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Original article

Masitinib, a c-kit/PDGF receptor tyrosine kinase inhibitor, improves disease control in severe corticosteroid-dependent asthmatics

Background: Masitinib is a tyrosine kinase inhibitor targeting stem cell factor receptor (c-kit) and platelet-derived growth factor (PDGF) receptor, which are expressed on several cell types including mast cells and bronchial structural cells, respectively. We hypothesized that c-kit and PDGF receptor inhibition may decrease bronchial inflammation and interfere with airway remodeling, which are crucial features of severe asthma.
Objectives: The primary endpoint was the percent change from baseline in oral corticosteroids after 16 weeks of treatment. Change in asthma control (asthma control questionnaire), exacerbation rate, pulmonary function tests, rescue medication requirement and safety were secondary endpoints.
Methods: A 16-week randomized, dose-ranging (3, 4.5, and 6 mg/kg/day), placebo-controlled study was undertaken in 44 patients with severe corticosteroid-dependent asthma who remained poorly controlled despite optimal asthma management.
Results: At 16 weeks of treatment, a comparable reduction in oral corticosteroids was achieved with masitinib and placebo (median reduction of −78% and −57% in the masitinib and placebo arms, respectively). Despite this similar reduction, the Asthma Control Questionnaire score was significantly better in the masitinib arm as compared to placebo with a reduction by 0.99 unit at week 16 ($P < 0.001$) *vs* 0.43 unit in the placebo arm. Masitinib therapy was associated with more transient skin rash and edema.
Conclusions: Masitinib, a c-kit and PDGF-receptor tyrosine kinase inhibitor, may represent an innovative avenue of treatment in corticosteroid-dependent asthma. These preliminary results warrant further long-term clinical studies in severe asthma (ClinicalTrials.gov Identifier: NCT00842270).

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Key words: asthma; c-kit; platelet-derived growth factor; mast cells; tyrosine kinase inhibitors.

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Abbreviations: ACQ, Asthma Control Questionnaire; AE, adverse events; CS, corticosteroids; EMEA, European Medicines Agency; FEV_1, forced expiratory volume in 1 s; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; ITT, intent-to-treat population; OCS, oral corticosteroids; PDGF, platelet-derived growth factor; PP, per-protocol population; SABA, short-acting beta2 agonist; SCF, stem cell factor; W16, week 16.

Most asthmatic patients can be satisfactorily managed by combining anti-inflammatory drugs and bronchodilators (1). Furthermore, a complete absence of response to corticosteroids in severe asthma is rare while reduced responsiveness, often described as corticosteroid-dependent asthma, is more common (2). Inhaled and oral corticosteroids are needed to control severe cases. These patients who remain symptomatic represent a major health problem and cause asthma-related health care costs (3).

Severe refractory asthma refers to patients who having followed an observation period of at least 6 months by an asthma specialist, remain difficult to control despite optimal management and an extensive re-evaluation of diagnosis (2). Factors that influence asthma control such as exposure to environmental hazards, co-morbidities, medication compliance and inhalation technique should be considered for diagnosis (2). Patients usually report recurrent symptoms, occurrence of exacerbations and a daily requirement of rescue medications (4). Although these patients represent only a small subpopulation, lack of disease control contributes markedly to their poor quality of life (2, 4). Finally, patients with severe asthma who require long-term oral steroid therapy usually comply with the treatment but are at higher risk of harmful side-effects (2).

Biological agents designed to interfere with immune targets have been widely explored (5), but many studies were disappointing (6). To date only omalizumab, an anti-immunoglobulin E antibody, has EMEA approval for severe allergic asthma (7). Nonetheless, a significant proportion of severe asthmatics are not allergic or are not controlled by this therapy and novel drugs are needed to treat severe refractory asthma (2, 6, 7).

Asthma is a chronic inflammatory condition, with bronchial recruitment, activation of inflammatory cells and enhanced release of mediators (1). Dendritic and mast cells are likely to play a major role in severe asthma (2, 4, 8, 9). These cells can be activated through the engagement of the stem cell factor (SCF) receptor c-kit (8, 9). Inhibition of the SCF/c-kit pathway leads to significant decrease of the mast cell population, histamine levels and eosinophile infiltration, interleukin-4 production and airway hyper-responsiveness *in vivo*(8), suggesting that SCF/c-kit may be a potential therapeutic target. Experimental data indicated that dendritic cells expressing nonfunctional c-kit elicited diminished allergic airway inflammation (8). Also, growth factors such as platelet-derived growth factor (PDGF) contribute to bronchial remodeling, a characteristic of severe asthma, and targeting PDGF receptor tyrosine kinase may be an interesting novel therapeutic option (10, 11).

