State-of-the-art overview on biological treatment for CRSwNP anno 2020

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Abbreviations:

CRS	chronic rhinosinusitis
NP	nasal polyps
CRSwNP	chronic rhinosinusitis with nasal polyps
SNOT-22	sinonasal outcome test 22
NCS	nasal congestion score
LOS	loss of smell
UPSIT	University of Pennsylvania Smell Identification Test
CT	computed tomography (Lund-Mackay score)
NPS	nasal polyp score
VAS	visual analogue scale

ABSTRACT

Background: The majority of patients with uncontrolled severe CRSwNP, asthma, and atopic dermatitis share a similar T helper 2 type inflammation underlying the phenotype. This so-called type 2 endotype has given rise to novel treatments targeting specific cytokines driving inflammation in CRSwNP like IL-4, IL-13, IL-5 and IgE. At present, the efficacy of several biological treatments has been demonstrated in CRSwNP, with similarities and differences in baseline characteristics of included patients and outcome parameters.

Aims: First comprehensive overview of efficacy of reported biologicals for CRSwNP based on published phase 2 and 3 data with focus on the clinically relevant outcome parameters at 16 to 25 weeks of therapy.

Methods: After literature search, an overview was made of the reported effects of dupilumab, mepolizumab and omalizumab treatment on patient relevant, i.e. nasal congestion, smell loss and SNOT-22 scores, and patient irrelevant outcome parameters, i.e. CT scan Lund-Mackay, smell test and nasal polyp scores. Therapy duration of 16 to 25 w was chosen for evaluation of efficacy.

Results: A direct comparison of efficacy between dupilumab, mepolizumab and omalizumab is challenging given differences in inclusion criteria, outcome parameters and time-points of analyses. However, consistent and major reduction of patient relevant and irrelevant outcome parameters are found in all studies with biologicals for CRSwNP, with most available data on dupilumab.

Conclusion: Despite the heterogeneity of protocols, dosages and time-points of analyses of biological trials in CRSwNP, this overview is the first to highlight and present outcomes of biological treatment in CRSwNP in a comprehensive way. Real-life data will generate more insight in the comparison of efficacy between the 3 biological molecules.

INTRODUCTION

EPOS2020 [1] provides the ENT community with guidance for better care of CRS, including integrated care pathways. The treatment plan for patients with severe uncontrolled CRSwNP has recently been enriched by the option of biological treatment [2]. The novel treatment option with biologicals targets one or more biomarkers of CRSwNP, i.e. IL-4, IL-13, IL-5 and IgE [3] that drive the inflammation in the sinonasal mucosa in CRSwNP. As a subgroup of CRSwNP remain uncontrolled despite surgery and/or oral corticosteroids [4], new therapeutic options are embraced by the Rhinology community and by the patients given the proven efficacy in several large-scale multi-center trials [5]. In 2019, the EUFOREA expert team published a consensus statement on the clinical criteria for consideration of biological treatment in CRSwNP [2], which were updated by the EPOS2020 expert panel [6].

In order to help the Rhinology community dealing with CRSwNP patients understand the differences and similarities in efficacy of the novel therapeutic options with biologicals, we have taken the initiative to help the community and provide an overview of reported study outcomes. For the sake of clarity, we focused on those outcome parameters that are mostly appreciated by the physicians, and divided them arbitrarily into patient relevant, i.e. of direct importance for the patient with impact for their quality of life (QoL), and patient irrelevant parameters, i.e. without direct impact on QoL.

We here provide a 2020 state-of-the art overview of literature on biological treatments for CRSwNP including a comprehensive overview and comparison of inclusion and exclusion criteria, and outcome parameters. An attempt was made to show efficacy across different studies and with different molecules with proven efficacy in CRSwNP patients.

MATERIALS and METHODS

The overall objective of this manuscript is to allow an overview of published data on efficacy of biologicals in CRSwNP anno 2020. For the sake of interest and clarify, we have selected 6 clinically relevant outcome parameters for analysis: nasal congestion and smell dysfunction scores, SNOT-22 scores, CT scan Lund-Mackay scores, smell test scores and nasal polyp score (NPS). The first 3 are considered patient relevant, and the latter 3 patient irrelevant outcome parameters. For the sake of simplification, the time-point of analysis was between 16 to 25 w.

Prisma search for inclusion of studies

This study was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommended guidelines [7]. Randomized placebo controlled double blinded trials of phase 2 and 3 were included. Phase 1, open label, retrospective and prospective uncontrolled studies were excluded. Only trials with known results were used in this analysis, therefore ongoing trials or studies with no published results could not be used. The study population consists of adult (minimum age of 18 years) patients with CRSwNP. The diagnosis of this condition was based on the European position paper on rhinosinusitis and NPs. [1] Biologicals used in trials on CRSwNP are dupilumab, mepolizumab, omalizumab, reslizumab and benralizumab. In this article an intervention with biologicals is defined as a treatment, if it consists at least two doses. Reslizumab was not included in this comparison as the only study fulfilling the qualifications administers only a single dose of treatment.[8] For benralizumab only ongoing trials were registered (OSTRO: clinicaltrial NCT03401229 and ORCHID: clinicaltrial NCT04157335) [9]. Results from these trials will make comparison for the use of benralizumab in CRSwNP possible in the future, yet no inclusion in this analysis is possible. Hence the three biologicals retained for this study are dupilumab, mepolizumab and omalizumab.

