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**Literature search results**

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**Search details**

Primary and secondary biologics failure as treatment for rheumatoid arthritis

**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 antibod*; "tumour necrosis factor" adj2 antibod*; “recombinant DNA”; monoclonal antibodies; exp MONOCLONAL ANTIBODY; infliximab; exp INFILIXIMAB; etanercept; exp ETANERCEPT; adalimumab; exp ADALIMUB; 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*; metaanaly*; META ANALYSIS; random* adj0 control* adj0 (trial OR study*); RANDOMIZED CONTROLLED TRIAL; RANDOMIZED CONTROLLED TRIALS; RANDOMISED CONTROLLED TRIAL; clinical adj0 (trial* OR study*); exp CLINICAL TRIAL; case (stud* OR report* OR series); CASE REPORT; CASE SERIES; CASE STUDIES; CASE STUDY; primary adj2 failure*; secondary adj2 failure*; primary adj2 responder*; secondary adj2 responder*; non-responder*; nonresponder*

**Evidence search string(s)**: (arthritis (rheumatoid OR deformans OR atrophic) OR polyarthritis 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"*) ("primary failure"* OR "secondary failure"* OR "primary responder"* OR ~nonresponder* OR non-responder*)
**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) (~“primary failure” OR ~“secondary failure” OR ~“primary responder” OR ~nonresponder)

**Summary**

Please find the results of the failure of biologic treatment for rheumatoid arthritis search modified by the inclusion of the terms primary failure and secondary failure. I have included research where patients have not responded to the primary treatment as well as those not responsive to multiple treatments.

**Guidelines**

NICE  
*Rheumatoid Arthritis* 2008

Scottish Medicines Consortium  
Tocilizumab (RoActemra) - for the treatment of moderate to severe active rheumatoid arthritis (RA) 2012

**Evidence-based reviews**

Biomed Central  
Evaluating the efficacy of sequential biologic therapies for rheumatoid arthritis patients with an inadequate response to tumor necrosis factor-alpha inhibitors 2011

ACR70-disease activity score remission achievement from switches between all the available biological agents in rheumatoid arthritis: a systematic review of the literature 2009

Evidence Updates  
Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate 2010

**Journal of Rheumatology**

Associations between tumor necrosis factor-alpha (TNF-alpha) -308 and -238 G/A polymorphisms and shared epitope status and responsiveness to TNF-alpha blockers in rheumatoid arthritis: a metaanalysis update 2010

**Published research**

1. Differential drug retention between anti-TNF agents and alternative biological agents after inadequate response to an anti-TNF agent in rheumatoid arthritis patients.  
**Author(s)** Du Pan SM, Scherer A, Gabay C, Finckh A  
**Citation**: Annals of the Rheumatic Diseases, June 2012, vol./is. 71/6(997-9), 0003-4967:1468-2060 (2012 Jun)  
**Publication Date**: June 2012  
**Abstract**: BACKGROUND: After inadequate response to an antitumour necrosis factor (aTNF) agent for treatment of rheumatoid arthritis (RA), rheumatologists can choose an
alternative aTNF or a biological agent with another mode of action (non-aTNF biological (non-aTNF-Bio)). OBJECTIVE: To compare drug retention rates of non-aTNF-Bio with alternative aTNF. METHODS: All patients within the Swiss RA cohort (SCQM-RA) treated with an alternative biotherapy after a prior inadequate response to aTNF were analysed. The drug retention of alternative aTNF was compared with non-aTNF-Bio using Cox proportional hazards models, adjusted for potential confounders. RESULTS: 1485 treatment courses after aTNF failure were available for analysis, 853 with alternative aTNF and 632 with non-aTNF-Bio. The median drug retention was 32 months (IQR 14-54) on non-aTNF-Bio versus 21 months (IQR 8-53) on alternative aTNF, or a 50% reduction drug discontinuation risk in favour of non-aTNF-Bio (adjusted hazard ratio (HR) for non-aTNF-Bio: 0.50 (95% CI 0.41 to 0.62)). This effect appears to be modified by the type of prior aTNF failure, with a larger difference in favour of non-aTNF-Bio in patients having experienced a primary failure with a previous aTNF (HR: 0.33 (95% CI 0.24 to 0.47), p<0.001). CONCLUSION: After inadequate response to aTNF, and particularly after primary failure, patients on a non-aTNF-Bio agent have significantly higher drug retention rates.

Source: Medline
Available in fulltext from EULAR Meeting Abstracts at Highwire Press
Available in fulltext from Annals of the Rheumatic Diseases at Highwire Press
Available in print at

2. Sustained elevation of interleukin-33 in sera and synovial fluids from patients with rheumatoid arthritis non-responsive to anti-tumor necrosis factor: possible association with persistent IL-1beta signaling and a poor clinical response.


Citation: Rheumatology International, May 2012, vol./is. 32/5(1397-401), 0172-8172;1437-160X (2012 May)
Publication Date: May 2012

Abstract: Although TNF inhibitors have dramatically improved the outcome of patients with rheumatoid arthritis, 30-40% of patients do not respond well to them and treatment needs to be changed. In an effort to discriminate good and poor responders, we focused on the change in serum and synovial fluid levels of interleukin (IL-) 33 before and after treatment with TNF inhibitors. They were also measured in synovial fluids from 17 TNF inhibitor-naive patients, and fibroblast-like synoviocytes (FLS) in culture from 6 patients and correlated with various pro-inflammatory cytokines. Serum levels of IL-33 at 6 months after treatment decreased significantly in responders, while they did not change in non-responders. Synovial fluid levels of IL-33 in 6 patients under treatment with TNF inhibitors stayed high in 3 who were refractory and slightly elevated in 2 moderate responders, while they were undetectable in one patient under remission. Among inflammatory cytokines measured in 17 synovial fluids from TNF inhibitor-naive patients, levels of IL-33 showed a significant positive correlation only to those of IL-1beta. IL-1beta increased IL-33 expression markedly in FLS in vitro, compared to TNF-alpha. IL-1beta might be inducing RA inflammation through producing pro-inflammatory IL-33 in TNF inhibitor-hypo-responders. Sustained elevation of serum and/or synovial levels of IL-33 may account for a poor response to TNF inhibitors, although how TNF inhibitors affect the level of IL-33 remains to be elucidated.

