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The Safety and Efficacy of Dupilumab for Chronic Rhinosinusitis with Nasal Polyposis: A Meta-Analysis

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ABSTRACT

To analyze and assess the safety and efficacy of dupilumab as an adjuvant treatment for chronic rhinosinusitis with nasal polyposis. Two authors independently searched 6 databases from inception until May 2021. We included and analyzed studies comparing dupilumab-treated (dupilumab) and placebo-treated (control) groups. The risk of bias was evaluated using the Cochrane Risk of Bias tool. Three studies, including 784 participants, were included. The dupilumab group showed significantly improved laboratory markers in serum and nasal secretions compared to the control group except for serum eosinophils. In addition, dupilumab showed higher efficacy for olfactory symptoms, disease-related symptoms (nasal congestion, sinusitis symptom severity, nasal polyp score), and radiologic findings (computed tomography score). However, there were no significant differences in treatment-related morbidities between the 2 groups. According to a meta-analysis of studies reporting laboratory and clinical results, dupilumab is a safe and effective treatment for patients suffering from chronic rhinosinusitis with nasal polyps.

Keywords: Biological products, dupilumab, antibodies, sinusitis, nasal polyps

Introduction

The prevalence of chronic rhinosinusitis with nasal polyps (CRSwNP) is estimated to be 4.2% in the United States,[1] 2.1% to 4.3% in Europe,[2] and 2.1% to 8.4% in Asia.[3,4] Chronic rhinosinusitis with nasal polyps has a worse prognosis than chronic rhinosinusitis without nasal polyps, and the majority of intractable CRSwNP cases show marked eosinophil and mast cell infiltration into the nasal mucosa and polyp tissue, which is a hallmark of T-helper 2 (Th2) cell inflammation. This Th2 cell immune response can be confirmed by local and systemic increases in type 2 cytokines, such as eosinophil cationic protein (ECP), eotaxin, interleukin (IL)-4, IL-5, and IL-13. Among them, IL-4, IL-5, and IL-13 are known to play important roles in the pathophysiology of CRSwNP.[5]

The traditional treatments used for CRSwNP are topical intranasal corticosteroids and short-course systemic steroids if the disease worsens.[6] Endoscopic polypectomy and/or sinus surgery have been recommended for patients who do not respond to medication. However, the underlying inflammatory process is not resolved even after the surgery, and the recurrence of symptoms and polyps is common.[7] Treatment directly targeting underlying type 2 inflammation may restore the balance of the immune system and induce immune tolerance via selective immunomodulation.[8] Dupilumab, the first monoclonal antibody targeting the IL-4 receptor alpha subunit, inhibits IL-4/IL-13 signaling and is approved as an add-on maintenance treatment in adult patients with refractory CRSwNP.[5] Recently, evidence for the safety and efficacy of dupilumab for CRSwNP has accumulated. This review aims to assess the efficacy and safety of dupilumab for CRSwNP in

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terms of endoscopic, clinical, and patient-reported outcomes, and treatment-related morbidity.

Methods

Search Strategy

The PubMed, SCOPUS, Embase, Web of Science, and Cochrane Central Register of Controlled Trials databases were searched from inception through to May 2021 for studies published in English. To optimize the search results, the search strategy combined the keywords "dupilumab," "chronic sinusitis," "chronic rhinosinusitis," "nasal polyp," and "polyps" with Boolean operators, with Medical Subject Headings terms used where appropriate.

Two independent reviewers screened the abstracts and titles of all candidate publications related to dupilumab for CRSwNP. If it was difficult to decide whether to include an article based on the abstract, a full-text review was conducted. The study protocol was registered on Open Science Framework (https://osf.io/7dsbv/).

Selection Criteria

Randomized controlled studies meeting the following inclusion criteria were reviewed. The study included patients who received dupilumab, and the effects of dupilumab were compared to those of control (placebo). Studies were not eligible if the treatment included other biologics, such as mepolizumab, omalizumab, reslizumab, or benralizumab, or if the article was a duplicate. We also excluded studies for which the outcomes were not clearly reported and those for which data could not be extracted and analyzed. Figure 1 is a schematic of the search strategy.

Main Outcome Measures

This study had 4 main outcome measures. First, laboratory markers were measured, including eosinophil, eotaxin-3, IgE, thymus and activation-regulated chemokine (TARC), and ECP, in serum or nasal secretions. Second, objective clinical indices were measured, including the endoscopic nasal polyp score (0-8; higher scores indicate worse outcomes), the Lund–Mackay (LMK) score (0-24; higher scores indicate more opacification on computed tomography), and UPSIT (University of Pennsylvania Smell Identification Test) (0-40; high scores (35–40) indicate a normal sense of smell). Third, clinical symptoms were measured using the 22-item Sinonasal Outcome Test (SNOT-22) (scores of 0-110; higher scores indicate poorer outcomes). Also, smell dysfunction (loss of smell) and nasal congestion or obstruction were assessed using a categorical scale (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms), and sinusitis symptom severity was assessed by a 10-point visual analog scale (higher scores indicate more severe symptoms). Treatment-related morbidities (adverse events (including those leading to treatment discontinuation) such as back pain, bronchitis, cough, epistaxis, headache, injection site problems, and nasopharyngitis) were also assessed. These outcomes were compared between the treatment group (dupilumab) and control group (placebo).