A structured summary of the review process is depicted in Figure 1. We searched the following databases: MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL) and Trip database. Search terms were adapted appropriately to suit each database structure. Beyond this first strategy, open search was performed. Additional records were identified, all clinical trials with or without published articles. The results of our search were collected until April 2020 with a filter for English language. This resulted in a total of 38 studies.
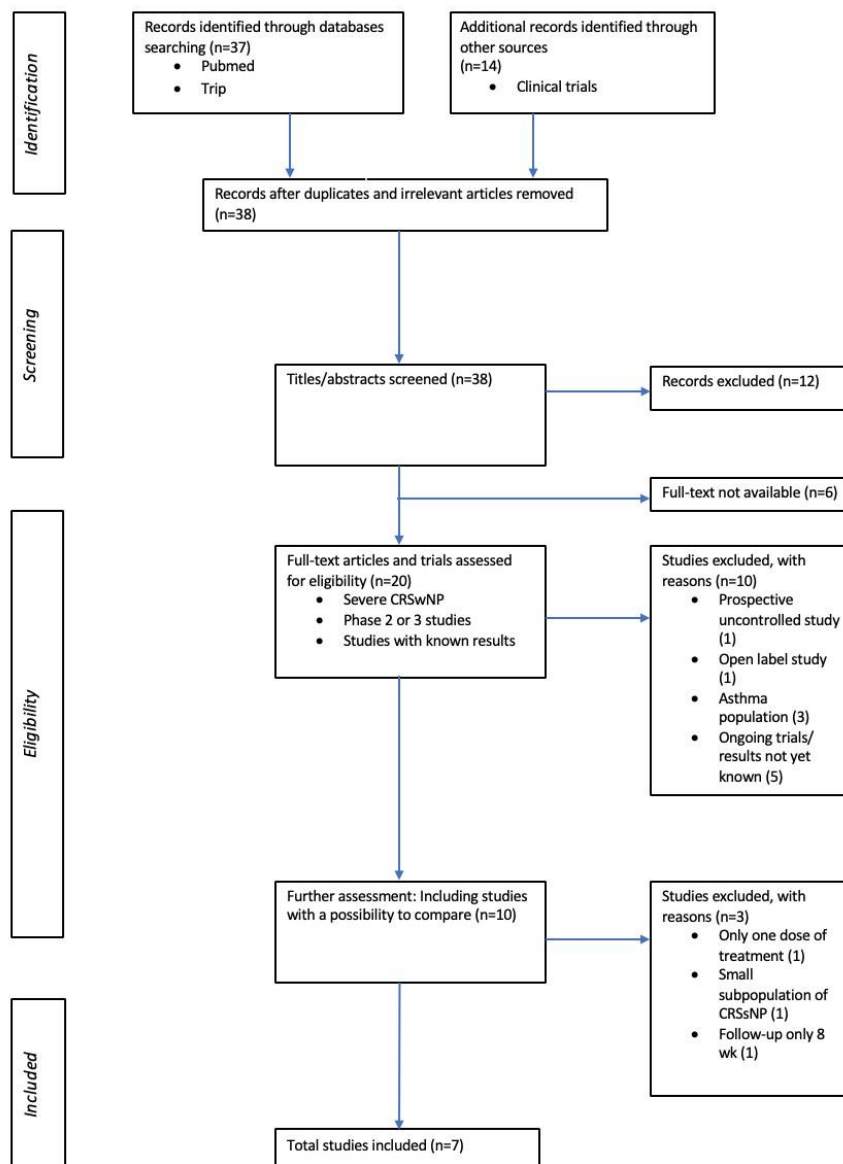
Figure 1: Prisma search for inclusion of studies

Further funneling of the 38 studies led to a final inclusion for analysis of 7 studies. An exploratory search for all applications of biologicals for CRSwNP was performed. First a restriction was made by screening title and abstract. Out of the 38 studies, 12 studies were excluded. 6 articles were excluded because no full text was available. For the remaining 20 studies full text was assessed for eligibility. This resulted in an exclusion of 10 studies for the following reasons: 1 prospective uncontrolled study, 1 open label study, 3 studies included a non-representative patient population (concerning asthma population), and 5 ongoing trials lacking study results. The last 10 studies were in addition screened for comparability. This screening excluded 3 more studies. The first study, as noted before, had only one administration dose [8]. The second one had a small subpopulation including CRS

without nasal polyposis. [10] The third excluded study had a patient follow-up time of only 8 weeks. This does not fit the time frame of the other studies, so comparison was not possible [11].

Overview of included studies

   The search strategy finally resulted in 7 studies that were included in this article. Table 1 shows a summary of these studies, including number of participants (n), dosing scheme and the outcome parameters available for the different treatment follow-up periods in time.

