EUFOREA expert board meeting on uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) and biologics: Definitions and management

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Uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) is the most bothersome phenotype of chronic rhinosinusitis; it is typically characterized by a type 2 inflammatory reaction and by comorbidities, including asthma, nonsteroidal anti-inflammatory drug–exacerbated respiratory disease, and allergies. Here, the European Forum for Research and Education in Allergy and Airway Diseases proposes structured definitions to enable communication between clinicians and provides a practical algorithm to define type 2 inflammation in CRSwNP in daily clinical practice. A rational approach for the treatment of uncontrolled severe CRSwNP is discussed; it consists of evaluating the perspective and risks of surgery and efficacy and adverse events of biologics on the basis of 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 in many countries within a short time. Further, suggestions for monitoring of the drug effects that support recognition of responders to the therapy and, subsequently, the decision regarding continuation or discontinuation of the biologic are proposed. (J Allergy Clin Immunol 2021;147:29-36.)

Key words: *Chronic rhinosinusitis, nasal polyps, endotypes, type 2 inflammation, sinus surgery, biologics, indication, patient selection*

Uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) with or without comorbidities—most frequently, asthma, nonsteroidal anti-inflammatory drug–exacerbated respiratory disease (N-ERD), and allergies—is a highly disabling

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Abbreviations used
AE: Adverse event
CRSwNP: Chronic rhinosinusitis with nasal polyps
DBPCRS: Double-blind placebo-controlled, randomized study
ESS: Endoscopic sinus surgery
EUFOREA: European Forum for Research and Education in Allergy and Airway Diseases
GCS: Glucocorticosteroid
HRQoL: Health-related quality of life
INCS: Intranasal corticosteroid
N-ERD: Nonsteroidal anti-inflammatory drug–exacerbated respiratory disease
NPS: Nasal polyp score

airway disease that is characterized by long-term disease burden, consecutive exposure of patients to long-term local and systemic corticosteroids, necessity of often-repeated poorly standardized surgical interventions, and (so far) lack of highly efficacious treatment approaches beyond surgery. The advent of biologic drugs for type 2 immune effectors such as IL-4, IL-5, and IL-13, as well as IgE, offer new approaches for physicians and hope for patients to manage this difficult disease.

The European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) is an international nonprofit organization with the aim of preventing and improving the burden of chronic respiratory diseases. ENT physicians, allergists, and pneumologists working in leading EU research institutes are part of EUFOREA; to include their view, ear, nose, and throat colleagues in the United States also took part in the expert board meeting at which this document was drafted. One patient diagnosed with CRSwNP, representing the patient perspective, was invited to add his opinion. Representatives of the pharmaceutical industry producing biologic drugs were asked to contribute their knowledge but were not involved in any strategic discussions or decisions on any criteria-related care pathway decisions.

The aim of the EUFOREA expert board meeting in Brussels on January 25, 2020, was to develop suggestions for the indication of currently and soon-to-be-available type 2 biologics in an individual patient, the monitoring and evaluation of efficacy, and the development of evidence-based care pathways for management of uncontrolled severe type 2 CRSwNP with or without comorbid asthma. The presence of internationally renowned specialists in the fields of otolaryngology, pulmonology, allergology, and immunology have substantially added to the discussion and decisions. At the Brussels meeting, the various definitions were discussed point by point until unanimity was reached. A draft of the document was subsequently written and submitted to 3 rounds of review by all authors. In each round of review, the changes made to the definitions and proposed algorithms were discussed and refined until they were approved unanimously.

The discussions focused on clear definitions to define phenotype and endotype, elaborate criteria to support decision-making processes, and develop care pathways based on evidence when available and best practice when not.

DEFINITIONS: HOW TO DEFINE UNCONTROLLED SEVERE TYPE 2 CRSwNP WITH COMORBID DISEASE?