Source: Medline
Available in print at


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-
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-TNFalpha agents 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-TNFalpha 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.

Source: Medline
Available in fulltext from EULAR Meeting Abstracts at Highwire Press
Available in fulltext from Annals of the Rheumatic Diseases at Highwire Press
Available in print at

4. 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.

Source: Medline
5. 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.

**Source:** Medline

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**Author(s)** Mori S, Ueki Y

**Citation:** Modern Rheumatology, December 2011, vol./is. 21/6(628-36), 1439-7595;1439-7609 (2011 Dec)

**Publication Date:** December 2011

**Abstract:** To characterize primary failure to infliximab and determine the efficacy of switching to tocilizumab in patients with rheumatoid arthritis (RA), we examined 24 RA patients who had started on infliximab therapy (3 mg/kg) as their first biological agent. Nine of the 24 patients were found to be primary nonresponders, defined as patients who had never achieved a 20% clinical improvement according to the American College of Rheumatology criteria (ACR20) during induction therapy. The remaining 15 patients had achieved an ACR20 response to infliximab, without any relapses, for at least the first 14 weeks. A higher baseline health assessment questionnaire score was markedly associated with primary unresponsiveness to infliximab (p = 0.0005). Six of the 9 primary nonresponders showed rapid clearance of infliximab: their trough concentrations of infliximab were under 1 mug/ml. The other 3 were classified as exhibiting the residual type of unresponsiveness, which was defined as unresponsiveness in patients who maintained serum infliximab levels above 1 mug/ml. Human antichimeric antibody was not detected in the rapid-clearance nonresponders. Dose escalation (5 mg/kg) was insufficiently effective. Primary nonresponders to infliximab were started on tocilizumab therapy (8 mg/kg, every 4 weeks), and their responses were assessed after 24 weeks of this second attempt at
therapy. All the nonresponders, except for a single rapid-clearance patient, had achieved an ACR20 clinical improvement at the time of assessment. In conclusion, primary nonresponders to infliximab can be classified into rapid-clearance and residual types, based on their trough concentrations of infliximab, but both types of nonresponders seem to benefit from an early decision to discontinue infliximab therapy and switch to tocilizumab.

Source: Medline
Available in print at

7. 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

8. Primary anti-TNF failures experience better clinical responses but similar health care utilization to a second anti-TNF agent than secondary failures: Analysis of the alberta rheumatoid arthritis biologics registry

Author(s) Maksymowych W., Russell A., Ohinmaa A., Charles Y., Jacobs P., Martin L., Barr S., Penney C., Sholter D.

Citation: Journal of Rheumatology, June 2011, vol./is. 38/6(1162-1163), 0315-162X (June 2011)
Publication Date: June 2011
Abstract: Objective: Meta-analysis of anti-TNF switching data from observational cohorts has concluded that responses are inferior in those switching due to primary as compared to secondary anti-TNF failures but limitations include small sample size of individual studies, failure to define response, and selection bias. We assessed the impact of switching anti-TNF agents at different time points in the Alberta Biologics Registry, an observational cohort of RA patients starting anti-TNF therapy in 2004, where collection of outcome data on all patients is requested by the Provincial pharmaceutical formulary. Methods: The Alberta Biologics Registry collects clinical, employment, and health economic data at baseline, 3 months, and every 6 months thereafter. Health-related quality of life is measured with the EQ-5D and self reported health care utilization is measured for the six months prior to each visit. We analyzed responses according to time of switch (3 month versus subsequent time points) and according to specific anti-TNF agent switches. Results:
From 1,222 patients in the registry, 649 patients had 27 month follow up assessment and 498 (76.7%) of these remained on the first anti-TNF during the study period. There were 28 (4.3%) primary failures and 123 (19%) secondary failures who switched a median of 15 months from baseline. The response rate to the second anti-TNF was somewhat better in the primary versus the secondary failures (p=NS) at 3 months after initiation of the second anti-TNF for HAQ, DAS, EQ-5D. By 27 months, switchers due to primary failures had attained comparable reductions in outcomes to non-switchers while changes in secondary failures were from 50% (HAQ) to 68% (EQ-5D) lower compared to non-switchers (p< 0.05). Health care utilization was significantly reduced in four measured parameters over 27 months: number of rheumatologist visits (-0.31 visits, p< 0.001), family physician visits (-0.95, p< 0.001), % having >= 1 outpatient visit (-0.22, p< 0.001), and % having day surgery (-0.026, p< 0.001). This reduction was comparable between switching groups and non-switchers. Conclusion: The results from this mandatory registry show that primary failures to anti-TNF show similar responses to patients responding to their first anti-TNF agent. Clinical responses in secondary failures are less optimal. Despite this, there is no significant difference between primary and secondary failures in the significant reduction in the health care utilization while receiving their second anti-TNF agent over the course of the 27 month follow up period.

Source: EMBASE
Available in print at

9. Switching rheumatoid arthritis treatments: An update

Author(s) Atzeni F., Sarzi-Puttini P., Gorla R., Marchesoni A., Caporali R.
Citation: Autoimmunity Reviews, May 2011, vol./is. 10/7(397-403), 1568-9972 (May 2011)
Publication Date: May 2011
Abstract: The first approved biological agents for the treatment of rheumatoid arthritis (RA) were tumour necrosis factor (TNF) antagonists, all of which improve disease signs and symptoms, and slow or prevent structural damage; however, they are not equally effective in all patients. About 30% of patients treated with a TNF agent fail to achieve an improvement of 20% in the American College of Rheumatology (ACR) criteria, and even more patients lose efficacy during therapy or experience adverse events. Switching to a second TNF inhibitor has become an established approach to patients who fail or are intolerant of treatment with the first. However, there is only one published large randomised clinical trial evaluating the benefits of switching TNF antagonists, and data from observational studies and clinical practice are conflicting. Many parameters influence switching TNF agents, including the type of failure or TNF antagonist. However, many RA patients can be successfully treated with a second TNF antagonist, especially those discontinuing the first because of secondary failure or adverse events. 2011 Elsevier B.V.
Source: EMBASE
Available in print at

10. 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. Characteristics associated with a better response were being a non-smoker. 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
Available in print at
Available in fulltext from Internal Medicine Journal at EBSCOhost

11. Secondary failure to treatment with recombinant human IL-1 receptor antagonist in Chinese patients with rheumatoid arthritis

Author(s) Bao J., Yue T., Liu W., Zhang Q., Zhou L., Xu H.-J., Dai S.-M.

