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EUFOREA Consensus on Biologics for CRSwNP with or without asthma

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Abstract

Novel therapies such as type 2 targeting biologics are emerging treatment options for patients with chronic inflammatory respiratory diseases fulfilling the needs of severely uncontrolled patients. The majority of patients with chronic rhinosinusitis with nasal polyps (CRSwNP) and over half of patients with asthma show a type 2 inflammatory signature in sinonasal mucosa and/or lungs. Importantly, both chronic respiratory diseases are frequent co-morbidities, ensuring alleviation of both upper and lower airway pathology by systemic biologic therapy. Type 2 targeting biologics such as anti-IgE, anti- IL4Rα, anti-IL5 and anti-IL5Rα have entered the market for selected pheno/endotypes of asthma patients and may soon also become available for CRSwNP patients. Given the high prevalence of chronic respiratory diseases and the high cost associated with biologics, patient selection is crucial in order to implement such therapies into chronic respiratory disease care pathways.

The European Forum for Allergy and Airway Diseases (EUFOREA) organized a multidisciplinary Expert Board Meeting to discuss the positioning of biologics into the care pathways for CRSwNP patients with and without comorbid asthma.

Introduction

Chronic rhinosinusitis (CRS) is a chronic inflammatory condition of the sinonasal cavities that affects 5-12% of the general population worldwide according to epidemiological studies (1-4). The European Position Paper on RhinoSinusitis and Nasal Polyps (EPOS) defines CRS clinically based on symptoms supported by signs of mucosal inflammation found on imaging or with nasal endoscopy (5). Recently, the prevalence of clinically based CRS has shown to be between 3-6.4% (6, 7). CRS is classically divided into a phenotype with and without nasal polyps (CRSwNP and CRSsNP, respectively). Using patient questionnaires to measure the prevalence of CRSwNP yielded estimates of 2.1% (France) to 4.3% (Finland), in Europe and 1.1% in China (13). CRSwNP comprises a heterogeneous group of patients who differ with respect to co-existing asthma, allergy, NSAID-exacerbated respiratory disease (NERD) (8), smoking, age of onset and disease severity (9-11). Asthma affects 30-70% of the CRSwNP patients (12-15). Conversely, the presence of nasal polyps is associated with the severity of asthma, regardless of smoking status ranging from 10-30% in mild asthma to 70 - 90% in severe asthma (16, 17). Both CRSwNP and asthma share common underlying pathophysiological mechanisms driving the disease (endotype) of which type 2 inflammation is the most prominent (14, 18-20). Type 2 inflammation is characterized by the presence of eosinophilic airway inflammation associated with type 2 -related cytokines (IL4, IL5 and/or IL13) and circulating and/or local IgE (14, 21) .

The management guideline in Europe for CRS, European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS), has been developed to provide physicians with comprehensive tables of levels of evidence and helpful management algorithms (5). In the US, similar consensus statements have been published in 2016 by Orlandi et al. (22).

The cornerstone of the management of both CRSwNP and asthma consists of anti-inflammatory treatment with local corticosteroids, aiming to achieve optimal disease control (5, 22, 23). When this is insufficient, short courses of oral corticosteroids are used (usually 30-60 mg for 14 days, sometimes reducing over time) (24, 25). Sinus surgery is the treatment option for CRSwNP patients in cases failing medical treatment (26-28). Recently, also more attention has been paid to the concept of “treatable traits”. Treatable traits have been postulated as a management concept which complements the traditional diagnostic labels like e.g. CRSwNP or CRSsNP, thereby focusing on therapy targeted to a patients’

individual disease-associated characteristics (29, 30). Typical treatable traits in the upper airways can be smoking, allergy, occupation and mucociliairy clearance deficits (31).

