Slovenian Medical Journal

Treatment with biologics in severe asthma and chronic rhinosinusitis

Biološka zdravila v sodobnem zdravljenju hudih oblik astme in kroničnega rinosinuzitisa

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Abstract

The concept of the common airway is a paradigm shift in the understanding of common diseases such as allergic rhinitis, chronic rhinosinusitis and asthma. These clinical entities share common epidemiology and probably some pathophysiological cornerstones. In asthma, airway obstruction and hyperresponsiveness can be well-controlled by local glucocorticoid therapy. Chronic rhinosinusitis with nasal polyps is treated by local glucocorticoids, prolonged systemic antibiotic administration, systemic glucocorticoid pulses and surgery. Suboptimal management of the disease in the upper airways can also lead to worsening of the condition in the lower airways. Patients with severe asthma and chronic rhinosinusitis with nasal polyps have persistent uncontrolled symptoms despite maximal treatment; however, receiving systemic glucocorticoids carries a growing risk for long-term side effects. Biologicals are the latest, next-generation treatment used in asthma and chronic rhinosinusitis with nasal polyps. These antibodies target only specific inflammation pathways. Therefore, they represent essentially personalized medicine. Different pathways seen in upper and lower airway diseases can be recognized by characteristic biomarkers. Ideally, early endotypization would help us select the particular type of endotype tailored treatment as quickly as possible.

Izvleček

Med pogoste kronične vnetne bolezni zgornjih in spodnjih dihalnih poti sodijo alergijski rinitis, kronični rinosinuzitis in astma. Bolezni so znotraj enotne dihalne pot med seboj epidemiološko in patofiziološko povezane. Pri večini bolnikov z astmo lahko preodzivnost in obstrukcijo dihalnih poti nadzorujemo z zdravili. Bolnike s kroničnim rinosinuzitisom z nosnimi polipi zdravimo z lokalnimi glukokortikoidi, sistemskimi antibiotiki v podaljšanem odmerjanju, pulzno s sistemskimi

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Key words: biologicals; asthma; chronic rhinosinusitis; oral glucocorticoid load; immunopathogenesi

Ključne besede: biološka zdravila; astma; kronični rinosinuzitis; breme oralnih glukokortikoidov; imunopatogenez

Received / Prispelo: 11. 1. 2021 | **Accepted / Sprejeto:** 31. 5. 202

Cite as / Citirajte kot: Skrgat S, Košak Soklič T, Urbančič J, Zidarn M. Treatment with biologics in severe asthma and chronic rhinosinusitis. Zdrav Vestn. 2022;91(3–4):150–60. **DOI:** https://doi.org/10.6016/ZdravVestn.3214

glukokortikoidi in kirurško. Slab nadzor bolezni zgornjih dihal lahko povzroči poslabšanje bolezni spodnjih dihal, saj jih v okviru enotne dihalne poti razumemo kot eno funkcionalno enoto. S pomočjo bioloških označevalcev je treba bolnike z astmo in/ali kroničnim rinosinuzitisom z nosnimi polipi razdeliti v endotipe. Z endotipizacijo bi utegnili v prihodnosti razkriti tudi patofiziološko ozadje bolezni in napovedati odziv na zdravljenje. Huda astma in hud kronični rinosinuzitis sta stanji, ko bolnikovih težav, kljub skrajnim oblikam zdravljenja, ne uspe več nadzorovati, sistemsko zdravljenje z glukokortikoidi pa povzroča obolevnost zaradi njihovih neugodnih učinkov. Biološka zdravila so protitelesa, ki predstavljajo bolj usmerjen način zdravljenja težkega rinosinusitisa z nosnimi polipi in težke astme. Vsako biološko zdravilo je tarčno zdravilo, ki zavira samo določene dele vnetne poti, zato gre za personalizirano zdravljenje bolezni dihalnih poti. Na aktivnost posameznih poti sklepamo iz klinične slike in nekaterih bioloških označevalcev. Dragoceno bi bilo zgodnje prepoznavanje dejavnikov in bioloških označevalcev ugodnega odziva, kar bi omogočilo hitrejšo in lažjo odločitev o načinih zdravljenja.

