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Diagnosis and Management of Suspected Idiopathic Pulmonary Fibrosis

Idiopathic Pulmonary Fibrosis

National Clinical Guideline Centre
Methods, evidence and recommendations June 2013

CG163 Idiopathic Pulmonary Fibrosis: Baseline Assessment Tool June 2013
The baseline assessment is an Excel spreadsheet that can be used by organisations to identify if they are in line with practice recommended in NICE guidance and to help them plan activity that will help them meet the recommendations.
http://www.nice.org.uk/nicemedia/live/14183/64132/64132.xls

Pirfenidone for Treating Idiopathic Pulmonary Fibrosis
NICE technology appraisal guidance 282 2013
1.1 Pirfenidone is recommended as an option for treating idiopathic pulmonary fibrosis only if:
the person has a forced vital capacity (FVC) between 50% and 80% predicted and the manufacturer provides pirfenidone with the discount agreed in the patient access scheme.

1.2 Treatment with pirfenidone that is recommended according to 1.1 should be discontinued if there is evidence of disease progression (a decline in per cent predicted FVC of 10% or more within any 12 month period).

1.3 People currently receiving pirfenidone that is not recommended according to 1.1 should have the option to continue treatment until they and their clinician consider it appropriate to stop.

NICE PATHWAY

This is in algorithm format from the National Institute for Clinical Effectiveness based on the 2013 guidance. Click n the yellow boxes for more information that then pops up.

Idiopathic pulmonary fibrosis overview
http://pathways.nice.org.uk/pathways/idiopathic-pulmonary-fibrosis

Managing idiopathic pulmonary fibrosis
Evidence – Systematic Reviews / Summaries

Adverse Events of Pirfenidone for the Treatment of Pulmonary Fibrosis: A Meta-Analysis of Randomized Controlled Trials
Chunguo Jiang et al Online PLOS one October 9, 2012 (accessed 8th August 2013)

Pirfenidone (PFD) is a novel antifibrotic agent approved for patients with pulmonary fibrosis. However, there are concerns regarding toxicity of the drug. In this meta-analysis, we analyzed the adverse events (AEs) of PFD for the treatment of pulmonary fibrosis.

Methods
We performed a systematic search of PubMed, Embase, ClinicalTrials.gov, and Cochrane Central Register of Controlled Trials for trials published between January 1999 and October 2011. Data extracted from literature were analyzed with Review manager 5.0.24.

Results
The results of six randomized controlled trials (1073 participants) revealed that the number of individuals who discontinued PFD therapy was significantly higher than patients receiving placebo. The PFD group had a significantly higher rate of gastrointestinal (nausea, dyspepsia, diarrhea, and anorexia), neurological (dizziness and fatigue), and dermatological (photosensitivity and rash) AEs compared to the placebo group.

Conclusions
PFD used for the treatment of pulmonary fibrosis is not so safe or well-tolerated. Notably, gastrointestinal, neurological and dermatological adverse effects were more common in patients receiving PFD therapy, and therefore appropriate precaution is needed.

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0047024

The Cochrane Central Register of Controlled Trials REVIEW
Incidence and Prevalence of Idiopathic Pulmonary Fibrosis: Review of the Literature
ABSTRACT: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing interstitial pneumonia of unknown aetiology. It is a rare disease, and its incidence and prevalence are not clear. Therefore, we sought to review the published evidence on the global epidemiology of IPF. A comprehensive review of English language literature was performed by searching Medline and EMBASE for studies on IPF epidemiology published between January 1990 and August 2011. Studies providing quantitative data on IPF incidence and/or prevalence were identified and key data collected. 15 studies reporting on the incidence and/or prevalence of IPF were identified and summarised. IPF prevalence estimates in the USA varied between 14 and 27.9 cases per 100,000 population using narrow case definitions, and 42.7 and 63 per 100,000 population using broad case definitions. In Europe, IPF prevalence ranged from 1.25 to 23.4 cases per 100,000 population. The annual incidence of IPF in the USA was estimated at 6.8–8.8 per 100,000 population using narrow case definitions and 16.3–17.4 per 100,000 population using broad case definitions. In Europe, the annual incidence ranged between 0.22 and 7.4 per 100,000 population. IPF prevalence and incidence increase with age, are higher among males and appear to be on the increase in recent years. IPF is an orphan disease that affects a potentially increasing number of people in Europe and the USA. The observed variability in IPF incidence and prevalence may be explained by the differences in diagnostic criteria used, case definition, study population and study design.

http://err.ersjournals.com/content/21/126/355.full.pdf
Title Six-Minute-Walk Test In Idiopathic Pulmonary Fibrosis: Test Validation And Minimal Clinically Important Difference.
Volume 183 Issue 9 Pages 1231-7
RATIONALE: The 6-minute-walk test (6MWT) is a practical and clinically meaningful
measure of exercise tolerance with favorable performance characteristics in various cardiac
and pulmonary diseases. Performance characteristics in patients with idiopathic pulmonary
fibrosis (IPF) have not been systematically evaluated.

