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Literature search results

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<td>Richard Bridgen</td>
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Search details

Biologics or anti-TNF treatment for rheumatoid arthritis. Failure of treatment.

Resources searched

NHS Evidence; TRIP Database; Cochrane Library; EMBASE; MEDLINE; Google Scholar

Database search terms: rheumatoid adj2 arthritis; RHEUMATOID ARTHRISTS; arthritis adj2 deformans; arthrosis adj2 deformans; chronic adj2 polyarthritis; chronic adj2 "poly arthritis"; RA; atrophic adj2 arthritis; psoriatic adj2 arthritis; biologic*; biosimilar*; anti-TNF; "anti TNF"; antiTNF; exp TUMOR NECROSIS FACTOR ANTIBODY; "tumor necrosis factor" adj2 antibody*; "tumour necrosis factor" adj2 antibody*; "recombinant DNA"; "monoclonal antibodies"; exp MONOCLONAL ANTIBODY; infliximab; exp INFliximAB; etanercept; exp ETANERCEPT; adalimumab; exp ADALIMUMAB; TNF adj2 inhibit*; exp TUMOR NECROSIS FACTOR INHIBITOR; abatacept; exp ABATACEPT; "fusion protein*"; recombinant adj2 protein; exp RECOMBINANT PROTEIN; exp HYBRID PROTEIN; treatment adj2 failure; exp TREATMENT FAILURE; therap* adj2 failure*; failure*; drug* adj2 failure*; medic* adj2 failure*; "no* improve*"; (treatment OR therap* OR medic* OR drug*) adj2 fail*; adult*; ADULT; aged; exp AGED; elder*; senior*; older adj0 (people OR person*); "middle age*"; MIDDLE AGED; "systematic review"; SYSTEMATIC REVIEW; meta-analysis*; metaanalys*; META ANALYSIS; random* adj0 control* adj0 (trial OR stud*); RANDOMIZED CONTROLLED TRIAL; RANDOMIZED CONTROLLED TRIALS; RANDOMISED CONTROLLED TRIAL; clinical adj0 (trial* OR stud*); exp CLINICAL TRIAL; case (stud* OR report* OR series); CASE REPORT; CASE SERIES; CASE STUDIES; CASE STUDY

Evidence search string(s): (arthritis (rheumatoid OR deformans OR atrophic) OR polyarthritos OR RA) (biologic* OR biosimilar* OR anti-TNF OR ((TNF OR “tumor necrosis factor” OR “tumour necrosis factor”) inhibit*)) OR “monoclonal antibody*” OR “fusion protein*” OR “recombinant protein*”) fail*

Google search string(s): (~“rheumatoid arthritis” OR polyarthritis OR RA) (~biologic OR ~biosimilar OR ~anti-TNF OR ((“tumor necrosis factor” OR “tumour necrosis factor”) ~inhibitor) ~failure

Summary

There is a lot of research on the efficacy or otherwise of biologic and anti-TNF treatments.
for rheumatoid arthritis. Given the broad nature of the search, and the large number of biologic treatments, I am not able to summarise further. I have interpreted failure to include adverse effects caused by the treatment as well as ineffectiveness of the treatment as a whole.

### Guidelines

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<th><strong>American College of Rheumatology</strong></th>
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<td>Recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis 2008</td>
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<td>Clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis 2007</td>
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<td>Management of rheumatoid arthritis (first 2 years) 2006</td>
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<td>Guideline for anti-TNF alpha therapy in psoriatic arthritis 2005</td>
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<td>A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview 2009</td>
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<td>EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs 2010</td>
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<td>Rheumatoid arthritis - drugs for treatment after failure of a TNF inhibitor 2010</td>
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<td>Rheumatoid arthritis: the management of rheumatoid arthritis in adults 2009</td>
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<td>Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis 2007</td>
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<td>Assessing, managing and monitoring biologic therapies for inflammatory arthritis: guidance for rheumatology practitioners 2009</td>
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<th><strong>Scottish Medicines Consortium</strong></th>
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<td>Abatacept (Orencia) - In combination with methotrexate, for the treatment of moderate to severe active rheumatoid arthritis 2011</td>
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<td>Certolizumab pegol (Cimzia) Resubmission - Moderate to severe active rheumatoid arthritis in adult patients 2010</td>
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Certolizumab pegol (Cimzia) - Rheumatoid arthritis 2010
Abatacept (Orencia) for active rheumatoid arthritis 2007
Rituximab (MabThera) - Severe active rheumatoid arthritis 2006
SIGN
Management of early rheumatoid arthritis 2011
STEPS
Adalimumab (Humira) for the Treatment of Rheumatoid Arthritis 2008

Evidence-based reviews

Database of Uncertainties about the Effects of Treatments (DUETs)
Biologics for rheumatoid arthritis 2010
Abatacept for rheumatoid arthritis 2009

Database of Abstracts of Reviews of Effects
Systematic review and meta-analysis: anti-tumor necrosis factor alpha therapy and cardiovascular events in rheumatoid arthritis 2012
Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation 2011
Clinical relevance of switching to a second tumour necrosis factor-alpha inhibitor after discontinuation of a first tumour necrosis factor-alpha inhibitor in rheumatoid arthritis: a systematic literature review and meta-analysis 2011
The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis 2008

Health Technology Assessment Database
Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation 2011
A systematic review and economic evaluation of the use of tumour necrosis factor-alpha (TNF-α) 2011
UK cost-utility analysis of rituximab in patients with rheumatoid arthritis that failed to respond adequately to a biologic disease-modifying antirheumatic drug. 2009
Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis 2007
Aggressive versus symptomatic therapy in established rheumatoid arthritis 2007
Clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis 2007
Long-term clinical and cost-effectiveness of infliximab and etanercept for rheumatoid arthritis 2007
Rheumatoid Arthritis: the Effectiveness of Infliximab and Eta... 2007

National Horizon Scanning Centre
Fostamatinib for rheumatoid arthritis ? second line 2012
Abatacept (Orencia) for active rheumatoid arthritis 2009
Tocilizumab (Actemra) for rheumatoid arthritis 2007

NHS Economic Evaluation Database
Assessing the cost-effectiveness of biologic agents for the management of moderate-to-severe rheumatoid arthritis in anti-TNF inadequate responders in Italy: a modelling
Published research

1. Switching between anti-TNF-alpha agents does not improve functional capacity in patients with long-standing and active rheumatoid arthritis.

Author(s) Soares MR, Reis Neto ET, Luz KR, Ciconelli RM, Pinheiro MM

Citation: Revista Brasileira de Reumatologia, January 2012, vol./is. 52/1(9-15), 0482-5004;1809-4570 (2012 Jan-Feb)

Publication Date: January 2012

Abstract: OBJECTIVES: To assess clinical response after switching between anti-tumor necrosis factor-alpha (anti-TNF-alpha) agents in patients with rheumatoid arthritis (RA). PATIENTS AND METHODS: This study included 99 patients diagnosed with RA American College of Rheumatology, 1987), on anti-TNF-alpha therapy, to assess the therapeutic response after 24 weeks. Switching was performed if, after 12 to 24 weeks, a severe adverse event was reported (toxicity: T) or if no reduction greater than 0.6 in the initial Disease Activity Score 28 (DAS28) occurred (inadequate response: IR). In case of IR, the patient was considered as primary failure (PF). Secondary failure (SF) was defined as loss of response after initial improvement. Remission (DAS28 < 2.6), low disease activity (between 2.61 and 3.2), and functional improvement [increase in the initial Health Assessment Questionnaire (HAQ) > 0.2] were assessed by use of linear regression analysis. The significance level adopted was P < 0.05. RESULTS: Switching was performed in 39 (39.4%) patients, especially due to PF (24.3%), SF (35.1%) and T (40.5%). The retention rate of the first agent was 60.1%, and the mean time for switching was 14.2 +/- 10.9 months. After switching, a tendency towards a decrease in DAS28 was observed (4.7 +/- 1.4; P = 0.08), but not in the HAQ (1.2 +/- 0.77; P = 0.11). Around 43% of the patients achieved good/moderate EULAR response. The major determinant of switching was a higher initial DAS28, independent of age, duration of disease, and functional capacity. CONCLUSION: Switching between anti-TNF-alpha agents is a valid strategy to control disease activity, despite the low likelihood of remission and no significant improvement in functional capacity.
2. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial.

Author(s) van Vollenhoven RF, Geborek P, Forslind K, Albertsson K, Ernestam S, Petersson IF, Chatzidionysiou K, Bratt J, Swefot study group

Citation: Lancet, May 2012, vol./is. 379/9827(1712-20), 0140-6736;1474-547X (2012 May 5)

Publication Date: May 2012

Abstract: BACKGROUND: Analysis of the Swedish Farmacotherapy (Swefot) trial at 12 months showed that the addition of an anti-tumour-necrosis-factor agent gave an improved clinical outcome compared with the addition of conventional disease-modifying antirheumatic drugs in patients with methotrexate-refractory early rheumatoid arthritis. Here we report the 2 year follow-up assessment.METHODS: In this randomised, non-blinded, parallel-group trial, we enrolled adult patients older than 18 years with rheumatoid arthritis and a symptom duration of less than 1 year from 15 rheumatology units in Sweden between December, 2002 and December, 2006. All patients were started on methotrexate. After 3-4 months, those who failed treatment were randomly assigned (1:1) to group A (conventional treatment; additional sulfasalazine and hydroxychloroquine) or group B (biological treatment; additional infliximab). Randomisation was done with a computer-generated sequence. We analysed clinical outcomes at months 18 and 24 by the response criteria of the American College of Rheumatology and the European League Against Rheumatism, and radiographs of patients' hands and feet at months 12 and 24 using the Van der Heijde modification of the Sharp score. Analysis was by intention to treat. This trial is registered with www.ClinicalTrials.gov, number NCT00764725.FINDINGS: Of 493 screened individuals, we enrolled 487, of whom 258 were randomly allocated to treatment. The proportion of patients in group B who received a EULAR-defined good response was non-significantly greater than it was in group A at 18 months (49 of 128 [38%] vs 38 of 130 [29%]) and at 24 months (49 of 128 [38%] vs 40 of 130 [31%]; p=0.204). After 24 months, radiological disease progression was greater in patients in group A than it was in those in group B (mean 7.23 [SD 12.72] vs 4.00 [10.0]; p=0.009). We recorded three serious adverse events: an extended generalised illness in group A, an extended febrile episode in group B, and a generalised illness in group B.INTERPRETATION: Additional biological treatment is a valid option for patients who fail initial methotrexate treatment. However, improved clinical outcomes after 12 months and better radiographical results after 24 months should be weighed against the absence of a convincing clinical difference at 24 months and substantially higher costs. Therefore, for many patients who fail initial methotrexate treatment, add-on treatment with disease-modifying antirheumatic drugs is an appropriate treatment option.FUNDING: Swedish Rheumatism Association, Stockholm County, and Schering-Plough/Merck Sharp and Dohme. Copyright Copyright 2012 Elsevier Ltd. All rights reserved.

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3. Psoriatic arthritis in two patients with an inadequate response to treatment with
tocilizumab.

Author(s) Ogata A, Umegaki N, Katayama I, Kumanogoh A, Tanaka T

Citation: Joint, Bone, Spine: Revue du Rhumatisme, January 2012, vol./is. 79/1(85-7), 1297-319X;1778-7254 (2012 Jan)

Publication Date: January 2012

Abstract: Psoriatic arthritis (PsA) is considered as one of the seronegative spondylarthropathies. Like rheumatoid arthritis (RA), the increased production of interleukin (IL)-6 suggests a pathogenic role of IL-6 in PsA. However, whether humanized anti-IL-6 receptor antibody such as tocilizumab (TCZ) might be effective for PsA as well as RA has yet to be determined. We report herein two cases of PsA treated using TCZ. Although, TCZ treatment resulted in disappearance of serum CRP in both patients, arthritis and skin lesions were not improved despite 6-month administration of TCZ. In contrast, tumor necrosis factor (TNF) inhibitor proved effective against arthritis and skin lesions in these patients. Collectively, these findings not only indicate that IL-6 has distinct pathological roles in RA and PsA, but also suggest that TNF inhibitor therapy (but not TCZ) is effective for arthritis and skin lesions of PsA. Copyright Copyright 2011 Societe francaise de rhumatologie. Published by Elsevier SAS. All rights reserved.

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4. Safety and effectiveness of rituximab in patients with rheumatoid arthritis following an inadequate response to 1 prior tumor necrosis factor inhibitor: the RESET Trial.

Author(s) Haraoui B, Bokarewa M, Kallmeyer I, Bykerk VP, RESET Investigators

Citation: Journal of Rheumatology, December 2011, vol./is. 38/12(2548-56), 0315-162X;0315-162X (2011 Dec)

Publication Date: December 2011

Abstract: OBJECTIVE: To evaluate the safety and effectiveness of rituximab (RTX) in combination with methotrexate in patients with active rheumatoid arthritis (RA) after failure of a single tumor necrosis factor-alpha (TNF-alpha) inhibitor. Changes in patient-reported outcomes after primary treatment or retreatment with RTX and factors determining retreatment in clinical practice were also evaluated.METHODS: In this phase 3b open-label, multicenter trial, patients received 2 slow infusions of RTX 1000 mg 14 days apart after premedication (primary treatment). Patients with a clinically relevant response could receive retreatment between 24 and 48 weeks. The primary endpoint was evaluation of safety. Secondary outcomes were safety of retreatment, effectiveness of primary treatment and retreatment, and changes in patient-reported outcomes after primary treatment or retreatment.RESULTS: Of 120 patients enrolled at 36 centers and receiving primary RTX treatment, 77 received retreatment, 112 completed the 24-week primary treatment period, and 25 completed the 48-week primary treatment and retreatment period following a single course of RTX. The most common adverse events were mild to moderate nausea, vomiting, nasopharyngitis, and headache. No infections or infusion reactions were considered life-threatening. At 24 weeks, 58%, 27%, and 7% of patients achieved American College of Rheumatology 20, 50, and 70 improvements, respectively, and similar improvements were seen after retreatment.CONCLUSION: RTX was well tolerated, with a low incidence of infusion reactions and infections. Efficacy results, including enhanced response in rheumatoid factor-positive patients, were comparable to those reported in the literature. Based on its efficacy and safety profile and retreatment schedule, RTX is an attractive treatment option for patients that have not responded to a single TNF-alpha inhibitor.

Source: Medline

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5. Treatment of refractory adult-onset Still's disease with tocilizumab: report of two cases and review of the literature.

**Author(s)** Thonhofer R, Hiller M, Just H, Trummer M, Siegel C, Dejaco C

**Citation:** Rheumatology International, December 2011, vol./is. 31/12(1653-6), 0172-8172;1437-160X (2011 Dec)

**Publication Date:** December 2011

**Abstract:** Adult-onset Still's disease (AOSD) is empirically treated with nonsteroidal anti-inflammatory drugs, corticosteroids, conventional disease-modifying antirheumatic drugs, tumor necrosis factor-blocking agents or anakinra. The monoclonal anti-interleukin (IL)-6 antibody tocilizumab (TOC) has recently been approved for the treatment of rheumatoid arthritis and may be an attractive therapeutic option for AOSD as well. We report two AOSD patients treated with TOC and review of the current data on the use of TOC in AOSD. TOC was applied to the first patient after failure of chloroquin, methotrexate, adalimumab and etanercept. The second patient received TOC because of inefficacious methotrextate treatment. TOC was well tolerated by both the patients, and no clinically significant side effects occurred. Including these two cases, a total of seven AOSD patients have been successfully treated with TOC so far. TOC may be a promising treatment option for AOSD patients refractory to conventional disease-modifying antirheumatic drugs anakinra and tumor necrosis factor-[Formula: see text].

**Source:** Medline

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6. Predictors of response to rituximab in patients with active rheumatoid arthritis and inadequate response to anti-TNF agents or traditional DMARDs.

**Author(s)** Narvaez J, Diaz-Torne C, Ruiz JM, Hernandez MV, Torrente-Segarra V, Ros S, Rodriguez de la Serna A, Diaz-Lopez C, Sanmarti R, Nolla JM

**Citation:** Clinical & Experimental Rheumatology, November 2011, vol./is. 29/6(991-7), 0392-856X;0392-856X (2011 Nov-Dec)

**Publication Date:** November 2011

**Abstract:** OBJECTIVES: Identifying early predictors of response to biological agents is important for both the individual patient and health economics. The aim here was to identify clinical variables that are easily assessed in clinical practice which are associated with a major response to rituximab (moderate to good EULAR response, according to DAS28 values) in patients with active rheumatoid arthritis and inadequate response to anti-TNF agents or traditional DMARDs.METHODS: Rituximab (2x1g, two weeks apart) was administered to 108 patients in four different Spanish hospitals. The primary efficacy endpoint was the percentage of patients who achieved a major response at six months. Potential predictors of a major response were identified using multivariate binary logistic regression models.RESULTS: At six months of treatment 75.9% of patients achieved a major response (24% good and 52% moderate). Comparing the clinical features at baseline between patients who did or did not achieve a major response, significant differences were found in rheumatoid factor (RF) and anti-CCP positivity, as well as in the number of failed anti-TNF agents prior to rituximab. While rituximab delivers clinical benefit in seronegative patients, the presence of RF and/or anti-CCP consistently enriches clinical responses. The multivariate analysis showed that the best model for predicting a major EULAR response to rituximab was comprised of the following two variables: the anti-CCP antibody positivity (p=0.045) and the number of previous anti-TNF agents used (p=0.028). Using a cut-off level for CCP of 300 U/ml we found that patients with an anti-CCP titre >300 U/ml were 3-4 times more likely to achieve a major EULAR response [odds ratio (OR): 3.38; 95% CI: 1.025-11.17]. By contrast, those patients who had failed to respond to 2 or more anti-TNF agents had a 72.5% lower probability of achieving a moderate to good EULAR response (OR: 0.275; 95% CI: 0.087-0.871) than did patients who had only failed to respond to one such agent.CONCLUSIONS: A lower number of previously-failed TNF blockers and high anti-CCP titre can help select the best candidates for RTX therapy in patients with RA.

**Source:** Medline

**Author(s)** Schmitz S, Adams R, Walsh CD, Barry M, FitzGerald O

**Citation:** Annals of the Rheumatic Diseases, February 2012, vol./is. 71/2(225-30), 0003-4967;1468-2060 (2012 Feb)

**Publication Date:** February 2012

**Abstract:** BACKGROUND: A number of tumour necrosis factor alpha (TNFalpha) antagonists (anti-TNFalpha) are available to treat rheumatoid arthritis. All of these have demonstrated considerable efficacy in placebo controlled trials, but few head-to-head comparisons exist to date. This work's objective is to estimate the relative efficacy among licensed anti-TNFs in patients who have had an inadequate response to methotrexate (MTX). Different outcome measures are used to highlight the advantages of continuous measures in such analyses.

**METHODS:** A systematic review identified randomised controlled trials comparing the efficacy of licensed anti-TNFalpha agents with placebo at 24 weeks in patients who have had an inadequate response to MTX. Relative efficacy was estimated using Bayesian mixed treatment comparison (MTC) models. Three different outcome measures were used: RR of achieving an American College of Rheumatology (ACR) 20 and ACR50 response and the percentage improvement in Health Assessment Questionnaire (HAQ) score.

**RESULTS:** 16 published trials were included in the analysis. All anti-TNFs show considerably improved efficacy over placebo. The MTC results also provide evidence of some differences in efficacy of the TNFalpha antagonists. Etanercept appears superior to infliximab and golimumab, and certolizumab to infliximab and adalimumab. ACR results indicate improved efficacy of certolizumab over golimumab. On HAQ analysis, adalimumab, certolizumab, etanercept and golimumab appear superior to infliximab, and etanercept shows improved efficacy compared with adalimumab.

**CONCLUSIONS:** There are differences in efficacy among the TNFalpha antagonists. In a MTC, a continuous outcome measure has more strength to detect such differences than a binomial outcome measure because of its enhanced sensitivity to change.

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8. Patients non-responding to etanercept obtain lower etanercept concentrations compared with responding patients.

**Author(s)** Jamnitski A, Krieckaert CL, Nurmohamed MT, Hart MH, Dijkmans BA, Aarden L, Voskuyl AE, Wolbink GJ

**Citation:** Annals of the Rheumatic Diseases, January 2012, vol./is. 71/1(88-91), 0003-4967;1468-2060 (2012 Jan)

**Publication Date:** January 2012

**Abstract:** OBJECTIVE: To investigate the relationship between serum etanercept levels and clinical response.

**METHODS:** In 292 etanercept-treated patients with rheumatoid arthritis clinical and pharmacological data were determined at baseline and after 1, 4 and 6 months of etanercept treatment. Differences in etanercept levels between good, moderate and European League Against Rheumatism (EULAR) non-responders were assessed after 6 months of therapy.

**RESULTS:** After 6 months of therapy etanercept levels were significantly higher in good responders (median (IQR) 3.78 (2.53-5.17)) compared with both moderate 3.10 (2.12-4.47) and EULAR non-responders 2.80 (1.27-3.93) (all p<0.05). There was a significant association between clinical response and serum etanercept levels (regression coefficient 0.54, 95% CI 0.21 to 0.86, p=0.001). When patients were
categorised into quartiles according to the height of etanercept levels, the lowest quartile (etanercept level <2.1 mg/l) comprised 40% of all non-responders. The highest quartile (etanercept level >4.7 mg/l) comprised 35% of all good EULAR responders. Anti-etanercept antibodies were detected in none of the sera. CONCLUSION: The authors demonstrated that lower etanercept levels were associated with non-response. Therapeutic drug monitoring and the possibility of the adjusted dosing regimes in the selected groups of patients should be investigated further as a possible tool to optimise treatment with etanercept.

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Author(s) Vasiliopoulos Y, Bagiatis V, Stamatopoulou D, Zisopoulos D, Alexiou I, Sarafidou T, Settas L, Sakkas L, Mamouris Z
Citation: Clinical & Experimental Rheumatology, July 2011, vol./is. 29/4(701-4), 0392-856X;0392-856X (2011 Jul-Aug)
Publication Date: July 2011
Abstract: OBJECTIVES: To investigate the possible influence of tumour necrosis factor-alpha (TNF), TNF receptor I (TNFR) and TNF receptor II (TNFRII) gene polymorphisms on anti-TNF treatment responsiveness, stratified by autoantibody status. METHODS: A Greek multi-centre collaboration was established to recruit a cohort of patients (n=100) with active RA treated with anti-TNF drugs. TNF g.-238G>A (rs361525), g.-308G>A (rs1800629), g.-857C>T (rs1799724), TNFRI c.36A>G (rs4149584) and TNFRII c.676T>G (rs1061622) polymorphisms were genotyped by PCRRFLP assays. Serum RF and anti-CCP antibody status were determined using commercially available kits. Single-SNP, haplotype and stratification by autoantibody status analyses were performed in predicting response to treatment by 6 months, defined as the absolute change in DAS28. RESULTS: 31 patients (31%) were defined as non-responders due to failure to fulfill the DAS28 criteria. 79% and 66% were RF and anti-CCP positive, respectively. None of the genotyped SNPs was alone associated with responsiveness to drug treatment. However, after stratification by autoantibody status, carriage of TNFRII c.676G allele was associated with poorer response to drug treatment in anti-CCP positive patients (p=0.03), after 6 months of anti-TNF therapy. CONCLUSIONS: In concordance with previous studies, genetic polymorphisms alone cannot be used to safely predict clinical response to anti-TNF therapy however the combination of genetic factors and autoantibody status warrants further investigation in larger independent cohorts.

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10. Soluble urokinase plasminogen activator receptor as a useful biomarker to predict the response to adalimumab in patients with rheumatoid arthritis in a Japanese population.

Citation: Clinical & Experimental Rheumatology, September 2011, vol./is. 29/5(811-5), 0392-856X;0392-856X (2011 Sep-Oct)
Publication Date: September 2011
Abstract: OBJECTIVES: To determine whether soluble urokinase plasminogen activator receptor is a useful biomarker to predict the response to adalimumab (ADA) in Japanese
patients with rheumatoid arthritis. METHODS: Rheumatoid arthritis (RA) patients administrated ADA (n=51) were classified as good responders (n=18) or nonresponders (n=9) according to the EULAR response criteria after 8 weeks of bi-weekly ADA administration. We examined the expression of cytokines and chemokines in these groups by antibody array methods. Positive results obtained by antibody array methods were further confirmed by ELISA. RESULTS: Antibody array has identified that the macrophage migration inhibitory factor (MIF), vascular endothelial growth factor (VEGF) and soluble urokinase plasminogen activator receptor (uPAR) decreased in the good responders to ADA whereas these changes were not observed in the non-responders. The decrement of serum uPAR was confirmed by ELISA in the good responders to ADA. Furthermore, serum uPAR at baseline was significantly high in non-responders compared with good responders. CONCLUSIONS: An antibody array is convenient for screening the expression of proteins of interest. Examination of serum uPAR at baseline and thereafter may be useful as a predictive biomarker for primary failure toward ADA in patients with RA.

Source: Medline
Available in print at ULHT journal article requests. Complete the online form to obtain articles.

11. Long-term safety, efficacy and inhibition of radiographic progression with abatacept treatment in patients with rheumatoid arthritis and an inadequate response to methotrexate: 3-year results from the AIM trial.


Citation: Annals of the Rheumatic Diseases, October 2011, vol./is. 70/10(1826-30), 0003-4967;1468-2060 (2011 Oct)

Abstract: OBJECTIVE: To evaluate abatacept treatment over 3 years in patients with rheumatoid arthritis (RA) refractory to methotrexate (MTX). METHODS: Patients randomised to abatacept or placebo (+MTX) during the 1-year double-blind period of the Abatacept in Inadequate responders to Methotrexate (AIM) trial received open-label abatacept (+MTX) in the long-term extension (LTE). Safety was assessed for patients who received >= 1 dose of abatacept, regardless of randomisation group. Efficacy was assessed for patients randomised to abatacept who entered the LTE. RESULTS: 433 and 219 patients were randomised and treated with abatacept or placebo, respectively; 378 and 161 entered the LTE. At year 3, 440/539 patients were ongoing. No unexpected safety events were observed in the LTE. By year 3, incidence rates of adverse event and serious adverse events were 249.8/100 and 15.1/100 patient-years, respectively. Incidence rates were generally stable over time. At year 3, 84.8%, 63.4% and 37.5% of patients achieved American College of Rheumatology (ACR) criteria of 20, 50 and 70, respectively, compared with 82.3%, 54.3% and 32.4% of patients at year 1. Mean changes in Genant-modified Sharp scores were reduced progressively over 3 years, with significantly greater inhibition during year 3 compared with year 2 (p=0.022 for total score). CONCLUSION: In MTX-inadequate responders with RA, abatacept provided consistent safety and sustained efficacy over 3 years. The data suggest an increasing inhibitory disease-modifying effect on radiographic progression.

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12. Highest clinical effectiveness of rituximab in autoantibody-positive patients with rheumatoid arthritis and in those for whom no more than one previous TNF antagonist has failed: pooled data from 10 European registries.

OBJECTIVE: To assess the 6-month effectiveness of the first rituximab (RTX) course in rheumatoid arthritis (RA) and to identify possible predictors of response.

METHOD: 10 European registries submitted anonymised datasets (baseline, 3- and 6-month follow-up) from patients with RA who had started RTX, and datasets were pooled and analysed. Heterogeneity between countries was analysed by analysis of variance. Predictors of response were identified by logistic regression.

RESULTS: 2019 patients were included (mean age/disease duration 53.8/12.1 years, 80.3% female, 85.6% rheumatoid factor (RF) positive and 76.8% (456/594 patients) anti-cyclic citrullinated peptide antibodies (anti-CCP) positive). For these patients an average of 2.7 disease-modifying antirheumatic drugs (DMARDs) (range 0-10) had failed, and RTX was given as the first biological agent in 36.6% of patients. There was significant heterogeneity between countries for several baseline characteristics, including the number of previous biological agents. Disease Activity Score based on 28 joint counts (DAS28) decreased from 5.8±1.4 at baseline to 4.2±1.4 at 6 months (p<0.0001) and 22.2%/42.5% achieved European League Against Rheumatism (EULAR) good/moderate response. Larger 6-month improvement in DAS28 was observed in RF-positive and anti-CCP-positive versus seronegative patients. The following predictors of EULAR good response at 6 months were identified in a multivariate analysis: anti-CCP positivity (OR=2.86, p=0.003), number of previous DMARDs (OR=0.84, p=0.06), <=1 previous biological agents (OR=1.89, p=0.04), baseline DAS28 level (OR=0.74, p=0.003).

CONCLUSION: In this large observational cohort of patients with RA treated with RTX, seropositive patients achieved significantly greater reductions in DAS28 at 6 months than seronegative patients. Effectiveness was best when RTX was used as the first biological agent or after failure of no more than one anti-tumour necrosis factor agent.

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13. The presence or absence of antibodies to infliximab or adalimumab determines the outcome of switching to etanercept.

Author(s) Jamnitski A, Bartelds GM, Nurmohamed MT, van Schouwenburg PA, van Schaardenburg D, Stapel SO, Dijkmans BA, Aarden L, Wolbink GJ

Citation: Annals of the Rheumatic Diseases, February 2011, vol./is. 70/2(284-8), 0003-4967;1468-2060 (2011 Feb)

Publication Date: February 2011

Abstract: OBJECTIVE: The aim of this study was to test the hypothesis that the reason for non-response (caused by immunogenicity or not) to a first tumour necrosis factor (TNF) inhibitor defines whether a second TNF inhibitor will be effective. METHODS: This cohort study consisted of 292 consecutive patients with rheumatoid arthritis (RA), all treated with etanercept. A total of 89 patients (30%) were treated previously with infliximab or adalimumab ('switchers'), and the remaining 203 (70%) were anti-TNF naive. All switchers were divided into two groups: with and without antibodies against the previous biological. Differences in clinical response to etanercept between switchers with and without antibodies and patients who were anti-TNF naive were assessed after 28 weeks of treatment using changes in Disease Activity Score in 28 joints (DAS28). RESULTS: After 28 weeks of treatment, response to etanercept did not differ between patients who were anti-TNF naive and switchers with anti-drug antibodies ([Greek capital Delta]DAS28=2.1 +/- 1.3 vs [Greek capital Delta]DAS28=2.0 +/- 1.3; p = 0.743). In contrast, switchers without anti-drug antibodies had a diminished response to etanercept treatment compared to patients who were TNF naive ([Greek capital Delta]DAS28 =1.2 +/-1.3 vs [Greek capital Delta]DAS28 =2.1 +/- 1.3; p = 0.001) and switchers with antibodies ([Greek capital Delta]DAS28 =1.2 +/-1.3 vs [Greek capital Delta]DAS28 = 2.0 +/- 1.3; p =
CONCLUSION: Patients with RA with an immunogenic response against a first TNF-blocking agent had a better clinical response to a subsequent TNF blocker compared to patients with RA without anti-drug antibodies. Hence, determining immunogenicity can be helpful in deciding in which patient switching could be beneficial and can be part of a personalised treatment regimen.

