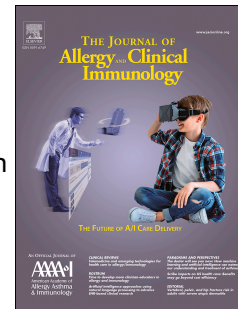


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EUFOREA Expert Board Meeting on Uncontrolled Severe Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) and Biologics: Definitions and Management

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EUFOREA Expert Board Meeting on Uncontrolled Severe Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) and Biologics: Definitions and Management

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43 Conflict of interest

44 CB Speaker and member of advisory boards for Sanofi-Aventis, Regeneron, Novartis, Genentech,
45 Glaxo, Astra-Zeneca, Stallergenes, ALK, Asit Biotech, Mylan, Allakos.

46 JH Consultant for ALK-Abelló, AstraZeneca, Sanofi Genzyme, GlaxoSmithKline, Genentech,
47 Intersect, Medtronic, Optinose, Novartis, Regeneron

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50 Regeneron, Sanofi Aventis, Stallergenes, Teva

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52 Aventis

53 SL Advisory board for and funding from AstraZeneca, Genentech Novartis, Genzyme,
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56 TEVA, MSD, Novartis.

57 JM Advisory board or speaker for ALK, AstraZeneca, Genentech, GlaxoSmithKline, Glenmark,
58 Menarini, Mitsubishi-Tanabe, MSD, Mylan-MEDA Pharma, Novartis, Regeneron Pharmaceuticals,
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70

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72

Abstract

Uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) is the most bothersome phenotype of chronic rhinosinusitis, typically characterized by a type 2 inflammatory reaction and by comorbidities including asthma, N-ERD and allergies. EUFOREA, the European Forum for Research and Education in Allergy and Airway Diseases, here proposes structured definitions to enable communication between clinicians and provides a practical algorithm to define type 2 inflammation in CRSwNP in daily clinic. A rational approach for the treatment of uncontrolled severe CRSwNP is discussed, evaluating the perspective and risks of surgery and efficacy and adverse events of biologics, based on currently available data. Further, possible combinations of surgery and biologics are discussed, and a rationale is provided. Here, it is of importance to adequately counsel the patient about both approaches to enable a decision-making process with an informed patient. Criteria for the selection of a biologic drug are provided, as several biologics for uncontrolled severe CRSwNP will be available within short time in many countries. Further, suggestions for monitoring of the drug effects are proposed, which support the recognition of responders to the therapy and consecutively the decision for continuation or discontinuation of the biologic.

Capsule Summary

An European Expert Opinion on Uncontrolled Severe Nasal Polyps (CRSwNP) is provided to support the selection of patients for Type 2 biologics and extended surgical interventions. Suggestions for the monitoring of the treatment response and considerations for treatment choices are offered based on current evidence.

Abbreviations

95	
96	AE(s): Adverse Event(s)
97	AQLQ: Asthma Quality of Life Questionnaire
98	CRS: Chronic Rhinosinusitis
99	CRSwNP/NP: Chronic Rhinosinusitis with Nasal Polyp
100	CSF: Cerebrospinal fluid
101	CT: Computed Tomography
102	DBPCR: Double-blind placebo-controlled, randomized study
103	ECP: Eosinophil Cationic Protein
104	EGPA: Eosinophilic Granulomatosis with Polyangiitis
105	ESS: Endoscopic Sinus Surgery
106	EUFOREA: European Forum for Research and Education in Allergy and Airway Diseases
107	FESS: Functional Endoscopic Sinus Surgery
108	GINA: Global Initiative for Asthma
109	GCS: Glucocorticosteroids
110	HRQoL: Health Related Quality of Life
111	IgE: Immunoglobulin E
112	IL: Interleukin
113	IL-4: Interleukin-4
114	IL-5: Interleukin-5
115	INCS: Intranasal Corticosteroids
116	MCID: Minimal Clinically Important Difference
117	MD: Medical Doctor
118	N(SAID)-ERD: Nonsteroidal anti-inflammatory drug - Exacerbated Respiratory Disease
119	NCS: Nasal Congestion Score
120	NPS: Nasal Polyp Score
121	OMU: Ostiomeatal Unit
122	PROs: Patient-related outcomes
123	SE-IgE: Specific IgE to <i>Staphylococcus aureus</i> enterotoxins
124	SNOT-22: 22-item Sino-Nasal Outcome Test
125	SPT: Skin Prick Test

126 UPSIT: University of Pennsylvania Smell Identification Test

127 VAS: Visual Analogue Scale

128

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129 **Introduction**

130 Uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP, nasal polyps) with or
131 without comorbidities, most frequently asthma, Nonsteroidal anti-inflammatory drug - Exacerbated
132 Respiratory Disease (N-ERD) and allergies, is a highly disabling airway disease which is
133 characterized by long-term disease burden, the consecutive exposure of patients to long-term local
134 and systemic corticosteroids, the necessity of often repeated poorly standardized surgical
135 interventions, and – so far – the lack of highly efficacious treatment approaches beyond surgery.
136 The advent of biologic drugs for type 2 immune effectors such as interleukins 4, 5 and 13 as well as
137 IgE offer new approaches for physicians and hope for patients to manage this difficult disease.

138 The European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) is
139 an international non-profit organization with the aim of preventing and improving the burden of
140 chronic respiratory diseases. ENT physicians, allergists, and pneumologists, working in leading EU
141 research institutes, are part of EUFOREA; US ENT colleagues also took part in the Expert Board
142 meeting drafting this document to include their view. One patient diagnosed with CRSwNP,
143 representing the patient perspective, was invited to add his opinion. Representatives of the
144 pharmaceutical industry producing biologic drugs were asked to contribute with their knowledge
145 but were not involved in any strategic discussions and decisions on any criteria-related care
146 pathway decisions.

147 The aim of the EUFOREA Expert Board meeting on January 25, 2020 in Brussels was to develop
148 suggestions for the indication of currently and in near future available type 2 biologics in an
149 individual patient, the monitoring and evaluation of efficacy, and the development of evidence-
150 based care pathways for the management of uncontrolled severe type 2 CRSwNP with or without
151 comorbid asthma. The presence of internationally renowned specialists in the fields of
152 otolaryngology, pulmonology, allergology, and immunology have substantially added to the
153 discussion and decisions. At the Brussels meeting the various definitions were discussed point by

154 point until unanimity was reached. Consecutively, a draft of the document was written and
155 submitted to three rounds of review by all authors. In each round of review, the changes made to the
156 definitions and proposed algorithms were discussed and refined until they were approved
157 unanimously.

