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SUPPORTING INFORMATION

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Comparing biologicals for severe chronic rhinosinusitis with nasal polyps: A network meta-analysis

To the Editor,

We read with special interest the systematic review (SR) by Agache et al.¹ on the efficacy and safety of biologicals in patients with severe chronic rhinosinusitis with nasal polyposis (CRSwNP).

Meta-analytical results were presented for the comparison between each biologic versus placebo, but indirect comparisons between different biologicals were not performed. Therefore, we aimed to complement this SR¹ with a network meta-analysis

TABLE 1 Randomized controlled trials (RCT) with monoclonal antibody (Mab) treatment of chronic rhinosinusitis with nasal polyps included in the network meta-analysis

Mab/biological	RCT/study period	Patients enrolled (n)/ treatment period	Inclusion criteria	Primary outcome
Anti-IgE/Omalizumab	POLYP 1 ¹ November 2017 to March 2019	138/24 weeks	Persistent bilateral nasal polyps; nasal congestion; impaired HRQoL; weight (30–150 kg); serum IgE (30–1500 IU/ml) AND ≥ 4 weeks of INCS before screening visit 1; total NPS ≥ 5 ; NCS ≥ 2 ; SNOT-22 score ≥ 20	Change from baseline to week 24 in endoscopic NPS and mean daily NCS
Anti-IgE/Omalizumab	POLYP 2 ¹ November 2017 to March 2019	127/24 weeks	Persistent bilateral nasal polyps; nasal congestion; impaired HRQoL; weight (30–150 kg); serum IgE (30–1500 IU/ml) AND ≥ 4 weeks of INCS before screening visit 1; total NPS ≥ 5 ; NCS ≥ 2 ; SNOT-22 score ≥ 20	Change from baseline to week 24 in endoscopic NPS and mean daily NCS
Anti-IL-5/Mepolizumab	BACHERT et al. ² May 2009 to December 2014	105/21 weeks	Severe recurrent bilateral nasal polyposis requiring surgery according to the predefined criteria of an endoscopic NPS of 3 or more in 1 nostril (and a minimum score of 2 on the other side) AND VAS nasal symptom score of greater than 7 OR Refractory to standard-of-care steroid therapy (received intranasal steroids for ≥ 3 months and/or received a short course of oral steroids) AND to have undergone at least 1 previous nasal polyp removal surgery	Number of patients no longer requiring surgery at week 25 based on a composite end point of endoscopic NPS and nasal polyposis severity VAS score
Anti-IL-5/Mepolizumab	SYNAPSE ³ May 2017 to December 2019	407/52 weeks	Nasal obstruction VAS > 5 and overall symptoms VAS > 7 and NPS ≥ 5 and at least 1 nasal surgery past 10 year AND INCS (mometasone) at least 8 week before screening; symptoms of CRS for at least 12 week before screening	Change from baseline in endoscopic NPS at 52 week and in mean nasal obstruction VAS score during weeks 49–52
Anti-IL-5 α /Benralizumab	TVERSKY et al. ⁴ 2018 to 2019	24/20 weeks	Average bilateral endoscopic NPS of at least 5 or more; eosinophil count of 300/ μ l or greater; refractory symptoms despite prior surgical or endoscopic polyp removal and at least one oral corticosteroid course over the previous 12 months	Reduction in endoscopic NPS at 20 weeks of therapy compared with baseline
Anti-IL-5 α /Benralizumab	CANONICA et al. ⁵ July 2017 to September 2019	153/24 weeks	Diagnosis of severe, eosinophilic asthma who had experienced ≥ 2 prior-year exacerbations; on high-dosage ICS plus an additional controller for ≥ 3 months before screening; ACQ-6 score of ≥ 1.5 ; documented post-bronchodilator reversibility of $\geq 12\%$ FEV ₁ ; and screening BEC ≥ 150 cells/ μ l; AND patients with physician-diagnosed NP of any severity ongoing at baseline who provided additional consent to participate in ANDHI NP substudy population	Response to SNOT-22, defined as having a minimum clinically important improvement (change from baseline of ≤ -8.9) in SNOT-22 at the end of treatment (week 24)

