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Evaluation of ongoing mepolizumab treatment in chronic rhinosinusitis with nasal polyps

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Abstract

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a multifactorial inflammatory disease of the mucous membranes of the nose and paranasal sinuses. Eosinophilic inflammation is described as a common endotype. The anti-interleukin-5 (IL-5) antibody mepolizumab was approved in November 2021 as an add-on therapy to intranasal glucocorticosteroids for the treatment of adults with severe CRSwNP when systemic glucocorticosteroids or surgery do not provide adequate disease control. While national and international recommendations exist for the use of mepolizumab in CRSwNP, therapy monitoring and follow-up documentation are required, and therapy discontinuation has not been adequately established yet. In this paper, recommendations for monitoring the course and efficacy of therapy as well as for reviewing the duration and possible termination of therapy are provided. For this purpose, a literature search was performed to analyze previous data on the treatment of CRSwNP with mepolizumab and to determine the available evidence by searching MEDLINE, PubMed, and the national and international trial and guideline registries and the Cochrane Library. Human studies published in the period up to and including October 2022 were considered. Based on the international literature and previous experience, recommendations for follow-up, adherence to therapy intervals and possible therapy breaks, as well as termination of therapy when using mepolizumab for the indication CRSwNP in the German health care system are given by an expert panel on the basis of a documentation sheet.

Keywords

Chronic rhinosinusitis, chronic rhinosinusitis with nasal polyps, biologics, eosinophilic inflammation, mepolizumab

Introduction

Chronic rhinosinusitis with nasal polyps

Chronic rhinosinusitis (CRS) with nasal polyps (NP; CRSwNP) is characterized by nasal obstruction, a feeling of pressure in the paranasal sinuses, loss of smell, and anterior and/or posterior rhinorrhea, among other symptoms.

All drug and surgical treatments available to date do not provide adequate disease control and recurrence prevention in some cases [1]. Oral glucocorticosteroid therapy is commonly used to control exacerbations, with a history of steroid-related side effects. Thus, there is an unmet need for new treatments to better control the disease. Advances in the understanding of the immunologic processes involved in type-2 inflammation, which accounts for approximately 80% of cases of CRSwNP in Europe [2, 3] and the U.S. [4, 5], have led to new opportunities for disease control. Monoclonal antibodies (mAbs) targeting eosinophilic or type-2 inflammation are also available for the treatment of CRSwNP in Europe with mepolizumab, omalizumab, and dupilumab.

International recommendations exist for the indication and in-label therapy of CRSwNP with biologics [1, 6–8] and also consensus recommendations and Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) guidelines specifically adapted to the German health care system [9, 10] for the use of dupilumab [11, 12], omalizumab [13, 14] and mepolizumab [15], also during the coronavirus disease 2019 (COVID-19) pandemic [16].

Prevalence of NP, pathophysiology, and current treatment

CRS is the second most common chronic disease in Europe and the U.S. [1]. CRSwNP, as the most severe subtype of CRS, accounts for the majority of health care costs with a prevalence of approximately 4% in the adult population of CRS [1], and is associated with significantly impaired health-related quality of life [17, 18]. In CRSwNP, recurrence is common despite adequate drug and surgical treatment [19]. Symptoms mainly include obstructed nasal breathing, loss of sense of smell, feeling of pressure around the face, and anterior and posterior rhinorrhea [7, 20–22].

Drug treatment of CRSwNP targets the underlying inflammation with the symptoms described above. Standard treatments include topical intranasal corticosteroids, short-term systemic corticosteroid (SCS) treatments, and endoscopic paranasal sinus surgery [7, 21, 23]. Treatment continues to include nasal lavage with brine solutions and antibiotics to treat any acute bacterial exacerbations. Sinus surgery is an option for patients whose symptoms persist despite appropriate drug treatment [7]. However, in addition to sinus surgery, drug treatment is always continued, primarily in the form of intranasal glucocorticosteroid (INCS) and nasal lavage.

Patients with severe CRSwNP have a recurrence rate of 40% within three years, even when multimodal treatment methods have been used [24], and of up to 80% within 12 years [24–26]. Therefore, additional treatment options are needed.

Patients with severe CRSwNP and comorbid asthma, aspirin-exacerbated respiratory disease (AERD), and eosinophilic inflammation are most affected by the disease. Of significance, these patients are more likely to require sinus surgery, have high corticosteroid use, and experience long-term recurrence than patients without these disease features [24, 26–29]. Patients with asthma and AERD account for 23% to 45% of all recurrences [30–32] respectively, and 10% to 16% [29, 31] of patients with severe CRSwNP. Biologic therapy targets type-2 inflammation. This is found in approximately 80% of patients with CRSwNP in Europe. Indications of type-2 inflammation are severe CRSwNP refractory to therapy, comorbid asthma, and a blood eosinophil count greater than 300 cells/μL [33]. In addition, previous mepolizumab studies in severe eosinophilic asthma suggest that patients with a blood eosinophil count of ≥ 150 cells/μL at baseline were more likely to benefit from mepolizumab therapy [34, 35], although blood eosinophil count has not yet been established as a clear biomarker of mepolizumab efficacy in CRSwNP [36].

Mechanism of action of mepolizumab

Advances in understanding the pathogenesis and immunological basis of CRSwNP enabled the development of mAbs as drugs (biologics) for this disease [3]. In CRSwNP, chronic inflammation is primarily determined by type-2 proinflammatory cytokines such as interleukin-5 (IL-5), IL-4, and IL-13, as well as high numbers of eosinophils in the surrounding tissue [7, 37]. CRSwNP is characterized by impaired barrier function of the epithelium and often by a type-2 inflammatory pattern, which can be observed in a similar form in bronchial asthma [38]. Activation of T lymphocytes and epithelial cells leads to the release of epithelial cytokines such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) [39]. These cytokines activate type-2 innate lymphoid cells (ILC2s), adaptive T helper (Th) cells, dendritic cells, and mast cells in tissues and promote type-2 inflammation. The subsequent type-2 immune responses are characterized by the production of IL-4, IL-5, IL-13 by ILC2, $CD8^+$ T cells expressing the prostaglandin DP2 receptor chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2; Tc2), and Th2 cells. IL-13 contributes significantly and directly to goblet cell hyperplasia in the respiratory epithelium and clinically often to dyscrinia and hypersecretion. IL-4 and IL-13 mediate a class switch to immunoglobulin E (IgE) production by B cells so that with increased activity of these cytokines in diseased tissues in asthma and CRSwNP, IgE antibodies are not only an expression of allergy but also of generic type-2 activation. IL-5 recruits eosinophils to the tissue. The increase in T cells, B cells, and plasma cells in the tissues with high levels of IgE in the mucosa characterizes this inflammatory response, which is further enhanced by the activation of mast cells and eosinophils. Increased levels of IL-4 and IL-13 observed proximally in the inflammatory cascade, and IL-5 and eosinophils observed distally, are considered hallmarks of the

inflammatory type-2 response in polyp tissue [40–43]. Therefore, these key cytokines have become targets for various mAbs as therapeutic agents (biologics).

