# Imatinib mesylate (Gleevec™) in the treatment of diffuse cutaneous systemic sclerosis: results of a 24-month open-label, extension phase, single-centre trial

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## ABSTRACT

**Objective.** *We aimed to assess the long-term safety and tolerability of imatinib in diffuse cutaneous systemic sclerosis (dcSSc).*

**Methods.** *In this open-label, single-arm, extension-phase clinical trial, patients continued imatinib for 24 months following 12 months of initial treatment.*

**Results.** *Seventeen patients were enrolled. Forty of 92 adverse events (AE) and 0/6 serious (S) AEs were possibly related to medication. The MRSS decreased from a median of 21 to 16, (p=0.002).*

**Conclusions.** *This study demonstrates long-term safety and tolerability of imatinib in a substantial proportion of patients with dcSSc. This is important in evaluating the relevance of this therapy in a chronic disease such as SSc.*

## Introduction

The therapies currently available to treat the skin disease associated with diffuse cutaneous Systemic Sclerosis (dcSSc) are not universally effective (1), and the treatment of scleroderma skin involvement is an important and unmet need. Transforming growth factor beta (TGF-β) and the platelet-derived growth factor (PDGF) are cytokines implicated in the pathological fibrosis of dcSSc (2, 3). Imatinib mesylate (Gleevec; Novartis Pharmaceuticals, Basel, Switzerland) is a tyrosine kinase inhibitor (TKI) with antagonistic activity against c-Abl, the PDGF receptor (PDGFR) and has been shown to interfere with both TGF-β and PDGF-mediated fibrosis in *in vitro* and in murine models of SSc as well as in gene expression studies (4, 5).

Several groups have studied imatinib in patients with dcSSc (6-9) and the results have been mixed. Adverse Events (AEs), especially fluid retention and gastrointestinal (GI) upset, were observed in all studies, and none definitively answered whether there is a role for imatinib in the treatment of dcSSc due to various study design limitations and flaws (10).

In our initial open-label, single-centre study, 24/30 patients completed 12 months of treatment (11). AEs were common but manageable in most cases with dose reduction or diuretic use. Twenty-four serious (S)AE were observed but most were not related to the medication. Patients demonstrated an improvement in the MRSS by 6.6 points or 22.4% at 12 months ($p$=0.001). Forced vital capacity (FVC) improved and diffusion lung capacity of carbon monoxide (DLCO) remained stable. We report here the results of a 24-month extension phase of this trial with such long-term safety data relevant in a chronic disease like dcSSc.

## Patients and methods

*Study design*

This was an investigator-initiated, phase IIa, single-centre, single-arm, open-label clinical trial in extension phase. The primary endpoint of this study was description of AEs and SAEs.

The protocol was approved by our institutional review board. Patients provided written informed consent. An independent data and safety monitoring board regularly reviewed safety data. The trial was registered at ClinicalTrials.gov (NCT00555581).

Patients who completed the initial phase of the trial were offered inclusion in the extension phase at their follow-up visit 3 months after stopping imatinib and within 6 months (12). Concomitant immunosuppressive therapy was not allowed. Enrolled patients were assessed every 3 months by history, physical examination including MRSS and blood-work. MRSS was

performed by the same examiner at each visit (RS or JG.) AEs were listed according to the National Cancer Institute's common terminology (12).

Baseline data at the time of enrolment into extension-phase is presented in Table I. The median disease duration since initial non-Raynaud's symptom of SSc was 3.5 (2.5, 4.75) years.76% were female. 29% of patients were anti-topoisomerase positive. 26% of patients had ILD, 6% of patients had pulmonary arterial hypertension, 100% of patients had some degree of GI involvement. Patients known to have myocardial involvement due to scleroderma or otherwise were excluded.

Annual echocardiography was performed to assess for cardiomyopathy. Pulmonary Function Test (PFT) and Computerised Tomography (CT) of the chest were performed as part of standard of care.

Patients were treated with imatinib from 100 to 400 mg daily by mouth. Dose modifications and interruptions were allowed for AE and were recorded.