OBJECTIVES: To assess the reliability, validity, and responsiveness of the 6MWT and
estimate the minimal clinically important difference (MCID) in patients with IPF.

METHODS: The study population included all subjects completing a 6MWT in a clinical trial
evaluating interferon gamma-1b (n = 822). Six-minute walk distance (6MWD) and other
parameters were measured at baseline and at 24-week intervals using a standardized
protocol. Parametric and distribution-independent correlation coefficients were used to
assess the strength of the relationships between 6MWD and measures of pulmonary
function, dyspnea, and health-related quality of life. Both distribution-based and anchor-
based methods were used to estimate the MCID.

MEASUREMENTS AND MAIN RESULTS: Comparison of two proximal measures of 6MWD
(mean interval, 24 d) demonstrated good reliability (coefficient = 0.83; P < 0.001). 6MWD
was weakly correlated with measures of physiologic function and health-related quality of
life; however, values were consistently and significantly lower for patients with the poorest
functional status, suggesting good construct validity. Importantly, change in 6MWD was
highly predictive of mortality; a 24-week decline of greater than 50 m was associated with a
fourfold increase in risk of death at 1 year (hazard ratio, 4.27; 95% confidence interval, 2.57-
7.10; P < 0.001). The estimated MCID was 24-45 m.

CONCLUSIONS: The 6MWT is a reliable, valid, and responsive measure of disease status
and a valid endpoint for clinical trials in IPF.

Intervention Review
Non-Steroid Agents For Idiopathic Pulmonary Fibrosis
Published Online: 8 SEP 2010
Idiopathic pulmonary fibrosis is a chronic progressive lung disease with poor outcome and
no effective treatment to date. This is an update of a Cochrane Review first published in
2003.
Objectives
To assess the efficacy of non-steroid agents in adults with idiopathic pulmonary fibrosis.

Selection criteria
Randomised studies comparing non-steroid drugs with placebo or steroids in adults with
idiopathic pulmonary fibrosis.

Main results
Fifteen trials involving 10 different drugs were included. Two trials enrolling 1156 patients
compared interferon gamma-1beta with placebo: interferon gamma-1beta did not
significantly improve survival (HR 0.88, 95% CI 0.47 to 1.64; P = 0.68). Four trials involving
1155 patients compared pirfenidone with placebo. Three trials, conducted in 1046 patients,
provided data on progression-free survival: pirfenidone significantly reduced the risk of
disease progression by 30% (HR 0.70, 95% CI 0.56 to 0.88, P = 0.002). Data on the effect of
pirfenidone on pulmonary function could only be assessed for two studies analysing 314
patients. Forced vital capacity or vital capacity was significantly improved by pirfenidone
(mean difference 0.08 L, 95% CI 0.03 to 0.13, P = 0.0006).
Authors’ conclusions
Based on available data, partly still unpublished, pirfenidone appears to improve progression-free survival and, to a lesser extent, pulmonary function in patients with idiopathic pulmonary fibrosis. More data are needed on overall survival and quality of life on treatment. From the studies in this review, interferon gamma-1beta has not been shown to affect survival. Other agents evaluated in single studies either failed to provide evidence for a benefit or need to be assessed.

Non-Steroid Agents for Idiopathic Pulmonary Fibrosis
Paolo Spagnolo et al Published Online: 8 SEP 2010

Background
Idiopathic pulmonary fibrosis is a chronic progressive lung disease with poor outcome and no effective treatment to date. This is an update of a Cochrane Review first published in 2003.

Objectives
To assess the efficacy of non-steroid agents in adults with idiopathic pulmonary fibrosis.

Selection criteria
Randomised studies comparing non-steroid drugs with placebo or steroids in adults with idiopathic pulmonary fibrosis.

Data collection and analysis
Two authors independently assessed trial quality, extracted data and assessed risk of bias. We contacted pharmaceutical companies to obtain missing information, if any. We combined survival outcomes using Peto odds ratios or hazard ratios (HR).

Main results
Fifteen trials involving 10 different drugs were included. Two trials enrolling 1156 patients compared interferon gamma-1beta with placebo: interferon gamma-1beta did not significantly improve survival (HR 0.88, 95% CI 0.47 to 1.64; P = 0.68). Four trials involving 1155 patients compared pirfenidone with placebo. Three trials, conducted in 1046 patients, provided data on progression-free survival: pirfenidone significantly reduced the risk of disease progression by 30% (HR 0.70, 95% CI 0.56 to 0.88, P = 0.002). Data on the effect of pirfenidone on pulmonary function could only be assessed for two studies analysing 314 patients. Forced vital capacity or vital capacity was significantly improved by pirfenidone (mean difference 0.08 L, 95% CI 0.03 to 0.13, P = 0.0006).

