

Editorial

More about masitinib

Ulrich A Walker

Basel University Department of Rheumatology, Felix Platter Spital, Burgfelderstrasse, 4012 Basel, Switzerland

Corresponding author: Ulrich A Walker, ulrich.walker@fps-basel.ch

Published: 13 July 2009

This article is online at <http://arthritis-research.com/content/11/4/120>

© 2009 BioMed Central Ltd

Arthritis Research & Therapy 2009, **11**:120 (doi:10.1186/ar2734)

See related research by Tebib *et al.*, <http://arthritis-research.com/content/11/3/R95>

Abstract

A dose-escalating phase II trial studied masitinib, an oral tyrosine kinase inhibitor, in 43 patients with rheumatoid arthritis. Masitinib induced American College of Rheumatology (ACR)20, ACR50 and ACR70 responses in 54%, 26% and 8% of patients, respectively. A placebo group was not included. Thirty-seven per cent of the patients withdrew before the 12-week end-point was reached, primarily because of adverse events. These findings are the first on the efficacy of tyrosine kinase inhibition in a sizeable population. Future work should focus on delineating the tyrosine kinase that is most important in maintaining rheumatoid activity and address potential long-term toxicities such as gonadal insufficiency, teratogenicity and cardiotoxicity.

Introduction

In the previous issue of *Arthritis Research and Therapy*, Jacques Tebib and coworkers [1] present the results of an open-label, uncontrolled, phase IIa trial of oral masitinib in patients with rheumatoid arthritis (RA). Masitinib is a tyrosine kinase inhibitor that was recently approved for veterinary use in dogs with unresectable mast cell tumours [2]. Masitinib is currently being developed for the treatment of gastrointestinal stromal and other tumours, but the trial presented here is the first report on the use of masitinib in non-oncological pathology.

The lead compound of such tyrosine kinase inhibitors is imatinib mesylate (Gleevec; Novartis Pharmaceuticals Corp, Basel, Switzerland). Imatinib is approved for the treatment of chronic myeloid leukaemia, in which it inhibits a tyrosine kinase produced by the bcr-abl fusion gene. In addition to the tyrosin kinase produced by bcr-abl, imatinib inhibits the tyrosine kinase signalling of other proteins, such as the receptors of platelet-derived growth factor (PDGF), stem cell factor and macrophage colony-stimulating factor, all of which have been implicated in the pathogenesis of RA [3,4]. In synovial fluid mononuclear cells derived from RA patients, imatinib was found to attenuate tumour necrosis factor (TNF)- α production [5]. Imatinib was also shown to induce mast cell

apoptosis in the rheumatoid synovium [6]. Synovial mast cells produce tissue destructive proteases and pro-inflammatory cytokines, most prominently TNF- α , and they therefore represent an interesting and novel target in the treatment of RA [7].

That imatinib has efficacy in RA has indeed been suggested in preclinical models and in human patients [4,8]. A phase II clinical trial of imatinib 400 mg/day in combination with methotrexate in RA has been completed (ClinicalTrials.gov identifier NCT00154336) [9], but the results of this trial have not yet been published.

Masitinib in rheumatoid arthritis

Tebib and coworkers [1] present the first study of masitinib in non-oncological pathology. Masitinib was given twice daily, either at an initial dose of 3 mg/kg per day or 6 mg/kg per day. Dose escalations were allowed during the 12-week study period. Half of the RA patients included had previously failed a TNF- α inhibitor.

American College of Rheumatology (ACR)20, ACR50 and ACR70 responses were achieved in 54%, 26% and 8% of the RA patients, respectively. With the higher initial masitinib dose, the median time to achieve an ACR20 response was 29 days and to achieve an ACR 50 response was 73 days. It should be noted, however, that the efficacy analysis of this phase II study is hampered by the lack of a placebo group. Thus, a significant proportion of the study population could have improved by regression to the mean and other effects.

With regard to safety, 37% of the patients included in the masitinib study withdrew before they reached the 12-week end-point, primarily because of adverse events. The overall incidence of adverse events was 91% and included rash (30%), oedema (mainly of the face; 26%), nausea (23%) and diarrhoea (18.6%). In 21% of individuals the adverse events

were severe. In some RA patients who were followed beyond week 12, however, no instances of rash, nausea, vomiting or diarrhoea were reported, although oedema persisted in a sizeable proportion.

Safety profile of tyrosine kinase inhibitors

The side-effect profile of masitinib appears to be similar to that observed in preclinical models and those of other tyrosine kinase inhibitors. The occurrence of diarrhoea with this drug class can be explained by the pharmacological activity on the stem cell factor receptor on Cajal cells in the intestine [10], whereas oedema is linked to PDGF receptor blockade in the periorbital region. The side effects were similar in the canine masitinib study [2] and commonly involved the gastrointestinal tract.

Several data suggest that tyrosine kinase inhibitors may have adverse effects that were not addressed in the human masitinib study. The canine study, for example, found hair loss to be among the most common side effects of masitinib. Stem cell factor and PDGF signalling pathways also appear to regulate the postnatal formation of spermatogonial stem cells and Leydig cells in rat testis [11]. When imatinib was given to male rodents, it reduced the litter size and led to permanently elevated serum levels of gonadotrophins, indicating latent testicular effects. In female laboratory animals, masitinib also reduced fertility. Imatinib has also been associated with ovarian insufficiency in humans [12]. Preclinical studies have demonstrated that imatinib is embryotoxic and causes defects of the skull bones. Malformations after imatinib exposure raise concerns of similar outcomes in human pregnancy [13]. Cardiac toxicity has been demonstrated with masitinib in rodents and with imatinib in clinical trials. Given the small study population, the short observation period and the methodology - which was inadequate for detecting the side effects discussed above - it is premature to conclude that masitinib is safe.