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Author(s) Devine EB, Alfonso-Cristancho R, Sullivan SD
Citation: Pharmacotherapy: The Journal of Human Pharmacology & Drug Therapy, January 2011, vol./is. 31/1(39-51), 0277-0008;1875-9114 (2011 Jan)
Publication Date: January 2011
Abstract: STUDY OBJECTIVE: To compare the efficacy of biologic disease-modifying antirheumatic drugs (DMARDs) versus placebo with or without methotrexate, in treating rheumatoid arthritis. DESIGN: Comparative effectiveness analysis using an indirect treatment comparison (ITC) method in a Bayesian framework. PATIENTS: Adults with rheumatoid arthritis who had been enrolled in randomized controlled trials (RCTs) and had never failed biologic DMARD therapy. MEASUREMENTS AND MAIN RESULTS: Two random-effects logistic regression models, representing 6 and 12 months of treatment, were created using RCTs identified in a literature search. Twenty-three RCTs (11,589 patients) were included in the 6-month model and 10 RCTs (6051 patients) in the 12-month model. Nine biologic DMARDs in five therapeutic drug classes were included in the 6-month model, and six biologic DMARDs in three classes were included in the 12-month model. Our efficacy end point was the American College of Rheumatology 50% improvement criteria. In the 6-month model, all biologic DMARDs and methotrexate were significantly more efficacious than placebo and ranked in the following order: certolizumab (median log odds ratio [OR] 2.6), tocilizumab (1.7), rituximab (1.6), infliximab (1.6), etanercept (1.4), adalimumab (1.4), golimumab (1.4), abatacept (1.2), anakinra (1.0), and methotrexate (0.8). Of 45 pairwise comparisons, certolizumab was significantly more efficacious than methotrexate, but no other comparisons were significant. The rank order in the 12-month analysis was certolizumab (median log OR 2.0), rituximab (2.0), adalimumab (1.4), infliximab (1.4), etanercept (0.9), abatacept (0.6), and methotrexate (0.8). Of the 21 pairwise comparisons, none were significant. The results of the model using therapeutic class revealed that each class was more efficacious than placebo. In pairwise comparisons, each class was more efficacious than methotrexate, but none was more efficacious than another. CONCLUSION: Use of emerging ITC methods enabled us to compare the efficacy of biologic DMARDs for the treatment of rheumatoid arthritis in the absence of direct head-to-head comparison trials. Our methods enabled us to rank order these treatments. Further analyses by drug and by therapeutic class suggest that biologic DMARDs are similarly efficacious.

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15. Subacute liver failure induced by adalimumab.

Author(s) Hagel S, Bruns T, Theis B, Herrmann A, Stallmach A
Citation: International Journal of Clinical Pharmacology & Therapeutics, January 2011, vol./is. 49/1(38-40), 0946-1965;0946-1965 (2011 Jan)
Publication Date: January 2011
Abstract: Most cases of liver toxicity associated with TNF-antagonists have been linked to
Infliximab and to a lesser extent to etanercept. So far only mild elevations of liver enzymes during therapy with adalimumab have been reported. In general, patients who developed ALT and AST elevations were asymptomatic and the abnormalities decreased or resolved with either continuation or discontinuation of adalimumab, or modification of concomitant medications. In this case report, we are presenting the first case of a patient without previous history of liver disease or concomitant risk factors for liver disease who developed subacute liver failure during therapy with adalimumab for psoriatic arthritis.

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16. Etanercept-induced necrotizing crescentic glomerulonephritis in two patients with rheumatoid arthritis.

Author(s) Kaneko K, Nanki T, Hosoya T, Mizoguchi F, Miyasaka N
Citation: Modern Rheumatology, December 2010, vol./is. 20/6(632-6), 1439-7595;1439-7609 (2010 Dec)
Publication Date: December 2010
Abstract: We present two patients with rheumatoid arthritis (RA) who developed necrotizing crescentic glomerulonephritis (NCGN) during etanercept therapy. Both patients developed proteinuria and hematuria, and one progressed to renal failure. Renal biopsy revealed NCGN. In both patients, nephritis improved following discontinuation of etanercept and administration of prednisolone. Physicians should be aware of etanercept-induced GN in patients with RA on anti-tumor necrosis factor therapy.

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Author(s) Matsuno H
Citation: Modern Rheumatology, December 2010, vol./is. 20/6(561-5), 1439-7595;1439-7609 (2010 Dec)
Publication Date: December 2010
Abstract: This study was carried out to determine the effectiveness of half-dose administration of etanercept in patients with rheumatoid arthritis (RA) who exhibited secondary loss of efficacy of infliximab. Seventeen patients were administered 25 mg of etanercept once weekly for at least 1 year after secondary loss of efficacy of infliximab. The mean duration of treatment with infliximab was 32.5 +/- 1.3 months. The patient cohort consisted of 3 males and 14 females, with a mean age of 56.3 +/- 11.4 years and mean weight of 57.2 +/- 10.9 kg. The mean duration of RA was 16.2 +/- 10.9 years. The mean Disease Activity Score 28 was decreased significantly, from 5.8 at the initiation of infliximab therapy to 3.6 at the end of observation. There were no withdrawals due to adverse reactions during the study period, although in 2 subjects the agent was changed to tocilizumab due to lack of effect, one after 18 months and the other after 36 months, and 1 subject withdrew after 18 months for financial reasons. A good response can be expected to a half dose of etanercept in patients with secondary loss of efficacy of infliximab. Reduction of the patient's cost burden also makes this a superior treatment.

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18. **Etanercept treatment in rheumatoid arthritis patients with chronic kidney failure on predialysis.**

**Author(s)** Cho SK, Sung YK, Park S, Bae SC

**Citation:** Rheumatology International, September 2010, vol./is. 30/11(1519-22), 0172-8172;1437-160X (2010 Sep)

**Publication Date:** September 2010

**Abstract:** Rheumatoid arthritis (RA) patients with chronic kidney failure are intolerant to most disease-modifying antirheumatic drugs (DMARDs) and NSAIDs due to their potential toxicities. Although the tumor necrosis factor (TNF) inhibitors have emerged as a highly effective treatment for RA, their safety and efficacy in RA patients with chronic kidney failure have not been well reported. We retrospectively evaluated the safety and efficacy of etanercept treatment in RA patients with chronic kidney failure. We describe three RA patients with chronic kidney failure who had been treated with DMARDs, steroids and NSAIDs, but were discontinued from these classical agents due to several side effects and nephrotoxicity. The patients were treated with 25 mg of etanercept once or twice a week. We evaluated disease activity and used decreasing renal function and increasing number of infections to monitor safety. All three patients improved after starting etanercept treatment and their steroid requirements were decreased. Linear relationships between Modification of Diet in Renal Disease study equation (MDRD) glomerular filtration rate (GFR) and time were observed. Thus, in all patients, the changes in GFR did not represent superimposed acute drug toxicity, but rather chronic progressive renal failure. These cases show that etanercept may be a safe and effective treatment option for RA patients with chronic kidney failure.

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19. **Formulary review of 2 new biologic agents: tocilizumab for rheumatoid arthritis and ustekinumab for plaque psoriasis.**

**Author(s)** Schafer JA, Kjesbo NK, Gleason PP

**Citation:** Journal of Managed Care Pharmacy, July 2010, vol./is. 16/6(402-16), 1083-4087;1083-4087 (2010 Jul-Aug)

**Publication Date:** July 2010

**Abstract:** BACKGROUND: Two autoimmune biologics were recently approved by the FDA: ustekinumab in September 2009 for the treatment of moderate to severe plaque psoriasis in adults who are candidates for phototherapy or systemic therapy and tocilizumab in January 2010 for adult patients with moderate to severe rheumatoid arthritis (RA) who have not responded adequately to 1 or more tumor necrosis factor (TNF) antagonist therapies. Both agents use new mechanisms of action and add to the growing group of autoimmune biologics.OBJECTIVE: To critically review the phase 3 trials for ustekinumab and tocilizumab and provide managed care considerations in the context of the 9 other biologic agents on the market in the United States that are used to treat moderate to severe RA or psoriasis.METHODS: A MEDLINE review was performed for articles published and available through January 2010 using keywords "ustekinumab" and "tocilizumab" with an emphasis on phase 3 trials. The literature search was limited to articles in English, clinical trials, randomized controlled trials, and research conducted in humans. Search results for ustekinumab included 8 articles of which 4 were excluded for not being psoriasis or psoriatic arthritis trials. Search results for tocilizumab included 16 articles of which 8 were excluded for not being RA trials or using biomarkers as primary endpoints. Additional information was obtained from the FDA website.RESULTS: Three phase 3 trials are available for ustekinumab. Ustekinumab demonstrated superior efficacy to placebo in 2 trials for the treatment of psoriasis. In a 12-week trial, ustekinumab 45 milligrams (mg) and...
90 mg demonstrated significantly higher rates of 75% improvement in the psoriasis area and severity index (PASI 75) (67.5% and 73.8%, respectively) compared with etanercept (56.8%) in the first phase 3 comparative psoriasis trial between autoimmune biologics (P < 0.05 for both comparisons). In a phase 3 trial of RA patients who had failed prior TNF antagonist therapy, a 20% improvement in signs or symptoms according to the American College of Rheumatology criteria (ACR 20) at week 24 was achieved by significantly more study participants in the tocilizumab 8 mg per kilogram (kg) (50.0%) and 4 mg per kg (30.4%) groups than the placebo group (10.1%, P < 0.001 for both tocilizumab groups compared with placebo). Safety data for ustekinumab are limited to use for less than 2 years, and the prescribing information contains warnings regarding infection and malignancy. Tocilizumab is associated with neutropenia, thrombocytopenia, and elevations in lipids and liver function tests. Tocilizumab has unique adverse events when compared with other autoimmune biologics and requires laboratory testing and careful monitoring.

CONCLUSIONS: Ustekinumab and tocilizumab are new additions to the treatment of autoinflammatory disease. The majority of safety data for both agents are from trials lasting 3 to 6 months. Published long-term safety data for tocilizumab are limited to less than 143 patients treated longer than 5 years, and safety data for ustekinumab are scant beyond 2 years of use; therefore, clinicians should exercise caution prior to widespread adoption. The comparative efficacy and safety trial of etanercept and ustekinumab brings important clinical information to decision makers. Tocilizumab is indicated after failure or intolerance to a TNF antagonist and has unique safety concerns. Managed care plans will consider the experience and long-term data of these agents along with efficacy data and cost when establishing management programs such as prior authorization or step therapy.

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Author(s) Suarez-Gestal M, Perez-Pampin E, Calaza M, Gomez-Reino JJ, Gonzalez A

Citation: Arthritis Research & Therapy, 2010, vol./is. 12/2(R72), 1478-6354;1478-6362 (2010)

Publication Date: 2010

Abstract: INTRODUCTION: We aimed to replicate the strong associations that a recent genome wide association study (GWAS) has found between 16 single nucleotide polymorphisms (SNPs) and response to anti-tumour necrosis factor (TNF) treatment in 89 patients with rheumatoid arthritis (RA). This study is very important because, according to published simulations, associations as strong as the reported ones will mean that these SNPs could be used as predictors of response at the individual level. METHODS: Disease activity score (DAS28) was evaluated in 151 anti-TNF treated patients with RA of Spanish ancestry at baseline and every 3 months thereafter. Genotypes of the 16 putative predictor SNPs were obtained by single-base extension. Association between the relative change in DAS28 and SNP genotypes was tested by linear regression. In addition, logistic regression was applied to compare genotypes in non-responders (n = 34) versus good-responders (n = 61) following the EULAR response criteria. RESULTS: None of the analyses showed any significant association between the 16 SNPs and response to anti-TNF treatments at 3 or 6 months. Results were also negative when only patients treated with infliximab (66.9% of the total) were separately analyzed. These negative results were obtained in spite of a very good statistical power to replicate the reported strong associations. CONCLUSIONS: We still do not have any sound evidence of genetic variants associated with RA response to anti-TNF treatments. In addition, the possibility we had envisaged of using the results of a recent GWAS for prediction in individual patients should be dismissed.

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21. Subfulminant hepatitis B during treatment with adalimumab in a patient with rheumatoid arthritis and chronic hepatitis B.

**Author(s)** Verhelst X, Orlent H, Colle I, Geerts A, De Vos M, Van Vlierberghe H

**Citation:** European Journal of Gastroenterology & Hepatology, April 2010, vol./is. 22/4(494-9), 0954-691X;1473-5687 (2010 Apr)

**Publication Date:** April 2010

**Abstract:** We report a case of reactivation of hepatitis B virus (HBV) infection with subacute liver failure during administration of adalimumab, followed by a literature review of all 19 published cases, with a focus on the effect of antiviral prophylaxis. Eight patients were given prophylaxis and had a good outcome. Of the 11 patients without prophylaxis, six patients developed a reactivation and needed to stop anti-TNFalpha therapy (P = 0.017). One patient developed an acute liver failure, necessitating urgent liver transplantation. One patient died. Administration of anti-TNFalpha therapy can lead to HBV reactivation, with a possible lethal outcome. High-risk patients and possibly all patients should be screened for hepatitis B surface antigen and anti-HBV core antibody before starting anti-TNFalpha therapy. Administration of antiviral prophylaxis proves beneficial in prevention of reactivation in hepatitis B surface antigen positive patients.

**Source:** Medline

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22. Adalimumab therapy in patients with active rheumatoid arthritis.

**Author(s)** Ancuta C, Ancuta E, Miu S, Iordache C, Belibou C, Chirieac R

**Citation:** Revista Medico-Chirurgicala a Societatii de Medici Si Naturalisti Din Iasi, July 2009, vol./is. 113/3(710-5), 0048-7848;0048-7848 (2009 Jul-Sep)

**Publication Date:** July 2009

**Abstract:** AIM: To evaluate efficacy and safety of adalimumab (ADA), a monoclonal anti-TNFalpha antibody, in rheumatoid arthritis (RA).MATERIAL AND METHOD: 5 years retrospective observational study on 70 active RA (ARA 1987 modified criteria; 48 women; mean age 52.6 +/- 11.7 years; mean disease duration 6.7 +/- 3.2 years, mean DAS28 6.5 +/- 1.3) treated with ADA (classic regimen). All patients have been assessed according to a standard protocol: (i) clinical (tender and swollen joints; pain; global disease evaluation), (ii) inflammatory and (iii) immune parameters (total antinuclear and anti-double stranded DNA antibodies), (iv) activity and functional scores, (v) response to therapy (EULAR), (vi) adverse events. Evaluation was performed at baseline and every 3 months. Statistical analysis was done in SPSS-13, p < 0.05.RESULTS: Statistical significant improve in RA activity (mean final DAS28 3.6 +/- 0.8, p < 0.05), functional scores (mean HAQ 1.3 +/- 0.3, p < 0.05) and decreased X-ray progression (Sharp score) have been reported; 60% RA were responders (mean EULAR 2.7 +/- 1.2), 35.7% in remission, while switching to another biological agent (14.28% ADA failure) was done in 20% cases, clinical, biological and radiological efficacy and favorable safety profile of ADA have been demonstrated in real life long-term administration in active RA.

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23. Rheumatoid factor positivity rather than anti-CCP positivity, a lower disability and a lower number of anti-TNF agents failed are associated with response to rituximab in rheumatoid arthritis.

OBJECTIVES: We explored clinical factors associated with a major response to rituximab (RTX) (e.g. ACR ≥50, and European League against Rheumatism (EULAR) moderate to good response) in patients with active long-standing RA and inadequate response to anti-TNF agents or traditional DMARDs.

METHODS: RTX was used in 110 RA patients in six different Italian centres. The mean disease activity score on 28 joints (DAS28) was 6.4 +/- 0.99 and the mean HAQ was 1.63 +/- 0.68 at baseline. Thirty-two patients (29.1%) underwent RTX after the failure of DMARD therapy, 37 (33.6%) had failed or were intolerant to at least two anti-TNF agents, and 41 (37.3%) had failed or were intolerant to one anti-TNF agent. Univariate and multivariate analyses were performed.

RESULTS: The number of previous anti-TNF agents (P = 0.043), HAQ (P = 0.023), RF positivity (P < 0.0001) and anti-cyclic citrullinated peptide (anti-CCP) positivity (P = 0.003) were associated with ACR response > or =50 between month +4 and month +6 after starting RTX by univariate analysis. Multivariate analysis confirmed that a lower HAQ, a lower number of anti-TNF agents failed before RTX and RF positivity, but not anti-CCP positivity, were the selected variables associated with an ACR response > or =50, with an accuracy of 84% of the model. Only RF positivity correlated with EULAR moderate to good response both in the univariate and in the multivariate analysis, with an accuracy of 79% of the model.

CONCLUSION: RF-positive rather than anti-CCP-positive RA patients with lower baseline disability and a lower number of previously failed TNF blockers may be the best candidates to RTX.

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24. The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial.


Citation: Annals of the Rheumatic Diseases, November 2009, vol./is. 68/11(1708-14), 0003-4967;1468-2060 (2009 Nov)

Publication Date: November 2009

Abstract: OBJECTIVE: To assess the safety, tolerability and efficacy of abatacept in patients with rheumatoid arthritis (RA) who had failed anti-tumour necrosis factor (TNF) therapy and were switched to abatacept directly or after completing washout.

METHODS: In this international, 6-month, open-label trial, patients had active RA, an inadequate response to anti-TNF therapy for 3 months or longer and a disease activity score in 28 joints (DAS28 (C-reactive protein; CRP) of 5.1 or greater. "Washout" patients discontinued anti-TNF therapy 2 months or longer pre-screening; "direct-switch" patients began abatacept (approximately 10 mg/kg) at their next scheduled anti-TNF therapy dose.

RESULTS: 1046 patients were treated (449 washout, 597 direct-switch; baseline characteristics were similar between groups). At 6 months, adverse events (AE; 78.0% vs 79.2%), serious AE (11.1% vs 9.9%) and discontinuations due to AE (3.8% vs 4.0%) and serious AE (2.0% vs 1.3%) were comparable in washout versus direct-switch patients. There were no opportunistic infections. At 6 months, in washout versus direct-switch patients, similar clinically meaningful improvements were seen in DAS28 (CRP) (≥ 1.2 unit improvement, 59.5% vs 53.6%, respectively; low disease activity state, 22.5% vs 22.3%; DAS28-defined remission, 12.0% vs 13.7%), physical function (health assessment questionnaire disability index > ≥0.22 improvement; 46.3% vs 47.1%) and health-related quality of life (mean
CONCLUSION: Abatacept demonstrated acceptable safety and tolerability and clinically meaningful efficacy over 6 months in patients with inadequate response to anti-TNF therapy. Results were comparable with or without a washout, supporting direct switching from anti-TNF therapy to abatacept as an option in clinical practice. Trial registration number: NCT00124982.

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25. An evidence-based assessment of the clinical significance of drug-drug interactions between disease-modifying antirheumatic drugs and non-antirheumatic drugs according to rheumatologists and pharmacists.

Author(s) van Roon EN, van den Bemt PM, Jansen TL, Houtman NM, van de Laar MA, Brouwers JR

Citation: Clinical Therapeutics, August 2009, vol./is. 31/8(1737-46), 0149-2918;1879-114X (2009 Aug)

Publication Date: August 2009

Abstract: BACKGROUND: Clinically relevant drug-drug interactions (DDIs) must be recognized in a timely manner and managed appropriately to prevent adverse drug reactions or therapeutic failure. Because the evidence for most DDIs is based on case reports or poorly documented clinical information, there is a need for better assessment of their clinical relevance.OBJECTIVE: This study evaluates the interdisciplinary agreement between rheumatologists and clinical (hospital) pharmacists in assessing the clinical relevance of DDIs with disease-modifying antirheumatic drugs (DMARDs) and non-DMARD medications.METHODS: Potential DDIs were identified from the medical literature using MEDLINE and EMBASE for the years 1968-2009. The following search terms were used for the key word, title, and abstract sections of the publications: interaction(s), DMARD, disease-modifying antirheumatic drug(s), antirheumatic, rheumatology, rheumatoid arthritis, and the names of the individual DMARDs of interest (abatacept, adalimumab, anakinra, auranofin, aurothioglucose, aurothiomalate, d-penicillamine, etanercept, gold, [hydroxy]-chloroquine, interleukin-1 receptor antagonist, IL1-RA, infliximab, leflunomide, methotrexate, rituximab, and sulfasalazine/sulphasalazine). Reference lists of the retrieved publications were searched for further information on potential DDIs. All pharmacodynamic or pharmacokinetic DDIs between a DMARD and a non-DMARD identified were included in the study, with the exception of evidence regarding DMARD doses higher than used in the treatment of rheumatoid arthritis and interactions with phytotherapeutic or homeopathic preparations. Using a standard information set for each DDI (eg, from product labeling, textbooks, and the medical literature), a group of rheumatologists and a group of clinical pharmacists independently assessed whether the individual drug-DMARD combinations interacted and whether they required immediate intervention. Both groups consisted of 3 members (2 men and 1 woman), aged 40 to 60 years, who had >5 years of clinical experience and were currently involved in clinical practice in large, nonacademic teaching hospitals in the Netherlands.RESULTS: Forty potential DDIs with DMARDs were retrieved and assessed by the 2 groups. For 30 (75%) of these, rheumatologists and clinical pharmacists agreed about the requirement for immediate intervention. Specifically, 17 drug combinations (43%) were judged to interact and to require immediate intervention, and 13 combinations (33%) were judged either not to interact or to interact but not to require immediate intervention. For 10 combinations (25%), rheumatologists and clinical pharmacists were not in agreement. Overall, agreement between the groups was good (kappa = 0.80) for judging whether the drug combinations were interactions, and agreement was fair (kappa = 0.39) for judging whether immediate intervention was required. Prospective analysis of the data showed that rheumatologists tended to recommend immediate intervention more often when the adverse reaction to the DDI involved an increased risk of toxicity of the DMARD. In contrast, clinical pharmacists more often advocated immediate intervention when the adverse reaction involved decreased effectiveness of the DMARD.CONCLUSION: For a subset of DMARD-drug combinations,
rheumatologists and clinical pharmacists differed in their assessments of clinical relevance.

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26. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial.

Citation: Lancet, August 2009, vol./is. 374/9688(459-66), 0140-6736;1474-547X (2009 Aug 8)
Publication Date: August 2009
Abstract: BACKGROUND: New treatment strategies for early rheumatoid arthritis are evolving rapidly. We aimed to compare addition of conventional disease-modifying antirheumatic drugs (sulfasalazine and hydroxychloroquine) with addition of a tumour necrosis factor antagonist (infliximab) to methotrexate in patients with early rheumatoid arthritis.METHODS: We undertook a randomised trial in 15 rheumatology units in Sweden. We enrolled patients with early rheumatoid arthritis (symptom duration <1 year) and administered methotrexate (up to 20 mg per week). After 3-4 months, those who had not achieved low disease activity but who could tolerate methotrexate were randomly allocated by computer addition of either sulfasalazine and hydroxychloroquine or infliximab. Primary outcome was achievement of a good response according to European League Against Rheumatism (EULAR) criteria at 12 months. Patients were followed up to 24 months; here, we present findings at 12 months. Analysis was by intention to treat and we used non-responder imputation. The Swefot (Swedish Pharmacotherapy) study is registered in the WHO database at the Karolinska University Hospital, number CT20080004.FINDINGS: 487 patients were initially enrolled. Of 258 who had not achieved low disease activity with methotrexate, 130 were allocated sulfasalazine and hydroxychloroquine and 128 were assigned infliximab. 32 of 130 (25%) patients allocated sulfasalazine and hydroxychloroquine achieved the primary outcome compared with 50 of 128 (39%) assigned infliximab (risk ratio 1.59 [95% CI 1.10-2.30], p=0.0160). Adverse events were balanced fairly well between the two groups and accorded with known adverse events of the drugs used. No deaths occurred in either group.INTERPRETATION: In patients with early rheumatoid arthritis in whom methotrexate treatment failed, addition of a tumour necrosis factor antagonist to methotrexate monotherapy is clinically superior to addition of conventional disease-modifying antirheumatic drugs.FUNDING: Swedish Rheumatism Association, Schering-Plough.
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27. Clinical and radiological efficacy of initial vs delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis.

Author(s) van der Kooij SM, le Cessie S, Goekoop-Ruiterman YP, de Vries-Bouwstra JK,
van Zeben D, Kerstens PJ, Hazes JM, van Schaardenburg D, Breedveld FC, Dijkmans BA, Allaart CF

Citation: Annals of the Rheumatic Diseases, July 2009, vol./is. 68/7(1153-8), 0003-4967;1468-2060 (2009 Jul)

Publication Date: July 2009

Abstract: OBJECTIVES: To compare the clinical and radiological efficacy of initial vs delayed treatment with methotrexate (MTX) and infliximab (IFX) in patients with recent onset rheumatoid arthritis (RA).METHODS: In a post hoc analysis of the BeSt study (for Behandel Strategieen, Dutch for treatment strategies), 117 patients who started initial MTX+IFX were compared with 67 patients who started MTX+IFX treatment after failing (disease activity score (DAS)>2.4; median delay to IFX: 13 months) on > or =3 traditional DMARDs. If the DAS remained >2.4, the protocol dictated IFX dose increases to 6, 7.5 and 10 mg/kg. In case of a DAS < or =2.4 for > or =6 months, IFX was tapered and finally stopped. We aimed to correct for allocation bias using propensity scores. Functional ability was measured by the Health Assessment Questionnaire (HAQ), radiological progression by Sharp/van der Heijde scoring (SHS).RESULTS: Baseline differences between the initial and delayed groups were no longer significant after propensity score adjustment. At 3 years after baseline, patients treated with initial MTX+IFX experienced more improvement in HAQ over time and were less likely to have SHS progression than patients treated with delayed MTX+IFX (p = 0.034). At 2 years after IFX initiation, more patients in the initial group compared with the delayed group could discontinue IFX after a good response (56% vs 29%, p = 0.008).CONCLUSIONS: The results of this post hoc analysis suggest that using MTX+IFX as initial treatment for patients with recent onset RA is more effective than reserving MTX+IFX for patients who failed on traditional DMARDs, with more HAQ improvement over time, more IFX discontinuation and less progression of joint damage.

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Author(s) Li S, Kaur PP, Chan V, Berney S

Citation: Clinical Rheumatology, July 2009, vol./is. 28/7(787-91), 0770-3198;1434-9949 (2009 Jul)

Publication Date: July 2009

Abstract: An understanding of the cytokine cascade in a rheumatoid joint has led to the development of new therapeutic options, including drugs targeting tumor necrosis factor-alpha (TNF-alpha). The safety profile of these agents in patients with hepatitis-induced liver disease, however, remains a concern because of risks associated with immune suppression. To examine the effect of three different TNF-alpha antagonists, infliximab, etanercept, and adalimumab, on serum transaminases and hepatitis viral load in patients with rheumatoid arthritis (RA) and concurrent hepatitis B (HBV) or hepatitis C (HCV). Medical records of 11 patients with diagnosis of RA and documented seropositivity for hepatitis B or hepatitis C were retrospectively reviewed for worsening of hepatic inflammation and viral proliferation as measured by a rise in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and viral load while using these agents. Three patients had RA with concurrent chronic HBV and eight patients had RA with concurrent chronic HCV. Seven patients remained on a single anti-TNF-alpha agent and four patients switched to a second anti-TNF-alpha agent due to treatment failure. Two patients showed a transient elevation in AST and/or ALT from normal, but in all 11 patients, AST and ALT levels were within one time the upper range of normal at the conclusion of the study. No significant increase in viral load was seen except one patient who showed a fourfold increase from baseline. Our case series supports results obtained from previous studies.
examining the safety of anti-TNF-alpha agents in patients with underlying hepatic disease. Use of these agents in patients with HBV or HCV may be associated with a transient transaminitis but appears to be safe overall. In both groups, frequent monitoring of serum transaminase levels and viral load is essential.

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29. Effectiveness and safety of etanercept in subjects with RA who have failed infliximab therapy: 16-week, open-label, observational study.

Author(s) Bingham CO 3rd, Ince A, Harauvi B, Keystone EC, Chon Y, Baumgartner S
Citation: Current Medical Research & Opinion, May 2009, vol./is. 25/5(1131-42), 0300-7995;1473-4877 (2009 May)
Publication Date: May 2009
Abstract: BACKGROUND AND OBJECTIVE: Tumor necrosis factor (TNF) antagonists, including etanercept (a soluble TNF receptor) and infliximab (an anti-TNF monoclonal antibody) are used in the treatment of patients with rheumatoid arthritis (RA). The purpose of this study was to evaluate the effectiveness and safety of 50 mg etanercept weekly in subjects with RA who have failed infliximab therapy. METHODS: This phase 4, multicenter, open-label, single-arm, 16-week observational study enrolled subjects who had experienced primary (failure to achieve an initial response) or secondary (failure to maintain an initial response) infliximab failures. Effectiveness was measured using European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) response criteria and laboratory assessments were used to evaluate levels of inflammation, lymphotoxin alpha, drug concentrations, and antibodies to infliximab. Safety endpoints included incidence of serious adverse events. Clinical trial registration: This trial was registered under U.S. National Institutes of Health ClinicalTrials.gov identifier NCT00099554. RESULTS: At week 16, over half (62%; 95% CI = 55, 69) of all subjects in the trial achieved a good or moderate EULAR response (DAS28) with etanercept. Using ACR criteria, after 16 weeks of etanercept therapy, 45% (95% CI = 38, 52) of all subjects had achieved an ACR20 response. Benefits were noted in tender and swollen joint counts, subject and physician global assessments, joint pain, and the Health Assessment Questionnaire. Outcomes were similar between subjects with primary and secondary infliximab failures. Levels of lymphotoxin alpha did not appear to affect response to etanercept. Potential limitations included the lack of a washout period, short duration of the trial, and the number of subjects who did not receive all doses of etanercept. CONCLUSION: In this open-label, uncontrolled study, subjects with moderate to severe RA who failed to respond or who lost their initial response to infliximab safely benefited from receiving etanercept.

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30. Pneumocystis jiroveci pneumonia in patients with rheumatoid arthritis treated with infliximab: a retrospective review and case-control study of 21 patients.

Citation: Arthritis & Rheumatism, March 2009, vol./is. 61/3(305-12), 0004-3591;0004-3591 (2009 Mar 15)
Publication Date: March 2009
Abstract: OBJECTIVE: To establish proper management of Pneumocystis jiroveci
pneumonia (PCP) in rheumatoid arthritis (RA) patients treated with infliximab. PCP has been observed in 0.4% of patients with RA treated with infliximab in Japan.

METHODS: Data from patients with RA (n = 21) who were diagnosed with PCP during infliximab treatment and from 102 patients with RA who did not develop PCP during infliximab therapy were collected from 14 rheumatology referral centers in Japan. A retrospective review of these patients and a case-control study to compare patients with and without PCP were performed.

RESULTS: The median length of time from the first infliximab infusion to the development of PCP was 8.5 weeks. At the onset of PCP, the median dosages of prednisolone and methotrexate were 7.5 mg/day and 8 mg/week, respectively. Pneumocystis jiroveci was microscopically identified in only 2 patients, although the polymerase chain reaction test for the organism was positive in 20 patients. The patients with PCP had significantly lower serum albumin levels (P < 0.001) and lower serum IgG levels (P < 0.001) than the patients without PCP. Computed tomography of the chest in all patients with PCP revealed ground-glass opacity either with sharp demarcation by interlobular septa or without interlobular septal boundaries. Sixteen of the 21 patients with PCP developed acute respiratory failure, but all survived.

CONCLUSION: PCP is a serious complication that may occur early in the course of infliximab therapy in patients with RA. For the proper clinical management of this infectious disease, physicians need to be aware of the possibility of PCP developing during infliximab therapy.

