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Chronic Rhinosinusitis—Could Phenotyping or Endotyping Aid Therapy?

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Abstract

Objectives: We reviewed the phenotyping and endotyping of chronic rhinosinusitis (CRS) and treatment options.

Methods: We searched PubMed, Google, Google Scholar, and the Proquest Central Database of the Kırıkkale University Library.

Results: Phenotypes are observable properties of an organism produced by the environment acting upon the genotype, that is, patients with a particular disorder are subgrouped according to common characteristics. Currently, CRS is usually phenotyped as being with (CRSwNP) or without (CRSsNP) nasal polyps. However, this is not immutable as some individuals progress from nonpolyp to polypoid CRS over time. Phenotypes of CRS are also based on inflammatory patterns, generally CRSwNP is eosinophilic, CRSsNP neutrophilic; but there is a spectrum, rather than a clear-cut division into 2 types. An endotype is a subtype of a condition defined by a distinct functional or pathobiological mechanism. Endotypes of CRS can be (1) nontype Th2, (2) moderate type Th2, and (3) severe type Th2 immune reactions, based on cytokines and mediators such as IL4, 5, 13. CRS endotyping can also include a (1) type 2 cytokine-based approach, (2) eosinophil-mediated approach, (3) immunoglobulin E-based approach, and (4) cysteinyl leukotriene-based approach. Subdivisions of CRSwNP can be made into nonsteroidal anti-inflammatory drug-exacerbated respiratory disease, allergic fungal sinusitis, and eosinophil pauci-granulomatous arteritis by testing. General treatment for all CRS is nasal douching. The place of surgery needs careful reconsideration. Endotype-directed therapies include glucocorticosteroids, antibiotics, aspirin, antifungals, anticytokines, and immunoglobulin replacement. The recognition of united airways and the co-occurrence of CRSwNPs and severe asthma should lead to common endotyping of both upper and lower airways in order to better direct therapy.

Conclusion: Endotyping can allow for the identification of groups of patients with CRS with a high likelihood of successful treatment, such as patients with a moderate type 2 immune reaction or those with acquired immune deficiency.

Keywords

chronic rhinosinusitis, endotypes, phenotypes, asthma, nonsteroidal anti-inflammatory drug-exacerbated respiratory disease, allergic fungal sinusitis, eosinophil pauci-granulomatous arteritis

Introduction

Chronic rhinosinusitis (CRS), characterized by persistent mucosal inflammation of the nose and paranasal sinuses, is one of the most prevalent chronic diseases.[1–4] The disease affects 10.9% of European and 13.4% of American people with impaired quality of life (QOL) and personal productivity.[5,6] Conservative treatment of CRS includes medical therapy for eliminating pathogenic bacteria, reducing inflammation. Nasal douching is undoubtedly helpful,[7] and most patients also receive topical glucocorticosteroids with benefit in CRS with

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nasal polyps (CRSwNPs), although effectiveness in CRS without nasal polyps (CRSsNP) is uncertain.[8]

Currently, patients who do not respond to medical therapy become candidates for sinus surgery.[1–4] However, evidence suggests that more intensive medical treatment is equally effective as surgery[9] and better for concomitant asthma in CRSwNPs. Also the place of surgery may be much earlier in the disease course.[10]

The best therapeutic option for patients with CRS, as for all diseases, probably involves precision medicine, with the individualized definitions of pathological mechanisms. This necessitates identifying the individual phenotypes and endotypes of CRS. For instance, defining the steroid-resistant phenotype in patients with CRS can avoid the potential side effects of corticosteroids.[11,12] Also, describing the endotypes of the disease is necessary due to the potential benefit of targeted biotherapeutic agents, such as anti-immunoglobulin E (IgE) and anti-cytokine antibodies.[13]

In this article, we review the phenotypes and endotypes of CRS. We searched PubMed, Google, Google Scholar, and the Proquest Central Database of the Kırıkkale University Library.