Main Points

- Eosinophilic chronic rhinosinusitis with nasal polyps (CRSwNP) is difficult to treat with traditional treatments.
- Dupilumab is the first monoclonal antibody approved as an add-on maintenance treatment for adult patients with refractory CRSwNP.
- This review aims to assess the efficacy and safety of dupilumab for patients with CRSwNP in terms of endoscopic, clinical, and patient-reported outcomes, and treatment-related morbidity.
- Dupilumab is considered a safe and effective treatment for patients suffering from CRSwNP.
- Additional research on indications, duration of treatment, long-term efficacy, and cost-effectiveness should be performed.

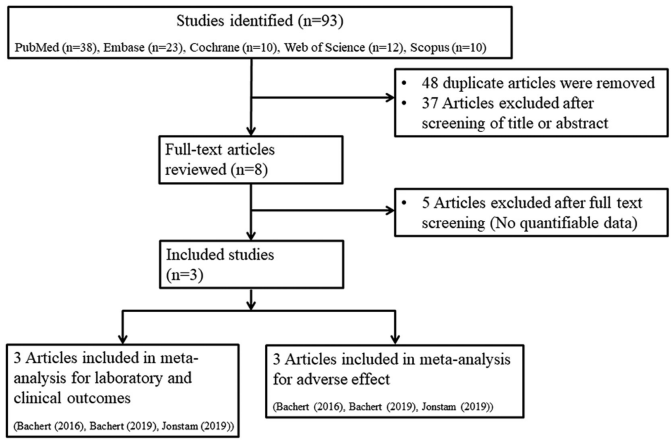

Figure 1. Schematic diagram of the search strategy.

Data Extraction and Risk of Bias Assessment

The data from the included studies were extracted, synthesized, and analyzed in a standardized manner.[8-10] Extracted data included the number of patients, grades, and *P*-values obtained for comparison of the magnitude of differences from baseline between the treatment and control groups. The risk of bias in each study was evaluated using the Cochrane Risk of Bias tool.[11]

Statistical Analysis

The meta-analysis was performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria). Standard mean differences (SMD) for continuous variables were analyzed. The SMD is a summary statistic used for meta-analyses of the same outcome measured using different continuous scales.[12] Individual mean differences (treatment–control) are weighted according to the size and standard deviation data of each study and provide an accurate estimate of the treatment effect (summarized as a single value, i.e., the SMD). Outcome analysis was based on odds ratios (ORs), calculated according to the Mantel–Haenszel method. An effect size of about 0.2 is considered small, while an effect size of about 0.5 is considered medium, and an effect size above 0.806 is considered large and clinically significant.[13,14]

Results

Three studies, including 784 participants, were included in the meta-analysis. The characteristics of the studies are presented

in Supplementary Table 1, and the results of the bias assessment are listed in Supplementary Table 2. Publication bias was not evaluated because the number of tests included was not sufficient for adequate evaluation of the funnel plot or advanced regression analysis.

Laboratory Markers

Changes from baseline of serum markers (eotaxin-3: SMD = −0.6725 (−0.9769; −0.3680); $P < .0001$, $I^2 = 84.7\%$; IgE: SMD = −0.8454 (−1.0700; −0.6207); $P < .0001$, $I^2 = 76.4\%$; TARC: SMD = −0.7772 (−0.8922; −0.6622); $P < .0001$, $I^2 = 26.9\%$) were significantly larger in the dupilumab than the control group, except for eosinophil (SMD = 0.1048 (−0.0709; 0.2806); $P = .2424$, $I^2 = 65.1\%$) (Table 1; Figure 2A–D). Significant inter-study heterogeneity was found in most outcomes during the treatment period ($I^2 > 50\%$).

The changes from baseline of nasal secretion markers (eotaxin-3: SMD= −0.5558 (−0.7421; −0.3696); $P < .0001$, $I^2 = 0.0\%$; IgE: SMD = −0.3945 (−0.5792; −0.2098); $P < .0001$ $I^2 = 0.0\%$; ECP: SMD = −0.3117 (−0.4958; −0.1276); $P = .0009$, $I^2 = 0.0\%$) during the treatment period were significantly larger in the dupilumab than the control group (Figure 3A–C). For most outcomes, no significant inter-study heterogeneity was seen during the treatment period. The overall analysis did not take the treatment period (16, 24, or 52 weeks) into account. Consequently, subgroup analyses were performed. The 16-week treatment subgroup included insufficient data for meaningful analysis, although eotaxin-3 and TARC tended to change more from baseline in the treatment than the placebo group. In the 24-and 52-week treatment subgroups, significant differences in the changes from baseline of eotaxin-3, IgE, and TARC were seen between the treatment and placebo groups.