The EUFOREA group agreed on the following definitions. *Severe* CRSwNP is defined as "bilateral CRSwNP with a nasal polyp score (NPS) of at least 4 of 8 points *and* persistent symptoms, including loss of smell and/or taste, nasal obstruction, secretion and/or postnasal drip, and facial pain or pressure, with the need for add-on treatment to supplement intranasal corticosteroids" (INCSs) (see Comment E1 in the Online Repository at www.jacionline.org). *Uncontrolled* CRSwNP is defined as "persistent or recurring despite long-term treatment with INCSs and having received at least 1 course of systemic corticosteroids in the preceding 2 years (or having a medical contraindication or intolerance to systemic corticosteroids) and/or previous sinonasal surgery (unless having a medical contraindication or being unwilling to undergo surgery) (see Comment E2 in the Online Repository at www.jacionline.org). CRSwNP with *comorbid disease* is defined as "nasal polyp disease with other coexisting type 2 inflammatory diseases such as asthma, N-ERD, atopic dermatitis/eczema, allergic rhinitis, urticaria, food allergy, or eosinophilic esophagitis" (see Comment E3 in the Online Repository at www.jacionline.org).

ENDOTYPING IN UNCONTROLLED SEVERE CRSwNP BASED ON CLINICAL SIGNS AND BIOMARKERS

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

Depending on the geographic region and ethnicity of the patient, CRSwNP is characterized by type 2 mucosal inflammation in approximately 15% to 85% of the patients.[1-6] Type 2 inflammation is clearly associated with more severe sinus disease and symptoms, asthma comorbidity, and recurrence of disease after surgery.[7,8] It is therefore of importance to differentiate type 2 from non–type 2 CRSwNP for prediction of the natural course of disease, response to medical and surgical interventions, and consequently long-term management and selection of therapeutic measures. For the indication of currently available type 2 biologics, including anti–IL-4 receptor alpha (dupilumab), anti-IgE (omalizumab), and anti–IL-5/Ra (mepolizumab and benralizumab), an underlying type 2 inflammation should be present (Fig 1) (see Comment E4 in the Online Repository at www.jacionline.org).

SINUS SURGERY, A BIOLOGIC APPROACH, OR A COMBINATION OF BOTH?

In a patient with uncontrolled severe type 2 CRSwNP, at a time point during the course of the patient's disease when he or she has experienced ineffective systemic glucocorticosteroid (GCS) therapy or surgery, a long-term plan should be formulated in cooperation with an informed patient. This plan needs to consider the endotype, comorbidities, and other possible treatment approaches for those comorbidities, as well as the treatment history

