Tyrosine kinase inhibitors in the treatment of systemic sclerosis  A systematic review

Kirsten I.M. Looman, Jordi de Winkel, Virgil A.S.H. Dalm

a Medical Student, Erasmus MC University Medical Center Rotterdam, The Netherlands
b Supervisor, Department of Immunology, Erasmus MC University Medical Center Rotterdam, The Netherlands
Correspondence: Kirsten Looman, e-mail: 367296kl@student.eur.nl

Abstract
Objective: The objective of this systematic review is to determine the efficacy and safety of tyrosine kinase inhibitors (TKIs) in the treatment of systemic sclerosis.

Methods: A systematic literature search for clinical trials that describe the efficacy of TKIs in the treatment of systemic sclerosis (SSc) was performed in MEDLINE. Our primary outcome measures included forced vital capacity (FVC %), modified Rodnan skin thickness score (MRSS) and diffusion capacity for carbon monoxide (DLCO). A quality assessment for the included studies was performed.

Results: Five clinical trials have been included, in which a total of 79 patients were treated with imatinib and 14 patients with placebo therapy. Two clinical trials reported significant improvement in skin disease and one showed FVC % improvement.

Conclusion: The studies did not provide enough evidence to conclude that the treatment with imatinib benefits all patients with SSc. The total dropout rate because of imatinib-related adverse events was 20%.

Introduction
Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by immune cell activation, vasculopathy and excessive fibrosis in various tissues.[1] Current treatment options are limited and include immunosuppressive therapies like methotrexate and mycophenolic acid. However, the mortality rate is approximately five- to eightfold higher than that of the general population, when adjusted for age and gender.[2] Pulmonary fibrosis and/or pulmonary hypertension are the main causes of mortality in patients with SSc.[2-4]

In the pathogenesis of systemic sclerosis transforming growth factor beta (TGFβ), Smad, Abelson kinase (c-abl) and platelet-derived growth factor receptor (PDGFR) play a crucial role.[1,5-8] In serum of SSc patients increased levels of fibroblast-stimulating autoantibodies such as cenpA, cenpB, scl-70 and platelet-derived growth factor (PDGF) are found when compared to healthy controls.[7]

Imatinib mesylate (Gleevec) was initially developed for the treatment of patients with chronic myeloid leukemia (CML). In CML imatinib mesylate inhibits the activity of the fusion protein Bcr-Abl, which is the main cause of disease in CML.[9] Imatinib mesylate is a tyrosine kinase inhibitor (TKI) that blocks the activity of c-abl, Smad1 and PDGF, hereby inhibiting the fibrotic response.[8]

An important feature in the development of fibrotic diseases is the overstimulation of the PDGFR and TGFβ-receptor pathways in fibroblasts that induce synthesis of extracellular matrix (ECM). Stimulation of TGFβ-receptors contributes to production of various types of collagen, fibronectin and actin.[8] Both PDGFR and TGFβ-receptor are transmembrane receptors that, after stimulation, form intracellular dimers through phosphorylation. These dimers activate protein complexes such as smad4 for TGFβ-receptor and the P13K-pathway for PDGFR. Smad proteins are intracellular proteins that are able to act as transcriptional factors via binding with the promoter region of a gene.[8]

Imatinib mesylate treatment results in dual inhibition of the PDGF and the TGFβ signalling pathway by blocking the downstream mediators smad3 and c-abl of TGFβ and by blocking PDGFR.[10] This is illustrated in figure 1. Imatinib mesylate has shown to be effective in murine and in in vitro models of fibrosis and was found to reduce collagen production.[10]
Systematic review

The first case-report of a patient with SSc responding to treatment with imatinib mesylate was published in 2008. [11] Subsequently, case-reports and the first clinical trials followed. However, definitive evidence of the efficacy and safety of imatinib mesylate has not been delivered. Therefore, it remains unclear what the current role of imatinib mesylate is in the treatment of SSc.

The main objective of this systematic review is to analyse all clinical trials that describe the efficacy and safety of tyrosine kinase inhibitors in the treatment of SSc.

