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EDITORIAL

Biological treatment in chronic rhinosinusitis with nasal polyposis



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Chronic rhinosinusitis (CRS) is defined as an inflammatory disorder of the nasal mucosa and mucosa of the paranasal sinuses[1], encountered in approximately 10.9% of the European population, according to the criteria proposed by the European Position Paper on Sinusitis (EPOS)[2]. A specific incidence and prevalence of CRS in our country is still unknown. Its high prevalence, duration of symptoms and the impact upon the quality of life determine an increased socio-economic burden. Taking into consideration that 85% of the CRS patients are aged between 18 and 65 years old, indirect costs associated with work absenteeism and decreased word productivity are significantly high[3].

The clinical classification can be made into two phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). In CRS etiopathogenesis, there are proposed three inflammatory pathways or endotypes which include the native T helper cells (Th1, Th2 and Th17), each being characterized by a different cytokine profile[4]. The last issue of the EPOS proposes a new classification of CRS in primary (localized and diffuse) and secondary diseases[2].

For the primary forms of CRS, the endotype – type 2 or non-type 2 – should be taken into consideration. In case of CRSwNP, type 2 inflammation is predominant, but other forms of inflammation can also be found. The effects of inflammation on the nasal mucosa are defined by formation of nasal polyps, hyperplasia of the goblet cells, which determine most of the associated symptoms.

The current therapeutic approach for chronic rhinosinusitis consists in medical therapy, for both phenotypes, with level A of evidence for nasal saline lavages, intranasal corticotherapy and systemic corticotherapy for acute recurrences. Medical management of CRS has a success rate of approximately 50%[5]. In refractory cases, the surgical approach is recommended, although surgery is not curative, but it alleviates nasal obstruction and facilitates the delivery of topical drugs to the paranasal sinuses. Different studies show that 10-30% of the patients who underwent surgery for CRS, will require a revision surgery[1,6]. Even with maximum medical treatment and proper surgical therapy, some patients still fail to achieve control of their symptoms. In such cases, the therapeutic options available are extremely limited. The risk of failure to respond to medical and surgical management is observed more frequently in patients with co-morbidities, such as asthma, non-steroids anti-inflammatory drugs intolerance, allergic fungal rhinosinusitis, and it is proportional to the endoscopic severity grade of the nasal polyps[4].

In the novel literature, there are several articles on the role of biologicals in refractory cases of chronic rhinosinusitis, aiming the Th1, Th2 and Th17 mediated inflammation. The previous conditions where immunobiologicals were first indicated include asthma, atopic dermatitis, inflammatory bowel diseases, idiopathic pulmonary fibrosis, scleroderma, rheumatoid arthritis. The proposed biological therapy for CRS has effect upon the Th2 inflammation, which is mediated by specific lymphocytes, such as IL-4, IL-5, IL-9 and IL-13 cytokines. The main cells involved in Th2 inflammation are eosinophils, associated with elevated IgE.

The principal reason for the development and

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use of biologicals in the treatment of CRS is the variable response of these patients to the same therapeutic approach, which can only be related to different individual physiopathological characteristics. Before initiating the biologic treatment, patients should be properly assessed for the severity of the disease, based on validated questionnaires. The biologicals should only be indicated for the patients who already had maximum medical treatment and adequate sinus surgery, but with persistent symptoms. A CT scan of the paranasal sinuses should be performed before administration, in order to establish the inflammation of the sinuses and the efficacy of the sinus surgery. The therapeutic response should be established both on subjective (improvement in nasal obstruction, sense of smell and rhinorrhea) and objective methods (nasal endoscopy and CT scan). The standard period for immunobiologicals is 12 months, related to the patients' symptoms. The first evaluation of patients is required to be performed at approximately 16 weeks. Failure to respond to the initial biological should imply the need to indicate another biological molecule, only if the patient continues to fulfil the inclusion criteria.

The update of the EPOS guideline from 2020 indicates specific criteria for biological therapy in CRSwNP, represented by at least three conditions from the following: proof of Th2 inflammation, the necessity for systemic corticosteroids (more than 2 cycles of systemic corticosteroids per year or prolonged use, more than 3 months) or a contraindication to use systemic corticosteroids, a moderate to severe disease (measured by the Visual Analogue Scale, with a score higher of 7, Sino-Nasal Outcome Test score higher than 40 points), smell disorders and associated asthma[2].

An important aspect is represented by the duration of biological therapy, which should take into account both the costs of the treatment and the clinical effectiveness. Cessation of treatment may induce recurrence of the nasal polyps due to the fact that biologicals are not a curative method for CRS and they cannot change the natural course of the disease. The European Forum for Research and Education in Allergy and Airway Diseases proposes 5 criteria upon which treatment efficacy can be evaluated[7]: reduction of the nasal polyps, need for systemic corticosteroid, improvement in the quality of life and sense of smell, reduction of the impact of co-morbidities. The therapeutic response should be assessed at 16 weeks and the therapy should be discontinued if there is no response in the aforementioned criteria.