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Author(s) Yokota K, Akiyama Y, Asanuma Y, Miyoshi F, Sato K, Mimura T
Citation: Rheumatology International, February 2009, vol./is. 29/4(459-61), 0172-8172;1437-160X (2009 Feb)
Publication Date: February 2009
Abstract: We report a Japanese male patient with intractable rheumatoid arthritis (RA), in whom tacrolimus was effective ultimately. Five years before the admission he was diagnosed as RA, which was resistant to various disease-modifying anti-rheumatic drugs (DMARDs). Two years before, administration of infliximab was initiated although the medicine failed to control RA. In spite of the multiple joint replacement, the RA disease activity worsened. Tacrolimus (1.5 mg/day) was administered. Twenty-four weeks of tacrolimus treatment reduced the disease activity score for 28 joints-erythrocyte sedimentation rate from 7.44 to 3.65. Herein, we present a patient with RA, who was successfully treated by tacrolimus, and in whom infliximab was not effective. Tacrolimus may be one of the drugs for RA patients refractory to the conventional treatments including methotrexate or tumor necrosis factor inhibitors.

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32. Basal anti-cyclic citrullinated peptide (anti-CCP) antibody levels and a decrease in anti-CCP titres are associated with clinical response to adalimumab in rheumatoid arthritis.

Author(s) Cuchacovich M, Catalan D, Wainstein E, Gatica H, Soto L, Aravena O, Pesce B, Sabugo F, Aguillon JC
Citation: Clinical & Experimental Rheumatology, November 2008, vol./is. 26/6(1067-73), 0392-856X;0392-856X (2008 Nov-Dec)
Publication Date: November 2008
Abstract: OBJECTIVE: To investigate the effect of adalimumab treatment on anti-cyclic citrullinated peptide antibodies (anti-CCP) in patients with rheumatoid arthritis
METHODS: 70 RA patients who failed treatment with disease modifying antirheumatic drugs (DMARDs) received 40 mg adalimumab subcutaneously every other week during 24 weeks. Serum samples were collected at baseline and at weeks 8, 16 and 24 before the corresponding adalimumab dose. The serum anti-CCP levels were tested by enzyme linked immunosorbent assay. RESULTS: At baseline, 52 of the 70 patients (74.3%) were positive for anti-CCP antibodies. 60% of the anti CCP positive patients and 44.4% of the anti CCP negative patients were ACR 20 responders at week 24 (p<0.049). The serum levels of anti-CCP antibodies decreased significantly after 24 weeks of adalimumab treatment only in those patients who met ACR 20 response criteria at week 24 (p<0.00044). Differences between baseline anti-CCP titers and those at 8, 16 and 24 weeks were all statistically significant (p<0.014, 0.003 and 0.019 respectively). No statistically significant changes in the anti-CCP levels were observed in patients who did not meet the ACR 20 response criteria. CONCLUSION: Basal anti-CCP antibodies levels correlate with clinical response to adalimumab. A decrease in anti-CCP levels on time was observed in patients showing also clinical improvement, suggesting that serum anti-CCP antibodies determination may be useful in assessing treatment efficacy in RA patients.

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33. Heart rate variability predicts anti-tumor necrosis factor therapy response for inflammatory arthritis.

Author(s) Holman AJ, Ng E

Citation: Autonomic Neuroscience-Basic & Clinical, December 2008, vol./is. 143/1-2(58-67), 1566-0702;1872-7484 (2008 Dec 5)

Publication Date: December 2008

Abstract: To consider autonomic status as a predictor of anti-tumor necrosis factor (TNF) treatment response for inflammatory arthritis, we conducted an exploratory, double-blind, 52-week study with 33 patients with rheumatoid (25) or psoriatic (8) arthritis using heart rate variability (HRV). All were assessed for parasympathetic, sympathetic, total power and tension index measures of autonomic reactivity at initiation of anti-TNF therapy with etanercept (15) or adalimumab (18). Clinical response was assessed at 6, 12, 26 and 52 weeks by internationally accepted outcome criteria (ACR20/50/70 and DAS28 response). Predictive value was demonstrated for all HRV assessments (p-value range 0.001-0.032), except sympathetic (p-value range 0.06-0.22), for ACR20, ACR50 and ACR70 at 52 weeks and at as early as 6 weeks for some measures. Only parasympathetic and tension index predicted DAS28 outcome (p-value range 0.009-0.024). Poor anti-TNF response was associated with low parasympathetic, low total power, high sympathetic and high tension index measures, a profile also predominant in the prior anti-TNF failure subset (12). In conclusion, this unique, exploratory study suggests that HRV may be a novel, useful predictor of response to anti-TNF therapy in patients with inflammatory arthritis, and emphasizes the importance of autonomic influence of autoimmune disease expression.

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34. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial.


Citation: Annals of the Rheumatic Diseases, November 2008, vol./is. 67/11(1516-23), 0003-4967;1468-2060 (2008 Nov)

Publication Date: November 2008

Abstract: OBJECTIVES: The phase III RADIATE study examined the efficacy and safety
of tocilizumab, an anti-IL-6 receptor monoclonal antibody in patients with rheumatoid arthritis (RA) refractory to tumour necrosis factor (TNF) antagonist therapy. METHODS: 499 patients with inadequate response to one or more TNF antagonists were randomly assigned to receive 8 mg/kg or 4 mg/kg tocilizumab or placebo (control) intravenously every 4 weeks with stable methotrexate for 24 weeks. ACR20 responses, secondary efficacy and safety endpoints were assessed. RESULTS: ACR20 was achieved at 24 weeks by 50.0%, 30.4% and 10.1% of patients in the 8 mg/kg, 4 mg/kg and control groups, respectively (less than p<0.001 both tocilizumab groups versus control). At week 4 more patients achieved ACR20 in 8 mg/kg tocilizumab versus controls (less than p = 0.001). Patients responded regardless of most recently failed anti-TNF or the number of failed treatments. DAS28 remission (DAS28 <2.6) rates at week 24 were clearly dose related, being achieved by 30.1%, 7.6% and 1.6% of 8 mg/kg, 4 mg/kg and control groups (less than p = 0.001 for 8 mg/kg and p = 0.053 for 4 mg/kg versus control). Most adverse events were mild or moderate with overall incidences of 84.0%, 87.1% and 80.6%, respectively. The most common adverse events with higher incidence in tocilizumab groups were infections, gastrointestinal symptoms, rash and headache. The incidence of serious adverse events was higher in controls (11.3%) than in the 8 mg/kg (6.3%) and 4 mg/kg (7.4%) groups. CONCLUSION: Tocilizumab plus methotrexate is effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNF antagonists and has a manageable safety profile. TRIAL REGISTRATION NUMBER: NCT00106522.

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35. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate.

Author(s) Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, Saldate C, Li T, Aranda R, Becker JC, Lin C, Cornet PL, Dougados M

Citation: Annals of the Rheumatic Diseases, August 2008, vol./is. 67/8(1096-103), 0003-4967;1468-2060 (2008 Aug)

Publication Date: August 2008

Abstract: OBJECTIVES: This double-blind trial evaluated the efficacy and safety of abatacept or infliximab vs placebo. The primary objective of this study was to evaluate the mean change from baseline in Disease Activity Score (based on erythrocyte sedimentation rates; DAS28 (ESR)) for the abatacept vs placebo groups at day 197. METHODS: Patients with rheumatoid arthritis (RA) and an inadequate response to methotrexate (MTX) were randomised 3:3:2 to abatacept (approximately 10 mg/kg every 4 weeks, n = 156), infliximab (3 mg/kg every 8 weeks, n = 165), or placebo (every 4 weeks, n = 110) and background MTX. Safety and efficacy were assessed throughout the study. RESULTS: Similar patient demographics and clinical characteristics were present at baseline between groups, with mean scores of approximately 1.7 for HAQ-DI and 6.8 for DAS28 (ESR). At 6 months, mean changes in DAS28 (ESR) were significantly greater for abatacept vs placebo (-2.53 vs -1.48, p<0.001) and infliximab vs placebo (-2.25 vs -1.48, p<0.001). For abatacept vs infliximab treatment at day 365, reductions in the DAS28 (ESR) were -2.88 vs -2.25. At day 365, the following response rates were observed for abatacept and infliximab, respectively: American College of Rheumatology (ACR) 20, 72.4 and 55.8%; ACR 50, 45.5 and 36.4%; ACR 70, 26.3 and 20.6%; low disease activity score (LDAS), 35.3 and 22.4%; DAS28-defined remission, 18.7 and 12.2%; good European League Against Rheumatism (EULAR) responses, 32.0 and 18.5%; and Health Assessment Questionnaire Disability Index (HAQ-DI), 57.7 and 52.7%. Mean changes in physical component summary (PCS) were 9.5 and 7.6, and mental component summary (MCS) were 6.0 and 4.0, for abatacept and infliximab, respectively. Over 1 year, adverse events (AEs) (89.1 vs 93.3%), serious AEs (SAEs) (9.6 vs 18.2%), serious infections (1.9 vs 8.5%) and discontinuations due to AEs (3.2 vs 7.3%) and SAEs (2.6 vs 3.6%) were lower with abatacept than...
CONCLUSIONS: In this study, abatacept and infliximab (3 mg/kg every 8 weeks) demonstrated similar efficacy. Overall, abatacept had a relatively more acceptable safety and tolerability profile, with fewer SAEs, serious infections, acute infusional events and discontinuations due to AEs than the infliximab group. Trial registration number: NCT00095147.

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Author(s) van der Bijl AE, Breedveld FC, Antoni CE, Kalden JR, Kary S, Burmester GR, Beckmann C, Unnebrink K, Kupper H

Citation: Clinical Rheumatology, August 2008, vol./is. 27/8(1021-8), 0770-3198;0770-3198 (2008 Aug)
Publication Date: August 2008

Abstract: This prospective open-label pilot study evaluated the effectiveness and safety of adalimumab and the relationship to antibodies against infliximab (IFX) in adult patients with active rheumatoid arthritis (RA) who had been treated previously with IFX and experienced treatment failure owing to lack or loss of response or intolerance. Patients self-administered adalimumab 40 mg subcutaneously every other week for 16 weeks, followed by maintenance therapy for up to Week 56. Measures of effectiveness included American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) response criteria, 28-joint Disease Activity Score, and the Health Assessment Questionnaire Disability Index. Serum IFX concentrations, human antichimeric antibody against IFX (HACA), adalimumab serum concentrations, antiadalimumab antibody, and safety also were assessed. Of the 41 enrolled patients, 37 completed 16 weeks and 30 completed 56 weeks of treatment. Patients experienced clinically meaningful improvements in all measures of RA activity, with greater response rates observed for patients who had experienced loss of initial response to or intolerance of IFX. At Week 16, 46% of patients achieved an ACR20 and 28% achieved an ACR50; 61% achieved at least moderate and 17% achieved a good EULAR response. Clinical benefit was maintained through Week 56 in all effectiveness parameters. Baseline HACA status did not significantly impact effectiveness. No new safety signals were observed; neither former IFX intolerance status nor baseline HACA status had a clinically relevant impact on adverse event frequency or severity. Adalimumab was effective and well-tolerated in patients with RA who previously failed IFX therapy, irrespective of reason for discontinuation and of HACA status.

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37. Anti-tumour necrosis factor treatment in patients with refractory systemic vasculitis associated with rheumatoid arthritis.


Citation: Annals of the Rheumatic Diseases, June 2008, vol./is. 67/6(880-4), 0003-4967;1468-2060 (2008 Jun)
Publication Date: June 2008
Abstract: OBJECTIVE: To assess anti-tumour necrosis factor (anti-TNF) agents in patients with refractory systemic rheumatoid vasculitis (SRV). METHODS: 1200 rheumatologists and internists were asked to provide medical files for patients with anti-TNF agents given as a second-line treatment for active SRV refractory to cyclophosphamide and glucocorticoids. RESULTS: We identified nine cases in which anti-TNF drugs were given for active SRV, despite previous treatment with a mean cumulative dose of 8.4 g of cyclophosphamide in association with high-dose glucocorticoids. The mean prednisone dose before anti-TNF therapy was 29.6 mg/day. After 6 months, six patients were in remission (complete in five, partial in one). The treatment failed in one patient and two patients stopped taking the anti-TNF treatment due to side-effects. Mean prednisone dose was reduced to 11.2 mg/day. Severe infection occurred in three patients. Relapses were observed in two patients. Remission was re-established by reintroducing anti-TNF therapy in one case and increasing the dose in the other. CONCLUSIONS: This study provides evidence of efficacy of anti-TNF therapy in adjunct to glucocorticoids for treating active refractory SRV. Remission was achieved in two-thirds of patients, with a significant decrease in prednisone dose, although there was a high rate of infection in these severely ill patients.

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38. Septic shock and community-acquired pneumonia associated with etanercept therapy.

Author(s) Nunez-Cornejo C, Borras-Blasco J, Gracia-Perez A, Rosique-Robles JD, Lopez-Camps V, Castera E, Abad FJ

Citation: International Journal of Clinical Pharmacology & Therapeutics, April 2008, vol./is. 46/4(193-7), 0946-1965;0946-1965 (2008 Apr)

Publication Date: April 2008

Abstract: OBJECTIVE: To report a case of septic shock and community-acquired pneumonia in a patient with psoriatic arthritis receiving treatment with etanercept. PATIENT DETAILS: A 65-year-old woman diagnosed as having psoriatic arthritis had received treatment with etanercept. Chest X-ray studies were normal and the tuberculin skin test was negative. Two months after etanercept therapy, the patient presented to our emergency department with fever, cough, chest pain and generalized weakness. Chest radiography revealed a right pulmonary infiltrate. Her condition rapidly deteriorated and she went into shock with a further drop in her blood pressure, tachycardia and tachypnea. She was intubated, mechanically ventilated and was treated with fluids, cardioversion and amiodarone. Empiric therapy with levofloxacin, amikacin and cefepime were initiated. In the urinalysis, the result of a rapid test for Streptococcus pneumoniae was positive. Etanercept treatment was suspended due to a possible adverse reaction associated with this drug. At the start of therapy her clinical condition improved slowly. On Day 28, the patient was afebrile and she was discharged from the intensive care unit. DISCUSSION: Most of the infections associated with etanercept therapy have been reported in patients with rheumatoid arthritis. Based on our observations, etanercept was the possible offender in the development of septic shock and respiratory failure in community-acquired pneumonia. There was a temporal relationship between exposure to the drug and onset of symptoms. Etanercept was the only drug administered before the septic shock developed. Based on the Naranjo algorithm, the adverse reaction could be considered possible. CONCLUSION: Patients initiated on etanercept should be counseled and receive appropriate screening before drug initiation. All febrile and newly occurring concomitant illnesses should be promptly evaluated. General practitioners should discontinue etanercept treatment and institute prompt and aggressive intervention if infection develops.

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**Author(s)** El-Hag K, Dercken HG, Prenzel R, Holzle E

**Citation**: Pneumologie, April 2008, vol./is. 62/4(204-8), 0934-8387;1438-8790 (2008 Apr)

**Publication Date**: April 2008

**Abstract**: BACKGROUND: TNF-alpha is known to play a decisive role as a pro-inflammatory cytokine in several autoimmune conditions. Its neutralisation by TNF-alpha antagonists such as infliximab (Remicade), a chimeric monoclonal anti-TNF-alpha antibody, may be beneficial in patients with active disease. These anticytokine drugs have been approved and are being increasingly used in the therapy of rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, psoriatic arthropathy and generalised psoriasis after established treatments have failed. Whenever therapy options are few, TNF-alpha antagonists are regarded as an effective, relatively safe and generally well-tolerated alternative, even if there is no detailed knowledge of their safety profile and possible long-term adverse events. In the respiratory tract an increased risk of viral, (myco-)bacterial, fungal and opportunistic infections has been observed. Furthermore, rare cases of severe fibrosing alveolitis in patients with concomitant immunosuppressant therapy or underlying lung disease have been reviewed recently.CASE: We present a case of drug-induced alveolitis following infliximab and azathioprine for the treatment of severe, generalised psoriasis and atopic eczema without pre-existing lung disease. Withdrawal of both drugs achieved clinical and functional stabilisation, and the addition of prednisolone resulted in a rapid improvement.CONCLUSION: As the pathophysiology of the pulmonary insult is unknown and since there are potentially serious adverse effects, we advise caution and close screening before and after initiation of TNF-alpha blockade, especially in patients with an underlying lung disease or with a combination of pneumotoxic agents.

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40. Treatment response to a second or third TNF-inhibitor in RA: results from the South Swedish Arthritis Treatment Group Register.

**Author(s)** Karlsson JA, Kristensen LE, Kapetanovic MC, Gulfe A, Saxne T, Geborek P

**Citation**: Rheumatology, April 2008, vol./is. 47/4(507-13), 1462-0324;1462-0332 (2008 Apr)

**Publication Date**: April 2008

**Abstract**: OBJECTIVES: To study treatment response rates of RA patients undergoing second- and third-line anti-TNF therapy and to identify baseline predictors of response to second-line treatment.METHODS: RA patients monitored in a prospective, observational study, having switched anti-TNF therapy once (first-time switchers, n = 337) or twice (second-time switchers, n = 36)—i.e. following failures with one antibody- and one receptor-type agent—between March 1999 and December 2006, were studied. Treatment responses at 3 months were assessed by the ACR and European League Against Rheumatism (EULAR) response criteria. Predictive potentials for response to second-line treatment of demographics, baseline disease activity measures, disease and treatment characteristics were analysed using logistic regression.RESULTS: ACR20 response was met by 51% of first-time and 35% of second-time switchers. Corresponding ACR50 rates were 27 and 18%; EULAR overall rates (EULAR good or moderate response) 71 and 58%; EULAR good rates 25 and 9% and 28-joint disease activity score (DAS28) remission rates 16 and 6%. Identified baseline predictors of response to second-line treatment were lower age and HAQ scores, elevated DAS28 values and having ceased the former anti-TNF treatment due to adverse events rather than inefficacy. No variable was predictive for all examined response criteria.CONCLUSIONS: Response rates of first-time anti-TNF switchers are somewhat below those of anti-TNF naive RA patients, while the markedly inferior response...
rates of second-time switchers suggest other therapeutic options to be considered in this situation. Identified baseline predictors of response may be useful indicators to second-line anti-TNF therapy, but vary depending on the response criteria set studied.

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**Author(s)** Donahue KE, Garthlehner G, Jonas DE, Lux LJ, Thieda P, Jonas BL, Hansen RA, Morgan LC, Lohr KN

**Citation:** Annals of Internal Medicine, January 2008, vol./is. 148/2(124-34), 0003-4819;1539-3704 (2008 Jan 15)

**Publication Date:** January 2008

**Abstract:** BACKGROUND: The comparative effectiveness of rheumatoid arthritis therapies is uncertain. PURPOSE: To compare the benefits and harms of disease-modifying antirheumatic drugs (DMARDs) for adults with rheumatoid arthritis. DATA SOURCES: Records limited to the English language and studies of adults were identified by using MEDLINE, EMBASE, The Cochrane Library, and International Pharmaceutical Abstracts from 1980 to September 2007. STUDY SELECTION: Two persons independently selected relevant head-to-head trials and prospective cohort studies with at least 100 participants and 12-week follow-up and relevant good- or fair-quality meta-analyses that compared benefits or harms of 11 drug therapies. For harms, they included retrospective cohort studies. DATA EXTRACTION: Information on study design, interventions, outcomes, and quality were extracted according to a standard protocol. DATA SYNTHESIS: Head-to-head trials (n = 23), mostly examining synthetic DMARDs, showed no clinically important differences in efficacy among synthetic DMARDs (limited to methotrexate, leflunomide, and sulfasalazine) or among anti-tumor necrosis factor drugs (adalimumab, etanercept, and infliximab). Monotherapy with anti-tumor necrosis factor drugs resulted in better radiographic outcomes than did methotrexate but no important differences in clinical outcomes (for example, 20%, 50%, or 70% improvement according to American College of Rheumatology response criteria). Various combinations of biological DMARDs plus methotrexate improved clinical response rates and functional outcomes more than monotherapy with either methotrexate or biological DMARDs. In patients whose monotherapy failed, combination therapy with synthetic DMARDs improved response rates. Numbers and types of short-term adverse events were similar for biological and synthetic DMARDs. The evidence was insufficient to draw conclusions about differences for rare but serious adverse events for biological DMARDs. LIMITATION: Most studies were short-term efficacy trials conducted in selected populations with few comorbid conditions. CONCLUSION: Limited available comparative evidence does not support one monotherapy over another for adults with rheumatoid arthritis. Although combination therapy is more effective for patients whose monotherapy fails, the evidence is insufficient to draw firm conclusions about whether one combination or treatment strategy is better than another or is the best treatment for early rheumatoid arthritis.

**Source:** Medline

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42. Effect of tumor necrosis factor alpha antagonists in a patient with rheumatoid arthritis and primary biliary cirrhosis.

Author(s): Spadaro A, Scrivo R, Riccieri V, Valesini G

Citation: Joint, Bone, Spine: Revue du Rhumatisme, January 2008, vol./is. 75/1(87-9), 1297-319X;1778-7254 (2008 Jan)

Publication Date: January 2008

Abstract: The proinflammatory cytokine tumor necrosis factor alpha seems to play a major role in the pathogenesis of both rheumatoid arthritis and primary biliary cirrhosis. We describe the case of a 46-year-old female patient with rheumatoid arthritis and concomitant primary biliary cirrhosis treated with anti-tumor necrosis factor alpha agents. During infliximab treatment we observed a poor clinical response and persistence of liver function test abnormalities. After infliximab interruption the levels of alkaline phosphatase dropped and had nearly reached normal values when etanercept was started. This new therapeutic regimen was well tolerated with joint clinical improvement and normalization of alkaline phosphatase. This single case shows that etanercept therapy maintained liver enzymes within the normal range and controlled the arthritis with a 30-month follow-up whereas infliximab did not account for similar results.

Source: Medline

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43. Effectiveness, predictive response factors, and safety of anti-tumor necrosis factor (TNF) therapies in anti-TNF-naive rheumatoid arthritis.


Citation: Journal of Rheumatology, December 2007, vol./is. 34/12(2334-42), 0315-162X;0315-162X (2007 Dec)

Publication Date: December 2007

Abstract: OBJECTIVE: To evaluate the effectiveness and safety of anti-tumor necrosis factor (anti-TNF) therapies in rheumatoid arthritis (RA), and to identify the factors involved in this response. METHODS: Dynamic prospective cohort study of patients with RA treated with anti-TNF under clinical practice conditions. Effectiveness was evaluated using Disease Activity Score (DAS) 28, European League Against Rheumatism (EULAR) response, Health Assessment Questionnaire (HAQ), and time to treatment failure. Prior adherence was evaluated retrospectively and safety was evaluated by adverse events (AE). The analysis was restricted to anti-TNF-naive patients. RESULTS: The study included 161 patients treated for RA during 6 years (60 infliximab, 79 etanercept, and 22 adalimumab). At 6 months, 15% reached a good EULAR response and 38% a moderate response. A mean decrease of -1.5 (p < 0.0001) was observed in the DAS28 and of -0.34 in the HAQ (p < 0.0001); however, women showed poorer progress in terms of DAS and HAQ. In the first year, 64.3% did not experience treatment failure and this figure was 50.5% after 2 years. In one-third, glucocorticoids were withdrawn and in the remainder the dose was reduced by 50%. Adherence to treatment, selection of etanercept, and intensification of infliximab were associated with a lower probability of premature failure in the multivariate model. AE were similar to other those in studies and no outstanding differences in safety were found between the 3 anti-TNF therapies. CONCLUSIONS: Anti-TNF treatments are effective and safe, reducing the activity of the disease, disability, and the need for corticosteroids. Patients who displayed good adherence prior to the anti-TNF treatment and were treated with etanercept or with increasing doses of infliximab had the best chance of displaying a response.

Source: Medline

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44. Heart failure among younger rheumatoid arthritis and Crohn’s patients exposed to TNF-alpha antagonists.

Author(s) Curtis JR, Kramer JM, Martin C, Saag KG, Patkar N, Shatin D, Burgess M, Xie A, Braun MM

Citation: Rheumatology, November 2007, vol./is. 46/11(1688-93), 1462-0324;1462-0324 (2007 Nov)

Publication Date: November 2007

Abstract: OBJECTIVES: New onset heart failure (HF) has been associated with the use of TNF-alpha antagonists etanercept and infliximab based upon spontaneous adverse event reports. HF clinical trials of these agents were stopped early due to futility or worsening of existing HF. A potential association between etanercept and infliximab and new onset HF has been studied minimally at a population level. METHODS: Using administrative claims from a large U.S. health care organization, we identified rheumatoid arthritis (RA) and Crohn's disease (CD) patients receiving infliximab or etanercept (exposed), and comparator cohorts of RA and CD patients receiving non-biologic immunosuppressives (unexposed). We studied adults < 50 years to reduce potential confounding related to common age-related comorbidities. Based on abstracted medical records of suspected HF cases, a physician panel adjudicated cases as definite, possible or no HF. RESULTS: Among 4018 RA and CD patients with mean duration follow-up of 18 months, 9 of 33 suspected HF cases (identified using claims data) were adjudicated as definite (n = 5) or possible (n = 4) HF. The relative risk of HF among TNF-alpha antagonist-treated RA and CD patients was 4.3 and 1.2, respectively (P = NS for both). The absolute difference in cumulative incidence of HF among infliximab or etanercept-exposed compared to unexposed patients was 3.4 and 0.3 cases per 1000 persons for RA and CD (P = NS), respectively, yielding a number needed to harm of 294 for RA and 3333 for CD. CONCLUSION: We found only a small number of presumed HF cases (n = 9, or 0.2%) in a large population of relatively young RA and CD patients. Although there was an increased relative risk of incident, HF that was not statistically significant among those exposed to TNF-alpha antagonists compared to those unexposed, larger cohorts are needed to provide more precise risk estimates and permit adjustment for potential confounding.

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45. Infliximab and methotrexate as induction therapy in patients with early rheumatoid arthritis.

Author(s) van der Bijl AE, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Ten Wolde S, Han KH, van Krugten MV, Allaart CF, Breedveld FC, Dijkmans BA

Citation: Arthritis & Rheumatism, July 2007, vol./is. 56/7(2129-34), 0004-3591;0004-3591 (2007 Jul)

Publication Date: July 2007

Abstract: OBJECTIVE: To evaluate the efficacy of infliximab plus methotrexate (MTX) as induction therapy in patients with early rheumatoid arthritis (RA). METHODS: Disease-modifying antirheumatic drug (DMARD)-naive patients with active, early RA who were included as group 4 of the BeSt study were initially treated with infliximab (3 mg/kg) in combination with MTX (25 mg/week). The Disease Activity Score (DAS) was measured every 3 months. In patients with persistent low disease activity (DAS <or=2.4) for at least 6 months, the infliximab dosage was tapered and finally discontinued; the MTX dosage then was tapered to 10 mg/week. In patients with a DAS of >2.4, the infliximab dosage was increased (maximum 10 mg/kg), and they were subsequently switched to another DMARD.
Except for intraarticular administration, corticosteroids were not permitted. Functional ability and the modified Sharp/van der Heijde score were determined after 2 years of therapy. RESULTS: Of the 120 patients, 67 responders (56%) had persistent low disease activity and discontinued infliximab after a median of 9.9 months, with a median MTX dosage of 10 mg/week after 2 years. Ten other patients experienced a disease flare after discontinuation and resumed infliximab after a median of 3.7 months. Thirteen patients did not achieve persistent low disease activity and received infliximab at various dosages. Treatment was unsuccessful in 30 patients. In the 67 responders, the progression of joint damage was lower than in the 30 patients in whom treatment failed. CONCLUSION: Fifty-six percent of patients with active early RA, initially treated with infliximab plus MTX, could discontinue infliximab after achieving a DAS of <or=2.4. Low disease activity was maintained in these patients while the MTX dosage was tapered to 10 mg/week.

Source: Medline
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46. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy.

Author(s) Genovese MC, Mease PJ, Thomson GT, Kivitz AJ, Perdok RJ, Weinberg MA, Medich J, Sasso EH, M02-570 Study Group

Citation: Journal of Rheumatology, May 2007, vol./is. 34/5(1040-50), 0315-162X;0315-162X (2007 May)

Publication Date: May 2007

Abstract: OBJECTIVE: To demonstrate the safety and efficacy of adalimumab for the treatment of active psoriatic arthritis (PsA) in patients with an inadequate response to disease modifying antirheumatic drugs (DMARD). METHODS: In a placebo controlled, double-blind, randomized, multicenter study, patients were treated for 12 weeks with subcutaneous injections of adalimumab 40 mg every other week (eow) or placebo, followed by a period of open-label treatment with adalimumab 40 mg eow. The primary efficacy endpoint was the percentage of patients who met the American College of Rheumatology (ACR20) core criteria at Week 12. Secondary efficacy measures included the modified Psoriatic Arthritis Response Criteria (PsARC) and assessments of disability, psoriatic lesions, and quality of life. For missing data, nonresponder imputation was used for ACR and PsARC scores and last observation carried forward for other measures. RESULTS: A total of 100 patients received study drug (51 adalimumab, 49 placebo). At Week 12, an ACR20 response was achieved by 39% of adalimumab patients versus 16% of placebo patients (p = 0.012), and a PsARC response was achieved by 51% with adalimumab versus 24% with placebo (p = 0.007). At Week 12, measures of skin lesions and disability were statistically significantly improved with adalimumab. After Week 12, open-label adalimumab provided continued improvement for adalimumab patients and initiated rapid improvement for placebo patients, with ACR20 response rates of 65% and 57%, respectively, observed at Week 24. Serious adverse events had similar frequencies during therapy with placebo (4.1%), blinded adalimumab (2.0%), and open-label adalimumab (3.1%). No serious infections occurred during adalimumab therapy. CONCLUSION: In this study of patients who had active PsA and a previous, inadequate response to DMARD therapy, adalimumab was well tolerated and significantly reduced the signs, symptoms, and disability of PsA during 12 weeks of blinded and 12 weeks of open-label therapy. Adalimumab also improved psoriasis in these patients.

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47. [Anakinra, a recombinant human IL-1 receptor antagonist, in clinical practice. Outcome in 60 patients with severe rheumatoid arthritis]. [Italian] Anakinra, antagonista umano ricombinante del recettore dell'IL-1, nella pratica clinica. Outcome in 60 pazienti con artrite reumatoide severa.
OBJECTIVE: We evaluated both the efficacy and safety of anakinra in daily routine rheumatoid arthritis clinical practice.

METHODS: We studied 60 cases, including patients with previous anti-TNF-alpha exposure, treated with anakinra (100 mg/daily s.c.) in combination with methotrexate (7.5-10 mg/week i.m.) or leflunomide (20 mg/die) in a two year observational study. Efficacy measures were assessed using the American College of Rheumatology (ACR) response criteria. Safety was evaluated according to a modified World Health Organization adverse reaction term dictionary.

RESULTS: At week 14, ACR 20% response criteria have been fulfilled by 53 (91.3%) out of 58 patients, 51 (87.9%) of them achieving also an ACR 50% and 15 (25.8%) an ACR 70% response. Thirteen patients touched 102 weeks of treatment: ACR 20% response was achieved in 92.3%, while ACR 50% and ACR 70% were respectively found in 84.6% and 38.4% of the cases. The mean decrease in HAQ score was 0.38, p<0.001. Of the 16 patients who were previously treated with anti-TNF-alpha blockers, 81.2% responded to anakinra. There was no significant difference in the ACR response between groups with and without previous anti-TNF-alpha exposure. Seventeen patients (28.3%) stopped anakinra because of side-effects (5%) or failure to respond (23.3%). Only 4 cases of pulmonary, of which 2 have been hospitalised, and 1 case with tuberculosis (previously treated with infliximab) were observed.

CONCLUSIONS: Our clinical experience confirms that anakinra is effective and safe in the treatment of rheumatoid arthritis. Anakinra seems also useful in patients with previous anti-TNF-alpha blockers failures. Even though major adverse events were rare, clinicians should be aware of such a possibility.

