Eosinophilic asthma with chronic rhinosinusitis/nasal polyps and biologic agents

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ABSTRACT

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The current understanding in severe asthma management is the targeted therapy approach with the evaluation of phenotypes and biomarkers. Therefore, personalized treatments are recently more prominent. Eosinophilic asthma with chronic rhinosinusitis/nasal polyps (CRSwNP) is one of the severe asthma phenotypes which needs a personalized treatment approach. Biological agents which specifically target type 2 (T2) high inflammation have been used in this severe asthma phenotype with a preferable safety profile. In the present review, biological agents in eosinophilic asthma with CRSwNP will be discussed.

Key words: *Severe asthma; eosinophilic asthma; chronic rhinosinusitis/nasal polyp; asthma phenotype; biologics*

ÖZ

Kronik sinüzit/nazal polipli eozinofilik astım ve biyolojikler

Ağır astımda hastalık yönetimi için yeni anlayış fenotip ve biyolojik belirteçlerin kullanılarak hedefe yönelik tedavilerin kullanılmasıdır. Bu nedenle günümüzde kişiselleştirilmiş tedaviler ön plana çıkmaktadır. Kronik rinosinüzit/nazal polipli (CRSwNP) eozinofilik astım da kişiselleştirilmiş tedavi gerektiren ağır astım fenotiplerinden birisidir. Bu ağır astım fenotipinde tip 2 (T2) high inflamasyonu spesifik bir şekilde hedefleyen ve güvenlik profilleri çok iyi olan biyolojik ajanlar kullanılmaya başlanmıştır. Bu derlemede CRSwNP'li ağır eozinofilik astımda kullanılma potansiyeli olan biyolojik tedaviler ele alınacaktır.

Anahtar kelimeler: *Ağır astım; eozinofilik astım; kronik rinosinüzit/nazal polip; astım fenotip; biyolojikler*

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Asthma patients who are not undercontrol despite treatment with high dose inhaled corticosteroid (ICS) and long-acting β2 agonist (LABA) in GINA step 5, need specific asthma management. As the first-line treatment in severe asthma, GINA the recommends addi-

tion of biologics (for T2 high asthma) and/or long-acting muscarinic antagonists to an ICS + LABA combination. Low dose oral corticosteroid (OCS) usage is recommended as "optional controller therapy" for the prevention of asthma attacks and maintaining asthma control in GINA step 5 (1,2). The controller options for patients who have uncontrolled severe eosinophilic asthma with CRSwNP despite GINA step 5 treatment are firstly biologic agents and then low dose OCS.

Chronic rhinosinusitis (CRS) affects 5%-12% of the general population. The prevalence of CRSwNP is between 1.1% and 4.3% (3). Asthma affects 30%-70% of CRSwNP patients. The presence of CRSwNP is associated with the severity of asthma, ranging from 10%-30% in mild asthma to 70%-90% in severe asthma (4,5). CRSwNP in approximately 85% represents a T2 inflammation (6). CRS and/or nasal polyps are frequently accompanying late-onset severe asthma and the management of this phenotype is quite complex.

Recently, biologic agents are considered preferable rather than low dose OCS in the management of uncontrolled severe eosinophilic asthma with CRSwNP, due to long term serious adverse effects of OCS. In this review, eosinophilic asthma with CRSwNP and suitable biologic agents for the treatment of this specific phenotype will be discussed (Figure 1).

Definations

Severe asthma: By this is meant that is uncontrolled despite adherence to maximal optimized therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased (1).