Table 1. Biologicals in CRSwNP: overview on available studies and outcome parameters									
Study	**n**	**dosing**	**Outcome parameters, treatment period**						
				SNOT-22	Nasal congestion score	Loss of smell	UPSIT	CT (LM score)	Nasal polyp score
			Time						
Dupilumab									
1 Bachert et al., JAMA, 2016 Phase 2	60	1:1 Subcutaneous injection of dupilumab or matched placebo. Dosing: single injection of 600 mg loading dose followed by 15 weekly doses of 300 mg. Add-0N: mometasone furoate nasal spray	16 wk (Study endpoint)	x	x	x	x	x	x
			4,8,12 wk	x			x		x
2 Bachert et al., Lancet, 2019 Phase 3	276	1:1 Subcutaneous injection of dupilumab or matched placebo. Dosing: 300 mg every 2 wk for 24 wk. Add-0N: mometasone furoate nasal spray	24 wk (Study endpoint)	x	x	x	x	x	x
			4,8,12,16,20 wk	x	x	x	x		x
3 Bachert et al., Lancet, 2019 Phase 3	448	1:1:1 Subcutaenous injection of dupilumab or matched placebo. Dosing: 300 mg every 2wk for 52 wk or 300 mg every 2 wk for the first 24 wk followed by injections every 4 wk until reaching 52 wk. Add-0N: mometasone furoate nasal spray	52 wk (Study endpoint)	x	x	x	x	x	x
			24 wk	x	x	x	x	x	x
			4,8,12,16,20 wk	x	x	x	x		x
Mepolizumab									
4 Bachert et al., J Allergy Clin Immunol, 2017 Phase 2	105	1:1 Intravenous infusion of mepolizumab or matched placebo. Dosing: 750 mg every 4wk for 6 doses. Add-ON: fluticasone propionate	25wk (Study endpoint)	x	x	x			x
			5,9,13,17,21 wk		x	x			x
Omalizumab									
5 Gevaert et al., J Allergy Clin Immunol, 2013 Phase 2	24	2:1 Subcutaneous injection of omalizumab or matched placebo. Dosing: every 2 or 4 wk based on total serum IgE levels and body weight (max. dose 375 mg) for 16w. Add-ON: /	16 wk (Study endpoint)		No baseline known	No baseline known		x	x
			4,8,12 wk		No baseline known	No baseline known			x
6 Gevaert et al., J Allergy Clin Immunol, 2020, POLYP2 Phase 3	127	1:1 Subcutaneous injection of omalizumab or matched placebo. Dosing: every 2 or 4 wk based on total serum IgE levels and body weight (dose 75-600 mg) for 24w. Add-ON: momethasone	16 wk		x				x
			24 wk	x	x	x	x		x
7 Gevaert et al., J Allergy Clin Immunol, 2020, POLYP1 Phase 3	138	1:1 Subcutaneous injection of omalizumab or matched placebo. Dosing: every 2 or 4 wk based on total serum IgE levels and body weight (dose 75-600 mg) for 24w. Add-ON: momethasone	16 wk		x				x
			24 wk	x	x	x	x		x

X : Data for this treatment period is given in the original study

▢: Data for this treatment period is chosen for analysis

Table 1: Biologicals in CRSwNP: overview on available studies and outcome parameters.

Inclusion criteria

Inclusion criteria in the 7 retained studies are heterogeneous. 4 out of 7 studies have main criteria for inclusion in common [12-14], i.e. eligible patients were aged older than 18 y with refractory bilateral nasal polyposis and chronic symptoms of CRS despite earlier treatment with intranasal corticosteroids. Patients were required to have a bilateral endoscopic nasal polyp score of at least 5 (maximum score of 8), and manifest at least 2 of the following symptoms prior to screening: nasal obstruction or nasal discharge and/or facial pain or pressure and a reduction/loss of smell. Where 4 out of 7 studies shared these inclusion criteria, the inclusion criteria of the other 3 studies slightly differed [15][16]. Gevaert et al, 2013 [15] included a patient population aged older then 18 years suffering CRSwNP and comorbid asthma for more than 2 years, without mention of severity of nasal polyposis or other additional symptoms. In the studies POLYP1 and POLYP2, severe CRSwNP is defined as persistent bilateral nasal polyps with a nasal polyp score of at least 5. Instead of defining additional symptoms, a SNOT-22 score of at least 20 and a nasal congestion score of at least 2 impairing the health-related QOL is needed to fulfil inclusion [16].

While the differences for inclusion of patients in the 7 studies were substantial, they were deemed sufficiently comparable for the sake of this overview.

Outcome parameters

In addition to differences in inclusion criteria, there is also a variety of outcome parameters reported in the published reports. In an attempt to compare efficacy of different biological molecules in CRSwNP a selection of outcome parameters for comparison was needed. The most frequently reported and clinically important parameters were chosen for reporting here. A distinction between patient-relevant and patient-irrelevant parameters was made. Patient-relevant parameters have a clinical impact on QOL as they are directly linked to the subjective burden experienced by the patient. Patient-irrelevant parameters are more objectively measured but not strictly correlating with symptom severity.

The following 6 outcome parameters have been chosen for evaluation: 22-item SinoNasal Outcome Test (SNOT-22) scores, nasal congestion scores (NCS), loss of smell test (LOS), University of Pennsylvania Smell Identification Test (UPSIT), Lund-Mackay CT score and nasal polyp score (NPS). Respectively the first 3 represent patient-relevant parameters and the last 3 are patient-irrelevant parameters.

The same definition of these 6 outcome parameters is used throughout the seven studies. The 22 questions of the SNOT-22 questionnaire are scored as 0 (no problem) to 5 (problem as worse as it can be) for each question with a total range from 0 to 110 (higher scores indicate poorer outcomes)[17]. Individual signs and symptoms, scored as LOS and NCS were captured daily by patients using a scale (0=no symptoms, 3=severe symptoms).[18] The UPSIT score ranges from 0 to 40 (higher scores of 35-40 indicate normal sense of smell and lower scores of 0-18 indicate anosmia)[19]. The Lund-Mackay CT score evaluates the patency of each sinus using a 0 to 2 scale (0=normal; 2=total opacification) and

has a total score range from 0 to 24 (higher scores indicate more opacification)[20]. The NPS is graded based on polyp size (recorded as the sum of the right and left nostril scores with a range of 0-8; higher scores indicate worse status)[15]. In contrast with other reviews concerning treatment of CRSwNP, the parameter NPS was concerned less important in this analysis. An objective improvement in NPS does not guarantee a better patient reported QOL [21].