Citation: Clinical Rheumatology, May 2011, vol./is. 30/5(697-701), 0770-3198;1434-9949 (May 2011)

Publication Date: May 2011

Abstract: The aim of this study is to assess the efficacy of anakinra, a recombinant human interleukin 1 receptor antagonist, plus methotrexate (MTX) in patients with active rheumatoid arthritis (RA) refractory to MTX therapy. A total of 54 patients with active RA, who were taking MTX at a stable dosage, were randomized to receive daily subcutaneous injections of anakinra (80 mg) or placebo. Clinical outcomes were assessed every 4 weeks for 24 weeks by using the criteria of the American College of Rheumatology. After 24 weeks, more patients achieved clinical benefits as determined by the ACR20 improvement treated with anakinra plus MTX compared with MTX alone (64% vs. 17%, P=0.004). In the anakinra group, an ACR50 response was observed in 38% and an ACR70 response in 17%. None of the patients treated with MTX alone achieved ACR50 or ACR 70 improvement. However, nine of 42 (21.4%) patients in the anakinra group, who showed therapeutic response initially, had secondary drug failure to anakinra therapy thereafter. A significant increase in mean DAS28 from baseline was found in the non-responders to anakinra compared with placebo (0.83+/−1.38 vs. -1.28+/− 0.78, P<0.001). Anakinra is effective in the treatment of patients with active RA by blocking IL-1. However, the efficacy of anakinra is soon lost in about one fifth of patients in spite of initial good response. Clinical Rheumatology 2011.

Source: EMBASE
Available in print at
Available in fulltext from Clinical Rheumatology at EBSCOhost

12. Effectiveness of rituximab in rheumatoid arthritis: Results from the British society for rheumatology biologics register (BSRBR)


Citation: Rheumatology, April 2011, vol./is. 50/(iii31), 1462-0324 (April 2011)

Publication Date: April 2011

Abstract: Background: Rituximab (RTX) in combination with methotrexate (MTX) has been licensed since 2006 for the management of severe active rheumatoid arthritis (RA) in patients who have failed at least one anti-tumour necrosis factor (anti-TNF) therapy. Published clinical trials have demonstrated the efficacy of RTX in improving both clinical
symptoms and patients' physical function. This study aimed to assess the effectiveness of RTX in RA patients treated in routine clinical practice by examining clinical and patient reported outcomes six months after receiving a first course of RTX. Methods: The analysis involved 550 RA patients registered with the BSRBR, who were starting RTX and were followed up for at least 6 months. Change in Disease Activity Score (DAS28) and European League Against Rheumatism (EULAR) response were used to assess the clinical response while change in Health Assessment Questionnaire (HAQ) score was used to assess the physical function of the patients 6 months after starting RTX. The change in DAS28 and HAQ was compared between seronegative and seropositive patients and anti-TNF naive patients versus anti-TNF failures. The response was also compared between patients receiving RTX in combination with MTX, other non-biologic disease modifying anti-rheumatic drugs (nbDMARDs) or no nbDMARDs. Results: The mean (S.D.) age of the cohort was 59 (12) years and 78% of the patients were females. The patients had a mean (S.D.) of 15 (10) years of disease duration. 16% were biologic naive while 84% were anti-TNF failures. 32% of the patients were seronegative and 68% were seropositive. The mean (95% CI) DAS28 at baseline was 6.2 (6.1, 6.3) which decreased to 4.8 (4.7, 4.9) at 6 months of follow up. 16% were EULAR good responders, 43% were moderate responders and 41% were non responders. The mean (95% CI) change in HAQ was -0.1 (-0.2, -0.1) (Table 1). The mean change in DAS28 was similar in seropositive and seronegative patients (p=0.18) while the anti-TNF naive patients showed a greater reduction in DAS28 scores than anti-TNF failures (p=0.05). Patients receiving RTX in combination with MTX showed similar changes in DAS28 and HAQ compared to patients receiving RTX alone or with other nbDMARDs. Conclusions: RTX has proven to be effective in the routine clinical practice. Anti-TNF naive patients seem to benefit more from RTX treatment than anti-TNF failures.

Source: EMBASE
Available in print at
Available in fulltext from Rheumatology at Highwire Press

13. Remission of rheumatoid arthritis by multiple large joint surgeries in partial responder for etanercept – A case report

Author(s) Kanazawa T., Nishida K., Hashizume K., Kadota Y., Nakahara R., Saito T., Ozaki T.

Citation: International Journal of Rheumatic Diseases, July 2010, vol./is. 13/(250), 1756-1841 (July 2010)

Publication Date: July 2010

Abstract: Case report: A 56 years old woman with rheumatoid arthritis (RA) showed high disease activity in spite of medical treatment by conventional disease modifying anti-rheumatic drugs including methotrexate (MTX). Infliximab (INF) in combination with MTX and corticosteroid was started from May 2004, and switched into etanercept (ETN) at a dose of 50 mg/week from October 2005 due to secondary failure of INF. She had multiple joints swelling and tenderness, and severe pain in both knee joints (Larsen grade IV at right knee joint and Larsen grade III at left knee joint) and right elbow (Larsen grade IV). Because activity of daily living was highly restricted and high disease activity (CRP 12.9, DAS28-ESR 6.96) continued, right total knee arthroplasty and right total elbow arthroplasty (TEA) was performed in January 2006 and May 2006, respectively, after temporally discontinuation of ETN. Although disease activity rapidly decreased, moderate disease activity (CRP 1.03, DAS28-ESR 3.86) and severe swelling of left knee joint continued 52 weeks after TEA. In July 2007, arthroscopic synovectomy on left knee joint was performed. At the final follow- up, disease activity showed a clinically relevant remission (CRP 0.56, DAS28-ESR 1.83) by ETN. Serum concentration of MMP-3 decreased from 542 before first surgery to 32.8. Each operated joint showed satisfactory clinical outcome with excellent range of motion (right knee: 0-125, left knee: 10-140, right elbow: 20-120). The treatment strategy for RA has dramatically changed over the past decade with introduction of biologic agents. Surgical treatment, however, still holds an important place against non-responders, as a local treatment especially for partial responders, or for patients who cannot use optimal medication due to complications or economic problems. In this case, surgical treatments for joints with active inflammation and destruction might contribute the enhancement of efficacy of ETN by reducing synovial volume as well as local TNF.
14. Lack of replication of genetic predictors for the rheumatoid arthritis response to anti-TNF treatments: a prospective case-only study

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

**Citation:** Arthritis research & therapy, 2010, vol./is. 12(2), R72, 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.