Phenotypes of CRS

The CRS phenotype is based on the presence (CRSwNP) or absence (CRSsNP) of nasal polyps (NPs) according to current recommendations (Figure 1).[12,13] Eosinophil-mediated TH2-high (IL-4-, IL-5-, and IL-13-high) cytokines are probably more related to Western NP disease, whereas CRSsNP has noneosinophilic disease mechanisms. The determination of polypoid tissue endoscopically with relative ease makes this phenotyping method still valid and practical.[11] However, caveats exist—patients with rhinitis may have CRS symptoms before actual polyps develop and not all polyps are eosinophilic. Asian NPs can be neutrophilic and may have a Th17 mechanism, though eosinophilic ones are becoming more common.[14] Three distinct phenotypes of CRSwNPs and asthma in China were recently described.[15]

Sinonasal fibroblasts were increased in CRSwNP and allergic fungal rhinosinusitis (AFRS) compared to control and CRSsNP in an American study.[16] Fibroblasts were associated with worse QOL but not with asthma.

Inflammatory Cell Profile (Neutrophilic and Eosinophilic CRS)

Quantifying eosinophil expression in nasal tissue or secretions constitutes an alternative approach. The intensity of eosinophilia, and its marker, serum periostin, in CRSwNPs correlates with disease severity and the likelihood of rapid recurrence of polyps following

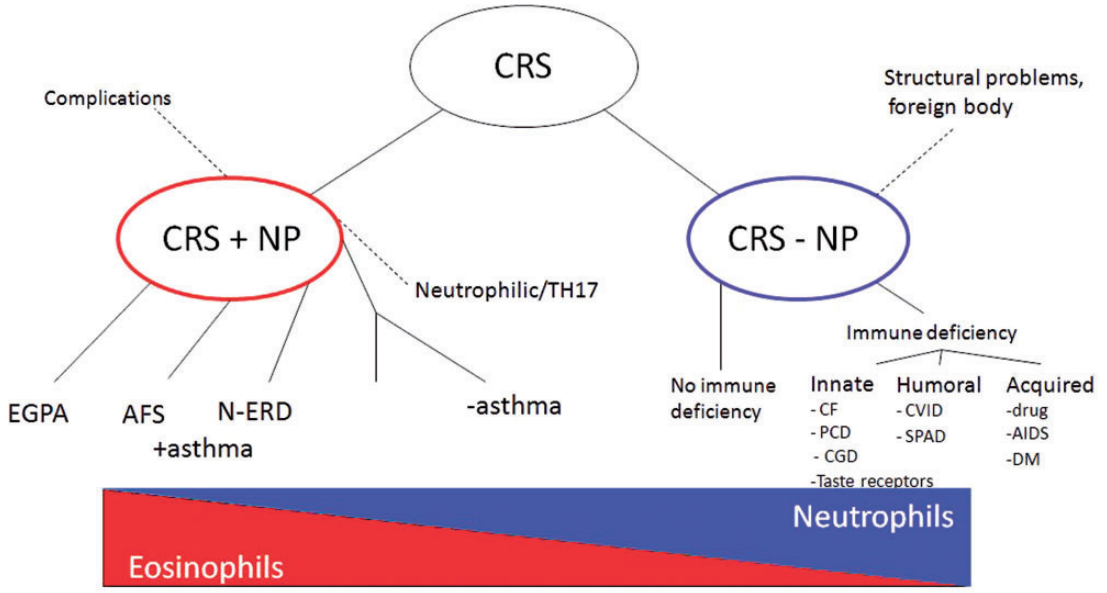

Figure 1. Phenotypes of CRS. This shows the basic division of CRS into that with CRSwNPs, or withoutCRSsNPs, nasal polyps. It also includes further phenotypes which can be clinically identified within these 2 divisions. Beneath this is the likely composition of inflammatory cells, with the most eosinophilic tissue occurring in eosinophilic pauci-granulomatous disease (EGPA). AFS, allergic fungal sinusitis; AIDS, acquired immune deficiency disorder, due to HIV, the human immune deficiency virus; CF, cystic fibrosis; CGD, chronic granulomatous disease; CVID, common variable immune deficiency; drug, immune deficiency caused by medication, eg, anti-TNF; DM, diabetes mellitus; EGPA, eosinophilic granulomatosis with polyangiitis; N-ERD, NSAID-exacerbated respiratory disease; PCD, primary ciliary dyskinesia; SPAD, specific polysaccharide antibody deficiency.

surgical or medical polypectomy as well as the severity of associated asthma[5,17–22] (Figure 1).