For each study, these 6 parameters were registered for all available treatment periods. In Table 1, 'X' means data for this parameter are available at a particular period of follow-up, and also gaps were found as most of the studies did not asses all 6 parameters. Some studies report variants of these parameters. In the study of Bachert et al. [13] subjective scoring of individual symptoms, scored as LOS and NCS were recorded differently than in other studies. A visual analogue scale (VAS) was used instead of scoring from 0-3 by MMS method (mild-moderate-severe). Conversion from VAS score to MMS score was performed here according to the following guideline were they define 'mild' as being 0-3 inclusive, 'moderate, as > 3-7 inclusive and 'severe' as >7-10 inclusive on the VAS scoring system [22]. In the same study, objective scoring of smell was performed by using Sniffing Sticks. No quantitative transposition from sniffing sticks score to UPSIT score could be done. This results in a missing value for smell quantification for this study [22].

Treatment period

In table 1, study parameters were set out for each given treatment period as reported in the 7 studies. Data were obtained from tables and extracted from graphs of the original studies. Treatment periods were heterogeneous and overlapping. Firstly, treatment periods shorter then 16 w were excluded as treatment outcomes shorter than 16 w were not considered relevant for this study [2]. Secondly, a time interval between 16 and 25 w was chosen for analysis. Although this interval covers 9 weeks, it was still considered comparable as in most studies the impact of the different treatment starts to reach a plateau after 14 w. Within this range, one point of analysis was chosen for each study. This resulted in more available data, as a single treatment period would decrease significantly the amount of available data for evaluation of efficacy. Thirdly, only one treatment period per study was chosen for the sake of simplicity of the data. In future, analysis of more time-points might be performed allowing evaluation of times of reaching efficiency levels.

Used data

For each study, analysis of the outcome parameters was done by reporting values at baseline and at the chosen treatment period. The data for the placebo group and the actively treated group were recorded separately, as their baselines slightly differed. Table 2 shows for each study these 4 data points per outcome parameter. Standard deviation was included, if reported in the original study. In this manner, improvement between treatment versus placebo could be compared, as the effect of placebo for some parameters can be important.

Data were obtained out of the 7 original studies using tables, text and extrapolation from graphs. Priority was given to information from tables. Direct figures for baseline and follow-up were given in tables for most of the studies. [12], [14](SINUS LIBERTY 24 AND LIBERTY 52) and [13] (for LOSS and NCS). In SINUS LIBERTY 52 [14] a pooled analysis was performed. For this particular study the table showed data for follow-up at 24 weeks in a pooled group of patients. This pooled treatment group include group A (n=150) and group B (n=145) treated with another dosing scheme. Baseline from group A and B differed, therefore a calculation to become mean baseline for group A and B together was performed. If absolute values at time of follow-up were missing, these data were calculated out of least square mean change from baseline. [16] and [13] (for NPS). The study of Gevaert et al [15] had not enough data available from tables or graphs. Only one table with baseline characteristics was given, lacking information about improvement after 16 weeks. Therefor, we derived data from the text, mentioning figures for improvement from baseline to 16 weeks. Note that in the text, other baseline characteristics were used then the ones mentioned in the table with baseline characteristics. Figures for SNOT-22 score were also derived from the text in [13]. They slightly differed from the figures mentioned in table E5 of the original article.

The following additional elements were taken into account. The study of Bachert et al, 2016 [12] report both AM and PM values for NCS and LOS. As they were similar, AM data was used in this analysis. Secondly, as noted before, conversion from VAS score to MMS score for NCS and LOS was performed in the study of Bachert et al, 2017. [13] Thirdly, although figures for NCS and LOS at the follow-up point of 16 weeks in the study of Gevaert et al, 2013 [15] were available, no data for these outcome parameters were reported in table 2. As no baseline was known, the effect of treatment over time could not be assessed.

Statistical analysis

Meta-analysis was performed for SNOT-22 and mean change from baseline of the nasal polyp score (NPS) in line with recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses (QUORUM) guidelines [23, 24]. For the other variables data were incomplete. Variables were analysed using mean differences (MD) for SNOT-22 and standardised mean differences (SMD) for NPS [25], with 95% confidence intervals (CIs). The results were pooled using either a fixed effect [26] or random effect model as appropriate [25]. Heterogeneity of the exposure effects was evaluated statistically using the I2 statistic to quantify heterogeneity across studies [27]. A I2 value of >50% was taken as evidence of substantial heterogeneity and in such cases a random effect model was used. A chi-squared test for heterogeneity was also performed and the 'p' values are presented.

When a study failed to present a standard deviation (SD), this statistic was either calculated from standard error of mean, 95% CI, t value or interquartile range [28]. Statistical analyses were performed using RevMan 5.3 software.

RESULTS

The 6 outcome parameters were evaluated as change from baseline in the active treatment versus placebo group (Fig 1-6), with each graph depicting the reported data of one parameter in the 7 studies. We chose to represent all data extracted from the individual studies, including baseline, treatment period, sample sizes and publication date on the Fig. legends.