48. Switching to etanercept in patients with rheumatoid arthritis with no response to infliximab.

Author(s) Di Poi E, Perin A, Morassi MP, Del Frate M, Ferraccioli GF, De Vita S

Citation: Clinical & Experimental Rheumatology, January 2007, vol./is. 25/1(85-7), 0392-856X;0392-856X (2007 Jan-Feb)

Publication Date: January 2007

Abstract: TNF-alpha is thought to play a pivotal role in the initiation and perpetuation of the chronic inflammatory process in rheumatoid arthritis. TNF-alpha blockers such as infliximab and etanercept are currently used in the treatment of active rheumatoid arthritis (RA) when traditional DMARDs have failed and are effective in a significant proportion of patients. However, about one third are non-responders to anti-TNF-alpha. The aim of this study was to verify whether rheumatoid patients, after failing infliximab, can benefit from etanercept. We analysed 18 patients with active RA with no response to at least 3 DMARDs and where infliximab therapy had failed. The patients had received infliximab associated with methotrexate: eleven of them did not show any significant response, while seven patients, after a good response, relapsed. Etanercept was then started. EULAR criteria of response were used with calculation of activity index DAS28 at baseline, after 2 weeks, 3 months and every third month until last follow-up. A moderate or good response was achieved with etanercept in 13 out of 18 patients. From our experience, etanercept can be considered as a good alternative choice when infliximab has failed.

Source: Medline

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Abstract: Infliximab, a chimeric monoclonal antibody that binds the tumor necrosis factor alpha (TNFalpha), is used in the treatment of rheumatoid arthritis (RA) and Crohn's disease (CD). Previous cases of significant secondary liver disease associated with infliximab treatment have been reported in patients with RA, CD, and psoriatic arthritis. Two additional patients with RA who developed a serious liver disease associated with infliximab treatment are reported here. A 39-year old RA patient was admitted with cholestatic liver disease after 8 months of treatment with infliximab. She had no history of hepatic diseases, exposure to hepatotoxic or illicit drugs, or alcohol abuse. A liver biopsy showed severe ductal proliferation with collapse and enucleation of the hepatocytes. Despite aggressive treatment with oral prednisolone, she developed hepatic failure. On the 45th day, a liver transplant was performed. The second patient, a 54-year old RA patient, was diagnosed with autoimmune hepatitis after 12 infliximab infusions. She fulfilled autoimmune hepatitis type 1 criteria. A liver biopsy disclosed an altered lobulillar structure with chronic inflammation and the formation of collagen bands. She was treated with prednisolone and azatioprine and a complete recovery was noted 1 month later. These cases should alert rheumatologists to the possibility of new adverse reactions (liver injury) associated with the use of TNFalpha blockers in an autoimmune setting.

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dropped out before week 14 due to adverse events (5) or patients' initiative (2). In patients with moderate response, the following disease course between infusion 4 and 5 was observed: improvement to good response 6, temporary response 6, stable disease activity 6, drop out 8. In moderate responders, interval reduction and dose increase resulted in a decrease in mean DAS28 from 5.1 to 3.6 \([P = 0.005, \text{mean interval 5.6 weeks, mean infliximab dose 4.8 mg/kg/8 week (endpoint)}]\) and from 4.1 to 3.6 \([P = 0.04, \text{mean infliximab dose 7.3 mg/kg/8 week (endpoint)}]\), respectively.

CONCLUSION: Three different patterns of disease activity were observed in moderate responders after 14 weeks of infliximab treatment, i.e. further improvement, no change in disease activity or a temporary response. Both interval reduction and dose increase significantly reduced disease activity, however, with different mean infliximab dosages. In good responders the response was often sustained over follow-up, whereas non-responders showed modest or no improvement despite dose adjustments.

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53. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate.


Citation: Arthritis & Rheumatism, September 2006, vol./is. 54/9(2817-29), 0004-3591;0004-3591 (2006 Sep)

Publication Date: September 2006

Abstract: OBJECTIVE: To establish the safety and efficacy of repeat infusions of tocilizumab (previously known as MRA), a humanized anti-interleukin-6 (IL-6) receptor antibody, alone and in combination with methotrexate (MTX), for the treatment of rheumatoid arthritis (RA).METHODS: The study group comprised 359 patients with active RA in whom the response to MTX was inadequate. During a stabilization period, these patients received their current dose of MTX for at least 4 weeks. Following stabilization, they were randomized to 1 of 7 treatment arms, as follows: tocilizumab at doses of 2 mg/kg, 4 mg/kg, or 8 mg/kg either as monotherapy or in combination with MTX, or MTX plus placebo.RESULTS: A 20% response (improvement) according to the American College of Rheumatology criteria (ACR20 response) was achieved by 61% and 63% of patients receiving 4 mg/kg and 8 mg/kg of tocilizumab as monotherapy, respectively, and by 63% and 74% of patients receiving those doses of tocilizumab plus MTX, respectively, compared with 41% of patients receiving placebo plus MTX. Statistically significant ACR50 and ACR70 responses were observed in patients receiving combination therapy with either 4 mg/kg or 8 mg/kg of tocilizumab plus MTX (\(P < 0.05\)). A dose-related reduction in the Disease Activity Score in 28 joints was observed from week 4 onward, in all patients except those receiving monotherapy with 2 mg/kg of tocilizumab. In the majority of patients who received 8 mg/kg of tocilizumab, the C-reactive protein level/erythrocyte sedimentation rate normalized, while placebo plus MTX had little effect on these laboratory parameters. Tocilizumab was mostly well tolerated, with a safety profile similar to that of other biologic and immunosuppressive therapies. Alanine transaminase and aspartate transaminase levels followed a sawtooth pattern (rising and falling between infusions). There were moderate but reversible increases in the nonfasting total cholesterol and triglyceride levels and reversible reductions in the high-density lipoprotein cholesterol and neutrophil levels. There were 2 cases of sepsis, both of which occurred in patients who were receiving combination therapy with 8 mg/kg of tocilizumab plus MTX.CONCLUSION: These results indicate that targeted blockade of IL-6 signaling is a highly efficacious and promising means of decreasing disease activity in RA.
54. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison.


Citation: Annals of the Rheumatic Diseases, October 2006, vol./is. 65/10(1357-62), 0003-4967:0003-4967 (2006 Oct)

Publication Date: October 2006

Abstract: OBJECTIVE: To compare the efficacy and safety of etanercept and sulfasalazine, alone and in combination, in patients with active rheumatoid arthritis despite sulfasalazine treatment.

METHODS: A double-blind, randomised study in adult patients with active rheumatoid arthritis despite stable sulfasalazine (2-3 g/day) treatment. The primary end point was a 20% response by the American College of Rheumatology (ACR) criteria at 24 weeks.

RESULTS: At baseline, the three treatment groups (sulfasalazine, n = 50; etanercept, n = 103; etanercept and sulfasalazine, n = 101) were comparable for demographic variables and disease activity. Lack of efficacy was the primary reason for discontinuation (sulfasalazine, n = 12; etanercept, n = 1; etanercept and sulfasalazine, n = 4; p<0.001). Significantly more patients receiving etanercept, alone or in combination (74% for each), achieved ACR 20 responses at 24 weeks than those receiving sulfasalazine (28%; p<0.01). Similarly, more patients in the etanercept groups achieved ACR 50 and ACR 70 responses than those in the sulfasalazine group (p<0.01). In the groups receiving etanercept, significant differences in the ACR core components were observed by week 2 compared with those receiving sulfasalazine alone (p<0.01). The incidences of several common adverse events (headache, nausea, asthenia) were lower with etanercept alone than with the combination (p<0.05), but infections and injection site reactions were higher with etanercept alone (p<0.05). The safety profiles of both etanercept treatment groups were comparable with previous experience of etanercept.

CONCLUSIONS: For all efficacy variables assessed, etanercept alone or in combination with sulfasalazine resulted in substantial and similar improvement in disease activity from baseline to week 24 compared with sulfasalazine alone in patients with active rheumatoid arthritis despite their sulfasalazine treatment. All three treatments were generally well tolerated.

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Author(s) Ruppert M, De Clerck L, van Offel J, Hubens G, Balliu L, Vaneerdeweg W

Citation: Acta Chirurgica Belgica, March 2006, vol./is. 106/2(225-7), 0001-5458;0001-5458 (2006 Mar-Apr)

Publication Date: March 2006

Abstract: Vasculitis leading to intestinal necrosis is a rare complication of rheumatoid arthritis. The introduction of anti-TNF treatment for methotrexate-resistant cases improved disease-control substantially in these often more aggressive forms of rheumatoid arthritis. As far as we know only two cases of severe vasculitis following anti-TNF treatment have been reported. We describe a 45-year old female patient with severe rheumatoid arthritis, who presented with an epileptic insult, renal failure and a quickly deteriorating general condition
due to intestinal vasculitis, while she had been receiving anti-TNF treatment for 6 months.

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56. An open label, single dose study to evaluate the safety, efficacy, and effects on CD25 expression of ciclosporin in patients with active rheumatoid arthritis despite treatment with methotrexate and infliximab.

Author(s) Sidiropoulos PI, Siakka P, Raptopoulou A, Mamoulaki M, Choulaki C, Koutala H, Kouroumal H, Kritikos H, Boumpas DT

Citation: Annals of the Rheumatic Diseases, April 2006, vol./is. 65/4(538-41), 0003-4967;0003-4967 (2006 Apr)

Publication Date: April 2006

Abstract: OBJECTIVE: To explore the safety, efficacy, and lymphocyte activation of a triple therapeutic regimen with infliximab, methotrexate (MTX), and ciclosporin A (CsA) by an open label, pilot study. PATIENTS AND METHODS: 19 patients (mean age 52.9 years) with active rheumatoid arthritis (mean DAS28 7.3) after a mean of 16.8 infliximab infusions and dose adjustments of both infliximab and MTX were enrolled. CsA was added to a stable therapeutic regimen. Disease activity was evaluated by the DAS28. Lymphocyte activation was evaluated by assessing CD25 expression on peripheral blood mononuclear cells (PBMCs). Primary end points were safety and efficacy according to the EULAR response criteria at 24 weeks. RESULTS: Eight patients (42%) discontinued treatment: adverse events (3), inefficacy (2) or non-compliance (2). One patient had a stroke and died. 5/11 (45%) patients who completed 24 weeks’ treatment were moderate responders. CD25 expression, both on unstimulated and phytohaemagglutinin stimulated PBMCs in five patients assessed, was reduced (mean (SD) values from 37 (34)% to 15 (10)% and from 50 (15)% to 29 (20)%, respectively). CONCLUSION: In this group of patients with refractory, highly active disease, addition of CsA reduced lymphocyte activation, and resulted in a modest response and a high rate of discontinuation. In such patients, other new approaches need to be explored.

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57. The effect of etanercept on anti-cyclic citrullinated peptide antibodies and rheumatoid factor in patients with rheumatoid arthritis.

Author(s) Chen HA, Lin KC, Chen CH, Liao HT, Wang HP, Chang HN, Tsai CY, Chou CT

Citation: Annals of the Rheumatic Diseases, January 2006, vol./is. 65/1(35-9), 0003-4967;0003-4967 (2006 Jan)

Publication Date: January 2006

Abstract: OBJECTIVE: To evaluate the changes in anti-cyclic citrullinated peptide antibodies (anti-CCP) and rheumatoid factor (RF) following etanercept treatment in patients with rheumatoid arthritis. METHODS: The study included 90 patients with rheumatoid arthritis who failed treatment with disease modifying antirheumatic drugs (DMARDs). All patients were allowed to continue treatment with DMARDs; 52 of them received etanercept as a twice weekly 25 mg subcutaneous injection for three months, and the others did not. Serum samples were collected at baseline and one month intervals during the treatment course. The serum levels of anti-CCP and RF were tested by enzyme linked immunosorbent assay and nephelometry, respectively. RESULTS: At baseline, 45 of the 52 etanercept treated patients (86.5%) and 32 of the 38 controls (84.2%) were positive for anti-CCP. Tests for RF were positive in 78.9% and 84.2% of patients with or without etanercept treatment, respectively. The serum levels of anti-CCP and RF decreased
significantly after a three month etanercept treatment (p = 0.007 and p = 0.006, respectively). The average decrease from baseline calculated for each individual patient in the etanercept treated group was 31.3% for anti-CCP and 36% for RF. The variation in anti-CCP was positively correlated with the variation in disease activity, swollen and tender joint counts, RF, and C reactive protein. CONCLUSIONS: Etanercept combined with DMARDs leads to a much greater decrease than DMARDs alone in the serum levels of anti-CCP and RF in rheumatoid arthritis, compatible with a reduction in clinical disease activity.

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58. The benefit/risk profile of TNF-blocking agents: findings of a consensus panel.
Author(s) Hochberg MC, Lebwohl MG, Plevy SE, Hobbs KF, Yocum DE
Citation: Seminars in Arthritis & Rheumatism, June 2005, vol./is. 34/6(819-36), 0049-0172;0049-0172 (2005 Jun)
Publication Date: June 2005
Abstract: OBJECTIVE: To review the benefits and risks associated with the use of the tumor necrosis factor (TNF)-blockers in various indications (eg, rheumatoid arthritis [RA], Crohn's disease [CD], psoriasis). METHODS: The members of the consensus panel were selected based on their expertise. Centocor, Inc provided an educational grant to the Center for Health Care Education to facilitate the consensus panel. Peer-reviewed articles discussing clinical studies and clinical experiences with TNF-blockers form the basis of this review. Emerging data that have not been peer-reviewed are also included. RESULTS: The TNF-blockers infliximab, etanercept, and adalimumab are all approved for treatment of RA. All 3 are effective, and there are currently no published data from head-to-head clinical trials to support using 1 agent over another. Preliminary data from small, retrospective studies indicate that switching among agents to overcome inadequate efficacy or poor tolerability is beneficial in some patients. The only TNF-blocker currently approved for the induction and maintenance of remission in CD is infliximab. Preliminary data indicate that etanercept and infliximab are effective in treating psoriasis. Some risks associated with TNF-blockers have become apparent, including congestive heart failure, demyelinating diseases, and systemic lupus erythematosus, but in most cases can be identified and managed. Several of these risks (eg, lymphoma and serious infections) are associated with either the condition per se or the concomitant medication use. Simple screening procedures help manage the risk of tuberculosis infection; however, it is recommended that physicians and patients be alert to the development of any new infection so that appropriate treatment may be initiated promptly. Rare infusion reactions, particularly with infliximab, may also be effectively managed. CONCLUSION: TNF-blockers are effective and may be safely used for short- and long-term management of RA or CD. TNF-blockers also show efficacy in other emerging indications.
Source: Medline
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59. Repeated infusions of low-dose infliximab plus methotrexate in psoriatic arthritis: immediate benefits are not maintained after discontinuation of infliximab.
Author(s) Covelli M, Scioscia C, Iannone F, Lapadula G
Citation: Clinical & Experimental Rheumatology, March 2005, vol./is. 23/2(145-51), 0392-856X;0392-856X (2005 Mar-Apr)
Publication Date: March 2005
Abstract: OBJECTIVE: To assess the long-term efficacy and tolerability of a therapy consisting of infliximab at low dosage plus methotrexate in patients with psoriatic arthritis
As a second objective, we assessed whether the improvement obtained after 54 weeks of infliximab could be maintained with methotrexate alone. METHODS: A group of 26 patients with peripheral PsA resistant to various DMARDs were treated with infliximab + methotrexate for 54 weeks. RESULTS: The clinical response after the induction period was constant and progressive, with a high percentage of patients achieving an ACR50 response. The ESR and CRP values also declined continuously and gradually, but only CRP returned to normal values. During the follow-up period after 54 weeks, infliximab was stopped and the improvement obtained lasted for 2-6 months. The secondary end point was not achieved, and an extension period was designed. Results at 78 weeks are presented. CONCLUSIONS: Open questions for treating patients with infliximab and methotrexate are the schedule and the length of the administration and how to preserve the improvement obtained after the drug discontinuation.

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60. Clinical efficacy of infliximab plus methotrexate in DMARD naive and DMARD refractory rheumatoid arthritis is associated with decreased synovial expression of TNF alpha and IL18 but not CXCL12.

Author(s) van Oosterhout M, Levarht EW, Sont JK, Huizinga TW, Toes RE, van Laar JM

Citation: Annals of the Rheumatic Diseases, April 2005, vol./is. 64/4(537-43), 0003-4967:0003-4967 (2005 Apr)

Publication Date: April 2005

Abstract: BACKGROUND: Tumour necrosis alpha (TNF alpha) blocking agents lead to pronounced clinical effects and reduced synovial infiltrate in rheumatoid arthritis. Laboratory and clinical studies suggest that TNF alpha independent pathways play a role in the disease. OBJECTIVES: To evaluate the immunopathological effects of combination therapy on rheumatoid synovial tissue in order to identify TNF alpha independent mechanisms. METHODS: 12 rheumatoid patients, including four DMARD (disease modifying antirheumatic drug) naive patients with early disease, were studied for the effect of combination therapy with infliximab and methotrexate on the synovial infiltrate. Biopsies and clinical assessments (DAS28) were carried out before the first and after the third infusion of infliximab. Synovial inflammation was scored semiquantitatively. Co-expression of CD38(+) cells was studied by an immunofluorescent double labelling technique. RESULTS: Marked clinical responses were associated with a global reduction in the synovial infiltrate and expression of cytokines, notably interleukin 18 and TNF alpha, but low grade disease activity persisted. There was no effect on the expression of CXCL12, and germinal centre-like structures were still detectable in synovial tissue in two patients after treatment. CD38(+) activated T cells were more resistant to treatment than CD38(+) plasma cells. No differences in clinical response or effects on synovial infiltrate were observed between DMARD refractory and DMARD naive patients. CONCLUSIONS: Persistent expression of CXCL12 and incomplete resolution of lymphocytic infiltrates after infliximab plus methotrexate indicates that TNF alpha independent mechanisms are operative in rheumatoid arthritis. This may contribute to low grade disease activity, even in DMARD naive patients with early disease.

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61. Adalimumab in rheumatoid arthritis after failed infliximab and/or etanercept therapy: experience with 18 patients.
62. Antineutrophil cytoplasmic antibody-associated necrotizing crescentic glomerulonephritis in a patient receiving treatment with etanercept for severe rheumatoid arthritis.

Author(s) Doulton TW, Tucker B, Reardon J, Velasco N

Citation: Clinical Nephrology, September 2004, vol./is. 62/3(234-8), 0301-0430;0301-0430 (2004 Sep)

Abstract: Etanercept is a tumor necrosis factor inhibitor used in the treatment of rheumatoid arthritis and, increasingly, in a range of other diseases. We report a case of necrotizing crescentic glomerulonephritis, associated with a positive antineutrophil cytoplasmic antibody, causing acute renal failure in a woman receiving treatment with etanercept for severe rheumatoid arthritis. Our patient was treated with steroids and cyclophosphamide following withdrawal of etanercept, with a good clinical response. Although reports of vasculitis in patients receiving treatment with etanercept are rare, this drug has been shown to up-regulate some aspects of immune function, and the possibility that this agent may precipitate or exacerbate vasculitis in some individuals has to be considered.

Source: Medline

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63. Safety of leflunomide plus infliximab combination therapy in rheumatoid arthritis.

Author(s) Godinho F, Godfrin B, El Mahou S, Navaux F, Zabraniecki L, Cantagrel A

Citation: Clinical & Experimental Rheumatology, May 2004, vol./is. 22/3(328-30), 0392-856X;0392-856X (2004 May-Jun)

Abstract: OBJECTIVE: To analyse the safety of leflunomide plus infliximab combination therapy, in adult rheumatoid arthritis (RA) patients. PATIENTS: A retrospective study of 17 adult patients with active RA (DAS 28 = 5.94 +/- 0.88 at baseline) who were treated with a combination of leflunomide plus infliximab after failure of treatment with other DMARDs. 13 patients were treated for a minimum of 3 months with leflunomide without toxicity before beginning infliximab. Treatment was begun simultaneously with both drugs in 4 patients. Side effects (clinical and biological) and efficacy (DAS 28) were evaluated at each infliximab infusion (3 mg/kg at week 0, 2, 6 and then every 8 weeks). RESULTS: Thirteen patients experienced 20 types of side effects and 8 of them stopped the combination therapy. The causes of discontinuation were congestive heart failure (1 case), hypertension with thoracic pain (2 cases), eczematous skin patches (2 cases) and neutropenia (3 cases). No death was registered. Nine RA patients continued the therapy with a median follow-up of 22 weeks. Only 4 of them experienced no side effects. Eight patients were positive for antinuclear antibodies (ANA) and 1 for double-stranded DNA (dsDNA) antibodies at study entry. After treatment, 13 and 5 patients tested positive respectively for ANAs and dsDNA antibodies. There was no relationship between discontinuation and ANA/dsDNA positivity. CONCLUSION: In this cohort, adverse events were not very different from those seen in patients on either treatment alone and the combination of leflunomide plus infliximab did not appear to be as badly tolerated as described in a previous study.

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64. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed.


**Citation:** Annals of the Rheumatic Diseases, May 2004, vol./is. 63/5(508-16), 0003-4967:0003-4967 (2004 May)

**Publication Date:** May 2004

**Abstract:** OBJECTIVE: To evaluate the efficacy and safety of monotherapy with adalimumab in patients with RA for whom previous DMARD treatment has failed. METHODS: In a 26 week, double blind, placebo controlled, phase III trial, 544 patients with RA were randomised to monotherapy with adalimumab 20 mg every other week, 20 mg weekly, 40 mg every other week, 40 mg weekly, or placebo. The primary efficacy end point was > or =20% improvement in the ACR core criteria (ACR20 response). Secondary efficacy end points included ACR50, ACR70, EULAR responses, and the Disability Index of the Health Assessment Questionnaire (HAQ DI). RESULTS: After 26 weeks, patients treated with adalimumab 20 mg every other week, 20 mg weekly, 40 mg every other week, and 40 mg weekly had significantly better response rates than those treated with placebo: ACR20 (35.8%, 39.3%, 46.0%, 53.4%, respectively v 19.1%; p< or =0.01); ACR50 (18.9%, 20.5%, 22.1%, 35.0% v 8.2%; p< or =0.05); ACR70 (8.5%, 9.8%, 12.4%, 18.4% v 1.8%; p< or =0.05). Moderate EULAR response rates were significantly greater with adalimumab than with placebo (41.5%, 48.2%, 55.8%, 63.1% v 26.4%; p< or =0.05). Patients treated with adalimumab achieved better improvements in mean HAQ DI than those receiving placebo (-0.29, -0.39, -0.38, -0.49 v -0.07; p< or =0.01). No significant differences were found between adalimumab and placebo treated patients for serious adverse events, serious infections, or malignancies. Injection site reaction occurred in 10.6% and 0.9% of adalimumab and placebo treated patients, respectively (p< or =0.05). CONCLUSION: Among patients with RA for whom previous DMARD treatment had failed, adalimumab monotherapy achieved significant, rapid, and sustained improvements in disease activity and improved physical function and was safe and well tolerated.

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65. [Etanercept in rheumatoid arthritis patients with a poor therapeutic response to infliximab]. [Spanish] Etanercept en pacientes con artritis reumatoide y escasa respuesta terapeutica a infliximab.

**Author(s)** Sanmarti R, Gomez-Puerta JA, Rodriguez-Cros JR, Albaladejo C, Munoz-Gomez J, Canete JD

**Citation:** Medicina Clinica, March 2004, vol./is. 122/9(321-4), 0025-7753;0025-7753 (2004 Mar 13)

**Publication Date:** March 2004

**Abstract:** BACKGROUND AND OBJECTIVE: Knowing the efficacy of tumor necrosis factor alpha (TNF-alpha) antagonists infliximab or etanercept in patients with rheumatoid arthritis (RA), when one of these agents has failed, has important clinical implications. The aim of this study was to evaluate the efficacy and safety of etanercept in patients with RA, who had previously failed to infliximab. PATIENTS AND METHOD: All patients with RA of our center, who were previously treated with infliximab and then switched to etanercept for...
at least 6 months were included. Several clinical and biological parameters of inflammatory activity along with the disease activity index DAS-28 were assessed at baseline, after 6 weeks, at the last infusion of infliximab and after 0, 3 and 6 months on etanercept. EULAR criteria of response to therapy were used. RESULTS: Fourteen RA patients (13 females) who fulfilled the inclusion criteria were selected. These patients had been treated with infliximab for a mean (SD) of 14.6 (8.3) months when this drug was stopped. Drug withdrawal owed to inefficacy in 12 patients and to adverse events in 2 patients. Most patients achieved a satisfactory clinical response within the first months of infliximab, with a subsequent loss of the therapeutic effects in spite of an increase in the infliximab dose or a reduction of the interval between infusions. In the group of 12 patients switched to etanercept because of infliximab inefficacy, a therapeutic response was achieved in 10 (83%) of them after 6 months of etanercept therapy. The DAS-28 score (SD) improved from 5.6 (1) to 4.3 (0.8) (p = 0.019). An even better therapeutic response to etanercept was observed in those patients with an initial poor response to infliximab. No serious adverse effects were recorded during etanercept treatment. CONCLUSIONS: Etanercept is an efficient and safe therapy in RA patients when infliximab treatment has failed.

Source: Medline

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Author(s) anonymous

Citation: Prescrire International, August 2003, vol./is. 12/66(127-32), 1167-7422;1167-7422 (2003 Aug)

Publication Date: August 2003

Abstract: There is no reference second-line treatment for patients with rheumatoid arthritis, juvenile chronic arthritis, psoriatic arthropathy or ankylosing spondylitis after failure or intolerance of a slow-acting antirheumatic drug such as methotrexate. Etanercept, a immunosuppressant targeting TNF-alpha (like infliximab), is now approved in France for use in these situations, with the exception of spondylitis. In the second-line treatment of adults with rheumatoid arthritis, the clinical evaluation dossier on etanercept contains data from dose-finding studies and two placebo-controlled trials involving patients in whom several single-agent treatments had failed. At a dose of 25 mg subcutaneously twice a week, etanercept worked partially in about half the patients. Without direct comparisons, the place of etanercept relative to other slow-acting antirheumatic drugs is difficult to establish. From indirect comparisons, etanercept seems a slightly better treatment option than infliximab. In the first-line treatment of rheumatoid arthritis, one trial showed that etanercept worked faster than methotrexate, but there was no significant difference between the two treatments after two years. Little is known about the efficacy of etanercept in patients with juvenile chronic arthritis who do not respond adequately to methotrexate. There are no comparative trials. One double-blind placebo-controlled trial showed that etanercept, when it worked, remained active for at least 7 months. In one trial, etanercept was more effective than placebo in patients with psoriatic arthropathy and ankylosing spondylitis who continued to receive their usual treatment, which included a slow-acting antirheumatic drug in about 50% of cases. More than 50% of patients treated with etanercept have a cutaneous reaction to the injection. These reactions are usually mild or moderate. Active pharmacovigilance is needed, given its mechanism of action, and previous notifications of a wide variety of adverse effects (even though it is sometimes difficult to establish a foolproof link between etanercept and the adverse effect). Long-term studies of large numbers of patients are needed to determine the precise risk of side effects including haematological, infectious, neurological, oncological and immunological effects. In practice, methotrexate remains the first-line treatment for inflammatory arthritis. Etanercept can be a useful second-line treatment, especially in juvenile chronic arthritis.

Source: Medline

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67. Case reports of heart failure after therapy with a tumor necrosis factor antagonist.

**Author(s)** Kwon HJ, Cote TR, Cuffe MS, Kramer JM, Braun MM

**Citation:** Annals of Internal Medicine, May 2003, vol./is. 138/10(807-11), 0003-4819;1539-3704 (2003 May 20)

**Publication Date:** May 2003

**Abstract:** **BACKGROUND:** Etanercept and infliximab are U.S. Food and Drug Administration-approved tumor necrosis factor (TNF) antagonists. **OBJECTIVE:** To describe adverse event reports of heart failure after TNF antagonist therapy. **DESIGN:** Case series. **SETTING:** The U.S. Food and Drug Administration's MedWatch program. **PATIENTS:** 47 patients who developed new or worsening heart failure during TNF antagonist therapy. **MEASUREMENTS:** Clinical and laboratory reports. **RESULTS:** After TNF antagonist therapy, 38 patients developed new-onset heart failure and 9 patients experienced heart failure exacerbation. Of the 38 patients with new-onset heart failure, 19 (50%) had no identifiable risk factors. Ten patients younger than 50 years of age developed new-onset heart failure after receiving TNF antagonists. After TNF antagonist therapy was discontinued and heart failure therapy was started in these 10 patients, 3 had complete resolution of heart failure, 6 improved, and 1 died. **CONCLUSION:** In a fraction of patients, TNF antagonists might induce new-onset heart failure or exacerbate existing disease.

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68. Rescue of combination therapy failures using infliximab, while maintaining the combination or monotherapy with methotrexate: results of an open trial.

**Author(s)** Ferraccioli GF, Assaloni R, Di Poi E, Gremese E, De Marchi G, Fabris M

**Citation:** Rheumatology, October 2002, vol./is. 41/10(1109-12), 1462-0324;1462-0324 (2002 Oct)

**Publication Date:** October 2002

**Abstract:** **OBJECTIVE:** To assess the possible clinical and biological rescue of rheumatoid arthritis (RA) in 16 patients who were still active despite intensive combination therapy after receiving infliximab following the Anti-Tumour necrosis factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) schedule. **METHODS:** Sixteen patients who were still active despite combination therapy with optimal doses of methotrexate (MTX 15-17.5 mg/week) and cyclosporin A (CsA 2.5-3.5 mg/day) received infliximab. Ten received their combination plus infliximab (Combi), and six received infliximab plus MTX alone (Mono). The follow-up was carried out for 30 weeks in all patients and for 46 weeks in eight. Efficacy and safety were examined. **RESULTS:** At entry, the mean disease activity score (DAS) was 5.6 (all patients had a DAS >3.7). After therapy, eight of 10 patients in Combi and four out of six in Mono showed an improvement of >50% in the initial swollen joint count, yet only one patient reached 50% improvement in the initial DAS after 30 weeks, and one patient had a DAS <2.4 (low disease activity). Of the eight patients who reached 46 weeks of follow-up, three showed an improvement in DAS of 50% and two had a DAS <2.4. When considering the change over time, the difference between DAS at entry and at week 30 was statistically significant only in patients receiving MTX plus CsA, while it was not significant in those receiving MTX only. Two patients developed recurrent febrile upper respiratory infections in the Combi therapy group, while two had a single febrile infection in the MTX alone group. Two patients became strongly anti-cardiolipin positive (IgM >40 MPL) and one developed a coronary syndrome. **CONCLUSION:** Infliximab can be added incrementally to MTX plus CsA, with favourable results in terms of efficacy and safety over time in severe rapidly aggressive and progressive RA. Finally, minor evidence emerged for a stronger efficacy of the Combi treatment compared with Mono.
69. Pneumocystis carinii pneumonia following a second infusion of infliximab.

**Author(s)**: Tai TL, O'Rourke KP, McWeeney M, Burke CM, Sheehan K, Barry M

**Citation**: Rheumatology, August 2002, vol./is. 41/8(951-2), 1462-0324;1462-0324 (2002 Aug)

**Publication Date**: August 2002

**Source**: Medline

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70. Sudden death in a patient without heart failure after a single infusion of 200 mg infliximab: does TNF-alpha have protective effects on the failing heart, or does infliximab have direct harmful cardiovascular effects?

**Author(s)**: de' Clari F, Salani I, Safwan E, Giannacco A

**Citation**: Circulation, May 2002, vol./is. 105/21(E183), 0009-7322;1524-4539 (2002 May 28)

**Publication Date**: May 2002

**Source**: Medline

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71. Delayed hypersensitivity reaction and acute respiratory distress syndrome following infliximab infusion.


