

## Review



# Biology and Function of Eosinophils in Chronic Rhinosinusitis With or Without Nasal Polyps

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## ABSTRACT

Chronic rhinosinusitis (CRS) with or without nasal polyposis is a complex medical condition characterized by varying patterns of chronic innate and adaptive mucosal inflammation. Treatment of CRS has been traditionally limited to corticosteroids and sinus surgery; however, novel biologics have more recently been evaluated as steroid- and surgery-sparing options. While it is clear that there are different subtypes or endotypes of CRS, perhaps the most frequent presentation involves the features of type 2 inflammation, including a prominent tissue eosinophilia component. The purpose of this review is to provide an update on eosinophil biology as well as on the potential contribution of eosinophils and their mediators to the pathophysiology of CRS, drawing mechanistic conclusions mainly from studies of human sinus mucosal tissues, nasal secretions, and benefits (or lack thereof) from the use of various pharmacotherapies. The unavoidable conclusion derived from this approach is that eosinophils themselves cannot fully explain the underlying pathophysiology of this complex disorder.

**Keywords:** Eosinophils; nasal polyps; sinusitis; biologics; inflammation

## INTRODUCTION

Eosinophils are a distinct lineage of granulocytic leukocytes whose presence in the blood and within certain tissues has been known for over a century. Since their discovery not just in humans but virtually all vertebrates, these unique cells with their distinct panoply of proteins, organelles and other features have been implicated in a wide variety of pathophysiologic and beneficial responses to their hosts.<sup>1-3</sup> Homeostatic contributions attributed to eosinophils range from roles in innate immune responses to parasitic invaders such as helminths to contributions to tissue repair, fat metabolism and other responses. In contrast, it has been widely appreciated that eosinophils can cause trouble: their increased number and activation are associated with a wide gamut of diseases including asthma, eczema, eosinophilic gastrointestinal disorders, hypereosinophilic syndromes and more, as well as the focus of this review, chronic rhinosinusitis (CRS) with or without nasal polyps (CRS<sub>NP</sub> and CRS<sub>SNP</sub>, respectively). For instance, in patients with Samter's triad, now known as aspirin-exacerbated respiratory disease, Dr. Samter himself stated in a 1961 review<sup>4</sup>: "Cells which are found in nasal polyps are not limited to any particular type, although lymphocytes are rare

entitled to a share of royalties received by Johns Hopkins University during development and potential sales of such products. Dr. Bochner is also a co-founder of Allakos, which makes him subject to certain restrictions under University policy. The terms of this arrangement are being managed by Johns Hopkins University and Northwestern University in accordance with their conflict of interest policies. W.W.S. served on a scientific advisory board for GlaxoSmithKline.

and eosinophils tend to occur in conspicuous numbers” and at the time, the leading theory was that eosinophils were “...indicators of antigen-antibody reactions of the immediate, histamine-releasing, type...[although] nasal polyps might be an exception from this rule.”

Fast forward to 2020 where, despite tremendous advances in knowledge and availability of drugs that target type 2 inflammation and even eosinophils themselves, our understanding of CRS pathophysiology with or without nasal polyposis including the role of eosinophils in these disorders remains unsatisfying.<sup>5</sup> What follows is an overview of eosinophil biology from the standpoint of its potential contributions to CRS pathophysiology, followed by a summary of what is known about eosinophils and their mediators in samples derived from patients with CRSwNP and CRSsNP. The review concludes with a discussion of lessons learned as a result of newer pharmacology capable of targeting type 2 inflammation and eosinophils in these diseases, finishing with examples of unanswered questions and ideas for future directions.

## EOSINOPHIL BIOLOGY IN RELATION TO CRS

When considering mechanisms of local eosinophil recruitment, retention, survival, and activation, several likely pathways come to mind. Those involved in their preferential recruitment almost certainly include cell surface adhesion molecules including P-selectin, beta 1 integrins, such as VLA-4, and beta 2 integrins, interacting with their respective counter-ligands expressed on inflamed endothelium of the sinus mucosa (P-selectin ligand [CD162], VCAM-1, and ICAM-1 respectively, plus others).<sup>6-8</sup> A separate subset of chemotactic factor receptors, such as CCR3, CRTh2, and CysLT1, allow for the preferential and directional migration of eosinophils into the extravascular compartment compared to most other circulating cells.<sup>2,6</sup> Beyond their selective accumulation, eosinophils display evidence of prolonged survival in nasal tissue, presumably due to their protection from cell death by locally produced cytokines such as interleukin (IL)-5 and granulocyte-macrophage colony-stimulating factor.<sup>9,10</sup>