Chronic rhinosinusitis: All CRS subjects met the criteria for CRS as defined by the American Academy of Otolaryngology-Head and Neck Surgery Chronic Rhinosinusitis Task Force; the diagnosis of CRS was based on the presence of clinical symptoms (i.e., nasal congestion, rhinorrhea, facial pressure, hyposmia) per-
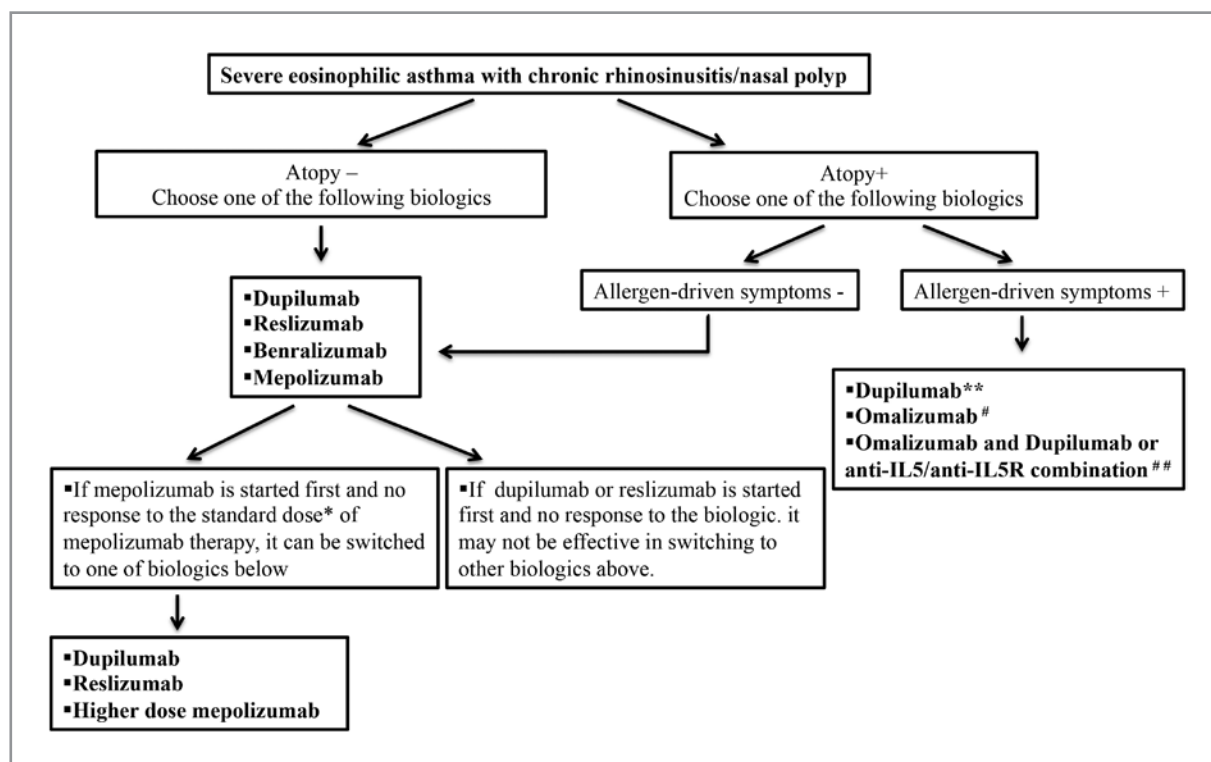

Figure 1. Decision tree for the biologic treatment of the severe eosinophilic asthma with chronic rhinosinusitis/nasal polyp
Abbreviations used: Ig: Immunoglobulin; SC: Subcutaneous; IL: Interleukin; IV: Intravenous; FeNO: Fractional exhaled nitric oxide; mg: Miligram; ppb: Parts per billion.
* 100 mg/month, SC.
** First option for patients who have also atopic dermatitis and high FeNO levels (≥ 25 ppb).
# If patient's atopy status is really appropriate, given the clinical history (childhood allergic asthma, comorbidities such as allergic rhinitis, and respiratory symptoms with exposure to aeroallergens) and patient has high FeNO levels (≥ 20 ppb).
Cost-effectiveness?

sisting for more than 12 weeks in addition to objective evidence of chronic inflammatory disease on paranasal sinus computed tomography (PNCT) imaging or nasal endoscopy (7).

CRSwNP: CRSwNP is characterized by the occurrence for more than 12 weeks of symptoms such as nasal discharge, stuffiness, facial pressure or pain, dysfunction or loss of the sense of smell, and cough from post-nasal drip. It is also characterized the polypoid inflammation filling the nasal cavity in the PNCT (8).