*Statistical analysis*

The primary endpoint was a description of AEs and SAEs. Paired *t*-tests, Wilcoxon signed-rank tests, and unpaired *t*-tests were used as indicated. The generalised estimating equation was used to analyse MRSS over the entire course of treatment. Statistical analysis was performed using SPSS software v.17.0.

**Table I.** Extension phase baseline demographic and disease-related data (n=17).

| Characteristic | |
|---|---|
| Age – median (IQR) | 49 (41, 54) |
| Sex, no. (%) female | 13 (76%) |
| Race, Ethnicity, no. (%) | |
| Caucasian | 11 (65%) |
| Hispanic | 2 (12%) |
| African American | 4 (23%) |
| Disease duration – median (IQR) | 3.5 (2.5, 4.75) |
| SHAQ-DI – median (IQR) | 1.3 (0.9, 1.6) |
| Autoantibody status (% of 17) | |
| Anti-topoisomerase positive – n (%) | 5/17 (29%) |
| Anti-RNA Polymerase 3 | 1/8 |
| U1-RNP | 1/9 |
| Anti-centromere | 0/5 |
| MRSS at initial baseline, median (IQR) | 27 (23, 40) |
| MRSS at extension baseline, median (IQR) | 24 (18, 31) |
| ILD at baseline - n (%) | 4 (26%) |
| Previous treatments* | None 2/17<br>Prednisone 9/17<br>Methotrexate 5/17<br>Hydroxychloroquine 4/17<br>Mycophenolate mofetil 3/17<br>Cyclophosphamide – 2/17<br>Tetracyclines 2/17<br>Penicillamine – 1/17<br>IVIG – 1/17<br>Thalidomide – 1/17 |
| Concomitant treatments | Prednisone ≤10 mg -2/17<br>Hydroxychloroquine – 2/17<br>Proton pump inhibitor - 13/17<br>Calcium channel blocker - 12/17 |

*Previous treatments were prior to enrolment in initial phase of study. Treatment with immunosuppressive or putative anti-fibrotic therapy was not allowed in the initial or extension phases of study.

## Results

Between February 2009 and December 2010, 17 of 24 eligible patients enrolled. Of those 7 who did not enrol, 5 were considered clinical responders with a mean initial MRSS improvement of -8.4. Three declined extension as they felt their disease was quiescent, 1 was not offered enrolment due to non-adherence with general medical recommendations, and the study was not available to 1 due to timing. Of the 5 responders, 1 had an increase in MRSS years later, but not all patients continued follow-up at our centre. Fifteen of 17 patients continued treatment for an additional 12 months and 13 for an additional 24 months.

Four patients withdrew from extension. One patient withdrew after 6 days of retreatment. This patient experienced substantial progression of disease during 4 months off imatinib and after enrolment, the treating physicians decided immunosuppressive treatment was most prudent. One patient discontinued due to an asymptomatic cerebral aneurysm noted incidentally which required surgical repair. One patient moved, and one was lost to follow-up. Safety data are included on all 17 patients enrolled.

*Adverse events*

There were 92 total AEs observed during the study period, of which 40 were considered to be possibly, probably, or definitely related to imatinib. Of these 40 AEs, 88% were grade 1 and 12% were grade 2. The most common AEs were fatigue and oedema, both seen in 35% of patients (Table II). Cardiomyopathy, which has been a concern with imatinib, was not seen when assessed with annual echocardiography. 29% of patients required dose adjustment during the extension phase, and the median dose taken as confirmed by pill count was 300 mg daily. The leading causes for dose adjustment or interruption were dyspepsia, fatigue, and oedema. Myalgia and mild CK elevation, not necessarily in association, were observed during the extension phase, but increasing muscle weakness was not observed as assessed by serial examination.

There were 6 SAEs (Table II) observed during the study period. No deaths occurred.

