Tyrosine kinase inhibitors for the treatment of fibrotic diseases such as systemic sclerosis: towards molecular targeted therapies

Distler, J H W; Distler, O
Tyrosine kinase inhibitors for the treatment of fibrotic diseases such as systemic sclerosis: towards molecular targeted therapies

Abstract

Systemic sclerosis (SSc) is a fibrosing connective tissue disease with significantly increased mortality. Therapeutic options to treat fibrosis are limited. The small molecule tyrosine kinase inhibitor imatinib and related drugs such as dasatinib and nilotinib target simultaneously two of the major profibrotic pathways, TGFbeta- and PDGF- signaling. Imatinib, dasatinib and nilotinib inhibit collagen synthesis in cultured fibroblasts and have potent anti-fibrotic effects in animal models of different fibrotic diseases. Moreover, several case reports, case series and uncontrolled studies on patients with SSc, mixed connective tissue disease, nephrogenic systemic fibrosis and in particular sclerodermatous graft versus host disease (cGvHD) report regression of fibrosis and good tolerability. However, the results of larger controlled trials, which are currently ongoing, are needed before any conclusions on efficacy and tolerability can be drawn. Until the results of these trials are available, we discourage off-label use of imatinib in single patients.
Tyrosine kinase inhibitors for the treatment of fibrotic diseases such as systemic sclerosis: towards molecular targeted therapies

J H W Distler and O Distler

Ann Rheum Dis 2010 69: i48-i51
doi: 10.1136/ard.2009.120196

Updated information and services can be found at:
http://ard.bmj.com/content/69/Suppl_1/i48.full.html

These include:

References
This article cites 37 articles, 18 of which can be accessed free at:
http://ard.bmj.com/content/69/Suppl_1/i48.full.html#ref-list-1

Article cited in:
http://ard.bmj.com/content/69/Suppl_1/i48.full.html#related-urls

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To order reprints of this article go to:
http://ard.bmj.com/cgi/reprintform

To subscribe to Annals of the Rheumatic Diseases go to:
http://ard.bmj.com/subscriptions
Tyrosine kinase inhibitors for the treatment of fibrotic diseases such as systemic sclerosis: towards molecular targeted therapies

J H W Distler,¹ O Distler²

ABSTRACT
Systemic sclerosis (SSc) is a fibrosing connective tissue disease with significantly increased mortality. Therapeutic options to treat fibrosis are limited. The small molecule tyrosine kinase inhibitor imatinib and related drugs such as dasatinib and nilotinib target simultaneously two of the major profibrotic pathways, TGFβ- and PDGF- signaling. Imatinib, dasatinib and nilotinib inhibit collagen synthesis in cultured fibroblasts and have potent anti-fibrotic effects in animal models of different fibrotic diseases. Moreover, several case reports, case series and uncontrolled studies on patients with SSc, mixed connective tissue disease, nephrogenic systemic fibrosis and in particular sclerodermatous graft versus host disease (cGvHD) report regression of fibrosis and good tolerability. However, the results of larger controlled trials, which are currently ongoing, are needed before any conclusions on efficacy and tolerability can be drawn. Until the results of these trials are available, we discourage off-label use of imatinib in single patients.

Systemic sclerosis (SSc) is a chronic disorder of the connective tissues that affects the skin and internal organs, including the lungs, kidneys, heart and gastrointestinal tract. Histological hallmarks in the skin of early stages of SSc are perivascular inflammatory infiltrates and microvascular changes such as capillary dilatation with subsequent rarefaction. In later stages, this leads to tissue fibrosis with an excessive accumulation of extracellular matrix. Tissue fibrosis disrupts the physiological tissue architecture and leads to dysfunction of the affected organs. Tissue fibrosis causes not only significant morbidity but, together with vascular manifestations such as pulmonary arterial hypertension, is also the major cause of death in patients with SSc. With pulmonary arterial hypertension and (lung) fibrosis accounting for up to 70% of SSc-related causes of death, the need for intensive preclinical and clinical research in these areas is clear. Herein, we focus on the molecular mechanisms of fibrosis and potential molecular targets for therapy.