Authors’ conclusions
Based on available data, partly still unpublished, pirfenidone appears to improve progression-free survival and, to a lesser extent, pulmonary function in patients with idiopathic pulmonary fibrosis. More data are needed on overall survival and quality of life on treatment. From the studies in this review, interferon gamma-1beta has not been shown to affect survival. Other agents evaluated in single studies either failed to provide evidence for a benefit or need to be assessed in larger randomised controlled trials.

**Intervention Review**

**Corticosteroids for Idiopathic Pulmonary Fibrosis**
Luca Richeldi et al
Editorial Group: Cochrane Airways Group
Published Online: 17 FEB 2010
Assessed as up-to-date: 28 JUN 2008

**Background**
Idiopathic pulmonary fibrosis (IPF) is a disease with significant morbidity and mortality. Patients' short survival time, high mortality, and generally rapid decline raise the importance of early treatment. Current guidelines suggest a combination of corticosteroids and immunosuppressants as "gold standard" for IPF treatment, although the evidence for this recommendation is weak. Based on animal models, it has been hypothesized a central role for aberrant wound healing following repeated epithelial lung injury, weakening the rationale for using corticosteroids in IPF, previously thought to be a chronic inflammatory disease.

**Objectives**
The aim of the review is to determine the efficacy of corticosteroids in the treatment of adults with familial and sporadic IPF.

**Selection criteria**
Randomised controlled trials (RCT) and controlled clinical trials (CCT) using corticosteroids alone for the treatment of adults with IPF.

**Data collection and analysis**
Abstracts of identified articles were retrieved and articles possibly fulfilling inclusion criteria were retrieved in full. Two reviewers would have independently assessed trial quality if there had been any included study.

**Main results**
Seventeen articles were selected as potentially eligible for meta-analysis. After further analysis of full text papers, no RCTs or CCTs were identified as suitable and therefore no data was available for inclusion in any meta-analysis. All studies were excluded due to inadequate methodologies.

**Authors' conclusions**
At present, there is no evidence for an effect of corticosteroid treatment in patients with IPF. On the other hand, other fibrotic lung diseases, such as non-specific interstitial pneumonia (NSIP), are reported to show a better response to corticosteroids. Making a clear distinction between IPF and other entities grouped under the umbrella term interstitial lung disease is, therefore, essential as this may have therapeutic and prognostic implications.

Centre For Reviews and Dissemination
Thiopurine S-Methyltransferase Testing In Idiopathic Pulmonary Fibrosis: A Pharmacogenetic Cost-Effectiveness Analysis
Hagaman JT, Kinder BW, Eckman MH
Centre For Reviews and Dissemination
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.
CRD summary
This study assessed the cost-effectiveness of testing the level of the enzyme thiopurine S-methyltransferase (TPMT) in the blood, before treatment with azathioprine, for patients with idiopathic pulmonary fibrosis. The authors concluded that TPMT testing before treatment was cost-effective. The methods and the reporting of the results were satisfactory. Some limitations were reported and should be considered, but the conclusions reached by the authors appear to be appropriate.
http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?LinkFrom=OAI&ID=22010000845

Pulmonary Hypertension in Idiopathic Pulmonary Fibrosis: A Review.
Pitsiou G, Papakosta D, Bouros D.
Idiopathic pulmonary fibrosis (IPF) is a progressive diffuse parenchymal disease with a poor prognosis. Pulmonary hypertension (PH) often complicates the course of IPF and may even be found in patients with preserved lung function. Possible pathogenetic mechanisms of PH in IPF include vascular destruction, pulmonary hypoxic vasoconstriction and vascular remodeling due to overexpression of cytokines and growth factors. PH in IPF patients is associated with decreased exercise capacity and a worse prognosis. Due to its prognostic significance, it seems important to investigate for PH in these patients. As the symptoms of PH in IPF are nonspecific, the development of PH in a patient with known IPF can be easily overlooked. Noninvasive methods provide clues for the diagnosis, but their sensitivity is limited. Doppler echocardiography is a useful tool for the detection of PH which also provides additional information regarding associated cardiac abnormalities. However, right heart catheterization remains the gold standard diagnostic test. Therapeutic options for PH in IPF are limited. Long-term oxygen administration for the correction of hypoxemia should be recommended. The availability of new pharmacological agents in the treatment of PH has raised the possibility of therapy in patients with IPF and associated PH. Whether these PH-targeted therapies may be of benefit in this patient group, in terms of improving functional outcomes and survival, remains uncertain.
http://www.karger.com/Article/Pdf/327918