*Modified Rodnan skin score*

During the 3-month period off imatinib

**Table II.** Adverse events.

| AE at least possibly related Event (in order of frequency) | SAE % pts | Event | Number | Attribution |
|---|---|---|---|---|
| Fatigue | 35.3 | Anaemia* | 1 | not related |
| Oedema | 35.3 | Pneumonia* | 1 | not related |
| Muscle Pain | 29.4 | renal failure* | 1 | not related |
| Nausea | 23.5 | hospitalisation for chest pain‡ | 1 | not related |
| Hand Cramping | 11.8 | hospitalisation for fundoplication procedure | 1 | not related |
| Diarrhea | 11.8 | hospitalisation for arterial blood clot | 1 | unlikely related |
| CPK Elevation | 11.8 | | | |
| Anaemia | 5.9 | | | |
| Constipation | 5.9 | | | |
| Cramps in feet | 5.9 | | | |
| Hair loss | 5.9 | | | |
| Hypocalcaemia | 5.9 | | | |
| Hypophosphataemia | 5.9 | | | |
| Lateral epicondylitis | 5.9 | | | |
| LFTs elevated (<2x normal) | 5.9 | | | |
| Menstrual irregularity | 5.9 | | | |
| Pyrosis | 5.9 | | | |
| Skin fragility | 5.9 | | | |
| Weight gain | 5.9 | | | |

Adverse Events: *These events occurred in a single patient who had experienced an MRSS improvement from 43 to 30 and the FVC from 58% to 78% predicted in the initial phase of the trial. During a four-month period off of imatinib the patient experienced a progression of disease characterised by worsening of anaemia, weight loss, inflammatory myositis, interstitial lung and skin disease, with MRSS increasing to 35. Since the patient had had a significant clinical improvement previously, imatinib was reinitiated, but then reconsidered in favour of an immunosuppressive regimen and the patient was withdrawn from the study. The patient was later (but within 3 months of last imatinib dose) hospitalised with pneumonia, anaemia, exacerbation of pre-existing inflammatory myositis, and exacerbation of scleroderma and ILD. This was treated with high-dose corticosteroids and cyclophosphamide and the patient later developed renal failure due to scleroderma renal crisis 3 months after discontinuation from the trial. ‡Patient was hospitalised for chest pain work-up that was related to GERD.

prior to enrolment in extension phase, the median MRSS (n=17) was not significantly different (23 to 24, $p$=0.10), but the range of change in MRSS during this period was from -4 to +9 demonstrating that some patients experienced a clinically important increase in the MRSS during this 3-month period off imatinib (Fig 1a.). During the extension period, the MRSS decreased from a median of 24 (IQR 18, 31) to 18 (13, 29) with an additional 12 months of imatinib ($p$=0.08, n=15), and from 21 (18, 28) to 16 (13, 24) with an additional 24 months of treatment ($p$=0.002, n=13) (Fig. 1b.).

*Pulmonary function testing*

PFTs were performed as part of standard clinical care and as such were performed on different machines, which introduces variability (13). Changes in PFT parameters are shown in Table III. During this 2-year extension phase, two patients developed incident mild ILD as defined by characteristic changes noted on HRCT accompanied by decline in DLCO. Neither patient was symptomatic. These 2 patients are included in the group without ILD at baseline.

*Additional outcomes and observations*

No significant change was observed in the SF-36 mental or physical component, SHAQ-DI, ESR, or Physician Global Assessment. Patients returned for a 3 month follow-up visit after discontinuing imatinib and no significant change in MRSS was observed during that period of time. Of the 13 patients who completed the trial, 8 patients have continued follow-up in the offices of RS or JG. Of those 8, 3 patients have had significant exacerbations of skin disease during an additional 6 to 12 months off of imatinib.