The overproduction of extracellular matrix (ECM) components in patients with SSc is mediated by activated fibroblasts, which produce increased amounts of different types of ECM proteins such as glycosaminoglycans, fibronectins and collagenas. The molecular mechanisms leading to tissue fibrosis are incompletely understood and the cause or trigger of SSc is unknown. However, remarkable advances have been made in the identification of key mediators and their intracellular signalling cascades. Interestingly, similar mechanisms also account for other fibrotic diseases such as graft-versus-host disease. These findings have direct translational implications, because drugs targeting these pathways are often in clinical use in other diseases. This review summarises the clinical and preclinical evidence of imatinib and other tyrosine kinase inhibitors targeting c-abl and platelet-derived growth factor (PDGF) receptors as novel antifibrotic treatment approaches in SSc.

RATIONALE BEHIND TYROSINE KINASE INHIBITORS AS AN ANTIFIBROTIC THERAPY
Imatinib mesylate (STI571, Gleevec/Glivec, Novartis Basel, Switzerland) is a small molecule tyrosine kinase inhibitor that binds to the ATP-binding pocket of abelson kinase (c-abl) and efficiently blocks its tyrosine kinase activity. Thus, target proteins of c-abl are no longer phosphorylated, and downstream effects of these activated target proteins, such as proliferation and anti-apoptotic effects, are blocked. c-abl by itself is an important downstream signalling molecule of transforming growth factor β (TGFβ). In cells deficient for c-abl, the induction of ECM proteins by TGFβ is strongly decreased. In addition to its effects on c-abl, imatinib interferes with PDGF signalling by blocking the tyrosine kinase activity of PDGF receptors. Imatinib inhibits also the tyrosine kinase activity of the gene product of the proto-oncogene c-kit and c-fms. Thus, imatinib mesylate targets simultaneously and rather selectively two major profibrotic pathways activated in SSc.

Besides its selectivity, favourable pharmacokinetics, long-standing clinical experience with imatinib in other indications and an acceptable profile of adverse effects provide an argument for the use of imatinib. Imatinib is an orally administered drug, that is readily absorbed and has to be taken one or more times daily, because of its long half-life of 13–16 h. Imatinib is currently widely used for the treatment of bcr-abl positive chronic myelogenous leukaemia and gastrointestinal stromal tumours, with more than 100 000 patients treated so far. Previous clinical trials on patients with chronic myelogenous leukaemia have suggested that imatinib is well tolerated with severe adverse side effects leading to discontinuation of the drug in <1% of patients. However, mild to moderate side effects are common and outside clinical trials, up to one-quarter of patients discontinue imatinib because of adverse effects. The major adverse events responsible for discontinuation are dose dependent and include oedemas, muscle cramps and creatine kinase elevations, uncontrollable diarrhoea and bone marrow toxicity. Furthermore, abl-kinase inhibitors...
might induce congestive heart failure, although the number of reported patients is low and most patients had pre-existing cardiac disease or a variety of cardiovascular risk factors. Nevertheless, these adverse effects need particular attention in clinical trials with patients with SSc because cardiac involvement is common in patients with SSc. The gastrointestinal tract is one of the most frequent organ manifestations in SSc, including intermittent diarrhoea, because of small bowel bacterial overgrowth, and a significant number of patients have coexisting myositis with creatine kinase elevations. In addition, mild to moderate oedema might be less well tolerated by patients with SSc with existing skin diseases than by patients with cancers.