Masitinib (AB1010; AB Science, Paris, France) and imatinib (Glivec, STI571; Novartis, Basel, Switzerland) are protein tyrosine kinase inhibitors, which potently and selectively inhibit c-kit and PDGF receptors (12). Accordingly, masitinib and imatinib are currently developed in various nononcologic chronic diseases characterized by chronic inflammation and remodeling (10–13). In this randomized, dose-ranging, placebo-controlled study, we assessed if a 16-week treatment with masitinib was a safe and efficient add-on option in corticosteroid-dependent severely asthmatic patients.

Methods

Patients

Patients, 18–75 years of age with a diagnosis of asthma for ≥3 years and severe uncontrolled disease for ≥1 year, and followed up at the same center for ≥1 year, were eligible for this study. Patients were required to have exhibited within 1 year of screening the following characteristics: (i) postbronchodilator reversibility in forced expiratory volume in 1 second (FEV_1) of ≥12%, (ii) to have experienced asthma symptoms more than once in 3 days for ≥3 months before screening despite continuous treatment with high-dose inhaled corticosteroids (beclometasone ≥1000 μg or equivalent), long-acting beta2 agonists and daily oral corticosteroids (10–50 mg of equivalent prednisolone, with stable dosage for at least 3 months) and (iii) patients had to be nonsmokers for at least 1 year with a prior tobacco consumption of < 10 pack-years. Exclusion criteria included (i) any other significant respiratory or cardiac disease, (ii) worsening of asthma symptoms requiring treatment with additional oral corticosteroids within 4 weeks of screening, (iii) any other infections, (iv) a history of acute infection requiring hospitalization or treatment with antibiotics within 2 weeks of screening, (v) rare variants of severe asthma such as Churg-Strauss syndrome or allergic bronchopulmonary aspergillosis, (vi) inadequate organ function (total bilirubin ≥1.5 times the upper limit of normal range, liver transaminases ≥ 2.5 times the upper limit of normal range, neutrophil count < 2500/ml and platelet count < 150 000/ml at baseline), and (vii) concomitant treatments with immunomodulatory drugs. Treatment with omalizumab was an exclusion criterion unless the drug was not taken for at least 4 months.

This study was submitted to the French authorities and conducted in France in accordance with the Declaration of Helsinki. Each participating investigator followed guidelines established for Good Clinical Practice. Approval was obtained from the Local Ethics Committees before study initiation and all patients provided written informed consent. Enrollment started in January 2006. This study was registered in clinical trial.gov under the trial registration number NCT00842270.

Study design

This was a Phase 2a, 16-week, double-blind, placebo-controlled, randomized, parallel group, multicenter study of daily oral masitinib conducted in 44 asthmatic patients with severe persistent asthma (see Table 1). Patients were randomly assigned to one of four groups for a 16-week treatment period: masitinib at 3, 4.5 or 6 mg/kg/day or placebo control. The trial consisted of three phases: corticosteroid dose remained constant during the first 4 weeks; over the following 8 weeks oral corticosteroid doses were decreased weekly according to a predefined schedule, until weaning or an asthma exacerbation occurred (see Table 2A and B); the final 4 weeks were a stabilization period for observation. Asthma exacerbation was defined as a deterioration of asthma symptoms requiring an emergency visit, hospitalization or an increase in oral corticosteroid treatment. In case an asthma exacerbation occurred, oral corticosteroid therapy was resumed at the level prior to this occurrence following the acute treatment phase.

Table 1. Baseline demographics, disease characteristics, and concomitant medications