Beyond their accumulation and prolonged survival within the nasal mucosa, perhaps more important is what eosinophils generate and release as part of their contribution to the inflammatory response. Despite the fact that mechanisms for eosinophil activation remain incompletely defined, it is known that eosinophils secrete a broad range of substances. Some are preformed and stored within granules. Indeed, particularly prominent within the eosinophil genome is evidence of commitment to production of eosinophil granule proteins. The crystalloid core of the specific granules contains major basic protein, while the granule matrix is the site of storage for eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), eosinophil peroxidase (EPX), secretory phospholipase A<sub>2</sub>, and more. Other proteins derived from human eosinophils include galectin-10, enzymes, cytokines, growth factors, and chemokines (**Table**).<sup>11</sup> Interestingly, many of these eosinophil granule proteins can be detected in nasal biospecimens,<sup>12,13</sup> and other proteins like galectin-10 (formerly known as Charcot-Leyden crystal [CLC] protein, comprising up to 10% of the total protein contained in eosinophils) have been shown to promote inflammation.<sup>14,15</sup>

In addition to protein mediators, eosinophils produce potent pro-inflammatory lipids generated via the metabolism of arachidonic acid. In one pathway, 5-lipoxygenase (5-LO) and 5-LO activating protein (FLAP) first convert arachidonic acid to 5-HETE which is then

**Table.** Eosinophil mediators

<b>Granule proteins</b>	<b>Cytokines</b>
Major basic protein (MBP)	IL-1 $\alpha$
MBP homolog (MBP2)	IL-2
Eosinophil cationic protein (ECP)	IL-3
Eosinophil-derived neurotoxin (EDN)	IL-4
Eosinophil peroxidase (EPX)	IL-5
Charcot-Leyden crystal (CLC) protein (Galectin 10)	IL-6
Secretory phospholipase A <sub>2</sub> (sPLA <sub>2</sub> )	IL-9
Bactericidal/permeability-inducing protein (BPI)	IL-10
Acid phosphatase	IL-11
Arylsulfatase	IL-12
$\beta$ -Glucuronidase	IL-13
	IL-16
	Leukemia inhibitory factor (LIF)
	Interferon- $\gamma$ (IFN- $\gamma$ )
	Tumor necrosis factor- $\alpha$ (TNF- $\alpha$ )
	GM-CSF
	APRIL
<b>Lipid mediators</b>	<b>Chemokines</b>
Leukotriene B <sub>4</sub> (negligible)	CXCL8 (IL-8)
Leukotriene C <sub>4</sub>	CCL2 (MCP-1)
5-HETE	CCL3 (MIP-1 $\alpha$ )
5,15- and 8,15-dihETE	CCL5 (RANTES)
5-oxo-15-hydroxy-6,8,11,13-ETE	CCL7 (MCP-3)
Platelet-activating factor (PAF)	CCL11 (eotaxin)
Prostaglandin E <sub>1</sub> and E <sub>2</sub>	CCL13 (ECP-4)
Thromboxane B <sub>2</sub>	
<b>Oxidative products</b>	<b>Growth factors</b>
Superoxide radical anion (OH <sup>-</sup> )	Nerve growth factor (NGF)
Hydrogen peroxide (H <sub>2</sub> O <sub>2</sub> )	Platelet-derived growth factor (PDGF)
Hypohalous acids	Stem cell factor (SCF)
	Transforming growth factor (TGF- $\alpha$ , TGF- $\beta$ )
<b>Enzymes</b>	
Collagenase	
Metalloproteinase-9	
Indoleamine 2,3-dioxygenase (IDO)	

Physiologic significance of these cytokines needs to be confirmed. Reproduced with permission.<sup>11</sup> APRIL, a proliferation-inducing ligand; ETE, eicosatetraenoic acid; GM-CSF, granulocyte-macrophage colony-stimulating factor; HETE, hydroxyeicosatetraenoic acid; IL, interleukin.

further converted to cysteinyl leukotriene C<sub>4</sub> (LTC<sub>4</sub>) by LTC<sub>4</sub> synthetase. Nasal polyps have significantly higher levels of 5-lipoxygenase, LTC<sub>4</sub> synthetase, and cysteinyl leukotrienes compared to healthy sinonasal mucosa.<sup>16</sup> More specifically, a significant correlation was reported between eosinophil-associated genes (*e.g.*, ECP and IL-5) and cysteinyl leukotrienes (*e.g.*, LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>).<sup>16,17</sup> Eosinophils produce higher levels of LTC<sub>4</sub> when primed with IL-5 or eotaxin both of which are known to be elevated in nasal polyps.<sup>16,17</sup> It is thus likely that eosinophils are one of the major producers of cysteinyl leukotrienes in CRSwNP. These mediators in turn can promote further eosinophil recruitment, mucus secretion, and increased vascular permeability.

