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ORIGINAL ARTICLE

Chronic rhinosinusitis with nasal polyposis: the role of personalized and integrated medicine

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Abstract. Chronic rhinosinusitis with nasal polyposis (CRSwNP) is a frequent disorder. From a clinical and an immunopathological point of view, different phenotypes and endotypes have been identified. The frequent comorbidity with asthma allowed to pave the way to the use of biological agents for the treatment of CRSwNP. Biological agents are targeted to antagonize IgE, interleukin (IL) 4, IL-5, and IL-13 at present. However, a correct and appropriate workup is mandatory, mainly concerning the exact definition of the specific pheno-endotype. The preliminary outcomes are promising, even though there is a need for well-established indications, criteria of responsiveness, duration, and safety. On the other hand, this personalized medicine could be fruitfully integrated with gold-standard medications, such as intranasal corticosteroids. As CRSwNP is a chronic disorder, treatment should be long-lasting, so complementary anti-inflammatory treatments could be opportunely integrated and/or alternated to steroids. (www.actabiomedica.it)

Key words: chronic rhinosinusitis, nasal polyposis, biological agents, corticosteroids, enoxolone, mannitol

Clinical and immunopathological background

Chronic rhinosinusitis (CRS) is a frequent disorder as it affects about 10-12% of the European population (1). CRS may be classified into 2 phenotypes based on endoscopy and computed tomography (CT) findings: CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP) (2). CRSwNP is defined by the presence of nasal polyps and by signs and symptoms lasting longer than 8–12 weeks (3,4). Nasal polyps are benign edematous masses in the nasal cavities, paranasal cavities, or both. Their occurrence depends on an exaggerated inflammatory reaction. As nasal polyps occupy space into nasal cavities they can cause nasal obstruction, rhinorrhea, postnasal drip, and hypo- or anosmia (5). The CRSwNP overall prevalence is approximately estimated to be 2% to 4% of the general population. Treatment options consist of local or systemic corticosteroids as the first-line choice, if ineffective there is the need for functional endoscopic sinus surgery. Especially patients with CRSwNP and comorbid asthma have a poor therapeutic response and a high recurrence rate, so the disease is more difficult to treat. Both CRSwNP and asthma share a serious impairment of quality of life (QoL) and cause a large financial burden for society (3). On the other hand, recent technological advances, mainly in the fields of genetics and engineering, increased the information concerning the phenotypes and the endotypes of chronic respiratory disorders, mainly concerning the type of inflammation and the type of immune response (6-9). This information could enable more targeted, effective, and efficient Precision Medicine (PM). PM refers to the "ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in

the biology or prognosis of those diseases they may develop, or in their response to a specific treatment" (10). Consequently, PM allows to stratify patients into subgroups and to tailor treatment based on their peculiar pheno-endotypes (11). This approach has been defined as Personalized Medicine (12).

From an epidemiological point of view, CRSwNP may be frequently associated with asthma: among patients with CRSwNP, approximately 30% have asthma and 15% have aspirin intolerance (13). Asthma is a chronic inflammatory disease of the lower airways characterized by bronchial inflammation, airway hyperresponsiveness, and usually reversible airflow obstruction, leading to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing (14). The disease has a high prevalence, ranging between 5-10% of the general population (15). Asthma frequently is associated with many comorbidities, including upper airways diseases, including rhinitis and rhinosinusitis (16, 17). In particular, the CRSwNP-asthma phenotype, characterized by the association of CRSwNP with asthma, is particularly severe (18).

Although some effective therapies exist for mild-moderate asthma, severe asthma remains difficult to treat, and the costs of the disease are relevant (19). A breakthrough in the treatment of severe asthma has been the discovery of biological agents. Indeed, it has been more than 15 years since the US Food and Drug Administration approved omalizumab for the therapy of moderate-to-severe perennial allergic asthma (20). At that time, the concept of removing one of the main triggers of asthma, such as IgE, excited the scientific and medical community. Indeed, 80% of children and 50% of adults have allergic asthma, such as an IgE-dependent bronchial inflammation, this approach could, therefore, lead to longstanding asthma remission for many patients. This lesson has been successively applied in the field of CRSwNP treatment (21,22). Many trials have been conducted using biologics for treating CRSwNP in these last years (23-26). However, there was a need for reflecting on the precise positioning of these biological therapies also for upper airway diseases (27, 28). In this regard, the European Forum for Research and Education in Allergy and Airway Diseases EUFOREA has nowadays provided a consensus on this issue (29).

