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Fevipirant in CRSwNP and comorbid asthma: Wrong target population or wrong PGD₂ receptor?

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Aspirin-exacerbated respiratory disease

Prior to the approval of dupilumab in 2019, the treatment of chronic rhinosinusitis with nasal polyposis (CRSwNP) was limited to topical and/or systemic steroids or surgical intervention. While biologic therapy has offered meaningful medical management options for CRSwNP, given their high cost and requirement for parenteral administration, novel medical treatments are sought. For the significant subset of patients with CRSwNP and co-morbid asthma, medical options that address upper and lower airway inflammation are of particular importance.

Prostaglandin (PG)_{D2} is a key inflammatory mediator produced by tissue resident mast cells and recruited inflammatory cells implicated in both asthma and CRSwNP. PGD₂ and PGD₂ metabolites have actions at three receptors: the D prostanoid (DP)₁ receptor, the DP₂ receptor also known as CRTH₂, and the thromboxane (TP) receptor. Each receptor facilitates unique and different functions of PGD₂ relevant in chronic airway inflammation. DP₁ is responsible for vasodilation, inhibition of platelet aggregation, Th0 cell polarization to Th2 cells by inhibition of dendritic cell(DC) IL-12 release, and DC migration(1), DP₂ contributes to inflammatory cell [group 2 innate lymphoid cells (ILC₂), eosinophils, basophils, T helper type 2 cells, macrophages] recruitment to sites of tissue inflammation and promotes ILC₂ survival and type 2 cytokine production(1, 2), and actions at the TP receptor facilitate bronchospasm(1). Both DP₁ and DP₂ receptors are implicated in anti-fibrotic actions of PGD₂ in bleomycin-induced pulmonary fibrosis models while DP₂ demonstrates a pro-fibrotic role in Hermansky-Pudlack syndrome-associated lung disease(1). These pro-inflammatory actions of PGD₂ support a potential therapeutic benefit from PGD₂ pathway inhibition in asthma and CRSwNP. The selective DP₂ antagonist, fevipiprant, showed promise with improvements in forced expiratory volume in one second (FEV)₁ and reductions in sputum eosinophils in phase II clinical trials in asthma. However, the development of fevipiprant in asthma was halted after phase III studies demonstrated safety but failed to achieve the targeted reductions in asthma exacerbations or improvements in FEV₁ among patients with moderate-to-severe and uncontrolled asthma.

In this issue of the *Journal*, Gevaert and colleagues report the results of THUNDER, a phase IIIb, multi-center, randomized controlled trial fevipiprant or placebo in 98 subjects with CRSwNP and concomitant asthma (3). Subjects with a total nasal polyp score of ≥ 4 despite 4 weeks of mometasone furoate nasal spray 200 μ g once daily were randomized 1:1:1 to add-on oral fevipiprant 150 or 450 mg or matched placebo once daily for 16 weeks. The primary endpoint was change from baseline to week 16 in nasal polyp score as assessed by the centralized, 2-reader, blinded review of rhinoscopy videos. Secondary endpoints included change in nasal congestion score, the Sino-nasal Outcome Test (SNOT)-22 and smell as assessed by the University of Pennsylvania Smell Identification Test (UPSIT). No asthma outcomes were reported. The sample size was determined based on a mean reduction of 1.5 in nasal polyp score in fevipiprant groups compared with placebo. This primary endpoint projection was optimistic. Currently approved biologic therapies have failed to achieve a mean reduction in change from baseline in nasal polyp score of 1.5 relative to placebo in study populations with higher starting nasal polyp scores(4). The fevipiprant dose, study duration, the requirement for background mometasone furoate, and selection of primary and secondary endpoints align with other recent studies of medical therapeutics in CRSwNP and other phase III studies of fevipiprant in asthma. Even with the aggressive primary endpoint target, the primary endpoint data are decisively negative across both fevipiprant doses. While the fevipiprant 450 mg dose demonstrated a significant improvement in smell over placebo by 4.5 points on the UPSIT, SNOT-22 failed to improve, and nasal congestion scores showed a trend towards worsening.

Post-hoc analyses of the primary endpoint and the secondary endpoint nasal congestion score stratified by baseline peripheral blood eosinophil count (cut-off 450 μ l) were also negative. Despite the mechanistic data to suggest benefit from DP2 antagonism in CRSwNP, these results from the first randomized controlled trial of fevipiprant in CRSwNP are negative.

