Imatinib mesylate (Gleevec) in the treatment of diffuse cutaneous systemic sclerosis: results of a 1-year, phase IIa, single-arm, open-label clinical trial

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ABSTRACT

Objective To assess the safety and effectiveness of imatinib mesylate in the treatment of diffuse cutaneous systemic sclerosis (dcSSc).

Methods In this phase IIa, open-label, single-arm clinical trial, 30 patients with dcSSc were treated with imatinib 400 mg daily. Patients were monitored monthly for safety assessments. Modified Rodnan skin scores (MRSS) were assessed every 3 months. Pulmonary function testing, chest radiography, echocardiography and skin biopsies were performed at baseline and after 12 months of treatment.

Results Twenty-four patients completed 12 months of therapy. 171 adverse events (AE) with possible relation to imatinib were identified; 97.6% were grade 1 or 2. Twenty-four serious AE were identified, two of which were attributed to study medication. MRSS decreased by 6.6 points or 22.4% at 12 months (p=0.001). This change was evident starting at the 6-month time point (Δ=-4.5; p<0.001) and was seen in patients with both early and late-stage disease. Forced vital capacity (FVC) improved by 6.4% predicted (p=0.008), and the diffusion capacity remained stable. The improvement in FVC was significantly greater in patients without interstitial lung disease. Health-related quality of life measures improved or remained stable. Blinded dermatopathological analysis confirmed a significant decrease in skin thickness and improvement in skin morphology.

Conclusions Treatment with imatinib was tolerated by most patients in this cohort. Although AE were common, most were mild to moderate. In this open-label experiment, improvements in skin thickening and FVC were observed. Further investigation of tyrosine kinase inhibition for dcSSc in a double-blind randomised placebo controlled trial is warranted.

ClinicalTrials.gov, NCT00555581

Systemic sclerosis (SSc) is a multisystem, fibrosing disorder in which vasculopathy, autoimmunity and inflammation lead to morbidity and increased mortality.1 Abnormal signalling through the transforming growth factor beta (TGFβ)2–4 and the platelet-derived growth factors5–8 axes contributes to this pathological fibrosis. Imatinib mesylate (Gleevec; Novartis Pharmaceuticals, Basel, Switzerland) is a tyrosine kinase inhibitor with activity against c-Abl, the platelet-derived growth factor receptor (PDGFR), and other tyrosine kinases and is a therapy of interest for SSc because of its ability to interfere with both TGFβ and platelet-derived growth factor signalling.9–10

Combined inhibition of both TGFβ and PDGFR signalling by imatinib has been shown to decrease the production of extracellular matrix proteins by both scleroderma and normal skin fibroblasts.11 In murine models of both early and established cutaneous fibrosis and pulmonary fibrosis, imatinib treatment was beneficial.12–14 Similar effects were seen with nilotinib and dasatinib, other tyrosine kinase inhibitors that also block c-abl and PDGFR.15

Case reports of the use of imatinib in patients with SSc16–18 and mixed connective tissue disease19 have suggested clinical benefit. In case series of other cutaneous fibrosing disorders, nephrogenic systemic fibrosis20 and chronic sclerodermatous graft versus host disease,21 22 imatinib also showed a potential antifibrotic effect on the skin. However, in a randomised, placebo controlled study of imatinib for idiopathic pulmonary fibrosis treatment was not beneficial.23

We report here the results of a single-centre, phase IIa, single-arm, open-label clinical trial assessing the safety and efficacy of imatinib in the treatment of diffuse cutaneous systemic sclerosis (dcSSc).

PATIENTS AND METHODS

Study subjects

Between September 2007 and March 2009, 30 patients were enrolled. All patients fulfilled the American College of Rheumatology classification criteria for SSc24 and had the diffuse subtype. Patients were stratified by disease duration defined as onset of first symptom of SSc apart from Raynaud’s phenomenon: group 1 (n=20) less than 4 years and group 2 (n=10) 4–10 years.

All subjects were over 18 years old, had a stable modified Rodnan skin score (MRSS) of 16 points or more in the month between screening and baseline visits, and had disease duration of less than 10 years. Exclusion criteria included treatment with immunosuppressive therapies 3 months before baseline (including prednisone equivalent >10 mg), pregnancy, serious medical conditions, diffusion capacity of carbon monoxide (DLCO) less than 30% predicted, or ejection fraction (EF) less than 50% (see supplementary material, available online only).