Arachidonic acid can also be metabolized via the cyclooxygenase pathway to generate a variety of prostaglandins. In particular, eosinophils have been reported to generate prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) and E<sub>2</sub> (PGE<sub>2</sub>) as well as thromboxane B<sub>2</sub>. PGE<sub>2</sub> is associated with anti-inflammatory effects and levels were lower in CRSwNP compared to healthy sinonasal mucosa.<sup>16,18</sup> Platelet activating factor (PAF) is another important lipid mediator that is generated from membrane-bound lysophosphatidylcholine following the liberation of

arachidonic acid. PAF is important in eosinophil recruitment and activation. While not as extensively studied in CRS to date, PAF levels in nasal polyps were significantly higher in patients who had higher numbers of tissue eosinophils,<sup>19</sup> suggesting eosinophils may be an important source.

## **EOSINOPHILS IN CRSWNP**

### **International geographic diversity in eosinophilic nasal polyps**

Historically, nasal polyps in Asia were predominantly characterized by a neutrophilic, not eosinophilic, cellular infiltrate.<sup>20</sup> However, over the past 2 decades, studies have documented a shift in this paradigm with rising numbers of eosinophilic nasal polyps observed in several Asian countries.<sup>21</sup> In one study from Korea, the prevalence of eosinophils detected in nasal polyps increased from 24% to 51% over a 17-year period.<sup>22</sup> Similar significant increases have been observed in Thailand, China, and Japan.<sup>23,24</sup> Perhaps not unexpectedly, as the prevalence of eosinophils in nasal polyps has increased, the proportion of neutrophils has declined.<sup>24</sup>

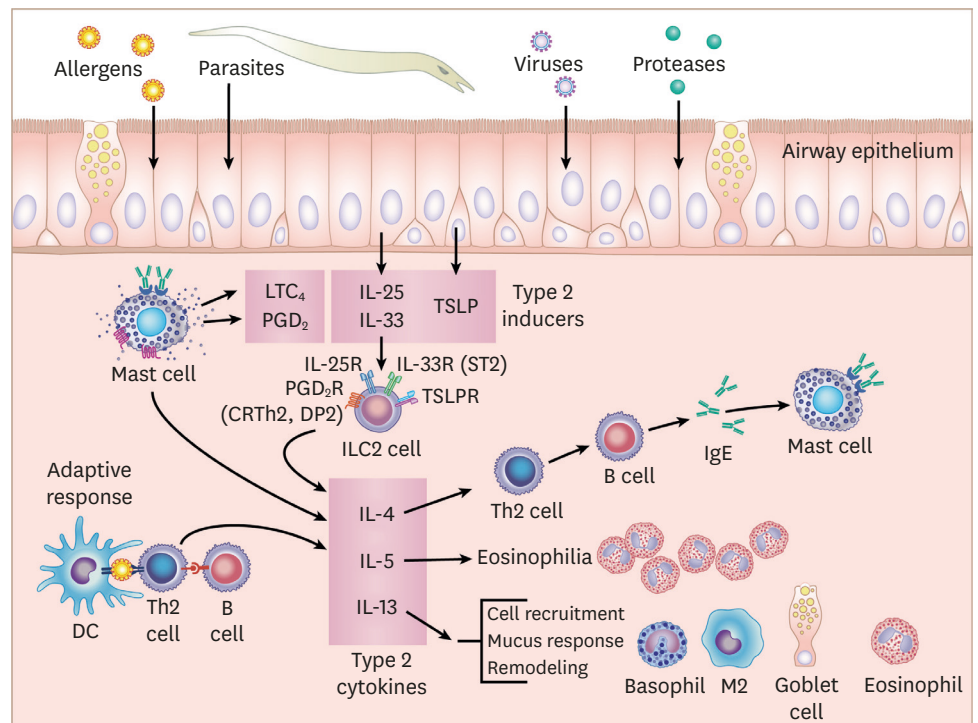
In contrast to Asia, patients with CRSwNP living in the United States (US) and Europe have been more extensively investigated. In these Western societies, it is well established that nasal polyps are predominantly characterized by a chronic type 2 inflammatory response with tissue eosinophilia (**Figure**).<sup>5,25</sup> Studies in the US, Belgium, and Australia found that over 70% of nasal polyps had significantly elevated levels of IL-5 or CLC.<sup>26,27</sup> This is in comparison to 61% and 20% of nasal polyps in Beijing or Chengdu, China being characterized by type 2 inflammation, respectively.<sup>27</sup> Taken together, while eosinophils can be found in nasal polyps, CRSwNP remains a geographically heterogeneous disease.