Clinical Markers

Changes from baseline of the endoscopic nasal polyp score (SMD = −1.1271 (−1.2587; −0.9954); $P < .0001$, $I^2 = 35.5\%$), LMK score (SMD = −1.8733 (−2.4963; −1.2504); $P < .0001$ $I^2 = 89.9\%$), and UPSIT score (SMD = 1.3320 (1.0583; 1.6058); $P < .0001$ $I^2 = 55.5\%$) were significantly larger in the dupilumab than the control group (Figure 4A–C). Significant inter-study heterogeneity was found in the LMK and UPSIT scores during treatment ($I^2 > 50\%$).

Table 1. Subgroup Analysis of the Effects of Dupilumab on Laboratory and Clinical Markers

	Effect Size (SMD, Laboratory Markers)			
	Eotaxin-3	**IgE**	**TARC**	**Eosinophil**
Overall results	−0.6725 (−0.9769; −0.3680); $I^2 = 84.7\%$	−0.8454 (−1.0700; −0.6207); $I^2 = 76.4\%$	−0.7772 (−0.8922; −0.6622); $I^2 = 26.9\%$	0.1048 (−0.0709; 0.2806); $I^2 = 65.1\%$
16 weeks	−1.7502 (−2.3510; −1.1493);NA	−2.2646 (−2.9218; −1.6075]; NA	−0.3780 (−0.8889; 0.1328); NA	0.1893 (−0.3180; 0.6965); NA
24 weeks	−0.4181 (−0.5803; −0.2558); $I^2 = 0.00\%$	−0.7209 (−0.8580; −0.5838); $I^2 = 0.0\%$	−0.7638 (−0.9302; −0.5974); $I^2 = 34.0\%$	0.2054 (0.0113; 0.3995) ;$I^2 = 52.8\%$
52 weeks	−0.4181 (−0.5803; −0.2558); $I^2 = 86.1\%$	−0.7325 (−0.8983; −0.5667); $I^2 = 0.0\%$	−0.8337 (−1.0011; −0.6662); $I^2 = 13.2\%$	−0.0638 (−0.3692; 0.2416); $I^2 = 72.3\%$

	Effect Size (SMD, Clinical Markers)						
	Nasal Polyp Score	**LMK Score**	**UPSIT**	**SNOT-22**	**Loss of Smell**	**Sinusitis Symptom Severity**	**Nasal Congestion or Obstruction**
Overall results	−1.1271 (−1.2587; −0.9954); $I^2 = 35.5\%$	−1.8733 (−2.4963; −1.2504); $I^2 = 89.9\%$	1.3320 (1.0583; 1.6058); $I^2 = 55.5\%$	−1.0082 (−1.1399; −0.8764); $I^2 = 24.2\%$	−1.1969 (−1.4785; −0.9152); $I^2 = 57.9\%$	−0.9632 (−1.2029; −0.7235); $I^2 = 50.3\%$	−0.9883 (−1.1137; −0.8630); $I^2 = 0.0\%$
16 weeks	−1.1164 (−1.6630; −0.5698); NA	−2.7571 (−3.4758; −2.0384); NA	1.7983 (1.1926; 2.4041); NA	−1.1304 (−1.6780; −0.5828); NA	−1.5271 (−2.1537; −0.9004); NA	−0.6160 (−1.1347; −0.0972); NA	−0.8954 (−1.4279; −0.3629); NA
24 weeks	−1.0530 (−1.2132; −0.8927); $I^2 = 41.2\%$	−1.5608 (−2.0926; −1.0291); $I^2 = 88.5\%$	1.2385 (1.0396; 1.4374); $I^2 = 27.6\%$	−0.9667 (−1.1292; −0.8042); $I^2 = 68.7\%$	−1.1376 (−1.4393; −0.8359); $I^2 = 68.7\%$	−1.0273 (−1.2540; −0.8007); $I^2 = 48.6\%$	−0.9682 (−1.1306; −0.8058); $I^2 = 36.9\%$
52 weeks	−1.3165 (−1.5712; −1.0619); NA			−1.0791 (−1.3261; −0.8321); NA			−1.0375 (−1.2498; −0.8252); NA

