Care about patients with chronic rhinosinusitis and type-2 inflammation

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MAIN TEXT:

Introduction

Chronic rhinosinusitis (CRS) is defined as a long-lasting (>12 weeks) inflammation of the nasal cavity and paranasal sinuses, characterized by symptoms of nasal blockage/congestion or nasal discharge, possibly associated to facial pain/pressure and a dysregulated sense of smell [1]. CRS is a generic term that may be useful to establish diagnosis, but widely incomplete to define the complexity of differing clinical patterns of the disease.

During the last 40 years, clinicians and researchers have underlined the importance of considering the subjective dimension of diseases to achieve a more global and coherent vision about the patient and the effects of the whole health-care process. This perspective was driven by the clinical necessity to go beyond the limits of 'disease-centered medicine' in order to reach a more global perspective of 'patient-centered medicine' [2]. In this perspective, any information directly provided by the patients about a health condition and its treatment (defined as Patient Reported Outcomes - PROs) represents a fundamental component of any treatment paradigm aimed to provide a personalized approach [3]. In 1948 the World Health Organization defined "health" as a state of complete physical, mental, emotional, and social well-being and not merely the absence of disease or infirmity [4]. According to it, we must be aware that patients with chronic rhinosinusitis barely fulfill this definition.

In the past 15 years, an expanding body of literature was built on CRS reporting its high socio-economic impact, reduced quality of life (QoL) and direct and indirect costs on societies, as also abundantly underlined in the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) [1]. CRS with nasal polyps (CRSwNP) is relatively common particularly in asthmatics, affecting about 2-4% of the general population [5-7], but with increasing prevalence among unselected asthmatics (7-15%) [8] and up to 50% in patients with severe asthma, particularly those with late-onset eosinophilic severe asthma [9]. The economic and social burden of rhinosinusitis, both acute and chronic, is enormous [10,11]. Costs of medication, hospitalization, physician's examinations and surgery account only for direct health care expenses, while there is a concurrent and likewise substantial indirect cost from absenteeism, disability and therefore loss in productivity and work performance [12]. Absenteeism and lower quality of life – according to SF-36 and other health-related QoL measures – are linked especially to some forms of rhinitis such as recurrent acute rhinosinusitis (RARS) and CRS both with and without polyps, with also high prevalence (15-25%) of related depression and anxiety [12]. In the USA, rhinosinusitis is in the top 10 most costly health conditions to employers. The current direct costs for the management of CRS are between $10 and $13 billion per year, with the highest direct costs in patients who had recurrent polyposis after surgery. Indirect costs from absenteeism and presenteeism

(decreased productivity at work) significantly add to the economic burden of the disease. Overall, in the USA, the total indirect costs related to CRS were estimated to be of $20 billion per year [1].

Moreover, the possible correlation between CRS and asthma can amplify the burden of both conditions synergistically [13]. Widely accepted is indeed the concept of rhinobronchial syndrome [14-16], which has been introduced to highlight the link between upper and lower airways pathophysiology.

In EPOS 2020 [1] a new concept has been emphasized, which is the multidisciplinary approach based on the precision medicine methodology. Precision medicine, that President Obama sustained in his 2015 Precision Medicine Initiative, was defined by him as "a bold new research effort to revolutionize how we improve health and treat disease" [17]. Precision medicine goes beyond the "one-size-fits-all" approach, taking into account individual differences in people's genes, environments and lifestyles. This concept was widely introduced with the paradigm of the "4-P Medicine": Prediction, Prevention, Personalization, Participation [18]. The first three Ps were introduced at the beginning of the century, then extended with the fourth one in 2008 by the molecular biologist and oncologist Leroy Hood [19]. This extension has been labeled as "a driving force for revolutionizing healthcare", since the individual's participation is the key to put into practice the other three aspects [20].

The same 4P paradigm has been applied to CRS [21-23]. Being a chronic disorder, the primary fact is that medicine cannot cure CRS patients, but it has the duty to improve its course, lower the impact on QoL and on social costs, also by means of predicting – hence avoiding – possible undesirable progression and maintaining wellness (Prevention). Participation is fundamental: it consists in keeping the patient at the core of the treatment plan, encouraging counselling to maintain adherence and compliance. In the whole scenario, as the response to treatment is influenced by several factors, patients stratification is fundamental to set the correct diagnostic and therapeutic path for each. Identifying markers that may be predictive of response means to actualize the concept of target therapy (Precision) and predicting the response to it (Prediction). On the basis of the model adopted for oncological patients, each clinic should establish a multidisciplinary team to plan the correct personalized treatment for CRS patients (Figure 1).