A recent histotype, basophilic CRSwNP, was found to be significantly correlated with eosinophilia and prognosis.[23]

It is those highly eosinophilic patients at the severe end of the disease spectrum who have asthma as well as CRS who are theoretically most likely to benefit from monoclonal antibodies directed against IL-5 or its receptor (eg, reslizumab, mepolizumab, benrolizumab). Considering that these subjects are the most costly in terms of health expenditure because of asthma exacerbations, hospitalization, and need for surgery, the provision of expensive, but effective, treatment should prove worthwhile both for their QOL and for the providers' pockets.

CRSsNPs can be associated with neutrophils in secretions but may have a mixed picture with some eosinophils, particularly if there is concomitant allergic rhinitis or eosinophilic nonallergic rhinitis is in progression to future CRSwNPs. As in rhinitis and CRSwNPs, a mixed etiology in CRS is possible.

Microbiome Phenotypes of CRS

Identification of the microbial environment in CRS may provide opportunities for directed antimicrobial treatment.[11] Hoggard et al.[24] reported that CRS patients with asthma and cystic fibrosis (CF) had reduced bacterial diversity and an increased bacterial load than patients without asthma and CF. Cope et al.[25] demonstrated different CRS microbiota states associated with varied NP risks according to distinct functional attributes and host immune responses.

Endotyping of CRS

Theoretically, in future, microarray-based studies would enable determination of the inflammatory endotype by means of detailed individual transcriptomic, proteomic, or metabolomic signature analyses. Recent initial steps consist of analysis of cytokine signatures of TH1, TH2, and TH17 inflammation.

CRS With Nasal Polyps

Much CRSwNP has a distinct phenotype probably due to the TH2- and IL-5-high endotype. Nearly, 85% of NPs display high IL-5 concentrations[26] and also sometimes concomitant expression of IL-17- and IFN-g-associated cytokines and IL-5.

The endotyping approach inspired clinicians to apply targeted therapies to diseases sharing identical pathological mechanisms. Bacteria, fungi, viruses, biofilms, and proteins trigger inflammation by activating T-helper (TH) cells.[26,27] Activated TH1, TH2, and TH17 cells produce a group of cytokines called interleukins that regulate the activity and the accumulation of blood cells such as eosinophils and basophils and cause an inflammatory response.[28] Targeted therapies are mainly focused on the type 2 cytokines IL-4, IL-5, and IL-13, as well as IgE. Phase I and II trials show the benefit of targeted therapy, and phase III studies are currently being conducted in the development of endotype-driven treatment.[29]

Bachert et al. reported that CRS phenotypes should be distinguished into endotype profiles according to the inflammatory patterns, including prominent cytokines, such as IL-5, and *Staphylococcus aureus* enterotoxin-specific IgEs.[30] These may have a predictive value for asthma comorbidity[31] and disease recurrence[32] and also may help to allocate the role of biologics including anti-IgE, anti-IL-5, and anti-IL-4 receptor α in individualized treatment.[33] The PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology previously summarized the detailed knowledge of phenotypes and endotypes in CRS.[34]

In a recent study, 3 endotypes of CRS including non-type 2, moderate type 2, and severe type 2 inflammation were defined by comparing the significant upregulation of cytokines and mediators in healthy versus diseased patients or in severe versus moderate disease.[35] In this study, while patients with a non-type 2 endotype profile had CRSsNP with little asthma comorbidity, CRSwNP patients had a moderate type 2 profile with increased asthma prevalence. The severe type 2 endotype was associated with higher tissue IgE concentrations and *S. aureus* enterotoxin-specific IgEs expression. Recently, serum biomarkers were found that can differentiate between non-type 2 and type 2 endotypes and also determine moderate versus severe type 2 endotypes.[36,37]