158 The discussions focused on clear definitions to define pheno- and endotype, the elaboration of
159 criteria to support decision making processes, and to develop care pathways based on evidence,
160 when available, and best practice when not.

161

162 **Definitions: How to define uncontrolled severe type 2 CRSwNP with comorbid disease?**

163 The EUFOREA group agreed on the following definitions:

164 Severe CRSwNP is defined as “bilateral chronic rhinosinusitis with nasal polyps (CRSwNP) with a
165 nasal polyp score (NPS) of ≥ 4 out of 8 points, and persistent symptoms including loss of smell
166 and/or taste, nasal obstruction, secretion and/or post-nasal drip, and facial pain or pressure, with the
167 need for add-on treatment to intranasal corticosteroids (INCS). (See Comment E1 in the Online
168 Repository)

169 Uncontrolled CRSwNP is defined as “persistent or recurring despite long-term INCS, and having
170 received at least one course of systemic corticosteroids in the preceding 2 years (or having a
171 medical contraindication or intolerance to systemic corticosteroids) and/or previous sinonasal
172 surgery” (unless having a medical contraindication or being unwilling to undergo surgery). (See
173 Comment E2 in the Online Repository)

174 CRSwNP with comorbid disease is defined as “nasal polyp disease with other co-existing type 2
175 inflammatory diseases such as asthma, N-ERD, atopic dermatitis/eczema, allergic rhinitis, urticaria,
176 food allergy or eosinophilic esophagitis”. (See Comment E3 in the Online Repository)

177 **Endotyping in uncontrolled severe CRSwNP based on clinical signs and bio-markers.**

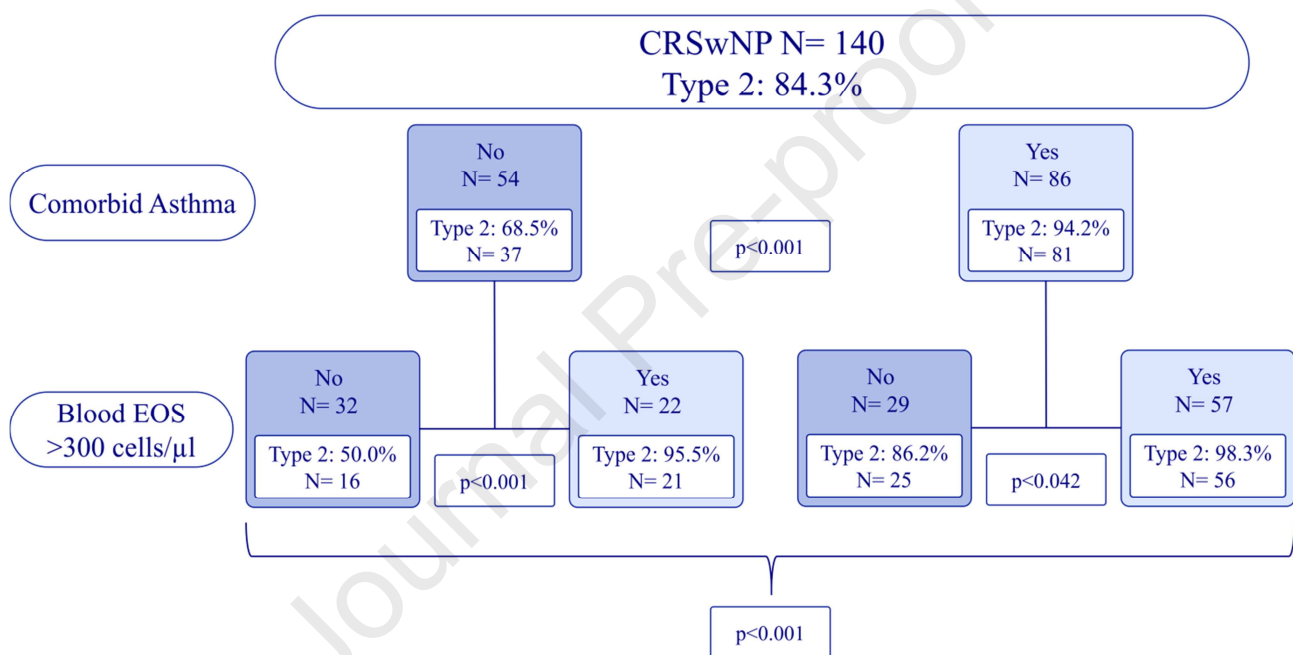
178 Endotyping refers to the identification of type 2 or non-type 2 immune reactions, as currently this
179 differentiation is clinically relevant in determining treatment with a biologic therapy. It may be
180 assumed that in the coming years, a further differentiation into type 1/type 3 immune reactions may
181 become relevant, as further biologics targeting other cytokines become available.

182 Depending on the geographic region and ethnicity of the patient, CRSwNP is characterized by type
183 2 mucosal inflammation in approximately 15 to 85% of the patients.¹⁻⁶ Type 2 inflammation is
184 clearly associated with more severe sinus disease and symptoms, asthma comorbidity and
185 recurrence of disease after surgery.^{7,8} It is therefore of importance to differentiate type 2 from non-

186 type 2 CRSwNP for the prediction of the natural course of disease, response to medical and surgical
 187 interventions, and consequently the long-term management and selection of therapeutic measures.
 188 For the indication of currently available type 2 biologics including anti-IL4 receptor alpha
 189 (dupilumab), anti-IgE (omalizumab) and anti-IL5/Ra (mepolizumab, benralizumab), an underlying
 190 type 2 inflammation should be present. (Figure 1) (See Comment E4 in the Online Repository)

191

192



193

194 **Figure 1**

195

196 Sinus surgery or a biologic approach, or a combination of both?

197 In a patient with uncontrolled severe type 2 CRSwNP, at a time point in the patient's course of
198 disease when the patient has experienced non-effective systemic GCS therapy or surgery, a long-
199 term plan should be formulated together with an informed patient. This plan needs to consider the
200 endotype, the comorbidities and possible other treatment approaches for those comorbidities, and
201 the former treatment history (surgeries, systemic GCS and their efficacy, duration of effect, and
202 adverse events).