Table 2 shows changes from baseline to treatment follow-up. For each parameter data at baseline are given for the placebo and the treatment group, with subsequent changes upon treatment. The 7 studies are listed per type of biological: 3 studies for dupilumab, 1 study for mepolizumab and 3 studies for omalizumab. The number representing the study corresponds with the study and accompanied number described in table 1. Standard deviation is included in the table if data from the original study is available. The way in which data was extracted from the original study into this table was described in the section materials and methods. If data was not available, it is mentioned as 'Not known'.

Table 2. Change from baseline to treatment follow-up in patients with CRSwNP treated with placebo or biological (dupilumab/mepolizumab/omalizumab)

		Study													
		Dupilumab						**Mepolizumab**		**Omalizumab**					
		1		**2**		**3**		**4**		**5**		**6**		**7**	
	P	N=30		N=133		N=153		N=51		N=8		N=65		N=66	
	T	N=30		N=143		N=295		N=54		N=16		N=62		N=72	
Endpoints		Baseline, Mean (SD)	Week 16, Mean (SD)	Baseline, Mean (SD)	Week 24, Mean (SD)	Baseline, Mean (SD)	Week 24, Mean (SD)	Baseline, Mean (SD)	Week 25, Mean (SD)	Baseline, Mean (SD)**	Week 16, Mean (SD)**	Baseline, Mean (SD)	Week 24, Mean (SD)*	Baseline, Mean (SD)	Week 24, Mean (SD)*
SNOT-22[a]	P	40,60 (19,90)	30,20 (19,60)	50,87 (20,22)	40,49 (23,06)	53,48 (21,85)	42,16 (23,26)	49,50 (19,10)	38,20 (24,50)	Not Known		59,80 (18,20)	53,25	60,50 (15,30)	51,92
	T	41,40 (18,20)	12,80 (11,00)	48,00 (20,16)	18,58 (14,92)	51,01 (21,05)	23,89 (18,77)	51,50 (17,00)	28,80 (22,00)			59,20 (20,50)	37,61	59,80 (19,70)	35,10
Nasal congestion score[b]	P	1,70 (0,70)	1,40 (0,70)	2,45 (0,55)	1,90 (0,85)	2,38 (0,54)	2,02 (0,77)	3***	2***	Not known		2,30 (0,60)	2,10	2,50 (0,60)	2,15
	T	1,70 (0,70)	0,70 (0,70)	2,26 (0,57)	0,94 (0,75)	2,46 (0,62)	1,19 (0,90)	3***	2***			2,30 (0,70)	1,60	2,40 (0,70)	1,51
Loss of smell[b]	P	2,80 (0,50)	2,50 (0,80)	2,73 (0,51)	2,50 (0,77)	2,72 (0,52)	2,49 (0,79)	3***	3***	Not known		2,80 (0,60)	2,67	2,80 (0,40)	2,57
	T	2,40 (0,90)	1,00 (1,00)	2,70 (0,57)	1,35 (0,99)	2,76 (0,59)	1,55 (1,02)	3***	2***			2,60 (0,80)	2,02	2,60 (0,80)	2,04
UPSIT[c]	P	15,60 (7,90)	16,20 (8,70)	14,44 (8,31)	14,56 (8,58)	13,78 (8,31)	13,30 (7,96)	Not known		Not known		13,10 (7,30)	13,54	13,90 (7,40)	14,53
	T	12,80 (8,30)	28,70 (8,20)	14,68 (8,66)	25,39 (9,49)	13,53 (8,20)	23,89 (9,21)					12,80 (7,60)	17,11	12,80 (7,90)	17,22
CT (LM score)[d]	P	18,70 (5,50)	17,90 (5,70)	19,55 (4,26)	18,97 (4,51)	17,65 (3,76)	17,73 (3,81)	Not known		17,80	18,30	Not known		Not known	
	T	18,60 (5,00)	9,40 (5,10)	18,55 (4,55)	10,89 (4,82)	18,12 (3,89)	12,86 (3,87)			17,60	13,60				
Nasal polyp score[e]	P	5,70 (0,90)	5,40 (1,50)	5,86 (1,31)	5,94 (1,44)	5,96 (1,21)	6,09 (1,19)	6,31 (0,88)	5,63*	6,00	5,88	6,10 (0,90)	5,79	6,30 (0,90)	6,36
	T	5,90 (1,00)	4,00 (1,90)	5,64 (1,23)	3,75 (1,98)	6,18 (1,22)	4,46 (1,89)	6,28 (0,88)	4,42*	6,00	3,33	6,40 (0,90)	5,50	6,20 (1,00)	5,12

P, placebo
T, treatment (dupilumab, mepolizumab, omalizumab)
N, number of patients in group
*Data calculated out of LS mean change from baseline, therefore SD not known
**SD not given
***Data extrapolated out of VAS scoring scoring system, therefore SD not known

[a]Range of 0 to 110 (higher scores indicate poorer outcomes) and a minimally clinically important difference of 8,90
[b]Symptoms were captured using a catergorical scale (0 = no symptoms, 1= mild symptoms, 2 = moderate symptoms, 3 = severe symptoms)
[c]Range of 0 to 40 (higher scores of 35-40 inidicate normal sense of smell)
[d]Range of 0 to 24 (higher scores indicate more opacification)
[e]Range of 0 to 8 (higher scores indicate worse outcomes)

Table 2: change from baseline to treatment follow-up in patients with CRSwNP treated with placebo or biological (dupilumab, mepolizumab, omalizumab).