Biological therapies have entered the market for patients with asthma almost 15 years ago with anti-IgE as first-line therapy for patients with severe allergic asthma (32) and urticaria (33-36). Recently, other monoclonal antibodies targeting type 2 inflammation (37) have been approved and are available now for patients with eosinophilic asthma (38-42), atopic dermatitis (43, 44) and urticaria (37, 43-47) . A number of trials have been done with biological therapies for CRSwNP (48-51). As these drugs enter the market, it necessitates the medical community to reflect on the positioning of these therapies in the current care pathways of the upper and lower airways (52, 53).

The European Forum for Allergy and Airway Diseases organized a multidisciplinary Expert Board Meeting on November 29th and 30th 2018 to develop proposals for the positioning of biologics into the care pathways for CRSwNP patients with or without asthma. Subsequently, a patient advisory board meeting was held to discuss the outcomes of the Expert Board Meeting.

Severity and the burden of uncontrolled disease in CRSwNP and asthma

CRSwNP has a severe impact on quality of life comparable to asthma (54, 55) and poses a significant burden on society (55, 56). In particular the loss of sense of smell is a debilitating and often underappreciated component and can significantly impact one's quality of life (57, 58).

The terms 'disease control' and 'disease severity' cannot be used interchangeably. In CRSwNP severity is defined by the impact of the symptoms on general quality of life and it can be measured with VAS and/or SNOT-22 (59). Uncontrolled disease in CRS is defined as persistent symptoms such as nasal blockage, mucopurulent rhinorrhea/postnasal drip, facial pain/headache, impaired sense of smell or sleep disturbance/fatigue, and/or diseased mucosa in the last three months or the need for long term antibiotics or systemic steroids in the last month (5, 59, 60). Few real-life studies have evaluated the burden of uncontrolled disease following these criteria. A study performed at an academic referral centre showed

that at least 40% of CRS patients are uncontrolled despite maximal medical and surgical treatment (61) .

The goal of CRS management is to achieve and maintain clinical control with minimal use of medication and associated side effects or surgical interventions. Additionally, the frequency of recurrence of nasal polyps and the need for systemic corticosteroids might be measures of disease control. In clinical practice systemic corticosteroids are used more frequently and for longer periods than proposed in guidelines (13, 61). Real-life studies are needed to determine the cumulative exposure to corticosteroids of patients with co-morbid CRSwNP and asthma. The side effects of repeated use of systemic corticosteroids were also identified by the patient advisory board as a major concern (62).

Symptomatic nasal polyp recurrence rates, defined as patients undergoing revision endoscopic sinus surgery, are reported to be 20% within a 5-year period after surgery (63, 64) but may be as high as 50% on endoscopic examination (63).

Type 2 disease is a strong predictor of recurrent disease with more than 50% of recurrences occurring in clusters with high eosinophilia (63-66).

The Global Initiative for Asthma (GINA) suggests assessing asthma severity retrospectively from the level of treatment required to control symptoms and exacerbations. Mild asthma is asthma that can be controlled with low dose inhaled corticosteroids. Severe asthma is defined as asthma that requires treatment with high-dosed inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to maintain symptom control (after other causes of lack of control, i.e., treatment adherence and inhalation technique have been addressed) or asthma that remains uncontrolled despite this (maximal) therapy (67).

There is a clear correlation between control of upper and lower airways in patients with CRS and asthma and many patients with severe asthma have comorbid CRSwNP, which should be addressed to optimize asthma control (68-70). To conclude, the management of CRSwNP and asthma patients who are uncontrolled despite medical and often surgical intervention remains a challenge. However, in recent years, there has been significant innovation and expansion in the treatment armamentarium since the advent of biological therapies.

Efficacy of biological treatment for CRSwNP and asthma

Omalizumab was the first biological therapy that entered the market for patients with moderate to severe allergic asthma. It has been shown to improve disease control, reduce the number of asthma exacerbations, the need for oral corticosteroid and rescue medication use (32, 71). In recent years, several other biologics (anti-IL5, anti-IL5R and anti-IL4Rα) have shown to be effective for treatment of severe asthmatics with a type 2 inflammatory signature (72, 73). In most countries, biologics are indicated in (moderate-)severe asthma with insufficient level of control despite high dose of inhaled corticosteroids combined with at least one other asthma medication and where severe exacerbations and/or oral corticosteroid dependent asthma have been demonstrated.