203 According to current patient rights, the patient must be informed about the aims, reasonable
204 expectations, and possible side effects and complications of all authorized treatments available for
205 the disease; this obliges the physician to inform the patient about available alternatives in case of
206 proposed surgery. The aim is to have an informed patient to share the decision making in this
207 situation; this gains importance with the complexity of the interventions available and the history of
208 former therapeutic approaches. (See Comment E5 in the Online Repository)

209 Surgical approaches can be differentiated into functional endoscopic sinus surgery (ESS)⁹⁻¹¹ with
210 the aim of opening all sinuses ("full house") and removing all nasal and sinus polyps but preserving
211 the sinus mucosa, and the nasalisation and reboot approaches¹²⁻¹⁴ aiming at the complete removal of
212 polyp and sinus mucosa from all sinuses involved. The latter always includes the maxillary and
213 ethmoidal sinuses, but may also include the frontal and sphenoidal sinuses, including the creation of
214 wide openings (mostly the Draf III frontal sinus approach and the sphenoid drill-out^{15,16} to
215 completely remove the sinus mucosa. It has been demonstrated that reboot surgery in severe
216 CRSwNP lead to less recurrence compared to conventional approaches^{12,17,18} and are followed by
217 an effective healing process with functional mucosa.^{12,19}

218 Should the patient and the physician choose for a biologic drug approach, the physician should
219 decide on the possible choices among the biologics and make a choice with the informed patient,
220 also considering drug availability and patient-relevant questions such as practical issues with drug

221 application. Before a surgical procedure under biologic protection should be planned, a period of 6
222 months – and eventually 12 months, if the patient’s response to the treatment is as expected or
223 better – should be considered to enable the physician to recognize the suitability of /the response to
224 the drug in an individual patient. A surgical procedure may not be considered necessary any more in
225 up to two thirds of the patients under biologic treatment.²⁰

226 If a surgical approach has been chosen aiming at long-term disease suppression, no biologic drug
227 should be considered for at least 6 months and would only be indicated in case of recurrence. A
228 fixed combination plan with surgery and biologic treatment starting in parallel or within short time
229 is not advised, as the response of the individual patient to the surgery or to the biologic is
230 impossible to evaluate. Approaches such as a limited surgery combined with application of a
231 biologic drug are not recommended as such approaches would lead to maximal costs and risks of
232 adverse events/complications in all patients. However, if a surgery has been performed and shows
233 to be insufficient to suppress nasal polyp growth and symptoms despite continuation of INCS, a
234 lower than 4 NPS might be sufficient to indicate a biologic treatment.

235 The recent SARS-CoV2 pandemic added further aspects for the choice of surgery vs. biologics, as
236 surgical procedures and repeated post-operative endoscopic debridement may impose a
237 considerable risk to the medical personnel.²¹

238

Evaluation of efficacy vs. adverse events/complications for surgery and biologics

a) Efficacy of biologics in Phase 3 trials:

There are currently three biologics which already finalized Phase 3 trials (2 parallel DBPCR studies with anti-IL4 receptor alpha, dupilumab, NCT02912468 and NCT02898454; 2 parallel DBPCR studies with anti-IgE, omalizumab, NCT03280550 and NCT03280537; one DBPCR trial with anti-IL5, mepolizumab, NCT03085797) and one drug still ongoing (benralizumab, NCT03401229).

These studies were all based on a similar study design and included a high number of participants (n=265 - 724). In all studies the effect of the biologic was compared to placebo added to a continuous treatment with intranasal corticosteroids throughout the whole study period. Dupilumab is the first biologic registered in the EU and US as an add-on treatment of severe CRSwNP, not sufficiently controlled by systemic corticosteroids and/or surgery. The patients recruited into the finalized studies had bilateral nasal polyps with a NPS (score) $\geq 5/8$, had asthma in 48-71%, and prior surgery in 54-100 % of subjects, and were symptomatic with impairment of smell and nasal obstruction as major symptoms.

In all Phase 3 trials, the primary endpoints (reduction in NPS and nasal congestion/obstruction score) were met with changes in the NPS between 0.7 (median, mepolizumab) and 2.4 (mean, dupilumab, Liberty 52w) over placebo after 52 weeks. NPS reductions at 24 weeks were from 0.7 (mean, omalizumab, mean of Polyp 1 and 2 studies) to 2.06 (mean, dupilumab, Liberty 24w). Of importance, smell was significantly improved with all drugs, however at different speed and magnitude; dupilumab demonstrated a strong and fast effect on smell, reducing the percentage of anosmic subjects from 76% at baseline to 26% after 24 weeks of treatment.²⁰ SNOT-22 reflecting disease-specific quality of life also improved significantly by 14 to 21 score points, clearly surpassing the Minimal Clinically Important Difference (MCID) of >8.9. dupilumab also showed a significant reduction in the CT-based Lund-Mackey-Score by 5 to 7.5 points. dupilumab and mepolizumab, in addition to the reduction in NPS and symptoms as well as quality of life,

264 demonstrated a reduction in the need of systemic corticosteroids and surgery over one year of
265 treatment vs. placebo. A reduction of at least one NPS point or more was achieved in 50 to 65% of
266 the verum-treated subjects over the trials.

267 Thus, these biologics offer a new treatment approach to many patients with type 2 CRSwNP
268 insufficiently controlled by intranasal corticosteroids; asthma or N-ERD comorbidity also needs to
269 be taken into consideration then. When surgery is considered, biologics should also be mentioned to
270 the patient as an alternative, or a combination of biologic and surgical approaches has to be
271 discussed, with the biologic treatment first for reasons discussed above. As there are no head to
272 head comparisons between these biologics at the moment, the choice of drug should be based on
273 availability, potential specific limitations such as eosinophil numbers or IgE levels (for
274 mepolizumab and omalizumab), responder rates and expected size of effects in responders.

