

EDITORIALS



Mast Cells and KIT as Potential Therapeutic Targets in Severe Asthma

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Mast cells and many of their secreted products have long been thought to contribute to the pathologic processes underlying asthma,^{1,2} but no clinical studies have assessed whether specifically targeting mast-cell survival or development would have therapeutic benefit in the treatment of this disorder. In this issue of the *Journal*, Cahill and colleagues³ report the results of a randomized, double-blind, placebo-controlled, phase 2, 24-week, proof-of-principle trial in which patients with severe, poorly controlled asthma were treated with the tyrosine kinase inhibitor imatinib, which can inhibit KIT,⁴ the major survival and growth factor for mast cells.² The total number of patients was small (62 patients underwent randomization per protocol); however, a significant effect of imatinib treatment was observed with regard to the prespecified primary outcome of improvement in airway hyperresponsiveness, assessed as the increase from baseline at 6 months in the methacholine PC₂₀, a measurement of the concentration of methacholine required to decrease the forced expiratory volume in 1 second (FEV₁) by 20%. The increase in PC₂₀ was 1.73 doubling doses in the imatinib group, as compared with 1.07 doubling doses in the placebo group (P=0.048). Patients in the imatinib group also had greater reductions in serum levels of the mast cell–derived protease tryptase than did patients in the placebo group (P=0.02), as well as a small improvement in lung function, measured as the FEV₁.

The authors were appropriately cautious in interpreting their findings, noting that their data

did not prove that the observed beneficial effects of imatinib reflected its effects on either KIT or mast cells, as opposed to actions on other imatinib-sensitive tyrosine kinases or on other KIT-expressing cells. Indeed, although decreases from baseline in the total numbers of tryptase-positive mast cells in the airways and the bronchial smooth muscle were greater in the imatinib group than in the placebo group, the differences between the groups were not significant (P=0.11 and P=0.07, respectively), nor was the correlation between increases in FEV₁ and reductions in the numbers of airway mast cells in endobronchial-biopsy samples significant (P=0.06). However, given that KIT can influence mast-cell functions (including enhancing the activation of the cell by IgE-dependent mechanisms) as well as survival,² and in light of a report that patients who receive long-term treatment with imatinib (for chronic myeloid leukemia) have marked reductions in numbers of tissue mast cells,⁵ the findings of Cahill et al. are consistent with the hypothesis that the benefit observed in the imatinib-treated group may have reflected, at least in part, the effects of imatinib on mast-cell numbers, functions, or both.

Although the findings reported are not clinically directive, do they make the case that, at least in some patients with asthma, “targeting” mast cells would be a good idea? The evidence that mast cells might represent important contributors to the pathogenesis of asthma is strong.^{1,2} Mast cells normally reside in the lungs, and on activation by IgE-dependent (i.e., “allergic”)

or other mechanisms, they can release a diverse spectrum of mediators that in turn can rapidly induce local effects on blood vessels, nerves, and mucous glands, as well as on epithelial cells, airway smooth-muscle cells, and immune cells.^{1,2} Moreover, a study involving one model of “chronic asthma” in mice has indicated that, at least in that context, mast cells also can contribute to the establishment of chronic inflammation in the airways, with cellular infiltrates that include neutrophils and eosinophils, as well as contribute to features of tissue remodeling that resemble those observed in association with “real” (i.e., human) asthma, including the development of increased numbers of mucus-secreting goblet cells in the airway epithelium and increased deposition of interstitial collagen.⁶

Do we therefore have the green light to go ahead and target mast cells, or perhaps even ablate them, in patients with asthma? I agree with Cahill et al. in thinking that the currently available evidence suggests that this should be studied further, but cautiously. First, as in other areas of so-called precision medicine, patient selection may be critical. As discussed by Cahill et al., studies involving mouse models^{6,7} and studies involving patients with severe asthma⁷ suggest that mast cells⁶ and interferon- γ ^{6,7} may have more critical pathogenic roles in forms of asthma that are characterized by the substantial involvement of neutrophils than they do in those with a type 2 helper T-cell–like immune response tissue signature, in which eosinophils are more prominent.⁸ Second, evolution has not endowed us with mast cells to fill our asthma clinics or to permit us to develop allergic disorders, which are now thought to affect 20 to 30% of the world’s people. In addition to potentially beneficial roles in host defense against parasites, mast cells and IgE also can contribute to innate and adaptive immune responses that increase survival among mice injected with certain arthropod or reptile venoms,⁹ and other beneficial roles of mast cells probably are yet to be discovered. Third, studies in mice suggest that even in the context of “asthma models,” some products of mast cells — in this case, the chymase-like protease, mouse mast cell

protease 4 — can function to limit the development of certain aspects of the associated pathologic processes.¹⁰

Yet in those unfortunate people in whom the functions of mast cells can be strongly implicated as contributing to disease, suppressing their function or reducing their numbers may indeed confer more benefit than harm, particularly if these cells can be targeted locally at sites of disease. It should go without saying that if agents were to be devised that can more specifically target mast cells than do drugs such as imatinib, and can do so safely, then testing such agents in the clinic will be of particular interest.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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DOI: 10.1056/NEJMe1702653

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