Parameters	Masitinib groups					
	3 mg/kg/day (*n* = 12)	4.5 mg/kg/day (*n* = 11)	6 mg/kg/day (*n* = 10)	All masitinib (*n* = 33)	Placebo (*n* = 11)	All (*n* = 44)
Female, *n* (%)	9 (75.0%)	7 (63.6%)	7 (70.0%)	23 (69.7%)	8 (72.7%)	31 (70.5%)
Age (years)	55 ± 14	49 ± 10	51 ± 13	52 ± 12	58 ± 15	53 ± 13
Body mass index (kg/m^2)	29 ± 8	29 ± 9	29 ± 9	29 ± 8	32 ± 6	30 ± 8
Disease duration (years)	24 ± 18	21 ± 14	29 ± 13	24 ± 15	18 ± 18	23 ± 16
Time since last exacerbation (months)	4 ± 2	4 ± 2	7 ± 11	5 ± 6	6 ± 9	5 ± 7
Prebronchodilator FEV1 (% of predicted)	51.9 ± 11.1	67.4 ± 10.8	60.6 ± 17.1	59.7 ± 14.3	58.9 ± 27.3	59.5 ± 18.1
ACQ score (1–7 scale)	2.8 ± 0.8	3.6 ± 1.1	3.1 ± 1.5	3.2 ± 1.1	3.4 ± 1.2	3.2 ± 1.1
OCS (equivalent prednisone, mg/day)	25 ± 11	22 ± 12	26 ± 12	24 ± 11	19 ± 11	23 ± 11
ICS, (equivalent beclometasone, µg/day)	1690 ± 1110	2850 ± 1376	3000 ± 1224	2470 ± 1340	2556 ± 1460	2492 ± 1352
SABA (number of puffs/day)	4.7 ± 3.8	3.6 ± 3.9	6.4 ± 7.8	5.0 ± 5.4	5.5 ± 3.7	5.1 ± 5.0
Other Concomitant asthma medications						
Long-acting beta2 agonist, *n* (%)	10 (83.3%)	10 (90.9%)	10 (100.0%)	30 (90.9%)	9 (81.8%)	39 (88.6%)
Leukotriene modifiers, *n* (%)	4 (33.3%)	4 (36.4%)	3 (30.0%)	11 (33.3%)	2 (18.2%)	13 (29.5%)
Theophylline, *n* (%)	3 (25.0%)	1 (9.1%)	3 (30.0%)	7 (21.2%)	4 (36.4%)	11 (25.0%)

ACQ, Asthma Control Questionnaire; CS, corticosteroids; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; OCS, oral corticosteroids; SABA, short-acting beta2 agonist; all values are mean ± SD.

Table 2 (A) Oral corticosteroids wean (ITT population). (B) Oral corticosteroids wean (subpopulation initially treated with >15 mg prednisone daily/ITT population)

(A)

Parameters	Masitinib groups				
	3 mg/kg/day (*n* = 12)	4.5 mg/kg/day (*n* = 11)	6 mg/kg/day (*n* = 10)	All masitinib (*n* = 33)	Placebo (*n* = 11)
Absolute change between W4 and W16					
Mean ± SD	−10.7 ± 19.2	0.2 ± 26.8	−12.2 ± 18.5	−8.0 ± 21.3	−7.0 ± 11.7
Median	−14.0	−7.5	−11.3	−12.3	−10.0
Q1; Q3	−20; −10	−12.5; −2.5	−25; −2.5	−20; −5	−10; 0
Min; Max	−32.5; 45.0	−18.8; 65.0	−40.0; 20.0	−40.0; 65.0	−25.0; 20.0
Percent change between W4 and W16					
Mean ± SD	−41 ± 113	2 ± 179	−46 ± 69	−30 ± 123	−49 ± 50
Median	−82	−56	−69	−78	−57
Q1; Q3	−100; −33	−97; −6	−100; −17	−100; −19	−100; 0
Min; Max	−100; 300	−100; 433	−100; 100	−100; 433	−100; 50
Patients weaned at W16	5 (41.7%)	2 (25.0%)	3 (37.5%)	10 (35.7%)	3 (27.3%)

(B)

Parameters	Masitinib groups				
	3 mg/kg/day (*n* = 9)	4.5 mg/kg/day (*n* = 4)	6 mg/kg/day (*n* = 6)	All masitinib (*n* = 19)	Placebo (*n* = 6)
Absolute change between W4 and W16					
Mean ± SD	−17 ± 9	−7 ± 8	−14 ± 22	−14 ± 14	−7 ± 16
Median	−20	−5	−16	−15	−8
Q1;Q3	−20; −13	−12; −3	−30; 0	−20; −5	−20; 0
Min; Max	−33; 0	−19; 0	−40; 20	−40; 20	−25; 20
Percent change between W4 and W16					
Mean ± SD	−68 ± 38	−33 ± 42	−40 ± 78	−52 ± 53	−28 ± 47
Median	−81	−19	−69	−65	−38
Q1;Q3	−100; −33	−59; −6	−100; 0	−100; −13	−57; 0
Min; Max	−100; 0	−94; 0	−100; 100	−100; 100	−83; 50
Patients weaned at W16	4 (44.4%)	0 (0.0%)	2 (33.3%)	6 (31.6%)	0 (0.0%)

Efficacy and safety evaluations

The primary objective was to measure the reduction of oral corticosteroid dose after 16 weeks of masitinib treatment. Secondary objectives were to monitor the change from baseline in symptomatic scores (asthma control questionnaire, ACQ), the FEV_1 and rescue medication intake when necessary. Efficacy and safety parameters were assessed at baseline, prior to administration of masitinib, at week 2 and then weekly from weeks 4 to 16. A possible treatment extension was part of the study protocol in case of clinical benefit.

