



Dupilumab in the treatment of chronic rhinosinusitis with nasal polyposis

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Chronic rhinosinusitis with nasal polyposis (CRSwNP) imparts a significant healthcare challenge, resulting in diminished quality of life for patients and high costs with resource utilization for disease management. Understanding of CRSwNP pathophysiology has progressively evolved and the identification of various inflammatory biomarkers has led to the development of monoclonal antibodies that target the underlying mechanisms of inflammation. Dupilumab, which targets IL-4 and IL-13 signaling, serves as a novel agent for CRSwNP treatment. Three clinical trials, NCT01920893, *SINUS-24* and *SINUS-52*, have shown that dupilumab improves both subjective patient-reported outcomes and objective physician-evaluated metrics for CRSwNP. The favorable findings have resulted in approval by the US FDA in June 2019 as the first biologic therapy for CRSwNP.

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Chronic rhinosinusitis (CRS) is a heterogeneous inflammatory disease of the nose and paranasal sinuses, affecting an estimated 12% of the adult population in the USA [1]. CRS is typically classified into phenotypes by the presence or absence of nasal polyps. CRS with nasal polyps (CRSwNP) is estimated to afflict 0.5–4.2% of the population with variations across geographic regions and ethnic backgrounds [2]. The diagnostic criteria emphasize a set of symptoms, consisting of hyposmia, facial pressure, nasal drainage and nasal congestion, for a duration of at least 12 weeks [3]. Objective evidence of inflammation by radiographic imaging or direct visualization is also required [3].

The mainstay for CRSwNP treatment relies on medical therapeutics. Saline irrigations and topical corticosteroids are recommended with strong high-level evidence [4]. Oral steroids, leukotriene inhibitors and oral antibiotics may also be prescribed, although the evidence is less robust [4]. Surgery is generally reserved for those failing appropriate medical management [4]. Despite the various medical and surgical options, many CRSwNP patients remain at risk for disease persistence and recurrence. In CRSwNP patients who undergo endoscopic sinus surgery, polyp recurrence has been found to be as high as 35% at 6 months and 40% at 18 months [5]. Up to 7% of patients may ultimately need revision endoscopic sinus surgery due to symptomatic disease recurrence [6]. With annual costs of treating CRS in the USA estimated at \$22 billion [7] and with surgical cases for CRSwNP requiring both time and technical resources [8], there remains ample opportunity to improve the efficacy and efficiency of CRSwNP management.

The challenges in managing CRSwNP are in part rooted in the complex pathophysiology of CRSwNP, which has been a subject of research over the past 20 years. A defective epithelial barrier and exogenous pathogens have been posited as potential causes of the mucosal inflammation characteristic of CRSwNP [9]. Immune dysregulation in the form of Type 2 inflammatory responses has furthermore been the focus of much research on CRSwNP [10]. Elevated Type 2 immune markers, including IL-4, IL-5 and IL-13, which result in the upregulation and activation of eosinophils, basophils and mast cells, are characteristic of many classic CRSwNP endotypes [11–13]. Because IL-4, IL-5 and IL-13 serve as important upstream regulators of Type 2 inflammatory responses, these interleukins have become promising targets of therapeutic agents for CRSwNP.

In this respect, dupilumab (Dupixent[®], Regeneron Pharmaceuticals, NY, USA) is an important example of a biologic agent for CRSwNP through the targeting of the IL-4 and IL-13 pathways. Prior to its use in CRSwNP,

dupilumab has proven efficacious in similar Type 2 inflammatory diseases, such as atopic dermatitis and allergic asthma. More recently, clinical research has specifically shown that dupilumab provides therapeutic utility in CRSwNP. For this reason, the US FDA in June 2019 approved dupilumab as the first biologic therapy for clinical use in patients ≥ 18 years with inadequately controlled CRSwNP. The recommended dosage for dupilumab as an add-on maintenance therapy is 300 mg given subcutaneously every other week. This review aims to describe the basis for using dupilumab in CRSwNP and presents an overview of recent data from three clinical trials which demonstrate the efficacy and safety of dupilumab for CRSwNP treatment.

Endotypes & targeted therapies in CRSwNP

Recent therapeutic options for CRSwNP have focused on inhibiting the underlying immune signaling involved with Type 2 inflammatory responses, which are also strongly exhibited in both asthma and allergy [13]. In particular, prior studies have shown that allergic asthma is closely associated with nasal polyposis as a comorbid disease [13]. Classificatory schemes for CRSwNP have thus emphasized the use of Type 2 inflammatory biomarkers to characterize disease endotypes. IL-5, IgE and *Staphylococcus aureus* enterotoxin-specific IgE, for example, have been identified at elevated levels in a predominant subgroup of individuals with CRSwNP [14]. Variable expressions of other biomarkers, including myeloperoxidase, IL-8, IL-6, IL-17, IL-22, IFN- γ and eosinophilic cationic protein, have further augmented the development of different CRSwNP endotypes [14,15]. The expression of markers among the endotypes has demonstrated a wide degree of overlap, suggesting that CRS may be better considered as a continuum with variable expression of inflammatory markers, as opposed to separate endotypes [16].