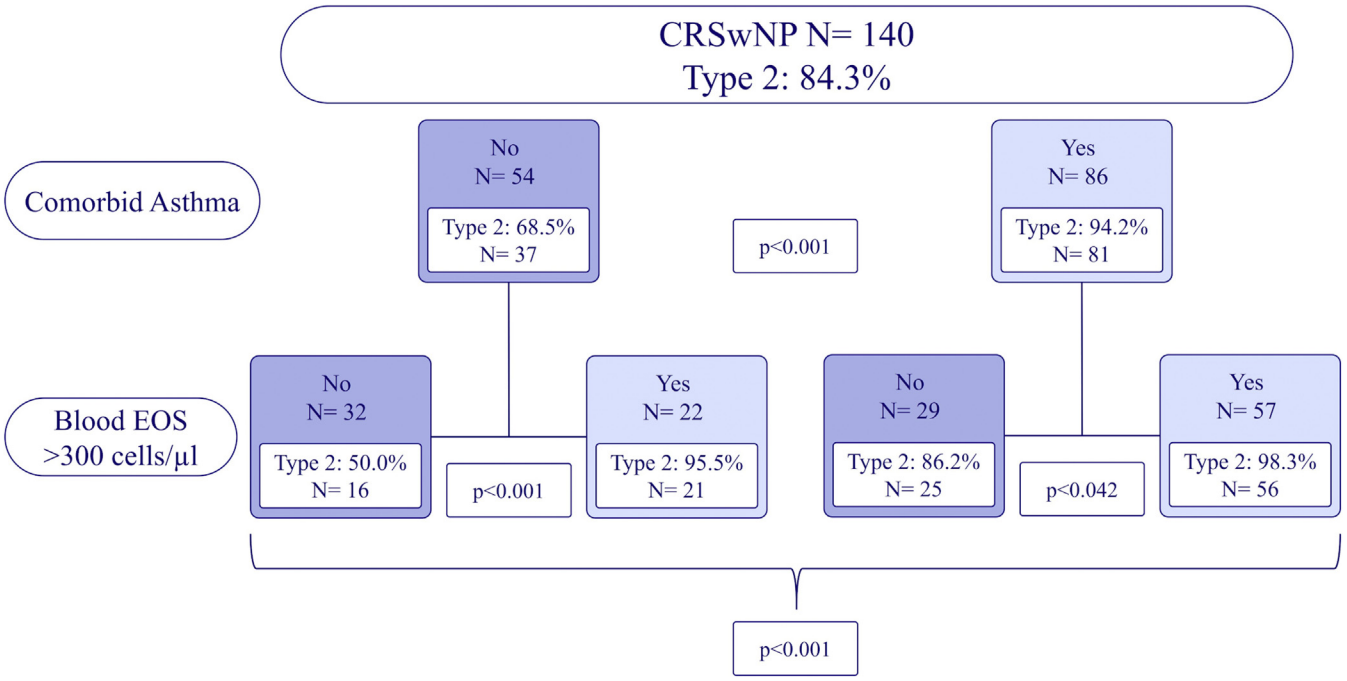

FIG 1. Identification of type 2 immune reactions within CRSwNP tissue (IL-5 positivity) based on clinical signs and blood eosinophil (EOS) original material from Ghent. Stepwise approach to identifying type 2 immune reactions: (1) ask whether comorbid asthma, allergy, or N-ERD is present, and (2) if the answer is no, consult the blood EOS count.

(operations, treatment with systemic GCSs and their efficacy, duration of effect, and adverse events [AEs]).

According to current patient rights, a patient must be informed about the aims, reasonable expectations, and possible side effects and complications of all authorized treatments available for the disease; this obliges the physician to inform the patient about available alternatives in the event of proposed surgery. The aim is to have an informed patient to share in the decision making in this situation, which gains importance with the complexity of the interventions available and the history of former therapeutic approaches (see Comment E5 in the Online Repository at www.jacionline.org).

Surgical approaches can be differentiated into functional endoscopic sinus surgery (ESS),[9-11] with the aim of opening all sinuses ("full house") and removing all nasal and sinus polyps but preserving the sinus mucosa, and the nasalization and reboot approaches,[12-14] with the aim of complete removal of polyp and sinus mucosa from all sinuses involved. The latter always includes the maxillary and ethmoidal sinuses, but IT may also include the frontal and sphenoidal sinuses, including the creation of wide openings (mostly the Draf III frontal sinus approach and the sphenoid drill-out[15,16] to completely remove the sinus mucosa). It has been demonstrated that reboot surgery in severe CRSwNP leads to less recurrence than do conventional approaches[12,17,18] and is followed by an effective healing process with functional mucosa.[12,19]

Should the patient and the physician opt for a biologic drug approach, the physician should decide on the possible choices among the biologics and make a choice with the informed patient, while also considering drug availability and patient-relevant questions such as practical issues with drug application. Before a surgical procedure under biologic protection is planned, a period of 6 months—and eventually 12 months if the patient's response to the treatment is as expected or better—should be considered to enable the physician to recognize the suitability of the response to the drug in the individual patient. In as many as two-thirds of the patients under biologic treatment, a surgical procedure may no longer be considered necessary .[20]

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

The recent SARS-CoV-2 pandemic has added further considerations for the choice of surgery versus biologics, as surgical procedures and repeated postoperative endoscopic debridement may impose a considerable risk to the medical personnel.[21]