Pulmonary Hypertension in Idiopathic Pulmonary Fibrosis: A Review.
Corte TJ, Wort SJ, Wells AU.
Pulmonary hypertension (PH) is a common in patients with idiopathic pulmonary fibrosis (IPF) referred for transplantation. When present, PH is associated with increased mortality, and may explain the deterioration of some patients with preserved pulmonary function. PH in IPF may develop as a consequence of, or disproportionate to the underlying fibrotic lung disease. The distinction between these two 'stages' of PH is essential as there are key differences in their pathophysiology, identification, and potential treatment options. Treatment advances in idiopathic pulmonary artery hypertension have focused attention on PH associated with underlying lung disease. We focus on pathogenetic mechanisms, identification of PH, and the potential for therapeutic intervention for PH in IPF. Although vascular ablation, and chronic hypoxia are both important in the aetiology of secondary PH, these mechanisms do not explain the development of disproportionate PH. In these patients, the early development of PH may be associated with increased fibrotic cell mediators,
abnormal vasculature or response to hypoxia, seen in IPF. Nocturnal and exercise desaturation are common in IPF, and may precede and contribute to the development PH. Therapeutic options for PH in IPF are limited, and there have been no controlled trials. Successful therapeutic intervention in pulmonary arterial hypertension, has led to suggestions that therapeutic intervention with PH specific therapy may be useful. However, controlled trials are warranted before therapy can be recommended. In the design of such trials, the distinction between secondary and disproportionate PH is essential.

**Challenges in Pulmonary Fibrosis. 1: Use of High Resolution CT Scanning Of the Lung for The Evaluation Of Patients With Idiopathic Interstitial Pneumonias.**

Gotway MB, Freemer MM, King TE Jr.

High resolution CT (HRCT) scanning has contributed significantly to the evaluation of patients with interstitial lung disease and is particularly useful in the diagnosis of idiopathic pulmonary fibrosis (IPF). The characteristic radiographic features of the idiopathic interstitial pneumonias on HRCT scans have been increasingly analysed and are now fairly well described. Based on current data, HRCT scanning can provide a confident, highly specific diagnosis of IPF in many patients with diffuse lung disease. This article reviews an organised approach to HRCT scanning and identifies the features that allow an accurate diagnosis of the idiopathic interstitial pneumonias to be made. The role of surgical lung biopsy is discussed in the diagnosis of cases when a definite HRCT diagnosis cannot be made.


**Research**

**Anti-Acid Treatment and Disease Progression in Idiopathic Pulmonary Fibrosis: An Analysis of Data from Three Randomised Controlled Trials**

Joyce S Lee et al The Lancet Respiratory Medicine, Volume 1, Issue 5, Pages 369 - 376, July 2013

**Summary**

**Background**

Abnormal acid gastro-oesophageal reflux is common in patients with idiopathic pulmonary fibrosis (IPF) and is considered a risk factor for development of IPF. Retrospective studies have shown improved outcomes in patients given anti-acid treatment. The aim of this study was to investigate the association between anti-acid treatment and disease progression in IPF.

**Methods**

In an analysis of data from three randomised controlled trials, we identified patients with IPF assigned to receive placebo. Case report forms had been designed to prospectively obtain data about diagnosis and treatment of abnormal acid gastro-oesophageal reflux in each trial. The primary outcome was estimated change in forced vital capacity (FVC) at 30 weeks (mean follow-up) in patients who were and were not using a proton-pump inhibitor or histamine-receptor-2 (H2) blocker.

**Findings**

Of the 242 patients randomly assigned to the placebo groups of the three trials, 124 (51%) were taking a proton-pump inhibitor or H2 blocker at enrolment. After adjustment for sex, baseline FVC as a percentage of predicted, and baseline diffusing capacity of the lung for carbon monoxide as a percentage of predicted, patients taking anti-acid treatment at baseline had a smaller decrease in FVC at 30 weeks (—0·06 L, 95% CI —0·11 to —0·01) than did those not taking anti-acid treatment (—0·12 L, —0·17 to —0·08; difference 0·07 L, 95% CI 0—0·14; p=0·05).
Interpretation
Anti-acid treatment could be beneficial in patients with IPF, and abnormal acid gastro-oesophageal reflux seems to contribute to disease progression. Controlled clinical trials of anti-acid treatments are now needed.