275 *b) Efficacy of surgery from available literature*

276 The efficacy of sinus surgery is difficult to evaluate as there are various forms of sinus surgery as
277 well as opinions on the extent of sinus surgery. For example, the term “sinus surgery” is used for
278 balloon dilation of a sinus ostium, a minimally invasive sinus surgery just aiming to open the sinus
279 drainage pathway, (functional) endoscopic sinus surgery to remove polyps from the nasal cavity and
280 sinuses, or following the mucosal concept approach removing all sinus mucosal tissue. Experts
281 agree that for CRSwNP, at least an endoscopic sinus surgery with opening of the ostiomeatal
282 complex, the maxillary and ethmoid sinuses with removal of nasal polyps and thickened sinus
283 mucosa should be performed. However, some recommend creating large sinus openings to all
284 sinuses including the frontal sinus such as described as “modified Lothrop”,²² and the complete
285 removal of the sinus mucosa described as “reboot surgery”.¹² Finally, there is variability in the
286 extent of sinus surgery, but also the quality of sinus surgery may vary substantially.

287 Due to these factors, the evidence for efficacy of endoscopic sinus surgery is and will remain low.
288 Most of the evidence will be retrospective, with only a few prospective cohort studies using a

common standardized surgical approach. Most evidence is based on one or few centres, possibly one prominent surgeon, and therefore not transferable to other centres, let alone “all surgeons or surgeries”. Data from the UK National Sinonasal Audit involving national centers demonstrated a surgical revision rate of 21% over 5 years.²³ A recent meta-analysis by Loftus et al reported a revision rate of <20% across the CRSwNP population at an average follow-up of 7.4 years, showing important differences between geographic regions (from 21.4% in Oceania to 14.90% in Asia) and comorbidities (22.6% in asthma vs 8.0% in nonasthmatic patients).²⁴ As it will remain difficult to perform prospective multicentre randomized trials of high quality for the efficacy of sinus surgery, international registries could be of some help to evaluate real life evidence.

Sinus surgery for nasal polyposis most often debulks and removes nasal polyps, but recurrence is likely after surgery (see Table E1 in the Online Repository); recurrence however does not necessarily translate into revision surgery. Therefore, is it imperative to post-operatively guide the patient and maintain postoperative medical treatment to prevent polyp recurrence. Even with postoperative topical corticosteroid medical therapy, the recurrence rate may be high. In a prospective cohort study of 244 patients with endoscopic sinus surgery, 40% of nasal polyps recurred within 18 months despite postoperative medical treatment.²⁵ Hence, there is a clear unmet need for other approaches to better manage patients with nasal polyposis.

c) AEs in Phase 3 trials with biologics

We here discuss adverse events related to recent Phase 3 trials of dupilumab,²⁰ omalizumab²⁶⁻²⁸ and mepolizumab,²⁹ reflecting the dosing schemes that will be relevant after registration. The proportion of patients who experienced ≥ 1 treatment-emergent AE was lower in the verum-treated compared to the placebo-treated patients. Most events across all studies were of mild-to-moderate intensity. AEs occurring in $\geq 3\%$ of patients include headache, dizziness, abdominal pain, nasopharyngitis, and injection site reactions, being slightly more frequent in the omalizumab treated vs. the placebo group; on the other hand, asthma exacerbations, nasal polyps and congestion occurred less frequent,

without significant differences between groups. Similarly, headache and nasopharyngitis, nasal polyps with need for treatment, upper respiratory tract infections and worsening of asthma were more frequent with placebo than with dupilumab, whereas cough, bronchitis, arthralgia, and injection site reactions were slightly more frequent in the two dupilumab groups than in placebo. None of the observations were significant. Conjunctivitis was reported in seven patients receiving dupilumab and in one patient receiving placebo; none of these cases were serious, severe, or associated with treatment discontinuation. Eosinophilia occurred in four patients: three developed eosinophilic granulomatosis with polyangiitis (EGPA) (one of them was a patient receiving placebo). In summary, biologics show a good tolerability without major AEs.

d) Complications of sinus surgery

About 100 000 persons are subjected to endoscopic-endonasal sinus surgery (ESS) every year in Europe, irrespective to the fact, that formal and comparative evidence of the long-term effectiveness of surgical procedures still is limited. ESS for CRS is technically demanding due to the narrow anatomical spaces, the individual and puzzling microanatomy in close proximity to delicate structures like the eye and brain. Surgeons performing ESS are faced with excusable and sometimes also avoidable mistakes and complications. These complications may be rated as “minor” or “major complication”.³⁰⁻³⁴ Some less severe adverse events may resolve spontaneously (e.g. mild orbital ecchymosis), others may cause persisting decrease in quality-of-life (e.g. dry nose feeling, crusting). Emergency revisional surgery may also be necessary (e.g. in case of dural defects or major orbital hematoma) and irreversible damage (e.g. blindness, death) may occur in rare cases. Referring to numerical data in literature, routine EES interventions are generally associated with minor complications in about 5% and major complications in 0.5–1%.³⁰ The number of endoscopic endonasal interventions is increasing in recent years revealing significant regional differences and individual technical as well as conceptual preferences.³⁵ Regardless of the fact that complication rates of endoscopic sinus surgery have generally decreased in the years after international adoption

339 of modern minimal-invasive techniques, the increased number and complexity of today's
340 interventions is still mirrored in actual reports on patient injuries.^{36,37}

341 **The patient perspective on biologics**

342 Patients, who have reached the limits of what current licensed treatment and techniques including
343 surgery can offer, often feel like they may never gain control of this difficult condition. For these
344 patients, biologics will represent an important new dimension in the way their condition is managed
345 and offer some hope that a level of disease control could be attainable.