Fig 1: Sino-Nasal Outcome Test 22

Fig 2: Nasal congestion score

Fig 3: Loss of smell

Fig 4: The University of Pennsylvania Smell Identification Test

Fig 5: CT scan (LM-score)

Fig 6: Nasal polyp score

Visualizing figures into graphs provides a clear view on improvement after treatment with biologicals. The placebo effects are larger for patient relevant (SNOT-22, LOS and NCS) then for patient irrelevant scores (UPSIT, CT Lund-Mackay and NPS). Beyond the placebo-effect a significant improvement of the different outcome parameters is observed by biological treatment. This improvement is seen for all 3 biologicals, although there seems a difference in magnitude.

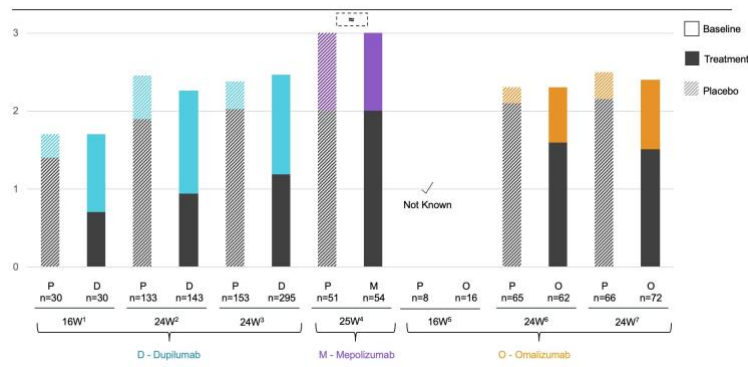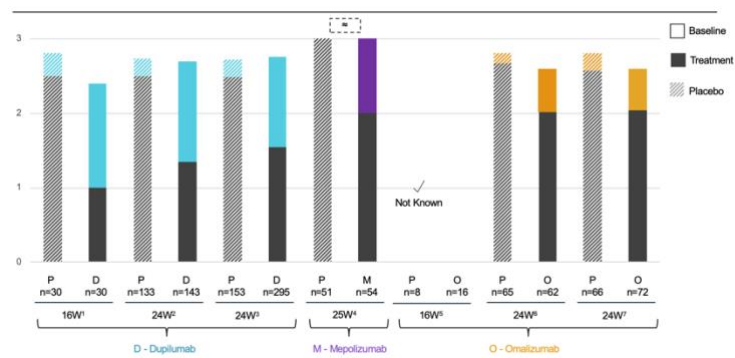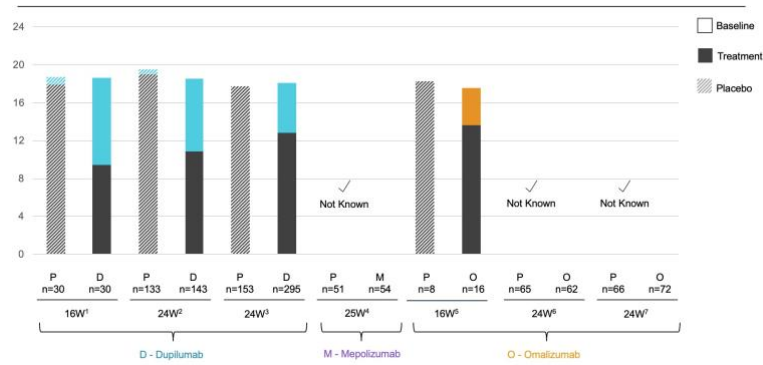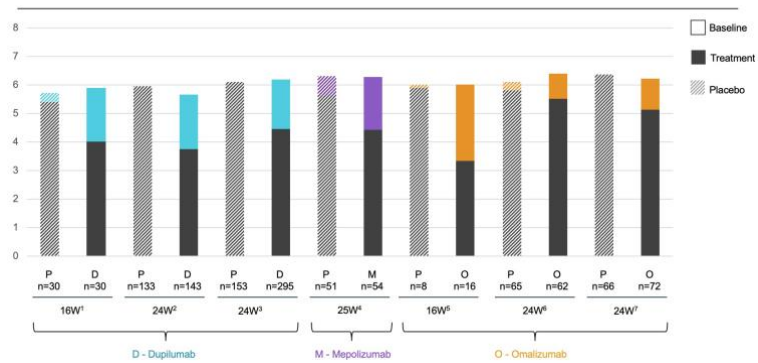The patient-relevant parameters are SNOT-22, NCS and LOS. Improvement levels of SNOT-22 score are important and significant in all studies. For SNOT-22 a meta-analysis could be performed including 6 studies. The SNOT-22 score (scale 0-110) at 16-25 weeks showed a significant and clinically relevant decrease of MD 17.97 (95% CI -**20.32 - -15.61**); 1054 participants; 6 studies; I2 = 28%), (Figure 7). There were no significant differences between the different biologicals (p=0.07). Fig 2 shows data for NCS. Impact is available for all 3 biologicals, although figures for the mepolizumab study should be interpreted with caution as the data were converted from VAS score to MMS. Dupilumab significantly reduced the NCS with 50 percent or more, where the effect of omalizumab is smaller. Fig 3 shows LOS data across studies. Dupilumab showed more improvement then omalizumab. For this parameter, data for mepolizumab was available, although less precise due to conversion from VAS score to MMS. The results for mepolizumab indicated an impact, in between the ones of dupilumab and omalizumab.