EVALUATION OF EFFICACY VERSUS AEs AND/OR COMPLICATIONS FOR SURGERY AND BIOLOGICS

Efficacy of biologics in phase 3 trials

There are currently 2 biologics for which phase 3 trials have already been finalized (2 parallel double-blind placebo-controlled, randomized studies [DBPCRSs] with the anti–IL-4

receptor-alpha dupilumab [NCT02912468 and NCT02898454], 2 parallel DBPCRSs with anti-IgE and omalizumab [NCT03280550 and NCT03280537]; and 1 DBPCRS with the anti–IL-5 mepolizumab [NCT03085797]); in addition, a study of 1 drug (benralizumab) is still ongoing (NCT03401229). These studies were all based on a similar study design and included a large number of participants (N = 265-724). In all these studies, the effect of the biologic was compared with that of placebo added to continuous treatment with INCSs throughout the whole study period. Dupilumab is the first biologic to be registered in the European Union and the United States as an add-on treatment of severe CRSwNP that has not been sufficiently controlled by systemic corticosteroids and/or surgery. The patients recruited into the phase 3 studies had bilateral nasal polyps with an NPS of at least 5 of 8; had asthma in 48% to 71% of cases; had prior surgery in 54% to 100 % of cases; and were symptomatic, with impairment of smell and nasal obstruction as major symptoms.

In all phase 3 trials, the primary end points (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. The NPS reductions at 24 weeks were from 0.7 (mean, omalizumab; mean of the POLYP 1 and POLYP 2 studies) to 2.06 (mean, dupilumab, Liberty 24w). Of importance, smell was significantly improved with all drugs, albeit at different speeds and magnitudes; 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] Scores on the 22-Item Sino-Nasal Outcome Test, which reflects disease-specific quality of life, also improved significantly (by 14 to 21 points), clearly surpassing the minimal clinically important difference of more than 8.9. Dupilumab also showed a significant reduction in the computed tomography–based Lund-Mackey score by 5 to 7.5 points. Dupilumab and mepolizumab, in addition providing a reduction in NPS and symptoms as well as quality of life, demonstrated a reduction in the need for systemic corticosteroids and surgery over the course of 1 year of treatment versus placebo. A reduction of the NPS by at least 1 point was achieved in 50% to 65% of the verum-treated subjects over the trials.

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

Efficacy of surgery from the available literature

The efficacy of sinus surgery is difficult to evaluate, as there are various forms of sinus surgery as well as opinions regarding the extent of sinus surgery. For example, the term *sinus surgery* is used for balloon dilation of a sinus ostium, which is a minimally invasive sinus surgery aiming just to open the sinus drainage pathway, whereas the aim of (functional) ESS is to remove polyps from the nasal cavity and sinuses, or following the mucosal concept approach, to remove all sinus mucosal tissue. Experts agree that for CRSwNP, at least ESS with opening of the ostiomeatal complex, the maxillary and ethmoid sinuses, with removal of nasal polyps and thickened sinus mucosa, should be performed. However, some recommend creating large sinus openings to all sinuses, including the frontal sinus such as described as "modified Lothrop,"[22] and the complete removal of the sinus mucosa described as "reboot surgery."[12] Finally, there is variability in the extent of sinus surgery; in addition, the quality of sinus surgery may vary substantially.

Because of these factors, the evidence for efficacy of ESS is and will remain low. 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 1 or few centers, possibly 1 prominent surgeon, and therefore not transferable to other centers, let alone "all surgeons or operations." 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 less than 20% across the population of individuals with CRSwNP 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 patients with asthma vs 8.0% in patients without asthma).[24] As it will remain difficult to perform prospective multicenter 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 after surgery is likely (see Table E1 in the Online Repository at www.jacionline.org); however, recurrence does not necessarily translate into revision surgery. Therefore, is it imperative to postoperatively 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 ESS, 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.

AEs in phase 3 trials with biologics

Here we discuss AEs related to recent phase 3 trials of dupilumab,[20] omalizumab,[26-28] and mepolizumab,[29] reflecting the dosing schemes that will be relevant after registration. The proportion of patients who experienced at least 1 treatment-emergent AE was lower in the verum-treated patients than in the placebo-treated patients. Most events across all studies were of mild-to-moderate intensity. AEs occurring in at least 3% of patients include headache, dizziness, abdominal pain, nasopharyngitis, and injection site reactions, being slightly more frequent in the omalizumab treated group than in the placebo group; on the other hand, asthma exacerbations, nasal polyps, and congestion occurred less frequently, 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 2 dupilumab groups than in the placebo group. None of the observations were significant. Conjunctivitis was reported in 7 patients receiving