346 It is important to understand that self-administering a subcutaneous injection may be a new and
347 possibly daunting prospect for a patient; however, most patients might be treated with home
348 injection. To give their full consent, an important part of both medical ethics and international
349 human rights law, to receiving a biologic, patients need to be informed and educated on a number of
350 factors relating to this treatment.³⁸ (See Comment E7 in the Online Repository)

351

352

Specific considerations for biologics

Selection of patients and predicting the response to a specific biologic drug

There are currently no parameters that could be used to predict the individual response of a patient to any of the biologics, specifically in uncontrolled severe CRSwNP following the definitions specified in this article. However, drug-specific rules need to be applied. (Figure 2a, 2b) (See Comment E8 in the Online Repository)

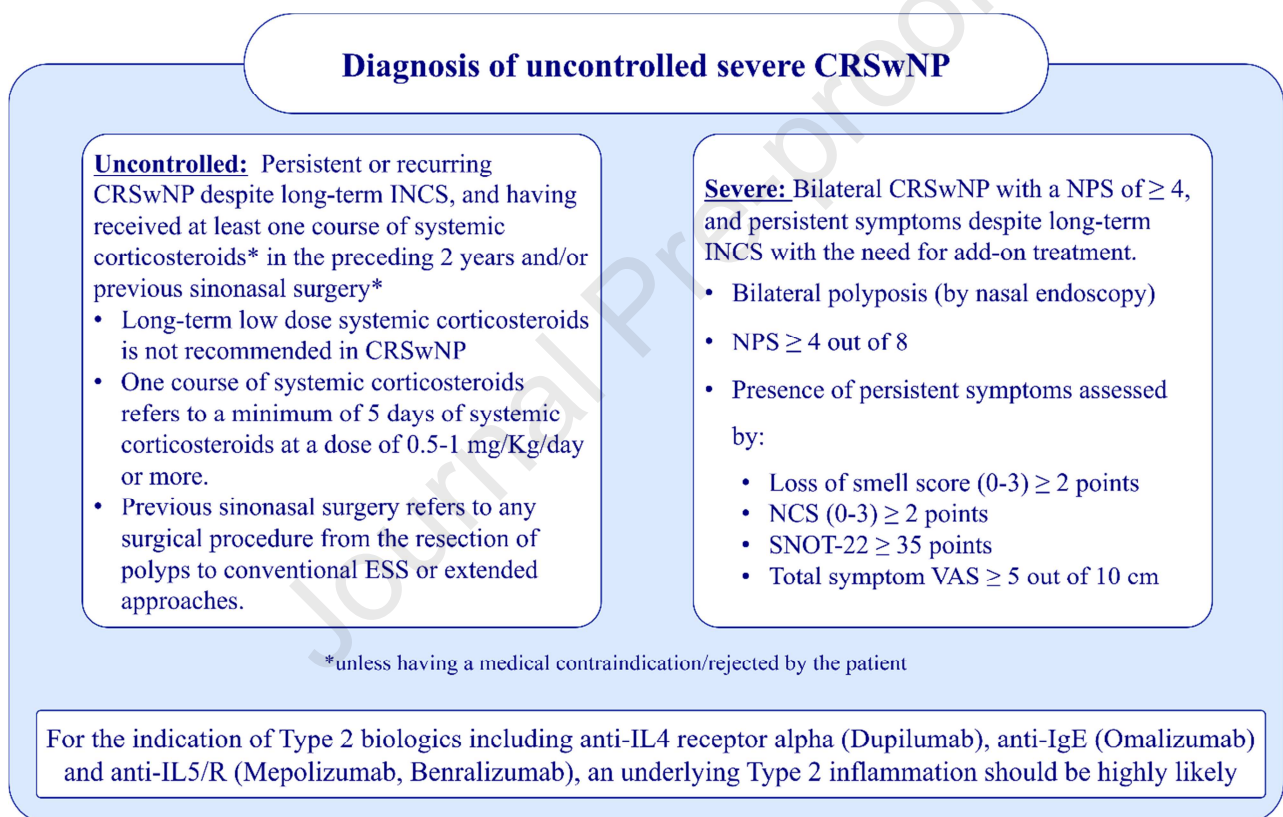


Figure 2a

Selection of a biologic drug and monitoring of its effectiveness

prediction of response in an individual patient is not possible today

- ✓ Confirm diagnosis of uncontrolled severe CRSwNP
- ✓ Check for comorbidity (asthma, N-ERD) and consequences
- ✓ Check that type 2 inflammation is highly likely
- ✓ Inform patient on treatment options, perspectives and risks
- ✓ Take decision on surgery or biologic drug with an informed patient
- ✓ Select biologic drug (note limitations applicable for specific drugs)

CRSwNP and ASTHMA:
collaboration with an
asthma specialist is
essential for the indication
and selection of biologics

After 6 months of treatment

Improvement of at least one symptom/score:

- Sense of smell: from anosmia to hyposmia/normosmia, smell score increase ≥ 0.5
- NCS: decrease by ≥ 0.5 or objective testing
- NPS: decrease by ≥ 1 by nasal endoscopy
- SNOT-22: reduction of ≥ 8.9 (minimal clinically important difference)
- VAS total symptoms: reduction of ≥ 2 cm

No

Stop - change to surgery or another biologic drug

Salvage surgery under biologic protection

Additional short course of systemic GCS

Yes

Improvement not acceptable to the patient

Improvement acceptable to the patient

Continue with biologic treatment

After 12 months of treatment

Adequate response (all of these definitions is fulfilled):

- NPS < 4 (total of both sides)
- NCS < 2
- VAS total symptoms < 5
- SNOT-22 score < 30

Further, there should be no current need for surgery or systemic GCS

No

Consider another biologic drug

Surgery

Yes

Continue with biologic treatment

362

363 **Figure 2b**

364 **Evaluation of the clinical response to a biologic within 6 months of treatment: “continue or**
365 **stop” suggestions**

366 EUFOREA has previously defined criteria to support patient selection for biologics and monitoring
367 the clinical response to treatment,³⁹ however, due to the developments in this fast-evolving field,
368 those criteria can now be replaced and detailed. When a biologic drug has been selected to treat
369 uncontrolled severe CRSwNP, it is important to monitor the response of the patient to the drug;
370 depending on the biologic drug and outcome measure used, non-responders may be expected in 25
371 to 50% of cases. To avoid inadequate treatment and associated unnecessary costs, a response to the
372 treatment should be expected within 6 months; there only is a small chance that drugs begin
373 meaningfully reducing disease burden after that time point.

374 Phase 3 studies with dupilumab and omalizumab^{20,26-28} have both demonstrated that the majority of
375 patients – but not all – reach a reduction of NPS and symptoms (including smell) of 75% or more of
376 the 24 week values within the first 8 – 12 weeks. A further reduction of disease burden after week
377 24, building up on the achieved reduction at that moment, has been demonstrated with dupilumab at
378 52 weeks of treatment. The group therefore decided on a 6-month period to evaluate the response of
379 an individual patient to a biologic and to define the “continue or stop” suggestions. When a clear
380 change for at least one symptom has been met, the therapy with the biologic drug may be continued.
381 In the other case, the patient does not show adequate response to the treatment within 6 months, and
382 the chance for a later response is small. The management strategy should be adapted accordingly
383 (change to surgery or another biologic drug in consideration with a well-informed patient). No
384 experience currently exists to advise on the order of biologics or the likelihood of response when
385 using a second biologic, which also may depend on the primary biologic used.