Mepolizumab was developed for the treatment of type-2 dependent eosinophilic disease [44]. Evidence of the efficacy of mepolizumab in eosinophilic airway disease was for severe eosinophilic bronchial asthma [45] with subsequent global approval in 2015 [46, 47].

Mepolizumab is a humanized anti-IL-5 mAb that prevents IL-5 from binding to its receptor on eosinophil granulocytes, mast cells, and other target cells and selectively inhibits eosinophilic inflammation [48].

Mepolizumab in CRSwNP

Mepolizumab (100 mg administered subcutaneously; s.c.) has been approved in several countries worldwide for the treatment of severe eosinophilic asthma and CRSwNP and has been approved at a dose of 300 mg for patients with eosinophilic granulomatosis with polyangiitis (EGPA) and hypereosinophilic syndrome (HES) [49–51].

The pivotal study for mepolizumab in CRSwNP was the SYNAPSE study—a randomized, double-blind, placebo-controlled, parallel-group phase III trial [52]. Detailed information about this study and the eligibility criteria have been published [53].

The phase III SYNAPSE trial demonstrated that mepolizumab reduced the size of NP and improved symptoms of nasal obstruction, reduced the actual number of sinus surgeries and use of SCS, improved sinonasal symptoms, and had an acceptable safety profile [53]. In addition, the initial results of SYNAPSE indicated that mepolizumab improved nasal obstruction in patients with high blood eosinophil counts [53]. This was explained by the IL-5-binding and eosinophil-blocking mechanism of action of mepolizumab [48]. Similar observations were made in patients with asthma and chronic obstructive pulmonary disease [34, 54].

Therefore, an exploratory analysis evaluated the efficacy of mepolizumab compared with placebo in adults with severe, bilateral CRSwNP who required revision surgery depending on the presence of comorbid asthma, comorbid AERD, and blood eosinophil count [55]. However, the extent to which blood eosinophil count can be seen as a potential biomarker of treatment success cannot be inferred from the available data on CRSwNP at the present time [36].

Adverse effects and safety of mepolizumab

The safety of mepolizumab is well established based on the collective collection of safety data in multiple phase III clinical trials not only for CRSwNP, but also for asthma and HES, EGPA, and in post-marketing surveillance [53, 56–59]. In general, mepolizumab was well tolerated in the studies presented, and no serious adverse effects occurred [60].

Vital signs, physical examinations, laboratory tests, and electrocardiograms were monitored in all studies and provided no evidence of adverse effects. Regarding CRSwNP, the SYNAPSE study confirmed the tolerability profile from previous studies. Serious adverse events occurred in 12 (6%) patients on mepolizumab and 13 (6%) on placebo. Also, the overall proportion of patients in whom adverse events were documented did not differ between the mepolizumab group [169 (82%)] and the placebo group [168 (84%)]. The most common adverse events in the study in both patient groups were nasopharyngitis, headache, epistaxis, and back pain [51, 53]. Systemic allergic reactions (type-I hypersensitivity reactions) were reported in 2 patients (< 1%) in the group receiving mepolizumab 100 mg and in no patients in the placebo group [51].

Dosage of mepolizumab in CRSwNP

Mepolizumab is applied s.c. and is therefore administered to patients every 4 weeks in a dose of 100 mg by the treating physician, but also by patients themselves.

After repeated s.c. administration, there was approximately 2-fold accumulation at steady-state with a bioavailability of 80% [61]. The effects of mepolizumab on blood eosinophils served as a pharmacodynamic parameter. In patients with CRSwNP, blood eosinophil counts decreased from a geometric mean at baseline of 390 cells/μL (n = 206) to 60 cells/μL (n = 126) by week 52 following a 100 mg dose of mepolizumab administered s.c. every 4 weeks for 52 weeks, an 83% reduction in geometric mean compared with placebo. This magnitude of reduction was observed within 4 weeks of treatment initiation and was maintained throughout the 52-week treatment period, demonstrating the onset and effect of mepolizumab on eosinophils [53, 61]. Current dosing recommendations state that if a dose is missed, it can be made up promptly. If the omission is not noticed until the time of the next dose, only the next dose is injected as scheduled and the missed dose must be omitted [62].

There is currently insufficient data on patient adherence to routine treatment and this will need to be investigated over time. Data on a possible extension of the injection interval are also lacking.

Evaluation of initial clinical response to mepolizumab in CRSwNP

Once therapy with a biologic has been initiated for the treatment of severe, uncontrolled CRSwNP, it is important to monitor the patient's response to the drug. Depending on the clinical endpoint used, non-responders can be expected in approximately 25% of cases in CRSwNP [6, 63].

Recommendations for the assessment of the initial response to therapy and subsequent follow-up have been made by an international expert panel [1], on which the guidelines given here for the German healthcare system are based. In order to achieve targeted and effective therapy, the principles of medical treatment in the German social insurance system (economical, expedient, expedient) were adhered to. In particular, this is also intended to avoid inappropriate treatment and the associated unnecessary costs.

For this purpose, the following recommendations for the different treatment phases of therapy with mepolizumab in CRSwNP are provided, which can be documented in a documentation sheet for the follow-up of the therapy—monitoring the course and efficacy of therapy and reviewing the duration and possible termination of therapy. These recommendations are based on both the pivotal phase III studies and the advancing knowledge about the use of mepolizumab in routine care as a now well-established treatment option. Here, the safety profile, the trade-off for treatment decision-making in the context of different treatment paradigms, and pharmacoeconomic aspects are also considered, taking into account the high cost of biologics.

A literature search was performed to analyze previous data on the treatment of CRSwNP with mepolizumab and to determine the available evidence by searching MEDLINE, PubMed, the national and international trial and guideline registries, and the Cochrane Library. Human studies published in the period up to and including October 2022 were considered.

Response to treatment with mepolizumab in CRSwNP is expected within 4–6 months

As previously outlined, steady-state concentrations for mepolizumab at recommended doses and injection intervals are achieved after approximately 4 weeks of treatment [53, 61]. We therefore recommend evaluating the success of therapy after 4–6 months, as it is expected that the first signs of therapeutic success will be detectable by this time.