The diversity in inflammatory markers highlights the multiple pathophysiologic mechanisms in CRSwNP and suggests that a single, universal therapeutic approach will be less likely to offer a comprehensive management strategy. The multiple biomarkers involved with the underlying causes of inflammation in CRSwNP have nonetheless provided ample opportunities for new pharmaceutical developments. To start, omalizumab, which is a monoclonal antibody that targets circulating IgE and is currently approved for use in moderate-to-severe asthma and chronic idiopathic urticaria, had been an intuitive medication for early trials for CRSwNP. Preliminary small sample size studies that evaluate the use of omalizumab for CRSwNP provided mixed results in regard to omalizumab's efficacy based on nasal polyp scores, computed tomography (CT) scores and quality-of-life measures [17,18]. However, recent Phase III clinical trials for this agent in CRSwNP subjects have met the two primary end points and key secondary end points.

Various monoclonal antibodies that target the IL-5 pathway and are presently used for asthma have also garnered attention for potential use in CRSwNP. In early trials, mepolizumab and reslizumab, which specifically target free circulating IL-5, have both demonstrated efficacy in reducing nasal polyp scores, among other objective and subjective outcome measurements [19,20]. Likewise, benralizumab has also shown early promise in its ability to target the IL-5 receptor, which is found on both eosinophils and basophils [21]. The most robust evidence for mepolizumab, reslizumab and benralizumab are related to their uses in asthma, but Phase III clinical trials examining the clinical efficacy of mepolizumab and benralizumab for CRSwNP are ongoing. At this time, the clinical trial for mepolizumab has completed subject enrollment, while enrollment in the clinical trial for benralizumab will soon be completed [22].

As an add on therapy to topical steroid for CRSwNP, dupilumab has emerged as a significant therapeutic option for CRSwNP by targeting the IL-4 and IL-13 inflammatory pathways, which are essential in the induction and perpetuation of the Type 2 inflammatory response. Produced with recombinant DNA technology, dupilumab is a fully human IgG4 monoclonal antibody that targets the IL-4 receptor- α (IL-4R α) subunit, which is common to both the IL-4 and IL13 receptors (Figure 1). Thus, as a receptor antagonist to IL-4 and IL-13 receptors, dupilumab inhibits the downstream effects of both IL-4 and IL-13 [23]. Dupilumab has been used in the USA for treatment of moderate-to-severe atopic dermatitis since March 2017 and for moderate-to-severe asthma since October 2018 [24,25]. For atopic dermatitis, the drug is administered as a subcutaneous injection, with a 600 mg loading dose followed by 300 mg dosed every other week [23]. For asthma with the eosinophilic phenotype or with oral corticosteroid dependence, the recommended dosage for dupilumab is either with an initial dose of 400 mg followed by 400 mg given every other week or an initial dose of 600 mg followed by 300 mg given every other week.