**Source:** EMBASE

Available in fulltext from Arthritis Research and Therapy at National Library of Medicine

15. Primary anti-TNF failures experience better clinical responses but similar health care utilization to a second anti-TNF agent than secondary failures: Analysis of the Alberta rheumatoid arthritis biologics registry

**Author(s)** Maksymowych W.P., Ohinmaa A., Martin L., Russell A.S., Barr S.G., Sholter D., Penney C.J.

**Citation:** Arthritis and Rheumatism, 2010, vol./is. 62(330), 0004-3591 (2010)

**Publication Date:** 2010

**Abstract:** Purpose: Meta-analysis of anti-TNF switching data from observational cohorts has concluded that responses are inferior in those switching due to primary as compared to secondary anti-TNF failures but limitations include small sample size of individual studies, failure to define response, and selection bias. We assessed the impact of switching anti-TNF agents at different time points in the Alberta Biologics Registry, an observational cohort of RA patients starting anti-TNF therapy in 2004, where collection of outcome data on all patients is requested by the Provincial pharmaceutical formulary. Methods: The Alberta Biologics Registry collects clinical, employment, and health economic data at baseline, 3 months, and every 6 months thereafter. Patients must attain either an ACR20 or EULAR response (>1.2) plus a HAQ response of > 0.22 units by 12 weeks and maintain this at each subsequent visit to continue to receive anti-TNF agent. Health-related quality of life is measured with the EQ-5D and self reported health care utilization is measured for the six months prior to each visit. We analyzed responses according to time of switch (3 month versus subsequent time points) and according to specific anti-TNF agent switches. Results: From 1,222 patients in the registry, 649 patients had 27 month follow up assessment and 498 (76.7%) of these remained on the first anti-TNF during the study period. There were 28 (4.3%) primary failures and 123 (19%) secondary failures who switched a median of 15 months from baseline. The response rate to the second anti-TNF was somewhat better in
VO2peak was 1067 mL/min before treatment and 1157 mL/min at week 24 (p=0.15). Mean the 6 centers that participated in the QoL and exercise capacity part of the trial. All had the EPO<100 vs. >100 IU/L, resp, P=0.04). 48 of the pts evaluated for response belonged to transfusion dependence, was significantly asso

ciating with response (RR 78% vs. 52% for EPO<500 IU/L received DAR 500mug once every 2 weeks for 12 weeks, G-CSF could be added in the absence of response at week 12, and response reevaluated at week 24. Responders at week 12 or 24 could continue treatment. Some of the recruiting centers accepted t

Citation: Blood, November 2009, vol./is. 114/22, 0006-4971 (20 Nov 2009)

Publication Date: November 2009

Abstract: Background. DAR is a hyperglycosylated erythroblastic stimulating agent (ESA) with prolonged half life. Previous studies have shown high erythroid response rates with DAR +/- G-CSF in anemia of lower risk MDS (Mannone et al, Br J Haem 2006) with improvement in quality of life (QoL) (Greenberg et al, Blood 2009). In addition, treatment with ESAs in lower risk MDS does not increase progression to AML and may improve survival (Park, Grabar, Kelaidi et al, Blood 2008; Jadersten et al, JCO 2008). To better document the clinical relevance of erythroid response in those pts, we explored whether physical performance was also improved, using a new regimen of DAR+/- G-CSF. Patients and methods. In this phase II study (clinicaltrials.gov ndegree NCT00443339), low and int-1 MDS pts with anemia and endogenous EPO level <100 IU but not IPSS or RARS 41%, RAEB 15%. Karyotype was favorable in 80%, intermediate in 20%. IPSS was low in 60%, int-1 in 40%. Median Hb was 92 g/L and 30% of the pts were RBC transfusion dependent (median 2 RBC units/month). Median endogenous EPO level was 60 IU/L. At the date of analysis, 77 and 65 pts were evaluable at weeks 12 and 24, respectively. Erythroid response rate at 12 weeks (according to IWG 2006 criteria) was 53% and reached 65% (after addition of G-CSF) at 24 weeks. Multivariate analysis for predicting response revealed that endogenous EPO level <100 IU but not IPSS or transfusion dependence, was significantly associated with response (RR 78% vs. 52% for EPO<100 vs. >100 IU/L, resp, P=0.04). 48 of the pts evaluated for response belonged to the 6 centers that participated in the QoL and exercise capacity part of the trial. All had the 6-min WT and QoL, and VO2peak evaluation could be assessed in 20 of them. Mean VO2peak was 1067 mL/min before treatment and 1157 mL/min at week 24 (p=0.15). Mean 6-min WT was 382 m at onset and 418 m at week 24 (p=0.06). A significant improvement in quality of life (QoL) (Greenberg et al, Blood 2009). In addition, treatment with ESAs in lower risk MDS does not increase progression to AML and may improve survival (Park, Grabar, Kelaidi et al, Blood 2008; Jadersten et al, JCO 2008). To better document the clinical relevance of erythroid response in those pts, we explored whether physical performance was also improved, using a new regimen of DAR+/- G-CSF. Patients and methods. In this phase II study (clinicaltrials.gov ndegree NCT00443339), low and int-1 MDS pts with anemia and endogenous EPO level <100 IU but not IPSS or RARS 41%, RAEB 15%. Karyotype was favorable in 80%, intermediate in 20%. IPSS was low in 60%, int-1 in 40%. Median Hb was 92 g/L and 30% of the pts were RBC transfusion dependent (median 2 RBC units/month). Median endogenous EPO level was 60 IU/L. At the date of analysis, 77 and 65 pts were evaluable at weeks 12 and 24, respectively. Erythroid response rate at 12 weeks (according to IWG 2006 criteria) was 53% and reached 65% (after addition of G-CSF) at 24 weeks. Multivariate analysis for predicting response revealed that endogenous EPO level <100 IU but not IPSS or transfusion dependence, was significantly associated with response (RR 78% vs. 52% for EPO<100 vs. >100 IU/L, resp, P=0.04). 48 of the pts evaluated for response belonged to the 6 centers that participated in the QoL and exercise capacity part of the trial. All had the 6-min WT and QoL, and VO2peak evaluation could be assessed in 20 of them. Mean VO2peak was 1067 mL/min before treatment and 1157 mL/min at week 24 (p=0.15). Mean 6-min WT was 382 m at onset and 418 m at week 24 (p=0.06). A significant improvement
in VO2 and 6-min WT at week 24 (vs baseline) was observed in 60% (p=0.058) and 70% (p=0.052) of responders compared to 0% and 19% of non responders, resp. Significant improvement of exercise capacity was associated with achievement of Hb level >110g/L. QoL tests were also improved in responders at week 24 compared to non responders at week 24 (p=0.04). No severe adverse events of treatment were reported. Conclusion: This regimen of DAR every 2 weeks yielded high response rates. An objective improvement in exercise testing with treatment was seen in 60 to 70% of responders, depending on the test used. This finding, and the QoL improvement also observed in responders, confirm the clinical relevance of anemia correction in that elderly population with lower-risk MDS.