1 Introduction

The airway, arbitrarily divided into upper and lower airways, has many common anatomical and immunological features. Inflammatory diseases affecting the upper and lower airways often have a similar immunopathophysiological basis, resulting in chronic inflammation. Drugs aimed at treating an immune-mediated inflammatory disease are useful in treating upper and lower airway diseases.

Asthma and chronic rhinosinusitis are increasingly understood as a syndrome with several subtypes, defined primarily by immunopathophysiological mechanisms. The phenotype describes visible and measurable characteristics based on genotype expression and interaction with the environment. New findings on the immunopathophysiology of asthma and chronic rhinosinusitis with nasal polyps have made it possible to identify their endotypes on the basis of the predominant mediators of inflammation and inflammatory cells, and drug response (1). An important shift towards personalised medicine for asthma and chronic rhinosinusitis with nasal polyps has enabled the development of biologics that target key immunopathophysiological mechanisms. Biologics have enabled treatment that is more tailored to subgroups of patients within a single diagnosis.

Asthma and chronic rhinosinusitis with nasal polyps are related diseases (2). As both diseases are very likely to start long before they are fully diagnosed, patients are so accustomed to the nasal symptoms that they do not even mention them in a conversation with a doctor if they are not asked about it (3). Eosinophilic inflammation is promoted by Th2 lymphocytes, Type 2 innate lymphoid cells (ILC2) and Type 2 cytotoxic lymphocytes (4). They are activated by cytokines originating from the epithelium in response to various stimuli from the environment. High T2 inflammation is characterised by a predominance of eosinophils, while low T2 inflammation may be dominated by neutrophils, or there may be a low number of inflammatory cells (1).

The review article describes the mechanisms of action of biologics currently available for the treatment of eosinophilic T2 airway inflammation, suggestions for their selection, and potential targets for biologics in the future.

2 Severe asthma

Asthma is characterised by chronic airway inflammation that is clinically manifested by overreaction and variable airway obstruction. In most patients, asthma can be managed with the right set of inhaled medications, which should always include inhaled glucocorticoids (5,6). In about 5% of people, asthma progresses extremely unfavourably and remains uncontrollable, despite the fact that the patient is prescribed high doses of inhaled glucocorticoids (IGC) and long-acting beta agonists (LABA) which they take diligently. Severe asthma is defined by the recommendations of the European Respiratory Society/American Thoracic Society (ERS/ATS) with the following criteria (7):

- The diagnosis of asthma has been unequivocally confirmed.
- Associated diseases are controlled as best as possible.
- The patient receives high doses of IGC and/or systemic glucocorticoids more than twice a year to regulate asthma symptoms. The ERS/ATS recommendations in Table 1 are taken into account when regarding high doses.
- The patient's condition worsens rapidly if the intake of systemic glucocorticoids or high doses of IGC are attempted to be reduced.

Compared to patients with regulated disease, patients with severe asthma are frequently treated in hospital, have systemic glucocorticoid (OGC) side effects, and poor quality of life (8).

In recent years, significant progress has been made in understanding the complex pathophysiology of asthma.

Table 1: High doses of IGC (inhaled glucocorticoids) in adult patients. Taken from the recommendations by the ERS/ATS, 2014 (7) and the recommendations by GINA, 2021 (5).

Inhaled glucocorticoid	Daily dose (mcg) ERS/ATS	Daily dose (mcg) GINA
beclomethasone	≥ 2000 powder or ≥ 1000 aerosol	≥ 1000 CFC or ≥ 400 HFA
budesonide	≥ 1600	≥ 800
ciclesonide	≥ 320	≥ 320
fluticasone propionate	≥ 1000	≥ 500 powder or ≥ 500 aerosol
fluticasone furoate (powder)		200
mometasone	≥ 800	≥ 400

Legend: ERS – European Respiratory Society; ATS – American Thoracic Society; CFC – chlorofluorocarbon; HFA – hydrofluoroalkane; GINA – Global Initiative for Asthma.