The rationale for the use of biologics in CRSwNP is based on the existence of clinical-morphological characteristics and unbalanced immune response, that define specific polyps phenotypes and endotypes (30). CRSwNP may be classified based on the polarization of the immune response type. Type 1 immune response is sustained by a Th1 polarization associated with neutrophilic infiltration and IFN-γ overproduction; this endotype is most common in Asia (31). Type 2 inflammatory response is defined by interleukin 4 (IL-4), IL-5, and IL-13 and a nasal infiltrate of eosinophils, mast cells, basophils, and T-helper 2 (Th2) cells; also, comorbidity with asthma and allergic diseases is frequent (32). Type 3 immune response is characterized by increased release of the IL-17 cytokine family and is associated with frequent exacerbations (33). It has to be noted that CRSwNP is a pleiomorphic disorder, for example, the type 1 NP may include other phenotypes, such as cilia motility defects, cystic fibrosis, and infectious sinus diseases (34). Consistently, type 2 NP may account for several CRSwNP phenotypes, including allergic fungal rhinosinusitis (AFRS) and NSAID-exacerbated (typically by aspirin) respiratory disease (N-ERD). In particular, AFRS and N-ERD phenotypes can display increased IL-4, whereas other eosinophilic polyp phenotypes can be associated with high IL-5 and IL-13 levels (34). AFRS is also characterized by overexpressed periostin. N-ERD patients show high levels of cysteinyl leukotriene and leukotriene C4 (LTC4), so novel treatments may be designed (35). Moreover, a mixed type 1 and type 2 endotype has been also reported as well as imbrications with type 3 endotype (36). A possible explanation for these pleiomorphic endotypes might depend on the plasticity of type 2 innate lymphoid cells (ILC2), which might define also most severe forms (37). ILC2 cells may induce and amplify type 2 inflammation apart allergic pathogenic mechanisms (38). In other words, an eosinophilic infiltrate may occur without allergic reaction: a typical example is a non-allergic rhinitis with eosinophils (NARES), characterized by nasal eosinophilia without sensitization (39). Based on this immunopathological background, the clustering analysis is very fruitful for identifying specific endotypes. Initial clustering analysis considered only symptoms and quality of life aspects (40,41). Successively, a se-

ries of immunological parameters were investigated in patients suffering from CRSwNP, including IL- 5, eosinophilic cationic protein (ECP), *S. aureus* enterotoxin (SE-IgE), and albumin to define endotypes (42).

Pragmatic approach

At present, physicians stratify the patients with CRSwNP to define the optimal therapeutic strategy and formulate an appropriate prognosis resorting, in current clinical practice, to nasal endoscopy and CT findings and clinical outcomes, including the severity of symptoms, their response to treatments and recurrence, and asthma comorbidity. This clinical approach has been used to create simple management algorithms based upon clinical parameters, such as the visual analogue scale (VAS) and the sino-nasal outcome test (SNOT-22) score (40, 41). Further, a series of biomarkers were investigated to improve diagnosis, response to treatment, and prognosis (28). Initially, tissue eosinophilia and IgE (classical type 2 biomarkers) were envisaged as predictors for corticosteroid sensitivity. Further, another type 2 biomarkers were evaluated in the context of the Precision Medicine approach. In this regard, sialic acid-binding Ig-like lectin 8 (Siglec-8), a surface receptor of type 2 immune cells, thymic stromal lipoprotein (TSLP), an epithelial cell-derived innate cytokine, and IL-25, a proinflammatory cytokine promoting type 2 inflammation, were considered the potential target of antagonism in clinical trials (42). The 24-h urinary LTC_4 has been proposed as a biomarker for N-ERD phenotype and consequently for identifying patients who could be potentially responder to leukotriene antagonists (43). Therefore, the biomarkers may be useful for applying the concepts of Precision Medicine and Personalized Medicine in the management of patients with CRSwNP (44). However, it has to be considered that there are still important limitations in daily practice. Indeed, a satisfactory biomarker has not been still identified for earlier and more aggressive surgical treatment, i.e. the reboot approach, for patients with severe type 2 CRSwNP (28, 45-47). Similarly, there is no reliable biomarker able to classify type 1 endotype, as well as anti-type 3 targeted biologics, that were ineffective in the asthma model (48).