In case of non-response with regard to individual or all parameters, therapy should still be continued, and re-evaluation should be performed after another 6 months. Both in the updated German AWMF guideline [2], as well as in the expert information, an evaluation of the therapy response after 24 weeks is recommended [64], and this recommendation for therapy evaluation 6 months after therapy initiation was also given internationally by a European expert group [1]. In contrast to the international position papers, the German guideline does not specify a fixed point in time for the evaluation of efficacy and thus allows for more flexible handling and strengthens the treating physician's freedom of therapy [2].

The chance that a response to treatment (reduction in disease burden) will still occur after 24 weeks/6 months in the absence of an effect under adequately administered mepolizumab treatment is low [1]. However, the data available from prospectively collected data is limited due to the recent approval.

Within the first 6 months, no concomitant medications (e.g., oral corticosteroids) or surgery other than topical INCS should be combined with mepolizumab, if possible, to distinguish response from nonresponse, except for emergency treatments and exacerbations. If additive immunosuppressive or modifying therapy was necessary during this period, a delayed efficacy assessment may be useful at a later time.

The treatment effect is defined as the changes in NP score (NPS), olfaction, and symptomatology, based on objectifiable symptom and endoscopy-based criteria. For individual patients, the decision to continue or discontinue treatment is made based on these criteria:

Objectifiable parameters for response to mepolizumab therapy at 6 months (at least 1 parameter should be fulfilled) [1]:

(1) Nasal obstruction: improvement in nasal congestion score (NCS; 0–3) by ≥ 0.5 or improvement in objective tests (e.g., increase in peak nasal inspiratory flow or nasal volume flow in active anterior rhinomanometry by ≥ 20 L/min, decrease in resistance and increase in hydraulic diameter).

(2) NPS: reduction of endoscopically determined NPS (0–8) by ≥ 1 score point compared with baseline.

(3) Sino-nasal outcome test 22 questionnaire (SNOT-22)/quality of life: reduction of SNOT-22 score (0–110) by ≥ 8.9 (validated minimal clinically relevant difference).

(4) Symptomatology in visual analogue score (VAS): reduction of VAS total symptoms (0–10 score points) by > 2.

(5) Olfaction: improvement in the 16-item Sniffin' Sticks identification test by ≥ 3 points (validated minimal clinically relevant difference).

If there is no sufficient response to treatment, the treatment strategy should be adapted accordingly, taking into account the patient's wishes (surgical intervention or switch to another biologic or other therapy, e.g., short-term administration of SCS) and, if necessary, referral of the patient to a rhinology center. Especially in the case of side asymmetric response, surgical intervention should be considered just to exclude secondary pathologies; however, such a pathology does not necessarily have to be present. Locally limited residual polyp findings are possible after biologic administration and can be addressed by adjunctive surgery if functionally relevant. Currently, no experience is available to adequately support a recommendation to switch to a specific biologic after frustrated use of a primary biologic. Therefore, the identical criteria for primary initial therapy should be applied in the selection here [12, 14, 15]. However, it seems logical to alternate between anti-IL-5, anti-IgE, and anti-IL-4 receptor (IL-4R) treatment principles. Here, prospectively collected data would be desirable.

There are also insufficient data on whether the continuation of biologic therapy in addition to paranasal sinus surgery improves the recurrence rate of uncontrolled CRSwNP after only a partial response with biologics. In the future, it should be systematically and prospectively assessed whether continued treatment with mepolizumab can prevent polyp recurrence after surgery in these patients in the long term, thus allowing them to maintain disease control after initial surgical treatment. Further monitoring of the various parameters should also be performed during the course of the disease in order to detect a decline in the effectiveness of the therapy.

After 12 months of treatment, a controlled state of CRSwNP with low symptom burden should be achieved so that treatment can be maintained in subsequent years. The following criteria for adequate response after 12 months of treatment with mepolizumab should be considered:

Objectifiable parameters for an evaluation of long-term mepolizumab therapy (≥ 12 months) [1]:

(1) All symptoms are only moderately pronounced or at least improved compared with the status prior to the start of therapy.

(2) Total NPS < 4 (summed on both sides).

(3) NCS < 2 (nasal passage allows near-normal breathing at rest).

(4) VAS total symptoms < 5.

(5) SNOT-22 value < 30.

(6) Currently, CRSwNP should not require administration of SCS or surgery for CRSwNP (except surgery to remove mechanical obstructions such as synechiae, mucocele, etc.).

If there is no sufficient response to biologics therapy after 12 months of treatment, we recommend discontinuation of biologics administration. If necessary, after critical re-evaluation of the clinical indication criteria as well as the character of the underlying inflammation (endotype), a switch to another biologic may be considered or additional/additive reoperation or short-term therapy with SCS may be considered.

However, once at least one of these criteria is met and there is no current need for surgery or SCS therapy, the patient is satisfied with the treatment, and no relevant side effects have occurred, treatment with the biologic can be continued.

In patients with an excellent response to mepolizumab in which therapy has been suspended, a follow-up with re-evaluation shall be performed after a time interval of a maximum of 6 months or when symptoms reappear.

Special instructions for the measurement of olfaction

In the pivotal studies for mepolizumab, the University of Pennsylvania smell identification test (UPSIT) [also "brief smell identification test" (B-SIT)] was used to objectify olfaction [65]. However, this test is hardly used in routine care in Europe. In contrast, the Sniffin' Sticks smell test is widely used [66, 67], a subjective, ortho-nasal olfactory test method. Felt-tip pens filled with odorants are used as the test instrument [66]. For a precise estimation of the total olfactory ability, the sum of the olfactory threshold test, the odor discrimination test, and the odor identification test (TDI) is formed. The examination of the TDI is very complex and is usually performed only in specialized centers. Nevertheless, the olfactory ability should be measured and not only asked. For the estimation of olfactory ability in clinical routine, the identification test with 12 pens or 16 pens is recommended. For a more detailed examination of olfaction (e.g., in rhinology centers or in studies), the threshold and discrimination ability should also be determined, with the threshold being the more important of the two parameters [68].

Combination of treatment with mepolizumab with other biologics in CRSwNP

Type-2 inflammatory comorbidities may respond very differently to one biologic, therefore in very rare cases, a combination of multiple type-2 biologics may be required. If, in close interdisciplinary collaboration, no single biologic can be identified that controls multiple co-existing type-2 diseases, the comorbidities should be independently treated according to guidelines. For example, patients sometimes show a very good response of CRSwNP to mepolizumab, while control of their asthma cannot be achieved with it and vice versa.