This, in turn, has led to the development of new options in the treatment of severe asthma. For patients whose asthma cannot be optimally managed at the primary and secondary levels, treatment in specialised units is appropriate, including an assessment of the suitability for the introduction of modern treatments. These include biologics and bronchial thermoplastics (9,10). Asthma is a heterogeneous disease with several phenotypes with different pathophysiological mechanisms and endotypes in the background (11-14). In defining the endotype, we basically distinguish between "T2 asthma" and "non-T2 asthma", which differ in cytokine expression. T2 asthma is characterised by Type 2 inflammation, in which the interleukins IL-4, IL-5, IL-13 are involved, and transmitted by CD4+ T helper cells 2-Th2, type 2 innate lymphoid cells (ILC-2) and type 2 CD8+ cytotoxic T cells (Tc2) (4,15). Therefore, the naming terminology of the endotype has recently changed from the Th2 endotype to the T2 asthma endotype. The essence of treatment is to influence specific cytokines and the pathways where these cytokines play key roles. When treating a patient, we therefore look for specific targets to which we direct biological treatment. This is considered personalised medicine for severe asthma (16).

2.1 Approach for a patient with T2 asthma

T2 inflammation or endotype is present in more than half of patients with severe asthma (16). In this endotype, there is an interaction between inhaled allergens, microbes and environmental pollutants on the one hand and the airway epithelium on the other. This interaction activates the innate immune response, the secretion of mediators (alarmins) such as thymic stromal lymphopoietin (TSLP), IL-25 and IL-33. This process subsequently triggers the T2 inflammation via Th2, ILC2 and Tc2 cells. The cytokines IL-4, IL-5, and IL-13 attract and activate basophils, eosinophils, and mast cells, form IgE from B lymphocytes, activate mucous glands, and cause airway smooth muscle contraction. The clinical consequences of this immunopathophysiological process are: bronchoconstriction, airway overreaction, mucus formation in the airway and airway remodelling (17,18).

T2 asthma includes allergic and non-allergic eosinophilic asthma. While allergen-specific IgE processes play an important role in allergic asthma, T2 cytokines play a predominant role in inflammation in non-allergic eosinophilic asthma. Eosinophils in the sputum and blood, serum IgE, and nitric oxide in exhaled air (NO) are recognised markers of T2 inflammation, which help us in choosing and predicting the response to biologics (19).

2.2 Biological markers and indicators of T2 asthma, useful in clinical practice

Cytokines involved in the pathophysiology of T2 inflammation are not measured in clinical practice. The biological markers we measure must be easily measurable and accessible. It is crucial then to infer from their presence the activity of a particular pathophysiological pathway and thus define the endotype of asthma in an individual patient. This is a personalised approach to the asthma patient and the foundation of the right choice of treatment for the patient (16).

2.2.1 Assessment of blood eosinophilia

Checking the level of blood eosinophilia is an easy way to determine the presence of a T2 asthma profile. Assessing eosinophilia in the blood gives a very good picture of inflammation at the airway level. Cytokines from the T2 profile promote the survival and maturation of eosinophils. These could also be measured in induced cough. Eosinophilia in induced cough reliably predicts the expression of the T2 inflammatory profile (20). A blood eosinophilia level between 250 and 300 cells/μL indicates a threshold that distinguishes between T2 and non-T2 asthma (20-23). As the technical procedure for obtaining an appropriate sample and result is demanding, it is not possible to make extensive use of

this investigation. It is saved only for specialised centres.

When assessing blood eosinophilia, it should always be checked whether the patient has been receiving systemic glucocorticoids, as this completely eradicates eosinophilia in the blood. In the most severe forms of asthma, when the patient also receives systemic glucocorticoids, the correlation between blood eosinophilia and mucosal eosinophilia at the airway level is therefore poor (24). This means that the patient does not have eosinophils in the blood when receiving systemic glucocorticoids, but they may be present in the airway mucosa.

