Dupilumab—A Potential New Biologic for Chronic Rhinosinusitis with Nasal Polyps

Kevin Hur and Robert C Kern

Department of Otolaryngology - Head and Neck Surgery, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

Chronic rhinosinusitis with nasal polyps (CRSwNP) affects up to 2% of the general population and oftentimes confers a significant burden for patients. Dupilumab is the first monoclonal antibody approved by the United States Food and Drug Administration for the treatment of CRSwNP. Dupilumab inhibits the interleukin-4 receptor \( \alpha \) (IL-4R\( \alpha \)) subunit, thereby obstructing the signaling of type 2 cytokines IL-4 and IL-13. By significantly decreasing the size of nasal polyps and improving the major symptoms associated with CRSwNP, dupilumab is an effective option, in addition to surgery and oral corticosteroids, for the treatment of CRSwNP refractory to intranasal steroids. The precise role for this drug in the management of refractory CRSwNP awaits further real-world experience.

Keywords

Dupilumab, biologic, chronic rhinosinusitis, nasal polyps, type 2 inflammation, endoscopic sinus surgery

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Corresponding Author: Robert C Kern, Department of Otolaryngology – Head and Neck Surgery, Feinberg School of Medicine, Northwestern University, 675 North St Clair Street, Suite 15-200, Chicago, Illinois 60611, USA. E:robert.kern@nm.org

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Pathophysiology of chronic rhinosinusitis with nasal polyps

About 85% of CRSwNP in areas outside of Asia exhibit type 2 inflammation, which explains the effectiveness of corticosteroids for CRSwNP, and the potential benefit of biologics which target elements of the this pathway. The process begins with epithelial signals that stimulate type 2 innate lymphocytes (ILC2 cells) and Th2 differentiation with the production of cytokines IL-4, IL-5, and IL-13. These cytokines invoke a cascade leading to the infiltration and/or activation of large numbers of eosinophils, mast cells, and basophils. In Asian countries, patients with CRSwNP tend to have a more neutrophilic cellular predominance. Less type 2 inflammation is observed in Asian CRSwNP, who exhibit predominantly type 1 and type 3 inflammation. In parallel, ILC1 and ILC3 cells are activated as well as the corresponding Th1 and Th17 subsets with release of the canonical cytokines interferon-\( \gamma \) and IL-17, respectively. Type 2 cytokines, IL-4, IL-5, and IL-13, influence several biological processes including immunoglobulin class switching to IGE and IgG4, mucus production, inflammatory cell chemotaxis with upregulation of vascular cell adhesion molecule-1, and the activation of eosinophils. The ILC
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cells, in general, function as the first-line defenders in the airway epithelial
barrier. The epithelial signals to ILC2s are well characterized and these cells
are also important sources of type 2 cytokines in CRSwNP, in addition to
the Th2 lymphocytes.13-15 Importantly, dupilumab targets cytokine activity
independent of the cellular source of the cytokines.

Nasal polyps are inflammatory outgrowths of the sinonasal mucosa and
are associated with marked tissue edema, diminished collagen, and
extracellular matrix degradation.16 The formation of polyps starts with local
inflammation which leads to the leakage of fibrogen from blood vessels
into the sinonasal tissue forming a matrix that traps proteins leading to
tissue edema.17 The type 2 cytokine IL-13 fosters formation of the fibrin
matrix, in part via inhibition of tissue plasminogen activator, which normally
would degrade the fibrin matrix. Inhibition leads to matrix stabilization,
with formation and growth of nasal polyps.18 IL-13 also leads to leakiness of
the epithelial barrier, which also fosters type 2 inflammation.6 It has been
hypothesized that this barrier remodeling in type 2 inflammation is a key
factor driving polyp recurrence.17

Asthma and CRSwNP frequently coexist and share a similar type 2
inflammatory pattern, especially in North America and Europe. As a result,
several biologics targeting the Th2 inflammatory pathway in asthma, such as
dupilumab, have also been investigated for the treatment of CRSwNP.