**Table III.** Results.

| | Extension Month 0 | Extension Month 24 | $p$-value |
|---|---|---|---|
| MRSS – median (IQR) | 21 (18,28) | 16 (13,24) | 0.002 |
| FVC –% predicted – median (IQR) (n=13) | 92 (73, 105) | 83 (68, 102) | 0.11 |
| DLCO -% predicted – median (IQR) (n= 13) | 77 (63, 108) | 74 (52, 91) | 0.012 |
| ILD* (n=4) | | | |
| FVC -% pred | 67 (60.5, 77.25) | 62.5 (56.75, 68) | 0.25 |
| DLCO -% pred | 60.5 (57, 63) | 50 (47, 52.75) | 0.125 |
| No ILD (n=9) | | | |
| FVC -% pred | 102 (92, 105) | 98 (83, 108) | 0.34 |
| DLCO -% pred | 100 (77, 110) | 83 (74, 93) | 0.078 |
| ESR (mm/hr) | 19 (9,36) | 21 (4.25, 40.25) | 0.97 |
| SHAQ-DI | 1.375 (1, 1.625) | 1.25 (0.875, 1.5) | 0.52 |
| SF36-MC | 81 (62.3, 85.8) | 61.9 (50.1, 82.4) | 0.075 |
| SF36-PC | 71.2 (54.8, 74.2) | 69.2 (45.6, 75.8) | 0.62 |
| Physician Global Assessment (100 mm) | 49.5 (34.0, 60.8) | 48.4 (18.6, 57.7) | 0.065 |
| VAS SOB (100 mm) median (IQR) n=13 | 0 (0,16.7) | 0 (0, 4.7) | 0.722 |

*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.