It remains unclear why fewer Asian patients historically had eosinophilic nasal polyps. Mahdavinia and colleagues<sup>28</sup> found that second-generation Asian patients with CRSwNP living in the US had reduced numbers of eosinophils and levels of ECP in their nasal polyps compared to Caucasian patients. This suggests that unique genetic factors may be important in either preventing (in Asian patients) or promoting (in Caucasian patients) tissue eosinophilia. However, such specific genes have yet to be identified. It is also unclear why there has been a more recent shift from a neutrophilic to eosinophilic inflammatory CRS pattern in Asia. One hypothesis to explain this is that the implementation of a more Westernized lifestyle in Asian countries is somehow contributing. Which particular aspect of a Westernized lifestyle is critical for this transition remains unclear, but it is likely that both genetic and environmental factors are involved.

### **Eosinophils as clinical biomarkers in CRSwNP**

As mentioned above, eosinophils are typically considered to be a hallmark of nasal polyps. However, the role these cells play in CRSwNP pathogenesis is not well understood. Nasal polyps are known to have increased levels of mediators important for eosinophil accumulation and survival (*e.g.*, IL-5 and IL-13) and chemotaxis (*e.g.*, eotaxin-1 and eotaxin-3) when compared to healthy sinonasal tissue.<sup>13,29</sup> As a result, it is possible that nasal polyp eosinophils may primarily be responding to the underlying enhanced type 2 inflammatory signals and thus serve as a metric for the degree of sinonasal disease severity.

To this end, patients with eosinophilic nasal polyps were found to have more severe sinus inflammation on sinus CT scan and nasal endoscopy compared to those with non-eosinophilic



**Figure.** Overview of type 2 inflammatory processes in chronic rhinosinusitis with nasal polyps. Type 2 inflammation is observed in the majority of patients with CRSwNP living in the US and Europe and in a growing number of patients with CRSwNP living in Asia. The epithelial cell-derived cytokines TSLP, IL-25, and IL-33 help promote the development of a type 2 inflammatory response. Increased numbers of eosinophils, mast cells, basophils, ILC2, and B cells are reported in nasal polyps as are elevated levels of common type 2 cytokines such as IL-4, IL-5, and IL-13. Together, these responses are all thought to contribute to CRSwNP pathogenesis. Novel treatment options targeting IL-4 and IL-13 signaling (dupilumab), eosinophils, (mepolizumab, reslizumab, benralizumab, antolizumab, dextransmethylglucosaminyl succinate) and IgE (omalizumab) are under investigation in CRSwNP. Figure reproduced with permission.<sup>25</sup> CRSwNP, chronic rhinosinusitis with nasal polyps; TSLP, thymic stromal lymphopoietin; IL, interleukin; ILC2, innate lymphoid cells type 2; IgE, immunoglobulin E; LTC<sub>4</sub>, leukotriene C<sub>4</sub>; PGD<sub>2</sub>, prostaglandin D<sub>2</sub>; DC, dendritic cell; TSLPR, thymic stromal lymphopoietin receptor.

nasal polyps.<sup>30</sup> In a separate study, tissue eosinophilia was also a predictor of nasal polyp recurrence following surgery, another indicator of more recalcitrant disease.<sup>31</sup> In a Chinese population, elevated tissue eosinophils were indicative of nasal polyp recurrence within 2 years after surgery.<sup>32</sup> The caveat to these observations is that there is currently no uniform consensus on how to define tissue eosinophilia.<sup>33</sup> Cutoffs ranging from greater than 5 to greater than 70 eosinophils per high power field have been used, making direct comparisons and interpretations between studies quite challenging. A recent meta-analysis of 11 studies comprising over 3,000 patients determined a cutoff of greater than 55 eosinophils per high power field showed the highest sensitivity and specificity for predicting recurrence of eosinophilic CRS.<sup>34</sup>