**PRECLINICAL EVIDENCE OF THE ANTIFIBROTIC EFFECTS OF IMATINIB**

Incubation of cultured fibroblasts from patients with SSc and healthy volunteers with imatinib strongly inhibited the synthesis of col1a1, col1a2 and fibronectin-1 on the mRNA as well as protein level by up to 90% at concentrations of 1.0 μg/ml. No changes of the expression of tissue inhibitors of metalloprotease and matrix metalloproteinases were seen that might have counterbalanced the decreased production of ECM proteins. Furthermore, treatment with imatinib completely prevented the development of fibrosis in the mouse model of bleomycin-induced dermal fibrosis. Treatment of mice with imatinib at doses of 50 mg/kg/day and 150 mg/kg/day had strong antifibrotic effects without toxic side effects. Imatinib prevented the differentiation of resting fibroblasts into myofibroblasts and dose dependently reduced the synthesis and accumulation of ECM in lesional skin. Imatinib also exerted potent antifibrotic effects in the tight-skin-1 (tsk-1) mouse model of SSc.11 Bleomycin-induced fibrosis is characterised by a strong infiltration of leukocytes with secondary activation of fibroblasts and resembles early, inflammatory stages of SSc. In contrast, fibroblasts isolated from tsk-1 mice show an endogenous activation with increased release of ECM and tsk-1 mice are used as a model system to mimic later stages of SSc. Treatment of tsk-1 mice with imatinib in doses of 150 mg/kg/day significantly reduced hypodermal thickening and differentiation of resting fibroblasts into myofibroblasts, and ameliorated the tsk-1 phenotype. In addition to experimental models of SSc, imatinib was also effective in different models of pulmonary, renal and liver fibrosis.12–14

In addition to prevention of fibrosis, imatinib might also be effective for the treatment of established fibrosis. We demonstrated recently that imatinib induces regression of pre-established fibrosis in a modified model of bleomycin-induced dermal fibrosis.15 Treatment with imatinib started 5 weeks after injection with bleomycin not only stopped further progression of dermal fibrosis despite ongoing challenge with bleomycin but also reduced dermal thickening to levels below that seen after 5 weeks of bleomycin. Thus, imatinib not only prevented progression but also induced regression of fibrosis. This is probably owing to the potent reduction of the synthesis of the ECM, which shifts the balance between synthesis of ECM and degradation of ECM towards degradation.

**FIRST CLINICAL REPORTS ON THE EFFECTS OF IMATINIB ON FIBROSIS**

The first clinical evidence for an antifibrotic effect of imatinib came from patients with chronic myelogenous leukaemia (CML) and concomitant bone marrow fibrosis. Two small clinical studies suggested that treatment of patients with CML with imatinib might lead to a regression of bone marrow fibrosis.16 Of note, the antifibrotic effect did not correlate with the cytogenetic response, suggesting an effect independent from the suppression of Philadelphia chromosome-positive cancer cells.16

Meanwhile, several case reports and small case series have reported on the efficacy and safety of imatinib in patients with SSc and other fibrosing connective tissue diseases.

We reported the successful treatment of pulmonary fibrosis with imatinib in a patient with anti-U1-antibody-positive mixed connective tissue disease.17 Before initiation of imatinib, the patient rapidly deteriorated despite treatment with corticosteroids and immunosuppressant agents. However, during a 20-week trial with 400 mg/day imatinib, the patient progressively improved. The New York Heart Association (NYHA) class changed from NYHA IV to NYHA II. The 6 min walking distance increased by 50 m and the carbon monoxide transfer factor increased from 26% predicted to 45% predicted. The arterial oxygen pressure increased from 64 mm Hg to 70 mm Hg at rest and from 50 mm Hg to 62 mm Hg after exertion. Ground-glass opacities decreased during treatment, whereas the reticular changes remained constant. However, no changes in forced vital capacity and total lung capacity were seen. The patient tolerated the treatment well and did not experience any adverse events apart from mild oedema.