In such a case, it may be necessary to separately indicate a specific biologic for each disease according to the respective approvals, ultimately resulting in a combination therapy of several biologics [69]. It is important that in such a case, each specialist group sets the indication for both CRSwNP and asthma in-label according to the approval. These are very individual therapeutic decisions. General recommendations for the combination of different biologics do not exist yet, nor is there any reason for safety concerns [69]. However, such multiple treatments have not yet been recorded systematically enough to be able to make valid statements. Data from biologics registries will hopefully provide the first scientific findings in a few years.

Conclusions

With the European approval of mepolizumab as add-on therapy with INCS for the treatment of adults with severe CRSwNP that cannot be adequately controlled with SCS and/or surgical intervention, an IL-5-addressing biologic will be available for the first time for the treatment of CRSwNP since 2021 and will be prescribable and reimbursable in Germany [70]. Mepolizumab represents an important advance in the treatment of CRSwNP and has been much needed for patients with this disease, as it avoids the adverse effects of the previously required use of SCS. With the approvals for omalizumab and dupilumab still available, biologics may open up the possibility of realizing the principle of "personalized medicine" for CRSwNP in the future [33]. AERD is often associated with CRSwNP, asthma, and respiratory hypersensitivity reactions following the use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs). In AERD, eosinophilic inflammation and the type-2 endotype are predominant, making biologics directed against IL-4/IL-13 and IL-5 of high clinical interest. Mepolizumab is very effective especially in CRSwNP patients with AERD. Aspirin therapy after aspirin desensitization (ATAD) is a well-established treatment option in AERD patients with CRSwNP. There are currently no known biomarkers that can predict the patient's response to ATAD or biologic therapy. Comorbidities such as cardiovascular disease or rheumatic diseases may favor a decision for an ATAD while ATAD is not the preferred option when there are absolute or relative contraindications to NSAID, such as a history of peptic ulcer disease, eosinophilic esophagitis (which may also be associated with AERD), renal insufficiency, anticoagulant use, and a history of coagulopathy [71]. These patients have an increased risk of acetylsalicylic acid (ASA)-related side effects, as long-term use of ASA decreases the synthesis of gastric prostaglandin I2 (PGI2) and causes insufficient regeneration of gastric mucosal cells, which can lead to gastric pain or ulceration. Bleeding may also occur as aspirin inhibits platelet function by acetylating cyclooxygenase [72]. Further prerequisites for starting ATAD or biological therapy are given: For ATAD, it is recommended that the patient should have stable/controlled bronchial asthma (FEV_1 > 70%) before starting therapy. The regulatory authorities have not defined any criteria in this regard for biologics.

Since biologics are cost-intensive preparations that in principle require a lifelong duration of therapy, compliance with the economic efficiency requirement of social security statute book (SGB) V § 12 is of particular importance for their use, especially in the German statutory health insurance (SHI) system. The contracting physician must provide the necessary, sufficient, and appropriate services at the lowest possible cost to the health insurance funds [12, 73]. This will always be the case when therapeutic alternatives have already been used unsuccessfully, or are not available due to side effects or, especially in the case of surgery, due to unacceptable burdens or risks [12, 73]. Comparative work now also exists on the cost-effectiveness of NNH surgery *versus* mepolizumab therapy for CRSwNP [74]. However, cost-benefit analyses in the true sense are still lacking. We have commented in detail on the use of the various biologics with approval in the indication area of CRSwNP and have developed documentation forms that enable the applying physician to prescribe with confidence [12, 14, 15].

These have recently been updated and adapted to the current situation [75]. They have also been further developed for an S2k guideline of the AWMF, which will be published shortly and is authoritative for the German-speaking area [10]. In the meantime, several years of experience in the treatment of a large number of patients have been gained, which makes it necessary to give corresponding recommendations for the follow-up documentation in the course of therapy, which are summarized in this position paper. Usually, a response of CRSwNP to treatment with mepolizumab can be expected within 4–6 months. In this case, assuming good tolerability, therapy should be continued unchanged. In case of only a partial response, treatment can also be continued, but re-evaluation is then required after 12 months of therapy at the latest. A combination of biologic treatment with short-term therapy with SCS or surgery is possible, but the greatest possible restraint should be exercised, especially in the use of SCS. The continuation of INCS application together with the biologic is always explicitly recommended, even in the case of clear therapeutic success, since mepolizumab was approved as an add-on therapy to INCS. If therapy success is still insufficient after 12 months, treatment should be discontinued, but a switch to another biologic can be considered. In case of a very good response to therapy with appropriate control of CRSwNP, a pause of

treatment under continued basic therapy with INCS can be considered after several years [76]. However, according to current knowledge, it must rather be assumed that disease control is successively lost again in this case, so close monitoring of the patient and resumption of the previously successful treatment is necessary in case of clinically relevant worsening of symptoms. An extension of the therapy intervals seems medically possible to the authors but currently does not correspond to the approved application intervals, resulting in an off-label use.

Due to the primarily inflammatory pathophysiology of CRSwNP and the disproportionately higher costs of biologics compared with other therapeutic options, it can be assumed that INCS will continue to represent the basic therapeutic agents in the future and that surgical therapies will also remain indispensable. The authors point out that the recommendations given here are consensus recommendations of our group of authors; a sufficient scientific data basis for all recommendations given does not yet exist, but this is expected for the coming years, especially from registry studies. We will therefore continuously adapt these recommendations to the state of the art.

Understanding about the immunologic basis of CRSwNP opens new non-surgical therapeutic approaches with biologics for patients with severe, uncontrolled courses. Mepolizumab is one of the currently three biologics approved for severe CRSwNP in adults that cannot be adequately controlled with systemic glucocorticosteroids and/or surgical intervention. Based on the scientific data and recommendations given, a safe and effective treatment is available if in-label use as an add-on therapy with INCS is assured. Recommendations for special clinical situations including follow-up, adherence to therapy intervals, possible therapy breaks, or discontinuation of therapy are provided based on current available evidence.