Given the limited ability for most physicians to rapidly, easily, and directly quantify the number of eosinophils in nasal polyps, studies have instead assessed whether peripheral blood eosinophil measures could serve as a biomarker for CRSwNP disease severity. In a Japanese study, the risk of disease recurrence following endoscopic sinus surgery was assessed in over 1,700 patients. Those patients with greater than 10% peripheral blood eosinophils were significantly more likely to have recurrence of their CRS than those patients with less than 10% eosinophils in their blood.<sup>35</sup> Similarly, other studies have reported that patients who had recurrence of nasal polyps following sinus surgery were more likely to have elevated peripheral eosinophils than those who did not report disease recurrence.<sup>36</sup>

### Eosinophils as effector cells in nasal polyps

In addition to serving as a biomarker for disease severity, it is also possible that eosinophils directly contribute to CRSwNP pathogenesis. A recent study from Yun and colleagues<sup>37</sup> found that eosinophils from nasal polyps have significantly higher levels of CD69 mRNA, a marker of cellular activation, than those from peripheral blood. Furthermore, the mean fluorescence intensity of CD69 on the surface of nasal polyp eosinophils as determined by flow cytometry significantly and positively correlated with nasal polyp size and degree of sinonasal inflammation on sinus CT scan.<sup>37</sup> Because CD69 is a reliable marker of eosinophil activation,<sup>38</sup> these data suggest that eosinophils recruited to nasal polyps are being activated, but it is unclear which factor(s) in nasal polyps is (are) responsible.

Once activated, eosinophils are known to release a variety of granule proteins. For instance, ECP, EPX, and EDN have all been reported to be elevated in nasal polyps compared to healthy sinonasal tissue, but how these proteins contribute to disease pathology is not fully known. A recent study by Tsuda and colleagues<sup>39</sup> stimulated human nasal epithelial cells with EDN and reported a subsequent up-regulation in MMP-9 expression as measured using RNA sequencing. MMP-9 is noted to be elevated in nasal polyps and is thought to contribute to tissue remodeling.<sup>40</sup> Eosinophils can also release extracellular traps containing nuclear-derived DNA through cytolytic extracellular trap cell death that may also contribute to disease pathogenesis especially in CRSwNP patients colonized with *Staphylococcus aureus*.<sup>41,42</sup> Finally, Persson and collaborators<sup>15</sup> showed that CLC protein/galectin-10 is readily detected in nasal polyps where, as a crystal, it can contribute to both innate and adaptive inflammatory responses.<sup>14</sup>

Another hallmark of nasal polyps is excessive fibrin deposition that can serve to trap plasma proteins and contribute to the mucosal edema observed in CRSwNP.<sup>43</sup> Fibrin is generated as an end product of the coagulation cascade and there is a significant correlation between fibrin levels and eosinophils in nasal polyps.<sup>44,45</sup> Eosinophils have been reported to express tissue factor which can initiate the extrinsic arm of the coagulation cascade, ultimately leading to fibrin formation.<sup>44</sup> In a subsequent study, tissue factor was found to co-localize with L-plastin on the surface of eosinophils in nasal polyps.<sup>45</sup> When L-plastin was knocked-out of a human eosinophil cell line, tissue factor could no longer translocate to the cell surface providing a potential mechanism for how eosinophils could be contributing to fibrin formation in CRSwNP.

### Eosinophils and clinical symptoms in CRSwNP

More work is needed to understand how factors involved in CRSwNP pathogenesis contribute to clinical symptoms. However, there are data suggesting a link between eosinophilia and smell loss. Patients with CRSwNP are significantly more likely to report smell loss than CRS patients without nasal polyps.<sup>46</sup> Studies have found a significant correlation between increased numbers of tissue eosinophils and olfactory dysfunction in CRSwNP.<sup>47</sup> Additionally, CLC gene expression was significantly elevated in the superior turbinate (near the olfactory cleft) of patients with CRSwNP compared to those without nasal polyps and CLC expression inversely correlated with olfactory threshold.<sup>48</sup> Whether CLC has direct effects on inducing smell loss or is instead a surrogate marker for another responsible process is the focus of future investigations.