Methods
Search strategy
A systematic literature search for relevant studies was conducted on 9 January 2014 in Medline/Pubmed. The following search criteria were used: “Scleroderma, Systemic”[Mesh] AND “Protein Kinase Inhibitors”[Mesh] AND Clinical trial[ptyp]. Only articles written in English were included. Additionally, our research was limited to human subjects. Our last search was performed on 27 January 2014.

Criteria for studies included in this review
Exclusively clinical trials that described the efficacy of TKIs in the treatment of SSc were included. There were no limitations in outcome measures used.

Study selection
We separately screened all abstracts and individually assessed full-text articles for eligibility. The articles were assessed according to the criteria mentioned under “criteria for studies included in this review”.

Data extraction
We analysed the outcome measures forced vital capacity (FVC%), modified Rodnan skin thickness score (MRSS) and diffusion lung capacity for carbon monoxide (DLCO) to compare the efficacy of imatinib mesylate on the skin and lungs reported in the included studies. The FVC%, MRSS and DLCO are commonly used parameters to define the severity of SSc. When the outcome parameters reported significant improvement, the treatment was considered effective.

Results
Overview of study characteristics
Our systematic literature search resulted in five relevant studies. [12-16] After application of the inclusion criteria these five articles remained. The characteristics of the studies are presented in table 1.

These studies together included 79 patients who were treated with imatinib mesylate and 14 patients on placebo therapy. All studies used the same TKI: imatinib mesylate, although different doses were used. In the study by Khanna et al.,[13] patients started at 100 mg/day and doses were increased with 100 mg every two weeks to a maximum of 600 mg/day. The mean ± SD dosage used was 445 ± 125 mg/day. The median dosage used was 400 mg/day. In the studies by Pope et al. [12] and Sabnani et al. [15] a dose of 200 mg/day was prescribed. In the studies performed by Prey et al. [14] and Spiera et al. [16] all patients started with a dose of 400 mg/day. However, in the study by Prey et al. at the end of the study the dose varied from 100-400 mg/day per patient. Patients were allowed to continue baseline therapy consisting of immunosuppressive agents, such as cyclophosphamide (CYC) in three studies.[12,14,15]

Four studies had a follow-up duration of twelve months. [13-16] The study of Pope et al. had a follow-up duration of six months.[12]

Various endpoints were described to measure the clinical improvement of SSc. Four studies used DLCO [13-16], three studies used FVC% [13,15,16] and four studies used MRSS. [12-14,16]

Overview of study results: efficacy
An overview of the study results on efficacy is presented in table 2.

A one-year phase I/II, open-label pilot trial performed by Khanna et al. reported an increase in FVC% and DLCO (respectively 1.74% and 1.46%). However, this increase was not significant (P>0.05).[13]
Table 1 - Study characteristics

<table>
<thead>
<tr>
<th>Author</th>
<th>QA*</th>
<th>Population (n)</th>
<th>Mean age of patients (years)</th>
<th>Gender (Female)</th>
<th>Dose of imatinib mesylate used</th>
<th>Duration of follow-up (months)</th>
<th>Outcome measures</th>
<th>Co-medication used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khanna et al.</td>
<td>2</td>
<td>20</td>
<td>46.1</td>
<td>65%</td>
<td>600 mg/day (started at 100 mg/day and increased 100 mg every 2 weeks)</td>
<td>12</td>
<td>DLCO**</td>
<td>No</td>
</tr>
<tr>
<td>Pope et al.</td>
<td>3</td>
<td>10</td>
<td>51</td>
<td>70%</td>
<td>200 mg/day</td>
<td>6</td>
<td>DLCO</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Prey et al.</td>
<td>5</td>
<td>28</td>
<td>48.9</td>
<td>61%</td>
<td>400 mg/day</td>
<td>12</td>
<td>DLCO</td>
<td>FVC, MRSS</td>
</tr>
<tr>
<td>Sabnani et al.</td>
<td>1</td>
<td>5</td>
<td>50</td>
<td>40%</td>
<td>200 mg/day</td>
<td>12</td>
<td>DLCO</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Spiera et al.</td>
<td>2</td>
<td>30</td>
<td>Median 48</td>
<td>80%</td>
<td>400 mg/day</td>
<td>12</td>
<td>DLCO</td>
<td>No</td>
</tr>
</tbody>
</table>