Exercise Capacity in Idiopathic Pulmonary Fibrosis: The Effect of Pulmonary Hypertension.
BACKGROUND AND OBJECTIVE:
Increased pulmonary arterial pressure (PAP) usually coexists with impaired lung function in IPF. Data on the effect of pulmonary hypertension (PH) on cardiopulmonary responses during exercise in IPF patients is very limited. We sought to investigate the impact of PH on exercise capacity and the correlation between systolic PAP (sPAP) and pulmonary function testing, as well as cardiopulmonary exercise parameters, in patients with IPF and PH.

METHODS:
Eighty-one consecutive patients with IPF, who were evaluated over a 6-year period, were retrospectively studied. Patients underwent pulmonary function testing, Doppler echocardiography and maximal cardiopulmonary exercise testing. PH was defined as sPAP > 35 mm Hg.

RESULTS:
PH was diagnosed in 57% of the patients. Categorization of patients according to severity of PH indicated a significant reduction in maximum work rate, peak O(2) uptake, anaerobic threshold and peak O(2) pulse in those with sPAP > 50 mm Hg. In IPF patients with PH, estimated sPAP correlated with peak O(2) uptake, anaerobic threshold, peak O(2) pulse and end-tidal CO(2) at anaerobic threshold, while the strongest correlation was between sPAP and ventilatory equivalent for CO(2) at anaerobic threshold (r = 0.611, P < 0.001). There were no differences in pulmonary function or exercise parameters indicative of lung volume reduction, across the patient categories, and none of these parameters correlated with sPAP.

CONCLUSIONS:
PH has a negative impact on exercise capacity in IPF patients. In IPF patients with PH, resting sPAP correlated with exercise parameters indicative of gas exchange and circulatory impairment, but not with defective lung mechanics.

Echocardiography, 6-Minute Walk Distance, and Distance-Saturation Product as Predictors of Pulmonary Arterial Hypertension in Idiopathic Pulmonary Fibrosis.
BACKGROUND:
Pulmonary arterial hypertension (PAH) is frequently seen in patients with idiopathic pulmonary fibrosis (IPF). We sought to examine the performance of echocardiography, 6-min walk test (6MWT) distance, distance-saturation product (DSP), and pulse oximetry (SpO2) in detecting underlying PAH in IPF.

METHODS:
626 lung transplanted patients from February 1990 to December 2007 were considered. Subjects with pre-transplant diagnosis of IPF were evaluated. Based on findings in pre-transplant right heart catheterization, the presence or absence of PAH was recorded. Right-ventricle systolic pressure, 6MWT distance, DSP, and lowest SpO2 during 6MWT were
compared in PAH and non-PAH groups. Receiver operating characteristic curves for each variable to assess prediction of PAH were constructed.

RESULTS:
131 patients were transplanted due to IPF. Of these 131 patients, 58 (44%) were eligible. PAH was diagnosed by right heart catheterization in 25 (43%) of 58 eligible patients. The mean pulmonary arterial pressure in PAH patients was 33 mm Hg, and 19 mm Hg in non-PAH patients (P = .001). 6MWT distance was 321 m in the PAH group, and 346 m in the non-PAH one (P = .38). DSP in PAH subjects was 272 meters% and 286 meters% in those with no PAH (P = .57). The lowest SpO2 in the PAH and non-PAH groups were 84% and 82%, respectively (P = .38). The diagnostic accuracy of the echocardiography exceeded that of the other variables (area under the curve 0.72).

CONCLUSIONS:
Right-ventricle systolic pressure measured by echocardiography, by 6MWT distance, by DSP, or by SpO2 performs poorly in detecting PAH in IPF. Measured by right heart catheterization, right-ventricle systolic pressure performs better to predict PAH in IPF.

Idiopathic Pulmonary Fibrosis And Emphysema: Decreased Survival Associated With Severe Pulmonary Arterial Hypertension.
Mejía M, et al

BACKGROUND:
It has been suggested that the presence of emphysema modifies the outcome of patients with idiopathic pulmonary fibrosis (IPF). In this article we compare clinical features, smoking history, pulmonary function, estimated systolic pulmonary artery pressure (eSPAP), and mortality in IPF with emphysema vs IPF without emphysematous changes.

METHODS:
A cohort of 110 IPF patients was evaluated. Clinical data were collected from clinical charts. High-resolution CT (HRCT) scans were examined by an expert blinded to clinical data, and patients were classified into the following two groups: patients with IPF with emphysema; and patients with IPF without emphysema. The Kaplan-Meier method, log-rank test, and Cox regression model were used for statistical analyses.