**Citation**: Inflammatory Bowel Diseases, May 2002, vol./is. 8/3(186-91), 1078-0998;1078-0998 (2002 May)

**Publication Date**: May 2002

**Abstract**: Infliximab, a chimeric human/murine monoclonal antibody directed against the proinflammatory cytokine tumor necrosis factor alpha, is an effective therapy for Crohn's disease (CD) and rheumatoid arthritis refractory to standard medical treatment. We report a case of adult respiratory distress syndrome associated with infliximab therapy. A 33-year-old white male presented with an exacerbation of CD and was treated with his second infliximab infusion (15 months following the first infusion). Within 7 days he developed
arthralgias, myalgias, and fever, followed by respiratory failure. He required intubation and mechanical ventilation. Open lung biopsy demonstrated eosinophilic pneumonia. Human antichimeric antibodies were present at high concentrations. An extensive investigation for infectious etiologies was negative. The patient was treated with intravenous corticosteroids, and fully recovered after a prolonged hospitalization. We review the infectious and immunologic complications of infliximab.

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72. Atrial fibrillation occurring in a patient taking etanercept plus methotrexate for rheumatoid arthritis.

Author(s) Wooten MD, Reddy GV, Johnson RD
Citation: Delaware Medical Journal, December 2000, vol./is. 72/12(517-9), 0011-7781:0011-7781 (2000 Dec)
Publication Date: December 2000
Abstract: A 57-year-old man with nodular rheumatoid arthritis was started on a combination of etanercept and methotrexate. After treatment for five months on this therapy, he presented with new-onset atrial fibrillation. While this report is anecdotal, any new drug warrants intense monitoring for unexpected toxicities in the post-marketing period. Etanercept is being tried in patients with congestive heart failure, where TNF-a seems to be increased. Further surveillance and caution are suggested in patients with known coronary artery disease or atrial dysrhythmia.

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73. Complication of etanercept treatment for rheumatoid arthritis - Purulent pericarditis caused by a commensal organism

Author(s) Taylor G.K., Elliott L., Sosin M.D., Soo S.S.
Citation: BMJ Case Reports, 2012, 1757-790X (2012)
Publication Date: 2012
Abstract: The patient presented with increasing fatigue and dyspnoea. The patient had medical history of rheumatoid arthritis for which she had been taking methotrexate for the past 15 years and etanercept for the past 6 years. Initial diagnosis was cardiac failure but further investigation by echocardiogram revealed a large pericardial effusion. Empirical piperacillin-tazobactam was started due to moderately raised inflammatory markers. Four hundred millilitre of frank pus was aspirated from the pericardial sac and antimicrobial treatment was changed to meropenem. Gram positive cocci were seen in the initial Gram stain, but conventional cultures remained negative. However, 16S ribosomal RNA gene sequencing of the pus sample detected the presence of Parvimonas micra genome. Reaccumulation of the effusion required further drainage where again P micra was detected by 16S ribosomal RNA gene sequencing. Two weeks of meropenem was completed followed by treatment with benzylpenicillin and metronidazole. Copyright 2012 BMJ Publishing Group. All rights reserved.

Source: EMBASE

74. Incidence of new-onset and flare of preexisting psoriasis during rituximab therapy for rheumatoid arthritis: Data from the French AIR registry

Author(s) Thomas L., Canoui-Poitrine F., Gottenberg J.-E., Economou-Dubosc A., Medkour F., Chevalier X., Bastuji-Garin S., Le Louet H., Farrenq V., Claudepierre P.
Citation: Journal of Rheumatology, May 2012, vol./is. 39/5(893-898), 0315-162X;1499-
Abstract: Objective: Psoriasis could be a paradoxical reaction to tumor necrosis factor-alpha antagonist therapy and it has been reported with rituximab therapy. Our objective was to assess the rates of new-onset and flare of preexisting psoriasis in patients taking rituximab for rheumatoid arthritis (RA). Methods: The nationwide multicenter prospective AutoImmunity and Rituximab (AIR) registry was set up in 2006 by the French Society for Rheumatology to collect data on patients taking rituximab for joint diseases. We identified patients with RA in the registry who had psoriasis listed as an adverse drug reaction, and we obtained additional information from their physicians if needed. We computed the incidence rates of new-onset and flare of preexisting psoriasis according to the rituximab exposure time. Results: Among the 1927 patients in the registry with RA, 2 had new-onset and 5 had flare of preexisting psoriasis after a median followup of 39.2 weeks. Incidence rates were 1.04/1000 person-years (95% CI 0.13 to 3.8) for new-onset psoriasis and 2.6/1000 person-years (95% CI 0.84 to 6.1) for flare of preexisting psoriasis. Rituximab rechallenge in the 2 new-onset cases and in 2 flare cases was not followed by recurrence or exacerbation of psoriasis. Two of the 5 flare cases developed after discontinuation of methotrexate. Conclusion: Despite the small number of cases observed, leading to wide CI, the incidence rates in our study do not support a causative role of rituximab therapy in new-onset or flare of preexisting psoriasis in patients with RA. Copyright 2012 The Journal of Rheumatology.

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75. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 Year follow-up of the randomised, non-blinded, parallel-group Swefot trial

Author(s) Van Vollenhoven R.F., Geborek P., Forslind K., Albertsson K., Ernestam S., Petersson I.F., Chatzidionysiou K., Bratt J.

Citation: The Lancet, May 2012, vol./is. 379/9827(1712-1720), 0140-6736;1474-547X (May 2012)

Publication Date: May 2012

Abstract: Background: Analysis of the Swedish Farmacotherapy (Swefot) trial at 12 months showed that the addition of an antitumour-necrosis-factor agent gave an improved clinical outcome compared with the addition of conventional disease-modifying antirheumatic drugs in patients with methotrexate-refractory early rheumatoid arthritis. Here we report the 2 year follow-up assessment. Methods: In this randomised, non-blinded, parallel-group trial, we enrolled adult patients older than 18 years with rheumatoid arthritis and a symptom duration of less than 1 year from 15 rheumatology units in Sweden between December, 2002 and December, 2006. All patients were started on methotrexate. After 3-4 months, those who failed treatment were randomly assigned (1:1) to group A (conventional treatment; additional sulfasalazine and hydroxychloroquine) or group B (biological treatment; additional infliximab). Randomisation was done with a computer-generated sequence. We analysed clinical outcomes at months 18 and 24 by the response criteria of the American College of Rheumatology and the European League Against Rheumatism, and radiographs of patients' hands and feet at months 12 and 24 using the Van der Heijde modification of the Sharp score. Analysis was by intention to treat. This trial is registered with www.ClinicalTrials.gov, number NCT00764725. Findings: Of 493 screened individuals, we enrolled 487, of whom 258 were randomly allocated to treatment. The proportion of patients in group B who received a EULAR-defined good response was non-significantly greater than it was in group A at 18 months (49 of 128 [38%] vs 38 of 130 [29%]) and at 24 months (49 of 128 [38%] vs 40 of 130 [31%]; p=0204). After 24 months, radiological disease progression was greater in patients in group A than it was in those in group B (mean 723 [SD 1272] vs 400 [100]; p=0009). We recorded three serious adverse events: an extended generalised illness in group A, an extended febrile episode in group B, and a generalised illness in group B. Interpretation: Additional biological treatment is a valid option for patients who fail initial methotrexate treatment. However, improved clinical
outcomes after 12 months and better radiographical results after 24 months should be weighed against the absence of a convincing clinical difference at 24 months and substantially higher costs. Therefore, for many patients who fail initial methotrexate treatment, add-on treatment with disease-modifying antirheumatic drugs is an appropriate treatment option. Funding: Swedish Rheumatism Association, Stockholm County, and Schering-Plough/Merck Sharp and Dohme.

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76. Case report: Safety and efficacy of tocilizumab in a patient with rheumatoid arthritis and chronic hepatitis C
Author(s) Iebba F., Di Sora F., Tarasi A., Leti W., Montella T., Montella F.
Citation: Case Reports in Medicine, 2012, vol./is. 2012/, 1687-9627;1687-9635 (2012)
Publication Date: 2012
Abstract: Tocilizumab is a monoclonal humanized anti-IL-6-receptor antibody used for the treatment of rheumatoid arthritis. The safety of tocilizumab in HCV patients is an open question. We report on safety and efficacy of tocilizumab in a 71-year-old female with rheumatoid arthritis and chronic hepatitis C. Monotherapy with tocilizumab (8mg/kg every 4 weeks, i.v.) was prescribed after the discontinuation, determined by clinical inefficacy, of anti-TNF-alfa agents (adalimumab and, subsequently, etanercept). We have registered an optimal and rapid clinical response to tocilizumab with early remission (SDAI 3.3 since 4 weeks). The safety was good with no adverse events and maintenance, during a six-month followup, of normal liver enzymes. These data suggest a good safety profile of tocilizumab in patients with rheumatoid arthritis and chronic hepatitis C virus pathology. Copyright 2012 Filippo Iebba et al.
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77. Psoriasis onset with tocilizumab treatment for rheumatoid arthritis
Author(s) Wendling D., Letho-Gyselinck H., Guillot X., Prati C.
Citation: Journal of Rheumatology, March 2012, vol./is. 39/3(657), 0315-162X;1499-2752 (March 2012)
Publication Date: March 2012
Source: EMBASE
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78. Effectiveness of rituximab in patients with rheumatoid arthritis: Observational study from the British society for rheumatology biologics register

Citation: Journal of Rheumatology, February 2012, vol./is. 39/2(240-246), 0315-162X;1499-2752 (February 2012)

Publication Date: February 2012

Abstract: Objective. To assess the effectiveness of rituximab (RTX) in patients with rheumatoid arthritis (RA) in routine clinical practice, and to identify predictors of 6-month response to RTX in patients for whom at least 1 anti-tumor necrosis factor-alpha (anti-TNF) therapy has failed. Method. The analysis involved 646 patients with RA registered with the British Society for Rheumatology Biologics Register (BSRBR) who were starting RTX and were followed for at least 6 months. Change in the 28-joint Disease Activity Score (DAS28), European League Against Rheumatism (EULAR) response, and proportions of patients achieving disease remission were used to assess the clinical response 6 months after starting RTX. Regression analyses were used to identify factors associated with the response in the patients for whom anti-TNF therapy had not worked. The models included baseline demographics, disease characteristics, baseline Health Assessment Questionnaire (HAQ), and drug history including biologic history. Results. The mean DAS28 at baseline was 6.2 (95% CI 6.1, 6.3), which decreased significantly to 4.8 (95% CI 4.7, 4.9) at the 6-month followup. Seventeen percent of the patients were EULAR good responders and 43% were moderate responders. Eight percent of the patients achieved disease remission. Subjects with higher baseline DAS28 score and those with positive rheumatoid factor (RF) status were significantly associated with a decrease in their DAS28 score (improvement), while women and patients with higher baseline HAQ score were less likely to improve. Conclusion. RTX has proven to be effective in routine clinical practice. When anti-TNF therapy fails, response to RTX was influenced by baseline DAS28 score, RF status, baseline HAQ score, and sex. The Journal of Rheumatology Copyright 2012. All rights reserved.

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79. Primary biliary cirrhosis in a rheumatoid arthritis patient treated with rituximab, a case-based review

Author(s) Polido-Pereira J., Rodrigues A.M., Canhao H., Saraiva F., Da Silva J.A.P., Fonseca J.E.

Citation: Clinical Rheumatology, February 2012, vol./is. 31/2(385-389), 0770-3198;1434-9949 (February 2012)

Publication Date: February 2012

Abstract: Primary biliary cirrhosis (PBC) is an autoimmune disease in which intrahepatic bile ducts are targeted by an immune-mediated injury. This disease tends to progress to fibrosis and cirrhosis with hepatic failure. The authors report a case of a 50-year-old rheumatoid arthritis (RA) patient, with erosions and seropositive for rheumatoid factor and anti-citrullinated peptide antibodies, with 18 years disease duration refractory to prednisolone and several disease-modifying antirheumatic drugs, either conventional or biological (adalimumab and etanercept). In April 2007, she started therapy with rituximab (RTX) with good European League Against Rheumatism response achieved 9 months later. In June 2008, she was admitted with intrahepatic cholestasis, steatorrhea, and spontaneous fractures of various ribs. After excluding cholelithiasis, as well as infectious and neoplastic diseases a liver biopsy was performed that was compatible with the diagnosis of PBC. The antinuclear antibodies (1/160) were positive as well as the antimitochondrial antibodies (1/640). Other antibodies were negative such as anti-SSA and anti-SSB. Afterwards, the patient started ursodesoxycholic acid 15 mg kg<sup>-1</sup> day<sup>-1</sup> with progressive improvement of cholestatic markers. A labial salivary gland biopsy was performed and showed findings compatible with the concomitant diagnosis of Sjogren's syndrome. Based on this clinical report, a detailed review of the clinical aspects of PBC is presented as well as its association with other immune-mediated inflammatory diseases, particularly, with RA. 2011 Clinical Rheumatology.
80. Efficacy of tocilizumab in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: The ROSE study

Author(s) Yazici Y., Curtis J.R., Ince A., Baraf H., Malamet R.L., Teng L.L., Kavanaugh A.

Citation: Annals of the Rheumatic Diseases, February 2012, vol./is. 71/2(198-205), 0003-4967;1468-2060 (February 2012)

Publication Date: February 2012

Abstract: Objectives: To evaluate efficacy of tocilizumab in US patients with moderate to severe active rheumatoid arthritis (RA) and inadequate clinical response to disease-modifying antirheumatic drugs (DMARD). Safety-related outcomes were also analysed.

Methods: The rapid onset and systemic efficacy study was a 24-week, randomised, double-blind trial. Patients were randomly assigned 2:1 to tocilizumab 8 mg/kg (n=412) or placebo (n=207) every 4 weeks while continuing background DMARD in both groups. Results: The primary efficacy endpoint, percentage of patients achieving ACR50 response at week 24, was higher with tocilizumab versus placebo (30.1% vs 11.2%; p<0.0001). Percentages of ACR20 and ACR50 responders were significantly higher with tocilizumab versus placebo as early as week 4 and continued to week 24; more patients in the tocilizumab versus placebo group also achieved ACR70 responses beginning at week 8 (p<0.01). Significant improvements associated with tocilizumab versus placebo were seen in routine assessment of patient index data responses, EULAR good response, DAS28 and percentages of patients achieving low disease activity and clinical remission (based on DAS28). A substudy examining early response to therapy showed improved patient global assessment of disease activity (p=0.005) and pain (p=0.01) and DAS28 (p=0.007) with tocilizumab versus placebo at day 7. Safety findings were consistent with the known tocilizumab safety profile; rates of serious infections (per 100 patient-years) were 7.87 (95% CI 4.30 to 13.2) and 1.20 (95% CI 0.03 to 6.66) in the tocilizumab and placebo groups, respectively. Conclusions: This study demonstrated the efficacy of tocilizumab in improving measures of disease activity in patients with RA who failed to respond adequately to DMARD therapy. Rapid improvement in clinical outcomes was demonstrated in a substudy as early as week 1 as shown by DAS28 scores, patient measures and C-reactive protein. Trial Registry no: NCT00531817.

Source: EMBASE

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81. Safety and effectiveness of rituximab in patients with rheumatoid arthritis following an inadequate response to 1 prior tumor necrosis factor inhibitor: The RESET trial

Author(s) Harauoi B., Bokarewa M., Kallmeyer I., Bykerk V.P.

Citation: Journal of Rheumatology, December 2011, vol./is. 38/12(2548-2556), 0315-162X;1499-2752 (December 2011)

Publication Date: December 2011

Abstract: Objective. To evaluate the safety and effectiveness of rituximab (RTX) in combination with methotrexate in patients with active rheumatoid arthritis (RA) after failure of a single tumor necrosis factor-alpha (TNF-alpha) inhibitor. Changes in patient-reported outcomes after primary treatment or retreatment with RTX and factors determining retreatment in clinical practice were also evaluated. Methods. In this phase 3b open-label, multicenter trial, patients received 2 slow infusions of RTX 1000 mg 14 days apart after premedication (primary treatment). Patients with a clinically relevant response could receive retreatment between 24 and 48 weeks. The primary endpoint was evaluation of
safety. Secondary outcomes were safety of retreatment, effectiveness of primary treatment and retreatment, and changes in patient-reported outcomes after primary treatment or retreatment. Results. Of 120 patients enrolled at 36 centers and receiving primary RTX treatment, 77 received retreatment, 112 completed the 24-week primary treatment period, and 25 completed the 48-week primary treatment and retreatment period following a single course of RTX. The most common adverse events were mild to moderate nausea, vomiting, nasopharyngitis, and headache. No infections or infusion reactions were considered life-threatening. At 24 weeks, 58%, 27%, and 7% of patients achieved American College of Rheumatology 20, 50, and 70 improvements, respectively, and similar improvements were seen after retreatment. Conclusion. RTX was well tolerated, with a low incidence of infusion reactions and infections. Efficacy results, including enhanced response in rheumatoid factor-positive patients, were comparable to those reported in the literature. Based on its efficacy and safety profile and retreatment schedule, RTX is an attractive treatment option for patients that have not responded to a single TNF-alpha inhibitor. The Journal of Rheumatology Copyright 2011. All rights reserved.

Source: EMBASE

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82. Treatment strategies in patients with rheumatoid arthritis for whom methotrexate monotherapy has failed: Data from the NOR-DMARD register

Author(s) Lie E., Van Der Heijde D., Uhlig T., Mikkelsen K., Kalstad S., Kaufmann C., Rodevand E., Kvien T.K.

Citation: Annals of the Rheumatic Diseases, December 2011, vol./is. 70/12(2103-2110), 0003-4967;1468-2060 (December 2011)

Publication Date: December 2011

Abstract: Objectives: To compare the effectiveness of adding synthetic disease-modifying antirheumatic drugs (sDMARDs) versus tumour necrosis factor alpha inhibitors (TNFi) to methotrexate (MTX) in patients with rheumatoid arthritis (RA) who were MTX inadequate responders (IR). Second, to examine outcomes in patients receiving MTX+TNFi for whom the MTX+sDMARD combination had also failed. Methods: Patients with RA (disease duration <= 5 years, MTX IR and naive to other DMARDs) starting treatment with MTX+TNFi or MTX+sDMARDs were included. From the latter group a subgroup of patients who went on to receive MTX+TNFi was identified. Results: Patients receiving MTX+TNFi (n=98) and MTX+sDMARDs (n=129) had similar baseline disease activity when starting combination therapy (mean Disease Activity Score 28 (DAS28) = 4.90 and 4.96, respectively). Three- and 6-month effectiveness and 2-year drug survival were better for MTX+TNFi than for MTX+sDMARDs: mean DAS28 was -1.61 versus -0.85 after 3 months (p<0.001) and -1.91 versus -1.03 after 6 months (p=0.01); DAS28<2.6 was reached by 29.0% versus 11.6% after 3 and 34.5% versus 12.9% after 6 months. Effectiveness was somewhat better with triple therapy than other MTX+sDMARD combinations but was generally inferior compared with MTX+TNFi. For the patients who received MTX+TNFi as a third step after MTX+sDMARDs had failed (n=38) there was a tendency towards lower remission rates, worse disease activity states and inferior drug survival compared with patients who received MTX+TNFi directly after the failure of MTX. Conclusions: Effectiveness was better for MTX+TNFi than for MTX+sDMARDs. Patients who started MTX+TNFi after two synthetic DMARD regimens had failed had a tendency to less favourable disease states after 3 months than patients who switched directly from MTX to MTX+TNFi.

Source: EMBASE

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83. Clinical relevance of switching to a second tumour necrosis factor-alpha inhibitor after discontinuation of a first tumour necrosis factor-alpha inhibitor in rheumatoid
Abstract: Objective: To assess the clinical relevance of switching to a second tumour necrosis factor (TNF)-alpha inhibitor after discontinuation of a first TNF-alpha inhibitor in patients with rheumatoid arthritis. Methods: A systematic literature search of MEDLINE, EMBASE and Cochrane database and Congress abstracts up to March 2009 retrieved all studies assessing the efficacy of switching to a second TNF-alpha inhibitor. Key words were rheumatoid arthritis AND failure OR switching AND TNFalpha inhibitors OR adalimumab OR etanercept OR infliximab. Efficacy was evaluated by American College of Rheumatology (ACR), European League Against Rheumatism (EULAR) response criteria and drug survival. A meta-analysis of the percentage of responders was carried out. Statistical heterogeneity was tested by the Q-test. Results: In the 32 relevant studies (4,441 patients) selected, the pooled percentage of ACR 20 responders (12 studies; 1,570 patients) was 55.1% (95% confidence interval, CI 48.2-62) and that of EULAR responders (15 studies; 2,665 patients) was 74.9% (95% CI 72.3-77.5). In the 19 studies analysing the efficacy by the reason to switch, the pooled percentage of ACR20 responders was 54.3% (95% CI 45.8-62.5) for switch because of lack of efficacy and 62.5% (95% CI 57.3-67.6) because of adverse events. The percentage of EULAR response was similar in both groups. Conclusion: This meta-analysis suggests that switching to a second TNFalpha inhibitor is clinically relevant in RA. Response to a second TNF-alpha inhibitor appears to be slightly better if the first TNF-alpha inhibitor was discontinued because of adverse events. Clinical and Experimental Rheumatology 2011.

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Available in print at ULHT journal article requests. Complete the online form to obtain articles.

84. "Paradoxical" adverse effects caused by anti-tumor necrosis factor-alpha biological drugs: Appearance of psoriasis in a patient treated with infliximab for rheumatoid arthritis

Author(s) Satriano R.A., Abbate G., Esposito S., Cassaglia B., Piccolo V., Baroni A.
Citation: Indian Journal of Dermatology, Venereology and Leprology, July 2011, vol./is. 77/4(536), 0378-6323;0973-3922 (July-August 2011)
Publication Date: July 2011
Source: EMBASE
Available in fulltext at EBSCOhost
Available in print at ULHT journal article requests. Complete the online form to obtain articles.

85. Persistence with anti-tumor necrosis factor therapies in patients with rheumatoid arthritis: Observations from the RADIUS registry

Author(s) Markenson J.A., Gibofsky A., Palmer W.R., Keystone E.C., Schiff M.H., Feng J., Baumgartner S.W.
Citation: Journal of Rheumatology, July 2011, vol./is. 38/7(1273-1281), 0315-162X;1499-2752 (July 2011)
Publication Date: July 2011
Abstract: Objective. To evaluate persistence with anti-tumor necrosis factor (TNF) therapy and predictors of discontinuation in patients with rheumatoid arthritis (RA). Methods. This retrospective analysis used data from RADIUS 1, a 5-year observational registry of patients with RA, to determine time to first- and second-course discontinuation of etanercept, infliximab, and adalimumab. First-course therapy was defined as first exposure to anti-TNF
therapy, and second-course therapy was defined as exposure to anti-TNF therapy after the first discontinuation. Kaplan-Meier survival analysis was used to assess persistence, log-rank tests were used to compare therapies, and Cox proportional hazards models were used to assess potential predictors of treatment discontinuation. Results. This analysis included 2418 patients. Mean persistence rates were similar among treatments [first-course: etanercept, 51%; infliximab, 48%; adalimumab, 48% (followup was 54 weeks for etanercept and infliximab and 42 weeks for adalimumab); second-course: 56%, 50%, 46%, respectively (followup was 36 weeks for etanercept and infliximab and 30 weeks for adalimumab)]. Discontinuations of first-course therapy due to ineffectiveness were similar among treatments (etanercept, 19%; infliximab, 19%; adalimumab, 20%) and discontinuations due to adverse events were significantly (p = 0.0006) lower for etanercept than for infliximab (etanercept, 14%; infliximab, 22%; adalimumab, 17%). Predictors from univariable analysis of first- or second-course therapy discontinuation included increased comorbidities (etanercept), female sex (infliximab), Clinical Disease Activity Index > 22 (infliximab), and a Stanford Health Assessment Questionnaire score > 0.5 (adalimumab). Conclusion. In this population, first- and second-course persistence was similar among anti-TNF therapies. First-course discontinuation due to adverse events was lower with etanercept compared with infliximab.

Source: EMBASE
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86. Salmonella septic arthritis following total knee arthroplasty for rheumatoid arthritis in a patient receiving etanercept

Author(s) Oe K., Wada T., Ohno H., Kushida T., Iida H.
Citation: Journal of Orthopaedic Science, 2011, vol./is. 16/2(258-262), 0949-2658;1436-2023 (2011)
Publication Date: 2011
Source: EMBASE
Available in print at ULHT journal article requests. Complete the online form to obtain articles.

87. Reactivation of chronic hepatitis B virus infection following rituximab administration for rheumatoid arthritis

Author(s) Pyrpasopoulou A., Douma S., Vassiliadis T., Chatzimichailidou S., Triantafyllou A., Aslanidis S.
Citation: Rheumatology International, March 2011, vol./is. 31/3(403-404), 0172-8172 (March 2011)
Publication Date: March 2011
Source: EMBASE
Available in fulltext at EBSCOhost
Available in print at ULHT journal article requests. Complete the online form to obtain articles.

88. Respiratory symptoms in a patient on anti-tumour necrosis factor therapy; Beware the negative enzyme linked immunosport (ELISpot) in suspected mycobacterial disease

Author(s) Mangat P., Taylor P., Abraham S.
Citation: QJM, January 2011, vol./is. 104/1(61-63), 1460-2725;1460-2393 (January 2011)
Publication Date: January 2011
Source: EMBASE
89. Patterns of biologic agent use, efficacy, safety and retention rates in a public hospital and private practice setting

Author(s) Katikireddi V., Hadwen T., Kubler P., Kevat S., Klestov A., Gunsberg M.

Citation: Internal Medicine Journal, May 2011, vol./is. 41/(26), 1444-0903 (May 2011)

Publication Date: May 2011

Abstract: Aim: To investigate the pattern of biologic use, efficacy, safety, retention rates and reasons for switching in adult rheumatoid arthritis patients for the first, second and third biologic agent in a single public hospital setting and associated private practices of the attending rheumatologists. Methods: Retrospective audit of adult rheumatoid arthritis patients currently or previously treated with a biological agent. 100 patients were identified and a comprehensive chart review was undertaken. Percentage improvement in total tender and swollen joint count and CRP and ESR was used as a measure of efficacy.

Results: Mean age of the population was 61.1 years. Mean disease duration was 14.2 years. 72.7% were seropositive. 86% were on prednisolone at baseline at a mean dose of 7.6 mg. 70% continued their initial biologic. The most common biologic prescribed was adalimumab followed by etanercept. Retention rates were 72.7% at 1 year, 60.6% at 2 years, 32.4% at 3 years, 13.2% at 4 years and 10.6% at 5 years. Mean duration of drug survival was 2.45 years. Reasons for discontinuation included secondary failure, followed by primary failure and side effects. The most common adverse event was infection with skin and respiratory the most frequent. Mean improvement in swollen and tender joint count was 73% with 59% improvement in mean CRP and 54.7% in mean ESR. Only 26.7% of patients reduced their prednisolone dose to less than half of baseline. Mean duration of biologic decreased with each successive biologic being 11.8 months for second and 7.1 months for third.

Conclusion: Biologic retention rates decrease with successive use of biological agents in rheumatoid arthritis. Treatment continuation was lower than randomised controlled trials. Identifying patient characteristics associated with an increased response rate may be beneficial in better targeting future therapy in rheumatoid arthritis.

Source: EMBASE

90. Baseline characteristics and effectiveness of treatment with infliximab in Canadian patients with rheumatoid arthritis: Comparison of an individual practice with the BioTRAC registry

Author(s) Faraawi R., Otawa S.

Citation: Journal of Rheumatology, June 2011, vol./is. 38/6(1166), 0315-162X (June 2011)

Publication Date: June 2011

Abstract: Objective: The efficacy of Infliximab (IFX) in Rheumatoid Arthritis (RA) has been well established in controlled clinical trials. Small area variations with respect to patient profile and outcomes may affect global assessment of real-life effectiveness. The aim of the current analysis is to compare the patient profile and outcomes of an Individual Rheumatology Practice cohort in Ontario to that of the entire Ontario and Canadian RA cohorts. Methods: The data for this analysis were obtained from BioTRAC, an observational prospective registry of adult RA patients initiated on IFX since 2002 and managed as per routine care. Results: A total of 70 RA patients were enrolled in the Individual Rheumatology Practice (IRP) between 2002 and 2010 while 695 patients comprised the total registry (Canadian) and 291 patients the Ontario cohort (ON). Patient baseline characteristics differed between the 3 cohorts with patients in the IRP cohort having significantly lower mean age (50.1 vs. 56.4 and 57 years in the IRP, Canadian and
ON cohorts, respectively), disease duration (5.7 vs. 11.1 and 9.4 years, respectively), ESR (25.5 vs. 33.8 and 37.1 mm/hr, respectively) HAQ (1.5 vs. 1.7 and 1.7, respectively), pain (50.9 vs. 58.8 and 59.1, respectively), Physician's Global Assessment of Disease Activity (PGA) (4.5 vs. 6.8 and 7.0, respectively), swollen joint count (SJ), and DAS28 (4.8 vs. 5.3 and 5.4, respectively) compared to the Canadian and ON cohorts. Regression analysis over time showed that morning (AM) stiffness, Patient's Global Assessment of Disease Activity (SGA), HAQ, tender joint count (TJC), SJC, and DAS28-CRP improved significantly in all cohorts without significant between-group differences. However, median time to discontinuation due to treatment failure (adverse event, disease progression, lack or loss of response) was significantly longer in this IRP cohort vs. Canadian (P=0.004) or ON (P=0.011) cohorts. After mean follow-up of 12.8, 13.0 and 13.3 months for the IRP, Canadian and Ontario cohorts ACR20/50/70 response rates were 54%/52%/52%, 49%/46%/43% and 40%/38%/33%, respectively. Conclusion: The results of this real-life observational study demonstrate that significant variation in patient baseline characteristics in individual rheumatology practices may exist within the BioTRAC registry. This may impact individual physician experience with respect to median time to discontinuation due to treatment failure. Nevertheless, treatment with IFX for up to 4 years is effective in reducing symptom severity and improving outcomes in patients with RA in this Individual Rheumatology Practice, Canadian and ON cohorts within the BioTRAC registry.

Source: EMBASE

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91. A retrospective analysis of responses to decitabine in therapy-related MDS patients

Author(s) Klimek V.M., Dolezal E.K., Tees M.T., Stein K., Nimer S.D.