## EOSINOPHILS IN CRSSNP

Despite comprising the largest subgroup of patients with CRS, less is known about the underlying mechanisms driving CRSSNP. Initially, this disease was considered to be a type

1 (or non-eosinophilic) inflammatory process. However, more recent studies have shown as many as half of US patients with CRSsNP have a type 2 inflammatory endotype with levels of CLC elevated above the 90% cutoff based on expression in control sinonasal tissue.<sup>46</sup> A similar type 2 inflammatory pattern was observed in approximately one-third of CRSsNP patients in Europe and in Beijing, China.<sup>27</sup>

There are many unanswered questions in regards to type 2 inflammation in CRSsNP. The factors driving this response are not well known. It is also unclear why CRSsNP and CRSwNP are both predominantly characterized by type 2 inflammation, but only the later condition is associated with nasal polyp growth. Future studies are needed to better define the cellular and molecular mechanisms contributing to CRSsNP pathogenesis and their impact on clinical disease.

## EFFECTS OF EOSINOPHIL-LOWERING AGENTS ON CRS

### Corticosteroids

Traditionally, corticosteroids have been the mainstay of medical treatment for patients with CRSwNP.<sup>49,50</sup> Corticosteroids can be administered locally within the sinonasal cavity through intra-nasal sprays, sinus rinses, or implanted devices, or systemically via oral or parental formulations. While a comprehensive review of how corticosteroids alter type 2 inflammatory responses is outside of the scope of this review, eosinophils are well established to be affected. Corticosteroids (both intranasal and oral) have been associated with significant reductions in eosinophil numbers as well as with reductions in ECP and IL-5 levels in nasal polyps.<sup>51,52</sup> Given the widespread mechanisms of action, it remains unclear if the clinical benefits of corticosteroids observed in CRSwNP are predominantly mediated solely through the reduction of eosinophils (which seems unlikely) or instead through a combination of this and other anti-inflammatory effects.

### Mepolizumab

Mepolizumab is a humanized monoclonal antibody that targets soluble IL-5 and is currently Food and Drug Administration (FDA) approved for the treatment of severe eosinophilic asthma and eosinophilic granulomatosis with polyangiitis. To date, there have been 2 clinical trials published that examined the safety and efficacy of mepolizumab in CRSwNP. In the first trial, 30 patients with severe CRSwNP were treated with either 2 doses of 750 mg mepolizumab intravenously or placebo over an 8-week period.<sup>53</sup> More patients noted a significant reduction in nasal polyp size who received mepolizumab (60%) than placebo (10%). However, no significant difference in sinonasal symptoms was reported between the 2 study arms. In a second study, 105 patients received either 750 mg of intravenously mepolizumab or placebo every 4 weeks for a total of 25 weeks.<sup>54</sup> All patients were also required to continue a daily topical corticosteroid for the duration of the study. Those receiving mepolizumab had significantly reduced nasal polyp size and sinonasal symptoms compared to placebo-treated controls, but only 30% of patients receiving the drug did not require additional sinus surgery.<sup>54</sup>

In both of these studies, mepolizumab was associated with a significant reduction in peripheral blood eosinophils as expected.<sup>53,54</sup> However, the number of eosinophils present in nasal polyp tissue before and after treatment was not directly assessed. Changes from the baseline levels of soluble IL-5 receptor alpha were significantly reduced in both serum and lavage following 8 weeks of mepolizumab compared to placebo, but there was a discrepancy

in ECP levels in that, after mepolizumab treatment, there was a significant reduction in ECP in serum, but not nasal lavage fluid compared to placebo.<sup>53</sup> This could suggest that the efficacy of intravenously mepolizumab within nasal polyps is not as great as it is in the peripheral blood. Additional mechanistic studies are thus needed to more directly assess how mepolizumab targets eosinophils within the sinonasal cavity and impacts clinical disease.

In contrast to CRSwNP, mepolizumab has been more extensively studied in severe asthmatics, but the primary outcomes of these clinical trials have understandably focused on the lower, not upper, respiratory tract. More recently, *post hoc* analyses have been performed on the subsets of patients with both severe asthma and CRSwNP. These have suggested that patients with both asthma and CRSwNP are more likely to have a greater clinical improvement in their asthma with mepolizumab than those without CRSwNP.<sup>55</sup> However, patients with both CRSwNP and asthma have been identified who have significant improvement in asthma symptoms, but not in sinonasal symptoms while on mepolizumab.<sup>56</sup> Taken together, this suggests that while patients with asthma and CRSwNP appear to be an endotype whose asthma will be more likely to respond to mepolizumab, their sinonasal disease may not equally improve. It is possible that mepolizumab affects eosinophils in the upper and lower respiratory tracts differently or that the mechanisms driving the inflammatory response in asthma and CRSwNP are not uniform. Further studies are needed to address these observations and a phase 3 clinical trial examining subcutaneous mepolizumab in severe CRSwNP is ongoing (NCT03085795).