Conclusions

Despite its preliminary nature, the results of the human masitinib trial are important in several respects. They represent the largest body of published data with regard to tyrosine kinase inhibition as a novel therapeutic approach in RA and they support clinically important roles for stem cell factor signalling and for other tyrosine kinases in the rheumatoid synovium. The results are also interesting with respect to the treatment of other rheumatic diseases, because tyrosine kinase antagonists are currently being investigated in the treatment of scleroderma and other fibrotic conditions.

Future investigations should address potential differences in the efficacy and safety profile of masitinib, imatinib and other tyrosine kinase inhibitors that are in clinical development. Differences between the individual members of the drug class may arise from their differential selectivity for the tyrosine kinase receptors and should be addressed. With

regard to masitinib, long-term clinical toxicology should address all target organs. The high frequency of reported side effects does not support an important role for masitinib in the first-line or second-line treatment of RA, but the compound may enrich our therapeutic armamentarium in recalcitrant cases.

Competing interests

The author declares that they have no competing interests.

References

1. Tebib J, Mariette X, Bourgeois P, Flipo RM, Gaudin P, Le Loet X, Gineste P, Guy L, Mansfield CD, Moussy A, Dubreuil P, Hermine O, Sibilia J: **Masitinib in the treatment of active rheumatoid arthritis: results of a multicentre, open-label, dose-ranging, phase 2a study.** *Arthritis Res Ther* 2009, **11**:R95.
2. Hahn KA, Ogilvie G, Rusk T, Devauchelle P, Leblanc A, Legendre A, Powers B, Leventhal PS, Kinet JP, Palmerini F, Dubreuil P, Moussy A, Hermine O: **Masitinib is safe and effective for the treatment of canine mast cell tumors.** *J Vet Intern Med* 2008, **22**:1301-1309.
3. Sandler C, Joutsiniemi S, Lindstedt KA, Juutilainen T, Kovanen PT, Eklund KK: **Imatinib mesylate inhibits platelet derived growth factor stimulated proliferation of rheumatoid synovial fibroblasts.** *Biochem Biophys Res Commun* 2006, **347**:31-35.
4. Ando W, Hashimoto J, Nampei A, Tsuboi H, Tateishi K, Ono T, Nakamura N, Ochi T, Yoshikawa H: **Imatinib mesylate inhibits osteoclastogenesis and joint destruction in rats with collagen-induced arthritis (CIA).** *J Bone Miner Metab* 2006, **24**:274-282.
5. Paniagua RT, Sharpe O, Ho PP, Chan SM, Chang A, Higgins JP, Tomooka BH, Thomas FM, Song JJ, Goodman SB, Lee DM, Genovese MC, Utz PJ, Steinman L, Robinson WH: **Selective tyrosine kinase inhibition by imatinib mesylate for the treatment of autoimmune arthritis.** *J Clin Invest* 2006, **116**:2633-2642.
6. Juurikivi A, Sandler C, Lindstedt KA, Kovanen PT, Juutilainen T, Leskinen MJ, Maki T, Eklund KK: **Inhibition of c-kit tyrosine kinase by imatinib mesylate induces apoptosis in mast cells in rheumatoid synovia: a potential approach to the treatment of arthritis.** *Ann Rheum Dis* 2005, **64**:1126-1131.
7. Eklund KK: **Mast cells in the pathogenesis of rheumatic diseases and as potential targets for anti-rheumatic therapy.** *Immunol Rev* 2007, **217**:38-52.
8. Eklund KK, Joensuu H: **Treatment of rheumatoid arthritis with imatinib mesylate: clinical improvement in three refractory cases.** *Ann Med* 2003, **35**:362-367.
9. **A Study of Imatinib 400 Mg Once Daily in Combination With Methotrexate in the Treatment of Rheumatoid Arthritis** [<http://www.clinicaltrials.gov/ct2/show/NCT00154336?term=NC T00154336&rank=1>]
10. Beckett EA, Ro S, Bayguinov Y, Sanders KM, Ward SM: **Kit signaling is essential for development and maintenance of interstitial cells of Cajal and electrical rhythmicity in the embryonic gastrointestinal tract.** *Dev Dyn* 2007, **236**:60-72.
11. Nurmio M, Kallio J, Toppari J, Jahnukainen K: **Adult reproductive functions after early postnatal inhibition by imatinib of the two receptor tyrosine kinases, c-kit and PDGFR, in the rat testis.** *Reprod Toxicol* 2008, **25**:442-446.
12. Christopoulos C, Dimakopoulou V, Rotas E: **Primary ovarian insufficiency associated with imatinib therapy.** *N Engl J Med* 2008, **358**:1079-1080.
13. Pye SM, Cortes J, Ault P, Hatfield A, Kantarjian H, Pilot R, Rosti G, Apperley JF: **The effects of imatinib on pregnancy outcome.** *Blood* 2008, **111**:5505-5508.