Abbreviations

AERD: aspirin-exacerbated respiratory disease

ATAD: aspirin therapy after aspirin desensitization

AWMF: Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften

CRS: chronic rhinosinusitis

CRSwNP: chronic rhinosinusitis with nasal polyps

IgE: immunoglobulin E

IL-5: interleukin-5

INCS: intranasal glucocorticosteroid

mAbs: monoclonal antibodies

NPS: nasal polyps score

NP: nasal polyps

s.c.: subcutaneously

SCS: systemic corticosteroid

SNOT-22: sino-nasal outcome test 22 questionnaire

Th: T helper

VAS: visual analogue score

Declarations

Author contributions

LK, JH, FK, SB, IC, and MC: Writing—review & editing, Writing—original draft. UFR, HO, AGB, AMC, T Huppertz, TKH, SD, TD, SS, HW, WS, HJW, BW, FB, JZ, CR, CAH, OGL, TS, C Bergmann, PW, OP, JG, MG, C

Beutner, ML, RKW, T Hildenbrand, ASH, and C Bachert: Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

B. Wollenberg has received honoraria and/or research funding from MSD, Sanofi, AstraZeneca, Novartis, and BMS Adboard outside of the present work. J. Hagemann states that he has received donations for lectures and fees for advisory boards from the companies Sanofi-Aventis, Novartis Pharma GmbH, and GlaxoSmithKline. A. M. Chaker performs consulting services (e.g., advisory boards, DSMBs), lectures, or other activities through the Technical University of Munich (TUM), or has performed clinical trials or received research funding through TUM from: Allergopharma, ALK-Abelló, AstraZeneca, Bencard/Allergen Therapeutics, GSK, HAL Allergie, Inmunotek, Novartis, Sanofi-Genzyme and Regeneron, Zeller AG, EIT Health, and BMBF. A. M. Chaker is also a functionary of EUFOREA, EAACI, AeDA, and DGAKI. H. Olze received honoraria and/or research grants from F. Hoffmann-La Roche Ltd., Sanofi-Aventis Deutschland GmbH, AstraZeneca GmbH, GlaxoSmithKline GmbH & Co. KG, and Novartis Pharma GmbH. L. Klimek reports grants and/or honoraria from Allergopharma, MEDA/Mylan, HAL Allergie, ALK-Abelló, LETI Pharma, Stallergenes, Quintiles, Sanofi, ASIT Biotech, Lofarma, Allergy Therapeut., AstraZeneca, GSK, and Inmunotek outside the submitted work; and membership in the following organizations: AeDA, DGHNO, German Academy of Allergology and Clinical Immunology, ENT-BV GPA, and EAACI. U. Förster-Ruhrmann received honoraria for lectures from Novartis, AstraZeneca, Sanofi, and GSK outside the present work. S. Strieth reports on grants from the German Research Foundation (DFG), Bonn, grants from the Stiftung Tumorforschung Kopf-Hals, Wiesbaden, grants and non-financial support from MED-EL AG, Innsbruck, personnel fee from Auris Medical, Basel, personnel fee from Merck Serono, Darmstadt, personnel fee Otonomy, Inc., San Diego (USA), personnel honorarium Nordmark Arzneimittel, Uetersen, grant Andreas Fahl Medizintechnik-Vertrieb, Cologne, grant Atos Medical, Troisdorf, grant Tracoe Medical, Nieder-Olm, grants from Heimomed Heinze, Kerpen, grants from Brom epithetik, Heidelberg, grants from Fresenius Kabi, Bad Hersfeld, personnel honorarium from Sanofi-Genzyme, Berlin, and personnel honorarium from ALK-Abelló Arzneimittel, Hamburg, outside the submitted work. M. Cuevas received honoraria and/or nonfinancial support from Novartis, Sanofi-Aventis, Allergopharma, HAL Allergie, LETI Pharma, AstraZeneca, GlaxoSmithKline, ALK-Abelló, Bencard Allergie, Stallergenes, and ROXALL outside of the submitted work and reports memberships with the following organizations: AeDA, DGHNO. A. G. Beule has received honoraria for lectures, consulting, or research activities from Allakos, AstraZeneca, BMS, GSK, Medtronic, MSD, Novartis, Olympus, Pharmalog, Pohl-Boskamp, and Sanofi-Aventis outside of the present work. O. Guntinas-Lichius has received honoraria from MED-EL, Merck, Novartis, MEDICE, and Merz, outside of this work; and he is a member of the following organizations: DGHNO, BVHNO. T. K. Hoffmann participates in honored advisory boards of Merck, MSD, and BMS, but thematically outside the scope of the present work. C. Bachert received honoraria/research grants from Sanofi, GSK, Novartis, AstraZeneca, and ALK outside the present work. H. Wrede reports speaking honoraria from Allergopharma, MEDA/Mylan, HAL Allergie, LETI Pharma, Stallergenes, Sanofi, Lofarma, Allergy Therapeut., GSK, outside the submitted work; and membership in the following organizations: AeDA, ENT-BV. T. Stöver received research and study funds as well as fees for lectures and/or consulting activities from MED-EL Elektromedizinische Geräte Deutschland GmbH and Cochlear Deutschland GmbH & Co. KG, outside the submitted work. There are memberships in the DGHNO-KHC, in the expert committee on medical devices and *in-vitro* diagnostics on behalf of the EU, in the advisory board of the Hörzentrum Oldenburg GmbH, in the task force "Living Practice Guidelines", in the advisory board of the Lower Saxony Center for Biomathematics, as chairman of the advisory board of the Foundation for Hearing and Speech Enhancement Friedberg and as co-editor of the journal *Laryngo-Rhino-Otologie*. C. Beutner reports honoraria from GSK, Sanofi, Novartis, and ALK-Abelló outside this work. M. Laudien supported and received support, speaking and consulting fees in the last 5 years from: Olympus Deutschland GmbH, Olympus Europa SE & CO. KG, Novartis Pharma GmbH, Sanofi-Aventis Deutschland GmbH, Brainlab Sales GmbH, GlaxoSmithKline GmbH & Co. KG, and the John Grube Foundation outside the present work. M. Gröger reports grants and lecture fees from Sanofi,

Novartis, AstraZeneca, and GSK, outside the submitted work. C. Bergmann reports grants and honoraria from GlaxoSmithKline (GSK), Sanofi-Aventis, Bencard Allergy GmbH/Allergy Therapeutics, HAL Allergie GmbH/HAL Allergy Holding B.V. outside this work. O. Pfaar acknowledges honoraria and/or study grants from ALK-Abelló, Altamira, Allergopharma, Stallergenes Greer, HAL Allergy Holding B.V./HAL Allergie, AAAAI, Bencard Allergie/Allergy Therapeutics, Lofarma, Biomay, Circassia, ASIT Biotech Tools S.A., Danish Consultancy, Laboratorios LETI/LETI Pharma, MEDA Pharma/MYLAN, Anergis S.A., Mobile Chamber Experts, Indoor Biotechnologies, GlaxoSmithKline, Astellas Pharma Global, EUFOREA, ROXALL, Novartis, Sanofi-Aventis and Sanofi-Genzyme, Med Update Europe, STREAMED UP, Pohl-Boskamp, Inmunotek S.L., Wiley and Sons, Paul Martini Foundation, Regeneron Pharmaceuticals Inc., RG Ärztefortbildung, Firma Meinhardt, PneumoLive, Institut für Disease Management, Deutsche Forschungsgesellschaft, Springer, Thieme, AstraZeneca, Deutsche Allergie-Liga, AeDA, IQVIA Commercial, Ingress Health, Wort & Bild Verlag, Verlag ME, Procter & Gamble, Alfried Krupp Krankenhaus, all outside the scope of this position paper; and he is a member of the Board/Excom of EAACI and a member of the Extended Board of DGAKI. Furthermore, he is the main author or co-author of various guideline and position papers in allergology and rhinology. A. S. Hoffmann received honoraria from GSK, Sanofi, and Novartis for lectures and advisory boards outside of this work. T. Hildenbrand reports on lecture fees from AstraZeneca and Novartis outside of this work. R. Weber has received honoraria for lecturing and consulting activities from GSK, InfectoPharm, KARL STORZ SE & Co. KG, NMP, Sanofi, Sidroga-Pharma, and Stryker. The other authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