Statistical design

As this was a phase 2a clinical trial, data were analyzed using descriptive statistics. However, tests were performed for exploratory purposes (Wilcoxon tests for continuous variables and Fisher exact tests for binary variables). The rate of patients having shown improvement in the primary outcome is presented in terms of percentage and, if applicable, exact 95% confidence intervals. Efficacy analyses were performed on intent-to-treat (ITT) and per-protocol (PP) populations. To extrapolate missing data the last-observation-carried-forward method was applied. The analysis of all safety variables was performed on the ITT population, which included all safety data from patients who received at least one dose of study treatment and had at least one safety variable assessed after treatment.

Results

Patient characteristics and disposition

Forty-four patients were included in this study, divided into 33 masitinib-treated (12, 11 and 10 patients received 3, 4.5 and 6 mg/kg/day, respectively) and 11 placebo-treated patients (see Table 1). All had poorly controlled severe refractory corticosteroid-dependent asthma with a mean prebronchodilator FEV_1 of 59 ± 18% relative to predicted value, a high ACQ score (3.2 ± 1.1) and an average of 5.1 ± 5.0 puffs short-acting beta2 agonists per day. In addition to oral corticosteroids of 23 ± 11 mg equivalent prednisone per day, baseline asthma therapy included high-dose inhaled corticosteroids (2492 ± 1352 μg equivalent beclometasone per day) and long-acting beta2 agonists in 88.6% of the population (see Table 1). Other asthma treatments included leukotriene receptor antagonists and theophylline in 29.5% and 25.0% of patients, respectively. Twenty-five out of the 44 patients received regularly high-dose oral corticosteroids (i.e. >15 mg equivalent prednisone per day).

Efficacy

All 44 patients were randomized in 15 centers. Fourteen patients (31.8%) dropped out prematurely before week 16 (W16), mainly due to adverse events (AE) (57%) or insufficient therapeutic efficacy (14%). The dropout rate was similar in the masitinib and placebo treatment groups. Thirty patients (68.2%) completed the 16-week study period. The different composition of the patient population at baseline between the three masitinib dose groups and the small sample size did not allow any intra-dose comparisons. Nevertheless, no consistent dose–effect relationship was observed throughout the different efficacy endpoints investigated. We therefore merged all data and compared masitinib-treated patients to placebo-treated patients.

No significant difference could be observed with respect to the corticosteroid weaning process and the number of patients weaned at W16 in both ITT and PP populations. Similarly, no difference between masitinib and placebo-treated patients was observed regarding the extent of the oral corticosteroid weaning in both ITT and PP populations. As shown in Table 2A, the ITT median change in oral corticosteroid doses was 12.3 mg *vs* 10.0 mg equivalent prednisone corresponding to a reduction of –78% and –57%, respectively, and the percentage of patients weaned from oral corticosteroids of 35.7% and 27.3% in the masitinib and placebo groups, respectively. Focusing on the patients receiving >15 mg equivalent prednisone per day, doses of oral corticosteroids were reduced by 52 ± 53% in masitinib-treated patients and 28 ± 47% in the placebo group ($P = 0.223$), with six patients (31.6%) weaned at W16 in the masitinib treatment groups *vs* none in the placebo arm ($P = 0.278$, see Table 2B). In parallel, the number of patients experiencing at least one exacerbation during the study period was 42.4% and 54.5% in the masitinib-treated and placebo groups, respectively. This corresponds to an exacerbation rate adjusted for patient exposure in the masitinib treatment group at W16 compared to baseline of 0.22 ± 0.59 *vs* 0.37 ± 0.53 exacerbation/month (i.e. a 40.5% reduction), and a number of exacerbations per patient of 0.5 ± 0.7 *vs* 0.9 ± 1.0 ($P = 0.275$), respectively.

An improved asthma control was observed in masitinib-treated patients. This assertion was reflected in the ACQ score, asthma symptoms and rescue medication intake reported by the patients. ITT analysis showed that masitinib-treated patients improved their ACQ score by 0.99 unit at W16 ($P < 0.001$, see Figs 1 and 2). This improvement of asthma control occurred during the stringent procedure of the corticosteroid wean. ACQ score changes were 0.56, 1.57 and 0.89 units in patients treated with 3, 4.5 and 6 mg/kg dose, respectively. A nonsignificant ACQ improvement of 0.43 units at W16 was also observed in the placebo treatment group.

