Imatinib for the treatment of rheumatic diseases

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There has been much speculation on the potential use of kinase inhibitors for the treatment of autoimmune rheumatic diseases. Investigations of small-molecule inhibitors of p38 mitogen-activated protein kinases (MAPK) and other kinase pathways have been limited by toxicities, however, data suggest that the small-molecule tyrosine kinase inhibitor imatinib mesylate could provide therapeutic benefit for a range of autoimmune rheumatic diseases including scleroderma, pulmonary arterial hypertension (PAH), spondyloarthropathies, and rheumatoid arthritis (RA). Imatinib is approved by the FDA for the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIST). Imatinib potently inhibits a select set of tyrosine kinases at submicromolar concentrations, including the platelet-derived growth factor receptor (PDGFR), c-kit, and ABL-related kinases; imatinib also potently inhibits c-fms and LCK at micromolar concentrations. Selective inhibition of one or more tyrosine kinases could provide a potent therapeutic option for a variety of autoimmune and inflammatory diseases, for which current therapies are insufficient.

Scleroderma is a fibrotic disease that affects the skin, and can also affect visceral organs. Data published in 2006 suggest that anti-PDGFR autoantibodies might have a critical role in driving fibrosis in scleroderma.[1] TGF-beta-stimulated signalling through Abl has also been identified as an important profibrotic pathway. Studies have demonstrated that imatinib inhibits fibrosis in rodent models of scleroderma[2] and thus, might provide benefit in patients with scleroderma.

PAH is characterized by pulmonary vasculature remodeling and intimal smooth muscle cell proliferation, which result in the constriction of pulmonary arteries. PDGFR and PDGF ligands are expressed in pulmonary vascular tissue.[3] PDGF ligands are implicated in PAH pathogenesis based on their ability to act as chemoattractants and smooth muscle cell activators. Schermuly *et al.* demonstrated that imatinib effectively inhibits smooth muscle cell proliferation, reverses pulmonary hypertension, and improves cardiac output and survival,[3] and there are at least four case reports of patients with PAH who exhibit clinical and hemodynamic benefits following the use of imatinib.[4]

RA is an autoimmune synovitis, and there are several case reports of patients with longstanding RA who have entered remission following the initiation of therapy with imatinib to treat CML or GIST.[5] An open-label study of imatinib in three patients with RA showed improvement following initiation of treatment with imatinib 200–400 mg per day.[5] PDGFR and it's ligands are upregulated in RA, and imatinib could provide benefit by reducing pannus formation. By inhibition of Fms and Kit, imatinib could also reduce TNF and the production of other proinflammatory cytokines. It has been shown that imatinib provides benefit in rodent models of RA.[6,7] Studies from our laboratory demonstrated that imatinib prevented development of and treated established collagen-induced arthritis. We also demonstrated that submicromolar concentrations of imatinib inhibited multiple tyrosine kinases and cellular responses that are central to the pathogenesis of RA, including PDGF-mediated proliferation of fibroblast-like synoviocytes, c-fms activation and macrophage production of tumor necrosis factor (TNF), and c-kit-mediated mast-cell release of TNF and interleukin (IL)-6.[6]

The presence of c-fms is critical for several functions in cells of the monocyte lineage, including macrophage and osteoclast differentiation, and priming macrophages to produce TNF in response to a second stimulus. TNF is a central pathogenic mediator in a variety of autoimmune diseases. Imatinib could provide benefit by inhibiting macrophage maturation and, thereby, TNF production and, in patients with diseases that involve bone destruction, by inhibiting the differentiation of monocytic precursor cells into osteoclasts.[7]

Mast cells express c-kit and are present at the sites of tissue injury in many autoimmune diseases. Activation of mast cells through c-kit

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induces the release of TNF, IL-6 and other proinflammatory cytokines. Inhibition of c-kit with imatinib or other small-molecule tyrosine kinase inhibitors could provide benefit in patients with inflammatory diseases in which mast cells contribute to pathogenesis.

Autoimmune diseases, although directed against distinct target tissues, share multiple pathogenic mechanisms. Imatinib and other tyrosine kinase inhibitors could provide benefit in a variety of autoimmune and inflammatory diseases, such as diseases in which TNF drives tissue injury, diseases characterized by fibroblast and muscle-cell proliferation, diseases mediated by mast cells, and diseases in which the activation of and immunoglobulin production by B cells have an important role.[6]

Imatinib might provide benefit in human autoimmune diseases including ankylosing spondylitis,[8] psoriasis[9] and Crohn's disease,[10] and clinical improvement has been observed in patients with spondyloarthropathies.[8] In rodent models of systemic lupus erythematosus, imatinib reduced glomerulosclerosis and increased survival. PDGF-stimulated mesangial cells have been implicated in lupus nephritis, and imatinib could provide benefit by inhibiting profibrotic signalling pathways. Despite case reports suggesting benefit, it is anticipated that the toxicity profile of imatinib will probably limit its use to autoimmune diseases that are organ-threatening or life-threatening. A 2006 study of patients with CML who were treated with 400 mg per day imatinib over 5 years showed that >40% of patients experienced edema, nausea, muscle cramps, musculoskeletal pain, and rashes.[11] A significant percentage of imatinib-treated patients also developed bone marrow suppression; 17% of patients exhibited neutropenia, 9% thrombocytopenia and 4% anemia.[11] Cardiotoxicity has also been described in imatinib-treated patients, and might be caused by mitochondrial and sarcoplasmic reticulum dysfunction secondary to inhibition of c-ABL.

Nevertheless, compared with the doses required to treat CML, GIST and other malignancies, we anticipate that significantly lower doses of imatinib and other small-molecule tyrosine kinases inhibitors could provide benefit in autoimmune diseases. CML and GIST arise from primary mutations in c-ABL and c-kit, and require relatively high doses of imatinib to inhibit proliferation of the malignant cells. By contrast, autoimmune diseases are not associated with mutations in these kinases, and wild-type kinases participate in the dysregulated cellular responses that mediate tissue injury. The inhibition constant (IC_{50}) of imatinib for wild-type kinases is significantly lower than that of the mutated kinases associated with malignancy, and low dose regimens could provide benefit in autoimmune diseases.

The ability of imatinib and other small-molecule inhibitors to inhibit multiple kinases could be important to their efficacy as a treatment for autoimmune diseases, and it is critical to define exactly which kinases and cellular responses mediate disease pathogenesis. This knowledge will facilitate the development of next generation inhibitors with increased specificity, and such inhibitors should provide more favorable therapeutic indices than imatinib. It is essential that therapeutic decision-making is evidence-based and guided by the results of rigorous clinical trials. Inhibition of tyrosine kinase pathways represents a potent and promising therapeutic approach, and in future could become a mainstay of therapy for patients with autoimmune and inflammatory rheumatic diseases.

Competing interests
The authors declared they have no competing interests.

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