If we are not careful, we can mistakenly define the patient as having non-T2 asthma and thus deprive him of treatment. Assessment of blood eosinophilia is currently the easiest way to check for the presence of T2 inflammation or distinguishing between T2 and non-T2 asthma.

2.2.2 NO (Nitric Oxide) in exhaled air

If the airway epithelium is exposed to IL-13 and IL-5, it secretes inducible NO synthase (iNOS), which stimulates the production of NO, which can be measured in exhaled air (FeNO). This is a non-invasive measurement that is performed according to a standardised procedure (25).

Data on the typical concentration, which is already indicative of T2 inflammation, are not very solid: FeNO>50 ppb in adults and >35 ppb in children indicate eosinophilic airway inflammation. However, FeNO measurements should actually be viewed in the broader context of the overall clinical picture of the patient, e.g. elevated levels above 45 ppb also indicate poor patient participation in the treatment with inhaled glucocorticoids (26). There are also reports of a reduction in the incidence of asthma exacerbations in pregnant women and individuals with more than one exacerbation of asthma per year if the dose of inhaled glucocorticoids is titrated using FeNO measurements in exhaled air (27,28).

Recent recommendations for the treatment of patients with severe asthma (5,6) identify the possibility of T2 inflammation in patients with FeNO>20 ppb. In these cases, it is considered that these are patients receiving high doses of inhaled glucocorticoids or even daily doses of systemic glucocorticoids. FeNO in exhaled air is therefore interpreted in a broader context, and monitoring the dynamics tells us much more than a single measurement. For example, biological drugs from the anti IgE and anti IL4/13 groups lower FeNO. If FeNO as a biological marker is elevated at baseline, it may in this case be a predictor of a favourable response to the biological therapy with drugs of these groups (23,29).

Measurement of NO in exhaled air means added value in cases where T2 asthma is suspected, even though the level of blood eosinophilia is low.

2.2.3 Total IgE

IgE concentrations are often determined by physicians in clinical practice to determine the atopic status. In reality, however, the role of IgE as a predictor of T2 inflammation in the airways is limited and not linked only to the atopic status, as non-atopics may also have a T2 cytokine profile (30).

Total IgEs are also a weak biological marker to define a favourable response to anti-IgE treatment. Measurements of local IgE in the respiratory mucosa would probably be a useful marker, but in clinical practice this is unattainable (31).

Specific IgE antibodies against environmental allergens indicate sensitisation to a specific allergen. In clinical practice, it is then necessary to assess whether the detected sensitisation is also clinically relevant. This means finding a link between sensitisation, allergen exposure and worsening of the symptoms of allergic rhinitis and/or asthma (32).

3 Allergic asthma

Allergic asthma is a disease associated with clinically significant sensitisation to aeroallergens that causes asthma symptoms and airway inflammation. It is a mediated T2 inflammation.

Allergic asthma usually begins in childhood; the disease in this early stage may be accompanied by atopic dermatitis and allergic rhinitis (33).

Inhalation of the aeroallergen causes acute bronchoconstriction, which triggers an immediate phase of the asthmatic response. This is followed by an inflammatory immune response that causes a late (delayed) phase of the asthmatic response (1).

Allergic asthma is probably the most common asthma phenotype. About 80% of children and 50% of adults with asthma have an allergic component to this disease. A family history of asthma is also common (34).

Allergic sensitisation to aeroallergens usually occurs after the age of two, so the prevalence of allergic asthma increases in childhood and adolescence. Etiopathogenesis involves an immune response to viral infection and aeroallergens in early childhood, and the risk is further increased in children with respiratory infections in the first year and with atopy. Allergic asthma is often

permanent and continues into adulthood (35,36).

In some patients, allergic asthma manifests itself in severe form in adulthood. History is crucial in the initial definition regarding differential diagnosis.