RESULTS:
The prevalence of emphysema in the IPF cohort was 28% (31 of 110 patients). IPF with emphysema was significantly associated with male gender (odds ratio [OR], 18; 95% confidence interval [CI], 2.7 to 773.7; p = 0.0003), and smoking (OR, 3.8; 95% CI, 1.36 to 11.6; p = 0.004). Patients with IPF and emphysema had a higher mean (+/- SD) decrease in oxygen saturation during rest and exercise (16.3 +/- 6.7% vs 13.5 +/- 4.6%, respectively; p = 0.04), a higher mean fibrosis HRCT scan score (1.75 +/- 0.36 vs 1.55 +/- 0.38, respectively; p = 0.015), a higher eSPAP (82 +/- 20 vs 57 +/- 15 mm Hg, respectively; p < 0.0001), and lower median survival time (25 vs 34 months, respectively; p = 0.01) than patients with IPF without emphysema. The Cox regression model showed that the two most important variables associated with mortality were FVC < 50% predicted (hazard ratio [HR], 2.6; 95% CI, 1.19 to 5.68; p = 0.016) and eSPAP >or= 75 mm Hg (HR, 2.25; 95% CI, 1.12 to 4.54; p = 0.022).

CONCLUSIONS:
IPF patients with emphysema exhibited higher mortality compared with those with IPF without emphysema. This dire prognosis seems to be at least partially associated with the development of severe pulmonary arterial hypertension.
Recent Advances in Idiopathic Pulmonary Fibrosis.
Idiopathic pulmonary fibrosis (IPF) remains the most common of the idiopathic interstitial pneumonias and portends a poor prognosis. Significant strides have been made in the approach to diagnosis and in the ability to predict outcome in the last few years. Advances in high-resolution CT (HRCT) scanning have allowed an accurate diagnosis obviating the need for surgical biopsy in many patients. Furthermore, HRCT scanning may aid in determining prognosis and identifying disease progression. The appropriate use of the HRCT scan requires a multidisciplinary iterative approach incorporating all available data to reach a final diagnosis. However, there remains great heterogeneity in disease progression. Pulmonary hypertension and acute exacerbations of IPF negatively influence prognosis and are increasingly a target of therapy. There has been an increase in the number of well-designed clinical trials of IPF that have focused on more specific targets. While no cure has yet been found, each trial expands our understanding regarding the natural course of the disease and the impact of targeted therapy. In the interim, lung transplantation, which appears to improve survival in a subset of IPF patients, remains the only intervention. The objective of this article is to review advances in the understanding of IPF and the evidence for the findings outlined above.

Amiodarone-Induced Skin Pigmentation and Pulmonary Fibrosis
Hospital Pharmacy Volume 37, Number 6, pp 615–618 2002 Facts and Comparisons Abstract — Amiodarone is a valuable drug for the treatment of supraventricular and ventricular arrhythmias. However, toxicity involving a variety of organs and tissues that limits the agent’s clinical use is not uncommon. This article presents the case of a patient who developed amiodarone-induced pulmonary fibrosis and blue-gray facial pigmentation. The authors emphasize awareness of amiodarone’s toxicity profile and the importance of appropriate treatment and followup care. Patients should be educated to take an active role in this process by monitoring themselves for symptoms of amiodarone-induced pulmonary toxicity, to aid in early diagnosis and help prevent fatal outcomes..

Efficacy and Safety of Oral Bosentan in Patients with Idiopathic Pulmonary Fibrosis
Completed
Public Title  Efficacy and Safety of Oral Bosentan in Patients With Idiopathic Pulmonary Fibrosis
Lay Summary  Endothelin-1 (ET-1) is expressed in a variety of pulmonary pathological conditions including pulmonary vascular disease and pulmonary fibrosis. Bosentan (an oral dual ET-1 receptor antagonist) could delay the progression of idiopathic pulmonary fibrosis (IPF), a condition for which no established treatment is available. The present trial investigates a possible use of bosentan, which is currently approved for the treatment of symptoms of pulmonary arterial hypertension (PAH) WHO class III and IV, to a new category of patients suffering from IPF. It was decided to offer Open Label treatment (bosentan) for patients willing to continue in the BUILD 1 study. (from ClinicalTrials.gov)

Open Label Extension Study in Patients with Idiopathic Pulmonary Fibrosis Who Completed Protocol AC-052-321/ BUILD 3 / NCT00391443 Completed

To include systematic reviews, reports summarising the evidence base etc. http://journal.publications.chestnet.org/data/Journals/CHEST/22152/zcb00709000010.pdf
Public Title  Open Label Extension Study in Patients With Idiopathic Pulmonary Fibrosis
Who Completed Protocol AC-052-321/ BUILD 3 / NCT00391443
Trial- Health Condition(s) or Problem  Idiopathic Pulmonary Fibrosis

Lay Summary  This Open-label extension study in patients with Idiopathic Pulmonary Fibrosis who completed protocol AC-052-321 / BUILD 3 (NCT00391443) will assess the long term safety and tolerability of bosentan in patients with idiopathic pulmonary fibrosis (IPF). (from ClinicalTrials.gov)