Source: EMBASE
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Available in fulltext from Blood at Highwire Press

17. 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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Available in print at
**18. 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, Haraoui 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.

**Source:** Medline

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**19. 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., Harauoi 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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20. Treatment options in patients with rheumatoid arthritis failing initial TNF inhibitor therapy: A critical review

Author(s) Rubbert-Roth A., Finckh A.

Citation: Arthritis Research and Therapy, April 2009, vol./is. 11/SUPPL. 1, 1478-6354;1478-6362 (06 Apr 2009)

Publication Date: April 2009

Abstract: Conventional disease-modifying antirheumatic drugs such as methotrexate are the mainstay of treatment for rheumatoid arthritis. More recently, biologic agents such as etanercept, infliximab and adalimumab, which act by inhibiting tumour necrosis factor (TNF), have become available. TNF inhibitors have proved to be very effective in patients not responding to conventional disease-modifying antirheumatic drugs. However, about 20% to 40% of patients treated with a TNF inhibitor fail to achieve a 20% improvement in American College of Rheumatology criteria, and more lose response over time (secondary failure or acquired therapeutic resistance) or experience adverse events following treatment with a TNF inhibitor. In this group of patients, therapeutic options were limited until recently and an established treatment approach was to switch from one TNF inhibitor to another. In recent years, therapeutic options in these patients have increased with the introduction of biologic agents with novel mechanisms of action, such as rituximab and abatacept. This review outlines the current evidence in support of the available treatment strategies in patients with an inadequate response or intolerance to an initial TNF inhibitor. 2009 BioMed Central Ltd.

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21. Non-responders to rituximab or tocilizumab after TNF-alpha inhibitor failure in the treatment of rheumatoid arthritis in the United Kingdom

Author(s) Lebmeier M., Shaw J., Koscielny V., Deeg M.

Citation: Arthritis and Rheumatism, 2009, vol./is. 60/(1026), 0004-3591 (2009)

Publication Date: 2009

Abstract: Purpose: Anti-TNF agents or rituximab (RTX) are routinely used in clinical practice after failure of a first or second anti-TNF agent in the treatment of rheumatoid arthritis (RA). Recently tocilizumab (TOC), an IL-6 antagonist, has been licensed for the treatment of RA, providing clinicians with potential further options for the treatment of patients failing anti-TNF therapy. In the absence of comparative data models may help to estimate the number of patients not responding to RTX and TOC after failure of a first anti TNF compared to a second anti-TNF. This may provide insights into the most appropriate treatment algorithms and highlight areas requiring further research. Method: An explorative analysis was conducted using a decision tree model. The model is based on data from RTX, and TOC clinical trials, as well as the British Society for Rheumatology Biologics Registry (BSRBR), which provides the most meaningful datasets on sequential use of
biologics to date. The model compares the failure rates for a second anti-TNF, RTX or TOC in patients that have not responded to a first anti-TNF. In the REFLEX trial patients receiving RTX after not responding to at least one anti-TNF 49% of patients did not respond to RTX treatment (defined as not achieving ACR20 response). The RADIATE trial was conducted in patients not responding to at least one TNF. In this trial 50% did not respond to TOC treatment. Failure rates for a second TNF were obtained from the UK BSR, reporting the proportion of patients failing a 2nd TNF to be 27%. These failure rates were applied in the model which also used UK prevalence data for RA to predict potentially anti TNF eligible patients. The prevalence of RA in the UK is reported to be 1.16% in women and 0.44% in men, resulting in potentially 385,266 RA patients. Results: The base case analysis calculated that 23,116 patients receive TNF inhibitor treatment, of which 4,221 can be expected to fail a first TNF inhibitor. If patients would receive RTX after the failure of a first anti-TNF, 2,068 can be expected to fail this regime. If they would receive TOC, 2,110 could be expected fail. If patients would receive a second anti-TNF, 1,140 may fail this treatment. We furthermore calculated failure rates for RTX and TOC after lack of response to a second anti-TNF using data from the same sources. No published data for anti TNF agents in this population is available. Using RTX after a second anti-TNF would result in 559 vs. 570 patients failing treatment. Conclusion: This exploratory analysis suggests that using 2 anti-TNFs sequentially, rather than switching to RTX or TOC after failure of only one anti-TNF may lead to fewer patients failing treatments. The data also suggests that RTX and TOC are equally effective when used after failure of a second anti-TNF agent. The model is based on limited data and further clinical comparative studies are needed.

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22. The importance of the baseline Disease Activity Score 28 in determining responders and non-responders to anti-TNF in UK clinical practice.