Regarding lung function parameters no statistically significant differences were observed between masitinib- and placebo-treated patients. Differences of baseline values between the three masitinib dose groups and the small sample size did not allow for an intra-dose comparison. No consistent dose relationship was observed throughout the different efficacy endpoints studied. Nineteen patients entered the extension phase for an average period of 11.4 ± 6.6 months, and at the time of this report 15 are still under drug treatment.

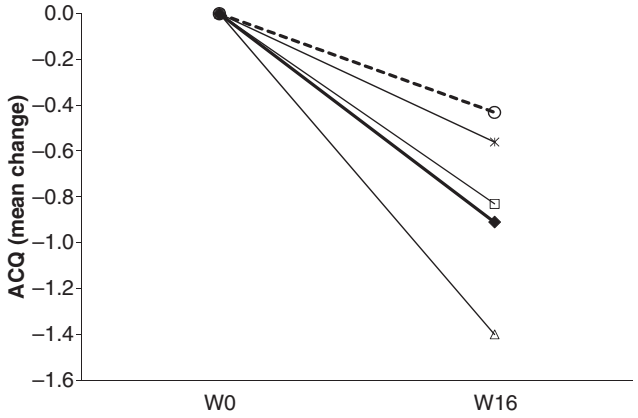

Figure 1. Mean absolute change in ACQ score (0–7 items), according to treatment group (ITT population). Change evaluated over 16-week study duration. Patients treated with masitinib experienced a statistically significant change from baseline in ACQ7 total score regardless of dose, while the placebo group showed no statistically significant change. Symbols: * = 3 mg/kg; Δ = 4.5 mg/kg, □ = 6 mg/kg for the treatment groups, ◆ = masitinib combined and ○ = placebo group.

Safety

In the event the study drug showed significant improvement for a patient a treatment extension was implemented. In these extension phases the follow-up of patients took place every four weeks during the first 3 months and then every 12 weeks until the end of the study. Overall the minimum and maximum period of drug administration ranged from 3 to 597 days. Of all patients treated with masitinib, regardless of dose, 93.9% experienced at least one AE *vs* 90.9% of the patients enrolled in the placebo treatment group.

The most frequent masitinib-related AEs reported were nausea (30.3%), skin rash (30.3%), peripheral edema (18.2%), diarrhea (18.2%), vomiting (12.1%), fatigue (12.1%) and pruritus (12.1%). These AEs were often transient and resolved spontaneously or with adequate treatment. No clear dose relationship could be established regarding event frequency with the exception of skin rash and edema, which showed an increased incidence with the high-dose regimens. Four patients exited the study during the first 2 weeks of treatment mainly due to gastrointestinal events. No placebo-treated patient but 10 patients (30.3%) receiving masitinib experienced severe AEs (excluding respiratory events). Among these, nine patients (27.3%) experienced severe drug-related AEs, leading to four of them (12.1%) withdrawing from the study.

One transient episode of severe neutropenia (< 500 cells/ml) was reported, which was detected after 28 days of treatment and resolved spontaneously without any study drug interruption or specific medical treatment. The vital signs and electrocardiogram of the patients showed no abnormalities.