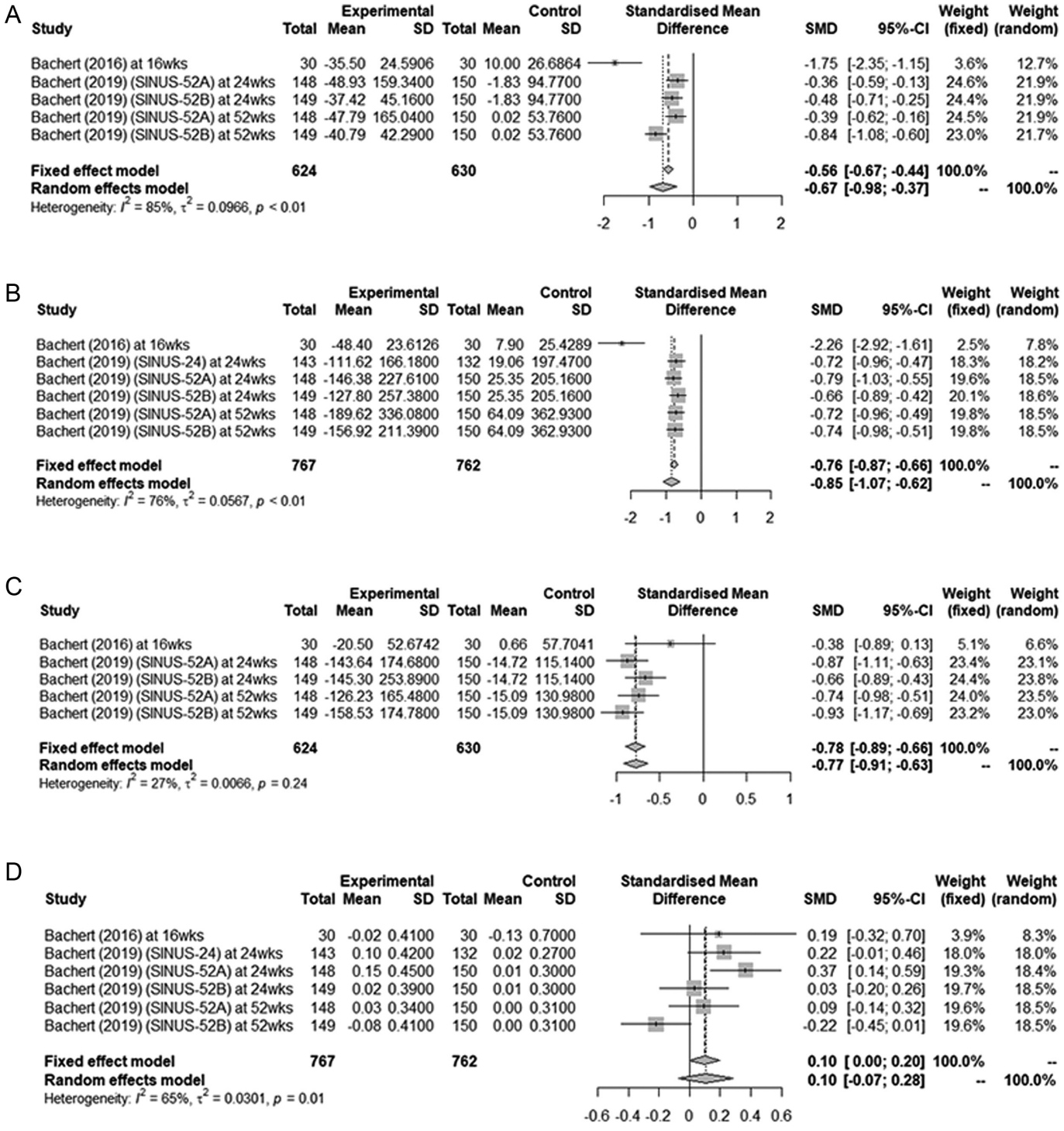

Figure 2. Changes from baseline of serum markers. (A) Eotaxin-3, (B) immunoglobulin E, (C) thymus and activation-regulated chemokine, and (D) eosinophils.

Regarding markers of clinical symptoms, the changes from baseline of SNOT-22 (SMD = –1.0082 (–1.1399; –0.8764) P < .0001, I^2 = 24.2%), loss of smell (SMD = –1.1969 (–1.4785; –0.9152) P < .0001, I^2 = 57.9%), sinusitis symptom severity (SMD = –0.9632 (–1.2029; –0.7235); P < .0001, I^2 = 50.3%), and nasal congestion or obstruction (SMD = –0.9883 (–1.1137; –0.8630); P < .0001, I^2 = 0.0%) scores were significantly larger in the dupilumab than the control group (Figure 4D–G). Significant inter-study heterogeneity was found in the loss of smell and sinusitis symptom severity during treatment (I^2 > 50%).

The 16- and 52-week treatment subgroups included insufficient data for meaningful analysis. However, all markers of clinical symptoms tended to change more from baseline in the treatment than the placebo group. In the 24-week treatment