Author(s) Smith N, Ding T, Butt S, Gadsby K, Deighton C

Citation: Rheumatology, September 2008, vol./is. 47/9(1389-91), 1462-0324;1462-0332 (2008 Sep)

Publication Date: September 2008

Abstract: OBJECTIVES: The NICE re-appraisal of anti-TNF requires demonstration of ongoing response, making the baseline 28-joint Disease Activity Score (DAS28) crucially important. A retrospective analysis of all RA patients on their first anti-TNF determined predictive factors for those classified as non-responders at 6 months according to current NICE guidelines. METHODS: The patients were divided into responders (DAS28 dropped by >1.2) and non-responders. These groups were compared for demographics, DAS28 at the two pre-assessments 1 month apart and at baseline. Exposure to intramuscular, oral and IA steroids in the 3 months period before the baseline DAS28 was recorded. RESULTS: At 6-month assessment in 256 patients, 82.8% were responders with no demographic differences between them and non-responders. Although the first pre-assessment score was not significantly different (6.8 vs 6.6), the second pre-assessment score (7.1 vs 6.7) and the baseline DAS (7.2 vs 6.3) were lower in the non-responders (P < 0.04 and P < 0.001, respectively). Comparing the differences in DAS28 from the first pre-assessment to baseline, the responders had increased by 0.4, and the non-responders had decreased by 0.4, (P < 0.001). If the first pre-assessment score had been taken as the baseline DAS28, then 9.4% of responders would be re-classified as non-responders, and 31.8% of non-responders would be re-classified as responders. The proportion of patients who had steroid treatment within the 3 months period before the baseline DAS28 did not differ significantly between the responders and non-responders (34% vs 41%, P = 0.38). CONCLUSION: Baseline DAS28 is critical in classifying responders at the 6-month assessment.

Source: Medline
Available in print at
Available in fulltext from Rheumatology at Highwire Press


**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 $^{99m}$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-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.

**Source:** EMBASE

Available in print at

24. Switching anti-TNF-alpha agents: What is the evidence?

**Author(s)** Erickson A.R., Mikuls T.R.

**Citation:** Current Rheumatology Reports, October 2007, vol./is. 9/5(416-420), 1523-3774;1534-6307 (October 2007)

**Publication Date:** October 2007

**Abstract:** The availability of biologic agents targeting tumor necrosis factor (TNF)-alpha represents a significant advance in the management of rheumatoid arthritis. Anti-TNF-alpha therapy has been associated with dramatic improvements in the clinical signs and symptoms of rheumatoid arthritis and has been shown to greatly retard the destructive process that too often characterizes this condition. Although effective and well-tolerated in a substantial proportion of patients, primary and secondary failures of anti-TNF-alpha strategies have been well described, affecting up to one-third to one-half of subjects treated with these agents. Switching from one anti-TNF-alpha agent to a second (or even third) anti-TNF-alpha therapy has emerged as a means of addressing treatment failures with this drug class. This review examines data addressing the practice of switching anti-TNF-alpha agents in the context of initial treatment failure, with a focus on data from peer-reviewed reports. Copyright 2007 by Current Medicine Group LLC.

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**Author(s)** Buch MH, Bingham SJ, Bryer D, Emery P
OBJECTIVE: Patients may cease therapy with anti-tumour necrosis factor (TNF) agents due to inefficacy at 12 weeks (termed primary non-response) or later. Until now, the extent of this later secondary non-response has not been clearly defined. We followed-up a substantial single-centre cohort to determine kinetics of this secondary loss of response. The licensed dose of 3 mg/kg was used throughout.

METHODS: Prospective data collection since anti-TNF therapy introduction in 1999 formed the basis of the analysis. Patients with rheumatoid arthritis who received infliximab as their first biologic agent, with at least 2 yrs follow-up were included. All relevant clinical data to calculate DAS-28 score and EULAR response were collected at 3, 6, 9, 12, 18 and 24 months. Reasons for cessation in those patients achieving a EULAR response at 3 months (secondary failures) were determined.

RESULTS: Of a total of 309 patients commenced on infliximab, 290 received this as their first biologic agent.; 195 commenced > or = 2 yrs ago. Efficacy data to identify EULAR responders at 3 months was available in 174 patients. Sixty-seven per cent achieved a 'moderate' or 'good' EULAR response; 25% failed to achieve a response, 8% developed toxicity within the first 12 weeks. Of the primary responders, over 55% subsequently ceased therapy in the first year, the predominant reason was a secondary loss of response; other reasons included high disease activity despite achieving a definable response, toxicity, and intercurrent illness. Subsequent loss of response in the second year was less pronounced.

CONCLUSIONS: This study of patients treated in clinical practice with infliximab demonstrated that secondary non-response occurred in around half the patients in the first year. The data highlight the need to continue development of other therapies as well as investigation of the underlying causes of this loss of response.

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Available in fulltext from Rheumatology at Highwire Press

26. 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.

Source: Medline
Available in print at

27. Therapy of patients with rheumatoid arthritis: outcome of infliximab failures switched to etanercept.

Author(s) Buch MH, Bingham SJ, Bejarano V, Bryer D, White J, Reece R, Quinn M, Emery P

Citation: Arthritis & Rheumatism, April 2007, vol./is. 57/3(448-53), 0004-3591;0004-3591 (2007 Apr 15)

Publication Date: April 2007

Abstract: OBJECTIVE: The role of alternative tumor necrosis factor (TNF) antagonist therapies in the context of failure of initial TNF antagonist therapy in patients with rheumatoid arthritis (RA) has yet to be clearly defined. The goal of this study was to determine the efficacy of etanercept in patients who failed to respond to infliximab.METHODS: Ninety-five patients with RA who failed to respond to infliximab and methotrexate were treated with etanercept (with continuation of concomitant methotrexate). Thirty-four patients never achieved a response to infliximab (primary nonresponse), 38 had an initial response to infliximab but relapsed (secondary nonresponse), and 23 demonstrated toxicity. Disease Activity Score in 28 joints (DAS28), European League Against Rheumatism (EULAR) response, and American College of Rheumatology (ACR) response were determined after 12 weeks of etanercept.RESULTS: After 12 weeks of etanercept, 38% of patients achieved an ACR 20% response (ACR20) on etanercept. Of these, 24% and 15% achieved ACR50 and ACR70 responses, respectively. In the primary infliximab nonresponse group, 42%, 30%, and 15% achieved ACR20, ACR50, and ACR70 responses, respectively; the percentages for the secondary nonresponse group were 34%, 21%, and 14%, respectively. Significant DAS28 reductions were observed in the entire cohort and nonresponse subtype groups. Sixty-one percent of the cohort achieved either a moderate or good EULAR score (67% of primary and 56% of secondary infliximab failures). No toxicity was observed in patients who stopped infliximab due to intolerance; 19 of 23 continued etanercept after week 12.CONCLUSION: This study confirms that etanercept is effective in patients who fail to respond to infliximab and suggests a higher response in patients who have never had a response to infliximab.