Blood and sputum eosinophilia: Although an established clear threshold for eosinophilic lower airway inflammation still does not exist, it is generally described based on blood or sputum eosinophil levels (9,10). Persistent eosinophilic airway inflammation is one of the best known distinctive disease patterns in asthma and is reflected with the eosinophil number of a minimum of 150-300 cells per µL in blood and/or more than 2-3% in sputum (11-15). In fact, blood and sputum eosinophil counts correlate, but blood eosinophil counts are not a stronger indicator of eosinophil counts in the sputum or airway wall (16,17). Although the blood eosinophil count is not a very strong indicator of airway eosinophilia, due to the easy testing method it is still being used in clinical studies (18). The current consensus is that in patients with asthma, a blood eosinophil count of greater than 150 cells/µL is a good indicator of T2 inflammation and diagnosis of eosinophilic asthma (19).

Asthma Phenotypes and Eosinophilic Asthma with CRSwNP

Recently, studies on asthma phenotypes and endotypes have been increasing. There is an evolution in asthma classification from simple subtyping, like intrinsic and extrinsic, towards phenotyping which is defined by clinical, laboratory, functional and inflammatory characteristics of the disease and response to treatment. It is now more important to understand asthma phenotypes as there is a new targeted treatment approach with the discovery of new biological agents that were developed for the treatment of underlying inflammation of asthma (20).

Asthma can be arranged into phenotypes according to its clinical and/or observable features. Triggers (allergens or aspirin hypersensitivity), inflammatory cells (eosinophilic, neutrophilic, paucigranulocytic) and comorbid nasal polyposis existence can be given as an example (21-24). Recently, cluster analysis has been used for phenotyping to define more objective criterias and abstain from bias (25-28). Asthma was classifed into 5 phenotypes as below in SARP (Severe Asthma Research Program) which is one of following cluster phenotyping programs: Mild early-onset allergic disease; Moderate early-onset allergic disease; Late-onset eosinophilic nonallergic disease; Severe early-onset eosinophilic allergic disease; Late-onset nonallergic neutrophilic severe asthma with fixed airflow (25). Another characteristic feature of the SARP Cluster 4 late-onset eosinophilic asthma is comorbid chronic rhinosinusitis with nasal polyposis, a feature known for many years and in some cases linked with aspirin and other NSAID hypersensitivity (29,30).

The phenotyping according to inflammation type is closer to asthma pathophysiology, but the underlying mechanism of this inflammation should also be evaluated. For example, in the eosinophilic asthma phenotype, if the main pathway of this inflammation can be determined and correlated with the patient's clinic then we can mention asthma endotypes. The endotype is defined by the correlation of heterogen asthma phenotypes with cellular, molecular, immunological and pathopysological mechanisms (such as atopic asthma with eosinophilia [Th2-mast cell-eosinophilia] or asthma with CRSwNP and eosinophilia [ILC2-IL4/IL5/IL13-eosinophilia], etc. Endotypes can provide more information about "precision medicine" and "personalized medicine" inlight of asthma pathophysiology (21,31,32). Eosinophilic asthma with CRSwNP has increased with the recognition that in this eosinophilic asthma subtype, high levels of the pro-eosinophilic cytokine IL-5 are produced by a unique population of T2 innate lymphoid cells (33). The main mechanisms are dysregulation of leukotriene synthesis, *Staphylococcus aureus* enterotoxin-specific IgE and chronic epithelial activation by agents such as superantigens and environmental pollutants, as well as by epithelium-derived innate cytokines (TSLP, IL-25, and IL-33), which stimulates type-2 innate lymphoid cell activation and overproduction of IL-5 (33-37). IL-4 and IL-13 are responsible for relasing chemokine eotaxin that causes the increase of vascular cell adhesion molecule-1 (VCAM-1) expression on the vascular system and enhances eosinophil migration to airway cells, play a role in asthma immunopathobiology (38-42). Hence, eosinophilic asthma with CRSwNP which is related to underlying T2 high inflammation pathways with clinical inflammatory phenotypes is both asthma endotype and asthma phenotype.

Eosinophilic Asthma with CRSwNP and Anti-IL5/Anti-IL5R

In patients with adult-onset asthma, those with high eosinophil counts were more likely to have a greater FENO values, have more sputum eosinophils, be taking oral steroids, have fixed obstruction, have worse lung function, and have a history of chronic rhinosinusitis and nasal polyposis (14,43,44). Both severe eosinophilic asthma and nasal polyposis are characterized by prominent local eosinophilic inflammation (45). IL-5 has an important role in nasal polyp pathogenesis. A nasal polyp is related to the increasing expresssion of IL-5 (45-47). The expression of IL-5 within nasal polyp tissue has been associated with asthma comorbidity (48). Thus, anti-IL5/anti-IL5R mAbs seem to be suitable in the treatment of this phenotype.