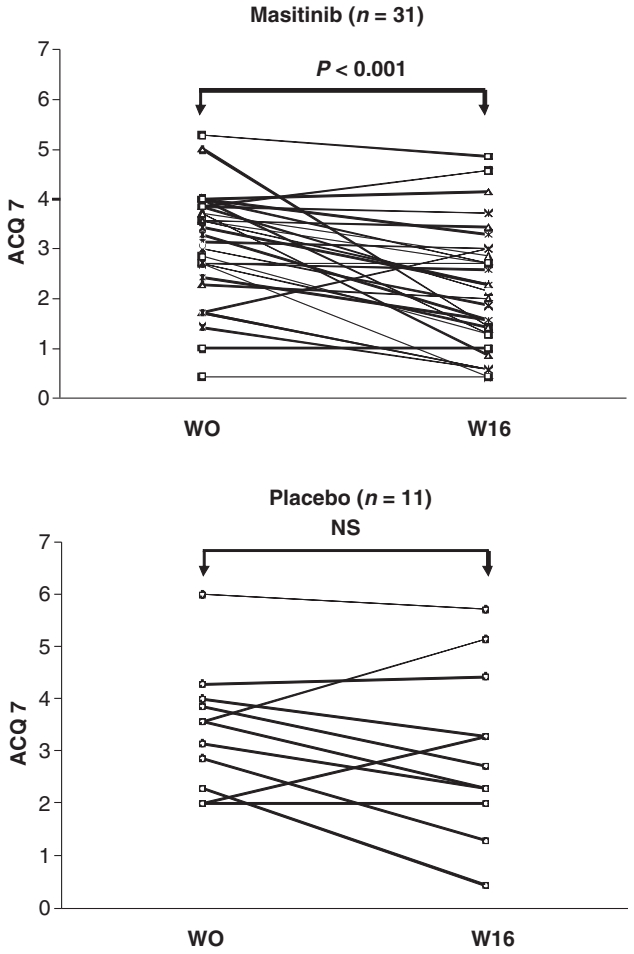

Figure 2. Absolute change in ACQ score, according to the ITT population. Upper panel: masitinib treatment group. Lower panel: placebo group. NS = nonsignificant, symbols: * = 3 mg/kg; Δ = 4.5 mg/kg, □ = 6 mg/kg for the treatment groups and ○ = placebo group.

Discussion

This is the first report on the use of the c-kit inhibitor masitinib in severe corticosteroid-dependent asthma. In a small group of well-characterized patients, this drug was able to improve asthma control (ACQ and frequency of severe exacerbations) despite the reduction of oral corticosteroid therapy. This effect was achieved with some drug-related AEs, which were mainly cutaneous and gastrointestinal. These preliminary proof-of-concept results suggest that masitinib warrants further long-term clinical studies in severe asthma.

Asthma is one of the most common chronic diseases worldwide. Approximately 5–10% of asthmatics present severe forms of the disease. Patients with inadequately controlled severe persistent asthma are at a particularly high risk of exacerbations, hospitalizations and death, and often have a severely impaired quality of life.

Although this group represents a relatively small fraction of the overall asthma population, they account for two-third of the asthma-related health care costs. This disproportionate use of healthcare resources points to a considerable unmet need of individual patients, and to health care providers (2–4).

Current management of asthma focuses on a stepwise approach tailored to disease severity and control (14). Patients with a severe type of asthma usually comply better with their drug prescriptions and are at a higher risk of harmful side-effects, which contrasts with the lack of efficacy as demonstrated by persistent poor control of the disease (2). These AEs are of particular concern for both patients and physicians as far as systemic corticosteroids are concerned. The unmet need of a better treatment of severe asthma calls for the development of innovative therapeutic approaches that take the expected risk/benefit ratio into account (2, 4).

Asthma is associated with chronic airway inflammation, which is classically, but not exclusively, eosinophilic in nature with infiltration of activated CD4 + lymphocytes, increased Th_2-cytokine (IL-4, IL-5, IL-13) expression, and mast cell infiltration of bronchial epithelium and submucosa including the airway smooth muscle layer (1, 2, 4). In addition, structural changes occur in the airway wall of severe asthmatic patients including subepithelial fibrosis, increased smooth muscle mass, enlargement of the submucosal glands, neovascularization and other epithelial abnormalities (1, 2, 4). These changes result in the development of persistent airflow obstruction, a feature mainly associated with severe forms of the disease (2, 4). Several new treatments that focused on inhibition of any single mediator failed to demonstrate convincingly their efficacy, with the exception of anti-immunoglobulin E therapy in a subset of patients with difficult-to-control severe allergic asthma, suggesting that IgE receptor expressing cells such as mast cells, basophiles, and to a lesser extent dendritic cells, are playing a role in asthma physiopathology (6, 7). The complexity and redundancy of the cytokine network was pointed out as the likely cause of failure of cytokine/anti-cytokine therapies (15). By contrast, tyrosine kinase inhibitors appear as a multi-target class of drugs with potential interest in complex diseases such as severe asthma (10). Therefore, inhibition of the c-kit tyrosine kinases, expressed on mast cells and other resident cells of the airways including dendritic cells, may reduce cell activation, thus, decreasing bronchial inflammation. In addition, PDGF receptor inhibition may reduce airway remodeling in severe asthma (10). Both imatinib mesylate and masitinib have recently been shown to abrogate allergic inflammation in a rodent model of asthma and the anti-proliferative activity of these agents may be of interest in the management of bronchial remodeling characteristic of severe refractory asthma (13, 16) (Hermine et al. unpublished observation).