Who can enter the trial  Inclusion Criteria: Patients should have completed all the assessments from the BUILD 3 (NCT00391443) end of study (EOS) visit. - Signed informed consent prior to initiation of any study-related procedures. - Women of childbearing potential must have a negative serum pregnancy test and use reliable methods of contraception during study treatment and for 3 months after study treatment termination. Exclusion Criteria: - Any major violation of protocol AC-052-321 / BUILD 3 (NCT00391443). - Pregnancy or breast-feeding. - AST and/or ALT > 3 times the upper limit of the normal range. - Any known factor or disease that might interfere with treatment compliance, study conduct or interpretation of the results, such as drug or alcohol dependence or psychiatric disease. - Known hypersensitivity to bosentan or any of the excipients.

Who cannot enter the trial  Inclusion Criteria: Patients should have completed all the assessments from the BUILD 3 (NCT00391443) end of study (EOS) visit. - Signed informed consent prior to initiation of any study-related procedures. - Women of childbearing potential must have a negative serum pregnancy test and use reliable methods of contraception during study treatment and for 3 months after study treatment termination. Exclusion Criteria: - Any major violation of protocol AC-052-321 / BUILD 3 (NCT00391443). - Pregnancy or breast-feeding. - AST and/or ALT > 3 times the upper limit of the normal range. - Any known factor or disease that might interfere with treatment compliance, study conduct or interpretation of the results, such as drug or alcohol dependence or psychiatric disease. - Known hypersensitivity to bosentan or any of the excipients.

What will happen  Drug; Bosentan; For patients who were administered Bosentan during BUILD 3 (NCT00391443): continue on same dose For patients who were administered placebo during BUILD 3 (NCT00391443): Oral Bosentan 62.5 mg for 4 weeks; maintenance dose: 125 mg ( 62.5 if patient weighs < 90 lbs.); 1; Tracleer

Primary aim  Extent of Exposure to Bosentan in Patients With Idiopathic Pulmonary Fibrosis (IPF)

Secondary Aim  Number of Patients Exposed to Bosentan Over Time; Start to end of study, up to 21 months; Yes; Numbers of participants exposed to bosentan treatment over time; Adverse Events (AE) Leading to Discontinuation of Study Drug.; Start to end of study, up to 21 months; Yes; Number of participants with at least one AE that led to permanent discontinuation of study treatment.; Treatment-emergent Serious Adverse Events (SAE); up to 21 months plus 28 days after the end of study drug; Yes; Number of participants with at least one SAE during the study.; Occurrence of Liver Function Test (LFT: Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST)) Abnormality.; up to 21 months, plus 24 hours after the end of study treatment; Yes; Number of participants with an increase in ALT and/or AST to > 3 times upper limit of normal during the study.

http://www.ukctg.nihr.ac.uk/trialdetails/NCT00631475
Interferon-Gamma1b Therapy in Idiopathic Pulmonary Fibrosis: A Meta-analysis
Bajwa EK, Ayas NT, Schulzer M, Mak E, Ryu JH, Malhotra A

Record Status
This is a systematic review that meets the criteria for inclusion on DARE

Bibliographic details

Indexing Status
Subject indexing assigned by NLM

MeSH
Humans; Interferon-gamma /therapeutic use; Pulmonary Fibrosis /drug therapy /mortality; Recombinant Proteins

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http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?LinkFrom=OAI&ID=12005000934

Dyspnea in Idiopathic Pulmonary Fibrosis: A Systematic Review
Ryerson CJ, Donesky DA, Pantilat SZ, Collard HR

Record Status
This is a systematic review that meets the criteria for inclusion on DARE.

Bibliographic details

http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?LinkFrom=OAI&ID=12012019093

Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis (CAPACITY): Two Randomised Trials
The Lancet, Volume 377, Issue 9779, Pages 1760 - 1769, 21 May 2011
Prof Paul W Noble et al

Summary
Background
Idiopathic pulmonary fibrosis is a progressive and fatal lung disease with inevitable loss of lung function. The CAPACITY programme (studies 004 and 006) was designed to confirm the results of a phase 2 study that suggested that pirfenidone, a novel antifibrotic and anti-inflammatory drug, reduces deterioration in lung function in patients with idiopathic pulmonary fibrosis.