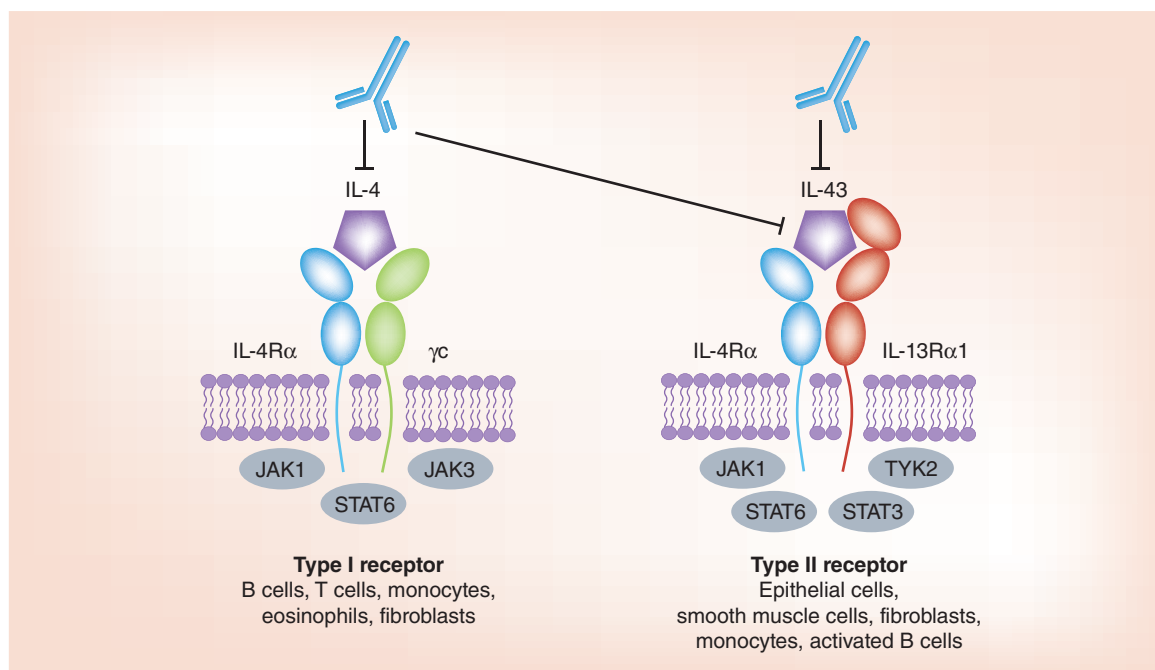


Figure 1. Mechanism of action of dupilumab. Dupilumab is a monoclonal antibody that directly binds to the IL-4 receptor- α (IL-4R α) subunit, which is common to both the IL-4 and IL-13 receptors. The combined inhibition of both IL-4 and IL-13 signaling pathways allows for the downregulation of Type 2 inflammatory responses, including eosinophil, mast cell and basophil recruitment, IgE synthesis and mucus hypersecretion.

Pharmacology of dupilumab

Administered through subcutaneous injections, dupilumab is absorbed by transcytosis into the lymphatic system, followed by delivery into the blood circulation via the thoracic duct [26]. The drug reaches its target tissue through convective transport, driven by hydrostatic pressure, osmotic gradients and permeability of the capillary endothelium. The drug follows nonlinear target-mediated pharmacokinetics, with systemic exposure increasing at a proportional factor greater than the corresponding dose increase [23,27]. The drug reaches a maximum concentration at 1 week and steady-state concentration at week 16 of administration [26]. This slow absorption is directly related to the slow drainage of lymph fluid into the circulation. The bioavailability is estimated at 64%, with a volume of distribution of 4.8 liters. The drug is nondetectable for about 10–13 weeks after final administration [23]. Despite the lack of formal investigation, renal impairment and hepatic impairment are not expected to affect drug concentrations significantly, as the compound undergoes breakdown into amino acids through lysosomal action in much the same way as native immunoglobulins do [23]. Lower drug trough concentrations are associated with higher body weight, although dose adjustment based on weight is not necessary.

While the effects of dupilumab are applied through the blockade of IL-4R α and the subsequent inhibition of the IL-4 and IL-13 inflammatory pathways, previous studies have demonstrated that the separate individual targeting of circulating IL-4 and IL-13 results in much less significant or even negligible, clinical benefits. For example, soluble IL-4 receptor compounds such as altrakincept were received with some initial promise for asthma, but subsequent studies failed to show a meaningful benefit [28]. Similarly, anrunkinumab, which targets IL-13, was evaluated in Phase II trials for asthma and ultimately did not demonstrate clinical efficacy [28]. While lebrikizumab, which also targets IL-13, initially demonstrated improvement in forced expiratory volumes (FEV1) [29], subsequent Phase III trials involving lebrikizumab failed to demonstrate significant efficacy in asthmatic patients [30,31]. Dupilumab's therapeutic utility thus relies on the combined inhibitory effects of IL-4 and IL-13 signaling.

Clinical efficacy of dupilumab

The clinical efficacy of dupilumab for CRSwNP has been evaluated in three clinical studies that were performed for the FDA-approval process. The relevant study outcomes of these three clinical trials – NCT01920893, SINUS-24 and SINUS-52 – are highlighted in Table 1. Additional assessments of the clinical effects of dupilumab on

Table 1. Completed trials of dupilumab in chronic rhinosinusitis with nasal polyposis.

Study	Population	Design	Treatments	Outcomes	Ref.
NCT01920893	- Symptomatic bilateral nasal polyps aged 18–65 - Failed 2 months of prior intranasal steroid use - No recent/multiple surgeries – no prior monoclonal antibody use	Randomized, double-blind, placebo-controlled study, Phase II	- Dupilumab 300 mg sc. weekly with intranasal mometasone - Placebo with intranasal mometasone	Greater improvement with dupilumab in: - NPS - Lund–Mackay score - Nasal airflow - CT volume of disease - SNOT-22 - UPSIT score - Diary symptoms - IgE - TARC	[32]
SINUS 24 (NCT02912468)	- Symptomatic bilateral nasal polyps >18 years old - Prior surgery and/or steroid use within 2 years - Severe disease as measured by endoscopy and symptoms	Randomized, double-blind, placebo controlled, Phase III	- Dupilumab 300 mg sc. bi-weekly with intranasal mometasone - Placebo with intranasal mometasone	Greater improvement with dupilumab in: - NPS - Lund–Mackay score - Nasal congestion - SNOT-22 - UPSIT score In dupilumab group: - Reduced need for systemic steroids - Reduced need for surgery to remove polyps	[33]
SINUS 52 (NCT02898454)	- Symptomatic bilateral nasal polyps >18 years old - Prior surgery and/or steroid use within 2 years - Severe disease as measured by endoscopy and symptoms	Randomized, double-blind, placebo controlled, Phase III	- Dupilumab 300 mg sc. bi-weekly with intranasal mometasone - Dupilumab 300 mg sc. bi-weekly for 24 weeks, then every 4 weeks for 28 weeks with intranasal mometasone - Placebo with intranasal mometasone	Greater improvement with dupilumab in: - NPS - Lund–Mackay score - Nasal congestion - SNOT-22 - UPSIT score In dupilumab group: - Reduced need for systemic steroids - Reduced need for surgery to remove polyps	[33]