The patient-irrelevant parameters are UPSIT, CT Lund-Mackay and NPS. In Fig 4, data for UPSIT were analysed. Only effects of dupilumab and omalizumab on UPSIT scores are represented here as data for mepolizumab are lacking. This objective scoring system shows that both dupilumab and omalizumab result in a significant improvement of sense of smell. The impact of dupilumab on smell is significantly more pronounced. An improvement of around 50 percent can be seen. Fig 5 shows data for CT Lund-Mackay scoring. Less figures are available for this parameter. No data for mepolizumab is given and for the study of omalizumab the patient group size is small. Within the dupilumab group the improvement range varies. NPS are presented in Fig 6, which is the only parameter reported in all 7 studies. A meta-analysis of NPS changes upon treatment could be performed including 6 studies. Because of high heterogeneity in NPS, only SMD could be calculated. The mean nasal polyp scores in these studies was around 6 indicating severe polyp disease. The SMD of the nasal polyp score at 16-25 weeks showed a significant reduction of 0.85 (**95% CI -1.06 - -0.64).**
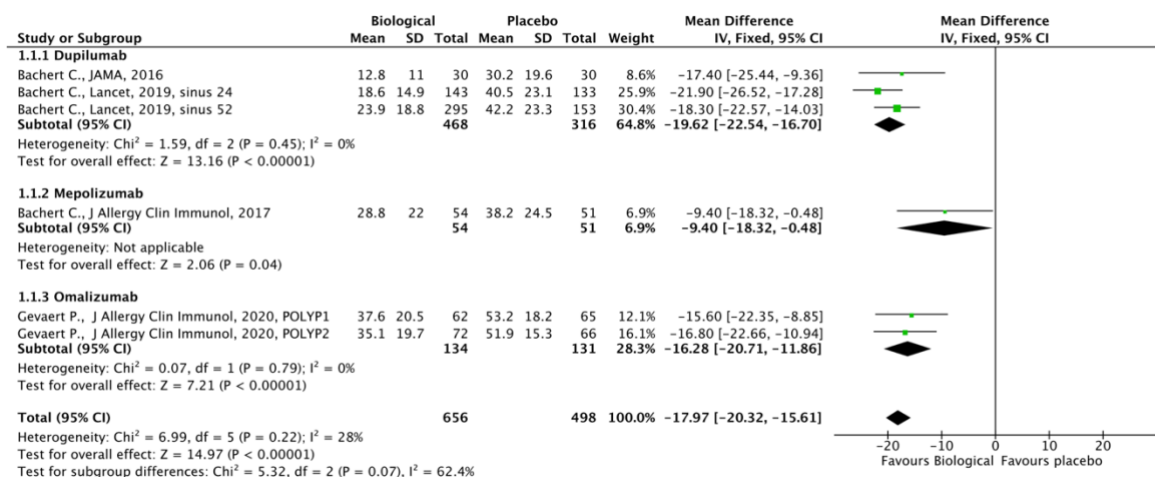
	Biological			Placebo				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.1.1 Dupilumab									
Bachert C., JAMA, 2016	12.8	11	30	30.2	19.6	30	8.6%	−17.40 [−25.44, −9.36]	
Bachert C., Lancet, 2019, sinus 24	18.6	14.9	143	40.5	23.1	133	25.9%	−21.90 [−26.52, −17.28]	
Bachert C., Lancet, 2019, sinus 52	23.9	18.8	295	42.2	23.3	153	30.4%	−18.30 [−22.57, −14.03]	
Subtotal (95% CI)			468			316	64.8%	−19.62 [−22.54, −16.70]	
Heterogeneity: Chi² = 1.59, df = 2 (P = 0.45); I² = 0%									
Test for overall effect: Z = 13.16 (P < 0.00001)									
1.1.2 Mepolizumab									
Bachert C., J Allergy Clin Immunol, 2017	28.8	22	54	38.2	24.5	51	6.9%	−9.40 [−18.32, −0.48]	
Subtotal (95% CI)			54			51	6.9%	−9.40 [−18.32, −0.48]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.06 (P = 0.04)									
1.1.3 Omalizumab									
Gevaert P., J Allergy Clin Immunol, 2020, POLYP1	37.6	20.5	62	53.2	18.2	65	12.1%	−15.60 [−22.35, −8.85]	
Gevaert P., J Allergy Clin Immunol, 2020, POLYP2	35.1	19.7	72	51.9	15.3	66	16.1%	−16.80 [−22.66, −10.94]	
Subtotal (95% CI)			134			131	28.3%	−16.28 [−20.71, −11.86]	
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%									
Test for overall effect: Z = 7.21 (P < 0.00001)									
Total (95% CI)			656			498	100.0%	−17.97 [−20.32, −15.61]	
Heterogeneity: Chi² = 6.99, df = 5 (P = 0.22); I² = 28%									
Test for overall effect: Z = 14.97 (P < 0.00001)									
Test for subgroup differences: Chi² = 5.32, df = 2 (P = 0.07), I² = 62.4%									

Fig. 7:Forest plot of the effect of biological vs placebo for SNOT-22 at completion of intervention (16-25 weeks) in patients with CRSwNP