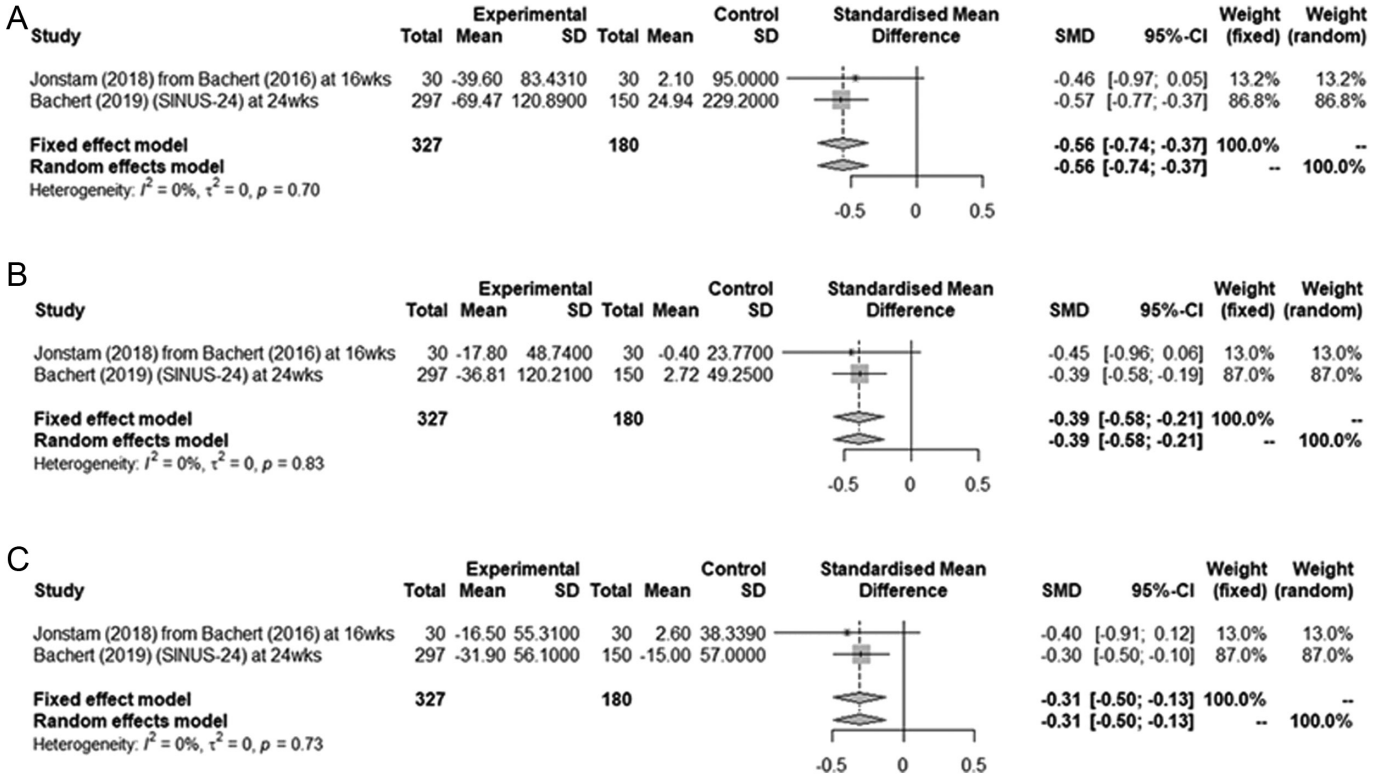

Figure 3. Changes from baseline of nasal secretion markers. (A) Eotaxin-3, (B) immunoglobulin E, and (C) eosinophil cationic protein.

subgroup, significant differences in the changes from baseline of all markers of clinical symptoms were seen between the treatment and placebo groups.

Treatment-Related Adverse Effects

There was no significant difference in the incidence of any type of adverse event (OR=0.7415 (0.5183; 1.0609), P=.1018, I^2 = 39.1%), including those leading to treatment discontinuation (OR=0.4140 (0.1395; 1.2282); P=.1119, I^2 = 55.3%), back pain (0.8788 (0.4365; 1.7693), P=.7175, I^2 = 12.7%), bronchitis (0.8551 (0.4483; 1.6309), P=.6346, I^2 = 47.9%), cough (0.9488 (0.5173; 1.7403), P=.8652, I^2 = 0.0%), epistaxis (1.0568 (0.3649; 3.0609), P=.9189, I^2 = 75.7%), headache (0.8017 (0.5216; 1.2322), P=.3135, I^2 = 0.0%), injection site problems (1.3673 (0.3145; 5.9453), P=.6765, I^2 = 79.3%), or nasopharyngitis (0.8882 (0.6452; 1.2228), P=.4674, I^2 = 0.0%), between the dupilumab and control groups (Figure 5A–I).

Discussion

We conducted a systematic review and meta-analysis to investigate the effectiveness of dupilumab for CRSwNP. Changes in laboratory and clinical markers differed significantly between the dupilumab and placebo groups regardless of the duration of treatment. The most common adverse events were nasal bleeding, nasopharyngitis, headache, recurrent nasal polyps, and exacerbation of asthma. Injection site erythema after dupilumab was uncommon. To the best of our knowledge, this is the first meta-analysis to assess the effectiveness of dupilumab for CRSwNP.