Trials with biological agents

Some trials provided evidence about the effectiveness of biologics in the treatment of CRSwNP. The first experience was conducted in patients with severe asthma and an (unexpected) improvement of NP was contemporarily observed. Consequently, different molecules were tested in this topic.

Omalizumab, an anti-IgE monoclonal, was the first experienced biologic in the treatment of patients with CRSwNP. A series of convincing proofs have been documented both by randomized controlled trials (21, 49, 50) and real-life studies (51). Interestingly, omalizumab was effective in treating NP also in non-allergic patients (21, 52). This outcome could open the possibility to explore new indications for this biological agent.

Mepolizumab is an anti-IL-5 monoclonal antibody that reduces peripheral and bronchial eosinophils in asthmatic patients (53). Mepolizumab has been investigated successfully also in patients with CRSwNP (54, 55). In particular, it has been recently reported that mepolizumab could reduce the need for sinus surgery (56).

Reslizumab is an anti-IL-5 monoclonal antibody that binds to IL-5, preventing it from binding the subunit of the IL-5 receptor. It has been evaluated the effects of Reslizumab on patients with asthma and self-reported nasal polyposis (57).

Benralizumab is an anti-IL-5 monoclonal antibody that binds to the α-chain of the IL-5 receptor initiating a direct, rapid depletion of eosinophils through enhancing the antibody-dependent cell-mediated cytotoxic pathway via the NK cells (58). A case report of severe asthma with eosinophilic CRS has been successfully treated with benralizumab (59).

Dupilumab is an anti-IL-4 monoclonal antibody which functions by targeting the alpha chain of IL-4Ra, a common receptor for both IL-4 and IL-13. These 2 cytokines play a prominent role in the Th2 pathway and pathogenesis of nasal polyp formation (60). In a randomized, double-blind, placebo-controlled phase 2 study of dupilumab in patients with CRSwNP with and without asthma, the dupilumab group experienced significant improvement in endoscopic, radiographic, and QoL endpoints relative to

placebo (61). These clinical changes were accompanied by a statistically significant reduction in circulating concentrations of the type 2 biomarkers, such as total serum IgE and eotaxin-3. More recently, it has been reported that dupilumab was able to reduce biomarkers of type 2 inflammation, including eotaxin, eotaxin 3, eosinophilic cationic protein, in polyps of patients with CRSwNP (62).

Biomarkers in clinical practice

These reported outcomes were encouraging and could pave the avenue to a new promising approach in patients with CRSwNP even though a need a precise classification of the patients is still mandatory (63). However, it has to be noted that CRSwNP is a multifaceted disease frequently characterized by multiple phenotypes and endotypes, that can imbricate between them. Patients with CRSwNP may belong to type 1, type 2, or type 3 endotype, but could display mixed phenotypes as well as multiple endotypes. In this regard, the identification of reliable biomarkers could be useful in precise phenotyping and allow the targeting of specific biologic mechanisms underlying the disease process. On the other hand, most of the investigated biomarkers are experimental and cannot be applied to routine practice. In this regard, it has been recently proposed a list of four biomarkers able to differentiate type 2 from non-type 2 inflammation: serum specific IgE, peripheral eosinophils, nasal cytology, and fractional exhaled nitric oxide (FeNO), that are easily available in daily clinical activity (64). Allergy is diagnosed by the demonstration of allergen-specific IgE production, in fact, IgE production, such as sensitization, is the *condicio sine qua non* to identify type 2 response (65). A real-world study showed that peripheral blood eosinophils correlated well with the presence of nasal eosinophils in patients with nasal symptoms, as assessed by nasal scraping and microscopic observation; consequently, peripheral eosinophils could be reasonably considered a biomarker for suspecting type 2 inflammation also at nasal level (66). Nasal cytology is a standardized procedure that can define the inflammatory phenotype of rhinitis, so allowing the precise diagnosis of rhinitis, mainly concerning the documentation of eosinophilic infiltrate (67). FeNO is a reliable biomarker able to identify type 2 bronchial inflammation as associated with eosinophil activation (68). Interestingly, NO can be measured also at nasal level (69). Also, type 2 immune response could be in turn stratified in two subgroups: the allergic endotype and the non-allergic endotype. To document sensitization, such as the production of allergen-specific IgE, could easily differentiate the two subgroups.