Endotypes of the CRSwNP phenotype have also been classified into 4 distinct but overlapping groups as follows: (1) type 2 cytokine-based, (2) eosinophil-based, (3) IgE-based, and (4) cysteinyl leukotriene-based.[38]

Different CRSwNP endotypes were also defined according to response to different therapies such as intranasal corticosteroids and biological agents.[28] Tomassen et al.[5] defined inflammatory endotypes of CRS according to cluster analysis of biomarkers including IL-5, IFN-γ, IL-17A, TNF-α, IL-22, IL-1β, IL-6, IL-8, cationic eosinophilic protein, myeloperoxidase, TGF-β1, IgE, *S. aureus* IgE specific for enterotoxin, and albumin in CRS patients. They concluded that distinct CRS clusters, classified according to diverse inflammatory mechanisms, provided a better delineation of CRS inflammatory mechanisms than phenotype determination alone. Turner[39] found that the Th2-associated cytokines, IL-5 and IL-13, are detectable in

sinonasal mucus, and their levels can be used to define Th2-high and Th2-low CRS.

A Chinese study used principal component analysis on 28 clinical variables and 39 mucosal cellular and molecular ones in 246 prospectively recruited Chinese CRS patients to identify 7 clusters.[40] Cluster 1 (13.01%) was comparable to the classic well-defined eosinophilic CRS with polyps, having severe disease and the highest proportion of difficult-to-treat CRS. Patients in cluster 2 (16.26%) and cluster 4 (13.82%) had relatively lower proportions of NPs and presented mild inflammation with moderate proportions of difficult-to-treat cases. Subjects in cluster 2 were highly atopic. Cluster 3 (7.31%) and cluster 6 (21.14%) were characterized by severe or moderate neutrophilic inflammation, respectively, and with elevated levels of IL-8 and high proportions of difficult-to-treat CRS. Cluster 5 (4.07%) was a unique group characterized by the highest levels of IL-10 and lacked difficult-to-treat cases. Cluster 7 (24.39%) demonstrated the lowest symptom severity, a low proportion of difficult-to-treat CRS, and low inflammation load. Difficult-to-treat CRS was associated with distinct clinical features and biomarkers in the different clusters.

Asthma

This is associated with more severe type 2 eosinophilic inflammation. In a recent UK analysis of 1470 study participants—221 controls, 553 CRSsNPs, 651 CRSwNPs, and 45 AFRS—the prevalence of asthma was 9.95%, 21.16%, 46.9%, and 73.3%, respectively.[41]

Asthma may precede CRSwNPs or follow the nasal disease, as is usual in nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD). The presence of asthma emphasizes the systemic nature of the problem and suggests the need for the consideration of the disease as a whole, see Figures 1 and 2.

CRSsNPs may coexist with bronchiectasis, in which case alpha 1 antitrypsin should be measured.

NSAID-Exacerbated Respiratory Disease

This includes asthma and recurrent nasal polyposis with sensitivity to cyclo-oxygenase 1 inhibiting analgesics (aspirin and most NSAIDs) and can be involved in CRSwNP endotypes.[27,42] The pathomechanism of aspirin-exacerbated respiratory disease is unknown but includes defects in eicosanoid metabolism with increased production of leukotrienes and reduced prostaglandins, including PGE2 which is bronchoprotective.[38,43]

Allergic Fungal Rhinosinusitis

AFRS constitutes approximately 5% to 10% of CRSwNP in immunocompetent hosts. Its geographical distribution includes areas with warm, wet climates such as the Southern United States and Western Australia. In AFRS, colonizing fungal species including *Aspergillus*, *Bipolaris*, *Curvularia*, and *Alternaria* species impair