Immunological mechanisms

Despite clearly distinguishable, CRS phenotypes do not provide full knowledge into the underlying cellular and molecular pathophysiologic mechanisms of the disease, which are increasingly relevant because of the different association with comorbidities and their responsiveness to treatments as corticosteroids, surgery and/or biological agents [1,23]. Indeed, CRS etiology is very complex to define. At the basis of CRSwNP, in Western countries, there is the so-called Type 2 inflammation and related cytokines. Type 2 immune responses are defined by the cytokines interleukin-4 (IL-4), IL-5, IL-9 and IL-13, which can be host protective, yet, when dysregulated, have pathogenic activity [24]. Type 2 immunity induces a complex response involving granulocytes (eosinophils, basophils), mastocytes, type 2-innate lymphoid cells (ILC2), IL-4- and/or IL-13-conditioned macrophages and T helper 2 (Th2) cells [24]. These cells are crucial to the pathogenesis of CRS and related disorders (asthma [25]), therefore, driving mechanisms that control intensity, maintenance and resolution of type 2 immunity are reasonably important regulators of disease progression and have to be fully understood for therapeutical purposes.

In the context of damaged airways epithelium as in CRSwNP, triggers that initiate and perpetuate type 2 inflammation may be different: viruses, bacteria, allergens, cigarette smoke, pollutants, etc. Yet, there is increasing evidence that viruses may enhance type 2 immunological response by stimulating epithelial expression of cytokines Thymic Stromal Lymphopoietin (TSLP), IL-25 and IL-33 [26,27]. In turn, these cytokines promote an intense cellular response by activating mast cells, ILC2 and Th2 that release IL-5, IL-13 and IL-4. The product of this immune cascade is the activation of eosinophils (by means of IL-5 and IL-13) and B-cells (through IL-4) [27]. IL-4 and IL-13 and their common receptor complex (IL-4Rα) are significantly elevated in CRSwNP. Despite sharing the same signaling pathway, they play distinct roles: IL-4 is mainly involved in the survival and proliferation of Th2 cells and isotype class switching of B cells to produce IgE, while IL-13 induces airway hyperreactivity and mucus hyperproduction, as well as smooth

muscle proliferation and fibrosis (i.e. tissue remodeling) [28,29]. IL-4 and IL-13 induce the abovementioned conditioned-state of macrophages, typical feature of CRSwNP [27].

Another molecule that in implicated in the pathogenesis of both CRSsNP and CRSwNP is transforming growth factor-β (TGF-β). TGF-β signals are fundamental in safe-guarding specific regulatory T cells (Treg) functions [30]. As Treg cells and TGF-β pathway are critical regulators of T cell tolerance, together they play important roles in the development of immune disorders, such as asthma and allergy [31]. In addition, TGF-β is a key factor in the remodeling process found in sinonasal mucosa with CRS. Specifically, TGF-β pathways were found to be upregulated in CRSsNP and downregulated in CRSwNP [32]. In the former scenario, TGF-β upregulation leads to induction of proliferation of fibroblasts, increased collagen deposition and extracellular matrix (ECM) production, as well as reduced metalloproteinases (MMP) activity, hence resulting in fibrosis and basement membrane thickening [33]. In CRSwNP, TGF-β downregulation contributes to greater MMP activity, degradation of ECM and deposition of albumin, which results in intense edematous stroma, subepithelial and perivascular inflammatory cells infiltration, formation of pseudocysts and polypoid degeneration [34].

Further mechanisms underlying CRS are complex and likely still unknown. As phenotyping is sometimes found insufficient to treatment efficacy, endotyping becomes necessary. In the scenario of Precision Medicine, identifying the specific pathophysiologic process of a patient's endotype may permit more effective treatments, better patient's outcomes and lower expenditures [35]. Also, defining the endotype is required to access the use of new targeted biotherapeutic molecules, such as anti-IgE and anti-cytokine monoclonal antibodies [36].