4 Eosinophilic, non-allergic asthma

Non-allergic eosinophilic asthma is a phenotype of asthma that occurs in adulthood. It typically occurs in the fourth or fifth decade of life. It is characterised by T2 eosinophilic inflammation in the airways, which persists despite treatment with inhaled glucocorticoids. Asthma is usually more difficult from the very beginning, there is also a tendency to develop airway remodelling and permanent obstruction, with the bronchodilator no longer achieving normalisation of lung function. Exacerbations of the disease are common, so patients often receive systemic glucocorticoids. Patients thus carry a significant glucocorticoid burden and side effects of systemic glucocorticoid therapy. A typical associated condition in eosinophilic non-allergic asthma is eosinophilic chronic rhinosinusitis with nasal polyps, which has the most severe course and numerous exacerbations. A special, clinically severe subgroup is patients with aspirin and nonsteroidal anti-inflammatory drug intolerance (37,38).

5 Chronic rhinosinusitis with nasal polyps

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic inflammation of the nasal mucosa and paranasal sinuses that lasts for more than 12 weeks. Endoscopically, nasal polyps are found bilaterally in the middle nasal passages, possibly with a thick discharge. Computed tomography (CT) or magnetic resonance (MRI) signs are sinus mucosal thickening and osteomeatal complex obstruction. Typical symptoms of CRSwNP are mucopurulent drainage, nasal congestion, partial or complete loss of smell, and facial pain or pressure in the paranasal sinuses (39,40). Patients with CRSwNP are treated with nasal glucocorticoids, systemic glucocorticoids in the form of short-term pulse therapy up to two times a year, systemic antibiotics in prolonged dosing, and surgically with endoscopic intervention and intensive rinsing of the nose and sinuses with large amounts of saline solution to remove inflammatory metabolites from the nose and paranasal sinuses (39).

5.1 Eosinophilic CRSwNP

Multiplied and activated degranulated mucosal eosinophil granulocytes, more than ten of which are in the high-power field (HPF), are characteristic of eosinophilic CRSwNP, which is usually accompanied by eosinophilic asthma beginning in adulthood. Patients have more severe symptoms, poorer quality of life, inadequate immune response, acute viral infections and frequent bacterial superinfections, and therefore re-exacerbations even after endoscopic surgical treatment (41-45). This is a T2 inflammation, where Th2 and ILC2 cells (46-48) participate, and double-negative (CD4– CD8–) T cells, which are also capable of secreting T2 inflammatory mediators, are multiplied and activated as well (49,50). In eosinophilic CRSwNP, the mucosa is infiltrated with lymphocytes and eosinophils. Remodelling of mucosal glands with hyperplasia, thickened basement membrane, squamous cell metaplasia, cilia loss, and submucosal oedema, are typical.

5.2 Severe CRSwNP

At least 20% of patients, despite appropriate drug treatment and surgical treatment, have severe CRSwNP with persistent disturbing severe symptoms with a score of five or higher on the visual analogue scale (VAS) from 0 to 10 (0 – asymptomatic condition and 10 – condition with unbearable symptoms) and endoscopic signs. Due to CRSwNP, these patients have a significantly poorer quality of life, which can also be seen in quality-of-life surveys such as Sino Nasal Outcome Test 22 (SNOT-22), adapted and validated for Slovenian patients (51). At the same time, they often have exacerbations even after endoscopic surgery and require systemic glucocorticoids at least twice a year, and more frequent reoperations (52,53).

6 Biologics

6.1 IgE-targeting biologics

Omalizumab is a humanised monoclonal anti-IgE antibody (mAb) that was the first biological drug to treat severe asthma. It has been on the market in Slovenia since 2009. It is used to treat severe allergic asthma, in which IgE antibodies play a key role. After exposure to an allergen, the immune system responds inappropriately to the antigen. In the sensitisation process, B lymphocytes are stimulated to produce specific IgE antibodies, which requires CD4+ helper T lymphocytes that produce IL-4. IgE antibodies circulate in the blood and bind to mast cells and basophils. Re-exposure to the allergen in inhaled air causes the release of pre-prepared mediators from mast cells. The result is an immediate allergic

Table 2: Severe chronic rhinosinusitis with nasal polyps: indicators of type 2 inflammation. Taken from Cardell LO, et al., 2020 (63).