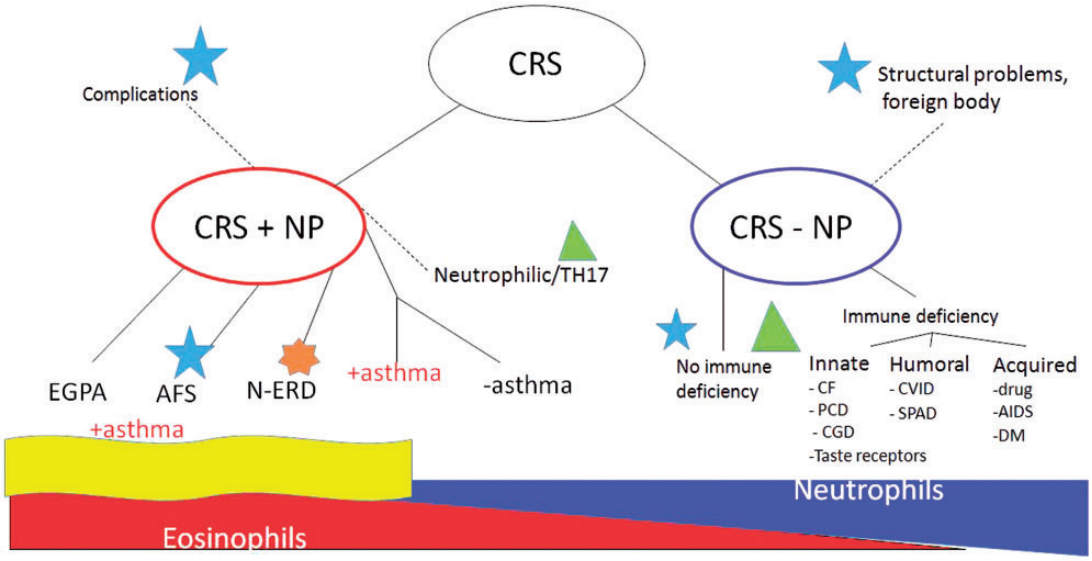

Figure 2. Specific therapies for CRS phenotypes. The areas in which surgery is likely to be particularly useful are indicated by blue stars and antibiotic therapy by green triangles. The likely place for new monoclonal antibodies is in highly eosinophilic patients with uncontrollable asthma (yellow flag). Aspirin desensitization (orange polygon) is effective in N-ERD and is considerably cheaper than all the new monoclonals. Patients with immune deficiency require therapy relevant to their condition, and this may include immunoglobulin replacement.

mucociliary clearance in paranasal sinus mucosa.[44] Fungal antigens may cause various inflammatory reactions including type I, type III, and type IV hypersensitivity that interrupt mucus drainage and subsequent fungal growth.[44,45] An association with N-ERD with an odds ratio for aspirin sensitivity among those with AFRS was 28.8 (confidence interval: 9.9–83.8); $P < .001$ was described in the UK survey.[41] AFRS may occur together with allergic bronchopulmonary apergillosis, a difficult-to-treat form of asthma.

CRS Without NPs

Although innate immunity is likely to have a pivotal role in the disease profile of CRSsNP,[46] TH1, TH2, and TH17 signatures can also exist, alone or in combination.[26] A proportion of sufferers have immune deficiency, either innate or acquired. Recent work suggests that bitter taste receptors are important in sensing bacterial quorum-forming molecules, then initiating ciliary beating and nitric oxide (NO) production. Inability to taste bitter substances is common in the population and is associated with CRSsNPs.[47]

Acquired immune deficiencies which present with CRS are usually humoral, involving reduced levels of immunoglobulins, subclasses, or a lack of specific antibody production.[13]

In children, immune deficiencies such as CF and primary ciliary dyskinesia (PCD) can present with CRS.[13] Low levels of nasal NO are present in both, particularly in PCD, and can alert the clinician to the need for further tests of ciliary function and ultrastructure.[48]