Citation: Leukemia Research, May 2011, vol./is. 35/(S70), 0145-2126 (May 2011)

Publication Date: May 2011

Abstract: Background: Therapy-related myelodysplastic syndrome (tMDS) patients (pts) are frequently treated with DNA methyltransferase inhibitors (DNMTI), but the response rate of tMDS to DNMTI therapy is not known. Materials and Methods: Adult Memorial Sloan-Kettering Cancer Center (MSKCC) tMDS pts who received decitabine (DAC) from 4/8/2002 to 10/18/2010 were analyzed for morphologic and cytogenetic responses. In addition, Eisai Inc. provided clinical data and response summaries for tMDS pts treated with DAC in the DACO-020 (5-day schedule) and D0007 (3-day schedule) clinical trials. A Waiver of Authorization was secured prior to the collection of data. Responses were assessed using the modified IWG MDS response criteria. Results: The 39pt (21M, 18F; median age 66, range 25-85) combined cohort included 25 MSKCC pts (1 3-day and 24 5-day DAC pts) and 14 Eisai pts (7 on the 3-day, 7 on the 5-day schedule). FAB subtypes included: RA, n=8; RARS, n=4; RAEB, n=17; RAEBt, n=7; CMML, n=3. IPSS subtypes were as follows: 2 (5%) IPSS Low Risk, 4 (10%) Int-1, 20 (51%) Int-2, and 13 (33%) High Risk. 85% (n = 33) had 2 or 3 significant cytopenias (by IPSS). Most pts had Poor Risk cytogenetics (n=27, 69%), vs. Good (n=8, 21%) or Intermediate Risk (n=4, 10%). Pre-DNMTI therapy included RBC (n = 7) or platelet (n =5) transfusions or both (n = 8), darbepoetin or epoetin alfa (n =19), lenalidomide (n= 1), and topotecan (n = 1). The MSKCC cohort included 8 pts who received tretinoin with 5-day DAC in a trial. Median number of cycles administered was 2 (range, 1-17). Best responses included: CR, n=5 (13%); PR, n=2 (5%); mCR, n=2 (5%); mCR plus HI, n=4 (10%); 2 trilineage HI, 1 HI-P+HI-N, 1 HI-P; HI, n= 5 (13%); SD, n=10 (26%); POD, n= 8 (21%); Failures (death before response evaluation), n = 3 (8%). Rate of CR + PR + mCR was 33% (n=13). ORR was 46%. Median time to best marrow morphologic and HI response was 2 cycles (range, 1-6). Cytogenetic responses included SCRs, and 5PRs. Median time to cytogenetic response was 3 cycles (range, 1-8). DNMTI was halted in 4 MSKCC pts due to the need to treat progressive primary malignancies. Conclusion: This retrospective analysis demonstrates that decitabine treatment can produce clinical and cytogenetic responses in tMDS. However, clinical trials of DNMTI combined with other epigenetic modifiers, or with agents having other mechanisms of action, should be considered for tMDS patients given their overall poor outcomes.
92. Efficacy and safety of abatacept therapy for rheumatoid arthritis in routine clinical practice

Author(s) Schiff M., Poncet C., Bars M.L.

Citation: International Journal of Clinical Rheumatology, October 2010, vol./is. 5/5(581-591), 1758-4272 (October 2010)

Publication Date: October 2010

Abstract: Aim: To evaluate treatment of rheumatoid arthritis with abatacept in the real-life clinic setting. Materials & methods: Patients who initiated abatacept at a single US clinic during an 18-month period were assessed in this observational, retrospective study. Patient retention, disease activity (Disease Activity Score 28 [DAS28] and Clinical Disease Activity Index [CDAI]: last observation carried forward analysis) and discontinuations due to adverse events were evaluated. Results: A total of 100 successive patients were included. At baseline, 97% had failed one or more anti-TNF therapy, mean DAS28 was 4.4 and CDAI was 32.9. At month 6, 80% remained on treatment. Seven out of 100 patients discontinued due to adverse events. For patients with available data, 44.1% (30/68) achieved Low Disease Activity State (<3.2), 32.5% (27/83) low CDAI (<10) and 33.8% (23/68) DAS28 remission (<2.6) at month 6. Conclusions: These real-world data are consistent with findings from clinical trials, and support abatacept as a therapeutic option. Further observations from larger cohorts of patients over longer treatment periods are now ongoing. 2010 Future Medicine Ltd.

Source: EMBASE

93. Anti-TNF-alpha agents are less effective for the treatment of rheumatoid arthritis in current smokers

Author(s) Abhishek A., Butt S., Gadsby K., Zhang W., Deighton C.M.

Citation: Journal of Clinical Rheumatology, January 2010, vol./is. 16/1(15-18), 1076-1608 (January 2010)

Publication Date: January 2010

Abstract: Objectives: To assess if smoking status at the time of commencing an anti-TNF-alpha agent for rheumatoid arthritis (RA) reduces the likelihood of achieving at least a moderate response on the European League Against Rheumatism (EULAR) response criteria at 3-month assessment. Methods: All patients with RA treated with their first anti-TNF-alpha agent at the Department of Rheumatology, Derby Hospital NHS Trust between April 2001 and October 2008 were included in this retrospective case control study. Information about age, gender, disease duration, body mass index, smoking status (current smoker, ex-smoker, and nonsmoker), comorbidities, oral prednisolone use, and 28 joint variables disease activity score (DAS28) at the time of commencing an anti-TNF-alpha agent was recorded. Details of rheumatoid factor (RF) and past and present disease modifying antirheumatic drugs were recorded. A case control study was carried out to examine possible baseline predictors of treatment effects at the 3-month assessment. Results: Results were available for 395 patients at 3-month assessment. According to the EULAR response criteria 42 patients failed to show at least a moderate response. After adjusting for confounders using multivariate analysis, current smoking at the time of commencing an anti-TNF-alpha agent reduced the chance of achieving at least a moderate response on the EULAR response criteria when compared with nonsmokers (aOR [95% CI] 0.20 [0.05-0.83], P = 0.03). Conclusion: RA patients who smoke are less likely to respond to an anti-TNF-alpha agent. Copyright 2010 by Lippincott Williams & Wilkins.

Source: EMBASE
94. Neuromeningeal tuberculosis in a patient with rheumatoid arthritis previously exposed to ineffective etanercept therapy and revealed by infliximab

Author(s) DaSilva V., Roux C.H., Bernard E., Brocq O., Albert C., Chami H., Grisot C., Allam Y., Dellamonica P., Euler-Ziegler L.

Citation: Journal of Rheumatology, February 2010, vol./is. 37/2(471-472), 0315-162X (February 2010)

Publication Date: February 2010

Source: EMBASE

95. Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumour necrosis factor (TNF) agents after previous failure of an anti-TNF agent?

Author(s) Finckh A., Ciurea A., Bruhlart L., Moller B., Walker U.A., Courvoisier D., Kyburz D., Dudler J., Gabay C.

Citation: Annals of the Rheumatic Diseases, February 2010, vol./is. 69/2(387-393), 0003-4967;1468-2060 (February 2010)

Publication Date: February 2010

Abstract: Background: Patients with rheumatoid arthritis (RA) with an inadequate response to TNF antagonists (aTNFs) may switch to an alternative aTNF or start treatment from a different class of drugs, such as rituximab (RTX). It remains unclear in which clinical settings these therapeutic strategies offer most benefit. Objective: To analyse the effectiveness of RTX versus alternative aTNFs on RA disease activity in different subgroups of patients. Methods: A prospective cohort study of patients with RA who discontinued at least one aTNF and subsequently received either RTX or an alternative aTNF, nested within the Swiss RA registry (SCQM-RA) was carried out. The primary outcome, longitudinal improvement in 28-joint count Disease Activity Score (DAS28), was analysed using multivariate regression models for longitudinal data and adjusted for potential confounders. Results: Of the 318 patients with RA included; 155 received RTX and 163 received an alternative aTNF. The relative benefit of RTX varied with the type of prior aTNF failure: when the motive for switching was ineffectiveness to previous aTNFs, the longitudinal improvement in DAS28 was significantly better with RTX than with an alternative aTNF (p=0.03; at 6 months, -1.34 (95% CI -1.54 to -1.15) vs -0.93 (95% CI -1.28 to -0.59), respectively). When the motive for switching was other causes, the longitudinal improvement in DAS28 was similar for RTX and alternative aTNFs (p=0.40). These results were not significantly modified by the number of previous aTNF failures, the type of aTNF switches, or the presence of cotreatment with a disease-modifying antirheumatic drug. Conclusion: This observational study suggests that in patients with RA who have stopped a previous aTNF treatment because of ineffectiveness changing to RTX is more effective than switching to an alternative aTNF.

Source: EMBASE

96. Sarcoidosis Appearing During Anti-Tumor Necrosis Factor alpha Therapy: A New "Class Effect" Paradoxical Phenomenon. Two Case Reports and Literature Review

Author(s) Massara A., Cavazzini L., La Corte R., Trotta F.

Citation: Seminars in Arthritis and Rheumatism, February 2010, vol./is. 39/4(313-319),
Objectives: To report 2 cases of sarcoidosis that developed during treatment with tumor necrosis factor alpha (TNFalpha) antagonists, infliximab and adalimumab, used for inflammatory rheumatic disease and to review previously reported cases. Methods: We describe 2 patients, the first with psoriatic arthritis, the second with rheumatoid arthritis, who developed noncaseating granulomas of the lungs consistent with sarcoidosis while being treated with anti-TNFalpha drugs. A retrospective review of the literature was performed using the PubMed database. Results: In our patients sarcoidosis developed after 2 years of continuous treatment with infliximab and adalimumab. Both patients presented with low-grade fever, chest pain, and dyspnea. The diagnosis of sarcoidosis was established by the typical well-formed noncaseating granulomas on transbronchial biopsy, after excluding all other granulomatous conditions. Following withdrawal of anti-TNFalpha agents and a brief course of steroids, the clinical picture resolved. Thirteen additional cases of sarcoidosis that developed after anti-TNFalpha treatment have been reported, and in 9 of these the causative agent was etanercept. Conclusions: The development of sarcoidosis during treatment with TNFalpha antagonists represents a rare and paradoxical adverse event. The occurrence of sarcoidosis with all 3 available agents suggests a new "class effect" probably linked to a cytokine disequilibrium in patients receiving anti-TNFalpha treatment. 2010 Elsevier Inc. All rights reserved.

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97. The effect of biologics on cardiovascular disease in patients with rheumatoid arthritis: A systematic literature review

Author(s) Westlake S.L., Colebatch A.N., Baird J., Kiely P., Quinn M., Choy E., Ostor A.J., Edwards C.J.

Citation: Rheumatology, April 2010, vol./is. 49/(i155), 1462-0324 (April 2010)

Abstract: Background: Patients with RA have an increased prevalence of cardiovascular disease (CVD). This is due to increased traditional risk factors and the effect of chronic inflammation. TNF antagonists are potent suppressors of inflammation and may reduce the risk of CVD. We performed a systematic literature review to determine whether TNF antagonists affect the risk of clinical CVD events in RA. Methods: We searched Medline, Embase, Cochrane database, DARE, HTA and Science Citation Index from 1980-2008. Papers were included if they assessed the relationship between the use of TNF antagonists and clinical CVD outcomes in RA. All articles were assessed for study quality. Results: 1840 abstracts were identified. Two reviewers independently assessed each title and abstract. 20 studies fulfilled the inclusion criteria: 1 RCT, 11 cohorts, 7 case-controls and 1 cross-sectional study(Table to be included in a poster). 7 studies considered all CVD events, 4 demonstrating a significant decreased CVD risk and 3 no change in risk. 7 studies assessed the association of TNF antagonists and MI; 2 demonstrated a significant decreased risk and 5 no difference. The study with the lowest risk of bias, showed a significantly lower risk of MI in TNF responders compared with non-responders. 3 studies considered stroke and TNF antagonists, two demonstrated no change in risk and 1 a reduced risk after 6 months of treatment. 6 studies considered heart failure (HF): 1 demonstrated a significantly increased risk of HF in elderly RA patients, 3 no difference in risk and 2 a significantly decreased risk of HF. In the study with the lowest risk of bias, a non-significant increased risk of HF was considered to be offset by the efficacy of TNF antagonists. Conclusions: For all CVD events there may be a decreased risk associated with use of TNF antagonists. For specific events, e.g. MI and HF the effect is less clear. Atherosclerosis is an inflammatory process, TNF antagonists would be expected to reduce the risk of CVD by decreasing the burden of systemic inflammation. There are several reasons this may not be apparent. Firstly, TNF antagonists may have adverse effects on traditional risk factors (lipids, etc.). Secondly MTX reduces the risk of CVD events, it is commonly used in combination with TNF antagonists and in some of the studies was used by controls. TNF antagonists may therefore have no additional benefit to MTX. In contrast
to MTX, TNF antagonists are often used late in the disease when significant irreversible damage has occurred. Finally the effect on CVD may depend on response to treatment as some of the studies demonstrated a lower risk of CVD events in responders compared with non-responders. To determine the true effect of TNF antagonists on CVD risk future studies should publish data on CVD risk factors and clinical events, this is particularly important in studies of early disease when the burden of inflammation has not been realised.

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98. Effectiveness and safety of etanercept in subjects with RA who have failed infliximab therapy: 16-Week, open-label, observational study

Author(s) Bingham III C.O., Ince A., Haraoui B., Keystone E.C., Chon Y., Baumgartner S.

Citation: Current Medical Research and Opinion, May 2009, vol./is. 25/5(1131-1142), 0300-7995;1473-4877 (May 2009)

Publication Date: May 2009

Abstract: Background and objective: Tumor necrosis factor (TNF) antagonists, including etanercept (a soluble TNF receptor) and infliximab (an anti-TNF monoclonal antibody) are used in the treatment of patients with rheumatoid arthritis (RA). The purpose of this study was to evaluate the effectiveness and safety of 50 mg etanercept weekly in subjects with RA who have failed infliximab therapy. Methods: This phase 4, multicenter, open-label, single-arm, 16-week observational study enrolled subjects who had experienced primary (failure to achieve an initial response) or secondary (failure to maintain an initial response) infliximab failures. Effectiveness was measured using European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) response criteria and laboratory assessments were used to evaluate levels of inflammation, lymphotoxin alpha, drug concentrations, and antibodies to infliximab. Safety endpoints included incidence of serious adverse events. Clinical trial registration: This trial was registered under U.S. National Institutes of Health ClinicalTrials.gov identifier NCT00099554. Results: At week 16, over half (62%; 95% CI = 55, 69) of all subjects in the trial achieved a good or moderate EULAR response (DAS28) with etanercept. Using ACR criteria, after 16 weeks of etanercept therapy, 45% (95% CI = 38, 52) of all subjects had achieved an ACR20 response. Benefits were noted in tender and swollen joint counts, subject and physician global assessments, joint pain, and the Health Assessment Questionnaire. Outcomes were similar between subjects with primary and secondary infliximab failures. Levels of lymphotoxin a did not appear to affect response to etanercept. Potential limitations included the lack of a washout period, short duration of the trial, and the number of subjects who did not receive all doses of etanercept. Conclusion: In this open-label, uncontrolled study, subjects with moderate to severe RA who failed to respond or who lost their initial response to infliximab safely benefited from receiving etanercept. 2009 Informa UK Ltd. All rights reserved.

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99. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: The FAST4WARD study

Author(s) Fleischmann R., Vencovsky J., Van Vollenhoven R.F., Borenstein D., Box J., Coteur G., Goel N., Brezinschek H.-P., Innes A., Strand V.
Background: Tumour necrosis factor alpha (TNFalpha) is a proinflammatory cytokine involved in the pathogenesis of rheumatoid arthritis (RA). Treatment with TNFalpha inhibitors reduces disease activity and improves outcomes for patients with RA. This study evaluated the efficacy and safety of certolizumab pegol 400 mg, a novel, poly-(ethylene glycol) (PEG)ylated, Fc-free TNFalpha inhibitor, as monotherapy in patients with active RA. Methods: In this 24-week, multicentre, randomised, double-blind, placebo-controlled study, 220 patients previously failing ≥1 disease-modifying antirheumatic drug (DMARD) were randomised 1:1 to receive subcutaneous certolizumab pegol 400 mg (n = 111) or placebo (n = 109) every 4 weeks. The primary endpoint was 20% improvement according to the American College of Rheumatology criteria (ACR20) at week 24. Secondary endpoints included ACR50/70 response, ACR component scores, 28-joint Disease Activity Score Erythrocyte Sedimentation Rate 3 (DAS28(ESR)3), patient-reported outcomes (including physical function, health-related quality of life (HRQoL), pain and fatigue) and safety. Results: At week 24, the ACR20 response rates were 45.5% for certolizumab pegol 400 mg every 4 weeks vs 9.3% for placebo (p<0.001). Differences for certolizumab pegol vs placebo in the ACR20 response were statistically significant as early as week 1 through to week 24 (p<0.001). Significant improvements in ACR50, ACR components, DAS28(ESR)3 and all patient-reported outcomes were also observed early with certolizumab pegol and were sustained throughout the study. Most adverse events were mild or moderate and no deaths or cases of tuberculosis were reported. Conclusions: Treatment with certolizumab pegol 400 mg monotherapy every 4 weeks effectively reduced the signs and symptoms of active RA in patients previously failing ≤1 DMARD compared with placebo, and demonstrated an acceptable safety profile. Trial registration number: NCT00548834.

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100. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: The RAPID 2 study. A randomised controlled trial


Citation: Annals of the Rheumatic Diseases, June 2009, vol./is. 68/6(797-804), 0003-4967;1468-2060 (June 2009)

Publication Date: June 2009

Abstract: Background: Certolizumab pegol is a PEGylated tumour necrosis factor inhibitor. Objective: To evaluate the efficacy and safety of certolizumab pegol versus placebo, plus methotrexate (MTX), in patients with active rheumatoid arthritis (RA). Methods: An international, multicentre, phase 3, randomised, double-blind, placebo-controlled study in active adult-onset RA. Patients (n = 619) were randomised 2:2:1 to subcutaneous certolizumab pegol (liquid formulation) 400 mg at weeks 0, 2 and 4 followed by 200 mg or 400 mg plus MTX, or placebo plus MTX, every 2 weeks for 24 weeks. The primary end point was ACR20 response at week 24. Secondary end points included ACR50 and ACR70 responses, change from baseline in modified Total Sharp Score, ACR core set variables and physical function. Results: Significantly more patients in the certolizumab pegol 200 mg and 400 mg groups achieved an ACR20 response versus placebo (p≤0.001); rates were 57.3%, 57.6% and 8.7%, respectively. Certolizumab pegol 200 and 400 mg also significantly inhibited radiographic progression; mean changes from baseline in mTSS at week 24 were 0.2 and -0.4, respectively, versus 1.2 for placebo (rank analysis p≤0.01). Certolizumab pegol-treated patients reported rapid and significant improvements in physical function versus placebo; mean changes from baseline in HAQ-DI at week 24 were
-0.50 and -0.50, respectively, versus -0.14 for placebo (p<=0.001). Most adverse events were mild or moderate, with low incidence of withdrawals due to adverse events. Five patients developed tuberculosis. Conclusion: Certolizumab pegol plus MTX was more efficacious than placebo plus MTX, rapidly and significantly improving signs and symptoms of RA and physical function and inhibiting radiographic progression. Trial registration number: NCT00175877.

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**Some additional results** *(may duplicate previous results)*

1. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial


**Citation:** The Lancet, August 2009, vol./is. 374/9688(459-466), 0140-6736 (14 Aug 2009)

**Publication Date:** August 2009

**Abstract:** Background: New treatment strategies for early rheumatoid arthritis are evolving rapidly. We aimed to compare addition of conventional disease-modifying antirheumatic drugs (sulfasalazine and hydroxychloroquine) with addition of a tumour necrosis factor antagonist (infliximab) to methotrexate in patients with early rheumatoid arthritis. Methods: We undertook a randomised trial in 15 rheumatology units in Sweden. We enrolled patients with early rheumatoid arthritis (symptom duration <1 year) and administered methotrexate (up to 20 mg per week). After 3-4 months, those who had not achieved low disease activity but who could tolerate methotrexate were randomly allocated by computer addition of either sulfasalazine and hydroxychloroquine or infliximab. Primary outcome was achievement of a good response according to European League Against Rheumatism (EULAR) criteria at 12 months. Patients were followed up to 24 months; here, we present findings at 12 months. Analysis was by intention to treat and we used non-responder imputation. The Swefot (Swedish Pharmacotherapy) study is registered in the WHO database at the Karolinska University Hospital, number CT20080004. Findings: 487 patients were initially enrolled. Of 258 who had not achieved low disease activity with methotrexate, 130 were allocated sulfasalazine and hydroxychloroquine and 128 were assigned infliximab. 32 of 130 (25%) patients allocated sulfasalazine and hydroxychloroquine and 128 were assigned infliximab. 32 of 130 (25%) patients allocated sulfasalazine and hydroxychloroquine achieved the primary outcome compared with 50 of 128 (39%) assigned infliximab (risk ratio 159 [95% CI 110-230], p=00160). Adverse events were balanced fairly well between the two groups and accorded with known adverse events of the drugs used. No deaths occurred in either group. Interpretation: In patients with early rheumatoid arthritis in whom methotrexate treatment failed, addition of a tumour necrosis factor antagonist to methotrexate monotherapy is clinically superior to addition of conventional disease-modifying antirheumatic drugs.

Funding: Swedish Rheumatism Association, Schering-Plough. 2009 Elsevier Ltd. All rights reserved.

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2. Increasing the infliximab dose in rheumatoid arthritis patients: A randomised, double blind study failed to confirm its efficacy

**Author(s)** Pavelka K., Jarosova K., Suchy D., Senolt L., Chrout K., Dusek L., Vencovsky J.

**Citation:** Annals of the Rheumatic Diseases, August 2009, vol./is. 68/8(1285-1289), 0003-4967;1468-2060 (August 2009)

**Publication Date:** August 2009

**Abstract:** Objective: To evaluate the effect of infliximab dose escalation in incomplete responders in a randomised controlled trial. Methods: 141 rheumatoid arthritis (RA) patients treated with infliximab for 12 months (3 mg/kg; intervals 0, 2, 6 and then 8 weeks) who responded to the drug (disease activity score in 28 joints (DAS28) decrease >1.2) but who were not in remission (DAS28 >2.6) were enrolled into the study. Patients were randomly assigned into arm A, 3 mg/kg, and arm B, 5 mg/kg infliximab every 8 weeks. Outcome measures included the DAS28, its components and C-reactive protein (CRP). Results: There were no significant differences in changes in the DAS28, its components, or CRP in patients in arms A and B during the 12 months of treatment. All patients showed a DAS28 decrease greater than 0.6 after 28 weeks. Eleven patients interrupted therapy in arm A and 14 in arm B. Infusion reactions and non-serious adverse events were observed in 4.2% and 28.2% of arm A patients and in 7.2% and 47.8% of arm B patients. The frequency of serious adverse events was comparable between arms A and B (16.9% and 15.9%, respectively), and the frequency of serious infections was not significantly greater in the higher dose group (5.8%) than in the lower dose group (5.6%). Conclusions: In this setting, increasing the infliximab dose from 3 mg/kg to 5 mg/kg in RA patients with residual disease activity did not improve efficacy but moderately increased toxicity. These data indicate that a switch to another biological treatment would be a more appropriate strategy in incomplete responders.

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3. Efficacy of tacrolimus in infliximab-refractory progressive rheumatoid arthritis

**Author(s)** Yokota K., Akiyama Y., Asanuma Y., Miyoshi F., Sato K., Mimura T.

**Citation:** Rheumatology International, February 2009, vol./is. 29/4(459-461), 0172-8172 (February 2009)

**Publication Date:** February 2009

**Abstract:** We report a Japanese male patient with intractable rheumatoid arthritis (RA), in whom tacrolimus was effective ultimately. Five years before the admission he was diagnosed as RA, which was resistant to various disease-modifying anti-rheumatic drugs (DMARDs). Two years before, administration of infliximab was initiated although the medicine failed to control RA. In spite of the multiple joint replacement, the RA disease activity worsened. Tacrolimus (1.5 mg/day) was administered. Twenty-four weeks of tacrolimus treatment reduced the disease activity score for 28 joints-erythrocyte sedimentation rate from 7.44 to 3.65. Herein, we present a patient with RA, who was successfully treated by tacrolimus, and in whom infliximab was not effective. Tacrolimus may be one of the drugs for RA patients refractory to the conventional treatments including methotrexate or tumor necrosis factor inhibitors. 2008 Springer-Verlag.

**Source:** EMBASE
4. Pericardial effusions on anti-TNF therapy for rheumatoid arthritis - A drug side effect or uncontrolled systemic disease?

Author(s) Edwards M.H., Leak A.M.

Citation: Rheumatology, 2009, vol./is. 48/3(316-317), 1462-0324;1462-0332 (2009)

Publication Date: 2009

Source: EMBASE

5. Use of tumor necrosis factor-alpha (TNF-alpha) antagonists infliximab, etanercept, and adalimumab in patients with concurrent rheumatoid arthritis and hepatitis B or hepatitis C: A retrospective record review of 11 patients

Author(s) Li S., Kaur P.P., Chan V., Berney S.

Citation: Clinical Rheumatology, 2009, vol./is. 28/7(787-791), 0770-3198 (2009)

Publication Date: 2009

Abstract: An understanding of the cytokine cascade in a rheumatoid joint has led to the development of new therapeutic options, including drugs targeting tumor necrosis factor-alpha (TNF-alpha). The safety profile of these agents in patients with hepatitis-induced liver disease, however, remains a concern because of risks associated with immune suppression. To examine the effect of three different TNF-alpha antagonists, infliximab, etanercept, and adalimumab, on serum transaminases and hepatitis viral load in patients with rheumatoid arthritis (RA) and concurrent hepatitis B (HBV) or hepatitis C (HCV). Medical records of 11 patients with diagnosis of RA and documented seropositivity for hepatitis B or hepatitis C were retrospectively reviewed for worsening of hepatic inflammation and viral proliferation as measured by a rise in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and viral load while using these agents. Three patients had RA with concurrent chronic HBV and eight patients had RA with concurrent chronic HCV. Seven patients remained on a single anti-TNF-alpha agent and four patients switched to a second anti-TNF-alpha agent due to treatment failure. Two patients showed a transient elevation in AST and/or ALT from normal, but in all 11 patients, AST and ALT levels were within one time the upper range of normal at the conclusion of the study. No significant increase in viral load was seen except one patient who showed a fourfold increase from baseline. Our case series supports results obtained from previous studies examining the safety of anti-TNF-alpha agents in patients with underlying hepatic disease. Use of these agents in patients with HBV or HCV may be associated with a transient transaminitis but appears to be safe overall. In both groups, frequent monitoring of serum transaminase levels and viral load is essential. Clinical Rheumatology 2009.

Source: EMBASE

6. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: Results from a 24-
Abstract: The phase III RADIATE study examined the efficacy and safety of tocilizumab, an anti-IL-6 receptor monoclonal antibody in patients with rheumatoid arthritis (RA) refractory to tumour necrosis factor (TNF) antagonist therapy. Methods: 499 patients with inadequate response to one or more TNF antagonists were randomly assigned to receive 8 mg/kg or 4 mg/kg tocilizumab or placebo (control) intravenously every 4 weeks with stable methotrexate for 24 weeks. ACR20 responses, secondary efficacy and safety endpoints were assessed. Results: ACR20 was achieved at 24 weeks by 50.0%, 30.4% and 10.1% of patients in the 8 mg/kg, 4 mg/kg and control groups, respectively (less than p<0.001 both tocilizumab groups versus control). At week 4 more patients achieved ACR20 in 8 mg/kg tocilizumab versus controls (less than p = 0.001). Patients responded regardless of most recently failed anti-TNF or the number of failed treatments. DAS28 remission (DAS28 <2.6) rates at week 24 were clearly dose related, being achieved by 30.1%, 7.6% and 1.6% of 8 mg/kg, 4 mg/kg and control groups (less than p = 0.001 for 8 mg/kg and p = 0.053 for 4 mg/kg versus control). Most adverse events were mild or moderate with overall incidences of 84.0%, 87.1% and 80.6%, respectively. The most common adverse events with higher incidence in tocilizumab groups were infections, gastrointestinal symptoms, rash and headache. The incidence of serious adverse events was higher in controls (11.3%) than in the 8 mg/kg (6.3%) and 4 mg/kg (7.4%) groups. Conclusion: Tocilizumab plus methotrexate is effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNF antagonists and has a manageable safety profile. Trial registration number: NCT00106522.

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7. Biologicals in rheumatology: Austrian experiences from a rheumatic outpatient clinic

Abstract: The efficacy of biological agents has been shown in several randomized clinical trials. However, little is known regarding the performance of these drugs in daily rheumatological care. Totally, 173 patients treated with biological agents (infliximab, etanercept, adalimumab, anakinra) were retrospectively analyzed between November 2001 and December 2005 at an Austrian rheumatic outpatient clinic. In total, 224 courses of treatment with biological agents were followed up. Among the 93 drug discontinuations observed, the most frequent causes were inefficacy (56.5%) and side effects (31.9%). In 74 patients (51%), the first biological agent was withdrawn after a median treatment period of 10.7 (range 0-80) months. A second biological agent was given to 36 patients, a third to 11 and a fourth to 3 patients. Our data underline the necessity of large observational studies to assess the full spectrum of patients treated with biological agents in clinical routine. 2008 Springer-Verlag.

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8. Uk cost-utility analysis of rituximab in patients with rheumatoid arthritis that failed to respond adequately to a biologic disease-modifying antirheumatic drug

Author(s) Kielhorn A., Porter D., Diamantopoulos A., Lewis G.

Citation: Current Medical Research and Opinion, September 2008, vol./is. 24/9(2639-2650), 0300-7995 (September 2008)

Publication Date: September 2008

Abstract: Objective: To evaluate the incremental cost effectiveness of rituximab in patients with rheumatoid arthritis that failed to respond adequately to tumour necrosis factor-alpha inhibitors (biologic disease-modifying antirheumatic drugs; bDMARDs). A cost-utility model has been developed to simulate the long-term incremental cost and benefits of rituximab using data from clinical trials and registries. Methods: The model estimates the lifetime disease progression of up to 10 000 hypothetical rheumatoid arthritis (RA) patients that failed one bDMARD. It compares cost and outcomes of two treatment sequences, representing the current UK standard both with and without rituximab. The population characteristics match those of the Randomised Evaluation of Long-term Efficacy of rituximab in RA (REFLEX) phase III randomised control trial. Clinical outcomes were based on an indirect comparison of published American College of Rheumatology response rates, adjusted for differences in placebo. To estimate medical resource use, health assessment questionnaire (HAQ) scores were grouped into five categories with UK registry data informing the average cost for each category. Quality-adjusted life years (QALYs) gained were mapped from disease severity (HAQ scores). Results: Compared to a standard UK treatment sequence (assuming the sequential use of bDMARDs) the introduction of rituximab led to a QALY gain of 0.526 years. The incremental cost-effectiveness ratios (ICERs) based on total direct medical cost were 11 601. Adding rituximab to a treatment sequence with no sequential use of biologic generates an ICER of 14 690. Conclusion: Rituximab has lower average annual treatment costs compared to other bDMARDs and is a highly cost-effective treatment option for patients who have failed to respond adequately to one bDMARD. The cost per QALY gained of rituximab falls well below commonly accepted thresholds within the UK. Potential weaknesses of the model include the paucity of data on the efficacy of bDMARDs or non-biologic DMARDs when used as second-line options; the lack of consensus about the most appropriate therapy in patients who fail all available bDMARDs; probable underestimation of the non-drug related medical costs; indirect measurement of QALY gains with rituximab therapy; and the necessity of synthesising data from a number of clinical trials with different populations and study drugs. 2008 Informa UK Ltd.

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9. An open-label pilot study of the effectiveness of adalimumab in patients with rheumatoid arthritis and previous infliximab treatment: Relationship to reasons for failure and anti-infliximab antibody status

Author(s) van der Bijl A.E., Breedveld F.C., Antoni C.E., Kalden J.R., Kary S., Burmester G.R., Beckmann C., Unnebrink K., Kupper H.