Surgical management: contemporary and future perspective

Despite the future probably lies in developing new drugs to target the abovementioned molecular pathways, to prevent recurrent sinus surgery or even avoid it, nowadays steroid therapy and surgery still play a relevant role in the treatment strategy of CRS. Anti-inflammatory therapies are at the forefront in the treatment of eosinophilic CRSwNP (E-CRSwNP) and, above all, corticosteroids, both intranasal and systemic (they contrast type 2 inflammation thus controlling both local and associated systemic effects of the disease) [37]. However, chronic and/or recurrent use of both systemic corticosteroids (particularly frequent in patients with CRSwNP and concomitant severe asthma [38]) and topical corticosteroids is associated with a relevant increased risk to develop adverse events (i.e.: type-2 diabetes, hypertension, glaucoma, osteoporosis...) [37,39] that may have also a dramatic burden in terms of health-care costs [40].

Along with steroids, sinonasal surgery improves nasal symptoms in patients with CRSwNP. Especially in patients with aspirin intolerance, allergic fungal rhinosinusitis (AFRS) and asthma, nasal polyposis is histologically dominated by dense eosinophilic infiltration: in these cases, a more aggressive surgical approach is required and is often combined with extensive postoperative use of corticosteroids to preserve good surgical results and prevent polyps regrowth [41]. Different "versions" of endoscopic sinus surgery exist and technique has evolved over time. Since 1984, Functional Endoscopic Sinus Surgery (FESS) has become the world gold standard in the management of sinonasal inflammatory disease unresponsive to medical therapy [41]. FESS, as it was originally presented, currently leaves some interpretative doubts. Based on its original principles, the aim of FESS is the rehabilitation of a sinus ventilation by exposure of its natural ostium without altering its profile, minimizing mucosal stripping and preserving anatomical landmarks (such as the middle turbinate) [41]. This "limited" surgery is especially adequate for larger sinuses (frontal and maxillary),that rarely require extensive manipulation. It precisely means to clear ethmoidal clefts, reestablishing ventilation and drainage of diseased large sinuses via their physiological routes[34]: the frontal recess for frontal sinus ventilation and the lateral wall of the middle meatus for maxillary sinus ventilation. Little deviations from the FESS paradigm take place, for example, when the maxillary sinus ostium is enlarged anteriorly and/or posteriorly (to the nasal fontanelle areas), still resulting in a window in its physiologic place. Over time, the concept of FESS has developed further. According to EPOS 2020 steering group [1], "full FESS" indicates sinus opening that includes anterior and posterior ethmoidectomy, large middle meatal antrostomies, sphenoidotomy and frontal opening (e.g. a Draf IIa procedure), still without damaging important landmark as the middle turbinate and mucosa in general. This is particularly applicable to compartmental sinusitis and

CRSsNP, and it can be applied to non-type 2 CRSwNP. The functionality criterion cannot be respected in severely extensive CSRwNP and in conditions characterized by type 2 inflammation, since limited surgery will not be effective in the long run. As disease becomes more severe, wider surgical resections turn out to be necessary: a large "ethmoidectomy box" with wide lateral fenestration to the maxillary sinus, extended upward to the frontal sinus and backward to the sphenoid. In many cases, the steadiness of the middle turbinate is compromised by both the destructive action of the disease and the extension of surgery. Being systematic in the endoscopic approach (ESS) implementation and in designing a targeted surgical treatment responds to the following needs: to create a surgical bed as wide as possible to help control recurrence with topical medications, to facilitate reintervention by simple polyps debridement, to minimize post-surgical restenosis.

In spite of great advancements in the biologics field for very severe and recurrent forms of polyposis, nowadays – and at least in the initial phase of a larger diffusion of these new drugs – few patients will have access to biological therapies. The first therapeutic attempt in complicated and relapsing CRSwNP will certainly be surgery. In 2018, a newly proposed approach (named "reboot approach" [42,43]) was introduced in the surgical scenario of severe recalcitrant CRSwNP, especially for cases who underwent multiple interventions. It aims to restore a non-inflammatory state of the epithelium by entirely removing the dysfunctional eosinophilic-infiltrated mucosa up to the periosteum of nasal and paranasal cavities, partially sparing the mucosa of the inferior conchas [42,43]. The procedure is accompanied by a Draf III or at least Draf IIb frontal drainage. The rationale is that removal of type 2 inflammatory environment might allow unaffected mucosa to grow and re-epithelize sinuses walls, markedly decreasing the risk of relapse.