Study design

This was an investigator-initiated phase IIa, single-centre, single-arm, open-label clinical trial. The primary objective of this study was to assess the safety and tolerability of imatinib in patients with dcSSc as assessed by the number of adverse events (AE) and serious adverse events (SAE). The primary
efficacy endpoint was change in the MRSS after 12 months of treatment. Secondary efficacy endpoints included change in forced vital capacity (FVC) and DLCO on pulmonary function testing (PFT) after 1 year of treatment, change in the short form 36 mental and physical components and change in scleroderma health assessment questionnaire disability index.

The protocol was approved by the institutional review board at the Hospital for Special Surgery and was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. Patients provided written informed consent before enrollment. An independent data and safety monitoring board regularly reviewed safety data. The trial was registered at ClinicalTrials.gov (NCT00555581).

Clinical outcomes
Patients were assessed at monthly visits for AE ascertainment, interval history, physical examination and clinical laboratories, and were to call our centre for issues between visits. AE were listed according to the National Cancer Institute’s common terminology.25 The MRSS was measured at screening, 1 month later at baseline and every 3 months. MRSS measurements were performed by the same physician at each visit (RS or both RS and JKG). PFT with measurement of FVC and DLCO were performed at baseline and following 12 months of therapy and are available on 22 completers.

Treatment
All patients were treated with imatinib at a target dose of 400 mg daily by mouth for 12 months. Dose modifications and interruptions were made for AE and were recorded. After 12 months of treatment, imatinib was stopped for 3 months. Patients were reassessed and offered entrance to an extension phase of the trial.

Dermatopathology
Four-millimetre punch biopsies of lesional forearm skin were performed before and after 12 months of treatment in 24 completers. The post-treatment biopsy was taken 1 cm adjacent to the original biopsy. Nineteen pairs were bisected. Half were formalin-fixed and paraffin-embedded, and half were stored for RNA extraction. The five final samples were prospectively reserved and submitted in entirety for RNA extraction to preserve adequate RNA quantity for microarray and follow-up confirmatory studies. The six patients who did not complete the study did not have follow-up biopsies. Sections were stained with H&E, anti-α-smooth muscle actin, Masson trichrome and elastin using standard techniques. A dermatopathologist (CM), blinded to before or after treatment status, compared the paired specimens.

Statistical analysis
The primary endpoint was a description of AE and SAE, and for this descriptive data are provided. No power calculation was performed for safety measurements, because there was no statistical analysis to be performed without a comparison group. The MRSS was the primary efficacy endpoint. Given a 5±8 unit difference in MRSS, based on a minimally clinically important difference of 5 points,26 a sample size of 30 was needed for a difference of 5 points, a sample size of 30 was needed for a two-sided alpha of 0.05 and 90% power. Analysis of all patients remaining on medication and reaching efficacy endpoints at months 3 (n=27), 6 (n=26), 9 (n=26) and 12 (n=24) is shown below as per our predefined protocol. A post-hoc modified intent-to-treat analysis including all patients with follow-up data, was also performed and was not different (not shown). In the case of missing data points, we utilised last observation carried forward. Paired t tests and Wilcoxon signed-rank tests were used to compare outcome measures before and after treatment, and unpaired t tests were used for comparisons between groups of patients. Statistical analysis was performed using SPSS software version 17.0.

RESULTS
Fifty-three patients were screened, 35 met entry criteria and five declined consent. Thirty patients started medication and 24 completed the study protocol. Baseline characteristics of the 30 subjects are summarised in table 1. Patients were categorised as having interstitial lung disease (ILD) if they had evidence of ground glass opacity and/or fibrosis on CT of the chest felt to be related to SSc in the opinion of the investigators and the treating physicians.

Three patients withdrew from the study in the first 3 months: two because of non-compliance and one developed...

Table 1 Baseline demographics, scleroderma related organ system involvement and previous treatments