In fact, the clinical efficacy of the anti-IL5/anti-IL5R mAbs (mepolizumab, reslizumab, benralizumab) has been reasonably consistent between studies and it is likely that the biologics have very similar effects on eosinophilic severe asthma (49-52). However, this asthma phenotype also has subtypes, like severe eosinophilic asthma with CRSwNP. We also should consider the possibility of different anti-IL5/anti-IL5R treatment responses within all different subtypes. Recent studies have demonstrated that targeting the IL-5 pathway may be efficacious in the treatment of asthma in a subgroup of patients with severe eosinophilic asthma with comorbid CRS (53-55). One of these studies, in a meta-analysis of DREAM and MENSA, assessed the efficacy of mepolizumab versus placebo in patients with severe eosinophlic asthma with or without nasal polyps at baseline. Data from both studies were combined using an inverse-variance weighted fixed-effects meta-analysis. Data are presented for combined 75 mg intravenous and 100 mg subcutaneous mepolizumab doses. A total of 884 patients were included in this analysis, of whom 120 (14%) had nasal polyps at baseline. Patients with nasal polyps had higher blood eosinophil counts at baseline than patients without nasal polyps. The reduction in exacerbations with mepolizumab compared with placebo was 59% for patients with nasal polyps and 48% for patients without nasal polyps. Mepolizumab improved ACQ-5, SGRQ, pre-bronchodilator and post-bronchodilator FEV$_1$ versus placebo in both groups, with larger point estimates in the nasal polyps group (53). In another study, a subphenotype which got more benefits from mepolizumab regarding asthma exacerbation reduction was defined. A supervised cluster analysis to determine which patients would benefit most from mepolizumab found

4 clusters. Cluster 2, which had patients with a history of nasal polyps and sinusitis, had a 53% reduction in exacerbations, whereas cluster 4 patients with obesity and high airway reversibility had a 67% reduction in exacerbations (56). The effect of benralizumab on this subphenotype was also assesed. A study showed that, compared with placebo, benralizumab reduced exacerbation rates by 42% for all patients, by 54% for patients with nasal polyps, and by 38% for patients without nasal polyps; and increased prebronchodilator FEV$_1$ by 0.128 L for all patients, by 0.272 L for patients with nasal polyps, and by 0.102 L for those without nasal polyps in the post-hoc pooled analysis of the Phase III SIROCCO and CALIMA trials. Similar trends were observed for efficacy measures of asthma symptoms and asthma-related quality of life. Benralizumab demonstrated enhanced clinical efficacy for patients with severe, uncontrolled eosinophilic asthma and nasal polyps (57). The efficacy of reslizumab on this subphenotype has been demonstrated in two studies. Reslizumab for the treatment of patients with severe, refractory, eosinophilic asthma was effective in improving lung function and trended toward greater asthma control, especially in patients with nasal polyps (58). In another study, in the post hoc analyses of pooled data from 2 BREATH phase 3 clinical trials, asthma-related outcomes in patients with comorbid, self-reported CRSwNP were examined. Add-on reslizumab treatment reduced the frequency of clinical asthma exacerbations by 83% versus placebo among patients with CRSwNP. Patients with CRSwNP treated with reslizumab add-on therapy also had significant improvements in lung function, as measured by forced expiratory volume in 1 second, compared with the placebo. Among patients with CRSwNP, reslizumab was also associated with improvements in patient-reported asthma control and asthma quality of life. Patients with eosinophilic asthma and self-reported CRSwNP are highly responsive to treatment with reslizumab for asthma-related outcomes. These findings suggest that a prospective investigation of reslizumab in this patient population is warranted (55). Although these three biological agents (mepolizumab, benralizumab, reslizumab) have a similar effect on eosinophilic asthma with CSRwNP phenotype, reslizumab seems more effective than the others. We believe, in severe eosinophilic asthma with CRSwNP, reslizumab (anti-IL5) could be an alternative treatment option in patients that were unresponsive to mepolizumab. We speculate that the mepolizumab treatment dose might be insufficient to suppress the tissue eosinophilia in these cases and reslizumab might be an alternative treatment option