An upcoming fascinating perspective could be represented by the combination of surgery and biological therapy for E-CRSwNP. In such manner, endoscopic surgery could be minimized to the true principles of FESS, supported by the effects of post-operative administration of targeted drugs.

Are biologics grabbing the spotlight?

As vastly proved, initial treatment of CRS includes topical and systemic corticosteroids, long-term antibiotics and surgical intervention. However, some patients suffer from a recalcitrant form of disease despite best practice. In recent years, the advancement in pharmaceutical therapies has reached application also in CRSwNP, with molecules (monoclonal antibodies) that specifically target the major players in the inflammation cascade of CRSwNP [36]. For what concerns the use of biologics, the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) suggested five criteria that should be satisfied to prescribe them in CRSwNP [44]. Besides having undergone sinus surgery, three criteria have to be met among the following: the evidence of type 2 inflammation, the need for systemic corticosteroids in the past 2 years, a significant impairment in quality-of-life because of the disease, reduced sense of smell and comorbid asthma. The fact that biologics may become an alternative to surgery is still a matter of discussion and it will be established after their approval for CRSwNP and post-marketing surveillance phase.

The critical players that have been targeted so far are IgE, IL-5, IL-4 and IL-13, as well as some of their receptors [36]. The continuous local activation of mast cells, basophils and dendritic cells by IgE can be reduced by selective binding to free circulating IgE, thanks to an anti-IgE antibody (omalizumab) [45]. Two pivotal old studies [45,46] in a small number of patients (<30) gave contradictory results, but very recently the first results of two phase III clinical trials (POLYP 1 and POLYP 2) showed that omalizumab significantly improved endoscopic, clinical and PROs in patients with corticosteroid-refractory CRSwNP [47].

Other drugs that block circulating IL-5 (mepolizumab and reslizumab) and therefore interrupting eosinophilic inflammation, have undergone testing through randomized controlled studies: the only large study that was conducted with 105 severe CRSwNP patients is by Bachert et al. [48], showing that mepolizumab reduced the need for sinonasal surgery compared to placebo. Significant improvement in symptoms (rhinorrhea, nasal blockage and hyposmia), quality of life (by means of Sino-nasal Outcome Test, SNOT-22, questionnaire), as well as increase in Peak Nasal Inspiratory Flow (PNIF) in patients treated with mepolizumab. Similarly, blood eosinophils decreased. Results of phase 3 trials for mepolizumab in CRSwNP are expected to be

published within a year [36]. Also, RCTs on benralizumab, a monoclonal antibody directed towards the alpha subunit of IL-5 receptor (IL-5Rα), are ongoing.

Interleukin-4 (IL-4) and interleukin-13 (IL-13) have overlapping biological effects because of their partly shared receptor complex [29]. IL-4 may interact with either a type I receptor (made of IL-4 receptor alfa, IL-4Rα, and the common γ-chain of the IL-2R) or a type II receptor (made of IL-4Rα and an IL-13 binding chain, IL-13Rα1). This type II receptor complex is also a functional receptor for IL-13, which is the reason or IL-4/IL-13 common pathways and functional properties [49]. Dupilumab is a monoclonal antibody against the IL-4Rα that inhibits both IL-4 and IL-13 signaling. Dupilumab significantly improved nasal polyp score (NPS), nasal congestion or obstruction, and sinus Lund-Mackay CT scores in two phase-3 big trials (SINUS-24 and SINUS-52) [50]. At the moment, it is the only monoclonal antibody approved for the treatment of CRSwNP [1,36].

Discussion

CRS is a heterogeneous disease, with at least two main clinical phenotypes (CRSwNP and CRSsNP), and it is characterized by a complex interaction between the degree of upper airway inflammation (mainly Type-2) and its clinical expression; genetic, environmental and behavioral factors, together with the presence of relevant comorbidities, contribute to determine the degree of disease severity (i.e.: recurrence rate after surgery, the need of systemic corticosteroid treatment...) and the its impact on patient's QoL and health-care related costs (Figure 2). For all these reasons, a more personalized approach, including a more precise disease endotypization, should be implemented in caring patients with CRS. In order to achieve this aim, a multidisciplinary team, including at least otolaryngologists, allegists/clinical immunologists, pulmunologists and phycologists, is mandatory (Figure 1), particularly in a era in which novel therapeutical approaches, such as biologic agents and innovative surgical treatments (i.e.: the so-called "reboot surgery") face the scenario of CRS management.