Currently, chronic rhinosinusitis is considered a chronic inflammatory disease rather than an infectious disease.[15] Both innate and adaptive immunity contribute to the inflammatory pathogenesis of chronic rhinosinusitis. Recently, classification systems and treatment strategies have been established according to the endotype of chronic rhinosinusitis rather than the anatomical classification.[16] Several studies have reported that most CRSwNP patients show a type 2-dominant endotype.[17,18] The main treatment for CRSwNP is nasal saline irrigation and intranasal corticosteroid sprays.[19] Functional endoscopic sinus surgery is recommended for patients with severe disease showing no response to systemic corticosteroids. However, studies have shown that the polyp recurrence rate is quite high after surgical intervention, ranging between 40% and 60%.[20,21] Polyps may recur after surgical removal if the underlying cause of the inflammation is not properly addressed.[6] Treatment success is considered to depend on appropriate therapy according to the underlying pathophysiology. Given the contribution of type 2 inflammation to the pathophysiology of CRSwNP, several biologic agents targeting type 2 inflammation, including anti-IgE (omalizumab), anti-IL-4/IL-13 (dupilumab), anti-IL-5 (mepolizumab), and anti-IL-5 receptor α (benralizumab) monoclonal antibodies, have or are currently being evaluated.[22] By targeting only the overexpressed immune response in CRSwNP, the side effects of systemic steroids, which are general immunosuppressive agents, can be avoided. Therefore, dupilumab could be a good option for patients who have difficulty using steroids due to various underlying diseases.

The stage of CRSwNP treatment at which dupilumab (and other biologics) should be added needs to be determined. As mentioned earlier, severe CRSwNP patients often show type 2 endotypes, but other endotypes are sometimes seen. In

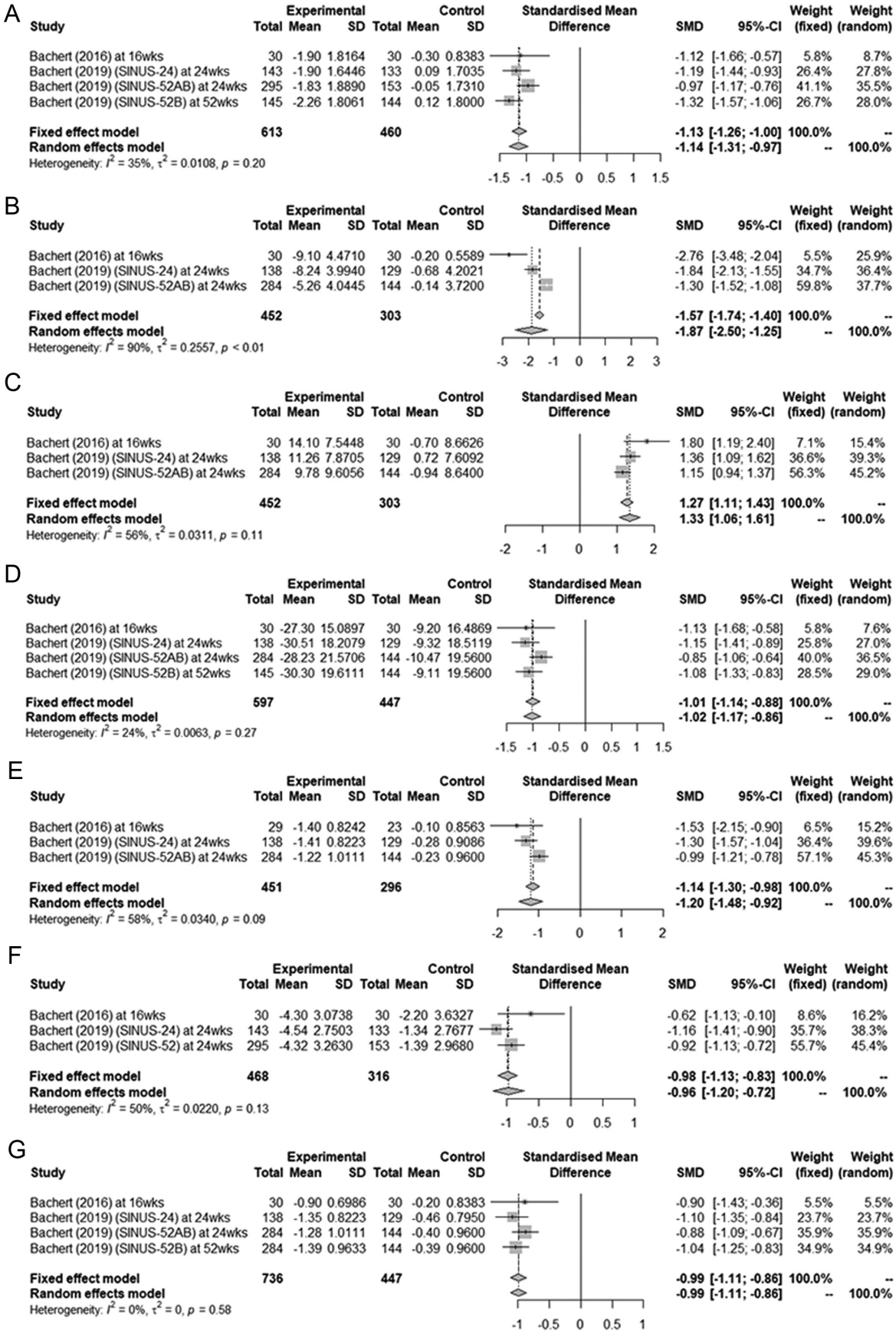

Figure 4. Changes from baseline of markers of clinical symptoms. (A) Nasal polyp score, (B) Lund–Mackay score, (C) University of Pennsylvania Smell Identification Test score, (D) 22-item Sinonasal Outcome Test score, (E) loss of smell score, (F) sinusitis symptom severity score, and (G) nasal congestion or obstruction score.