The definition and characteristics of the enrolled subjects in the present trial fulfilled all criteria for patients with severe uncontrolled asthma according to the GINA guidelines (14). Patients were already cared for by experts at specific centres for their disease and accordingly most of the potential confounding factors, including poor compliance with the regimen had been investigated and corrected (2). No difference in the decreased use of systemic corticosteroid was observed between the treated and placebo populations, indicating that the required corticosteroid dose was lower in both groups, as reported in most of the asthma corticosteroid-dependent trials (17, 18). Taking into account that the present study did not include a run-in phase during which the oral corticosteroid doses could have been reduced in order to verify that patients were truly dependent on corticosteroids, the weaning results could be misleading.

In an attempt to overcome this potential bias, a subgroup analysis was performed in patients receiving the highest daily dose of corticosteroids (> 15 mg) at baseline. In those patients, doses of oral corticosteroids were reduced by $52 \pm 53\%$ in masitinib-treated patients *vs* $28 \pm 47\%$ in the placebo group and six patients were weaned off oral corticosteroids at W16 in the masitinib treatment groups *vs* none in the placebo group.

In addition, asthma control, assessed with a validated questionnaire such as ACQ that has been widely used in clinical trials (19), improved significantly in the masitinib-treated group as compared to placebo, for a similar reduction in corticosteroid therapy. Similar trends were observed with asthma exacerbations. The significant benefit observed in the masitinib-treated patients on the control of their disease is comparable to the effect observed in previous studies in less severe cases and the improvement in asthma control reached the minimal clinically important change described for this score (19). It should be emphasized that improvement in asthma control has been rarely reported in severe asthmatic patients to date, indicating the potential interest of masitinib to the population studied. As is true for other studies in severe asthma, including agents recently approved for the management of such patients, there was no significant change in lung function in this trial (7).

Exacerbations are a common manifestation in patients with poorly controlled severe asthma, and they increase the risk of mortality (20). In the present study, the rate of asthma exacerbation was reduced in the masitinib-treated patients as compared to placebo, further demonstrating the potential for improved control despite overall reduction in long-term oral corticosteroid therapy. This parameter is presumably relevant as exacerbations are common and contribute to the burden of severe asthma. Of note, omalizumab therapy was approved for the treatment of severe, difficult-to-control allergic asthma, based on an improved exacerbation rate in a population with severe asthma (7) highlighting the possible

importance of tyrosine kinase inhibitor masitinib in severe asthma.

A majority of AEs associated with masitinib are skin-related, mostly transient, and of variable intensity. Our present data confirm that skin rash and edema were the most frequent side-effects when using masitinib in severe corticosteroid-dependent asthma. These side-effects appeared early in the first weeks of therapy and were mostly of mild intensity leading to discontinuation in a few cases. Such side-effects have been previously described for masitinib and other tyrosine kinase inhibitors, and were found to be manageable through the use of antihistamine and a transient increase in corticosteroid therapy (21). Another risk associated with masitinib was severe neutropenia. According to a safety database consisting of >450 masitinib-treated patients, severe neutropenia occurred in 1% of the patient population (data not shown), a similar proportion to that observed with imatinib in recent surveys (22). In the present study, we observed one asymptomatic and fully reversible episode of neutropenia and there was no increase of infections in the group of masitinib-treated patients. This is an important observation since severe asthmatics are at a higher risk for recurrent pneumonias and infections especially when they receive long-term systemic corticosteroids (23). One can argue that the short-term duration of the present study may limit the relevance of the analysis of the safety data.

Recent studies indicate that imatinib and other tyrosine kinase inhibitors may be cardiotoxic (22, 24, 25). This has been mainly demonstrated in an experimental model of mice chronically exposed to imatinib (25). In humans chronically exposed to imatinib, a registry of patients treated for chronic myeloid leukemia has demonstrated that 1% of the exposed patient population developed heart failure, which occurred mainly in predisposed individuals (22). The mechanisms of this AE were related to the specific effect of imatinib on Bcr-Abl, which was demonstrated in the rodent study, emphasizing the relevance of novel tyrosine kinase inhibitors that target c-kit and PDGF, but not Bcr-Abl (25). Masitinib shows these properties and offers higher c-kit specificity, does not block 'dirty kinases' such as Src, VEGFR or Abl, and therefore has not been implicated with cardiac side-effects to date, as previously suggested for other tyrosine kinase inhibitors such as imatinib mesylate, dasatinib or sunitinib (24).