The first proof-of-concept studies in CRSwNP using anti-IgE, anti-IL5 and anti-IL4Rα strategies also showed promising results and have been summarized earlier (51, 74). Recent larger scale studies showed a moderate reduction in the need for surgery following treatment with anti-IL5 in patients with CRSwNP (49). It was stated earlier that asthma is a frequent co-morbidity in patients with CRSwNP. All trials with biologics in CRSwNP also showed a positive impact on the lower airways with significant changes in either AQLQ, ACQ-5 or FEV_1 in patients with co-morbid asthma (48, 49, 75). Each of these biologics are tested in phase III clinical trials for CRSwNP patients with results to be expected in 2019. Preliminary data suggest a significant positive impact on quality of life, especially on the sense of smell and reduction in the need for surgery and systemic corticosteroid treatment.

Indications for biologics

The high burden of uncontrolled disease, the recurrence of nasal polyps after sinus surgery and the side effects associated with repeated courses of oral corticosteroids all underline the need for novel therapies. Given that biologics come with a high cost for the health care system, careful selection of patients is highly recommended. The EUFOREA expert team has put forward **five criteria** that are important in the decision to prescribe biologics in CRSwNP with prior sinus surgery (Figure 1):

- Evidence of type 2 inflammation (biological biomarker)
- Need for systemic corticosteroids in the past 2 years

- Significant quality of life impairment
- Significant loss of smell
- Diagnosis of comorbid asthma

It was concluded that biologics are indicated in patients with bilateral nasal polyps who had undergone sinus surgery in the past and meet 3 of the above criteria.

There was an extensive discussion whether there is a role for biologics in patients without previous sinus surgery. If these patients meet the criteria for severe asthma, they might fulfill the eligibility criteria to receive biological treatment by their pulmonologist.

In patients with severe CRSwNP and mild-moderate asthma, the question as to whether biologics may become a valid alternative for sinus surgery is difficult to answer before the approval and introduction of biologics into the market. Whilst most patients are keen to avoid surgery if possible, the effectiveness of biologics in preventing or reducing the need for surgery is yet to be established. The current evidence shows a significant but incomplete, relatively modest, reduction in polyp size suggesting that a notable proportion of patients might still need surgery despite treatment with a biological (38-40). On the other hand, given that repeated surgeries cannot prevent recurrence in CRSwNP subjects with type 2 inflammation, and in line with the principles of precision medicine that patients also will share in decision making, it is likely that biologics will in time become an alternative for sinus surgery as currently performed.

To date, one study evaluated omalizumab versus sinus surgery in patients with grade 3 CRSwNP and asthma (50). It was concluded that omalizumab is equally effective in reducing SNOT-22 at 16 weeks to sinus surgery. However, large scale studies are needed to confirm these findings in order to decide upon whether or not biologics could be a valid alternative to primary sinus surgery.

Therefore, it was concluded that patients who have never had sinus surgery need to meet at least 4 of the above criteria in order to be eligible for biological treatment.

Finally, indications **not to initiate type 2 biological treatment** were defined as follows:

- CRSsNP and lack of signs of type 2 inflammation
- Cystic fibrosis
- unilateral nasal polyps
- mucoceles
- general contra-indications for biological treatments, such as immunodeficiencies
- patient-related factors such as non-compliance to therapy

Defining response to biologics

Despite significant efficacy of biologics on various clinical and patient-reported outcome measures in the overall study population, considerable variability in the degree of response to such therapies is seen. These observations underpin the need to identify treatment responders as well as non-responders. The following criteria were agreed by the expert team to define response to biological therapy after 1 year (Figure 2):

- Reduced nasal polyp size
- Reduced need for systemic corticosteroids
- Improved quality of life
- Improved sense of smell
- Reduced impact of co-morbidities

Three categories of response were defined: poor (1-2 criteria), good (3-4 criteria) or excellent (5 criteria). It was proposed to assess the response to treatment after 16 weeks in order to decide upon continuation of the treatment (early stopping rule). The group felt that ethically and clinically, an assessment point was required to avoid unnecessary continuation of a treatment which was not working and had chosen 16 weeks after discussion, but recognize that this will be validated/may change when further information becomes available from ongoing trials. It should be noted that real-life studies are currently lacking to confirm the 16-week early stopping time point.