Personalized and integrated treatments

As previously discussed, the current challenge for the doctor managing patients with CRSwNP is the choice of the more appropriate therapy for the single patient, hopefully, according to the approach proposed by the Precision Medicine and the Personalized Medicine. In this regard, a multidisciplinary board of the EUFOREA suggested the positioning of biologics in this topic (29). First, a careful selection of patients was recommended: five prescriptive criteria were identified: i) evidence of type 2 inflammation, ii) need of systemic corticosteroids in the past two years, iii) significant QoL impairment, iv) significant hyposmia, and v) asthma comorbidity. Contraindications could be CRSsNP diagnosis, non-type 2 inflammation, cystic fibrosis, unilateral polyps, mucoceles, immunodeficiency, and factors associated with scarce compliance. Another relevant point was the recognition of criteria for defining response to biological therapy after one year: reduced nasal polyp size, reduced need for systemic corticosteroids, improved QoL, improved olfaction, and reduce the impact of comorbidities (29).

At present, biologic agents for CRSwNP could be therefore prescribed exclusively in patients with severe asthma. Moreover, as carefully pointed out by the Consensus, a multidisciplinary integrated care pathway should be performed in clinical practice. A thorough evaluation of both upper and lower airways should be done at every visit, monitoring symptoms, available biomarkers, airway function, and control medications use.

On the other hand, it has to be underlined that the enthusiastic interest obtained by biological agents

should not obfuscate the relevant importance of the so-called small molecule drugs (SMD), as recently highlighted by an EAACI Taskforce on Immunopharmacology (70). SMD is an umbrella definition that includes several medications belonging to different classes, such as topical and systemic corticosteroids, antagonists of leukotrienes, β2-agonists, antimuscarinic agents, mast cell stabilizers, and other active compounds (70). In this regard, intranasal corticosteroids represent the first-line choice in the management of CRSwNP (3, 4). Intranasal corticosteroids could be opportunely integrated with biologics.

There are different topical corticosteroid molecules, all of them are effective in reducing nasal inflammation. However, mometasone furoate nasal spray (MFNS) has a specifical indication for the treatment of nasal polyps in adult patients (71, 72). Its anti-inflammatory and anti-allergic has been documented also in the model of experimental allergic rhinitis (73). Also, its efficacy and safety have been proved by more than 20 years of presence on the market. There is also recent evidence that MFNS is effective in the postoperative management of CRSwNP (74). The long-lasting use of MFSN is safe as it does not affect the DNA of nasal mucosal cells (75). Also, MFSN is well-tolerated in the pediatric population and pregnant women (76, 77).

On the other hand, it has to keep in mind that CRSwNP is a chronic disease, thus prolonged corticosteroid treatment should be required to control the patients and to prevent a recurrence. In this regard, complementary treatments could be favourably integrated to spare the corticosteroid use. The intranasal route is the preferable and different medical devices are currently available. In this regard, Narivent® is a medical device containing enoxolone and mannitol. Enoxolone is the 18-β-glycyrrhetinic acid, it exerts potent anti-inflammatory and immunomodulatory activity as documented in *in vitro* studies (78, 79). Also, it has been demonstrated that enoxolone reduced nasal eosinophilia in children with allergic rhinitis acting on the cytokine HMGB1 (80). Enoxolone was also able to improve the nasal mucociliary transport time (81). Mannitol is a well-known osmotic anti-oedema agent. Clinical studies have demonstrated that this medical device was able to significantly improve the severity of nasal congestion (82, 83).

Conclusive remarks

Biological agents are a promising therapy for CRSwNP that could be adequately addressed to selected patients after a careful workup. However, conventional anti-inflammatory therapy should continue to be prescribed as effective, safe, and cheap. Of course, biologics and intranasal corticosteroids could be integrated between them. Moreover, as CRSwNP is a chronic disorder, non-steroidal active compounds could be effectively and safely integrated and/or alternated to intranasal corticosteroids and other anti-inflammatory ancillary treatment. Therefore, personalized and integrated therapies could be favourably prescribed in patients with CRSwNP.

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