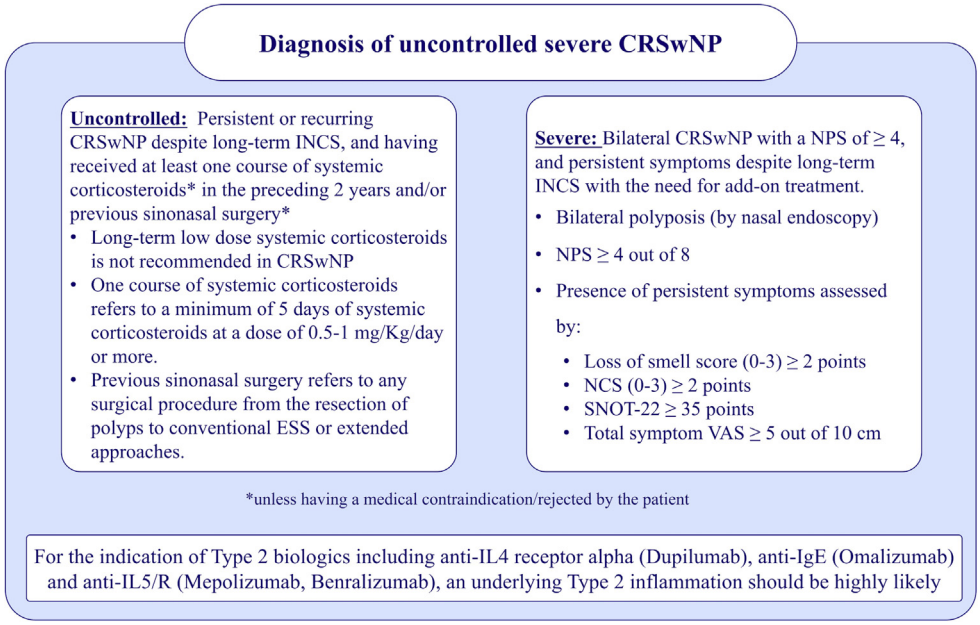

FIG 2. A, Patient selection criteria. **B,** Selection and monitoring of biologics. *ESS,* Endoscopic sinus surgery; *GCS,* glucocorticosteroid; *INCS,* inhaled corticosteroid; *NCS,* nasal congestion score; *NPS,* nasal polyp score; *SNOT-22,* 22-Item Sino-Nasal Outcome Test; *VAS,* visual analog scale.

dupilumab and in 1 patient receiving placebo; none of these cases were serious, severe, or associated with treatment discontinuation. Eosinophilia occurred in 4 patients: 3 of them developed eosinophilic granulomatosis with polyangiitis (1 of them was a patient receiving placebo). In summary, biologics show a good tolerability without major AEs.

Complications of sinus surgery

About 100,000 persons undergo endonasal ESS every year in Europe, irrespective of the fact that formal and comparative evidence of the long-term effectiveness of surgical procedures is still limited. ESS for chronic rhinosinusitis is technically demanding because of the narrow anatomic spaces and the individual and puzzling microanatomy in close proximity to delicate structures such as 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 complications.[30-34] Some less severe AEs may resolve spontaneously (eg, mild orbital ecchymosis); others may cause a persistent decrease in quality of life (eg, dry nose, crusting). Emergency revisional surgery may also be necessary (eg, in case of dural defects or major orbital hematoma), and irreversible damage (eg, blindness, death) may occur in rare cases. With regard to numeric data in the literature, routine EES interventions are generally associated with minor complications in about 5% of cases and major complications in 0.5% to 1%.[30] The number of endoscopic endonasal interventions has been 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 ESS have generally decreased in the years since international adoption of modern minimally invasive techniques, the increased number and complexity of today's interventions are still mirrored in actual reports on patient injuries.[36,37]

The patient perspective on biologics

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

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

SPECIFIC CONSIDERATIONS FOR BIOLOGICS

Selection of patients and prediction of 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 those with uncontrolled severe CRSwNP following the definitions specified in this article. However, drug-specific rules need to be applied (Fig 2, *A* and *B* and see Comment E8 in the Online Repository at www.jacionline.org).

