Prostaglandin D-2

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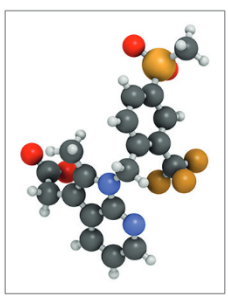
Prostaglandin D_2: the end of a story or just the beginning?



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Tremendous progress has been made in the treatment of asthma over the past decade. The development of monoclonal antibodies against IgE, interleukin-5 (IL-5) or its receptor, or the IL-4 receptor in particular has been a game changer, for a selected group of patients. These biologics all target the allergic or type 2 side of the spectrum of asthma, but even within the severe allergic or type 2 high asthma population these drugs do not completely prevent exacerbations, reducing their frequency by around 40–60%. Additionally, they must be administered intravenously or subcutaneously, and are costly. In short, there are multiple reasons for expanding the range of treatment options for patients with severe asthma.

In *The Lancet Respiratory Medicine*, Christopher Brightling and colleagues[1] present the results of the LUSTER-1 and LUSTER-2 randomised controlled trials of fevipiprant, an oral non-steroidal antagonist of the prostaglandin D_2 receptor 2 (DP_2 receptor). Prostaglandin D_2 is an arachidonic acid metabolite produced by prostaglandin D_2 synthase, released from mast cells, eosinophils, and several airway structural cells, with potent activity on eosinophils, neutrophils, mast cells, T helper 2 (Th2) cells and type 2 innate lymphoid cells. High urinary prostaglandin D_2 metabolites correlate with low lung function in asthma. Preliminary studies done in guinea pigs indicate that prostaglandin D_2 mobilises eosinophils from bone marrow, activates eosinophil migration, and supports eosinophil recruitment into the lungs in response to allergen exposure.[2]

Fevipiprant is the first DP_2 receptor antagonist to be evaluated in a phase 3 trial. It was tested before in two phase 2 studies, where it showed improvements in FEV_1 of 112–207 mL, depending on the dose and subgroup, next to improvements in asthma control.[3,4] Interest in fevipiprant was, however, most spurred by a small mechanistic study of 61 participants, from Leicester, UK, published in *The Lancet Respiratory Medicine* in 2016, which found a remarkable 4·3% reduction in sputum eosinophilia next to improvements in inflammatory and structural abnormalities in biopsies, and a 160 mL difference in FEV_1.[5] Since increased eosinophil numbers, in blood or airways, have a clinically meaningful association with the likelihood of asthma exacerbations, the authors designed a larger and longer study primarily aimed at reducing asthma exacerbations; notably, a similar strategy of shifting the focus away from FEV_1 was instrumental to the development of anti-IL-5 biologics, which are now part of mainstream asthma treatment.[6]

The LUSTER trials were two replicate studies done in adolescents and adults with severe asthma (GINA Steps 4 and 5), two thirds of whom had blood eosinophil counts of 250 cells per µL or higher. Oral fevipiprant (150 mg and 450 mg once daily) was compared with placebo over 52 weeks. The primary efficacy endpoint, a reduction in the annualised rate of moderate to severe asthma exacerbations with fevipiprant versus placebo, was not met in either trial, on either dose. Changes in pre-bronchodilator FEV_1 were also non-significant, but significant improvements in post-bronchodilator FEV_1 of 60–120 mL were shown, depending on the dose and subgroup. Small improvements in asthma control were also observed with the 450 mg dose.

So, after high expectations, what explains these results? The study was well designed and executed, although it should be noted that the assumptions for power calculations were not met. An exacerbation frequency of 1·5 per year in the placebo group, although lower than the selection criterion of at least two exacerbations in the previous year, was not achieved (the frequency in the placebo group was 0·95 exacerbations per year), leaving less room for improvement.

Central to the LUSTER trials was the premise that blood eosinophilia closely reflects the likelihood of asthma exacerbations, and that fevipiprant would reduce eosinophilia and hence reduce the frequency of exacerbations, especially in the two-thirds of participants who were pre-selected to have increased eosinophil counts at baseline. Contrary to this premise, patients without eosinophilia above the preset 250 cells per µL did not report a higher number of asthma exacerbations in the previous year. Most importantly, in the pooled analyses, the high eosinophil group had a 23% reduction in exacerbations versus 22% in the overall population, with the 450 mg dose.

How sure are we that fevipiprant should be targeted to patients with higher eosinophil counts (>250 cells per µL), or even those with very high eosinophil counts (>450 cells per µL)? This is a relevant question because a 22% overall

reduction in exacerbation frequency is not trivial, although it is lower than that anticipated in a population of patients with type 2-high allergic asthma when compared with the effects seen with biologics. In less selected severe asthma populations, such improvements in exacerbation frequency and FEV_1 have formed the basis for the registration of new, long-acting inhaled drugs for asthma.[7,8] Similarly, in chronic obstructive pulmonary disease, such reductions of 15–25% in exacerbation frequency are deemed worthwhile, and led to guideline recommendations for these drugs.

Why does the overall effect seem to be as good in non-eosinophilic populations as in those with eosinophilia (>250 cells per µL)? Prostaglandin D_2 has broader chemoattractant activity, activating human Th2 cells and macrophages to secrete neutrophil chemokines, and contributes to neutrophilic inflammation in animal models.[9,10] Not all cases of severe asthma or severe exacerbations are eosinophilic, as there are probably multiple pathways towards eosinophilia, and it is conceivable that the activity in the neutrophil pathway at least partially explains the 22% overall exacerbation rate reduction observed in the LUSTER trials. Unfortunately, sputum cell eosinophils and neutrophils were not measured at baseline or during exacerbations in the LUSTER trials. Such information could have proven useful to understanding the results observed.

Perhaps, we should not yet close the book on prostaglandin D_2 antagonism, but instead consider adding a new chapter.

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