FIGURE LEGENDS:

Figure 1 - Multidisciplinary approach to patients with chronic rhinosinusitis

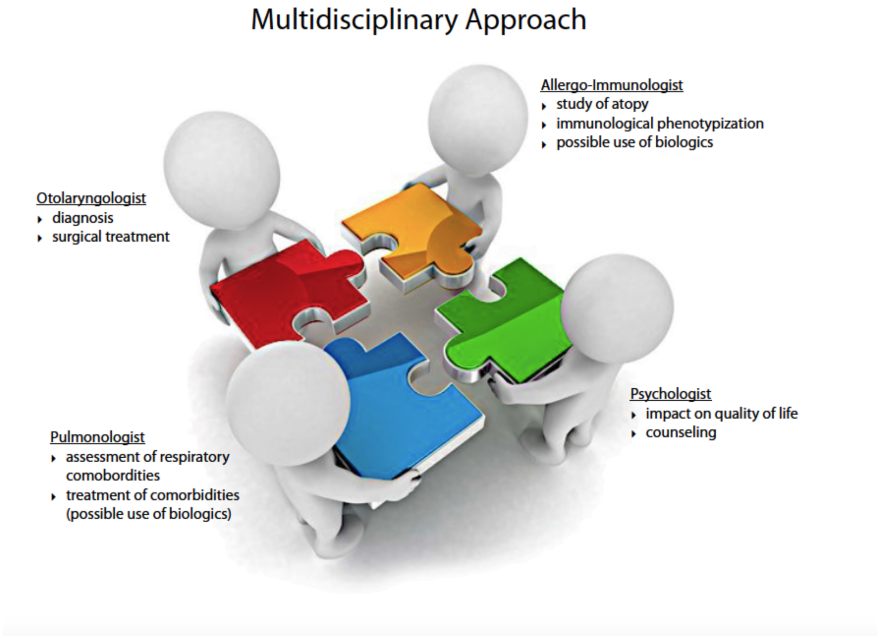
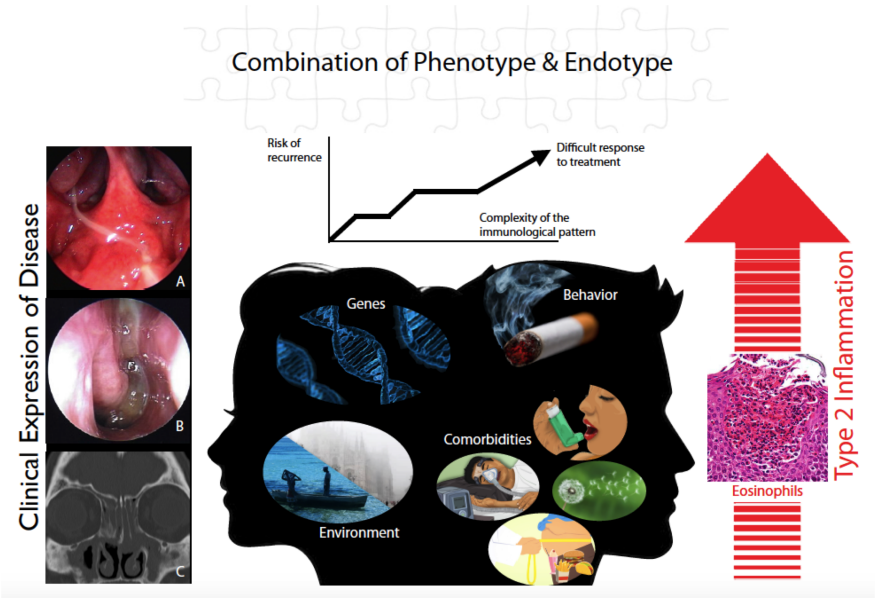


Figure 2 - Genetic, environmental and behavioral factors contribute, together with comorbidities, to determine the degree of upper airway Type-2 inflammation, with consequences on clinical expression and severity

(i.e.: recurrence after surgical treatment) of chronic rhinosinusitis. A: Post-nasal drip, as an example of pure upper airway inflammatory involvement; B: Chronic rhinosinusitis with nasal polyps, a more structured inflammatory condition; C: CT-scan with extendend chonic rhinosinusitis with concomitant bone remodeling as consequence of chronic inflammation.



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