Duplicumab mechanism of action

Duplicumab binds IL-Rα and inhibits IL-4R signaling induced by both IL-4 and
IL-13, down-regulating type 2 inflammation.19 IL-4 and IL-13 exert their actions
through three different combinations of shared receptors: one type I and
two type II complexes (note that these type I and II complexes are completely
unrelated to type 1, 2 and 3 inflammation terminology).19 Unfortunately, data
are scant on the precise mechanism of action of dupilumab. Duplicumab
has been shown to inhibit IgE production by B cells after being treated with
IL-4, and inhibit IL-25-induced allergic airway inflammation and eosinophilic
esophagitis in a mouse model.19 The IL-4Rα subunit antibody could either
inhibit the binding of IL-4 to the type I receptor complex, or inhibit the
assembly of the type II receptor complex by preventing the recruitment of
the IL-4Rα subunit by the IL-13Rα1 upon the binding of the latter to IL-13.
The impact of an IL-4Rα subunit antibody on the respective receptor is
likely influenced by the ratio of IL-4Rα and IL-13Rα1 subunits in the target
cells. If dupilumab preferentially suppressed IL-4 binding to IL-4Rα, then its
effects would primarily manifest as suppressive of Th2 cell differentiation
but not necessarily IL-13-driven type 2 inflammation in target tissues. The
reverse would be true if dupilumab primarily suppressed IL-13 binding to
the IL-4Rα and IL-13Rα1 subunit.

The clinical impact of which receptor complex dupilumab specifically binds
to may be the observation in some patients with allergic tissue inflammation,
such as asthma and eczema. Thus, if dupilumab differentially impacted the
assembly of the type I receptor, the “leakage” of type II receptor signaling
may explain, to some extent, the resistance of some patients to therapy.
In reverse, a preference for the type II receptor may impact the capacity
of dupilumab to directly act on Th2 cell-like Treg cells, which express the
type I receptor, to restore their function.14 However, future studies on the
interaction of dupilumab with the respective receptor complexes are
needed to clarify the exact mechanism of this biologic.

Therapeutic trials

In 2019, dupilumab was approved by the FDA for the treatment of CRSwNP
after a phase II trial and two phase III clinical trials. In this section, we will
review the results of these studies.

A phase II, double-blind, placebo-controlled, randomized study evaluating
dupilumab in 60 patients with CRSwNP was published in 2016 by Bachert
et al. demonstrating reduction of nasal polyp burden at 16 weeks follow-
up. Patients who had CRSwNP refractory to intranasal corticosteroids
underwent either 300 mg of dupilumab subcutaneously weekly or placebo
for 16 weeks with a 600 mg loading dose. Both groups used mometasone
furoate nasal spray twice daily for the duration of the study. Eligible patients
had bilateral nasal polypsis with at least extension inferior to the middle
turbinate bilaterally and had symptoms of chronic sinusitis. There was a
significant improvement in the dupilumab group compared to the placebo
group with a least squares (LS) mean difference in the nasal polyp score by
-1.6 points on a 0–8 scale (95% confidence interval [CI] -2.4 to -0.7, p<0.001).
Lund-Mackay CT score by -8.8 points (95% CI -11.1 to -6.6, p<0.001),
Sinonasal Outcome Test (SNOT)-22 score by -18.1 points (95% CI -25.6 to
-10.6, p<0.001), and the University of Pennsylvania Smell Identification Test
(UPSIT) score by 14.8 points (95% CI 10.9 to 18.7, p<0.001). In patients with
asthma, dupilumab significantly improved percentage of the forced vital
capacity predicted and asthma control compared to placebo. There was
also a decrease in total IgE and eotaxin-3. The phase II trial demonstrated
significant statistical improvement in both objective and subjective
outcomes in patients with CRSwNP who received dupilumab for 16 weeks.
However, the clinical significance of these differences still needs to be
further investigated as there is not a validated minimum clinically important
difference (MCID) for most outcomes measured in the dupilumab clinical
trials. Only the SNOT-22 has a validated MCID (≥8.5), which was exceeded in
all trials discussed in this section.20