* QA: Quality assessment score  
** DLCO: Diffusion capacity for carbon monoxide  
*** FVC: Forced vital capacity  
**** MRSS: Modified Rodnan skin thickness score  
***** TLC: Total lung capacity

Table 1 presents the study characteristics, including: QA, number of patients included, patient characteristics, dose of imatinib mesylate used, the duration of follow-up and the outcome measures used.

Table 2 - Efficacy and adverse events reported

<table>
<thead>
<tr>
<th>Author</th>
<th>FVC after follow-up</th>
<th>MRSS after follow-up</th>
<th>DLCO after follow-up</th>
<th>Number of patients discontinued due to AE/SAE</th>
<th>AE**</th>
<th>SAE***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khanna et al.</td>
<td>+ 1.74% (P&gt;0.05)</td>
<td>Improved 3.9 units</td>
<td>Improved 1.46%</td>
<td>7 out of 20</td>
<td>5 out of 20</td>
<td>3 out of 20</td>
</tr>
<tr>
<td>Pope et al.</td>
<td>ND*</td>
<td>Improved 0.7 units</td>
<td>ND</td>
<td>5 out of 10</td>
<td>In 7 out of 10</td>
<td>ND</td>
</tr>
<tr>
<td>Prey et al.</td>
<td>ND</td>
<td>No significant</td>
<td>0.00 (-0.10 - 0.10)</td>
<td>1 out of 28</td>
<td>53 (imatinib)</td>
<td>1 patient</td>
</tr>
<tr>
<td>Sabnani et al.</td>
<td>+ 80-89% of predicted in one patient</td>
<td>ND</td>
<td>same patient 43-50% of predicted</td>
<td>3 out of 5</td>
<td>3 patients</td>
<td>0</td>
</tr>
<tr>
<td>Spiera et al.</td>
<td>Improved from a mean of 82.9±21.1% to 89.3±25.2% predicted (p=0.008)</td>
<td>Improved 6.6 points (95% CI)</td>
<td>Improved from 78.0±22.9% to 83.5±29.2% (p=0.12)</td>
<td>0 out of 30</td>
<td>total 358 AE</td>
<td>Total of 24 SAE related to imatinib</td>
</tr>
</tbody>
</table>

* ND: Not defined, the clinical trial did not include this outcome.  
** AE: Adverse event(s)  
*** SAE: Severe adverse event(s)

Table 2 presents the results of efficacy of all clinical trials included. The number of AEs and the number of patients discontinued due to AE/SAE reported are also shown. FVC, MRSS, DLCO are outcome measures for efficacy.
Spiera et al. conducted a one-year phase IIa, single-arm, open-label clinical trial.[16] In this study, FVC% significantly improved from a mean of 82.9±21.1% to 89.3±22.5% predicted (p=0.008) and the DCLO improved insignificantly from 78.0±22.9% to 83.5±29.2% (p=0.12).

Furthermore, Spiera and colleagues found that patients without interstitial lung disease showed significantly better results for treatment with imatinib mesylate than patients with interstitial lung disease (ILD).[16] In Spiera et al. patients without ILD improved on average 10.4% point with respect to their FVC% (-3.3 to 18.2; p=0.01). Patients with ILD remained stable with an average increase of 2.1% point.[16]

The phase II double-blinded randomized controlled trial performed by Prey et al.[14] did not demonstrate any significant increase in FVC% or DCLO.

Sabnani et al. included five patients with restrictive lung disease in their study.[15] Four of these patients had severe restrictive lung disease and one had mild restrictive lung disease. Only the patient with mild restrictive lung disease showed improvement. This patient improved 80-89% in FVC% and 43-50% of predicted in DCLO.[15]

Pope et al. performed a six-month, randomized, double blind, placebo-controlled pilot study, which did not measure lung function parameters but only parameters regarding cutaneous SSc.[12] The results regarding skin sclerosis will be mentioned further on.