Assessed outcomes in the network meta-analysis	Asthmatic patients enrolled <i>n</i> (%)	AERD <i>n</i> (%)	Previous nasal polyp surgery <i>n</i> (%)	Serum total IgE (IU/ml), mean (SD)	Blood eosinophils (cells/ μ l), mean (SD)
One surgery or more One course of systemic steroids or more NPS SNOT-22 UPSIT	Placebo: 32 (48.5) OMA: 42 (58.3)	Placebo: 11 (16.7) OMA: 16 (22.2)	Placebo: 40 (60.6) OMA: 39 (54.2)	Placebo: 162.0 (141.2) OMA: 159.9 (139.0)	Placebo: 358.6 (305.2) OMA: 334.4 (264.7)
One surgery or more One course of systemic steroids or more NPS SNOT-22 UPSIT	Placebo: 39 (60.0) OMA: 38 (61.3)	Placebo: 21 (32.2) OMA: 24 (38.7)	Placebo: 40 (61.5) OMA: 39 (62.9)	Placebo: 196.1 (200.6) OMA: 184.1 (201.9)	Placebo: 357.4 (196.2) OMA: 310.8 (176.6)
One surgery or more NPS SNOT-22	Placebo: 38 (75) MEPO: 44 (81)	—	Placebo: 51 (100) MEPO: 54 (100)	—	Placebo: 470 (0.57 SD log) MEPO: 500 (0.71 SD log)
One surgery or more One course of systemic steroids or more NPS SNOT-22 UPSIT	Placebo: 149 (74) MEPO: 140 (68)	Placebo: 63 (31) MEPO: 45 (22)	Placebo: 201 (100) MEPO: 206 (100)	—	Placebo: 400 (0.91 SD log) MEPO: 390 (0.88 SD log)
NPS SNOT-22 UPSIT	Placebo: 12 (100) BENRA: 10 (83)	Placebo: 8 (67) BENRA: 3 (25)	Placebo: 12 (100) BENRA: 12 (100)	Placebo: 470 ($\pm$ 772) BENRA: 208 ($\pm$ 225)	Placebo: 846 ($\pm$ 592) BENRA: 698 ($\pm$ 412)
—	Placebo: 57 (100) BENRA: 96 (100)	Placebo: 11 (19.3) BENRA: 22 (22.9)	Placebo: 41 (71.9) BENRA: 69 (71.9)	Placebo: 125.2 (range: 9.2–7820.2) BENRA: 147.6 (range: 4.6–6292.3)	Placebo: 500 (range: 80–3900) BENRA: 515 (range: 90–7970)

TABLE 1 (Continued)

Mab/biological	RCT/study period	Patients enrolled (n)/ treatment period	Inclusion criteria	Primary outcome
Anti-IL-5Rα/Benralizumab	OSTRO ⁶ January 2018 to July 2020	413/48 weeks	Bilateral nasal polyps, NPS ≥5 with unilateral scores ≥2, symptoms despite maintenance INCS, history of SCS use and/or surgery for nasal polyps, moderate to severe nasal blockage, SNOT-22 total score ≥30	Change from baseline to week 40 in total NPS and biweekly mean NBS
Anti-IL-4Rα/Dupilumab	SINUS-24 ⁷ December 2016 to July 2018	276/24 weeks	Bilateral nasal polyps and symptoms of chronic rhinosinusitis despite INCS therapy, receiving SCS in the preceding 2 years OR previous sinonasal surgery AND NPS of at least 5 and at least two of the following symptoms: nasal congestion or obstruction, loss of smell, or nasal discharge (anterior or posterior)	Change from baseline in endoscopic NPS and nasal congestion severity (based on monthly average of daily score recorded by patients) at 24 weeks
Anti-IL-4Rα/Dupilumab	SINUS-52 ⁷ November 2016 to November 2018	448/52 weeks	Bilateral nasal polyps and symptoms of chronic rhinosinusitis despite INCS therapy, receiving SCS in the preceding 2 years OR previous sinonasal surgery AND NPS of at least 5; at least two of the following symptoms: nasal congestion or obstruction, loss of smell or nasal discharge (anterior or posterior)	Change from baseline in endoscopic NPS and nasal congestion severity (based on monthly average of daily score recorded by patients) at 24 weeks