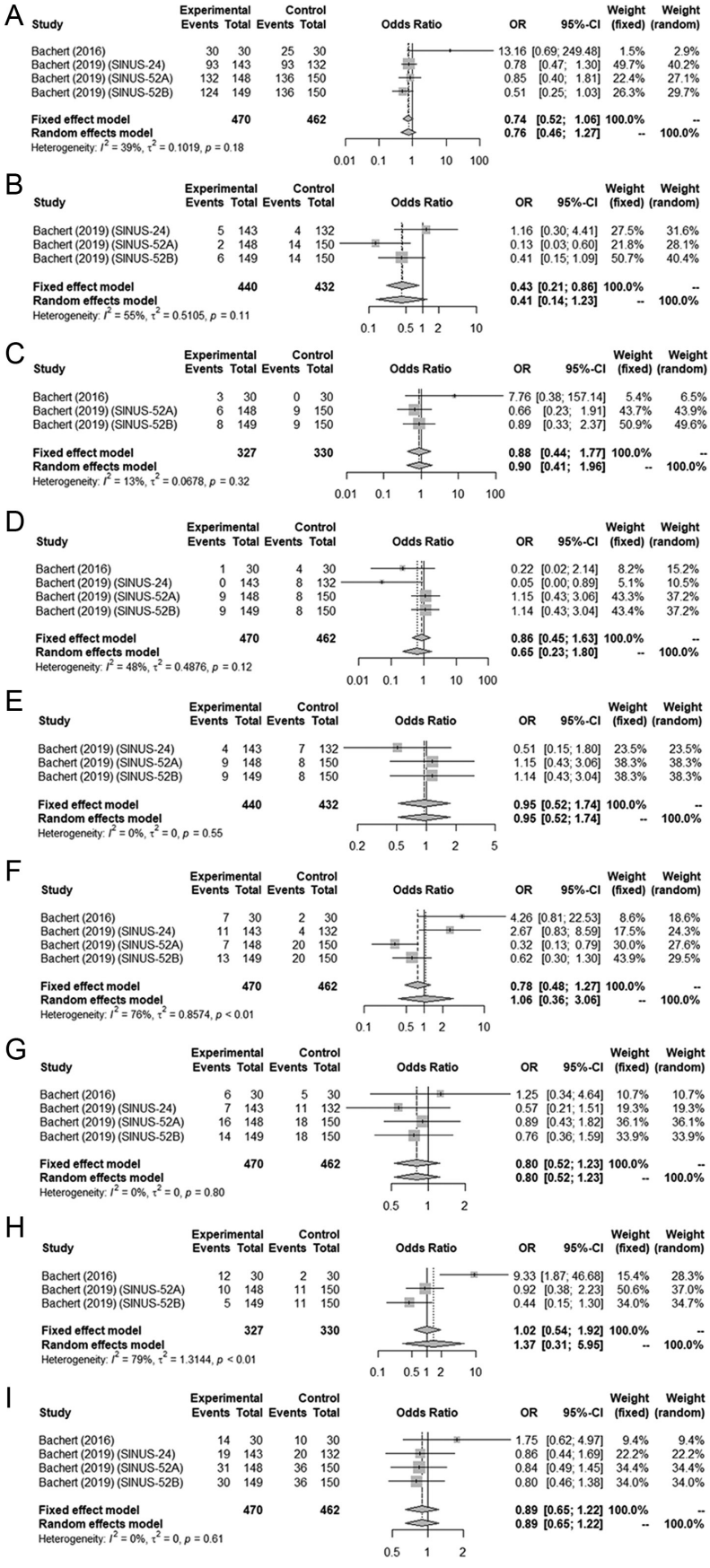

Figure 5. Treatment-related adverse events. (A) All types of adverse events, (B) adverse events leading to treatment discontinuation, (C) back pain, (D) bronchitis, (E) cough, (F) epistaxis, (G) headache, (H) injection site problem, and (I) nasopharyngitis.