CT: Computed tomography; NPS: Nasal polyp score; sc.: Subcutaneous; SNOT-22: Sino-nasal outcome test score; TARC: Thymus and activation regulated chemokine; UPSIT: University of Pennsylvania Smell Identification test score.

sinonasal symptoms in patients with comorbid atopic dermatitis and chronic inflammatory conditions of the sinonasal compartments were also performed – SOLO 1 & 2, CHRONOS and CAFÉ, which were Phase III clinical trials for dupilumab in specifically atopic dermatitis. The relevant data from the pooled data from the literature in atopic dermatitis are summarized.

NCT01920893

Study design

NCT01920893 was a Phase II randomized, double-blind, placebo-controlled study conducted in the USA and Europe evaluating the efficacy of dupilumab in treating subjects with CRSwNP [32]. A total of 60 subjects, aged 18–65, with symptomatic bilateral nasal polyps who failed 2 months of prior intranasal steroid use, were enrolled between August 2013 and March 2014. Of these subjects, 50% had comorbid asthma. All subjects received 4 weeks of mometasone furoate nasal sprays (MFNS) prior to being randomized to 16 weeks of concurrent MFNS and dupilumab or placebo. The dosing regimen of dupilumab was a loading dose of 600 mg followed by 15 weekly injections of 300 mg. The subjects were additionally followed for 16 weeks after completion of the 16-week treatment of dupilumab or placebo.

The primary outcome measurement was the change in endoscopic nasal polyp score, with secondary outcome measures including the change in Lund–Mackay CT score, change in maxillary sinus volume occupied by disease, change in Sino-nasal outcome test (SNOT-22) score, change in University of Pennsylvania smell identification test (UPSIT) score and change in peak nasal inspiratory flow. Additionally, subjects recorded a diary with daily symptom scores, subjects with asthma received an asthma specific questionnaire and FEV1 testing and all subjects had measures of IgE, eosinophil count, serum thymus and activation regulated chemokine (TARC) and eotaxin-3 collected.

Outcomes

Subjects in the dupilumab group demonstrated overall improved objective and subjective parameters when compared with subjects in the placebo group. The least squares mean difference in change in endoscopic nasal polyp score, which ranged from 0 (no polyps) to 8 (large polyps in bilateral nostrils), was -1.6 favoring dupilumab. The CT score, with a scale ranging from 0 to 24, also improved a greater degree in the dupilumab group, with a least squares mean difference of -8.8 favoring dupilumab. The volume of disease occupying the maxillary sinus and peak nasal airflow also decreased to a greater degree in the dupilumab group, with a least squares mean difference of -32.2 and 33.1 l/min, respectively, favoring dupilumab [32].

The SNOT-22 score improved to a greater degree in the dupilumab group, with a least means squared difference in improvement of -18.1 and the UPSIT sense of smell and diary-recorded symptom scores also improved to a greater degree in the dupilumab group [32]. Most of these improvements were sustained after cessation of dupilumab in the 16-week follow-up period [32]. In the 35 patients with asthma, those receiving dupilumab experienced a greater improvement in FEV1, with a least squares mean difference of 7.2 [32]. In regards to biomarkers, serum IgE, serum TARC and plasma eotaxin-3 all decreased to a greater degree through the first 12 weeks of the study and IgE and TARC maintained this difference through 16 weeks [32]. Eosinophil counts transiently increased in the dupilumab group but overall were unchanged compared with placebo at 16 weeks [32].

This trial demonstrated the efficacy of dupilumab in combination with MFNS for refractory CRSwNP. Objective measures of disease burden, subjective measures of symptom severity and biomarker measures of inflammatory activity all decreased to a greater degree in the treatment group receiving dupilumab. Although the period of examination was relatively short, the results of this study highlighted a potential role for dupilumab as combination therapy in CRSwNP.