Could selection of the wrong study population or disease state explain a negative study? PGD₂ is particularly relevant in the aspirin-exacerbated respiratory disease (AERD) subgroup of CRSwNP and comorbid asthma. At baseline, subjects with AERD have elevated urinary PGD₂ metabolites compared with aspirin-tolerant subjects with asthma, levels which inversely correlate with the aspirin-induced decline in FEV1(5). PGD₂ levels increase acutely during aspirin-induced reactions during which peak PGD₂ levels correlate with increases in nasal congestion scores and reductions in FEV1 and blood eosinophils(5, 6). The acute rise in PGD₂ levels following aspirin ingestion is associated with the acute influx of DP2/CRTH2+ cells out of the blood into the nasal mucosa which is then reversed on high-dose aspirin therapy when PGD₂ levels fall and blood DP2/CRTH2+ cells increase(7). Moreover, high-dose aspirin therapy suppression of PGD₂ in subjects with AERD is understood as one mechanism of high-dose aspirin therapy benefit in AERD(7). Such data support targeting the PGD₂ pathway could benefit the acute cyclooxygenase-1 inhibitor induced respiratory reactions and the chronic baseline inflammation associated with AERD.

Regrettably, the THUNDER study population was not enriched for subjects with AERD. The randomization of only one subject with AERD is unfortunate and a bit unexpected given 10-16% of subjects with CRSwNP and comorbid asthma have AERD(8). Phase III studies of dupilumab in CRSwNP included 28% of the study population with AERD(9). It raises the question of a study population with limited PGD₂-driven pathology or undiagnosed AERD. Additionally, no assessment of baseline systemic or respiratory tract PGD₂ levels were performed, despite the clinical availability of a laboratory test for the measurement of a urinary PGD₂ metabolite. The opportunity to assess the clinical utility of fevipiprant in a study population with high levels of PGD₂ and/or AERD was missed. Lacking a baseline assessment of the PGD₂ pathway, we are left to question whether the wrong study population was targeted. Alternatively, the importance of DP2/CRTH2+ cell recruitment to the nasal polyp tissue and its contribution to the signs and symptoms of CRSwNP may be overestimated. Another investigational product depleted nasal polyp tissue eosinophils yet failed to reduce nasal polyp size providing strong support nasal polyp size is independent of tissue eosinophilia(10). The lack of post-fevipiprant treatment biopsies was a missed opportunity to evaluate the impact of DP2 antagonism on tissue resident and recruited inflammatory cells (i.e. mast cells, ILC2) in nasal polyp tissue and the role of these DP2/CRTH2+ inflammatory cells in nasal polyp size.

Phase II and III studies of fevipiprant in asthma showed modest positive clinical effects but have fallen short of the clinically and statistically significant mark. The most promising data have come from study cohorts enriched for atopy and eosinophilia. No studies have yet enriched for patients with elevations in PGD₂. One conclusion from phase II and III studies of fevipiprant is that the ideal target population for DP2 antagonism has not yet been identified. Alternatively, the clinical trial results from fevipiprant may indicate that broader inhibition of the PGD₂ pathway is required to see therapeutic benefit in type 2 airway inflammation diseases (Figure 1). Based on our current understanding of receptor mechanisms, the inclusion of DP1 and TP receptor antagonism would be more likely to yield measurable clinical change in nasal congestion scores and lung function respectively. Have studies targeted the wrong population or

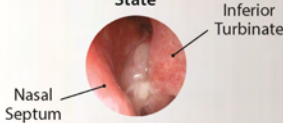
wrong receptor? Future studies enriched for AERD and paired with mechanistic assessments of the PGD₂ pathway are required before fevipiprant is excluded as a viable therapeutic in CRSwNP.

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Figure Legend:

Inhibition of the prostaglandin (PG)D₂ pathway in chronic rhinosinusitis with nasal polyposis and asthma. Data on the clinical efficacy of DP2/CRTH2 antagonism available from the phase IIIb THUNDER clinical trial in CRSwNP and comorbid asthma presented on the left (black font). Proposed clinical efficacy of broad PGD₂ pathway receptor antagonism presented on the right (blue font) based on preclinical and translational studies. Arrows denote an increase (↑) or decrease (↓) in the listed outcome measure. SNOT-22 – sinonasal outcome test-22, FEV₁ – forced expiratory volume in one second, Eos – eosinophil, Baso – basophil, TH₂ – T helper type 2 cell, ILC2 – group 2 innate lymphoid cell.

	Impact of DP2/CRTH2 Receptor Antagonist	Hypothesized Impact with Broad PGD2 Pathway Antagonist (DPI/DP2/TP Receptors)
Baseline State 	No Change	↓
Nasal Polyp Score 	No Change/↑	⇕
Nasal Congestion Score		
SNOT-22 Score	No Change	⇕
Sense of Smell	↑	↑
Nasal Polyp Tissue Type 2 Inflammation 	Not Assessed (⇕Hypothesized)	⇕
FEV₁ 	↑/↑↑	↑↑
Sputum 	↓	↓
Asthma Exacerbations 	↓	⇕