Clinical indicators	Probability of T2 inflammation	Diagnostics
tissue eosinophilia over 10 eosinophils/HPF	certain T2 inflammation	histological, clinical (biopsy)
aspirin intolerance	certain T2 inflammation	clinical
bilateral CRSwNP without comorbidity	high	clinical, endoscopic
allergic sensitisation	very high	clinical
the need for systemic glucocorticoids once or several times a year	very high	clinical
bilateral CRSwNP without comorbidity	high	clinical
Biological markers	**Probability of T2 inflammation**	**Diagnostics**
blood eosinophilia >150	very high	laboratory
elevated serum polyclonal IgE	very high	laboratory
serum IgE against staphylococcal enterotoxin	certain T2 inflammation	laboratory

Legend: CRSwNP – Chronic rhinosinusitis with nasal polyps; HPF – high power field.

reaction in the airways. This is followed by the formation of lipid mediators and the release of cytokines, resulting in a slower inflammatory phase or late phase characterised by the accumulation of neutrophils, eosinophils and macrophages. Omalizumab prevents the binding of the patient's IgE to mast cells and basophils because it occupies sites on IgE antibodies that bind to high-affinity FceRI receptors on mast cells and basophils. The result is a reduction in the release of inflammatory mediators and thus a reduced allergic response (54,55). Omalizumab is effective in both severe allergic asthma (56) and uncontrolled allergic rhinitis (57). Clinical studies have shown that omalizumab may reduce the number of asthma exacerbations due to viral infections as well. The clinical response to treatment appears to be associated with accelerated interferon (IFN) production, allowing the ability to alter the antiviral effect (58). The clinical effects of omalizumab are summarised in Table 2. If it proves ineffective after the first 16 weeks, it may be switched to another biologic without a break in between (59).

The basic facts in the introduction of omalizumab in a patient with severe allergic asthma (5,6) are the following:

- It is registered for patients with severe allergic asthma.
- Total IgE should be between 30-1500 IU/ml.
- Greater clinical effect is expected when NO is greater than 20 ppb and blood eosinophilia is above 260 cells/μL.
- It is administered subcutaneously every two or four weeks (depending on cIgE concentration and body weight).
- The success of the clinical response is assessed after approximately four months.
- IgE concentrations are not measured when monitoring efficacy. Although basal periostin and free IgE are biological markers of the effectiveness of omalizumab (60), they are not measured in clinical practice.
- The chance of anaphylaxis is 0.1-0.2%, so the patient should have a self-help kit with them.
- The patient is observed for two hours during the first three applications, later on for 30 minutes. If the patient tolerates the drug well, they can also take it themselves in a home environment with indirect supervision.

6.2 Biologics targeting the cytokine IL-5 (mepolizumab, reslizumab) and the cytokine receptor IL-5 (benralizumab) in severe eosinophilic non-allergic asthma

IL-5 (interleukin 5) is a cytokine involved in the maturation of eosinophils and their excretion from the bone marrow, attraction to the mucosa, activation and survival of eosinophils. By inhibiting this pathway, anti-IL-5 drugs reduce eosinophilic inflammation in the bronchial mucosa (40). Mepolizumab and reslizumab are antibodies that bind to IL-5 and prevent IL-5 from binding to

Table 3: Efficacy of biologics for the treatment of T2 asthma. Taken from McGregor MC, et al., 2019 (16).