Further analyses of the study population

Subsequent publications have further analyzed different parameters in the above study population. Jonstam *et al.* investigated the biochemical efficacy of dupilumab, as nasal secretions from all 60 patients and nasal polyp tissue from ultimately 12 patients were collected for analysis of cytokines, IgE, eosinophilic cationic protein (ECP) and eotaxin-3 [34]. Eotaxin-3 and total IgE in the nasal secretions of patients receiving dupilumab decreased significantly compared with those from the placebo group, while the decrease in ECP did not reach statistical significance [34]. In the analysis of polyp tissue, total IgE, ECP, eotaxin-2, eotaxin-3, IL-13 and PARC were significantly lower in the dupilumab group by the end of treatment than in the placebo group, whereas IL-6, IL-1 β , IL-4, eotaxin-1, IL-5, IL-10, IL-17, IL-33, TNF- α or TARC were not significantly different between groups at the end of treatment [34]. The results of this analysis further support the efficacy of this drug at the pharmacodynamic level, with a local tissue reduction in several biomarkers of Type 2 inflammation, building upon the previously reported reduction in systemic biomarkers.

Laidlaw *et al.* further analyzed the 19 subjects from NCT01920893 who demonstrated aspirin-exacerbated respiratory disease (AERD), a subgroup of CRSwNP patients with comorbid asthma and aspirin intolerance. The pathophysiology is unique in AERD, resulting from primarily elevated cysteinyl leukotrienes levels as opposed to the adaptive immune response. Evidence nonetheless points to elevated IL-4 playing a role in the overexpression of cysteinyl leukotriene [13]. CD45⁺ CD4⁻ IL-4 producing cells were found to be elevated in patients with AERD and likely reflect the important role of the mast cell in the pathogenesis. In the subgroup analysis by Laidlaw *et al.*, AERD subjects receiving dupilumab demonstrated statically significant improvements in endoscopic nasal polyp scores, Lund–Mackay scores, SNOT-22 scores, UPSIT score and symptomatic scores, when compared with subjects receiving placebo [35]. The results from this subsequent analysis suggest that dupilumab may provide therapeutic utility in AERD, which is regarded as an especially challenging CRSwNP subgroup to manage.

SOLO 1 & 2, CHRONOS & CAFÉ

SOLO 1, SOLO 2, CHRONOS and CAFÉ were Phase III investigations of dupilumab in the treatment of atopic dermatitis. As a part of the pooled subgroup analysis from these clinical trials, 1171 subjects with atopic dermatitis were evaluated for treatment effect on sinonasal symptoms, given the possibility of higher Type 2 inflammatory disease activity [36]. The change in SNOT-22 scores was used as a measure of response of sinonasal symptoms to treatment with dupilumab. Dosing schedules varied in the studies from weekly to biweekly dosing of 300 mg of dupilumab [36]. In both weekly and biweekly dupilumab groups, the SNOT-22 score improved to a greater degree compared with that from the placebo group, with a least squares mean change of 10.83 in the weekly group, 9.89

in the biweekly group and 5.10 in the placebo group [36]. There was not a significant difference between the groups receiving weekly or biweekly dosing administrations. Because these studies were designed to evaluate dupilumab in the treatment of atopic dermatitis, no other formal investigations of CRSwNP were included. The subjective improvements related to sinonasal symptoms, however, are still notable.

SINUS-24

Study design

In this Phase III randomized, placebo-controlled clinical trial, 276 adult subjects with bilateral CRSwNP were randomized to receive either biweekly dupilumab, dosed at 300 mg, with MFNS or placebo with MFNS over a 24-week period between December 2016 and July 2018 [33]. Subjects received either dupilumab or placebo at scheduled visits for the first 8 weeks, after which they were permitted to administer the medication at home. Subjects were followed for an additional 24 weeks after completion of the study treatment. The primary end points were the change in nasal polyp score and change nasal congestion severity, the latter of which was measured by averaging daily symptom scores over 1-month intervals. Secondary end points included changes in Lund–Mackay scores, UPSIT scores, serum biomarker levels, FEV1, SNOT-22 and asthma control questionnaire (ACQ-6) scores. Endoscopic scores and Lund–Mackay scores were graded centrally in a blinded fashion.

Outcomes

Overall, 5% of the total subjects did not complete the study; adverse events were the most common reason to drop out. As measured by the least square mean difference, dupilumab significantly improved nasal polyp scores (-2.06), nasal congestion (-0.89), CT Lund–Mackay scores (-7.44), SNOT-22 (-21.12) and UPSIT scores (+10.56) when compared with placebo. The total symptom score, which consisted of a composite of congestion, loss of smell and rhinorrhea, furthermore decreased to a greater degree in the dupilumab group, with a least squares mean difference of -2.61.

Nasal polyp scores were further analyzed based on the percentage of responders and nonresponders to dupilumab. When a 1-point change in nasal polyp score was used to define a response to dupilumab, the clinical trial found 65% of patients receiving dupilumab were considered responders, compared with 17.3% of placebo patients. When a therapeutic response was measured by a 2-point change, 46.2% of patients receiving dupilumab were considered responders, compared with 4.5% of placebo patients. In the subsequent subgroup analysis, which was based upon variables that included age, gender, region, territory, race, ethnicity, weight, body mass index, prior systemic corticosteroid use, prior nasal polyp surgery, comorbid asthma and comorbid AERD, only Hispanic ethnicity was associated with a response that did not statistically favor dupilumab in terms of nasal congestion and nasal polyp scores. The remaining variables failed to demonstrate an association with ultimate response to dupilumab. It should be noted, however, that only six patients of Hispanic ethnicity were included in the study and any meaningful conclusions about ethnicity as a prognostic factor for dupilumab are thus limited. Other factors that may predict which patients may be responders or nonresponders to dupilumab are not available with the current data.