In conclusion, this proof-of-concept study showed that masitinib was safe in patients with severe asthma. In addition, it improved asthma control by alleviating daily symptoms and reducing asthma exacerbations despite the reduction of systemic exposure to corticosteroids. These observations suggest that c-kit and to a lesser extent PDGFR inhibition should be considered as a potential new treatment for severe asthma. Therefore, further long-term studies enrolling a larger cohort of patients with severe asthma are highly warranted.

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References

1. Busse WW, Lemanske RF Jr. Asthma. N Engl J Med 2001;**344**:350–362.
2. Chanez P, Wenzel SE, Anderson GP, Anto JM, Bel EH, Boulet LP et al. Severe asthma in adults: what are the important questions? J Allergy Clin Immunol 2007;**119**:1337–1348.
3. Godard P, Chanez P, Siraudin L, Nicoloyannis N, Duru G. Costs of asthma are correlated with severity: a 1-yr prospective study. Eur Respir J 2002;**19**:61–67.
4. Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults. Lancet 2006;**368**: 780–793.
5. Barnes PJ. New drugs for asthma. Nat Rev Drug Discov 2004;**3**:831–844.
6. Bousquet J, Chiron R, Humbert M. Biologics in asthma: difficulties and drawbacks. Expert Opin Biol Ther 2008;**8**:1921–1928.
7. Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy 2005;**60**:309–316.
8. Reber L, Da Silva CA, Frossard N. Stem cell factor and its receptor c-Kit as targets for inflammatory diseases. Eur J Pharmacol 2006;**533**:327–340.

9. Krishnammorty N, Oriss TB, Paglia M, Fei M, Yarlagadda M, Vanhaesebroeck B et al. Activation of c-kit in dendritic cells regulates T helper cell differentiation and allergic asthma. Nat Med 2008;**14**:565–573.
10. Ingram JL, Bonner JC. EGF and PDGF receptor tyrosine kinases as therapeutic targets for chronic lung diseases. Curr Mol Med 2006;**6**:409–421.
11. Chung KF, Hew M, Score J, Jones AV, Reiter A, Cross NC et al. Cough and hypereosinophilia due to FIP1L1-PDGFRA fusion gene with tyrosine kinase activity. Eur Respir J 2006;**27**: 230–232.
12. Hahn KA, Oglivie G, Rusk T, Devauchelle P, Leblanc A, Leblanc A et al. Masitinib is safe and effective for the treatment of canine mast cell tumours. J Vet Intern Med 2008;**22**: 1301–1309.
13. Berlin AA, Hogaboam CM, Lukacs NW. Inhibition of SCF attenuates peribronchial remodeling in chronic cockroach allergen-induced asthma. Lab Invest 2006;**86**:557–565.
14. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2007; http://www.ginasthma.org.
15. Barnes PJ. New drugs for asthma. Nat Rev Drug Discov 2004;**3**:831–844.
16. Perros F, Montani D, Dorfmuller P, Durand-Gasselin I, Tcherakian C, Le Pavec J et al. Platelet derived growth factor expression and function in idiopathic pulmonary arterial hypertension. Am J Respir Crit Care Med 2008;**178**: 81–88.
17. Nizankowska E, Soja J, Pinis G, Bochenek G, Sladek K, Domagala B et al. Treatment of steroid-dependent bronchial asthma with cyclosporin. Eur Respir J 1995;**8**:1091–1099.
18. Lock SH, Kay AB, Barnes NC. Double-blind, placebo-controlled study of cyclosporin A as a corticosteroid-sparing agent in corticosteroid-dependent asthma. Am J Respir Crit Care Med 1996;**153**:509–514.
19. Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med 2006;**100**:616–621.
20. Johnston NW, Sears MR. Asthma exacerbations. 1: epidemiology. Thorax 2006;**61**:722–728.
21. Valeyrie L, Bastuji-Garin S, Revuz J, Bachot N, Wechsler J, Berthaud P et al. Adverse cutaneous reactions to imatinib (STI571) in Philadelphia chromosome-positive leukemias: a prospective study of 54 patients. J Am Acad Dermatol 2003;**48**:201–206.
22. Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, Gattermann N et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 2006;**355**: 2408–2417.
23. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. J Allergy Clin Immunol 2007;**119**: 405–413.
24. Chen MH, Kerkelä R, Force T. Mechanisms of cardiac dysfunction associated with tyrosine kinase inhibitor cancer therapeutics. Circulation 2008;**118**: 84–95.
25. Kerkelä R, Grazette L, Yacobi R, Iliescu C, Patten R, Beahm C et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nat Med 2006;**12**:908–916.