Almost all studies reviewed the effect of imatinib mesylate on skin sclerosis. The MRSS improved in the study by Khanna et al.[13] with 3.9 points (P<0.001). Spiera et al.[16] found a 6.6-point increase (95%CI -4.5 to -8.7).

Both Pope et al.[12] and Prey et al.[14] did not report any significant difference in MRSS after follow-up.

Although there are some positive results in reduction of skin involvement, the studies with the most power of evidence based on our quality assessment did not report any success. Previous studies suggested the use of imatinib mesylate in lower dosages in order to minimalize adverse events while maintaining the reduction of skin involvement.[17] The studies included in this review did not confirm these findings.

### Overview of study results: safety

In our review 20% of the patients discontinued the study because of AEs.

In terms of treatment-related AEs, the following was found. Three studies reported patients who discontinued the study due to AEs or SAEs.[12,13,15]

Khanna et al. reported seven patients who discontinued the study, of which five patients discontinued because of AEs and three patients because of SAEs. One of these patients had both AEs and SAEs. Of the five patients reported with AEs two were also reported to have discontinued the study because of the underlying SSc. Three patients were found to develop SAEs. Of these SAEs, two were related to the underlying disease. The other SAE patient stopped the imatinib mesylate treatment because of dyspnea and generalized edema that was resistant to treatment with diuretics.[13]

In the study of Pope et al., five out of ten patients discontinued the study because of AEs. These AEs included fluid retention, weakness, nausea, vomiting and chest pain. Pope et al. study was stopped because even after reintroduction of medication of lower dosage a lack of tolerability remained.[12]

All patients tolerated the combination therapy of imatinib mesylate and CYC in the study of Sabnani et al.[15] Only one patient had periods of required intermittent discontinuation because of fluid retention due to imatinib mesylate.

In the study by Prey et al. two patients discontinued treatment as result of an AE. One of these patients terminated participation because of SAEs (anasarca) and the other temporarily quit treatment because of AEs (edema).[14]

In contrast, Spiera et al. found one imatinib-related SAE, which was fluid overload with bilateral pleural effusions.[16] Common AEs, which required dose adjustment, were musculoskeletal complaints, fluid retention, gastrointestinal complaints, intercurrent illness and constitutional symptoms.

The most frequently reported adverse events were edema and gastro-intestinal complaints.[12-14,16] Both were very likely found as result of imatinib mesylate usage. Khanna et al.[13] reported a general rash in a patient. This rash disappeared after terminating imatinib mesylate therapy, and reappeared when the therapy was resumed.

Tachyarrhythmia/ cardiomyopathy is a serious AE described in patients treated with imatinib mesylate for CML. In the studies we included this SAE was reported in one patient of the study of Spiera.[16]

An overview of the study results on AE-related study discontinuation is also presented in table 2.

### Discussion

Despite the promising results of preclinical studies and case reports, substantial benefit of imatinib mesylate in the treatment of SSc has not been proven by the clinical trials included.

One weakness of this review is the inclusion of mostly open-label clinical trials. This is due to the fact that placebo-controlled trials are difficult to perform for a rare disease like SSc. Conclusions about efficacy and safety are uncertain due to lack of a control group.

Firstly, spontaneous improvements in skin scores are seen in patients with early stage diffuse cutaneous SSc[18], which emphasizes the need for randomized controlled trials. Most autoimmune diseases know periods of exacerbation and remission and this phenomenon might explain the fluctuation in MRSS rather than effective treatment.