Subgroup analysis of subjects defined by comorbid asthma, previous sinonasal surgery and AERD revealed that the improvement in nasal polyp scores and other metrics were similar to the general study group. Both symptom and nasal polyp scores, however, worsened once dupilumab was discontinued after the initial 24 weeks of treatment. This raises the question about the optimal duration of treatment, as both objective and subjective measures began to approach placebo values after subjects were off dupilumab therapy for several weeks. Based on the available data, the answer regarding the recommended duration of treatment is not clear. Current practice favors continuing dupilumab for at least 52 weeks, as 24 weeks alone did not seem sufficient. Future studies should examine whether a longer duration of treatment may lead to immunomodulatory effects in CRSwNP pathogenesis.

SINUS-52

Study design

Like SINUS-24, SINUS-52 was a Phase III randomized, placebo-controlled trial that examined dupilumab treatment in combination with daily MFNS for adult subjects with CRSwNP refractory to routine intranasal corticosteroid therapy. Unlike SINUS-24, subjects in SINUS-52 were randomized into three groups and were treated for 52 weeks, after which they were followed for an additional 12 weeks [33]. Between November 2016 and November 2018, a total of 448 patients were randomized to receive 300 mg of dupilumab subcutaneously biweekly for 52 weeks, 300 mg dupilumab biweekly for 24 weeks followed by every 4 weeks for the next 28 weeks or placebo

Table 2. Adverse effects of dupilumab compared with placebo in reported in clinical trials.

	Frequency in dupilumab (%)	Frequency in placebo (%)
Nasopharyngitis	47	33
Injection site reactions	6–40	4–7
Headache	20	17
Epistaxis	7.7	3
Arthralgia	3	1
Conjunctivitis	2	1
Gastritis	2	1
Insomnia	1	<1
Eosinophilia	1	<1
Toothache	1	<1

biweekly for 52 weeks. Subjects were permitted to self-administer their designated medication beginning at week 10.

The changes in nasal polyp score, nasal congestion, UPSIT smell test, Lund–Mackay score, SNOT-22, levels of blood and nasal biomarkers, ACQ-6 score and FEV1 were as outcome measurements for SINUS-52. Measurement of nasal ECP, eotaxin-3 and total IgE were unique to the SINUS-52 protocol. SNOT-22 was recorded at an additional time point of 24 weeks and the ACQ-6 was given at 24 weeks.

Outcomes

Overall, 11% of all subjects did not complete the study; adverse events were cited as the most common reason for study withdrawal. At 24 weeks of treatment, dupilumab at 300 mg biweekly demonstrated a least square mean difference was improved in nasal polyp score (-1.80), nasal congestion (-0.87), Lund–Mackay score (-5.13), total symptom score (-2.44), SNOT-22 score (-17.36) and UPSIT score (+10.52) when compared with placebo. These improvements were more pronounced at 52 weeks with least square mean differences of -2.40 for nasal polyp score, -0.98 for nasal congestion, -6.94 for Lund–Mackay score, -20.96 for SNOT-22 score and +10.30 for UPSIT score. After 24 weeks, the subjects receiving dupilumab on the biweekly dosage showed improved Lund–Mackay scores and nasal polyp scores then the subjects receiving dupilumab at 4-week intervals (least mean squares different of 0.53 vs -0.31 and -1.37 vs -0.62, respectively). All measured secondary end points, including ACQ-6, FEV1 and local and systemic biomarkers of inflammation also showed significant improvements with use of dupilumab when compared with placebo. In NCT01920893, SINUS-24 and SINUS-52, improvements in patient-reported nasal congestion and nasal polyp scores were evident as early as 4 weeks of therapy [32,33]. A 4-week period may thus serve as a reasonable benchmark as the treatment duration before subjective and objective responses to the drug may be assessed.

Similar to SINUS-24, nasal polyp scores were further analyzed based on percentage of responders and nonresponders. Using a 1-point change in nasal polyp score to define improvement, the SINUS-52 found that 62% of patients receiving dupilumab were considered responders, compared with 10.5% of placebo patients. When a 2-point change was used, 46.1% of patients receiving dupilumab were considered responders, compared with 0.7% of placebo patients. In the subgroup analysis of SINUS-52, no particular variable, including age, gender, ethnicity, prior corticosteroid use, prior sinus surgery and comorbid asthma or AERD, was predictive of an unfavorable response to dupilumab.