386 Within these first 6 months, no drugs other than topical GCS should be administered together with
387 the biologic to be able to differentiate response from no response. (See Comment E9 in the Online
388 Repository)

389 **The treatment response has been verified within 6 months:**

390 There are several options in this situation, depending on the remaining burden of disease:

391 If the degree of partial response is considered acceptable to the patient, continuation of the drug
392 over another 6 months is advised and follow-up at 12 months planned. It is expected that a further
393 reduction of the nasal polyp burden and relief of the patient's symptoms can be achieved.

394 If control of the disease is not acceptable to the patient, an additional short course of systemic GCS
395 may be considered with the patient immediately reducing burden of disease under continuation of
396 drug application. It has been determined that the drug is effective in this patient, and its continuation
397 can be justified.

398 As an alternative, "salvage surgery under biologic protection" may be considered to reduce the
399 remaining mass of polyps and burden of disease under continuation of the biologic. Again, the
400 drug's effectiveness in this patient has been demonstrated and its continuation can be justified.

401 However, the long-term benefit of surgery in this situation has only anecdotally been demonstrated.
402 (See Comment E10 in the Online Repository)

403

404 Uncontrolled comorbid severe CRSwNP

405 CRSwNP negatively impacts health related quality of life (HRQoL) and a greater burden is seen in
406 patients with higher disease severity or presence of comorbidities.⁴⁰ (See Comment E11 in the
407 Online Repository) In a cluster analyses based on HRQoL, 10% of the patients visiting a tertiary
408 health care center had the highest impact on their HRQoL. These patients were characterized by
409 greater numbers of comorbid conditions (asthma, eczema, N-ERD), a greater number of previous
410 sinus surgeries, reduced lung function, and greater severity of symptoms. These findings identify
411 uncontrolled comorbid severe CRSwNP patients,⁴¹ since this subgroup has received multiple
412 treatments including surgery and continue to have high symptom burden. These patients would
413 contribute the most to the total economic burden of CRSwNP patients, including both direct and
414 indirect costs, driven by greater health care utilization. Other published evidence on both direct and
415 indirect cost burden has shown higher costs in patients with greater severity of disease, presence of
416 comorbidities, and those being prescribed oral treatments or receiving sinus surgery.⁴²⁻⁴⁴

417 Although there is a significant unmet need for patients with severe nasal polyps, the pharmaco-
418 economic rationale for the use of biologics needs to be further developed. Of particular interest for
419 decision making will be the identification of relevant patient subgroups, and guidelines which can
420 inform the most appropriate use for biologics in the treatment pathway for nasal polyps. QoL
421 improvements and the avoidance of surgical interventions will drive cost effectiveness assessments
422 (value for money) in making pharmaco-economic assessments of biologics. The avoidance of
423 surgery will have an impact on both direct costs as well as utility gains (avoidance of complications,
424 time off work, adverse effects, recovery, etc.), both of which need further quantification.

425

References

1. Wang X, Zhang N, Bo M, Holtappels G, Zheng M, Lou H et al. Diversity of TH cytokine profiles in patients with chronic rhinosinusitis: A multicenter study in Europe, Asia, and Oceania. *J Allergy Clin Immunol* 2016;138:1344–1353.
2. Tomassen P, Vandeplas G, Van Zele T, Cardell L-O, Arebro J, Olze H et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol* 2016;137:1449-1456.e4.
3. Zhang Y, Gevaert E, Lou H, Wang X, Zhang L, Bachert C et al. Chronic rhinosinusitis in Asia. *J Allergy Clin Immunol* 2017;140:1230–1239.
4. Wang E-T. Eosinophilic chronic rhinosinusitis in East Asians. *World J Clin Cases* 2014;2:873.
5. Cao PP, Li HB, Wang BF, Wang SB, You XJ, Cui YH et al. Distinct immunopathologic characteristics of various types of chronic rhinosinusitis in adult Chinese. *J Allergy Clin Immunol* 2009;124(3):478-484.e4842.
6. Zhang N, Van Zele T, Perez-Novo C, Van Bruaene N, Holtappels G, DeRuyck N et al. Different types of T-effector cells orchestrate mucosal inflammation in chronic sinus disease. *J Allergy Clin Immunol* 2008;122:961–968.
7. Bachert C, Zhang N, Cavaliere C, Weiping W, Gevaert E, Krysko O. Biologics for chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol* 2020;145:725–739.
8. Bachert C, Zhang L, Gevaert P. Current and future treatment options for adult chronic rhinosinusitis: Focus on nasal polyposis. *J Allergy Clin Immunol* 2015;136:1431–1440.
9. Stammberger H, Posawetz W. Functional endoscopic sinus surgery - Concept, indications and results of the Messerklinger technique. *Eur Arch Oto-Rhino-Laryngology* 1990;247:63–76.
10. Orlandi RR, Kingdom TT, Hwang PH, Smith TL, Alt JA, Baroody FM et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. *Int Forum Allergy Rhinol*