Abbreviations: ACQ-6, Asthma Control Questionnaire-6; AERD, aspirin-exacerbated respiratory disease; BEC, blood eosinophil count; DSS, difficulty with sense of smell; EQ5D, EuroQoL-5 dimension questionnaire; FEV1, Forced expiratory volume in 1 s; FVC, Forced vital capacity; HRQoL, Health-related quality of life; ICS, inhaled corticosteroid; INCS, intranasal corticosteroid; LMS, Lund-Mackay score; LoS, loss of smell; NBS, nasal blockage score (score 0–5 obtained as a subset question from the SNOT-22 survey data); NCS, Nasal congestion score; NP, nasal polyp; NPS, nasal polyp score; PEFR, Peak expiratory flow rate; SCS, systemic corticosteroid; SNOT-22, Sino-Nasal Outcome Test-22; TNSS, Total Nasal Symptom Score; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analogue scale.

¹Gevaert P, Omachi TA, Corren J, et al. Efficacy and safety of omalizumab in nasal polyposis: two randomized phase III trials. *J Allergy Clin Immunol*. 2020;146(3):595–605. 10.1016/j.jaci.2020.05.032. ²Bachert C, Sousa AR, Lund VJ, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: randomized trial. *J Allergy Clin Immunol*. 2017;140(4):1024–1031. 10.1016/j.jaci.2017.05.044. ³Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2021;9(10):1141–1153. 10.1016/S2213-2600(21)00097-7. ⁴Tversky J, Lane AP, Azar A. Benralizumab effect on severe chronic rhinosinusitis with nasal polyps (CRSwNP): a randomized double-blind placebo-controlled trial. *Clin Exp Allergy*. 2021;51(6):836–844. 10.1111/cea.13852. ⁵Canonica GW, Harrison TW, Chanez P, et al. Benralizumab improves symptoms of patients with severe, eosinophilic asthma with a diagnosis of nasal polyposis. *Allergy*. 2021. 10.1111/all.14902. ⁶Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of benralizumab in chronic rhinosinusitis with nasal polyps: a randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2021. 10.1016/j.jaci.2021.08.030. ⁷Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicenter, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet*. 2019;394:1638–1650. 10.1016/S0140-6736(19)31881-1.

(NMA) providing indirect comparisons between different biologicals, and updating it with three additional randomized controlled trials (RCTs).^{2–4}

We included all RCTs evaluated in the SR by Agache¹ assessing the efficacy of biologicals in patients with CRSwNP treated for more than 16 weeks,⁵ and measuring the following outcomes: need for surgery, need for systemic steroids, Sino-Nasal Outcome Test-22 (SNOT-22), University of Pennsylvania Smell Identification Test (UPSIT) score and nasal polyp score (NPS). In addition, we searched for further eligible RCTs by (i) searching MEDLINE (between September 2020 and September 2021) with the same query

as Agache,¹ and (ii) hand-searching abstracts of 2021 international allergy meetings (Figure S1).

We performed NMA, calculating pooled risk ratios for binary outcomes and mean differences for continuous outcomes. As, for every comparison, evidence was either direct or indirect, we were not able to assess inconsistency. Heterogeneity was assessed using the I^2 statistic, with $I^2 > 50\%$ indicating severe heterogeneity. In each analysis, whenever a study resulted in more than one publication, we included the one with the longest duration of treatment. Sources of heterogeneity were explored by leave-one-out sensitivity analyses and subgroup analyses. The latter were performed according to