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28. Imaging and serum analysis of immune complex formation of radiolabelled infliximab and anti-infliximab in responders and non-responders to therapy for rheumatoid arthritis.

Author(s) van der Laken CJ, Voskuyl AE, Roos JC, Stigter van Walsum M, de Groot ER, Wolbink G, Dijkmans BA, Aarden LA

Citation: Annals of the Rheumatic Diseases, February 2007, vol./is. 66/2(253-6), 0003-4967;0003-4967 (2007 Feb)

Publication Date: February 2007

Abstract: BACKGROUND: Many patients with rheumatoid arthritis are currently successfully treated with infliximab (anti-tumour necrosis factor); however, about 30% of the patients do not respond to infliximab. One of the postulated hypotheses of not responding is the fast clearance of infliximab due to the development of infliximab-anti-infliximab complexes.OBJECTIVE: To investigate the in vivo mechanism of not responding and the role of human anti-chimeric antibodies (HACAs) by using radiolabelled infliximab.METHODS: Two responding and two non-responding patients with rheumatoid arthritis, infused with radiolabelled infliximab, were investigated by both imaging and serum analysis.RESULTS: Images showed predominant presence of infliximab in blood up to 24
h, with a trend of faster blood clearance and of higher liver/spleen uptake in a non-responding patient. Clinically inflamed joints showed uptake of the drug. The HACA level in the non-responders was high (1641 and 1008 U/ml), but low or not detectable in responders. Various sizes of antibody complexes, including very large ones, were observed in a non-responder who developed a serious infusion reaction. CONCLUSION: Formation of infliximab-anti-infliximab complexes were found in non-responders due to the presence of large amounts of HACA. This finding, supported by both imaging and serum analysis data, may explain failure of infliximab treatment.

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29. 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
Available in print at

30. Titration of infliximab treatment in rheumatoid arthritis patients based on response patterns.

Author(s) Flendrie M, Creemers MC, van Riel PL
Citation: Rheumatology, January 2007, vol./is. 46/1(146-9), 1462-0324;1462-0324 (2007 Jan)
Publication Date: January 2007
Abstract: OBJECTIVES: To observe the course of the disease activity in rheumatoid arthritis (RA) patients treated with the standard infliximab dosing regimen and to adjust treatment guided by the pattern of disease activity. METHODS: All RA patients starting infliximab treatment were included and observed for at least 37 weeks. At infusion 4 (week 14), European League Against Rheumatism response was assessed. In moderate responders the dose was unchanged and the disease activity was carefully observed. In case of stable disease activity, the dose was increased at infusion 5 (week 22). In case of a temporary response the interval was reduced. Paired t-testing was applied to the disease activity score with 28-joint counts (DAS28) at week 22 and study endpoint. RESULTS: A total of 76 patients were included. Response after 14 weeks: good 22 (29%) patients, moderate 26 (34%) patients, and non-response in 21 patients. Seven patients (9%)
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 \([P = 0.005\), mean interval 5.6 weeks, mean infliximab dose 4.8 mg/kg/8 week (endpoint)] and from 4.1 to 3.6 \([P = 0.04\), 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.

Source: Medline
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31. Individualized monitoring of drug bioavailability and immunogenicity in rheumatoid arthritis patients treated with the tumor necrosis factor alpha inhibitor infliximab.

Author(s) Bendtzen K, Geborek P, Svenson M, Larsson L, Kapetanovic MC, Saxne T

Citation: Arthritis & Rheumatism, December 2006, vol./is. 54/12(3782-9), 0004-3591;0004-3591 (2006 Dec)

Publication Date: December 2006

Abstract: OBJECTIVE: Infliximab, an anti-tumor necrosis factor alpha (anti-TNFalpha) antibody, is effective in the treatment of several immunoinflammatory diseases. However, many patients experience primary or secondary response failure, suggesting that individualization of treatment regimens may be beneficial. This study was undertaken to investigate whether serologic monitoring of infliximab bioavailability and immunogenicity in individual patients would be useful in optimizing treatment regimens to improve efficacy and tolerability.

METHODS: To avoid the use of solid-phase assays, two radioimmunoassays were developed: one for measurement of levels of anti-infliximab antibody, and a functional one for measurement of TNFalpha binding due to infliximab. Sera from 106 randomly selected rheumatoid arthritis patients were tested within 6 months of therapy initiation, and associations between findings of serum assays and disease activity, infusion reactions, and treatment failure occurring within 18 months were assessed.

RESULTS: Trough serum infliximab levels after the first 2 intravenous infusions of infliximab at 3 mg/kg varied considerably between patients (range 0-22 microg/ml). At this stage, only 13% of the patients were anti-infliximab antibody positive. With subsequent infusions, the frequency of antibody positivity rose to 30% and 44% (at 3 months and 6 months, respectively), accompanied by diminished trough levels of infliximab. Indeed, low infliximab levels at 1.5 months predicted antibody development and later treatment failure. There were highly significant correlations between high levels of antibodies and later dose increases, side effects, and cessation of therapy. High baseline disease activity, judged by C-reactive protein level and Disease Activity Score, was associated with low levels of infliximab at the early stage of treatment and later development of anti-infliximab antibodies. Cotreatment with methotrexate resulted in slightly reduced antibody levels after 6 months; other disease-modifying antirheumatic drugs and prednisolone had no effect.

CONCLUSION: Development of anti-infliximab antibodies, heralded by low preinfusion serum infliximab levels, is associated with increased risk of infusion reaction and treatment failure. Early monitoring may help optimize dosing regimens for individual patients, diminish side effects, and prevent prolonged use of inadequate infliximab therapy.

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32. Lack of efficacy of a third tumour necrosis factor alpha antagonist after failure of a
soluble receptor and a monoclonal antibody.