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Availability of data and materials

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References

1. Agache I, Song Y, Alonso-Coello P, Vogel Y, Rocha C, Solà I, et al. Efficacy and safety of treatment with biologicals for severe chronic rhinosinusitis with nasal polyps: a systematic review for the EAACI guidelines. Allergy. 2021;76:2337–53.
2. Ren L, Zhang N, Zhang L, Bachert C. Biologics for the treatment of chronic rhinosinusitis with nasal polyps - state of the art. World Allergy Organ J. 2019;12:100050.
3. Tomassen P, Vandeplas G, Van Zele T, Cardell LO, Arebro J, Olze H, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. J Allergy Clin Immunol. 2016;137: 1449–56.E4.
4. Chaaban MR, Walsh EM, Woodworth BA. Epidemiology and differential diagnosis of nasal polyps. Am J Rhinol Allergy. 2013;27:473–8.

5. Staudacher AG, Peters AT, Kato A, Stevens WW. Use of endotypes, phenotypes, and inflammatory markers to guide treatment decisions in chronic rhinosinusitis. Ann Allergy Asthma Immunol. 2020; 124:318–25.
6. Bachert C, Han JK, Wagenmann M, Hosemann W, Lee SE, Backer V, et al. EUFOREA expert board meeting on uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) and biologics: definitions and management. J Allergy Clin Immunol. 2020;147:29–36. Erratum in: J Allergy Clin Immunol. 2021;147:1981–2.
7. 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.
8. Hellings PW, Fokkens WJ, Bachert C, Akdis CA, Bieber T, Agache I, et al.; ARIA and EPOS working groups. Positioning the principles of precision medicine in care pathways for allergic rhinitis and chronic rhinosinusitis – a EUFOREA-ARIA-EPOS-AIRWAYS ICP statement. Allergy. 2017;72:1297–305.
9. Stuck BA, Beule A, Jobst D, Klimek L, Laudien M, Lell M, et al. Guideline for "rhinosinusitis"—long version. HNO. 2018;66:38–74. German. Erratum in: HNO. 2019;67:561–2.
10. Pfaar O, Beule AG, Laudien M, Stuck BA, erweiterte Leitliniengruppe, Biologika bei CRScNP. Treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) with monoclonal antibodies (biologics): S2k guideline of the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), and the German College of General Practitioners and Family Physicians (DEGAM). HNO. 2023;71: 256–63. German.
11. Klimek L, Beule AG, Förster-Ruhrmann U, Becker S, Chaker A, Huppertz T, et al. Positionspapier: hinweise zur patienteninformation und -aufklärung vor anwendung von biologika bei chronischer rhinosinusitis mit polyposis nasi (CRSwNP) – empfehlungen des Ärzteverbandes Deutscher Allergologen (AeDA) und der Deutschen Gesellschaft für HNO-Heilkunde, Kopf- und Halschirurgie (DGHNOKHC) – teil 1: dupilumab. Laryngorhinootologie. 2020;99:761–6. German.
12. Klimek L, Förster-Ruhrmann U, Becker S, Chaker A, Strieth S, Hoffmann TK, et al. Positionspapier: anwendung von biologika bei chronischer rhinosinusitis mit polyposis nasi (CRSwNP) im Deutschen gesundheitssystem – empfehlungen des Ärzteverbandes Deutscher Allergologen (AeDA) und der AGs Klinische Immunologie, Allergologie und Umweltmedizin und Rhinologie und Rhinochirurgie der Deutschen Gesellschaft für HNO-Heilkunde, Kopf- und Halschirurgie (DGHNOKHC). Laryngorhinootologie. 2020;99:511–27. German.
13. Förster-Ruhrmann U, Beule AG, Becker S, Chaker AM, Huppertz T, Hagemann J, et al. Positionspapier: hinweise zur patienteninformation und -aufklärung vor anwendung von biologika bei chronischer rhinosinusitis mit nasenpolypen (CRSwNP) – teil 2: omalizumab – empfehlungen des Ärzteverbandes Deutscher Allergologen (AeDA) und der Deutschen Gesellschaft für HNO-Heilkunde, Kopf- und Halschirurgie (DGHNOKHC). Laryngorhinootologie. 2021;100:864–72. German.
14. Klimek L, Förster-Ruhrmann U, Beule AG, Chaker AM, Hagemann J, Huppertz T, et al. Positionspapier: empfehlungen zur anwendung von omalizumab bei chronischer rhinosinusitis mit polyposis nasi (CRSwNP) im Deutschen gesundheitssystem – empfehlungen des Ärzteverbandes Deutscher Allergologen (AeDA) und der AGs Klinische Immunologie, Allergologie und Umweltmedizin und Rhinologie und Rhinochirurgie der Deutschen Gesellschaft für HNO-Heilkunde, Kopf- und Halschirurgie (DGHNOKHC). Laryngorhinootologie. 2021;100:952–63. German.
15. Klimek L, Förster-Ruhrmann U, Beule AG, Chaker AM, Hagemann J, Huppertz T, et al. Positionspapier: empfehlungen zur anwendung von mepolizumab bei chronischer rhinosinusitis mit polyposis nasi (CRSwNP) im Deutschen gesundheitssystem - empfehlungen des Ärzteverbandes Deutscher Allergologen (AeDA) und der AGs Klinische Immunologie, Allergologie und Umweltmedizin und Rhinologie und Rhinochirurgie der Deutschen Gesellschaft für HNO-Heilkunde, Kopf- und Halschirurgie (DGHNOKHC). Laryngorhinootologie. 2022;101:284–94. German.