Assessed outcomes in the network meta-analysis	Asthmatic patients enrolled n (%)	AERD n (%)	Previous nasal polyp surgery n (%)	Serum total IgE (IU/ml), mean (SD)	Blood eosinophils (cells/ μ l), mean (SD)
One surgery or more One course of systemic steroids or more NPS SNOT-22	Placebo: 136 (67.0) BENRA: 142 (68.6)	Placebo: 59 (29.1) BENRA: 62 (30.0)	Placebo: 149 (73.4) BENRA: 151 (72.9)	Placebo: 251 ($\pm$ 549) BENRA: 214 ($\pm$ 344)	Placebo: 445.7 ($\pm$ 245.1) BENRA: 448.3 ($\pm$ 364.6)
One surgery or more One course of systemic steroids or more NPS SNOT-22 UPSIT	Placebo: 79 (59%) DUPI: 82 (57%)	Placebo: 38 (29) DUPI: 46 (32)	Placebo: 99 (74%) DUPI: 99 (69%)	Placebo: 222.5 (269.1) DUPI: 202.0 (282.3)	Placebo: 440 (310) DUPI: 440 (350)
NPS SNOT-22 UPSIT (24 weeks)	Placebo: 91 (59) DUPI q2w-q4w: 91 (63) DUPI q2w: 85 (57)	Placebo: 44 (29) DUPI q2w-q4w: 41 (28) DUPI q2w: 35 (23)	Placebo: 88 (58) DUPI q2w-q4w: 85 (59) DUPI q2w: 88 (59)	Placebo: 227.80 (267.13) DUPI q2w-q4w: 282.28 (463.72) DUPI q2w: 210.82 (256.78)	Placebo: 450 (360) DUPI q2w-q4w: 400 (300) DUPI q2w: 450 (390)

the duration of treatment (20–24 weeks vs. $\geq$ 40 weeks), percentage of patients with asthma, percentage of patients with previous nasal polyp surgery, baseline mean IgE levels, and baseline mean eosinophil levels.

We included data from nine RCTs (Table 1; Tables S1 and S2). Meta-analytical results are displayed in Table 2 and Figure S2. Dupilumab was the only biologic which, for all outcomes and comparisons, displayed significant improvements compared with placebo. It was also the only biologic significantly associated with smell improvement compared with all other biologics. Heterogeneity was found to be severe for all assessed outcomes, except need

for surgery and SNOT-22. Results of subgroup analyses and leave-one-out sensitivity analyses are displayed in Tables S3 and S4, respectively—these results were overall consistent with our main analyses, with heterogeneity decreases being observed in some subgroups.

Our results suggest that anti-IL-4R α target therapy displays more effectiveness than anti-IL-5/IL-5R α and anti-IgE biologics. Two recent NMA^{6,7} comparing different biologics in CRSwNP patients had equally favored dupilumab. However, all these results should be carefully interpreted due to the high heterogeneity observed. The latter likely results from differences in participants'

TABLE 2 Results of a network meta-analysis comparing nine RCTs with different T2-targeting biologicals (anti-IL-4R α , anti-IL-5, anti-IgE, anti-IL-5R α) in chronic rhinosinusitis with nasal polyps, according to outcomes and duration of treatment. The table should be read as RR or MD of “drug listed in the row” versus “drug listed in the column” for each outcome