Safety & tolerability of dupilumab

In all clinical trials for dupilumab, the biologic agent has been found to be well tolerated in subjects (Table 2). Adverse effects have overall been mild in severity. In NCT01920893, adverse effects were experienced in both placebo and dupilumab groups, with greater prevalence in nasopharyngitis, headache and injection site reactions; injection site reactions were notably more frequent in the dupilumab group (40 vs 7%) [32]. Nasopharyngitis occurred in 47% of the dupilumab group compared with 33% of the placebo group and headache was similar in dupilumab (20%) compared with placebo (17%). No serious adverse events were related to dupilumab in the study and two of 30 patients receiving dupilumab discontinued the drug due to constipation and injection site reaction [34].

The pooled results from both SINUS-24 and SINUS-52 revealed that adverse events were generally more common in the placebo group than the dupilumab group [33]. Nasopharyngitis was the most common adverse event observed overall. In SINUS-24, epistaxis was a more common adverse event occurring in the dupilumab group when compared with the placebo group (7.7 vs 3%, respectively). Adverse reactions seen in 1–3% subjects receiving dupilumab have also included arthralgia, gastritis, insomnia and toothache [23].

The safety of dupilumab has also been demonstrated in the literature for atopic dermatitis. In three major Phase III trials, the incidence of adverse events was similar between placebo and dupilumab groups [37]. Only 2–3% of subjects discontinued dupilumab in SOLO1, SOLO2 and CHRONOS trials, compared with 8% of subject in the placebo groups [37]. Similar adverse reactions were reported as in the CRSwNP trials, including nasopharyngitis, upper respiratory tract infections and injection site reactions [37].

Conjunctivitis was reported as an adverse reaction related to dupilumab in the previous clinical trials for atopic dermatitis, but these associations were not significant in the clinical trials specifically for asthma and CRSwNP [37]. Additionally, no reports of conjunctivitis were seen in patients receiving dupilumab in clinical studies for eosinophilic esophagitis [38]. As such, conjunctivitis may be related to the pathophysiology of atopic dermatitis itself with disease–drug specific interactions. The incidence of conjunctivitis in the atopic dermatitis studies was associated with severity of the atopic dermatitis and a prior history of conjunctivitis [38]. While the exact pathophysiology is unknown, several hypotheses have been proposed and include alteration in *Demodex* mites, disruption of conjunctival lymphoid tissue and decreased number of goblet cells with associated mucus from the drop in IL-13 stimulation [38].

The only listed contraindication for dupilumab is known hypersensitivity to the drug itself or one of its ingredients. Less than 1% of patients have experienced hypersensitivity reactions in the previous clinical trials. Beyond the above adverse effects, patients with conditions with high eosinophils, such as eosinophilic granulomatosis with polyangiitis, may experience disease exacerbations related to the transient increase in eosinophils associated with dupilumab administration [23]. Additionally, patients with helminthic infections, which often rely on Type 2 mediated processes for disease control, were excluded from the studies evaluating dupilumab. Caution has been recommended in treating patients with parasitic infections with dupilumab.

Regulatory affairs in use of dupilumab

Dupilumab is currently approved for three major indications: atopic dermatitis, asthma and CRSwNP. Details regarding the indications of dupilumab as an add-on maintenance treatment for inadequately controlled CRSwNP have been mentioned above. For atopic dermatitis, dupilumab is approved in the USA for patients ≥ 12 years old with moderate-to-severe disease not controlled with topical prescription therapies or if those therapies cannot be used [23]. In Europe, the agent is approved for adults and more recently adolescents with moderate-to-severe atopic dermatitis who are candidates for systemic therapy. In Japan, it is approved for adults with atopic dermatitis not adequately controlled with existing therapies [39].

For asthma, dupilumab is approved in the USA as add-on maintenance therapy in patients ≥ 12 years old with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma [23]. In Europe, the indications are similar: patients ≥ 12 years old with severe asthma [39]. These patients exhibit Type 2 inflammation with elevated blood eosinophils or elevated fractional exhaled nitric oxide [39].

The economics of dupilumab are relevant. The list price for a 4-week supply of the medication is \$3019.50 [39]. By comparison, the cost of treating CRSwNP with index endoscopic sinus surgery followed by medical therapy for a 1-year duration is estimated at \$11,166 [40]. Patients who require revision surgery in that same year can expect an additional cost of \$13,129 [40]. Insurance coverage varies for dupilumab, but many patients whose commercial insurance covers the drug pay less than \$100 monthly [39]. Cost of treatment should be a component in the decision-making process, but it should be considered in the setting of severity of disease, previous treatments attempted, risks associated with both medical and surgical therapy and patient preference.