Two phase III studies have also been conducted, LIBERTY NP SINUS-24
and LIBERTY NP SINUS-52 (Table 1), which also assessed dupilumab as
adjuvantive therapy to mometasone furoate nasal spray.43 In SINUS-24,
subjects were randomized to two arms, either dupilumab 300 mg every
2 weeks or placebo every 2 weeks for 24 weeks. In SINUS-52, subjects
were randomized to either dupilumab 300 mg weekly for 24 weeks then
evry 4 weeks for 28 weeks, dupilumab 300 mg every 2 weeks for 52
weeks, or placebo every 2 weeks for 52 weeks. In both studies combined,
724 patients with severe CRSwNP (mean polyp size 5.97, scale 0–8; nasal
congestion score 2.40, scale 0–3), demonstrated significant improvement
in both co-primary endpoints with dupilumab every 2 weeks. The nasal
polyp score LS mean difference compared to placebo (p<0.0001) were
-2.06 (95% CI -2.43 to -1.69) and -1.80 (95% CI -2.10 to -1.51) in SINUS-24
and SINUS-52, respectively. The nasal polyp score LS mean difference (p<0.0001) was -0.89 (95% CI -1.07 to -0.71) and -0.87 (95% CI
-1.03 to -0.71) in SINUS-24 and SINUS-52, respectively. Radiographic
findings improved compared to placebo (p<0.0001) with Lund-Mackay
score LS mean difference -7.44 (95% CI -8.35 to -6.53) and -5.13 (95% CI
-5.80 to -4.46) in SINUS-24 and SINUS-52, respectively. SNOT-22 LS mean
difference (p<0.0001) was -21.12 (95% CI -25.17 to -17.06) and -17.36 (95%
CI -20.87 to -13.85) in SINUS-24 and SINUS-52, respectively. In SINUS-24,
treatment effects gradually diminished in the 12-week follow-up period
following drug discontinuation with worsening of the nasal polyp score.
Table 1: Summary of selected endpoints in LIBERTY NP SINUS-24 and SINUS-52 at 24 weeks

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>LS mean difference versus placebo</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SINUS-24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral nasal poly size (0–8)</td>
<td>-2.06</td>
<td>-2.43</td>
<td>-1.69</td>
</tr>
<tr>
<td>Nasal congestion score (0–3)</td>
<td>-0.89</td>
<td>-1.07</td>
<td>-0.71</td>
</tr>
<tr>
<td>Lund–Mackay CT score (0–24)</td>
<td>-7.44</td>
<td>-8.35</td>
<td>-6.53</td>
</tr>
<tr>
<td>Sinonasal Outcome Test (SNOT-22)</td>
<td>10.56</td>
<td>8.79</td>
<td>12.34</td>
</tr>
<tr>
<td>SINUS-52</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral nasal poly size (0–8)</td>
<td>-1.80</td>
<td>-2.10</td>
<td>-1.51</td>
</tr>
<tr>
<td>Nasal congestion score (0–3)</td>
<td>-0.87</td>
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</tr>
<tr>
<td>Lund–Mackay CT score (0–24)</td>
<td>-5.13</td>
<td>-5.80</td>
<td>-4.46</td>
</tr>
<tr>
<td>Sinonasal Outcome Test (SNOT-22)</td>
<td>10.52</td>
<td>8.98</td>
<td>12.07</td>
</tr>
<tr>
<td>SNOT-22 score (scale 0–110)</td>
<td>-17.36</td>
<td>-20.67</td>
<td>-13.85</td>
</tr>
</tbody>
</table>

CI = confidence interval; CT = computed tomography; LS = least squares; SNOT = Sinonasal Outcome Test; UPSIT = University of Pennsylvania Smell Identification Test.

Safety profile

Dupilumab is associated with side effects that should be discussed with all patients prior to treatment. In the phase II clinical trial, the most common adverse events in the dupilumab group were nasopharyngitis (47%), injection-site reactions (40%), and headache (20%). The most frequent adverse events reported in the 24 week pooled phase III trials (SINUS-24 and SINUS-52) for the dupilumab group were nasopharyngitis (13%), headache (7%), epistaxis (6%), and injection-site erythema (6%). Interestingly, all adverse events were more commonly reported in the placebo group (74%) versus the treatment group (69%).

Serious adverse events reported in the treatment arm included eosinophilia in three patients. One patient developed eosinophilic granulomatosis with polyangiitis while being treated with dupilumab, and another patient developed eosinophilia associated with arthralgia, asthma exacerbation, and insomnia during dupilumab treatment. Whether there is a relationship between eosinophilia and dupilumab is still unknown; however, eosinophilic granulomatosis with polyangiitis has been reported as a rare event in the administration of other biologics that target the type 2 inflammatory pathway, such as omalizumab. Whether eosinophilic granulomatosis with polyangiitis was a pre-existing condition unveiled by the cessation of systemic steroids during biologic therapy, or was secondary to the biologic itself, is unclear. Further research is necessary to clarify this possible relationship. Measuring a baseline blood eosinophil level prior to treatment and during treatment with dupilumab should be considered to monitor for this possible adverse event.

Conclusion

With consistent improvement in both objective and subjective outcomes, dupilumab is an effective nonsurgical therapeutic option in the treatment of CRSwNP not adequately controlled with nasal steroid sprays, oral corticosteroids, or surgery. The approval of dupilumab for CRSwNP patients represents a key development in the likely increasing role biologics will play in the management of patients with CRSwNP.