	Mepolizumab	Omalizumab	Benralizumab	Placebo
2.1. All studies				
A. One surgery or more^a—RR [95% CI]				
Dupilumab	0.26 [0.06;1.05]	0.03 [0.01;0.14]	0.14 [0.03;0.63]	0.15 [0.04;0.52]
Mepolizumab	—	0.10 [0.03;0.38]	0.35 [0.18;0.68]	0.57 [0.31;1.07]
Omalizumab	—	—	5.21 [1.18;23.05]	5.72 [1.76;18.61]
Benralizumab	—	—	—	1.10 [0.44;2.73]
B. One course of systemic steroids or more^b—RR [95% CI]				
Dupilumab	0.44 [0.28;0.70]	0.11 [0.03;0.44]	0.39 [0.25;0.62]	0.30 [0.22;0.43]
Mepolizumab	—	0.26 [0.07;0.98]	0.89 [0.58;1.36]	0.69 [0.51;0.92]
Omalizumab	—	—	3.45 [0.90;13.18]	2.67 [0.72;9.83]
Benralizumab	—	—	—	0.77 [0.58;1.05]
C. Nasal polyp score^c—MD [95% CI]				
Dupilumab	-1.34 [-2.01;-0.68]	-1.36 [-1.92;-0.80]	-1.75 [-2.43;-1.07]	-2.23 [-2.62;-1.83]
Mepolizumab	—	-0.02 [-0.68;0.65]	-0.41 [-1.18;0.36]	-0.88 [-1.42;-0.35]
Omalizumab	—	—	-0.39 [-1.07;0.29]	-0.87 [-1.26;-0.47]
Benralizumab	—	—	—	-0.48 [-1.03;0.08]
D. UPSIT score^c—MD [95% CI]				
Dupilumab	16.25 [6.94;25.56]	13.71 [6.72;20.71]	15.25 [5.24;25.27]	17.55 [12.59;22.51]
Mepolizumab	—	-2.54 [-11.84;6.76]	-1.00 [-12.74;10.74]	1.30 [-6.58;9.18]
Omalizumab	—	—	1.54 [-8.46;11.54]	3.84 [-1.09;8.77]
Benralizumab	—	—	—	2.30 [-6.40;11.00]
E. SNOT-22 score^d—MD [95% CI]				
Dupilumab	-7.55 [-12.03;-3.07]	-5.36 [-6.06;-4.67]	-13.49 [-14.33;-12.66]	-20.99 [-21.37;-20.62]
Mepolizumab	—	2.19 [-2.32;6.69]	-5.95 [-10.47;-1.42]	-13.44 [-17.91;-8.98]
Omalizumab	—	—	-8.13 [-9.08;-7.19]	-15.63 [-16.21;-15.05]
Benralizumab	—	—	—	-7.50 [-8.25;-6.75]
2.2. Studies with duration of treatment of 20–24 weeks				
A. One surgery or more^e—RR [95% CI]				
Dupilumab	0.19 [0.07;0.51]	0.03 [0.01;0.11]	NA	0.15 [0.06;0.39]
Mepolizumab	—	0.14 [0.05;0.39]	NA	0.78 [0.64;0.95]
Omalizumab	—	—	NA	5.72 [2.04;16.10]
Benralizumab	—	—	—	NA
B. One course of systemic steroids or more^b—RR [95% CI]				
Dupilumab	NA	0.11 [0.03;0.44]	NA	0.30 [0.22;0.43]
Mepolizumab	—	NA	NA	NA
Omalizumab	—	—	NA	2.67 [0.72;9.83]
Benralizumab	—	—	—	NA
C. Nasal polyp score^c—MD [95% CI]				
Dupilumab	-0.86 [-1.85;0.12]	-1.07 [-1.55;-0.59]	-1.53 [-2.15;-0.92]	-1.93 [-2.27;-1.60]
Mepolizumab	—	-0.20 [-1.19;0.78]	-0.67 [-1.73;0.39]	-1.07 [-1.99;-0.15]
Omalizumab	—	—	-0.47 [-1.08;0.15]	-0.87 [-1.20;-0.53]
Benralizumab	—	—	—	-0.40 [-0.92;0.12]

TABLE 2 (Continued)

	Mepolizumab	Omalizumab	Benralizumab	Placebo
D. UPSIT score ^c —MD [95% CI]				
Dupilumab	NA	13.71 [6.72;20.71]	15.25 [5.24;25.27]	17.55 [12.59;22.51]
Mepolizumab	—	NA	NA	NA
Omalizumab	—	—	1.54 [−8.46;11.54]	3.84 [−1.09;8.77]
Benralizumab	—	—	—	2.30 [−6.40;11.00]
E. SNOT-22 score ^c —MD [95% CI]				
Dupilumab	−7.80 [−22.73;7.13]	−3.62 [−9.00;1.76]	−5.94 [−11.37;−0.51]	−19.20 [−22.99;−15.41]
Mepolizumab	—	4.18 [−10.76;19.12]	1.86 [−13.10;16.82]	−11.40 [−25.84;3.04]
Omalizumab	—	—	−2.32 [−7.77;3.13]	−15.58 [−19.40;−11.76]
Benralizumab	—	—	—	−13.26 [−17.15;−9.37]
2.3. Studies with duration of treatment of ≥40 weeks				
A. One surgery or more ^b —RR [95% CI]				
Dupilumab	NA	NA	NA	NA
Mepolizumab	—	NA	0.35 [0.18;0.68]	0.38 [0.23;0.64]
Omalizumab	—	—	NA	NA
Benralizumab	—	—	—	1.10 [0.72;1.69]
B. One course of systemic steroids or more ^b —RR [95% CI]				
Dupilumab	NA	NA	NA	NA
Mepolizumab	—	NA	0.89 [0.58;1.36]	0.69 [0.51;0.93]
Omalizumab	—	—	NA	NA
Benralizumab	—	—	—	0.77 [0.58;1.05]
C. Nasal polyp score ^b —MD [95% CI]				
Dupilumab	−1.59 [−1.92;−1.26]	NA	−1.92 [−1.97;−1.87]	−2.39 [−2.42;−2.36]
Mepolizumab	—	NA	−0.33 [−0.66;0.01]	−0.80 [−1.13;−0.47]
Omalizumab	—	—	NA	NA
Benralizumab	—	—	—	−0.48 [−0.51;−0.44]
D. SNOT-22 score ^b —MD [95% CI]				
Dupilumab	−7.26 [−12.00;−2.52]	NA	−13.46 [−14.20;−12.72]	−20.96 [−21.32;−20.60]
Mepolizumab	—	NA	−6.20 [−10.96;−1.44]	−13.70 [−18.42;−8.98]
Omalizumab	—	—	NA	NA
Benralizumab	—	—	—	−7.50 [−8.14;−6.86]