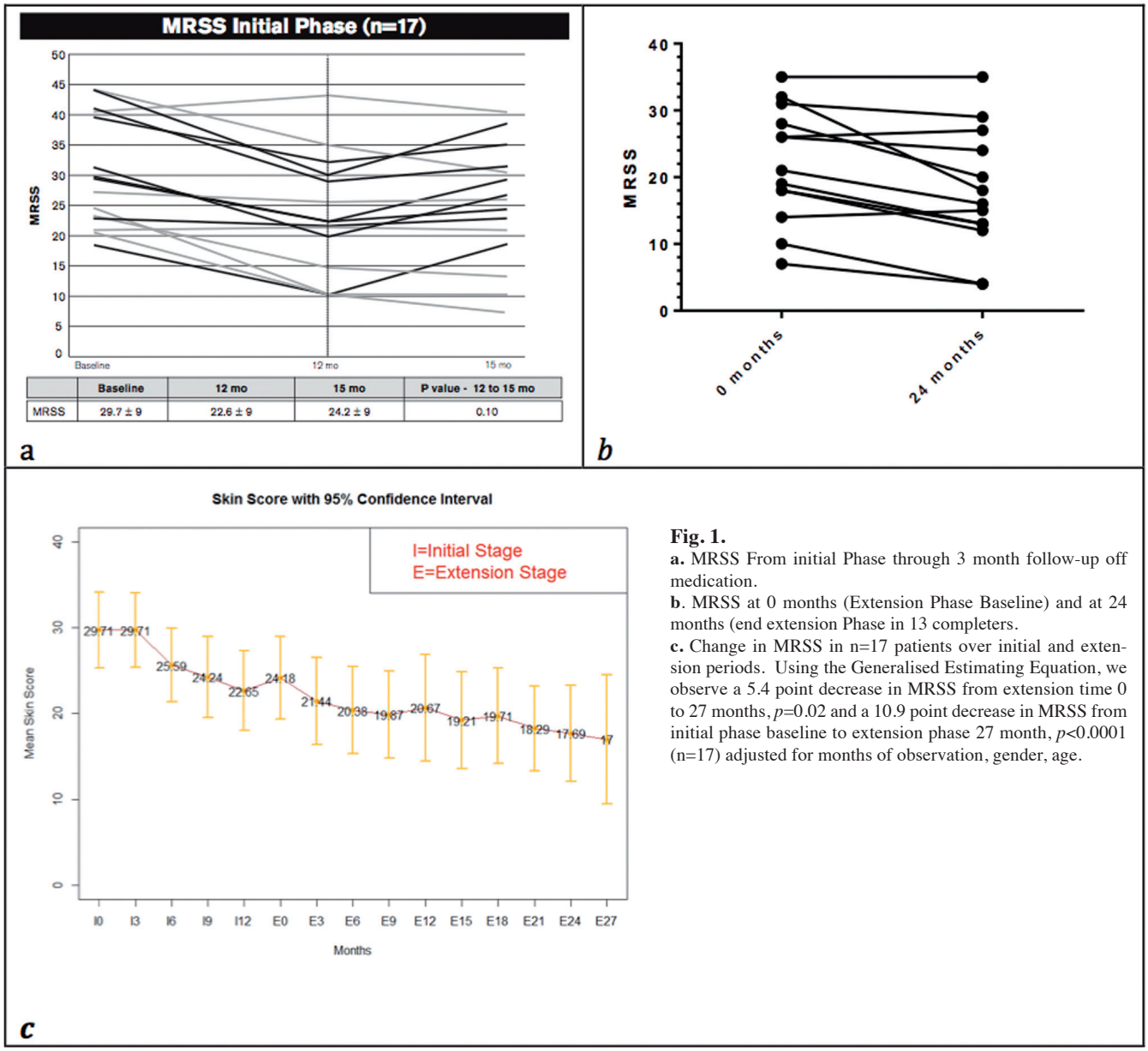


**Fig. 1.**
**a.** MRSS From initial Phase through 3 month follow-up off medication.
**b**. MRSS at 0 months (Extension Phase Baseline) and at 24 months (end extension Phase in 13 completers.
**c.** Change in MRSS in n=17 patients over initial and extension periods. Using the Generalised Estimating Equation, we observe a 5.4 point decrease in MRSS from extension time 0 to 27 months, $p$=0.02 and a 10.9 point decrease in MRSS from initial phase baseline to extension phase 27 month, $p$<0.0001 (n=17) adjusted for months of observation, gender, age.

## Discussion

Tyrosine kinase inhibition has emerged as a therapeutic approach of interest in scleroderma. To date, most studies addressing this strategy have evaluated imatinib, but due to study design limitations none have definitively demonstrated efficacy or inefficacy of the drug. In this 2-year open-label, extension study of 17 patients, relative safety was observed with a lower rate of AEs and SAEs than in the initial phase. This is likely to be due in part to patient selection with those with difficulty tolerating imatinib (whether due to medication or disease-related issues) discontinuing during the initial phase. Over the entire 3-year period of observation, oedema, CK elevations, fatigue and GI side effects were less of a problem as time went on. This points to the observation that tolerability issues may be seen when the medication is first initiated, but may resolve with time as with many other medications used in the treatment of rheumatic disease. Cardiotoxicity has been a potential concern with imatinib (14); however, this was not observed in these patients based on serial echocardiography, which may not exclude asymptomatic or subclinical cardiac effect. The present study is the longest and largest description of the use of imatinib in the dcSSc population. Side effects in this study were manageable in the majority of patients enrolled. Although this study with its open-label design does not answer whether imatinib is efficacious in the treatment of dcSSc, it does offer reassurance with respect to the long term safety and tolerability of its use in patients with dcSSc. This is important to demonstrate in a chronic disorder like scleroderma which requires long-term treatment.

We observed a significant improvement in the MRSS with a median improvement of 5 points at 24 months in those who completed this study. This observation is inconclusive given the uncontrolled study design and the observation that the MRSS tends to improve both with time (15) and in the context of clinical trials (16). It is interesting

to note that a subset of our patients demonstrated exacerbation of MRSS after discontinuing the medication; this would not be expected if improvement of MRSS related only to natural history of skin disease. Given that this was only seen in a subset of patients, it also points to a potentially heterogeneous response to medication. A potentially heterogeneous response is further supported by the observation that baseline patterns of gene expression in the skin were different between those who responded to imatinib and those who did not (17). Differential levels of target activation have been observed in different animal models of fibrosis which had divergent responses to TKIs (18). It is conceivable that different patients may have different levels of target activation, although this was not assessed in our study. We did observe a degree of decline in pulmonary function testing in this study as well as two incident cases of ILD. There were methodological issues with PFTs performed as part of standard clinical care, and this observation is not conclusive.

In summary, this study shows tolerability of long term imatinib treatment in a subset of dcSSc patients. Signals of potential efficacy with imatinib have been observed by our group as well as others and deserve more conclusive investigation.

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