Evaluation of the clinical response to a biologic within 6 months of treatment: "continue or stop" suggestions

EUFOREA has previously defined criteria to support patient selection for biologics and monitoring of the clinical response to treatment,[39] however, because of the developments in this fast-

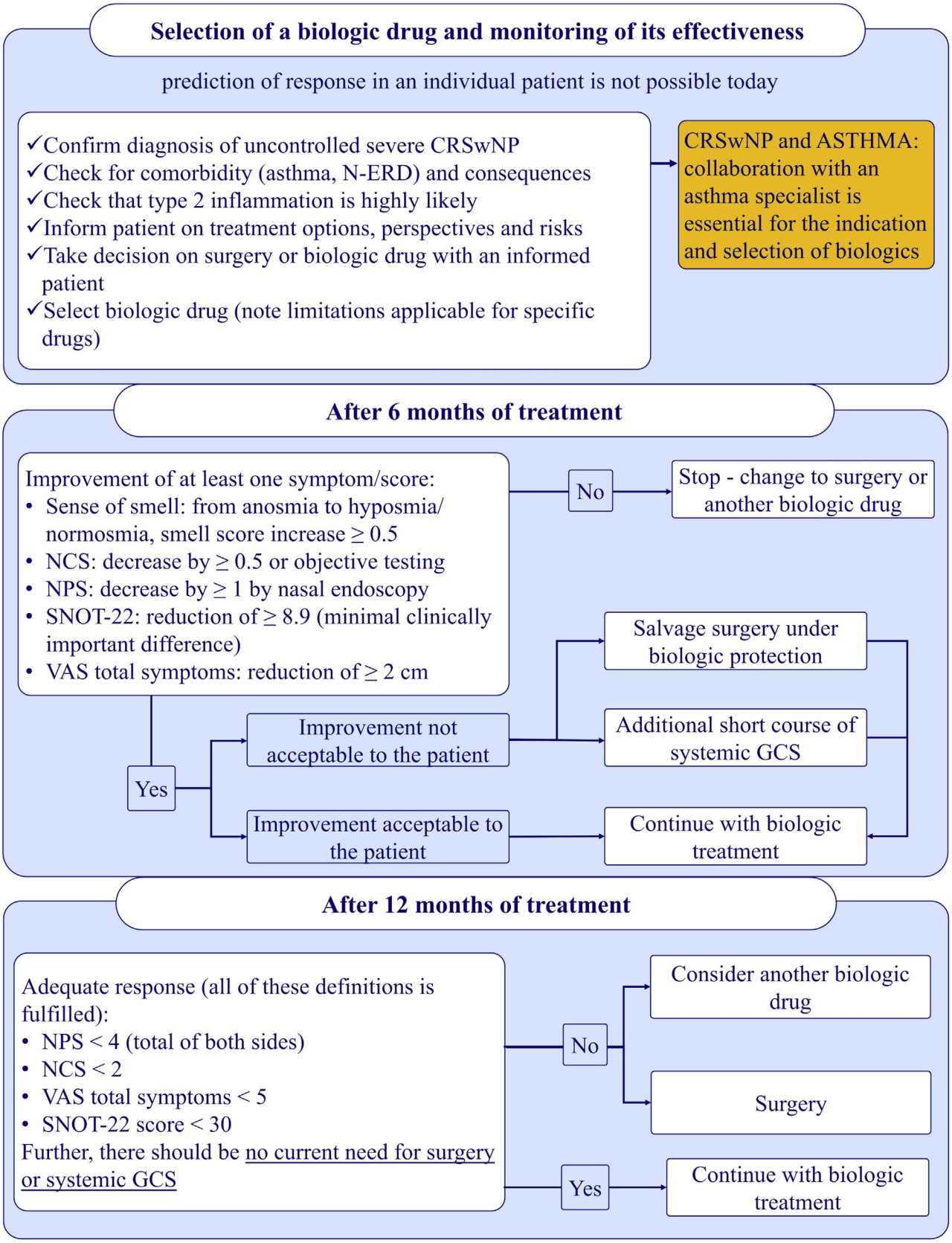

FIG 2. Continued.

evolving field, those criteria can now be replaced and detailed. When a biologic drug has been selected to treat uncontrolled severe CRSwNP, it is important to monitor the patient's response to the drug; depending on the biologic drug and outcome measure used, nonresponders may be expected in 25% to 50% of cases. To avoid inadequate treatment and associated unnecessary costs, a response to the treatment should be expected within 6 months; there is only a small chance that drugs will begin meaningfully reducing disease burden after that time point.