- 2016;6 Suppl 1:S22-209.
11. Wigand ME. Transnasal, endoscopic sinus surgery for chronic sinusitis. I. A biomechanical concept of the endonasal mucosa surgery (author's transl). [German]Transnasale, endoskopische Chirurgie der Nasennebenhöhlen bei chronischer Sinusitis. I. Ein bio-mechanisch. HNO 1981;29:215–221.
12. Alsharif S, Jonstam K, van Zele T, Gevaert P, Holtappels G, Bachert C. Endoscopic Sinus Surgery for Type-2 CRS wNP: An Endotype-Based Retrospective Study. Laryngoscope 2019;129:1286–1292.
13. Jankowski R. NASALISATION: TECHNIQUE CHIRURGICALE. J Fr d'Oto-Rhino-Laryngologie 1995;44:221–226.
14. Jankowski R, Rumeau C, Nguyen DT, Gallet P. Updating nasalisation: From concept to technique and results. Eur Ann Otorhinolaryngol Head Neck Dis 2018;135:327–334.
15. Schick B, Draf W. The frontal sinus. In: Rhinology and Facial Plastic Surgery. Springer Berlin Heidelberg 2009:567–573.
16. Van Zele T, Pauwels B, Dewaele F, Gevaert P, Bachert C. Prospective study on the outcome of the sphenoid drill out procedure. Rhinology 2018;56(2):178-182.
17. Anderson P, Sindwani R. Safety and efficacy of the endoscopic modified Lothrop procedure: a systematic review and meta-analysis. Laryngoscope 2009;119:1828–1833.
18. Shirazi MA, Silver AL, Stankiewicz JA. Surgical outcomes following the endoscopic modified lothrop procedure. Laryngoscope 2007;117:765–769.
19. Georgalas C, Hansen F, Videler WJM, Fokkens WJ. Long terms results of Draf type III (modified endoscopic Lothrop) frontal sinus drainage procedure in 122 patients: a single centre experience. Rhinol J 2011;49:195–201.
20. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE 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 multicentre, randomised,

- double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet* 2019;394:1638–1650
21. Jian L, Yi W, Zhang N, Wen W, Krysko O, Song WJ, Bachert C. Perspective: COVID-19, implications of nasal diseases and consequences for their management. *J Allergy Clin Immunol* Jul;146(1):67-69.
22. Draf W. Endonasal micro-endoscopic frontal sinus surgery: The fulda concept. *Oper Tech Otolaryngol - Head Neck Surg* 1991;2:234–240.
23. Hopkins C, Slack R, Lund V, Brown P, Copley L, Browne J. Long-term outcomes from the english national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. *Laryngoscope* 2009;119:2459–2465.
24. Loftus CA, Soler ZM, Koochakzadeh S, Desiato VM, Yoo F, Nguyen SA, Schlosser RJ. Revision surgery rates in chronic rhinosinusitis with nasal polyps: meta-analysis of risk factors. *Int Forum Allergy Rhinol* 2020;10(2):199-207.
25. DeConde AS, Mace JC, Levy JM, Rudmik L, Alt JA, Smith TL. Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. *Laryngoscope* 2017;127:550–555.
26. A Clinical Trial of Omalizumab in Participants With Chronic Rhinosinusitis With Nasal Polyps - Full Text View - ClinicalTrials.gov.
<https://clinicaltrials.gov/ct2/show/NCT03280550> (accessed 19 Apr2020).
27. Gevaert P, Omachi, TA, Corren J, Mullol J, Han J, Lee SE et al.. Efficacy and safety of omalizumab in patients with chronic rhinosinusitis with nasal polyposis: results from two, multicenter, randomized, double-blind, placebo-controlled phase III trials (POLYP 1 and POLYP 2). *JACI* 2020, in press
28. An Extension Study of Omalizumab in Participants With Chronic Rhinosinusitis With Nasal Polyps - Full Text View - ClinicalTrials.gov.
<https://clinicaltrials.gov/ct2/show/NCT03478930> (accessed 19 Apr2020).
29. Effect of Mepolizumab in Severe Bilateral Nasal Polyps - Full Text View -

- ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT03085797> (accessed 19 Apr2020)
30. Hosemann W, Draf C. Danger points, complications and medico-legal aspects in endoscopic sinus surgery. *GMS Curr Top Otorhinolaryngol Head Neck Surg* 2013;12:Doc06.
31. Kowalski ML, Agache I, Bavbek S, Bakirtas A, Blanca M, Bochenek G, et al. Diagnosis and management of NSAID-Exacerbated Respiratory Disease (N-ERD)-a EAACI position paper. *Allergy*. 2019 Jan;74(1):28-39.
32. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology* 2020;58:1–464.
33. Siedek V, Pilzweiger E, Betz C, Berghaus A, Leunig A. Complications in endonasal sinus surgery: A 5-year retrospective study of 2,596 patients. *Eur Arch Oto-Rhino-Laryngology* 2013;270:141–148.
34. Chang JR, Grant MP, Merbs SL. Enucleation as Endoscopic Sinus Surgery Complication. *JAMA Ophthalmol* 2015;133:850–852.
35. Toppila-Salmi S, Rihkanen H, Arffman M, Manderbacka K, Keskimäki I, Hytönen ML. Regional differences in endoscopic sinus surgery in Finland: A nationwide register-based study. *BMJ Open* 2018;8(10):e022173.
36. Blomgren K, Aaltonen LM, Lehtonen L, Helmiö P. Patient injuries in operative rhinology during a ten-year period: Review of national patient insurance charts. *Clin Otolaryngol* 2018;43:7–12.
37. Ramakrishnan VR, Kingdom TT, Nayak J V., Hwang PH, Orlandi RR. Nationwide incidence of major complications in endoscopic sinus surgery. *Int Forum Allergy Rhinol* 2012;2:34–39.
38. Satyanarayana Rao KH. Informed Consent: An Ethical Obligation or Legal Compulsion? *J Cutan Aesthet Surg*. 2008 Jan; 1(1): 33–35.
39. Fokkens WJ, Lund V, Bachert C, Mullol J, Bjermer L, Bousquet J, et al. EUFOREA consensus on biologics for CRSwNP with or without asthma. *Allergy* 2019

Dec;74(12):2312-2319.