16. Klimek L, Becker S, Buhl R, Chaker AM, Huppertz T, Hoffmann TK, et al. Positionspapier: empfehlungen zur behandlung der chronischen rhinosinusitis während der COVID-19-pandemie im Deutschen gesundheitssystem – empfehlungen des Ärzteverbandes Deutscher Allergologen (AeDA) und der Deutschen Gesellschaft für HNO-Heilkunde, Kopf- und Halschirurgie (DGHNO-KHC) – diese empfehlungen basieren auf dem EAACI positionspapier "treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) in the COVID-19 pandemics – an EAACI position paper", Allergy, 2020 und wurden auf die situation im Deutschen gesundheitswesen angepasst. Laryngorhinootologie. 2020;99: 356–64. German.
17. Kim J, Naclerio R. Therapeutic potential of dupilumab in the treatment of chronic rhinosinusitis with nasal polyps: evidence to date. Ther Clin Risk Manag. 2020;16:31–7.
18. Lange B, Holst R, Thilsing T, Baelum J, Kjeldsen A. Quality of life and associated factors in persons with chronic rhinosinusitis in the general population: a prospective questionnaire and clinical cross-sectional study. Clin Otolaryngol. 2013;38:474–80.
19. Wynn R, Har-El G. Recurrence rates after endoscopic sinus surgery for massive sinus polyposis. Laryngoscope. 2004;114:811–3.
20. Hox V, Delrue S, Scheers H, Adams E, Keirsbilck S, Jorissen M, et al. Negative impact of occupational exposure on surgical outcome in patients with rhinosinusitis. Allergy. 2012;67:560–5.
21. Passali D, Cingi C, Cambi J, Passali F, Muluk NB, Bellussi ML. A survey on chronic rhinosinusitis: opinions from experts of 50 countries. Eur Arch Otorhinolaryngol. 2016;273:2097–109.
22. Stevens WW, Schleimer RP, Kern RC. Chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol Pract. 2016;4:565–72.
23. 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. 2018;57:32–42.
24. Vlaminck S, Vauterin T, Hellings PW, Jorissen M, Acke F, Van Cauwenberge P, et al. The importance of local eosinophilia in the surgical outcome of chronic rhinosinusitis: a 3-year prospective observational study. Am J Rhinol Allergy. 2014;28:260–4.
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. 2016;127: 550–5.
26. Rosati D, Rosato C, Pagliuca G, Cerbelli B, Della Rocca C, Di Cristofano C, et al. Predictive markers of long-term recurrence in chronic rhinosinusitis with nasal polyps. Am J Otolaryngol. 2019;41:102286.
27. Loftus CA, Soler ZM, Koochakzadeh S, Desiato VM, Yoo F, Nguyen SA, et al. Revision surgery rates in chronic rhinosinusitis with nasal polyps: meta-analysis of risk factors. Int Forum Allergy Rhinol. 2019; 10:199–207.
28. McHugh T, Snidvongs K, Xie M, Banglawala S, Sommer D. High tissue eosinophilia as a marker to predict recurrence for eosinophilic chronic rhinosinusitis: a systematic review and meta-analysis. Int Forum Allergy Rhinol. 2018;8:1421–9.
29. Stevens WW, Peters AT, Hirsch AG, Nordberg CM, Schwartz BS, Mercer DG, et al. Clinical characteristics of patients with chronic rhinosinusitis with nasal polyps, asthma, and aspirin-exacerbated respiratory disease. J Allergy Clin Immunol Pract. 2017;5:1061–70.E3.
30. Klossek JM, Neukirch F, Pribil C, Jankowski R, Serrano E, Chanal I, et al. Prevalence of nasal polyposis in France: a cross-sectional, case–control study. Allergy. 2005;60:233–7.
31. Philpott CM, Erskine S, Hopkins C, Kumar N, Anari S, Kara N, et al.; CRES group; Erskine S, Philpott C, Clark A, Hopkins C, Robertson A, Ahmed S, et al. Prevalence of asthma, aspirin sensitivity and allergy in chronic rhinosinusitis: data from the UK National Chronic Rhinosinusitis Epidemiology study. Respir Res. 2018;19:129.

32. Seybt MW, McMains KC, Kountakis SE. The prevalence and effect of asthma on adults with chronic rhinosinusitis. Ear Nose Throat J. 2007;86:409–11.
33. Gevaert P, Omachi TA, Corren J, Mullol J, Han J, Lee SE, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. J Allergy Clin Immunol. 2020;146:595–605. Erratum in: J Allergy Clin Immunol. 2021;147:416.
34. Dalal AA, Duh MS, Gozalo L, Robitaille MN, Albers F, Yancey S, et al. Dose-response relationship between long-term systemic corticosteroid use and related complications in patients with severe asthma. J Manag Care Spec Pharm. 2016;22:833–47.
35. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al.; MENSA Investigators. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371: 1198–207. Erratum in: N Engl J Med. 2015;372:1777.
36. Lipworth B, Chan R, Misirovs R, Stewart K. Mepolizumab response in severe chronic rhinosinusitis with nasal polyps is dissociated from blood eosinophil levels. J Allergy Clin Immunol. 2022;149:1817.
37. Radabaugh JP, Han JK, Moebus RG, Somers E, Lam K. Analysis of histopathological endotyping for chronic rhinosinusitis phenotypes based on comorbid asthma and allergic rhinitis. Am J Rhinol Allergy. 2019;33:507–12.
38. Schleimer RP. Immunopathogenesis of chronic rhinosinusitis and nasal polyposis. Annu Rev Pathol. 2016;12:331–57.
39. Hulse KE. Immune mechanisms of chronic rhinosinusitis. Curr Allergy Asthma Rep. 2016;16:1.
40. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet. 2017;389:2287–303.
41. Busse WW, Maspero JF, Rabe KF, Papi A, Wenzel SE, Ford LB, et al. Liberty asthma QUEST: phase 3 randomized, double-blind, placebo-controlled, parallel-group study to evaluate dupilumab efficacy/ safety in patients with uncontrolled, moderate-to-severe asthma. Adv Ther. 2018;35:737–48.
42. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med. 2018;378:2486–96.
43. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med. 2018;378:2475–85.
44. Smith DA, Minthorn EA, Beerahee M. Pharmacokinetics and pharmacodynamics of mepolizumab, an anti-interleukin-5 monoclonal antibody. Clin Pharmacokinet. 2011;50:215–27.
45. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012;380: 651–9.
46. Fala L. Nucala (mepolizumab): first IL-5 antagonist monoclonal antibody FDA approved for maintenance treatment of patients with severe asthma. Am Health Drug Benefits. 2016;9:106–10.
47. Keating GM. Mepolizumab: first global approval. Drugs. 2015;75:2163–9.
48. Emma R, Morjaria JB, Fuochi V, Polosa R, Caruso M. Mepolizumab in the management of severe eosinophilic asthma in adults: current evidence and practical experience. Ther Adv Respir Dis. 2018; 12:1753466618808490.
49. Schwaab J, Lübke J, Reiter A, Metzgeroth G. Idiopathic hypereosinophilic syndrome—diagnosis and treatment. Allergo J Int. 2022;31:251–6.
50. Highlights of prescribing information [Internet]. GlaxoSmithKline; [cited 2022 Mar 11]. Available from: https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL-IFU-COMBINED.PDF