**Author(s)** Solau-Gervais E, Laxenaire N, Cortet B, Dubucquoi S, Duquesnoy B, Flipo RM

**Citation:** Rheumatology, September 2006, vol./is. 45/9(1121-4), 1462-0324;1462-0324 (2006 Sep)

**Publication Date:** September 2006

**Abstract:** OBJECTIVE: Some studies have highlighted the potential benefits of switching from infliximab to etanercept, or after failure of one or the other treatment. To our knowledge, no study has assessed the potential benefits of using the three anti-TNF-alpha agents that are currently available. The objective of this retrospective study was to assess the response to treatment in RA patients who had received the three anti-TNF-alpha agents, namely infliximab, etanercept and adalimumab. METHODS: Among a cohort of 364 patients undergoing biological treatments since the year 2000, 284 had been treated with only one anti-TNF-alpha agent. Our assessment focused on the records of 70 patients who had received at least two anti-TNF-alpha agents. Twenty of the 70 patients had received all three anti-TNF-alpha agents (infliximab, etanercept and adalimumab). Effectiveness was assessed using the 28-joint Disease Activity Score (DAS28), and adverse events were reported for each anti-TNF-alpha treatment. RESULTS: Of the 70 patients who had received two anti-TNF-alpha agents, 32 had switched from an antibody to a soluble receptor; 45% of them had a good clinical response to the soluble receptor. Thirty patients had switched from a soluble receptor to an antibody; 45% of them had a good clinical response to the antibody. Only eight patients had switched from an antibody to another antibody with an efficiency score of 33%. Of the 20 patients who had received three anti-TNF-alpha agents, seven had stopped receiving the third anti-TNF-alpha agent due to lack of effectiveness. In this group of non-responders to the third anti-TNF-alpha treatment, all patients except one had stopped receiving the two previous anti-TNF-alpha agents, without adverse events, for lack of effectiveness. These patients were deemed resistant to anti-TNF-alpha therapy. CONCLUSIONS: Resistance to anti-TNF-alpha agents is rare. The lack of effectiveness of a soluble receptor and of one of the anti-TNF-alpha antibodies predicts the lack of effectiveness of the third anti-TNF-alpha treatment.

**Source:** Medline

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

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

**Citation:** Rheumatology, August 2005, vol./is. 44/8(1026-31), 1462-0324;1462-0324 (2005 Aug)

**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 per cent 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.

**Source:** Medline
Available in print at
Available in fulltext from Rheumatology at Highwire Press

34. C-reactive protein as a predictor of infliximab treatment outcome in patients with rheumatoid arthritis: defining subtypes of nonresponse and subsequent response to etanercept.

**Author(s)** Buch MH, Seto Y, Bingham SJ, Bejarano V, Bryer D, White J, Emery P

**Citation:** Arthritis & Rheumatism, January 2005, vol./is. 52/1(42-8), 0004-3591;0004-3591 (2005 Jan)

**Publication Date:** January 2005

**Abstract:** OBJECTIVE: Nonresponse to anti-tumor necrosis factor alpha in patients with rheumatoid arthritis (RA) is poorly understood. The aims of this study were to define nonresponse patterns using infliximab and C-reactive protein (CRP) profiles, to assess the predictive power of a CRP response for outcome, and to correlate these findings with subsequent response to etanercept.METHODS: We studied 207 patients with resistant RA who were started on treatment with infliximab. After 12 weeks, the American College of Rheumatology 20% improvement criteria (ACR20) were used to classify patients as responders (ACR20 response or greater) or nonresponders (NRs). The NRs were further subdivided into 3 groups according to the CRP response at weeks 2, 6, and 12. Within the NR group, those with a suppressed CRP at week 12 continued taking infliximab for a further 12 weeks; those without a CRP response were switched to etanercept, and the ACR response at 12 weeks was calculated.RESULTS: At week 12, 54% of patients achieved an ACR20 response, and 46% failed to achieve a response. Of the NRs, 63% demonstrated a significant reduction in the CRP level at week 12, 59% of whom achieved an ACR20 response at week 24 on continuation of infliximab. Of the patients who did not demonstrate a significant reduction in the CRP level after the first infusion, 86% failed to show a biochemical or ACR20 response by week 12. Twenty-four percent of the NRs had a temporary reduction in the CRP level, and 13% of the NRs showed no CRP reduction. Seventy-five percent of these NRs switched to etanercept, and 68% of this group achieved an ACR20 response at week 12 (51% achieved an ACR50 response), with a CRP response in 63%.CONCLUSION: Infliximab NRs comprise subtypes with distinct CRP patterns. Failure to suppress the CRP at week 2 identified the majority of patients who were NRs at week 12. CRP suppression at week 12 in the NRs was associated with a late clinical improvement with infliximab treatment (24 weeks), whereas failure to suppress the CRP at week 12 was associated with a good response on switching to etanercept.

**Source:** Medline
Available in fulltext from Arthritis and Rheumatism at the ULHT Library and Knowledge Services’ eJournal collection

35. Switching of tumour necrosis factor-alpha antagonists in patients with spondyloarthritides

**Author(s)** Spadaro A.

**Citation:** European Musculoskeletal Review, January 2001, vol./is. 6/1(30-32), 1754-5072:1754-5080 (February 2011)

**Publication Date:** January 2001

**Abstract:** Tumour necrosis factor-alpha (TNFalpha) antagonists (adalimumab, etanercept and infliximab) have demonstrated effectiveness in controlling disease activity in spondyloarthritides, such as psoriatic arthritis and ankylosing spondylitis. Nevertheless, in controlled and observational studies with TNFalpha blockers, a variable percentage of patients, withdraw from therapy because of failure (primary or secondary lack of efficacy) or
poor tolerability. In the case of treatment failure with one agent, switching to the other agent may also be rational due to the different chemical structures and mechanisms of action of available TNFalpha blockers. Moreover, the rationale for switching is supported by the evidence of beneficial effects reported in patients resistant or intolerant to TNFalpha antagonists. This suggests that treatment with another anti-TNFalpha agent (monoclonal antibody or recombinant soluble TNF receptor) may be appropriate and leads to a prompt and sustained response, with the majority of patients tolerating these drugs well. Touch Briefings 2011.

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A Rubbert-Roth, A Finckh - Arthritis Res Ther, 2009 - biomedicalcentral.com

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