due to its dose adjusted according to the patient's weight. Also, mepolizumab has been shown to be an effective treatment for nasal polyposis. In this study, the dosage of the given drug was 750 mg, higher than the asthma indication (59). Based on this evidence, increasing the drug dose of mepolizumab before discontinuation might also be an alternative option in this group of asthma patients. However, there is a need for studies that evaluate the comparative effects of mepolizumab 100 mg and 750 mg on this phenotype. In addition, we need high-quality evidence and comparative real-life studies of these biological agents (mepolizumab, reslizumab, benralizumab) to prove this hypothesis in patients with severe eosinophilic asthma with CRSwNP.

Eosinophilic Asthma with CRSwNP and Anti-IL4α

Dupilumab (anti-IL4α) also was considered and discussed as an alternative treatment option in patients with severe eosinophilic asthma with CRSwNP. Targeting the common subunit of the IL-4 and IL-13 receptors has the advantage of blocking multiple other pathways. Although a high blood eosinophil level is still a predictor of response, other predictors, including high FeNO levels, oral steroid dependence, and presence of Type2 comorbidities such as atopic dermatitis and nasal polyposis, may also influence the choice of this biologic" (41). Patients with asthma and comorbid CRS may gain additional benefits from dupilumab treatment as it targets type 2 inflammation associated with these comorbid conditions (42). In a study, Dupilumab 200 mg/300 mg reduced annualized severe exacerbation rates by 63%/61%, respectively, in patients with CRS, and by 42%/40% in patients without CRS (all p< 0.001 vs. placebo) (42). With dupilumab treatment, the magnitude of reductions in severe asthma exacerbations and the improvement in FEV_1 from baseline was greater in the CRS subgroup than the in non-CRS subgroup. This greater reduction may be due to the simultaneous symptom control of type 2 mediated inflammation of both upper and lower airways by dupilumab leading to improvements in both CRS and asthma outcome measures (42). The findings reported here support and extend the data obtained from a previously published proof-of-concept, phase 2, randomized, placebo-controlled study of dupilumab in patients with CRS and NP (60). Adding dupilumab 300 mg q2w to intranasal corticosteroid therapy significantly reduced the burden of NP while improving FEV_1 and asthma control, as well as a sense of smell, sinus computed tomography scans, and quality of life in patients with CRS, NP, and

comorbid asthma. Phase 3 studies of dupilumab in CRS and NP have recently been completed, confirming and extending these positive results (61,62).

Eosinophilic Asthma with CRSwNP and Anti-IgE

There are some difficulties in the management of asthma with nasal polyp. Both conditions have similarities like airway eosinophilia, local IgE production and Th2 cytokine profile. Therefore, some studies to evaluate the effect of anti-IgE mAb, omalizumab, in this phenotype have been conducted. In one of these studies, omalizumab has been shown to have positive effects on asthma symptoms and quality of life. However, the primary end point of this study was the reduction in total nasal endoscopic polyp scores after 16 weeks. Secondary end points included a change in sinus computed tomographic scans, nasal and asthma symptoms. There was a significant decrease in total nasal endoscopic polyp scores after 16 weeks in the omalizumab-treated group. Omalizumab had a beneficial effect on airway symptoms (nasal congestion, anterior rhinorrhea, loss of sense of smell, wheezing, and dyspnea) and on quality-of-life scores, irrespective of the presence of allergy. Although omalizumab showed an improvement on asthma symptoms and quality of life in one of the studies, there is not enough evidence to conclude about omalizumab's effect on this subphenotype due to some limitations such as low patient numbers, high drop out ratio in placebo arm, and the evaluation of nasal polyp was the primary endpoint (63).