### Reslizumab

Reslizumab is another humanized monoclonal antibody targeting soluble IL-5 that is currently FDA approved for the treatment of severe eosinophilic asthma. There are less clinical studies evaluating reslizumab as compared to mepolizumab in CRSwNP. In a small double-blind placebo-control safety and pharmacokinetic study, one dose of reslizumab was administered and, 4 weeks later, half of the study patients (n = 12) had a significant reduction in nasal polyp size.<sup>57</sup> Those patients that noted the most improvement with reslizumab were those with the highest levels of IL-5 in their nasal lavage fluid. At the time of this writing, there are no other studies listed on [clinicaltrials.gov](https://clinicaltrials.gov) to further assess the effects of reslizumab in CRSwNP.

### Benralizumab

Benralizumab is a humanized monoclonal antibody that targets the IL-5 receptor alpha chain. Unlike targeting soluble IL-5, this agent can induce antibody-dependent cellular cytotoxicity that can result in eosinophil depletion. Additionally, this antibody can target and deplete basophils as they too can express IL-5 receptors. In the US, benralizumab is FDA approved for the treatment of severe asthma only. As with mepolizumab, benralizumab has been extensively studied in asthmatics. A *post hoc* analysis found that benralizumab treatment was associated with even lower asthma exacerbation rates in patients with both CRSwNP and asthma compared to those with asthma alone.<sup>58</sup> The effect of benralizumab on sinonasal symptoms and nasal polyp size remains unclear, but there are 2 ongoing phase 3 clinical studies in CRSwNP (NCT03450083 and NCT03401229).

### Dupilumab

Dupilumab is a human monoclonal antibody that targets the IL-4 receptor alpha chain and blocks the downstream signaling of IL-4 and IL-13. By nature of its target, dupilumab would be expected to have broader anti-inflammatory effects when compared to other biologics



more specifically directed towards eosinophils. In the US, dupilumab is currently the only FDA approved biologic for the treatment of patients with CRSwNP.

In phase 3 clinical trials (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52), patients with severe uncontrolled CRSwNP were treated with either dupilumab or placebo for 24 or 52 weeks.<sup>59</sup> For the duration of the studies, all participants also used a daily intra-nasal corticosteroid spray. Compared to placebo, patients treated with dupilumab noted a significant reduction in nasal polyp size and reported significant improvement in sinonasal symptoms including sense of smell. Nasal polyps and symptoms worsened again following discontinuation of the drug suggesting that dupilumab is suppressing but not permanently modulating the underlying inflammatory response.

The specific mechanisms for how dupilumab exerts its clinical effects in CRSwNP remain unclear. Protein levels of ECP, eotaxin-3, and IL-5 were reduced in nasal lavage fluid after 24 weeks of dupilumab compared to pre-treatment levels.<sup>59</sup> Plasma levels of eotaxin-3 were also reduced at 24 weeks compared to pre-treatment levels, with an earlier phase 2 clinical trial reporting decreases as early as 2 weeks of treatment.<sup>60</sup> Type 2 inflammatory mediators were also measured in biopsies of nasal polyps as part of another phase 2 clinical trial for dupilumab in CRSwNP.<sup>61</sup> In this study, ECP, eotaxin-2, and eotaxin-3 levels were significantly reduced in nasal polyp tissues after week 16 of treatment compared to baseline. Taken together, these data suggest that one potential mechanism of action for dupilumab is by reducing pro-eosinophilic inflammatory mediators.

Paradoxically, however, while nasal polyp size was reduced within 8 weeks of treatment and nasal congestion improved as soon as 4 weeks into therapy, an increase in peripheral blood eosinophilia was reported that peaked at 16 weeks then returned to baseline by the end of the study.<sup>59</sup> One hypothesis to explain this is that dupilumab inhibited the recruitment of eosinophils from the peripheral blood into nasal polyps, causing their temporary rise in the circulation. However, patients with higher peripheral blood eosinophil counts ( $> 300/\mu\text{L}$ ) did not have significantly better responses to dupilumab than those with eosinophil counts  $< 300/\mu\text{L}$ . This observation is in contrast to prior clinical trials of dupilumab in asthmatics where patients with  $> 300$  eosinophils/ $\mu\text{L}$  had improved benefits compared to those with  $< 150/\mu\text{L}$ .<sup>62</sup> In summary, it remains unclear what direct impact dupilumab may have on tissue eosinophils. While this drug may reduce eosinophil tissue accumulation and subsequent release of traditional pro-eosinophil mediators, it is likely that it also targets other inflammatory pathways downstream of IL-4 and IL-13 signaling to improve clinical disease.