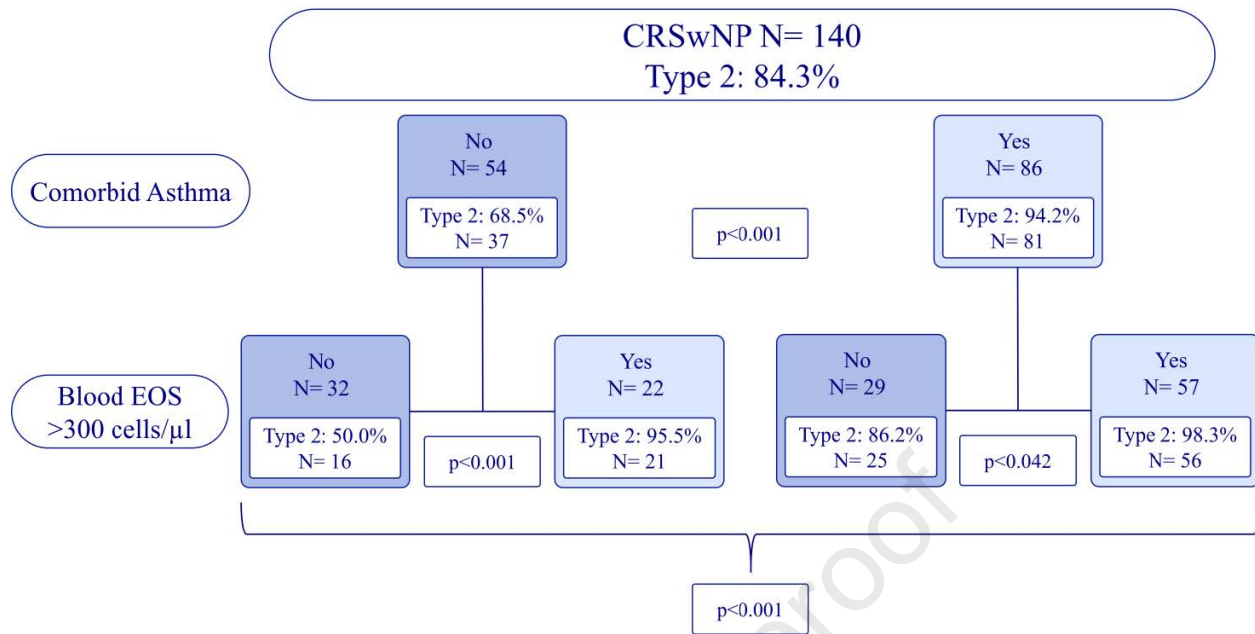
40. Khan A, Vandeplas G, Huynh TMT, Joish VN, Mannent L, Tomassen P et al. The Global Allergy and Asthma European Network (GALEN rhinosinusitis cohort: a large European cross-sectional study of chronic rhinosinusitis patients with and without nasal polyps. *Rhinology* 2019;57(1):32–42.
41. Khan A, Huynh TMT, Vandeplas G, Joish VN, Mannent LP, Tomassen P et al. The GALEN rhinosinusitis cohort: chronic rhinosinusitis with nasal polyps affects health-related quality of life. *Rhinology* 2019;57(5):343–351.
42. Velez F, Sacks H, Messina J, Kozma C, Maline D, Mahmoud R. Estimating the current cost of endoscopic sinus surgery in the US - a claims-based approach. *Value in Health* 2018;21:1.
43. Smith KA, Orlandi RR, Rudmik L. Cost of adult chronic rhinosinusitis: A systematic review. *Laryngoscope* 2015;125(7):1547–1556.
44. Bhattacharyya N. Assessing the additional disease burden of polyps in chronic rhinosinusitis. *Ann Otol Rhinol Laryngol* 2009;118(3):185–189.

545 **Figure Legends:**

546 **Figure 1:** Identification of type 2 immune reactions within CRSwNP tissue (IL-5 positivity) based
547 on clinical signs and blood eosinophils (original material from Ghent. Stepwise approach to identify
548 Type 2 immune reactions: 1) Ask for comorbid asthma, allergy and N-ERD 2) If negative, consult
549 blood eosinophil count

550 **Figure 2:** a) Patient selection criteria b) Selection and Monitoring of Biologics

551



Diagnosis of uncontrolled severe CRSwNP

Uncontrolled: Persistent or recurring CRSwNP despite long-term INCS, and having received at least one course of systemic corticosteroids* in the preceding 2 years and/or previous sinonasal surgery*

- Long-term low dose systemic corticosteroids is not recommended in CRSwNP
- One course of systemic corticosteroids refers to a minimum of 5 days of systemic corticosteroids at a dose of 0.5-1 mg/Kg/day or more.
- Previous sinonasal surgery refers to any surgical procedure from the resection of polyps to conventional ESS or extended approaches.

Severe: Bilateral CRSwNP with a NPS of ≥ 4 , and persistent symptoms despite long-term INCS with the need for add-on treatment.

- Bilateral polyposis (by nasal endoscopy)
- NPS ≥ 4 out of 8
- Presence of persistent symptoms assessed by:
 - Loss of smell score (0-3) ≥ 2 points
 - NCS (0-3) ≥ 2 points
 - SNOT-22 ≥ 35 points
 - Total symptom VAS ≥ 5 out of 10 cm

*unless having a medical contraindication/rejected by the patient

For the indication of Type 2 biologics including anti-IL4 receptor alpha (Dupilumab), anti-IgE (Omalizumab) and anti-IL5/R (Mepolizumab, Benralizumab), an underlying Type 2 inflammation should be highly likely

Selection of a biologic drug and monitoring of its effectiveness

prediction of response in an individual patient is not possible today

- ✓ Confirm diagnosis of uncontrolled severe CRSwNP
- ✓ Check for comorbidity (asthma, N-ERD) and consequences
- ✓ Check that type 2 inflammation is highly likely
- ✓ Inform patient on treatment options, perspectives and risks
- ✓ Take decision on surgery or biologic drug with an informed patient
- ✓ Select biologic drug (note limitations applicable for specific drugs)

CRSwNP and ASTHMA:
collaboration with an
asthma specialist is
essential for the indication
and selection of biologics

After 6 months of treatment

Improvement of at least one symptom/score:

- Sense of smell: from anosmia to hyposmia/normosmia, smell score increase ≥ 0.5
- NCS: decrease by ≥ 0.5 or objective testing
- NPS: decrease by ≥ 1 by nasal endoscopy
- SNOT-22: reduction of ≥ 8.9 (minimal clinically important difference)
- VAS total symptoms: reduction of ≥ 2 cm

No

Stop - change to surgery or another biologic drug

Yes

Improvement not acceptable to the patient

Improvement acceptable to the patient

Salvage surgery under biologic protection

Additional short course of systemic GCS

Continue with biologic treatment

After 12 months of treatment

Adequate response (all of these definitions is fulfilled):

- NPS < 4 (total of both sides)
- NCS < 2
- VAS total symptoms < 5
- SNOT-22 score < 30

Further, there should be no current need for surgery or systemic GCS

No

Consider another biologic drug

Surgery

Yes

Continue with biologic treatment