According to the specific molecule action, the main biologic therapies can be divided in: anti-IgE monoclonal antibodies (Omalizumab), anti-IL5 (Mepolizumab, Reslizumab, Benralizumab), anti-IL4 and anti-IL13 (Dupilumab), anti-IL-13 (Lebrikizumab, Tralokinumab). The molecules are being either in use, either investigated in the US and in the European Union for the patients with severe chronic rhinosinusitis[8,9].

The first biological treatment to receive approval from FDA for the treatment of CRSwNP (July 2019) was Dupilumab, an anti-IL-4 monoclonal antibody which targets the alpha chain of IL-4Ra, a common receptor for both IL-4 and IL-13, with an important role in the Th2 pathway and pathogenesis of respiratory diseases. Although not officially in use in Romania, Dupilumab is indicated as an add-on therapy in the treatment of severe asthma, insufficient controlled with high doses of inhaled corticosteroids; also, Dupilumab is used in CRSwNP when systemic corticosteroids and surgery do not provide adequate disease control.

The clinical studies showed that the treatment with Dupilumab was associated with significant improvements in the evolution of chronic rhinosinusitis. Subjective evaluation revealed reduction of SNOT-22 score and disease severity score (VAS), from the point of view of nasal congestion / obstruction at 4–6 months. The nasal polyp score was significantly reduced, using Lund-Mackay evaluation score, as well as the improvement in asthma control and forced expiratory volume in 1 second (FEV1). It was also the only monoclonal antibody shown to significantly improve olfaction as measured by UPSIT (University of Pennsylvania Smell Identification Test) score[3].

Although Dupilumab was the first biological approved by the FDA for the treatment of CRS, Omalizumab was the first biological studied for this disease. Omalizumab is an anti-IgE monoclonal antibody, recommended for use in moderate to severe forms of asthma and allergic rhinitis, by reducing serum levels of IgE, the numbers of IgE receptors and tissular eosinophils (nasal and bronchial), the number of mastocytes and B and T lymphocytes. Also, it is used in patients with CRSwNP as an add-on therapy when intranasal corticotherapy does not offer adequate disease control[5]. In December 2020, Omalizumab was approved by the FDA for the treatment of specific cases of CRS[8]. The studies demonstrated that patients treated with Omalizumab had a significantly improvement in the symptoms and the endoscopic scores. In the Journal of Allergy and Clinical Immunology, an extensive study on the efficacy, safety and durability of responses to Omalizumab in adults with CRSwNP has been published[10]. Cessation of Omalizumab

was associated with gradual increase in polyp and nasal obstruction scores, which indicates the non-permanent effects of the biological therapy.

The first biological proven to be efficient in the treatment of CRS stimulated the study of additional antibodies, such as anti-IL-5 molecules, represented by Mepolizumab, Reslizumab and Benralizumab, which were previously used for the treatment of asthma. In July 2021, FDA approved the use of Mepolizumab for the treatment of CRSwNP.

Like any other therapeutic options, biologicals may have adverse effects and the physicians should weigh the potential side effects and the benefits and inform the patients. The most frequently encountered adverse effects of biologicals were headache, rhinopharyngitis, local reactions and asthma worsening[10].

Development of new therapeutic strategies comes with the necessity of considering the main costs. The perfect health system would allow the practicians to indicate therapies, irrespective of costs, if in the benefit of the patients. The studies showed that the therapy with biologicals is 10 times more expensive than the standard medical and surgical treatment. Therefore, this treatment should only be initiated in specific cases, as recommended by the international guidelines, for example the patients who fail medical and surgical treatment and those with comorbidities (asthma, aspirin intolerance).

Chronic rhinosinusitis represents an important health problem, and the emergence of biologicals is only one step further into providing control of the disease. IL-33 is a novel cytokine involved in the Th2 inflammatory pathway and targets antibodies (AMG 282 and etokimab) which may have significant impact upon the mechanisms of CRS. Thymic stromal lymphopoietin (TSLP) is a IL-7 cytokine derived from the epithelial cells, which acts on Th2 inflammatory pathway and it stimulates dendritic cells to transform CD41 cells into Th2 cells.

One can conclude that immunobiologicals are similar to "Promised Land" for a patient with CRSwNP, because they may influence the inflammatory pathways without significant side effects. There are still questions about the long-term efficacy and about the cost-effectiveness relationship, but the current guidelines show an important advance in this field.

Even if the future of treatment of chronic rhinosinusitis sounds good, nevertheless, in Romania, there is a lack of legal base regarding the administration of biologicals in CRSwNP, despite their proven effect upon Th2 inflammation, both in the US and several EU states.

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