Methods
In two concurrent trials (004 and 006), patients (aged 40—80 years) with idiopathic pulmonary fibrosis were randomly assigned to oral pirfenidone or placebo for a minimum of 72 weeks in 110 centres in Australia, Europe, and North America. In study 004, patients were assigned in a 2:1:2 ratio to pirfenidone 2403 mg/day, pirfenidone 1197 mg/day, or placebo; in study 006, patients were assigned in a 1:1 ratio to pirfenidone 2403 mg/day or placebo. The randomisation code (permuted block design) was computer generated and stratified by region. All study personnel were masked to treatment group assignment until after final database lock. Treatments were administered orally, 801 mg or 399 mg three times a day. The primary endpoint was change in percentage predicted forced vital capacity
(FVC) at week 72. Analysis was by intention to treat. The studies are registered with ClinicalTrials.gov, numbers NCT00287729 and NCT00287716.

Findings

In study 004, 174 of 435 patients were assigned to pirfenidone 2403 mg/day, 87 to pirfenidone 1197 mg/day, and 174 to placebo. In study 006, 171 of 344 patients were assigned to pirfenidone 2403 mg/day, and 173 to placebo. All patients in both studies were analysed. In study 004, pirfenidone reduced decline in FVC (p=0·001). Mean FVC change at week 72 was −8·0% (SD 16·5) in the pirfenidone 2403 mg/day group and −12·4% (18·5) in the placebo group (difference 4·4%, 95% CI 0·7 to 9·1); 35 (20%) of 174 versus 60 (35%) of 174 patients, respectively, had a decline of at least 10%. A significant treatment effect was noted at all timepoints from week 24 and in an analysis over all study timepoints (p=0·0007). Mean change in percentage FVC in the pirfenidone 1197 mg/day group was intermediate to that in the pirfenidone 2403 mg/day and placebo groups. In study 006, the difference between groups in FVC change at week 72 was not significant (p=0·501). Mean change in FVC at week 72 was −9·0% (SD 19·6) in the pirfenidone group and −9·6% (19·1) in the placebo group, and the difference between groups in predicted FVC change at week 72 was not significant (0·6%, −3·5 to 4·7); however, a consistent pirfenidone effect was apparent until week 48 (p=0·005) and in an analysis of all study timepoints (p=0·007). Patients in the pirfenidone 2403 mg/day group had higher incidences of nausea (125 [36%] of 345 vs 60 [17%] of 347), dyspepsia (66 [19%] vs 26 [7%]), vomiting (47 [14%] vs 15 [4%]), anorexia (37 [11%] vs 13 [4%]), photosensitivity (42 [12%] vs 6 [2%]), rash (111 [32%] vs 40 [12%]), and dizziness (63 [18%] vs 35 [10%]) than did those in the placebo group. Fewer overall deaths (19 [6%] vs 29 [8%]) and fewer deaths related to idiopathic pulmonary fibrosis (12 [3%] vs 25 [7%]) occurred in the pirfenidone 2403 mg/day groups than in the placebo groups.

Interpretation

The data show pirfenidone has a favourable benefit risk profile and represents an appropriate treatment option for patients with idiopathic pulmonary fibrosis.

Study of the Effects of High-Dose N-Acetylcysteine (NAC) in Idiopathic Pulmonary Fibrosis (IPF)

Completed

Public Title Study of the Effects of High-Dose N-Acetylcysteine (NAC) in Idiopathic Pulmonary Fibrosis (IPF)
Acronym IFIGENIA
Source of Record URL http://clinicaltrials.gov/show/NCT00639496

Trial- Health Condition(s) or Problem Pulmonary Fibrosis
Lay Summary The purpose of this study is to determine whether NAC added to prednisone, and azathioprine has a better effect on lung function, radiology and clinical condition than placebo + prednisone in combination with azathioprine after 6 and 12 months. (from ClinicalTrials.gov)
http://www.ukctg.nihr.ac.uk/trialdetails/NCT00639496
Additional Information

TA282 Idiopathic Pulmonary Fibrosis - Pirfenidone: Costing Template 24 April 2013
A costing template has been produced that can be used by health communities to assess the local impact of implementing the guidance, based on the local population. The national assumptions used in the template can be altered to reflect local circumstances.
http://www.nice.org.uk/nicemedia/live/14156/63677/63677.xls

Oral N-Acetylcysteine for Idiopathic Pulmonary Fibrosis
Unlicensed and Off-label Medicines Report No.4

London New Drugs Group APC/DTC Briefing Document
PIRFENIDONE
December 2011
http://www.medicinesresources.nhs.uk/upload/Pirfenidone_Dec%202011.pdf

Patient Information

Pulmonary Fibrosis (Idiopathic)
NHS patient resource
http://www.nhs.uk/Conditions/pulmonary-fibrosis/Pages/Introduction.aspx

Pulmonary Fibrosis - it takes your breath away
http://pulmonaryfibrosistrust.org/

Pulmonary Fibrosis.org.uk
This site is here to help people with people affected by Pulmonary Fibrosis and those working to fight it.
http://www.pulmonaryfibrosis.org.uk/