Conclusion & future perspective

Dupilumab is the first biologic agent that has received FDA approval as a treatment option for CRSwNP. Other biologics targeting IL-5, IgE and IL-33 pathway are currently under investigation for clinical utility and safety in CRSwNP management. The European Forum for Allergy and Airway Diseases recently released a consensus statement on the use of biologics in CRSwNP [41]. This expert panel proposed five criteria that should be factored into decision-making on when to use biologics: evidence of Type 2 inflammation (biologic biomarker), the need

Executive summary

Chronic rhinosinusitis

- With a prevalence up to 12% and annual costs of treating estimated at US \$22 billion, the disease is an important healthcare issue.
- Although patients with nasal polyps are a smaller subset of chronic rhinosinusitis patients, nasal polyps are more difficult to treat, with a higher recurrence rate, up to 40%, after endoscopic sinus surgery.
- With the higher recurrence rate comes increased need for repeat surgeries and alternative therapies, with associated increased costs and adverse outcomes.

Pathophysiology & endotypes

- The pathophysiology of nasal polyps is complex and multifactorial, but a TH2 driven response is an important component. Immune signaling involving IL-4, IL-5 and IL-13 is important in driving this response.
- Recent evidence points to a diversity of expression of the immune signaling within patients suffering from nasal polyps and the concept of endotypes has important implications for treatment. Namely, a uniform therapeutic approach is unlikely to be effective for all patients. Rather, targeted therapies based on expression of immune/inflammatory markers is likely to be more successful.
- The growing field of monoclonal antibodies has made possible a targeted approach. Despite this, use of these pharmaceuticals in chronic rhinosinusitis has remained limited at this point.

Dupilumab

- Targets the signaling of both IL-4 and IL-13 by blocking the IL-4 receptor α subunit. Expands upon previous attempts to block IL-4 and IL-13 independently in asthma trials, which were generally not successful.
- Previously approved for the treatment of atopic dermatitis and asthma.
- Given subcutaneously weekly or biweekly. Follows nonlinear target-mediated pharmacokinetics with absorption driven by the lymphatic system.

Efficacy & safety of dupilumab in treating nasal polyps**NCT01920893**

- Randomized, double blind, placebo-controlled trial of patients receiving weekly dupilumab with intranasal mometasone compared with placebo with intranasal mometasone over 16 weeks. The dupilumab group had greater improvement in nasal polyp score, with a least squares mean difference in change of -1.6 favoring dupilumab.
- Secondary outcomes including Lund–Mackay score, CT volume of disease, nasal airflow, SNOT-22, UPSIT and symptoms as recorded by diary all improved to a greater degree in the dupilumab group. Markers of disease, including IgE and TARC also decreased to a greater degree in the dupilumab group.

SINUS 24

- Randomized, double blind placebo-controlled trial of biweekly dupilumab with intranasal mometasone given over 24 weeks.
- The dupilumab group had greater improvements in nasal polyp score, Lund–Mackay score, nasal congestion, SNOT-22 score and UPSIT scores. They also required less systemic steroids and fewer endoscopic surgeries to remove polyps.

SINUS 52

- Randomized, double blind placebo-controlled trial of biweekly dupilumab with intranasal mometasone compared with biweekly dupilumab transitioning to q4 week dosed dupilumab with intranasal mometasone.
- The dupilumab group had greater improvements in nasal polyp score, Lund–Mackay score, nasal congestion, SNOT-22 score and UPSIT scores. They also required less systemic steroids and fewer endoscopic surgeries to remove polyps.

Safety

- The drug is well tolerated. More common adverse effects include injection site reactions, nasopharyngitis, headache and epistaxis. Conjunctivitis is a rare, but notable side effect, more common in atopic dermatitis studies.

Conclusion & future perspective

- The accumulating evidence led to dupilumab's approval in June 2019 for the treatment of chronic rhinosinusitis with nasal polyps.
- Future studies will seek to examine dupilumab's long-term efficacy and safety. The use of dupilumab as a monotherapy or in comparison to other monoclonal antibodies should also be investigated.
- Development of a test to determine a patient's inflammatory endotype may help practitioners better select patients appropriate for dupilumab as well as other monoclonal antibodies available based on targeting specific signaling pathways.

to use systemic corticosteroids in the past 2 years, significant quality of life impairment, significant loss of smell and diagnosis of comorbid asthma. The group concluded that biologics are indicated in patients with bilateral CRSwNP meeting three of the previous criteria in addition to having had a prior endoscopic sinus surgery. In those patients who have not undergone previous sinus surgery, it was recommended that four of the five previous criteria be met before initiating biologic therapy. Contraindications for use of biologic treatments include lack of Type 2 inflammation, cystic fibrosis, unilateral nasal polyps, mucocoeles, noncompliance and immunodeficiencies. As the field of biologics continues to expand its indications for CRSwNP, a concerted effort to incorporate these therapeutic agents into the existing management strategies for CRSwNP will be essential to ensure both effective and cost-effective care.

Dupilumab provides an additional therapeutic option for CRSwNP, which remains a challenging condition with significant health-related costs. In one Phase II and two Phase III studies, dupilumab has demonstrated significant improvements in disease severity as assessed by symptom scores, biomarker measures of disease activity and physician assessment of disease burden. Its potential role in CRSwNP management represents an exciting development in the use of targeted therapy for disease management.

Financial & competing interests disclosure

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