| Parameter                              | Age, in years, median (range) |
|----------------------------------------|------------------------------|
|                                       | Median                       |
|                                       | Minimum, maximum             |
| Sex, n (%)                             | 48                           |
| Women                                  | 18                           |
| Men                                    | 71                           |
| Race, ethnicity, n (%)                 | 24 (80%)                     |
| White, non-Hispanic                    | 22 (73%)                     |
| White, Hispanic                        | 4 (13%)                      |
| African-American                       | 4 (13%)                      |
| Disease duration, n, mean±SD           | 3.4±2.3 years                |
| Whole group, n=30                      | 2.1±1.2 years                |
| Early group, n=20 (0–4 years)          | 6.1±1.8 years                |
| Later group, n=10 (4–10 years)         | 9 (30%)                      |
| Anti-Scl70 positive, n (%)             | 30.3±8.7                     |
| MRSS at baseline                       |                              |
| Organ involvement, n (%)               |                              |
| Gastrointestinal                       |                              |
| ILD                                    | 28 (93%)                     |
| Pulmonary artery Hypertension          | 16 (53%)                     |
| Cardiac                                | 3 (10%)                      |
| Renal                                   | 1 (3%)                       |
| Myopathy                               | 10 (33%)                     |
| Arthritis                              | 22 (73%)                     |
| Raynaud’s phenomenon                   | 30 (100%)                    |
| Digital ulceration                     | 24 (80%)                     |
| Previous treatment, n (%)              |                              |
| Corticosteroids                        | 14 (46.7%)                   |
| Methotrexate                           | 9 (30.0%)                    |
| Mycophenolate motefol                  | 6 (20.0%)                    |
| Cyclophosphamide                       | 5 (16.7%)                    |
| Penicillamine                          | 3 (10.0%)                    |
| IVIG                                    | 3 (10.0%)                    |
| Plaquenil                              | 4 (13.3%)                    |
| Colchicine                             | 2 (6.7%)                     |
| Thalidomide                            | 2 (6.7%)                     |
| Minocycline                            | 2 (6.7%)                     |
| Autologous stem cell transplant        | 1 (3.3%)                     |
| Oral collagen                          | 1 (3.3%)                     |
| Phototherapy                           | 3 (10%)                      |
| No previous treatment                  | 7 (23.3%)                    |

ILD, interstitial lung disease; IVIG, intravenous immunoglobulin; MRSS, modified Rodnan skin score.
an inflammatory myopathy that required immunosuppression. One patient withdrew after 3 months because of myalgia and fatigue, and one patient withdrew after 11 months because of the development of multiple medical issues (described below). One patient died after 11 months on medication. Safety data are included on all 30 patients enrolled.

### Safety outcomes

#### Adverse events

There were 358 total AE captured during the study period, of which 171 were considered to be possibly, probably, or definitely related to imatinib. All AE at least possibly related to imatinib and occurring in more than one patient are presented in table 2. Of these 171 AE, 72.5% were grade 1, 25.1% were grade 2 and 2.4% were grade 3 or 4 in severity. The most common AE was oedema, which was seen in 80% of patients. Fluid-related issues required the addition of furosemide in 60% of patients and dose adjustment in 30%. All AE captured regardless of attribution are required hospitalisation for diuresis. This episode occurred in the context of the patient receiving fluid resuscitation for a severe haemorrhoidal bleed. The patient subsequently tolerated reintroduction and treatment with imatinib 300 mg daily with concomitant furosemide administration.

### Chest radiography and echocardiography

Postero-antero and lateral chest radiographs and transthoracic two-dimensional echocardiograms were performed at baseline and after 12 months of treatment. Twenty-three of 24 chest radiographs were unchanged. One patient with ILD developed increased infiltrates on the follow-up study, which was further evaluated with high resolution CT and found to be unchanged from baseline.

Three patients had echocardiographic changes during the course of the trial, two of which were of clinical significance. One patient, who did not complete the trial, developed cardiomyopathy with congestive heart failure at a point when she had largely discontinued the medication. The patient’s treating physicians felt the cardiomyopathy was a result of ischaemic heart disease and was tachyarrhythmia mediated, and the investigators attributed this SAE as possibly related to imatinib. Two additional patients had declines in EF as noted on surveillance echocardiography from baseline normal EF to EF of 50–55%. One patient followed up with a cardiac MRI and was found to have a normal EF of 60%. The other patient underwent a multigated image acquisition scan, which confirmed the decline in EF. This patient had experienced disease progression in pulmonary, gastrointestinal and cutaneous manifestations, and the cardiomyopathy was felt to be most likely related to the progression of disease.

### Modified Rodnan skin score

There was a significant improvement of the MRSS over the course of 1 year with treatment with imatinib. At 12 months...
but there was no difference between the groups with respect to the change in DLCO (p=0.19; table 4). Differences were not seen in PFT changes based on disease duration or based on anti-
scl70 status.

Additional outcomes
Outcomes regarding health-related quality of life measures are shown in table 4, with significant improvements or stabil-
ity in multiple parameters. There was no correlation between change in FVC and change in MRSS (Spearman’s rank correla-
tion −0.071).