Note: Regarding each outcome, the relative risk should be interpreted as "how many times the risk of patients undergoing one biologic compares to that of patients undergoing other biologic." For example, the risk of patients undergoing dupilumab ending up receiving one surgery or more is 0.26 times that of patients undergoing mepolizumab. The mean difference corresponds to the difference of average values of the outcome variable when comparing patients undergoing one versus another biologic. Lower values of the Nasal Polyp Score and of the SNOT-22 score, as well as higher values of the UPSIT score, indicate better chronic rhinosinusitis control.

Abbreviations: CI, confidence interval; MD, mean difference; NA, not assessed (no data on included primary studies); RR, relative risk; SNOT, Sino-nasal Outcome Test; UPSIT, University of Pennsylvania Smell Identification Test.

^aHeterogeneity: $I^2 = 70\%$ ($p = .036$), Inconsistency: Not possible to assess.

^bHeterogeneity and inconsistency: Not possible to assess.

^cHeterogeneity: $I^2 = 99\%$ ($p < .001$), Inconsistency: Not possible to assess.

^dHeterogeneity: $I^2 = 32\%$ ($p = .210$), Inconsistency: Not possible to assess.

^eHeterogeneity: $I^2 = 0\%$ ($p = .897$), Inconsistency: Not possible to assess.

inclusion criteria, and outcomes' definitions. For example, studies differently defined "need for surgery" as effectively undergoing surgery or indication for surgery. In another example, studies assessing mepolizumab appeared to assess more severe patients than those assessing other biologics (eg, on the frequency of

previous surgery). To partly address these differences, we performed subgroup and leave-one-out sensitivity analyses. In the leave-one-out sensitivity analyses, we observed that removal of specific studies could have a distinct impact on the different outcomes in terms of heterogeneity modification, further pointing to

the methodological and clinical differences among included primary studies.

There is not only a need to standardize outcomes' definitions but also to define minimal clinically important differences (MCID), which can help establish the need to start biologic treatment and accompanying treatment responses. To the best of our knowledge, MCIDs have only been described for SNOT-22,¹ somehow limiting the clinical interpretation of results for other outcomes.

In conclusion, in this NMA we compared different biologicals for CRSwNP. Our report differs from previous studies^{1,6,7} by performing NMA solely including studies with a minimal duration of treatment >16 weeks,⁵ exploring sources of heterogeneity (eg, assessing subgroups based on the frequency of asthma, previous surgeries, or type 2 inflammation), and by focusing on the identification of limitations and unmet needs in CRSwNP RCTs. Such needs include homogenization of inclusion criteria, standardization of relevant outcomes (eg, "need for surgery" and "use of systemic CS," which should be clearly defined and assessed in all studies), need for considering different CRSwNP endotypes, simultaneous analyses of the responses of the upper and lower airway in subjects with associated asthma and concomitant cost assessment. Finally, RCTs directly comparing biologicals are needed to overcome the limitations of indirect comparisons and to assess the real-life effectiveness of each biologic.

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest to disclose.

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