Biologics	Asthma exacerbations	Discontinuance of OGC	Pulmonary function	Side Effects
Omalizumab	reduced by about 25%	reduces IGC dosage, less solid evidence that it reduces OGC	minimal improvement	in 0.1-0.2% risk of anaphylaxis
Mepolizumab	reduced by about 50%	reduces the burden of OGC, discontinuation of OGC from basic treatment (14%)	no change	rarely causes anaphylaxis, may cause reactivation of herpes zoster
Reslizumab	reduced by about 50–60%	no assessment	improved	0.3% risk of anaphylaxis
Benralizumab	reduced by 25–60%	reduction of OGC use, discontinuation of OGC treatment (50%)	improved	in rare cases, hypersensitivity reaction
Dupilumab	reduced by 50–70%	reduction of OGC dosage, discontinuation of OGC (50%)	improved	pain at the injection site, transiently elevated peripheral blood eosinophilia (4-14%)

Legend: OGC – oral glucocorticoids; IGC – inhaled glucocorticoids.

its eosinophil receptor. Benralizumab binds to the alpha subunit of the IL-5 receptor on eosinophils and basophils. IL-5 thus cannot bind to its receptor. In addition, benralizumab acts on natural killer cells; the end result is apoptosis of eosinophils (61).

Better clinical response to these drugs is expected with more pronounced eosinophilia, higher exacerbations over the past year, and dependence on systemic glucocorticoids.

Anti-IL-5 drugs registered for the treatment of severe eosinophilic asthma:

- **Mepolizumab** – given subcutaneously, 100 mg once every four weeks. The blood eosinophil count at baseline is 150/300 cells/μL or more. The patient may give it to himself/herself at home.
- **Reslizumab** – given intravenously 3 mg/kg once every four weeks. The blood eosinophilia count at baseline is 400 cells/μL or more.
- **Benralizumab** – given subcutaneously, 30 mg every four weeks three times in a row, then every eight weeks. The blood eosinophilia count at baseline is 300 cells/μL or more. The patient may give it to himself/herself at home.

6.3 Anti-IL-4/IL-13

Dupilumab is an antibody that targets the IL-4 alpha receptor. It inhibits signalling of both IL-4 and IL-13, two key cytokines that maintain the maturation of B lymphocytes and the formation of IgE, attract inflammatory cells, stimulate hyperplasia of mucous gland cells (goblet cells) in the mucosa and mucus formation, promote thickening of the basement membrane, deposition of fibrin (formation of nasal polyps) and collagen (fibrosis). IL-4 and IL-13 modulate excessive airway responsiveness and eventually remodelling them. This results in poorer efficacy of standard treatment (with bronchodilators and glucocorticoids) (62).

The key clinical effects in **patients with asthm**a are summarised in Table 2. Il-13 and Il-4 are involved in the synthesis of iNOS (inducible NO synthase), so elevated NO in exhaled air is a predictor of a favourable response to dupilumab. Candidates for treatment with dupilumab are also patients with **severe chronic rhinosinusitis with nasal polyps** who have already undergone endoscopic surgery on the sinuses and who meet three of the following five criteria:

- positive indicators of type 2 inflammation (Table 2) (63);
- they require pulse treatment with systemic glucocorticoids at least once a year or for which systemic glucocorticoids are contraindicated;
- significantly poorer quality of life (SNOT-22> 40);
- loss of smell;
- concomitant asthma.

Patients who are not candidates for endoscopic surgical treatment must meet four of the five criteria listed above (64). Patients are not candidates for surgical treatment if they are incapable of undergoing it due to

severe concomitant diseases. If the patient does not opt for the proposed surgical treatment that the physician believes would benefit him/her, the prescription of biologics should be assessed by a multidisciplinary team (pulmonologist, allergist, and ENT specialist) based on the expected benefits and risks to the patient.

6.4 Choice of biologics in the treatment of severe forms of asthma and severe CRSwNP

All five biologics available appear to reduce the incidence of asthma exacerbations by about 50% (Table 3). They are more effective in patients who have higher levels of eosinophils in their blood. As the main role of anti IL-5 is limited to maturation, release in the bone marrow, survival, and attraction of eosinophils to the mucosa, the drug is also expected to be effective in those patients with the airway obstruction, symptoms and severity of the disease being maintained by mucosal eosinophilia (16).

For CRSwNP, treatment with anti IL-5 has been shown to be successful in clinical trials, but not all patients respond well to the treatment, or the effect on CRSwNP becomes unnoticeable after several years of treatment (39,65).