Dermatopathology
The median skin thickness decreased with treatment from 2.23
mm (IQR 2.0–2.95) to 2.0 mm (1.81–2.36) as measured from
the granular cell layer to the dermal subcutaneous interface or
the greatest depth on H&E (p<0.01). There was a signifi-
cant increase in the number of appendageal structures (hair follicles
plus eccrine glands) counted per vertical section from two (one
to four) to three (two to six); p=0.03. All specimens before treat-
ment exhibited changes typical of scleroderma including thick
and hyalinised collagen bundles with decreased interstitial
spaces. Nine of the pretreatment specimens exhibited artefact
from overfi xation, which precluded comparative assessment
with the post-treatment specimen. Of the 10 assessable speci-
mens, seven exhibited a qualitative decrease in the thickness
of collagen bundles and increase in interstitial spaces (fi gure 2).
One specimen had increased sclerodermatous characteristics
and two were unchanged. The morphological differences cor-
responded to MRSS improvement with the mean change in
MRSS in the group with histological improvement being −8.8

Figure 1 Modified Rodnan skin score (MRSS) over the duration of the trial in all patients on treatment. At baseline the MRSS was 30.3±8.7
(n=30). After 3 months of imatinib therapy the MRSS was 29.9±9.4 compared with a baseline mean of 30.4±9.1 in this group (n=27); p=0.428.
After 6 months the MRSS was 26.1±9.1; p<0.001 compared with baseline mean of 30.6±9.2 in this group (n=26). After 9 months the MRSS was
25.3±9.7; p<0.001 (n=26). After 12 months of treatment the mean MRSS was 22.8±10.2 compared with a baseline MRSS of 29.4±8.6 in this
group (n=24); p<0.001. (A) As bar chart and (B) as individual patient plots. Black line is mean trendline.
making attribution of improvements in clinical outcomes as well as of AE and SAE uncertain. Furthermore, this was a heterogeneous population in terms of disease duration, organ system involvement and previous treatment history, making it difficult to compare this experience with trials including only early active SSc patients.

While patients in our trial had relatively early disease (mean disease duration 3.4 years), we prospectively elected to enroll 10 patients with later disease (4–10 years), appreciating that this subgroup is also in need of better therapies. Their inclusion in this pilot study was necessary to establish the tolerability and safety of this potentially antifibrotic therapy in later-stage patients, which would be requisite for their inclusion in future controlled studies. We recognise that including this subgroup adds to the difficulty in interpreting the significance of the improvements observed in our trial. Encouragingly, however, similar improvements were also seen in patients with very early (<18 months) disease duration. Nevertheless, definitive conclusions regarding efficacy cannot be drawn from an open-label

| Subgroup (n) | MRSS at baseline mean (SD) | MRSS at 12 months mean (SD) | Mean change in MRSS (SD) | p Value | % Change in MRSS |
|--------------|----------------------------|-----------------------------|--------------------------|---------|------------------|
| Duration of disease <18 months (n=8) | 26.8 (9.6) | 18.9 (11.6) | −7.9 (5.2) | 0.006 | −29.5 |
| Duration of disease <4 years (n=17) | 28.8 (9.0) | 23.0 (11.2) | −5.8 (5.1) | <0.001 | −20.1 |
| Duration of disease 4–10 years (n=7) | 30.9 (7.9) | 22.3 (8.0) | −8.6 (4.1) | <0.001 | −27.8 |
| All completers (n=24) | 29.4 (8.6) | 22.8 (10.2) | −6.6 (4.7) | <0.0001 | −22.4 |

MRSS, modified Rodnan skin score.

**DISCUSSION AND CONCLUSIONS**

Tyrosine kinase inhibition has emerged as a therapeutic approach of interest in scleroderma and other fibrosing disorders. This study represents the largest prospective trial of imatinib in dcSSc reported to date. Our results indicate acceptable safety and tolerability, and suggest the potential efficacy of imatinib for cutaneous and pulmonary manifestations of dcSSc, as well as benefit in patient-derived subjective outcomes. The strengths of this study include the number of patients treated, its prospective design and its relatively long duration. The obvious weakness is the open-label design and lack of a control group, making attribution of improvements in clinical outcomes as well as of AE and SAE uncertain. Furthermore, this was a heterogeneous population in terms of disease duration, organ system involvement and previous treatment history, making it difficult to compare this experience with trials including only early active SSc patients.