Kay and High reported impressive responses of two patients with nephrogenic systemic fibrosis treated with imatinib in doses of 400 mg/day.18 In the first patient, the modified Rodnan skin score (mRSS) decreased from 42 to 16 within 15 weeks. In the second patient, a decrease of the mRSS from 12 to 2 occurred within 12 weeks. In parallel with the mRSS, reduced accumulation of the ECM and decreased expression of type I procollagen was seen in skin biopsy specimens of these patients. Of note, skin thickening rapidly reoccurred in both patients within a few weeks of stopping imatinib, probably because of the persistent accumulation of gadolinium. However, the fibrotic changes regressed again upon reintroduction of imatinib.

Similar successful case reports and case series with imatinib have been reported for patients with treatment-resistant SSc.19,20 In general, skin fibrosis appeared to be more responsive than lung fibrosis in these case series.21 Chung et al reported beneficial effects in two patients with SSc treated with imatinib at doses of 200 mg/day.22 The first patient was diagnosed with SSc 3 years before and deteriorated with progressive pulmonary and dermal fibrosis despite treatment with cyclophosphamide. After 3 months treatment with imatinib, the mRSS decreased from 56 to 21 and pulmonary disease stabilised. The second patient was newly diagnosed with SSc and imatinib was initiated owing to intolerance of other therapeutic approaches. Within the 6 months of receiving imatinib, her mRSS decreased from 36 to 20. Both patients tolerated imatinib well and no major side effects were reported. Chang and coworkers performed molecular analyses on skin biopsy specimens taken from both patients before and after treatment with imatinib. They demonstrated that PDGF receptor and c-abl were phosphorylated and thereby activated in lesional skin before treatment and that imatinib strongly decreased the phosphorylation of both targets.23 Moreover, they identified an imatinib-responsive signature specific to diffuse SSc by gene expression
profiling, suggesting that imatinib targets a gene expression programme that is dysregulated in diffuse SSC.

Additional evidence for an antifibrotic effect of imatinib comes from two recent studies reporting on the effects of imatinib on the refractory sclerodermatous graft-versus-host disease (cGvHD).21–24 cGvHD is a rather common adverse event after allogeneic stem cell transplantation. Similar to SSC and other fibrotic treatments, current therapeutic approaches are unsatisfactory and the mortality of affected patients is high. Sclerodermatous cGvHD shares many clinical features with SSC and mice undergoing bone marrow transplantation with a minor HLA mismatch resulting in murine sclerodermatous cGvHD are often used as a murine model of SSC.25–28

One study reports on 19 patients with refractory cGvHD for whom at least two previous treatment approaches had failed.24 The organs involved were skin in 17 patients, lungs in 11 patients and bowel in 5 patients. The doses of imatinib given in this study were relatively low and ranged from 50 to 200 mg/day. The rate of imatinib-related severe adverse events was acceptable and imatinib was discontinued in three patients owing to toxicity. Imatinib was discontinued in an additional three patients owing to a lack of efficacy and in two patients owing to relapse of malignancy. The response rates were remarkable with seven complete remissions and eight partial remissions, defined as at least 50% improvement after 6 months. Skin fibrosis, as analysed by the mRSS, improved in all but two patients with a mean reduction from 38 (range 18–51) to 8 (range 0–36) after 6 months of treatment. Similarly, lung function scores improved in seven out of 11 patients and remained stable in the other four patients.

The other study reported on the treatment of 14 patients with refractory cGvHD.25 The doses of imatinib in this study were higher, with the majority of patients taking 400 mg imatinib a day. Four patients had to discontinue imatinib owing to drug intolerance. Seven patients responded to imatinib with an improvement of the mRSS of >90% in four of them including two patients with complete resolution of any clinically assessable skin fibrosis. The authors also noted a significant reduction of the corticosteroid dosage.

Although both trials were uncontrolled and non-blinded, the regression of the fibrotic changes in imatinib-treated patients with sclerodermatous cGvHD is impressive and suggests that imatinib might be effective for the treatment of sclerodermatous cGvHD.