Asthma symptoms, the number of salbutamol rescue/week, the number of moderate/severe exacerbations, ACT score, and pulmonary function were significantly improved by the omalizumab in a retrospective, observational, multicentric real-life study evaluating the efficacy of omalizumab in CRSwNP eosinophilic asthma phenotype. In parallel, the sino-nasal clinical outcomes (symptoms, number of acute rhinosinusitis) and the sinus computed tomographic images were significantly improved without an important effect on the nasal endoscopy polyps score. The serum levels of eosinophils were significantly decreased after six months of treatment by omalizumab (64). On the other hand, it has been showed that CRSwNP existence can reduce omalizumab's efficacy in severe allergic asthma (65). Thus, omalizumab seems not to be the first treatment option in patiets having severe eosinophilic asthma with CSRwNP due to lack of enough evidence and lack of large randomised, double-blind, placebo-controlled studies on this condition.

Which Biologic Agent Should be Used in Severe Atopic Eosinophilic Asthma with CRSwNP

In clinical practice, especially mixed inflammatory-clinical phenotypes like atopic, severe eosinophilic asthma with CRSwNP, challenge clinicians in choosing the appropriate mAb. In the GINA severe asthma guideline, suggestions were made on which biologic agents should be given for the type 2 high asthma phenotype and it was emphasized that the factors determining the response to treatment should be taken into consideration. It is proposed to consider starting first with an anti-IL5/anti-IL5R in patients with uncontrolled severe asthma with blood eosinophil ≥ 300 cells/mL if; a) Higher blood eosinophils (strongly predictive), b) Higher number of severe exacerbations in previous year (strongly predictive), c) Adult-onset asthma, d) Nasal polyposis, e) maintenance OCS at baseline (1). Patients with severe atopic eosinophilic asthma with CRSwNP, have higher blood eosinophil levels, frequent exacerbation history, and CRSwNP. Therefore, anti-IL5/anti-IL5R should be the drug of choice in this phenotype of severe asthma group due to possible higher benefit from the treatment eventhough the patients have atopy. On the other hand, anti-IL4α may also be used in patients with uncontrolled severe severe eosinophilic/Type 2 asthma with blood eosinophils ≥ 150/μL or FeNO ≥ 25 ppb or need for maintenance OCS if: a) higher blood eosinophils, b) higher FeNO, c) moderate/severe atopic dermatitis, d) nasal polyposis (1). Higher blood eosinophils and nasal polyps which are common predictive factor for both mAbs. Hence, anti-IL4α can be used as a first treatment option for patients who have severe eosinophilic asthma with CRSwNP and atopy, atopic dermatitis or high FeNO levels.

Anti-IgE should be started in patients with uncontrolled severe asthma who are sensitized to inhaled allergen(s) in skin prick testing or specific IgE. The factors that may predict a good response to anti-IgE mAb are as follows: (a) blood eosinophils ≥ 260/μL, (b) FeNO ≥ 20 ppb, (c) allergen-driven symptoms, and (d) childhood-onset asthma. Theoretically anti-IgE can be used in severe atopic eosinophilic asthma with CRSwNP. However, what is important here is whether the patient's atopy status is really appropriate, given the clinical history (childhood allergic asthma, comorbidities such as atopic dermatitis/allergic rhinitis, and respiratory symptoms with exposure to aeroallergens). We think that starting anti-IgE therapy based only on atopy (determination of positivity with skin prick testing and/or determination of specific IgE to common aeroallergens) may not be the ideal approach and that

the clinical history should be taken into consideration. On the other hand, CRSwNP existence can reduce omalizumab's efficacy in severe allergic asthma; which is also mentioned in the previous section. Therefore, anti-IL4Rα or anti-IL5/anti-IL5R should be preferred for patients who do not have concordant clinical manifestations of atopy or not having childhood-onset atopic asthma in severe atopic/eosinophilic asthma with CRSwNP. If the patient has atopic clinical manifestations and asthma with childhood-onset, omalizumab and anti-IL4Rα or anti-IL5/anti-IL5R combination can be suitable but there may be a need for cost-effectiveness studies on this condition.

CONCLUSION

Anti-IL5/anti-IL5R or anti-IL4Rα should be the drug of choice in severe eosinophilic asthma with CRSwNP. Reslizumab and dupilumab seem to stand out in this preference. However, real-life comparative studies are needed to show which of these biological agents should be chosen as the first choice biologic treatment in severe eosinophilic asthma with CRSwNP.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this articles.

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