51. Annex I: summary of product characteristics [Internet]. GlaxoSmithKline; [cited 2022 Mar 11]. Available from: https://www.ema.europa.eu/en/documents/product-information/nucala-epar-product-information_en.pdf
52. Effect of mepolizumab in severe bilateral nasal polyps [Internet]. GlaxoSmithKline; [cited 2022 Mar 11]. Available from: https://clinicaltrials.gov/ct2/show/NCT03085797
53. Han JK, Bachert C, Fokkens W, Desrosiers M, Wagenmann M, Lee SE, et al.; SYNAPSE study investigators. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021;9:1141–53.
54. Pavord ID, Chanez P, Criner GJ, Kerstjens HAM, Korn S, Lugogo N, et al. Mepolizumab for eosinophilic chronic obstructive pulmonary disease. N Engl J Med. 2017;377:1613–29.
55. Bachert C, Sousa AR, Han JK, Schlosser RJ, Sowerby LJ, Hopkins C, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps: treatment efficacy by comorbidity and blood eosinophil count. J Allergy Clin Immunol. 2022;149:1711–21.E6.
56. Gleich GJ, Roufosse F, Chupp G, Faguer S, Walz B, Reiter A, et al.; HES Mepolizumab Study Group. Safety and efficacy of mepolizumab in hypereosinophilic syndrome: an open-label extension Study. J Allergy Clin Immunol Pract. 2021;9:4431–40.E1.
57. Khatri S, Moore W, Gibson PG, Leigh R, Bourdin A, Maspero J, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. J Allergy Clin Immunol. 2018;143:1742–51.E7.
58. Stein ML, Collins MH, Villanueva JM, Kushner JP, Putnam PE, Buckmeier BK, et al. Anti–IL-5 (mepolizumab) therapy for eosinophilic esophagitis. J Allergy Clin Immunol. 2006;118:1312–9.
59. Wechsler ME, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA, et al.; EGPA Mepolizumab Study Team. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. N Engl J Med. 2017; 376:1921–32.
60. Leung E, Al Efraij K, FitzGerald JM. The safety of mepolizumab for the treatment of asthma. Expert Opin Drug Saf. 2017;16:397–404. Erratum in: Expert Opin Drug Saf. 2017;16:421.
61. Highlights of prescribing information [Internet]. GlaxoSmithKline; [cited 2022 Nov 24]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761122s006,125526s018lbl.pdf
62. Nucala - gebrauchsinformation für anwender - 100 mg injektionslösung im fertigpen [Internet]. GlaxoSmithKline; [cited 2022 Nov 24]. Available from: https://gskpro.com/content/dam/global/hcpportal/de_DE/produktinformationen/nucala/GI_Nucala_Fertigpen_102022.pdf
63. Gallo S, Castelnuovo P, Spirito L, Feduzi M, Seccia V, Visca D, et al. Mepolizumab improves outcomes of chronic rhinosinusitis with nasal polyps in severe asthmatic patients: a multicentric real-life study. J Pers Med. 2022;12:1304.
64. Fachinformation: nucala 100 mg injektionslösung im fertigpen/in einer fertigspritze; nucala 40 mg injektionslösung in einer fertigspritze [Internet]. GlaxoSmithKline; [cited 2022 Nov 24]. Available from: https://gskpro.com/content/dam/global/hcpportal/de_DE/produktinformationen/nucala/FI_Nucala_Injektionsl%C3%B6sung_im_Fertigpen_in_einer_Fertigspritze_100%20mg_40%20mg_102022.pdf
65. Doty RL, Shaman P, Kimmelman CP, Dann MS. University of Pennsylvania smell identification test: a rapid quantitative olfactory function test for the clinic. Laryngoscope. 1984;94:176–8.
66. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' Sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Senses. 1997;22:39–52.
67. Oleszkiewicz A, Schriever VA, Croy I, Hähner A, Hummel T. Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. Eur Arch Otorhinolaryngol. 2018;276:719–28.
68. Whitcroft KL, Cuevas M, Haehner A, Hummel T. Patterns of olfactory impairment reflect underlying disease etiology. Laryngoscope. 2017;127:291–5.

69. Lommatzsch M, Suhling H, Korn S, Bergmann KC, Schreiber J, Bahmer T, et al. Safety of combining biologics in severe asthma: asthma-related and unrelated combinations. Allergy. 2022;77:2839–43.
70. Tragende gründe: zum beschlussdes Gemeinsamen Bundesausschusses über eine änderung der arzneimittel-richtlinie: anlage XII – nutzenbewertung von arzneimitteln mit neuen wirkstoffen nach § 35a des fünften buches sozialgesetzbuch (SGB V) mepolizumab (neues anwendungsgebiet: chronische rhinosinusitis mit nasenpolypen) [Internet]. Berlin: Gemeinsamen Bundesausschusses; [cited 2022 My 19]. Available from: https://www.g-ba.de/downloads/40-268-8516/2022-05-19_AM-RL-XII_Mepolizumab_D-746_TrG.pdf
71. Klimek L, Dollner R, Pfaar O, Mullol J. Aspirin desensitization: useful treatment for chronic rhinosinusitis with nasal polyps (CRSwNP) in aspirin-exacerbated respiratory disease (AERD)? Curr Allergy Asthma Rep. 2014;14:441.
72. Klimek L, Pfaar O. Aspirin intolerance: Does desensitization alter the course of the disease? Immunol Allergy Clin North Am. 2009;29:669–75.
73. Koennecke M, Klimek L, Mullol J, Gevaert P, Wollenberg B. Subtyping of polyposis nasi: phenotypes, endotypes and comorbidities. Allergo J Int. 2018;27:56–65.
74. Codispoti CD, Mahdavinia M. A call for cost-effectiveness analysis for biologic therapies in chronic rhinosinusitis with nasal polyps. Ann Allergy Asthma Immunol. 2019;123:232–9.
75. Klimek L, Förster-Ruhrmann U, Beule AG, Chaker AM, Hagemann J, Klimek F, et al. Indicating biologics for chronic rhinosinusitis with nasal polyps (CRSwNP). Allergo J Int. 2022;31:149–60.
76. van der Lans RJL, Fokkens WJ, Adriaensen GFJPM, Hoven DR, Drubbel JJ, Reitsma S. Real-life observational cohort verifies high efficacy of dupilumab for chronic rhinosinusitis with nasal polyps. Allergy. 2021;77:670–4.