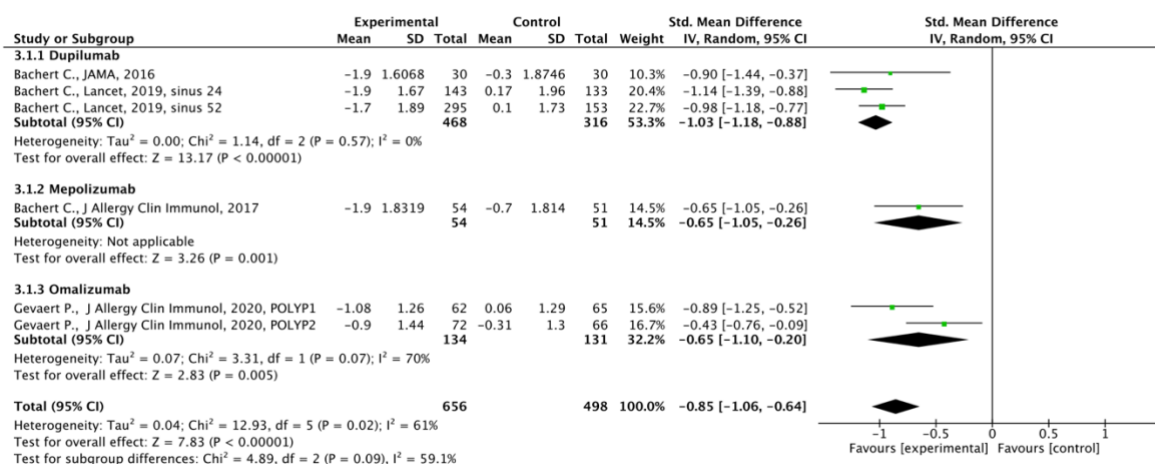| | Experimental | | | Control | | | | Std. Mean Difference | |
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
3.1.1 Dupilumab									
Bachert C., JAMA, 2016	−1.9	1.6068	30	−0.3	1.8746	30	10.3%	−0.90 [−1.44, −0.37]	
Bachert C., Lancet, 2019, sinus 24	−1.9	1.67	143	0.17	1.96	133	20.4%	−1.14 [−1.39, −0.88]	
Bachert C., Lancet, 2019, sinus 52	−1.7	1.89	295	0.1	1.73	153	22.7%	−0.98 [−1.18, −0.77]	
Subtotal (95% CI)			468			316	53.3%	−1.03 [−1.18, −0.88]	
Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 2 (P = 0.57); I² = 0%									
Test for overall effect: Z = 13.17 (P < 0.00001)									
3.1.2 Mepolizumab									
Bachert C., J Allergy Clin Immunol, 2017	−1.9	1.8319	54	−0.7	1.814	51	14.5%	−0.65 [−1.05, −0.26]	
Subtotal (95% CI)			54			51	14.5%	−0.65 [−1.05, −0.26]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 3.26 (P = 0.001)									
3.1.3 Omalizumab									
Gevaert P., J Allergy Clin Immunol, 2020, POLYP1	−1.08	1.26	62	0.06	1.29	65	15.6%	−0.89 [−1.25, −0.52]	
Gevaert P., J Allergy Clin Immunol, 2020, POLYP2	−0.9	1.44	72	−0.31	1.3	66	16.7%	−0.43 [−0.76, −0.09]	
Subtotal (95% CI)			134			131	32.2%	−0.65 [−1.10, −0.20]	
Heterogeneity: Tau² = 0.07; Chi² = 3.31, df = 1 (P = 0.07); I² = 70%									
Test for overall effect: Z = 2.83 (P = 0.005)									
Total (95% CI)			656			498	100.0%	−0.85 [−1.06, −0.64]	
Heterogeneity: Tau² = 0.04; Chi² = 12.93, df = 5 (P = 0.02); I² = 61%									
Test for overall effect: Z = 7.83 (P < 0.00001)									
Test for subgroup differences: Chi² = 4.89, df = 2 (P = 0.09), I² = 59.1%									

Fig. 8: Forest plot of the effect of biological vs placebo on standard mean difference of the nasal polyp score at completion of intervention (16-25 weeks) in patients with CRSwNP

DISCUSSION

To the best of our knowledge, this is the first report providing the ENT and Rhinology community with a comprehensive overview of the reported efficacy of different biological molecules in CRSwNP care. The newly released European Guidelines for treatment of CRSwNP recommend biological treatment when specific criteria are being met [1]. Overall, one can observe consistent efficacy across the studies involving 3 different biological molecules, which underscores the good news of a new therapeutic era in CRSwNP care with a non-surgical options besides corticosteroids and antibiotics. In addition to the efficacy, the size of efficacy is challenging to directly compare given the heterogeneity of the included patients, difference in time intervals of reported studies, and inconsistency in outcome parameters across studies. Effect sizes of dupilumab, mepolizumab and omalizumab seem large enough to reflect the major reduction in symptom burden as experienced by patients. Of note, the effect sizes of dupilumab on objective and subjective parameters of smell loss are impressive and reflect the clinical experience of major reduction of smell impairment in treated patients. An important aspect of interpretation of the biological data in CRSwNP, is that patients receiving the placebo injections are not receiving placebo but rather on standard of care, i.e. nasal corticosteroids and saline douching. Another important aspect relates to the outcomes of surgery versus biological treatment for CRSwNP, where no comparative trial has been conducted so far. It is no hard to understand that the medical approach using biologicals and the surgical approach with endoscopic sinus surgery both have health economic, efficacy and safety issues that need to be discussed with the patients at the time of elaboration of the treatment plan.

Real-life registries, comparative trials and/or endotype-driven treatment plans will all provide the answers to the multiple questions that are still open today, like responder rates of CRSwNP patients treated with biologicals, optimal duration of treatment with/without recurrence of disease after stopping the treatment, treatment of biologicals in relation to sinus surgery for CRSwNP, and optimal timing of biological treatment in the disease process taking into account preventive and curative considerations.

FINANCIAL DISCLOSURE

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