Positioning of biologics in the chronic respiratory disease integrated care pathway

New developments in understanding pathophysiology and treatment require new care pathways. Recently, integrated care pathways incorporating the different phenotypes and endotypes have been proposed (76, 77). Although, as we speak, biologics do not yet have an indication for CRSwNP, we can expect this to happen in the very near future.

Implementing integrated care pathways into daily clinical practice requires both collaboration between first, second and third line of care as well as across specialties (ENT, pulmonology, allergology). Patients pointed out during the advisory board meeting that awareness about CRS and nasal polyps and best-practice management options are unsatisfactory. Thus, it is the patients' perception that timely referral to a specialist is often delayed. Education of both patients and primary care physicians is thought to facilitate timely and accurate diagnosis of patients with CRSwNP and/or asthma. Because there are indications that early treatment of CRS may prevent asthma and further healthcare use (78), appropriate management at the right level of care may eventually prevent further development of disease and be highly cost-effective. Patients with a high-risk phenotype (asthma and NERD) should be referred to specialist centers early in their disease to optimize multidisciplinary management.

Many patients will predominantly have upper or lower airway diseases. However, it is recommended that every patient with CRS gets at least one systematic evaluation for asthma and allergy preferably by a validated questionnaire and if at risk for asthma, spirometry to assess lung function; skin prick test or measurement of specific blood IgE, and measurement of blood eosinophil counts. Similarly, for patients with asthma it is recommended that every patient is evaluated for upper airway problems (rhinitis or CRS) and allergy preferably by a validated questionnaire; nasal endoscopy, skin prick test or measurement of specific blood IgE; and measurement of blood eosinophil counts. However, a subgroup of patients with severe CRS and asthma may benefit from an intensified collaboration between ENT and pulmonologist and where appropriate allergologist.

Remarkably, only a few of the physicians in the Expert Board admitted to having a multidisciplinary outpatient clinic in place. Notwithstanding this, recommendations of the Board included the development of a multidisciplinary integrated care pathway and subsequent implementation in daily practice with systematic evaluation of both upper and

lower airways at every visit; treatment adjustments with attention to the full unified airways; regular measurement of type 2 biomarkers; and monitoring of the use of systemic corticosteroids.

Conclusion and unmet research needs

A multidisciplinary EUFOREA Expert Board Meeting and patient advisory board came together under the auspices of the European Forum for Research and Education in Allergy and Airway Diseases. The participants formulated a proposal for the positioning of biologics into the care pathways for CRSwNP with or without asthma patients. Criteria for and against the use of biologics and response criteria were defined (Figure 1 and 2).

A series of unmet needs for future research were identified:

- Evaluation of biological treatment in CRSsNP with signs of type 2 inflammation
- Biomarker research to identify responders to biological treatments
- Evaluation of the disease modifying effect of biological treatments
- Evaluation of required duration of treatment and discontinuation criteria
- Protocols of long-term treatment
- Interplay between biologics and sinus surgery
- Health-economic research

Figure legends

Figure 1: Indications for biological treatment in patients with CRSwNP: Proposal of the EUFOREA multidisciplinary Expert Board Meeting

Figure 2. Response criteria for biological treatment in patients with CRSwNP: Proposal of the EUFOREA multidisciplinary Expert Board Meeting

Author contributions:

All authors contributed to the discussion that was the base for this document and approved of the content.

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