IL-4 and Il-13 affect B lymphocyte maturation and IgE secretion, attraction of eosinophils and other inflammatory cells, goblet cell hyperplasia, accumulation of mucus, fibrin and collagen, smooth muscle contraction, and bronchial overreaction. Therefore, anti IL4/13 is expected to have a broader effect, not limited to mucosal eosinophilia (66).

Patient's baseline clinical characteristics and biomarkers and/or a combination of both would help predict the response to an individual biological drug. Certain things are already known, but otherwise this field is still a professional and research challenge:

- **Omalizumab** – patients with severe allergic asthma, elevated exhaled NO above 20 and blood eosinophilia above 260 cells/μL respond to it better;
- **Anti-IL-5** – patients who have blood eosinophilia, chronic rhinosinusitis and nasal polyps, suboptimal lung function, who often require systemic glucocorticoids and experience frequent exacerbations, respond better.

It would be valuable to know the prognostic factors of a favourable response soon after initiating treatment. This way, it would be clear before the four-month period whether to continue the treatment or not.

In severe forms of asthma, clinical evaluation after four months of treatment is crucial. Most important is the information on the reduction in the incidence of disease exacerbations that would require systemic glucocorticoids (Table 3). In patients who had required continuous baseline dosing of systemic glucocorticoids prior to the introduction of biologics, the key factor is whether we have been able to discontinue OGC and/or at least significantly reduce its dosing. In this way, the burden of treatment with systemic glucocorticoids is reduced.

6.5 Asthma without severe T2 inflammation

In Slovene, the term "non-T2 asthma" is still used by us in the profession. Asthma in which T2 inflammation is not expressed includes: neutrophilic and paucigranulocytic asthma, which are caused by the activation of Th1 and Th17 cells. Increased secretion of IL-17 has been described in patients with moderate to severe asthma (20). These patients respond poorly to systemic glucocorticoids and are usually slightly older at diagnosis, are not atopic, respond less well to beta agonists, and are often associated with obesity and complications of systemic glucocorticoid therapy. There are currently no biologics for this subtype of asthma, and possible therapeutic approaches include the introduction of tiotropium, macrolides, and bronchial thermoplasty (67,68).

Lifestyle changes are important, including complete abstinence from active and passive smoking and weight loss (69).

6.6 Non-eosinophilic CRSwNP

Only a small proportion of patients with CRSwNP have a non-eosinophilic endotype with neutrophilic infiltration and mixed type 1 and type 3 inflammation. Type 1 inflammation is mediated by Th1, ILC1, Tc1, and NK cells; mainly interferon gamma (IFN-γ) is secreted. Type 3 inflammation is mediated by Th17, Tc17 and ILC3, and type 3 cytokines are IL-17 and IL-22 (4,48,69,70). Nasal or systemic glucocorticoids are not effective in these patients. Treatment is endoscopic surgery with copious rinsing with saline in large amounts or with higher pressure. Quitting smoking is extremely important (39).

7 Biologics in the near future

With an improved understanding of the immunopathogenesis of asthma today, we can see other inflammatory pathways that can be identified as therapeutic

targets for new biologics. Among them, we recognise targets IL-25, Il-33 and alarmin TSLP (thymic stromal lipoprotein). Tezepelumab is an antibody against TSLP, the use of which is clinically demonstrated by a reduced incidence of asthma exacerbations independent of peripheral eosinophilia, IgE and NO in exhaled air (71).

8 Conclusion

Severe forms of asthma and chronic rhinosinusitis with nasal polyps share some immunopathogenetic features. Biological therapy of airway diseases represents a revolution in the treatment of patients with severe asthma; the latest biologics are also effective in patients with severe chronic rhinosinusitis with nasal polyps. It is crucial that patients who are candidates for this type of treatment are identified as soon as possible, thus reducing the burden of adverse side effects of treatment with systemic glucocorticoids and improving their quality of life. This also saves patients with chronic rhinosinusitis with nasal polyps from having to have reoperations.

Conflict of interest

None declared.

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