While patients in our trial had relatively early disease (mean disease duration 3.4 years), we prospectively elected to enroll 10 patients with later disease (4–10 years), appreciating that this subgroup is also in need of better therapies. Their inclusion in this pilot study was necessary to establish the tolerability and safety of this potentially antifibrotic therapy in later-stage patients, which would be requisite for their inclusion in future controlled studies. We recognise that including this subgroup adds to the difficulty in interpreting the significance of the improvements observed in our trial. Encouragingly, however, similar improvements were also seen in patients with very early (<18 months) disease duration. Nevertheless, definitive conclusions regarding efficacy cannot be drawn from an open-label

![Figure 2](image_url)
experience, especially noting that spontaneous improvements in skin scores can be seen even in patients with early stage dcSSc in clinical trials or observational studies. Although the blinded dermatopathological assessments support our clinical findings, attribution of these improvements to treatment is uncertain without a longitudinal control group.

A large number of AE and SAE were recognised during this 1-year trial, which may relate in part to our patients’ significant disease burden. However, 80% of patients enrolled were able to complete a full year of therapy. This number compares favourably to what has been observed in other clinical trials in scleroderma, but not surprisingly is less than expected to complete a full year of therapy. This number compares favourably to what has been observed in other clinical trials in scleroderma, but not surprisingly is less than expected to complete a full year of therapy.

In conclusion, this study represents the largest and longest double-blind placebo controlled trial in idiopathic pulmonary fibrosis. Side effects were common, but most patients tolerated the medication. Signals of potential efficacy were observed in MRSS, FVC and patient-derived quality of life indices. These findings cannot be definitively attributed to medication effect in an uncontrolled trial but deserve further investigation. A prospective randomised, double-blind, placebo controlled trial is warranted to define more clearly whether there is a role for tyrosine kinase inhibition in the treatment of dcSSc.