Citation: Clinical Rheumatology, August 2008, vol./is. 27/8(1021-1028), 0770-3198 (August 2008)

Publication Date: August 2008

Abstract: This prospective open-label pilot study evaluated the effectiveness and safety of adalimumab and the relationship to antibodies against infliximab (IFX) in adult patients with active rheumatoid arthritis (RA) who had been treated previously with IFX and experienced treatment failure owing to lack or loss of response or intolerance. Patients self-administered adalimumab 40 mg subcutaneously every other week for 16 weeks, followed by maintenance therapy for up to Week 56. Measures of effectiveness included American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) response criteria, 28-joint Disease Activity Score, and the Health Assessment
Questionnaire Disability Index. Serum IFX concentrations, human antichimeric antibody against IFX (HACA), adalimumab serum concentrations, antialdimumab antibody, and safety also were assessed. Of the 41 enrolled patients, 37 completed 16 weeks and 30 completed 56 weeks of treatment. Patients experienced clinically meaningful improvements in all measures of RA activity, with greater response rates observed for patients who had experienced loss of initial response to or intolerance of IFX. At Week 16, 46% of patients achieved an ACR20 and 28% achieved an ACR50; 61% achieved an at least moderate and 17% achieved a good EULAR response. Clinical benefit was maintained through Week 56 in all effectiveness parameters. Baseline HACA status did not significantly impact effectiveness. No new safety signals were observed; neither former IFX intolerance status nor baseline HACA status had a clinically relevant impact on adverse event frequency or severity. Adalimumab was effective and well-tolerated in patients with RA who previously failed IFX therapy, irrespective of reason for discontinuation and of HACA status. The Author(s) 2008.

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10. A case of autoimmune hepatitis exacerbated by the administration of etanercept in the patient with rheumatoid arthritis
Author(s) Harada K., Akai Y., Koyama S., Ikenaka Y., Saito Y.
Citation: Clinical Rheumatology, August 2008, vol./is. 27/8(1063-1066), 0770-3198 (August 2008)
Publication Date: August 2008
Abstract: A 50-year-old woman was admitted for active rheumatoid arthritis (RA). She was found to have RA 1 year prior to this admission. Past history was unremarkable and she had no family history for rheumatic diseases. As nonsteroidal anti-inflammatory drug (NSAID) and methotrexate were not effective, etanercept was started (25 mg, twice a week). Mild elevation of alanine transaminase (ALT) and aspartate transaminase (AST) was found as an outpatient, and it was considered to be NSAID-induced liver injury. Two weeks after the first dose of etanercept, she developed progressive elevation of AST and ALT with right upper quadrant tenderness and hepatomegaly. Etanercept was discontinued and liver biopsy was performed, which demonstrated portal-area-dominant lymphoplasmacytic inflammatory cell infiltration. She was diagnosed as autoimmune hepatitis (AIH). Glucocorticoid was started with normalized liver function and stable joint symptoms. AIH was thought to be acutely aggravated by the administration of etanercept. Clinical Rheumatology 2008.
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11. Tumor necrosis factor-alpha antagonist use and heart failure in elderly patients with rheumatoid arthritis
Author(s) Setoguchi S., Schneeweiss S., Avorn J., Katz J.N., Weinblatt M.E., Levin R., Solomon D.H.
Citation: American Heart Journal, August 2008, vol./is. 156/2(336-341), 0002-8703;1097-6744 (August 2008)
Publication Date: August 2008
Abstract: Background: Clinical trials have shown that tumor necrosis factor-alpha antagonists (TNFAs) confer little benefit, and some may cause potential harm in advanced heart failure (HF). Although TNFAs had significant benefits in treating rheumatoid arthritis (RA), little is known whether the drugs pose an increased risk of HF in older patients with
Methods: A cohort study was conducted using data from Medicare and drug benefit programs in 2 states (1994-2004). We identified patients with RA aged >=65 who received TNFα or methotrexate (MTX). The cohort was divided into patients with and without previous HF. We considered demographic variables, cardiovascular risk factors, RA severity-related measures, and other comorbidities. The primary end point was hospitalization with HF. We used stratified Cox proportional hazards regression to estimate the adjusted effect of TNFαs on HF hospitalization. Results: The cohort consisted of 1,002 TNFα users and 5,593 MTX users. There were 59 HF admissions during 1,680 person-years of TNFα use and 227 HF admissions during 10,623 person-years of MTX use. Comparing TNFα with MTX users, the adjusted hazard ratio for HF hospitalization was 1.70 (95% confidence interval 1.07-2.69). We found similar results in patients with and without previous HF. Among patients with previous HF, the adjusted hazard ratio for death was 4.19 (95% confidence interval 1.48-11.89). Conclusions: TNFαs may increase the risk of both first hospitalization and exacerbation of HF in elderly patients with RA. The potential for residual confounding in our study cannot be ruled out; larger and more detailed studies are needed to confirm the findings. 2008 Mosby, Inc. All rights reserved.

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12. Acute psychosis in three patients receiving anti-tumour necrosis factor-alpha therapy

Author(s) McGregor L., Saunders S.A., Hunter J.A., Murphy E.
Citation: Rheumatology, August 2008, vol./is. 47/8(1254-1255), 1462-0324;1462-0332 (August 2008)
Publication Date: August 2008
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Citation: Nederlands Tijdschrift voor Geneeskunde, July 2008, vol./is. 152/30(1672-1677), 0028-2162 (26 Jul 2008)
Publication Date: July 2008
Abstract: Objective. To investigate the in vivo mechanism of non-responding to infliximab treatment of patients with rheumatoid arthritis (RA) and the role of anti-infliximab antibodies by using radiolabeled infliximab. Design. Descriptive and comparative study. Method. Two responding and two non-responding RA patients were infused with radiolabeled infliximab. Subsequently imaging investigations and serum analysis were performed at set times. Results. The scintigrams showed that the labelled infliximab was mainly present in the blood until 24 h after infusion. There was a trend of faster blood clearance and higher liver and spleen uptake of <sup>99m</sup>Tc-infliximab in one non-responding patient. Labelled infliximab was taken up by inflamed joints. The anti-infliximab level was high (1008 and 1641 U/ml) in the non-responders and low or not detectable in the responders. Sucrose gradients of serum revealed antibody complexes in both non-responders. Various sizes of antibody complexes, including very large ones, were observed in one non-
A responder who developed a serious infusion reaction. Conclusion. Infliximab-anti-infliximab immune complexes were found to form in RA non-responders due to the presence of significant quantities of anti-infliximab. This finding may partly explain the failure of the infliximab treatment.

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14. Pyoderma Gangrenosum in a patient with seronegative rheumatoid arthritis during therapy with adalimumab: Toxic effects of adalimumab or failure of adalimumab to prevent the onset of this phenomenon?

**Author(s)** Stichenwirth M., Riedl E., Pehamberger H., Tappeiner G.

**Citation:** Archives of Dermatology, June 2008, vol./is. 144/6(817-818), 0003-987X;0003-987X (June 2008)

**Publication Date:** June 2008

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15. Rituximab in rheumatoid arthritis following anti-TNF-associated tuberculosis

**Author(s)** Burr M.L., Malaviya A.P., Gaston J.H., Carmichael A.J., Ostor A.J.K.

**Citation:** Rheumatology, May 2008, vol./is. 47/5(738-739), 1462-0324;1462-0332 (May 2008)

**Publication Date:** May 2008

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16. Occurrence of cold agglutinin disease in RA patient during etanercept therapy successfully treated with rituximab

**Author(s)** Malesci D., La Montagna G.

**Citation:** Rheumatology, May 2008, vol./is. 47/5(734-735), 1462-0324;1462-0332 (May 2008)

**Publication Date:** May 2008

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17. Sarcoidosis occurring during anti-TNF-alpha treatment for inflammatory rheumatic diseases: Report of two cases

Author(s) Toussirot E., Pertuiset E., Kantelip B., Wendling D.

Citation: Clinical and Experimental Rheumatology, May 2008, vol./is. 26/3(471-475), 0392-856X (May/June 2008)

Publication Date: May 2008

Abstract: Anti-TNF-alpha agents have been tried in cases of refractory sarcoidosis, giving favourable results. Thus, the occurrence of a granulomatous disease in a patient receiving such drug seems paradoxical. We describe 2 patients with inflammatory rheumatic disease, the first with ankylosing spondylitis, the second with rheumatoid arthritis, under anti-TNF-alpha treatment (infliximab and etanercept respectively) who developed non-caseating granulomas of the lungs and lymph nodes consistent with the diagnosis of sarcoidosis. Limited and various similar cases have been reported. It is generally considered that these granulomatous diseases are related to the anti-TNF-alpha agent. Copyright Clinical and Experimental Rheumatology 2008.

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18. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy

Author(s) Genovese M.C., Schiff M., Luggen M., Becker J.-C., Aranda R., Teng J., Li T., Schmidely N., Le Bars M., Dougados M.

Citation: Annals of the Rheumatic Diseases, April 2008, vol./is. 67/4(547-554), 0003-4967 (April 2008)

Publication Date: April 2008

Abstract: Objective: To evaluate the safety and efficacy of abatacept during 2 years of the ATTAIN (Abatacept Trial in Treatment of Anti-TNF Inadequate responders) trial in patients with rheumatoid arthritis. Methods: Patients completing the 6-month, double-blind period were eligible to enter the long-term extension; patients received abatacept ~10 mg/kg, plus disease-modifying antirheumatic drugs. Safety and efficacy (American College of Rheumatology (ACR) criteria responses, DAS28 (C-reactive protein), HAQ-DI, SF-36, Medical Outcomes Study Sleep Problems Index, fatigue VAS) were assessed through 2 years. Results: 317 patients (218 from the abatacept and 99 from the placebo group) entered and 222 (70%) completed 18 months of long-term extension treatment. The incidence and type of adverse events were consistent between the double-blind and cumulative (double-blind plus long-term extension) periods. Rates of serious adverse events were 25.6 and 23.4 per 100 patient-years in the double-blind versus cumulative period. At 6 months and 2 years, using non-responder analyses, ACR responses in abatacept-treated patients were: ACR 20, 59.4% and 56.2%; ACR 50, 23.5% and 33.2%; ACR 70, 11.5% and 16.1%; HAQ-DI responses were 54.4% and 47.9%. At 6 months and 2 years, using post-hoc as-observed analyses, the percentage of patients (95% confidence interval) achieving DAS28 (C-reactive protein) low disease activity score (<3.2) and DAS28 (C-reactive protein)-defined remission (<2.6) increased from 18.3% (13.0, 23.5) to 32.0% (24.6, 39.4) and 11.1% (6.8, 15.3) to 20.3% (13.9, 26.6). Clinically meaningful improvements in SF-36, pain, fatigue and sleep problems were also maintained throughout the 2 years of abatacept treatment. Conclusion: No unique safety observations were reported during open-label exposure. Improvements in the signs and symptoms of rheumatoid arthritis, physical function and health-related quality of life observed after 6 months, were maintained throughout the 2 years in this population with difficult-to-treat disease.

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19. Treatment response to a second or third TNF-inhibitor in RA: results from the South Swedish Arthritis Treatment Group Register

**Author(s)** Karlsson J.A., Kristensen L.E., Kapetanovic M.C., Gulfe A., Saxne T., Geborek P.

**Citation:** Rheumatology (Oxford, England), April 2008, vol./is. 47/4(507-513), 1462-0332 (Apr 2008)

**Publication Date:** April 2008

**Abstract:** OBJECTIVES: To study treatment response rates of RA patients undergoing second- and third-line anti-TNF therapy and to identify baseline predictors of response to second-line treatment. METHODS: RA patients monitored in a prospective, observational study, having switched anti-TNF therapy once (first-time switchers, n = 337) or twice (second-time switchers, n = 36) -- i.e. following failures with one antibody- and one receptor-type agent -- between March 1999 and December 2006, were studied. Treatment responses at 3 months were assessed by the ACR and European League Against Rheumatism (EULAR) response criteria. Predictive potentials for response to second-line treatment of demographics, baseline disease activity measures, disease and treatment characteristics were analysed using logistic regression. RESULTS: ACR20 response was met by 51% of first-time and 35% of second-time switchers. Corresponding ACR50 rates were 27 and 18%; EULAR overall rates (EULAR good or moderate response) 71 and 58%; EULAR good rates 25 and 9% and 28-joint disease activity score (DAS28) remission rates 16 and 6%. Identified baseline predictors of response to second-line treatment were lower age and HAQ scores, elevated DAS28 values and having ceased the former anti-TNF treatment due to adverse events rather than inefficacy. No variable was predictive for all examined response criteria. CONCLUSIONS: Response rates of first-time anti-TNF switchers are somewhat below those of anti-TNF naive RA patients, while the markedly inferior response rates of second-time switchers suggest other therapeutic options to be considered in this situation. Identified baseline predictors of response may be useful indicators to second-line anti-TNF therapy, but vary depending on the response criteria set studied.

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20. Three significant cases of neutropenia with etanercept [3]

**Author(s)** Wenham C., Gadsby K., Deighton C.

**Citation:** Rheumatology, March 2008, vol./is. 47/3(376-377), 1462-0324;1462-0332 (March 2008)

**Publication Date:** March 2008

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22. Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis

**Author(s)** Donahue K.E., Gartlehner G., Jonas D.E., Lux L.J., Thieda P., Jonas B.L., Hansen R.A., Morgan L.C., Lohr K.N.

**Citation:** Annals of internal medicine, January 2008, vol./is. 148/2(124-134), 1539-3704 (15 Jan 2008)

**Publication Date:** January 2008

**Abstract:** BACKGROUND: The comparative effectiveness of rheumatoid arthritis therapies is uncertain. PURPOSE: To compare the benefits and harms of disease-modifying antirheumatic drugs (DMARDs) for adults with rheumatoid arthritis. DATA SOURCES: Records limited to the English language and studies of adults were identified by using MEDLINE, EMBASE, The Cochrane Library, and International Pharmaceutical Abstracts from 1980 to September 2007. STUDY SELECTION: Two persons independently selected relevant head-to-head trials and prospective cohort studies with at least 100 participants and 12-week follow-up and relevant good- or fair-quality meta-analyses that compared benefits or harms of 11 drug therapies. For harms, they included retrospective cohort studies. DATA EXTRACTION: Information on study design, interventions, outcomes, and quality were extracted according to a standard protocol. DATA SYNTHESIS: Head-to-head trials (n = 23), mostly examining synthetic DMARDs, showed no clinically important differences in efficacy among synthetic DMARDs (limited to methotrexate, leflunomide, and sulfasalazine) or among anti-tumor necrosis factor drugs (adalimumab, etanercept, and infliximab). Monotherapy with anti-tumor necrosis factor drugs resulted in better radiographic outcomes than did methotrexate but no important differences in clinical outcomes (for example, 20%, 50%, or 70% improvement according to American College of Rheumatology response criteria). Various combinations of biological DMARDs plus methotrexate improved clinical response rates and functional outcomes more than monotherapy with either methotrexate or biological DMARDs. In patients whose monotherapy failed, combination therapy with synthetic DMARDs improved response rates. Numbers and types of short-term adverse events were similar for biological and synthetic DMARDs. The evidence was insufficient to draw conclusions about differences for rare but serious adverse events for biological DMARDs. LIMITATION: Most studies were short-term efficacy trials conducted in selected populations with few comorbid conditions. CONCLUSION: Limited available comparative evidence does not support one monotherapy over another for adults with rheumatoid arthritis. Although combination therapy is more effective for patients whose monotherapy fails, the evidence is insufficient to draw firm conclusions about whether one combination or treatment strategy is better than another or is the best treatment for early rheumatoid arthritis.

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23. Generalized pustulosis induced by adalimumab in a patient with rheumatoid arthritis - A therapeutic challenge

**Author(s)** Kucharekova M., Winnepenningcx V., Frank J., Poblete-Gutierrez P.

**Citation:** International Journal of Dermatology, 2008, vol./is. 47/SUPPL. 1(25-28), 0011-9059;1365-4632 (2008)

**Publication Date:** 2008

**Abstract:** Tumor necrosis factor-alpha (TNF-alpha) inhibitors such as adalimumab are increasingly used in the treatment of chronic inflammatory diseases, including rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. In Europe, this group of drugs also has been approved for therapy of moderate to severe psoriasis recently. With increased
application of adalimumab, the possible adverse effects occurring in the course of treatment steadily gained more attention. Among these, infection and localized skin eruptions are the most common. Usually, the cutaneous symptoms rapidly resolve after discontinuation of the drug. Here, however, we report on a woman with rheumatoid arthritis who developed a therapy-refractory, generalized pustular rash during treatment with adalimumab. After different unsuccessful therapeutic attempts, only a combined treatment with prednisone, methotrexate, and cyclosporine eventually led to marked improvement. To the best of our knowledge, this is the first report on a generalized, therapy-resistant pustulosis as an adverse effect of adalimumab. 2008 International Society of Dermatology.

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24. Pyoderma gangrenosum developing during therapy with TNF-alpha antagonists in a patient with rheumatoid arthritis
Author(s) Vandevyvere K., Luyten F.P., Verschueren P., Lories R., Segaert S., Westhovens R.
Citation: Clinical Rheumatology, December 2007, vol./is. 26/12(2205-2206), 0770-3198 (December 2007)
Publication Date: December 2007
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25. Limited efficacy of conventional DMARDs after initial methotrexate failure in patients with recent onset rheumatoid arthritis treated according to the disease activity score
Citation: Annals of the Rheumatic Diseases, October 2007, vol./is. 66/10(1356-1362), 0003-4967 (October 2007)
Publication Date: October 2007
Abstract: Objectives: To determine the efficacy of subsequent disease modifying antirheumatic drug (DMARD) therapies after initial methotrexate (MTX) failure in patients with recent onset rheumatoid arthritis (RA), treated according to the DAS for 2 years. Methods: In groups 1 and 2 of the BeSt study, 244 RA patients were initially treated with MTX 15-25 mg/ week. Patients who discontinued MTX because of insufficient clinical response (disease activity score, DAS >2.4) or toxicity were classified as "MTX failures." In group 1, these patients switched to sulfasalazine (SSA), then leflunomide and finally to MTX + infliximab (IFX). In group 2, "MTX failures" added SSA to MTX, then hydroxychloroquine (HCQ), then prednisone, and eventually switched to MTX + IFX. "MTX successes" were patients who achieved a DAS <=2.4 after 2 years while still on MTX monotherapy. Total Sharp/van der Heijde score (TSS) progression from 0-2 years was assessed in "MTX failures" versus "MTX successes." Results: After 2 years, 162/244 patients (66%) had discontinued MTX because of insufficient response or toxicity. Of these, 78% also failed on SSA (adding or switching), 87% subsequently failed on leflunomide (in group 1), and 64% on MTX + SSA + HCQ (in group 2). 34 of 48 patients (71%) in groups 1 and 2 were successfully treated with MTX + IFX. After 2 years, regardless of the "success" on subsequent DMARDs, "MTX failures" had a median TSS progression of 3 units (mean 9) versus 1 unit (mean 3) in "MTX successes" (p = 0.007). Conclusion: After failure on initial MTX, treatment with subsequent conventional DMARDs is unlikely to result in a DAS <=2.4 and allows progression of joint damage.

Author(s) Rogan M.P., Thomas K.

Citation: Journal of Medical Case Reports, September 2007, vol./is. 1/, 1752-1947;1752-1947 (05 Sep 2007)

Publication Date: September 2007

Abstract: A 78-year-old white male from Iowa in the United States of America receiving the anti-tumor necrosis factor (TNF) agent infliximab therapy for rheumatoid arthritis developed a cheek ulcer which failed to respond to empiric antibiotic therapy. He subsequently presented with progressive respiratory failure from miliary coccidioidomycosis which proved fatal. The patient vacationed in Arizona 6 months previously and likely contracted the organism there as Iowa is not an endemic area for coccidioidomycosis. Respiratory failure from miliary infiltration is an uncommon presentation of coccidioidomycosis. Physicians should be aware of the importance of travel history and potential for life-threatening coccidioidomycosis in patients receiving tumor necrosis factor inhibitors. 2007 Rogan and Thomas; licensee BioMed Central Ltd.

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27. A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases

Author(s) Weisman M.H., Paulus H.E., Burch F.X., Kivitz A.J., Fierer J., Dunn M., Kerr D.R., Tsuji W., Baumgartner S.W.

Citation: Rheumatology, July 2007, vol./is. 46/7(1122-1125), 1462-0324;1462-0332 (July 2007)

Publication Date: July 2007

Abstract: Objective. To evaluate the safety of etanercept in patients with rheumatoid arthritis (RA) and concomitant comorbidities. Methods. The safety of etanercept (25mg twice weekly) in RA patients with at least one comorbidity (i.e. diabetes mellitus, chronic pulmonary disease, recent pneumonia, recurrent infections) was evaluated in a 16-week placebo-controlled, randomized, double-blinded study. The primary endpoint was the incidence of medically important infections (MIIs; defined as those resulting in hospitalization or treatment with intravenous antibiotics). Results. Data from 535 patients were analysed; the study was terminated early because of slow enrolment and lower than predicted incidence of infections. Serious adverse events (5.9% placebo, 8.6% etanercept) were most commonly observed in the cardiovascular system. Six patients (1 placebo; 5 etanercept) died during the study; four deaths were attributed to cardiovascular events. The numerically higher mortality in the etanercept group was not statistically significant [relative risk (95% CI) = 5.06 (0.59, 42.99)] but remains unexplained. No etanercept-related increase in the incidence of MIIs (3.7% placebo, 3.0% etanercept) or overall infections was observed in the total study population or in subgroups of patients who were >=65 yrs of age, had diabetes or had chronic pulmonary disease. Conclusions. Etanercept was generally well tolerated by RA patients with comorbidities. Serious adverse events and deaths occurred more frequently in the etanercept group but event numbers were small and CIs were broad, preventing reliable conclusions from being drawn. Although the study
had limited statistical power, the incidence of MIIs in these patients was not increased by etanercept treatment. The Author 2007. Published by Oxford University Press on behalf of the British Society for Rheumatology. All rights reserved.

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28. Development of active tuberculosis following initiation of infliximab despite appropriate prophylaxis [3]

**Author(s)** Raychaudhuri S., Shmerling R., Ermann J., Helfgott S.

**Citation:** Rheumatology, May 2007, vol./is. 46/5(887-888), 1462-0324;1462-0332 (May 2007)

**Publication Date:** May 2007

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29. Serious liver disease induced by infliximab

**Author(s)** Tobon G.J., Canas C., Jaller J.-J., Restrepo J.-C., Anaya J.-M.

**Citation:** Clinical Rheumatology, April 2007, vol./is. 26/4(578-581), 0770-3198 (April 2007)

**Publication Date:** April 2007

**Abstract:** Infliximab, a chimeric monoclonal antibody that binds the tumor necrosis factor alpha (TNFalpha), is used in the treatment of rheumatoid arthritis (RA) and Crohn's disease (CD). Previous cases of significant secondary liver disease associated with infliximab treatment have been reported in patients with RA, CD, and psoriatic arthritis. Two additional patients with RA who developed a serious liver disease associated with infliximab treatment are reported here. A 39-year old RA patient was admitted with cholestatic liver disease after 8 months of treatment with infliximab. She had no history of hepatic diseases, exposure to hepatotoxic or illicit drugs, or alcohol abuse. A liver biopsy showed severe ductal proliferation with collapse and enucleation of the hepatocytes. Despite aggressive treatment with oral prednisolone, she developed hepatic failure. On the 45th day, a liver transplant was performed. The second patient, a 54-year old RA patient, was diagnosed with autoimmune hepatitis after 12 infliximab infusions. She fulfilled autoimmune hepatitis type 1 criteria. A liver biopsy disclosed an altered lobular structure with chronic inflammation and the formation of collagen bands. She was treated with prednisolone and azathioprine and a complete recovery was noted 1 month later. These cases should alert rheumatologists to the possibility of new adverse reactions (liver injury) associated with the use of TNFalpha blockers in an autoimmune setting. Clinical Rheumatology 2006.

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30. Failure of etanercept to control extra-articular manifestations of rheumatoid arthritis

Author(s) Hall S.J.L., Hickling P.

Citation: Journal of Clinical Rheumatology, February 2007, vol./is. 13/1(54), 1076-1608 (February 2007)

Publication Date: February 2007

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31. Anakinra, a recombinant human IL-1 receptor antagonist, in clinical practice. Outcome in 60 patients with severe rheumatoid arthritis [Italian] Anakinra, antagonista umano ricombinante del recettore dell’IL-1, nella pratica clinica. Outcome in 60 pazienti con artrite reumatoide severa

Author(s) Botsios C., Sfriso P., Furlan A., Ostuni P., Biscaro M., Fiocco U., Todesco S., Punzi L.

Citation: Reumatismo, January 2007, vol./is. 59/1(32-37), 0048-7449 (2007 Jan-Mar)

Publication Date: January 2007

Abstract: OBJECTIVE: We evaluated both the efficacy and safety of anakinra in daily routine rheumatoid arthritis clinical practice. METHODS: We studied 60 cases, including patients with previous anti-TNFalpha exposure, treated with anakinra (100 mg/daily s.c.) in combination with methotrexate (7.5-10 mg/week i.m.) or leflunomide (20 mg/die) in a two year observational study. Efficacy measures were assessed using the American College of Rheumatology (ACR) response criteria. Safety was evaluated according to a modified World Health Organization adverse reaction term dictionary. RESULTS: At week 14, ACR 20% response criteria have been fulfilled by 53 (91.3%) out of 58 patients, 51 (87.9%) of them achieving also an ACR 50% and 15 (25.8%) an ACR 70% response. Thirteen patients touched 102 weeks of treatment: ACR 20% response was achieved in 92.3%, while ACR 50% and ACR 70% were respectively found in 84.6% and 38.4% of the cases. The mean decrease in HAQ score was 0.38, p<0.001. Of the 16 patients who were previously treated with anti-TNFalpha blockers, 81.2% responded to anakinra. There was no significant difference in the ACR response between groups with and without previous anti-TNFalpha exposure. Seventeen patients (28.3%) stopped anakinra because of side-effects (5%) or failure to respond (23.3%). Only 4 cases of pulmonitis, of which 2 have been hospitalised, and 1 case with tuberculosis (previously treated with infliximab) were observed. CONCLUSIONS: Our clinical experience confirms that anakinra is effective and safe in the treatment of rheumatoid arthritis. Anakinra seems also useful in patients with previous anti-TNFalpha blockers failures. Even though major adverse events were rare, clinicians should be aware of such a possibility.

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Author(s) Boulton J.G., Bourne J.T.

Citation: Rheumatology, January 2007, vol./is. 46/1(178-179), 1462-0324;1462-0332 (January 2007)

Publication Date: January 2007

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33. Acute progression of interstitial lung disease: A complication of etanercept particularly in the presence of rheumatoid lung and methotrexate treatment [7]

**Author(s)** Lindsay K., Melsom R., Jacob B.K., Mestry N.

**Citation:** Rheumatology, August 2006, vol./is. 45/8(1048-1049), 1462-0324;1462-0332 (August 2006)

**Publication Date:** August 2006

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34. Efficacy and safety of leflunomide alone and in combination with methotrexate in the treatment of refractory rheumatoid arthritis

**Author(s)** Antony T., Jose V., Paul B., Thomas T.

**Citation:** Indian Journal of Medical Sciences, August 2006, vol./is. 60/8(318-326), 0019-5359 (01 Aug 2006)

**Publication Date:** August 2006

**Abstract:** BACKGROUND: Rheumatoid arthritis patients who develop refractoriness are left with no alternatives other than leflunomide and costly biological response modifiers. Leflunomide, though effective, was associated with adverse events and has not been extensively studied in the Indian population. AIMS: Determination of safety and efficacy of leflunomide alone and if not useful, in combination with methotrexate in patients refractory to conventional disease-modifying agents. SETTING AND DESIGN: Open labeled clinical trial with leflunomide [100 mg, OD x 3 days followed by 20 mg, OD x 6 months], if no improvement at three months, combined with methotrexate [5-7.5 mg, OD x 3 months] at a tertiary care hospital. MATERIALS AND METHODS: The primary endpoint in the improvement in EULAR criteria and secondary endpoints were patient and physician global evaluation, incidence of remission and biochemical and clinical adverse events. STATISTICAL ANALYSIS: Chi square test or Fisher's exact test and parametric and non-parametric repeat measure ANOVA were used for analysis. RESULTS: Among 84 patients who were included in the study, leflunomide showed improvement and remission in 52 [62%] and 6 [7%] in six months, by intention to treat analysis. Adverse events were observed in 15, discontinuation in 5 and 24 dropped out. With combination in 11 patients, there was improvement and remission in nine [91%] and one [9%] after three months. Adverse events were observed in six and one discontinued. CONCLUSIONS: If regular monitoring of hepatic function and hematological parameters are performed, leflunomide is an effective and safe drug in the Indian population in resistant rheumatoid arthritis patients, especially if used alone.

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35. Etanercept-induced dermatitis in a patient with rheumatoid arthritis [8]

Author(s): Lai-Cheong J., Warren R., Bucknall R., Parslew R.

Citation: Journal of the European Academy of Dermatology and Venereology, May 2006, vol./is. 20/5(614-615), 0926-9959;1468-3083 (May 2006)

Publication Date: May 2006

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36. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: Results of a phase IIb randomized, double-blind, placebo-controlled, dose-ranging trial


Citation: Arthritis and Rheumatism, May 2006, vol./is. 54/5(1390-1400), 0004-3591 (May 2006)

Publication Date: May 2006

Abstract: Objective. To examine the efficacy and safety of different rituximab doses plus methotrexate (MTX), with or without glucocorticoids, in patients with active rheumatoid arthritis (RA) resistant to disease-modifying antirheumatic drugs (DMARDs), including biologic agents. Methods. A total of 465 patients were randomized into 9 treatment groups: 3 rituximab groups (placebo [n = 149], 500 mg [n = 124], or 1,000 mg [n = 192] on days 1 and 15) each also taking either placebo glucocorticoids, intravenous methylprednisolone premedication, or intravenous methylprednisolone premedication plus oral prednisone for 2 weeks. All patients received MTX (10-25 mg/week); no other DMARDs were permitted. Results. Significantly more patients who received 2 500-mg or 2 1,000-mg infusions of rituximab met the American College of Rheumatology 20% improvement criteria (achieved an ACR20 response) at week 24 (55% and 54%, respectively) compared with placebo (28%; P < 0.0001). ACR50 responses were achieved by 33%, 34%, and 13% of patients, respectively (P < 0.001), and ACR70 responses were achieved by 13%, 20%, and 5% of patients (P < 0.05). Changes in the Disease Activity Score in 28 joints (-1.79, -2.05, -0.67; P < 0.0001) and moderate to good responses on the European League Against Rheumatism criteria (P < 0.0001) reflected the ACR criteria responses. Glucocorticoids did not contribute significantly to the primary efficacy end point, ACR20 response at 24 weeks. Intravenous glucocorticoid premedication reduced the frequency and intensity of first infusion-associated events; oral glucocorticoids conferred no additional safety benefit. Rituximab was well tolerated; the type and severity of infections was similar to those for placebo. Conclusion. Both rituximab doses were effective and well tolerated when added to MTX therapy in patients with active RA. The primary end point (ACR20 response) was independent of glucocorticoids, although intravenous glucocorticoid premedication improved tolerability during the first rituximab infusion. 2006, American College of Rheumatology.

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37. Relapsing oligoarticular septic arthritis during etanercept treatment of rheumatoid arthritis

Author(s): Mor A., Mitnick H.J., Greene J.B., Azar N., Budnath R., Fetto J.

Citation: Journal of Clinical Rheumatology, April 2006, vol./is. 12/2(87-89), 1076-1608
Abstract: Septic arthritis is a commonly reported complication of rheumatoid arthritis (RA). Tumor necrosis factor alpha (TNF-alpha) plays an important role in host defense against infection. Inhibition of its activity could therefore be anticipated to augment the risk of infection. Both opportunistic and bacterial infections have been described in patients with RA treated with anti-TNF-alpha therapy. We describe a patient who experienced 2 episodes of septic arthritis. Both occurred while the patient was on etanercept. Recurrence developed despite prolonged parenteral antibiotic. To our knowledge, this is the first report of relapsing oligoarticular methicillin-sensitive Staphylococcus aureus septic arthritis despite prolonged antibiotic treatment in a patient receiving etanercept therapy. Our case underscores the advisability of discontinuing TNF-alpha blockade in patients with septic arthritis during prolonged antimicrobial therapy. Copyright 2006 by Lippincott Williams & Wilkins.