### **Omalizumab**

Omalizumab is a humanized monoclonal antibody that binds to soluble immunoglobulin E (IgE). It is currently approved for the treatment of severe asthma and chronic spontaneous urticaria. Despite modifying several aspects of a type 2 inflammatory response, omalizumab has not been shown to directly target eosinophils. In nasal polyps, however, significant correlations were reported between levels of total IgE and levels of IL-5, ECP, and number of eosinophils.<sup>63</sup> The use of omalizumab in CRSwNP has been the focus of several investigations, but a meta-analysis of 3 such trials found no significant difference in nasal polyp size between omalizumab and placebo-treated patients.<sup>64</sup> However, some studies evaluating patients with both CRSwNP and asthma found omalizumab significantly improved sinonasal symptoms and reduced nasal polyp size.<sup>65-67</sup> Two recently completed phase 3 clinical trials of omalizumab in CRSwNP reported that omalizumab significantly improved endoscopic, clinical, and patient-reported outcomes

after 24 weeks.<sup>68</sup> Taken together, the effectiveness of omalizumab in CRSwNP suggests that factors other than eosinophils are also important in driving disease pathogenesis.

### Antolimab

Another biologic therapy under development that directly targets eosinophils is a humanized monoclonal antibody directed against Siglec-8, a cell surface receptor selectively expressed by human eosinophils and mast cells.<sup>69,70</sup> This is a non-fucosylated humanized IgG1 antibody called antolimab, formerly known as AK002. Both *in vitro* and *in vivo*, Antolimab has been shown to possess antibody-dependent cellular cytotoxicity activity, and phase 1 and phase 2 clinical trials consistently demonstrated its ability to deplete eosinophils from blood and tissues.<sup>70,72</sup> Whether antolimab has any beneficial effects in CRS is not yet known.

### Dexpramipexole

On the small molecule front, dexpramipexole is an interesting oral agent because of its unanticipated ability to selectively reduce eosinophil numbers in the blood, although this takes a few weeks to manifest.<sup>73</sup> While the exact mechanism of action remains uncertain, its ability to reduce eosinophil numbers in some but not all patients with hypereosinophilic syndrome has been demonstrated.<sup>74</sup> Particularly relevant to this review is the study by Laidlaw *et al.*<sup>75</sup> that explored the impact of dexpramipexole in CRSwNP. Remarkably, a 6-month open-label trial of dexpramipexole reduced blood eosinophils by 94% (n = 13). In parallel, 12 of these 13 subjects underwent nasal polyp biopsies before and after 6 months of drug treatment, and a 97% reduction in tissue eosinophils was seen. Despite these profound changes, polyp size as well as various clinical endpoints failed to improve. While this was a relatively small study, these findings strongly suggest that selectively targeting eosinophils does not have as profound of an impact as one might have been anticipated.

## SUMMARY AND CONCLUSIONS

In CRS, there is ample, convincing evidence that eosinophil-derived mediators, granule proteins, CLC, and other substances are overly abundant in most forms of the disease, but especially so in CRSwNP. Levels of specific eosinophil-related molecules tend to correlate with clinical parameters such as disease severity, making them useful disease biomarkers. Drugs like corticosteroids, dexpramipexole and several biologics are known to either directly or indirectly reduce tissue (and blood) eosinophils. However, despite all fingers being pointed at the eosinophil as a central effector in CRS disease pathogenesis, reductions in eosinophils do not always result in clinical improvement. Additional studies using biologics that selectively and virtually completely eliminate eosinophils are needed to better clarify the specific role of eosinophils in CRS. In the meantime, it remains possible that eosinophils and other effector cells, are all culprits. It is the hope that the knowledge gained from selective precision medicine approaches (including targeted biologics) in CRS will lead to new avenues of investigation and ultimately a better understanding of the specific mechanisms contributing to CRS pathogenesis. Until then, the eosinophil remains a suspect in the crime of CRS, but has not yet been convicted.

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