studies of asthma and atopic dermatitis patients, to whom biologic agents were administered before CRSwNP onset, type 2 inflammation biomarkers had limitations in determining individual responses to biologics and prognoses.[16,23,24] The European Position Paper on Rhinosinusitis and Chronic Rhinosinusitis 2020 suggested biologics were indicated when 3 or more of the following 5 criteria were satisfied in patients who had already undergone surgery: evidence of type 2 inflammation (tissue eosinophil level ≥10/HPF, blood eosinophil level ≥250 cells/mm,[3] or total IgE level ≥100 kU/L), a need for systemic steroids (≥2 cycles of systemic corticosteroid per year, long-term use (>3 months) or contraindication to systemic steroid), lowered quality of life (SNOT-22 score ≥40), anosmia, and comorbid asthma.[16] However, indications for biologic agents need to be further refined. In addition, a dosing period should be established to ensure a sufficient effect. In cases of CRSwNP, the established dosing regimen for dupilumab involves active administration of the drug every 2 weeks for 24 weeks, before switching to administration according to a 4-week interval. However, after discontinuation of dupilumab, some patients exhibit clinical signs of recurrence of polyposis, similar to when oral steroids are stopped.[8] These cases suggest that the natural history of CRSwNP might not be altered by dupilumab and show that long-term treatment could be needed to control the disease. Finally, the estimated cost of treatment is high, at about $36 000 a year.[25,26] Therefore, cost-benefit analysis is needed for individual cases.

Although this study provides evidence supporting the use of dupilumab in patients with CRSwNP, there were some limitations to the analysis. First, the small number of studies analyzed, and their relatively short follow-ups, limited the generalizability of the results. The small number of studies reflected our desire to include only high-quality randomized controlled trials; although the number of articles was small, bias was likely minimal. Nevertheless, larger comparative studies or well-designed randomized clinical trials using validated tools are still needed. Second, standardization of the treatment periods is needed. In the SINUS-52 study of Bachert et al[8] treatment efficacy gradually increased during the treatment period, and the maximum effects were not seen until after 52 weeks. Thus, dupilumab may exert therapeutic effects for more than 52 weeks. Third, only the efficacy of dupilumab administered in combination with topical steroids was evaluated, so the efficacy of dupilumab as a monotherapy remains unclear; dupilumab without intranasal corticosteroid treatment should be evaluated.[4,8]

Conclusion

Dupilumab appears safe and effective for treating type 2 inflammation in patients with intractable CRSwNP, with minimal side effects. However, additional research on indications, duration of treatment, long-term efficacy, and cost-effectiveness should be performed.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.H.K., S.H.H.; Design – D.H.K., S.H.H.; Supervision – S.W.K., M.A.B.; Funding – D.H.K., S.W.K., S.H.H.; Materials – D.H.K., S.W.K., M.A.B., S.H.H.; Data Collection and/or Processing – S.W.K., M.A.B.; Analysis and/or Interpretation – D.H.K., S.H.H.; Literature Review – S.W.K., M.A.B.; Writing – D.H.K., S.H.H.; Critical Review – D.H.K., S.W.K., M.A.B., S.H.H.

Declaration of Interests: The authors have no conflict of interest to declare.

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Supplementary Table 1. Summary of the Studies Included in the Meta-Analysis

Study (Year)	Sample Size	Age (Mean, Range, or Standard Deviation)/Sex (Ratio of Male to Female)	Study Design	Comparison	Outcome Measure Analyzed	Risk of Bias of Randomized Studies
Bachert (2016)	60	Dupilumab group (age: 47.4 (9.8) years (18 males:12 females)/placebo 49.3 (9.1) years /(16 males and 14 females)	Randomized controlled	Dupilumab group (16 weeks) vs placebo group	Clinical symptomatic markers and serum markers	Risk of bias (low risk)
Jonstam (2018)	60	Dupilumab group (age: 47.4 (9.8) years (18 males:12 females)/placebo 49.3 (9.1) years /(16 males and 14 females)	Randomized controlled	Dupilumab group (16 weeks) vs placebo group	Nasal secretion markers	Risk of bias (low risk)
Bachert (2019)	LIBERTY NP SINUS-24 (276)	LIBERTY NP SINUS-24 (24 weeks treatment)	Randomized controlled	Dupilumab group (24 weeks) vs placebo group	Clinical symptomatic markers, nasal secretion markers, and serum markers	Risk of bias (low risk)
		Dupilumab group (age: 52 (39-61) years (88 males:55 females)/placebo 50 (41-60) years/(70 males and 63 females)				
	LIBERTY NP SINUS-52 (298)	LIBERTY NP SINUS-52 (52 weeks treatment)				
		Dupilumab group (age: 53 (42-63) years (87 males:58 females)/placebo 53 (44-61) years/(95 males and 58 females)		Dupilumab group (52 weeks) vs placebo group		

Supplementary Table 2. Methodological Quality of the Randomized Controlled Trials (RCTs)

Study (Year)	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data Addressed	Free of Selective Reporting	Free of Other Bias
Bachert (2016)	Yes	Yes	Yes	Yes	Yes	Yes	Risk of bias (low risk)
Jonstam (2018)	Yes	Yes	Yes	No	Yes	Yes	Risk of bias (low risk)
Bachert (2019)	Yes	Yes	Yes	Yes	Yes	Yes	Risk of bias (low risk)

"Yes" indicates "low risk of bias"; "No" indicates "high risk of bias"; "?" indicates "unclear risk of bias."