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38. Infliximab-induced scleredema in a patient with rheumatoid arthritis

Author(s) Ranganathan P.

Citation: Journal of Clinical Rheumatology, December 2005, vol./is. 11/6(319-322), 1076-1608 (December 2005)

Publication Date: December 2005

Abstract: A 52-year-old patient with rheumatoid arthritis (RA) developed scleredema-like skin induration after treatment with the tumor necrosis factor alpha (TNFalpha) blocking agent, infliximab. Skin induration occurred within a few weeks of initiation of infliximab, resolved with discontinuation of the drug, and recurred with rechallenge with the drug, implicating infliximab as the offending agent. Laboratory evaluation revealed a high titer of human antichimeric antibodies (HACA). The skin induration improved within a few weeks of discontinuation of infliximab and did not recur with the use of etanercept. Scleredema has been reported in association with bacterial and viral infections, diabetes mellitus, and monoclonal gammopathies. Infliximab use should be added to the list of potential associations with scleredema. This effect appears possibly specific to infliximab and may be related to the development of HACA because it did not occur with the use of etanercept in this patient. In addition, there appears to be a complex relationship between TNFalpha and tumor growth factor beta (TGF-beta), a cytokine which promotes collagen synthesis and deposition. TNFalpha blockade with infliximab may affect TNFalpha-TGF-beta interactions and may be implicated in the development of scleredema in this case. Copyright 2005 by Lippincott Williams & Wilkins.

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Author(s) Bennett A.N., Wong M., Zain A., Panayi G., Kirkham B.W.

Citation: Rheumatology, September 2005, vol./is. 44/9(1199-1200), 1462-0324 (01 Sep 2005)

Publication Date: September 2005

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40. Adsorptive granulocyte/monocyte apheresis for the treatment of refractory rheumatoid arthritis: An open pilot multicentre trial

**Author(s)** Sanmarti R., Marsal S., Valverde J., Casado E., Lafuente R., Kashiwagi N., Rodriguez-Cros J.-R., Erra A., Reina D., Gratacos J.

**Citation**: Rheumatology, September 2005, vol./is. 44/9(1140-1144), 1462-0324 (01 Sep 2005)

**Publication Date**: September 2005

**Abstract**: Objective. To assess the efficacy and safety of adsorptive granulocyte and monocyte apheresis (GCAP) in patients with refractory rheumatoid arthritis (RA). Methods. Patients with active and refractory RA were treated with weekly GCAP sessions using a column filled with acetate beads (Adacolumn) over five consecutive weeks. Clinical assessments and response to therapy were analysed at weeks 5, 7, 12 and 20 in an open multicentre trial. The primary outcome measure of clinical response was 20% improvement in the American College of Rheumatology criteria (ACR20) at week 20. EULAR (European League Against Rheumatism) response criteria, based on the disease activity score for 28 joints (DAS28) and disability using the Health Assessment Questionnaire (HAQ), were also assessed. Results. Of 27 patients, 81.5% were women with mean disease duration of 14.4 yr. The mean number of previous disease-modifying antirheumatic drugs (DMARDs) was 3.7, and 48.1% of patients had previously failed on biologicals. On an intention-to-treat basis, 40.7% of patients achieved an ACR20 and 44.4% a therapeutic EULAR response at week 20. These percentages were 50 and 54.5% in 22 patients who completed the trial. In the 10 completers who had previously failed on biologicals, an ACR response was achieved in four patients (ACR20, two; ACR50, one; ACR70, one). A significant decrease was recorded in different ACR response components, including the tender joint and swollen joint counts, pain score and patient and physician global disease assessments, as well as the DAS28 index; most of them improved after week 5. ESR and CRP, but not the HAQ score, had decreased significantly at week 20. The treatment was well tolerated and only one serious adverse event related to the study procedure was documented (sepsis due to a catheter infection). Conclusions. GCAP treatment led to significant clinical improvement in a subset of patients with RA who had failed to respond to DMARDs or biologicals. Further large, placebo-controlled studies are warranted to fully assess the therapeutic value of GCAP for refractory RA. The Author 2005. Published by Oxford University Press on behalf of the British Society for Rheumatology. All rights reserved.

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41. Adalimumab in clinical practice. Outcome in 70 rheumatoid arthritis patients, including comparison of patients with and without previous anti-TNF exposure

**Author(s)** Bennett A.N., Peterson P., Zain A., Grumley J., Panayi G., Kirkham B.

**Citation**: Rheumatology, August 2005, vol./is. 44/8(1026-1031), 1462-0324;1462-0332 (August 2005)

**Publication Date**: August 2005

**Abstract**: Objective. To assess the efficacy and safety of the fully human recombinant monoclonal anti-TNF antibody adalimumab in routine clinical practice, including comparison of patients with and without previous anti-TNF exposure. Methods. We prospectively studied the outcome of 70 rheumatoid arthritis patients treated with adalimumab in normal
clinical practice. The primary outcome measures were Disease Activity Score 28 (DAS28), EULAR (European League Against Rheumatism) response and Health Assessment Questionnaire (HAQ). Results. Seventy-seven percent achieved a EULAR response (26% good, 51% moderate) and 19% were in remission. The mean decrease in DAS28 was 2.1 (6.3-4.2; $P<0.001$). The mean decrease in HAQ score was 0.34 (2.07-1.73; $P<0.001$), 66% achieving a clinically significant decrease of greater than 0.22. Twenty-three per cent stopped treatment because of side-effects (7%) or failure to respond (16%). Of the 26 patients who had previously tried 29 biologicals, 65% responded to adalimumab. There was no significant difference in the change in mean DAS ($P = 0.69$) or HAQ ($P = 0.88$) between groups with and without previous anti-TNF exposure. Of the 13 patients with previous secondary failure to infliximab, 77% responded to adalimumab. Patients with previous secondary failure had significantly better improvement in DAS ($P = 0.023$) than patients with previous primary failure. Conclusion. Our clinical experience confirms that adalimumab is effective and safe in the treatment of RA. It also shows adalimumab is effective in patients with previous biological failures, particularly patients with secondary failure to infliximab. The Author [2005]. Published by Oxford University Press on behalf of the British Society for Rheumatology. All rights reserved.

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42. Update on the British Society for Rheumatology guidelines for prescribing TNFalpha blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001)

Author(s) Ledingham J., Deighton C.

Citation: Rheumatology, February 2005, vol./is. 44/2(157-163), 1462-0324 (February 2005)

Publication Date: February 2005

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43. A Norwegian DMARD register: Prescriptions of DMARDs and biological agents to patients with inflammatory rheumatic diseases

Author(s) Kvien T.K., Heiberg M.S., Lie E., Kaufmann C., Mikkelsen K., Nordvag B.-Y., Rodevand E.

Citation: Clinical and Experimental Rheumatology, 2005, vol./is. 23/5 SUPPL. 39(S188-S194), 0392-856X (2005)

Publication Date: 2005

Abstract: Information concerning the effectiveness of drug therapy cannot be obtained only from randomized controlled clinical trials, due to limitations such as a short time frame and narrow inclusion and exclusion criteria. Therefore, complementary longitudinal observational studies performed in a real life setting are required. NOR-DMARD, a Norwegian 5-center register, was established in December 2000. All DMARD prescriptions to patients with inflammatory arthropathies are included, and patients are followed.
longitudinally with a variety of assessments. As of 2005, 4683 DMARD regimens have been included. Methotrexate is the most commonly used DMARD in rheumatoid arthritis and psoriatic arthritis. The proportions of patients who have received anti-TNF drugs in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile arthritis and other diseases have been 22.5, 21.6, 53.8, 36.9 and 9.7%, respectively. The proportion of patients receiving anti-TNF drugs is considerably higher in 2004 than earlier, and criteria for prescribing anti-TNF drugs appear to be trending toward patients with less severe and active disease. Confounding by indication or channeling bias represents a challenge for the group comparisons of longitudinal effectiveness data, but can be addressed by modern statistical techniques. The NOR-DMARD register may in the future provide comparative real life effectiveness data that may also be used in cost-effectiveness analyses. Copyright Clinical and Experimental Rheumatology 2005.

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44. Delayed multiple injection site reaction in a rheumatoid arthritis patient treated with etanercept [2]

Author(s) Rajakulendran S., Deighton C.

Citation: Rheumatology, December 2004, vol./is. 43/12(1588-1589), 1462-0324 (December 2004)

Publication Date: December 2004

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45. Antineutrophil cytoplasmic antibody-associated necrotizing crescentic glomerulonephritis in a patient receiving treatment with etanercept for severe rheumatoid arthritis

Author(s) Doulton T.W.R., Tucker B., Reardon J., Velasco N.

Citation: Clinical Nephrology, September 2004, vol./is. 62/3(234-238), 0301-0430 (September 2004)

Publication Date: September 2004

Abstract: Etanercept is a tumor necrosis factor inhibitor used in the treatment of rheumatoid arthritis and, increasingly, in a range of other diseases. We report a case of necrotizing crescentic glomerulonephritis, associated with a positive antineutrophil cytoplasmic antibody, causing acute renal failure in a woman receiving treatment with etanercept for severe rheumatoid arthritis. Our patient was treated with steroids and cyclophosphamide following withdrawal of etanercept, with a good clinical response. Although reports of vasculitis in patients receiving treatment with etanercept are rare, this drug has been shown to up-regulate some aspects of immune function, and the possibility that this agent may precipitate or exacerbate vasculitis in some individuals has to be considered. 2004 Dustri-Verlag Dr. K. Feistle.

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46. Etanercept (Enbrel) in patients with rheumatoid arthritis with recent onset versus
established disease: Improvement in disability

Author(s) Baumgartner S.W., Fleischmann R.M., Moreland L.W., Schiff M.H., Markenson J., Whitmore J.B.

Citation: Journal of Rheumatology, August 2004, vol./is. 31/8(1532-1537), 0315-162X (August 2004)

Publication Date: August 2004

Abstract: Objective. To compare etanercept-induced improvement in disability of patients with recent onset of rheumatoid arthritis (RA) to that of patients with established RA. Methods. Health Assessment Questionnaire (HAQ) scores were collected over 3 years in 2 groups of patients with RA who were treated with etanercept. The first group consisted of 207 patients with recent onset RA (mean duration of 1 year) who had not previously received methotrexate, and the second group consisted of 464 patients with established RA (mean duration of 12 years) who had failed one or more disease-modifying antirheumatic drugs. Results. Baseline demographics and disease characteristics were similar in the 2 groups, except for HAQ scores and C-reactive protein levels, which were higher in the established RA group. Patients in both groups showed rapid and sustained clinical responses with etanercept therapy, but patients with recent onset RA showed significantly greater improvement in HAQ scores compared with patients with established RA. The difference in magnitude of HAQ score improvement between groups was observed as early as week 2 after initiation of etanercept and persisted throughout the 3-year time frame. At year 3, significantly more patients with recent onset RA had a HAQ score of zero (26%) versus those with established RA (14%, p = 0.0095). Conclusion. Although etanercept therapy significantly improved disability scores in both groups, patients with recent onset of RA showed greater benefit in HAQ scores than patients with established RA. These results support prompt treatment of RA at an early stage of disease to minimize patient disability.

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47. The efficacy of switching from etanercept to infliximab in patients with rheumatoid arthritis

Author(s) Hansen K.E., Hildebrand J.P., Genovese M.C., Cush J.J., Patel S., Cooley D.A., Cohen S.B., Gangnon R.E., Schiff M.H.

Citation: Journal of Rheumatology, June 2004, vol./is. 31/6(1098-1102), 0315-162X (June 2004)

Publication Date: June 2004

Abstract: Objective. To describe the degree of clinical benefit in patients with rheumatoid arthritis (RA) who receive infliximab therapy after lack of efficacy with etanercept. Methods. In a retrospective study among 6 centers primarily designed to assess the safety of infliximab in combination with leflunomide, a standardized chart review form was used to collect data on 93 patients with RA. During that study, it was noted that some of these patients had switched from etanercept to infliximab. In this study, we compared the response of subjects switching from etanercept to infliximab (n = 20) to that of subjects receiving infliximab with no prior tumor necrosis factor (TNF) therapy (n = 73). Results. The swollen and tender joint count, patient and physician global assessments, morning stiffness, and C-reactive protein all improved substantially in both groups, with no statistical difference in the degree of benefit between the groups. At the time of chart review, switchers had received a statistically higher dose of infliximab than controls (4.4 vs 3.19 mg/kg; p = 0.006) with a total of 5.7 and 5 infusions, respectively. Conclusion. In this retrospective study, previous lack of efficacy with etanercept did not predict lack of efficacy with infliximab. Indeed, the degree of clinical improvement was similar in both groups, although switchers were receiving a higher dose of infliximab at the time of chart review. Our findings suggest that clinical response may differ between anti-TNF agents, and lack of response to one agent may not predict a lack of response to another.

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48. Safety of leflunomide plus infliximab combination therapy in rheumatoid arthritis

**Author(s)** Godinho F., Godfrin B., El Mahou S., Navaux F., Zabraniecki L., Cantagrel A.

**Citation:** Clinical and Experimental Rheumatology, May 2004, vol./is. 22/3(328-330), 0392-856X (May/June 2004)

**Publication Date:** May 2004

**Abstract:** Objective. To analyse the safety of leflunomide plus infliximab combination therapy, in adult rheumatoid arthritis (RA) patients. Patients. A retrospective study of 17 adult patients with active RA (DAS 28 = 5.94 +/- 0.88 at baseline) who were treated with a combination of leflunomide plus infliximab after failure of treatment with other DMARDs. 13 patients were treated for a minimum of 3 months with leflunomide without toxicity before beginning infliximab. Treatment was begun simultaneously with both drugs in 4 patients. Side effects (clinical and biological) and efficacy (DAS 28) were evaluated at each infliximab infusion (3 mg/kg at week 0, 2, 6 and then every 8 weeks). Results. Thirteen patients experienced 20 types of side effects and 8 of them stopped the combination therapy. The causes of discontinuation were congestive heart failure (1 case), hypertension with thoracic pain (2 cases), eczematous skin patches (2 cases) and neutropenia (3 cases). No death was registered. Nine RA patients continued the therapy with a median follow-up of 22 weeks. Only 4 of them experienced no side effects. Eight patients were positive for antinuclear antibodies (ANA) and 1 for double-stranded DNA (dsDNA) antibodies at study entry. After treatment, 13 and 5 patients tested positive respectively for ANAs and dsDNA antibodies. There was no relationship between discontinuation and ANA/dsDNA positivity. Conclusion. In this cohort, adverse events were not very different from those seen in patients on either treatment alone and the combination of leflunomide plus infliximab did not appear to be as badly tolerated as described in a previous study. Copyright Clinical and Experimental Rheumatology 2004.

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49. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed


**Citation:** Annals of the Rheumatic Diseases, May 2004, vol./is. 63/5(508-516), 0003-4967 (May 2004)

**Publication Date:** May 2004

**Abstract:** Objective: To evaluate the efficacy and safety of monotherapy with adalimumab in patients with RA for whom previous DMARD treatment has failed. Methods: In a 26 week, double blind, placebo controlled, phase III trial, 544 patients with RA were randomised to monotherapy with adalimumab 20 mg every other week, 20 mg weekly, 40 mg every other week, 40 mg weekly, or placebo. The primary efficacy end point was >=20% improvement in the ACR core criteria (ACR20 response). Secondary efficacy end points included ACR50, ACR70, EULAR responses, and the Disability Index of the Health Assessment Questionnaire (HAQ DI). Results: After 26 weeks, patients treated with adalimumab 20 mg every other week, 20 mg weekly, 40 mg every other week, and 40 mg weekly had significantly better response rates than those treated with placebo: ACR20 (35.8%, 39.3%, 46.0%, 53.4%, respectively v 19.1%; p<0.01); ACR50 (18.9%, 20.5%, 22.1%, 35.0% v 8.2%; p<0.05); ACR70 (8.5%, 9.8%, 12.4%, 18.4% v 1.8%; p<0.05). Moderate EULAR response rates were significantly greater with adalimumab than with placebo (41.5%, 48.2%, 55.8%, 63.1% v 26.4%; p<0.05). Patients treated with adalimumab achieved better improvements in mean HAQ DI than those receiving placebo (-0.29, -0.39, -0.38, -0.49 v -0.07; p<0.01). No significant differences were found between
adalimumab and placebo treated patients for serious adverse events, serious infections, or malignancies. Injection site reaction occurred in 10.6% and 0.9% of adalimumab and placebo treated patients, respectively (p<=0.05). Conclusion: Among patients with RA for whom previous DMARD treatment had failed, adalimumab monotherapy achieved significant, rapid, and sustained improvements in disease activity and improved physical function and was safe and well tolerated.

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50. The impact of escalating conventional therapy in rheumatoid arthritis patients referred for anti-tumour necrosis factor-alpha therapy

**Author(s)** Bingham S.J., Buch M.H., Tennant A., Emery P.

**Citation:** Rheumatology, March 2004, vol./is. 43/3(364-368), 1462-0324 (March 2004)

**Publication Date:** March 2004

**Abstract:** Objective. To assess the impact of escalating conventional therapy in patients with RA who satisfy BSR/NICE criteria for biologics. Methods. A total of 308 consecutive patients referred to a tertiary centre for biological therapy between January 1999 and February 2001 were studied prospectively. They were considered by their own consultant to have failed standard therapy. Prior to biologics, conventional therapy was escalated to include combination and parenteral methotrexate treatment. Patients were assessed at 12-weekly intervals for 1 yr and therapy was changed if response was not satisfactory. The subsequently released BSR/NICE biologic eligibility criteria were applied retrospectively. Response (disease activity, disability and quality of life) to escalated therapy in those patients who did or did not satisfy current eligibility criteria were compared. Results. In total, 159 satisfied BSR/NICE criteria and would have been eligible for immediate treatment with biologics [DAS28 > 5.1, failed methotrexate (20 mg/week or lower dose owing to toxicity) and one other DMARD]; however, 93 of these responded to escalated conventional therapy and did not require biologics [significant improvement (P < 0.01) in disease activity, disability and quality of life]. However, mild disease activity (DAS28 < 3.2) was only achieved in 7% of these patients at 12 months. Conclusions. Although over half the patients who satisfied standard criteria for biologics responded satisfactorily to escalated therapy, only a minority achieved mild disease activity. The savings achieved by treating with conventional therapies need to be weighed against the risk of persistent disease activity. British Society for Rheumatology 2003; all rights reserved.

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51. Etanercept in rheumatoid arthritis patients with a poor therapeutic response to infliximab [Spanish] Etanercept en pacientes con artritis reumatoide y escasa respuesta terapeutica a infliximab

**Author(s)** Sanmarti R., Gomez-Puerta J.A., Rodriguez-Cros J.R., Albaladejo C., Munoz-Gomez J., Canete J.D.

**Citation:** Medicina clinica, March 2004, vol./is. 122/9(321-324), 0025-7753 (13 Mar 2004)
BACKGROUND AND OBJECTIVE: Knowing the efficacy of tumor necrosis factor alpha (TNF-alpha) antagonists infliximab or etanercept in patients with rheumatoid arthritis (RA), when one of these agents has failed, has important clinical implications. The aim of this study was to evaluate the efficacy and safety of etanercept in patients with RA, who had previously failed to infliximab.

PATIENTS AND METHOD: All patients with RA of our center, who were previously treated with infliximab and then switched to etanercept for at least 6 months were included. Several clinical and biological parameters of inflammatory activity along with the disease activity index DAS-28 were assessed at baseline, after 6 weeks, at the last infusion of infliximab and after 0, 3 and 6 months on etanercept. EULAR criteria of response to therapy were used.

RESULTS: Fourteen RA patients (13 females) who fulfilled the inclusion criteria were selected. These patients had been treated with infliximab for a mean (SD) of 14.6 (8.3) months when this drug was stopped. Drug withdrawal owed to inefficacy in 12 patients and to adverse events in 2 patients. Most patients achieved a satisfactory clinical response within the first months of infliximab, with a subsequent loss of the therapeutic effects in spite of an increase in the infliximab dose or a reduction of the interval between infusions. In the group of 12 patients switched to etanercept because of infliximab inefficacy, a therapeutic response was achieved in 10 (83%) of them after 6 months of etanercept therapy. The DAS-28 score (SD) improved from 5.6 (1) to 4.3 (0.8) (p = 0.019). An even better therapeutic response to etanercept was observed in those patients with an initial poor response to infliximab. No serious adverse effects were recorded during etanercept treatment.

CONCLUSIONS: Etanercept is an efficient and safe therapy in RA patients when infliximab treatment has failed.

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52. Modelling the cost-effectiveness of etanercept in adults with rheumatoid arthritis in the UK

Author(s) Brennan A., Bansback N., Reynolds A., Conway P.

Citation: Rheumatology, January 2004, vol./is. 43/1(62-72), 1462-0324 (January 2004)

Publication Date: January 2004

Abstract: Objectives. This model examines the cost-effectiveness of etanercept monotherapy under British Society for Rheumatology guidelines, i.e. adults previously failing two disease-modifying anti-rheumatic drugs (DMARDs). It compares a DMARD sequence with etanercept third line against the same sequence excluding etanercept. Method. The 6-monthly trend in Health Assessment Questionnaire (HAQ) disability score is simulated for 10 000 patients' lifetimes using clinical trial data and published literature. Switching to the next treatment is triggered by lack of response, loss of efficacy or adverse events. Patient mortality depends on rheumatoid arthritis life-tables and on epidemiological evidence relating reduced risk to HAQ improvement. Regression of HAQ/EuroQol (EQ-5D) utility provides quality-adjusted life years (QALY) gained. Primary analysis includes drug costs, monitoring and hospitalizations. Results. The central estimate cost per QALY is 16 330. Sensitivity analyses (7 800 to 42 000) showed long-term HAQ progression (etanercept, DMARDs, non-responders) as most sensitive variables. The inclusion of potential avoided nursing home admissions and indirect costs/lost employment further improves the cost-effectiveness. Conclusions. For adults in the UK, the results suggest that etanercept is cost-effective when compared with non-biologic agents. The National Institute for Clinical Excellence has accepted that etanercept is cost-effective and recommended its availability for use in patients who have failed at least two DMARDs. This model was an important component of that decision. The model is further suitable for use for a wide range of other cost-effectiveness questions in rheumatoid arthritis.

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53. Efficacy of anti-tumour necrosis factor alpha therapy with etanercept in chronic polyarthritis [Norwegian] Behandling med etanercept ved kronisk polyartritt

Author(s) Bakland G., Nordvag B.Y., Nossent H.C.

Citation: Tidsskrift for den Norske Laegeforening, September 2003, vol./is. 123/18(2561-2564), 0029-2001 (25 Sep 2003)

Publication Date: September 2003

Abstract: Background. In randomised trials, treatment with anti-tumour necrosis factor alpha drugs has been shown to be efficacious for patients with rheumatoid arthritis. We analysed the effectiveness and toxicity of etanercept treatment in our day-to-day rheumatology practice at the University Hospital of Northern Norway. Material and methods. Patients with active polyarthritis who had failed at least three different disease-modifying anti-rheumatic drugs including methotrexate and/or combination therapy were consecutively included in an open study when they started etanercept therapy (25 mg twice per week subcutaneously). During follow up we noted the number of swollen and tender joints, took visual analogue scores (0 - 100 millimetre) for pain and global well-being, administered the Modified Health Assessment Questionnaire, performed laboratory tests, and took note of side effects. Results. Between April 1999 and July 2001, etanercept treatment was initiated in 71 patients. An ACR-20 response (20% improvement according to American College of Radiology criteria) occurred in 57% of patients after one month of treatment and in 70% after three months, ACR-50 response in 24% and 42%, and ACR-70 response in 6% and 20%. While half of all patients reported side effects, only five patients (7%) discontinued treatment because of them. Interpretation. Etanercept is effective therapy for many patients with severe chronic polyarthritis in clinical practice. Short-term side effects occur more frequently than reported and seem less frequent with concomitant methotrexate therapy. Long-term side effects are still unknown and require close monitoring.

Source: EMBASE

54. Toward a definition and method of assessment of treatment failure and treatment effectiveness: The case of leflunomide versus methotrexate

Author(s) Wolfe F., Michaud K., Stephenson B., Doyle J.

Citation: Journal of Rheumatology, August 2003, vol./is. 30/8(1725-1732), 0315-162X (01 Aug 2003)

Publication Date: August 2003

Abstract: Objective. Time to treatment discontinuation (TTD) is an accepted method of assessing treatment effectiveness in the community, but is susceptible to channeling bias and secular and cohort effects. In addition, TTD does not consider the addition of new disease modifying antirheumatic drugs (DMARD) to insufficiently effective therapies. We expand the definition of treatment failure to include discontinuation or addition of a second DMARD (1) to examine leflunomide (LEF) versus methotrexate (MTX) effectiveness in clinical practice; (2) to obtain an estimate of overall clinical effectiveness; and (3) to identify factors associated with treatment successes and failure. In addition, (4) we test the feasibility of performing a clinical trial using a longitudinal data bank. Methods. Using the National Data Bank for Rheumatic Diseases longitudinal data bank, 1431 patients with rheumatoid arthritis (RA) who began taking LEF or MTX as part of their routine medical care were followed from 1998 through 2001. None of the 1431 patients had received either treatment previously. Patients were assessed at 6 month intervals for periods up to 36 months by mailed questionnaires concerning DMARD therapy and demographic and RA severity factors. Kaplan-Meier survivor functions and Cox regression analyses were used to
assess treatment failure, defined as time to discontinuation or to the addition of a second DMARD. Results. For 756 patients taking LEF, the failure rate was 55.5 per 100 patient-years, and the median time to failure was 15 (95% CI 13, 17) months. For 675 patients taking MTX the failure rate was 57.3 per 100 patient-years, and the median failure time was 14 (95% CI 12, 18) months. These differences were not statistically significant. The overall rate of discontinuation was 68.7% of the failure rate. Discontinuation was predicted by adverse effects [hazard ratio 1.76 (95% CI 1.51, 2.04)] and by clinical status prior to starting DMARD, and these results were not affected by specific DMARD treatment. Discontinuation was more common with LEF, and addition of a second DMARD was more common with MTX. More than 77% of treatment failures, defined by use of additional therapy, resulted in starting anti-tumor necrosis factor treatment rather than a conventional DMARD. Conclusion. In an observational clinical trial using a contemporary longitudinal data bank, with time to treatment failure as the outcome, LEF and MTX had equal effectiveness as measured by time to treatment failure. Treatment failure rates were substantially greater than noted historically. Given the availability of many efficacious additional treatment options, this increase in failure rate appears to reflect a greater propensity to discontinue and/or add therapy.

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combination plus infliximab (Combi), and six received infliximab plus MTX alone (Mono). The follow-up was carried out for 30 weeks in all patients and for 46 weeks in eight. Efficacy and safety were examined. Results. At entry, the mean disease activity score (DAS) was 5.6 (all patients had a DAS > 3.7). After therapy, eight of 10 patients in Combi and four out of six in Mono showed an improvement of > 50% in the initial swollen joint count, yet only one patient reached 50% improvement in the initial DAS after 30 weeks, and one patient had a DAS <2.4 (low disease activity). Of the eight patients who reached 46 weeks of follow-up, three showed an improvement in DAS of 50% and two had a DAS < 2.4. When considering the change over time, the difference between DAS at entry and at week 30 was statistically significant only in patients receiving MTX plus CsA, while it was not significant in those receiving MTX only. Two patients developed recurrent febrile upper respiratory infections in the Combi therapy group, while two had a single febrile infection in the MTX alone group. Two patients became strongly anti-cardiolipin positive (IgM >40 MPL) and one developed a coronary syndrome. Conclusion. Infliximab can be added incrementally to MTX plus CsA, with favourable results in terms of efficacy and safety over time in severe rapidly aggressive and progressive RA. Finally, minor evidence emerged for a stronger efficacy of the Combi treatment compared with Mono.

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57. Etanercept and infliximab for rheumatoid arthritis

Author(s)

Citation: Drug and Therapeutics Bulletin, 2001, vol./is. 39/7(49-51), 0012-6543 (2001)
Publication Date: 2001

Abstract: Etanercept (Enbrel - Wyeth) and infliximab (Remicade - Schering Plough) belong to a new class of drugs that block the effects of tumour necrosis factor-alpha (TNF-alpha), a mediator of inflammation. Both are licensed for the treatment of patients with active rheumatoid arthritis who have responded inadequately to disease-modifying antirheumatic drugs (DMARDs). Here, we consider whether etanercept and infliximab offer advantages.

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58. A double blind, placebo controlled study of a platelet activating factor antagonist in patients with rheumatoid arthritis

Author(s) Hilliquin P., Chermat-Izard V., Menkes C.-J.

Citation: Journal of Rheumatology, August 1998, vol./is. 25/8(1502-1507), 0315-162X (August 1998)
Publication Date: August 1998

Abstract: Objective. To evaluate the efficacy and tolerance of a platelet activating factor-acether (PAF) antagonist, BN 50730, in patients with rheumatoid arthritis (RA). Methods. A total of 56 patients with active RA were enrolled in a multicenter, double blind, placebo controlled Study of BN 50730. Patients received either BN 50730 (40 mg orally bid) or placebo for 84 days. Results. Treatment with BN 50730 resulted in no improvement and was no more effective than placebo in improving clinical and biological indices of RA activity. Adverse events were observed in the 2 treatment groups, and BN 50730 was generally well tolerated. Conclusion. PAF antagonist BN 50730 at a daily dose of 80 mg was ineffective in the treatment of RA.
59. New approaches to biological immunomodulation therapy of rheumatoid arthritis: neutralization of basic cytokines [Russian] Novye podkhody k biologicheskoj immunomoduliruuschchej terapii revmatoidnogo artrita: neitralizatsiia osnovnykh tsitokinov

Author(s) Lukina G.V., Sigidin I.A., Skurkovich S.V., Skurkovich B.S.

Citation: Terapevticheskii arkhiv, 1998, vol./is. 70/5(32-37), 0040-3660 (1998)

Publication Date: 1998

Abstract: AIM: Investigation of efficacy of antibodies ot interferons in rheumatoid arthritis (RA) versus relevant efficacy of the tumor necrosis factor (TNF), comparison of the above cytokines in monotherapy and combined treatment. MATERIALS AND METHODS: An open controlled randomized trial of clinical benefit and tolerance of anticytokine antibodies was performed in a group of RA patients at stage II, III and IV (1, 20 and 4 patients, respectively). The activity degree II and III was in 10 and 15 patients, respectively. All the patients had articular functional insufficiency of the second degree. 21 patients failed previous therapy with basic drugs including immunodepressants. RESULTS: The anticytokine antibodies proved to be highly effective in RA. Positive changes in the disease activity were achieved early after the end of the 5-day course in 88% of patients. The most definite immediate therapeutic effect was noted in usage of TNF antibodies both in monotherapy and in combination with other anticytokines. Long-term effect was the best in patients given antibodies to interferon gamma. Interferon-alpha antibodies produced weaker effect. The combined treatment had no advantages over the monotherapy. CONCLUSION: A significant therapeutic effect of antibodies to interferon-gamma is indicative of an important role of this cytokine in RA pathogenesis. Anticytokine antibodies are promising as a component of combined therapy of patients with resistant RA.

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Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease
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