### References
1. Varga J, Abraham D. Systemic sclerosis: a prototypic multisystem fibrotic disorder. J Clin Invest 2007;117:557–67.
2. Varga J, Whitfield ML. Transforming growth factor-beta in systemic sclerosis (scleroderma). Front Biosci (Schol Ed) 2009;4:226–35.
3. Leask A, Abraham DJ. TGF-beta signaling and the fibrotic response. FASEB J 2004;18:816–27.
4. Higley V, Persichitte K, Chu S, et al. Immunochemical localization and serologic detection of transforming growth factor beta 1. Association with type I procollagen and inflammatory cell markers in diffuse and limited systemic sclerosis, morphea, and Raynaud’s phenomenon. Arthritis Rheum 1994;37:278–88.
5. Trojanowska M. Role of PDGF in fibrotic diseases and systemic sclerosis. Rheumatology (Oxford) 2008;47(Suppl 5):v2–4.
6. Klareskog L, Gustafsson R, Scehynius A, et al. Increased expression of platelet-derived growth factor type B receptors in the skin of patients with systemic sclerosis. Arthritis Rheum 1998;41:1534–41.
7. Baroni SS, Santillo M, Bevilacqua E, et al. Stimulatory autoantibodies to the PDGF receptor in systemic sclerosis. N Engl J Med 2006;354:2667–76.
8. Dragun D, Distler JH, Riemekasten G, et al. Stimulatory autoantibodies to platelet-derived growth factor receptors in systemic sclerosis: what functional autobody could learn from receptor biology. Arthritis Rheum 2009;60:907–11.
9. Distler JH, Distler O. Intracellular tyrosine kinases as novel targets for anti-fibrotic therapy in systemic sclerosis. *Rheumatology (Oxford)* 2008;47(Suppl 5):v10–11.
10. Rosenbloom J, Castro SV, Jimenez SA. Narrative review: fibrotic diseases: cellular and molecular mechanisms and novel therapies. *Ann Intern Med* 2010;152:759–66.
11. Distler JH, Jungel A, Huber LC, et al. Imatinib mesylate reduces production of extracellular matrix and prevents development of experimental dermal fibrosis. *Arthritis Rheum* 2007;56:311–22.
12. Daniels CE, Wilkes MC, Edens M, et al. Imatinib mesylate inhibits the profibrogenic activity of TGF-beta and prevents bleomycin-mediated lung fibrosis. *J Clin Invest* 2004;114:1308–16.
13. Akhmetshina A, Venalis P, Dees C, et al. Treatment with imatinib prevents fibrosis in different preclinical models of systemic sclerosis and induces regression of established fibrosis. *Arthritis Rheum* 2008;60:219–24.
14. Li M, Abdollahi A, Gröne HJ, et al. Late treatment with imatinib mesylate ameliorates radiation-induced lung fibrosis in a mouse model. *Radiat Oncol* 2009;4:66.
15. Akhmetshina A, Dees C, Fieclelyte M, et al. Dual inhibition of c-ABL and PDGF receptor signaling by dasatinib and nilotinib for the treatment of dermal fibrosis. *FASEB J* 2008;22:2214–22.
16. van Daele PL, Dik WA, Thio HB, et al. Is imatinib mesylate a promising drug in systemic sclerosis? *Arthritis Rheum* 2008;58:2549–52.
17. Sfi kakis PP, Gorgoulis VG, Katsiari CG, et al. Imatinib for the treatment of refractory, diffuse systemic sclerosis. *Rheumatology (Oxford)* 2008;47:735–7.
18. Chung I, Fiorentino DE, Benbarak MJ, et al. Molecular framework for response to imatinib mesylate in systemic sclerosis. *Arthritis Rheum* 2009;60:584–91.
19. Distler JH, Manger B, Spriewald BM, et al. Treatment of pulmonary fibrosis for twenty weeks with imatinib mesylate in a patient with mixed connective tissue disease. *Arthritis Rheum* 2008;58:2538–42.
20. Kay J, High WA. Imatinib mesylate treatment of nephrogenic systemic fibrosis. *Arthritis Rheum* 2008;58:2543–8.
21. Magro L, Mothy M, Catteau B, et al. Imatinib mesylate as salvage therapy for refractory sclerotic chronic graft-versus-host disease. *Blood* 2009;114:719–22.
22. Olivieri A, Locatelli F, Zucca M, et al. Imatinib for refractory chronic graft-versus-host disease with fibrotic features. *Blood* 2009;114:709–18.
23. Daniels CE, Lasky JA, Limper AH, et al. Imatinib treatment for idiopathic pulmonary fibrosis: randomized placebo-controlled trial results. *Am J Respir Crit Care Med* 2010;181:604–10.
24. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980;23:581–90.
25. Trott A, Colevas AD, Sztzer A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* 2003;13:76–81.
26. Khanna D, Forst DE, Hays RD, et al. Minimally important difference in diffuse systemic sclerosis: results from the d-penicillamine study. *Ann Rheum Dis* 2006;65:1325–9.
27. Gordon JK, Magid SK, Maki RG, et al. Elevation of creatine kinase in patients treated with imatinib mesylate (Gleevec). *Leuk Res* 2010;34:827–9.
28. Franceschini A, Tomaghi L, Benemacher V, et al. Alterations in creatine kinase, phosphate and lipid values in patients with chronic myeloid leukemia during treatment with imatinib. *Haematologica* 2008;93:317–18.
29. Amjadi S, Maranian P, Forst DE, et al. Course of the modified Rodnan skin thickness score in systemic sclerosis clinical trials: analysis of three large multicenter, double-blind, randomized controlled trials. *Arthritis Rheum* 2009;60:2490–8.
30. Herrick AL, Lunt M, Whidby N, et al. Observational study of treatment outcome in early diffuse cutaneous systemic sclerosis. *J Rheumatol* 2010;37:116–24.
31. Denton CP, Minkel PA, Forst DE, et al. Recombinant human anti-transforming growth factor beta1 antibody therapy in systemic sclerosis: a multicenter, placebo-controlled phase II/II trial of CAT-192. *Arthritis Rheum* 2007;56:323–33.
32. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006;354:2655–66.
33. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum* 2006;54:3962–70.
34. Clements PJ, Forst DE, Wong WK, et al. High-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis: analysis of a two-year, double-blind, randomized, controlled clinical trial. *Arthritis Rheum* 1999;42:1194–203.
35. Johnson JR, Broz P, Cohen M, et al. Approval summary: imatinib mesylate capsules for treatment of adult patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase. *Clin Cancer Res* 2003;9:1972–9.
36. Atallah E, Durand JB, Kantarjian H, et al. Congestive heart failure is a rare event in patients receiving imatinib therapy. *Blood* 2007;110:1233–7.
37. Wells AU, Behr J, Silver R. Outcome measures in the lung. *Rheumatology (Oxford)* 2008;47(Suppl 5):v48–50.