OTHER TYROSINE KINASE INHIBITORS OF C-ABL AND PDGF RECEPTOR

Recently, dasatinib (Sprycel, Bristol-Myers-Squibb, New York, New York, USA) and nilotinib (Tasigna, Novartis), two novel inhibitors of abl-kinases and PDGF receptors have been approved for the treatment of bcr-abl positive CML with resistance or intolerance to imatinib. Dasatinib and nilotinib are small-molecule tyrosine kinase inhibitors, which can be administered orally.29–33 Like imatinib, nilotinib selectively inhibits the tyrosine kinase activity of abl-kinases, PDGF receptor and c-kit. Dasatinib is less selective and inhibits additionally the structurally related family of src-kinases.34 Both, dasatinib and nilotinib inhibit the activity of abl-kinases much more potently than imatinib and are effective in most cell lines resistant to imatinib.35 The spectrum of adverse effects of dasatinib and nilotinib differs from that of imatinib and patients with intolerance to imatinib can often be switched safely to nilotinib or dasatinib.30–37 Thus, dasatinib and nilotinib might be interesting candidates for the treatment of patients who cannot tolerate imatinib. Indeed, incubation of cultured fibroblasts with dasatinib or nilotinib potently decreased the synthesis of ECM proteins without compensatory changes of the tissue inhibitors of metalloproteinase or matrix metalloproteinas.38 Furthermore, treatment of mice with dasatinib or nilotinib dose dependently reduced the development of dermal fibrosis in the mouse model of bleomycin-induced dermal fibrosis. Thus, dasatinib and nilotinib might be interesting alternatives to imatinib.

CONCLUSION

Mortality is significantly increased in SSC. Despite extensive research, therapeutic options for antifibrotic treatments are very limited. So far, a significant antifibrotic effect has only been demonstrated for cyclophosphamide, but the effect is mild at best and treatment with cyclophosphamide is accompanied by a significant toxicity. Preclinical data suggest that the small-molecule inhibitor imatinib and related drugs such as dasatinib and nilotinib, which target selectively and simultaneously TGFβ and PDGF signalling pathways, have potent antifibrotic effects.

First case reports, case series and uncontrolled studies on patients with SSC, mixed connective tissue disease, nephrogenic systemic fibrosis and, in particular, sclerodermatous cGvHD are promising. However, at least for SSC, the course of the disease is variable with spontaneous regression of dermal fibrosis in several patients. Thus, the reported regression of fibrosis might reflect the spontaneous course of the disease in individual patients and not a response to imatinib. In addition, the possibility of a publication bias cannot be excluded, as long, controlled and/or prospective studies are not available.

An appropriate assessment of toxicity is necessary in a larger number of patients to exclude relevant adverse effects in patients with SSC, who frequently have SSC-related cardiac pathologies. In addition, gastrointestinal side effects and myalgias might be more common in patients with SSC because of gastrointestinal and muscular involvement in this disease. Oedema might also be more common and more severe in patients with SSC owing to pre-existing microangiopathy.

It needs to be strongly emphasised that no definite conclusions about safety and efficacy can be drawn from the published reports and that the safety and efficacy of imatinib can only be investigated in larger controlled clinical trials that are currently ongoing (see http://www.clinicaltrials.gov (accessed 1 September 2009) for details). We recommend the inclusion of patients in larger clinical trials and strictly discourage uncontrolled off-label use of imatinib or other tyrosine kinase inhibitors in single patients, until the toxicity profile has been established or the results of the ongoing clinical trials are available.

Competing interests: OD has consultancy relationships and/or has received research funding from Actelion, Pfizer, Encysive, FibroGen, Ergonex, NioDi and Biotium in the area of potential treatments of scleroderma and its complications. He has received lecture honoraria from Actelion, Pfizer, Encysive and Ergonex. JD has consultancy agreements and/or has received research funding from Novartis, Ergonex, Bayer, Celgene and BMS.

Provenance and peer review: Not commissioned; externally peer reviewed.

REFERENCES


45. Cannell E, Dassatinib is effective in imatinib-resistant CML. Lancet Oncol 2007;8:286.