Phase 3 studies with dupilumab and phase 3 studies with omalizumab[20,26-28] have both demonstrated that the majority of—but not all—patients reach a reduction of their NPS and symptoms (including smell) of 75% or more of the 24 week values within the first 8 to 12 weeks. A further reduction of disease burden after week 24, building on the achieved reduction at that moment, has been demonstrated with dupilumab at 52 weeks of treatment. The group therefore decided on a 6-month period for evaluation of an individual patient's response of to a biologic and to determine the continue or stop suggestions. When the requirement of a clear change for at least 1 symptom has been met, the therapy with the biologic drug may be continued. Otherwise, the patient does not show adequate response to the treatment within 6 months and the chance for a later response is small. The management strategy should be adapted accordingly (change to surgery or to another biologic drug in consideration with a well-informed patient). No experience currently exists to advise regarding the order of biologics or the likelihood of response when using a second biologic, which also may depend on the primary biologic used.

Within these first 6 months, no drugs other than topical GCSs should be administered together with the biologic so as to be able to differentiate a response from no response (see Comment E9 in the Online Repository at www.jacionline.org).

When the treatment response has been verified within 6 months

There are several options in this situation, depending on the remaining burden of disease. If the degree of partial response is considered acceptable to the patient, continuation of the drug for another 6 months is advised and follow-up at 12 months is planned. It is expected that a further reduction of the nasal polyp burden and relief of the patient's symptoms can be achieved. If the level of control of the disease is not acceptable to the patient, an additional short course of a systemic GCS may be considered with the patient immediately experiencing reduction of the burden of disease under continuation of drug application. It has been determined that the drug is effective in this patient, and its continuation can be justified.

As an alternative, "salvage surgery under biologic protection" may be considered to reduce the remaining mass of polyps and burden of disease under continuation of the biologic. Again, the drug's effectiveness in this patient has been demonstrated and its continuation can be justified. However, the long-term benefit of surgery in this situation has been demonstrated only anecdotally (see Comment E10 in the Online Repository at www.jacionline.org).

Uncontrolled comorbid severe CRSwNP

CRSwNP negatively affects health-related quality of life (HRQoL), and a greater burden is seen in patients with higher disease severity or presence of comorbidities[40] (see Comment E11 in the Online Repository at www.jacionline.org). In a cluster analyses based on HRQoL, 10% of the patients visiting a tertiary health care center experienced the greatest impact on their HRQoL. These patients were characterized by greater numbers of comorbid conditions (asthma, eczema, N-ERD), greater numbers of previous sinus surgeries, reduced lung function, and greater severity of symptoms. These findings identify patients with uncontrolled comorbid severe CRSwNP[41] because this subgroup has received multiple treatments, including surgery, and they continue to have high symptom burden. These patients would contribute the most to the total economic burden of patients with CRSwNP, including both direct and indirect costs driven by greater health care utilization. Other published evidence on both direct and indirect cost burden has shown higher costs in patients with greater severity of disease, in those with comorbidities, and in those being prescribed oral treatments or receiving sinus surgery.[42-44]

Although there is a significant unmet need among patients with severe nasal polyps, the pharmacoeconomic rationale for the use of biologics needs to be further developed. Of particular interest for decision making will be the identification of relevant patient subgroups and guidelines that can inform the most appropriate use for biologics in the treatment pathway for nasal polyps. Improvements in quality of life and avoidance of surgical interventions will drive cost-effectiveness assessments (value for money) in making pharmacoeconomic assessments of biologics. The avoidance of surgery will have an impact on both direct costs and utility gains (avoidance of complications, time off work, adverse effects, recovery, etc), both of which need further quantification.

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