Furthermore, the study population included patients with heterogeneous underlying syndromes and different phases of SSc. This probably has effects on the outcome of the efficacy of therapy in SSc. This was shown in the study of Sabnani et al.[15] where only the patient with mild restrictive lung disease showed improvement. In further research, defining specific groups could lead to more definitive conclusions.
In addition, the patients included have had different treatment for SSc before and during imatinib mesylate therapy. It was shown by The Scleroderma Lung Study in 2009 that previous use of immunosuppressive agents like CYC can affect the efficacy outcome of the studies.[19]

The clinical significance of improvement of lung disease in relation to imatinib mesylate is hard to interpret because of the variability between patients. Not all subjects with SSc-associated interstitial/restrictive lung disease have been administered the same dose of imatinib mesylate. We expect that progressive lung involvement will eventually result in fibrosis, which is not reversible in its end-stage. In the early stages of SSc, the inflammation and fibroblast activation are more pronounced and the treatment has more benefit. In the end-stage of fibrosis, fibroblasts possibly exert their effects via more paracrine and autocrine pathways. For this reason medication may have less benefit in end-stage SSc.

Many of the AEs described are most likely related to the underlying SSc rather than imatinib mesylate. Prey et al. showed the same AEs in the imatinib mesylate group as in the placebo group, for example infections and haematotoxicity.[14] The studies showed heterogeneity in AEs, which could be related to heterogeneity of SSc. Future cohort studies should give more definitive conclusions about AEs of imatinib mesylate in the treatment of SSc patients.

Finally, most patients treated with imatinib mesylate did not respond to regular treatment. It is possible that patients that have not responded to previous treatment modalities are less likely to respond to imatinib mesylate. However, we tried to minimize these limitations of the review by performing a QA and include all published clinical trials until now.

Clinical trials that were randomized, double blinded, described the withdrawals and dropouts, included a control group and/or included more than ten patients contribute to minimizing the limiting items mentioned above.

Quality assessment
The study of Prey et al.[14] was found to be the clinical trial with the highest quality. Prey et al.[14] has a QA of 5 (randomized, double-blind, description of withdrawals and dropouts, control group, study population of more than 10 patients). The QA of Pope et al.[12] was 3 (randomized, double blind, placebo-controlled). The QAs of Khanna et al.[13]and Spiera et al.[16] were 2.

Sabnani et al.[15] has the lowest QA with a QA of 1 (description of withdrawals and dropouts). The low number of patients included should be taken into account because false conclusions can be drawn. Studies with a low total number of patients included are less likely to find a significant result and deliver poor level of evidence.

This suggests that studies with the highest QA are also most likely to present the most reliable result, which in this case is also not in favour of treating SSc patients with imatinib mesylate. Prey et al.[14] did not find any significant difference in all three outcome measures.

Conclusion
Even when taking into account the limitations of the included clinical trials, we can conclude the following.

Firstly, two out of five studies showed significant improvement in MRSS [13,16], one out of five studies showed significant improvement in FVC%.[16] These studies do not provide enough evidence to conclude that the treatment with imatinib mesylate offers benefit for all patients with SSc, especially when taking into account the QA for these studies.

However, the case reports of Tamaki et al.[17] and Van Daele et al.[11] showed that imatinib mesylate had a promising effect for cutaneous involvement. Future randomized controlled trials should provide clarity about the effect of imatinib mesylate for cutaneous involvement.

Second, the AE of imatinib mesylate in the treatment of SSc with the highest incidence is edema, followed by gastro-intestinal discomfort. Many studies reported adverse events and had a high rate of withdrawals or dropouts because of AEs. However, many of the AEs described are very possibly correlated to the underlying SSc and not (fully) caused by imatinib mesylate. In our review 20% of the patients discontinued the study because of AEs directly related to imatinib mesylate. Considering the severity of SSc this stands in proportion.

We recommend performing prospective randomized trials with larger study populations in the future. Due to the fact that SSc has a heterogeneous presentation, these trials should differentiate between the presentation and phase of SSc in the patients included. Groups treated with imatinib mesylate should be compared to a group treated with imatinib mesylate plus immunosuppressive agents, a group treated with only immunosuppressive agents and a placebo-controlled group.

Until further larger studies are performed we consider the use of imatinib mesylate therapy in individual SSc patients with skin involvement when regular treatment options have failed.

References