Treatment Options in CRS

In the future, it is likely that the endotyping of CRS can enable the indication of the most favorable individualized treatment modality, including medical therapy, surgery, or biologic agents (Figure 2).[38]

Surgery

Once the initial therapy for CRS, surgery now has largely been relegated to use when medical treatment has failed.[13] It involves an endoscopic approach to the ostiomeatal complex where sinus ventilation and drainage mainly occur and allows for better access of continuing medical therapy and distribution of NO. It is very rarely curative and is not superior to medical treatment.[9]

A recent paper[10] suggests that this delayed approach may be wrong and that patients with a short history prior to operation have longer remissions. However, this cannot be taken at face value because there was no detailed phenotyping of the subjects involved, and the remission rates vary markedly according to the disease type.

Certain phenotypes, such as allergic fungal sinusitis, need operative removal of the initiating allergen. Structural problems, such as a very deviated nasal septum, which restrict the access of treatment also require intervention, as do complications.[13]

Phenotype impacts upon surgical results. In a recent study from the Mayo Clinic,[49] all CRS subtypes demonstrated clinically meaningful improvement in postoperative 22-item Sino-Nasal Outcome Test (SNOT-22) scores following endoscopic sinus surgery (ESS). The overall revision ESS rate was 4% (3.5% in CRSwNP). AFS, N-ERD, and eosinophilic granulomatosis with polyangiitis (EGPA) groups demonstrated low revision rates, while immunodeficiency and granulomatosis with polyangiitis patients required more revision surgery.

Conversely, in the European experience, polyps in the highly eosinophilic CRSwNPs group, particularly N-ERD, tend to recur rapidly after operation, which itself can initiate or exacerbate asthma. Therefore, medical polypectomy with oral plus topical corticosteroid is preferable to repeated surgery.[13] Recent observations from the GALEN consortium suggest that in refractory CRSwNPs QOL is worse in those with prior surgery and worsens with the number of endoscopic operations (Holland S, personal communication), indicating a refractory group in whom monoclonal antibody therapy may be necessary.

In CRSsNPs patients, unresponsive to initial surgery may undergo multiple further operative procedures, sometimes resulting in the empty nose syndrome if turbinates are removed.[50] It would seem preferable to seek out the underlying mucosal or immune problem rather than operate multiple times.

Medical

Medical treatment options for CRS include nasal irrigation, topical and/or systemic antibiotics, oral or topical corticosteroids, antileukotrienes, antifungals, anti-IgE, anti-IL-5/IL-5 receptor, and anti-IL-4/IL-13.[11]

Nasal Douching

Using saline douching is effective in all forms of CRS[7] and should be encouraged as a daily routine. Recently, addition of corticosteroid directly into the douche has been advocated—an off label using—but there is no evidence to show whether this is preferable to use both separately. One paper suggests a lack of effect on adrenal function when 0.25 mg of budesonide and 5 mL of saline were used in each nostril once daily for 30 days.[15] Whether this remains true for higher doses and higher volumes is uncertain because wider access of

corticosteroid to the mucosa is likely to result in greater systemic absorption, compare the differential between fluticasone drops (0.06% systemically absorbed) and spray (<5% systemically absorbed). A comparative study is needed with an audit of outcomes and adrenal effects.

Corticosteroids

Oral and topical corticosteroids are commonly administered treatment modalities for CRS[13,51–53] with a reported response rate between 50% and 80%.[11,54,55] The mechanism of steroid response in CRS is presumably due to the induction of eosinophilic apoptosis.[55,56] More recent data demonstrated that an eosinophil-high TH2 lymphocyte signature is an essential factor for corticosteroid benefit.[57–59] This probably explains some negative studies in CRSsNPs.[60,61] Corticosteroids have a greater impact on type 2 inflammatory reactions than non-type 2 responses;[54] however, resistance to glucocorticoid treatments have been observed in type 2 CRSwNP patients,[55] as in asthma.[62] These subjects may be rendered responsive by calcitriol therapy which can also affect fibroblasts.[16] Endotyping could be useful for determining those who would benefit from calcitriol.

The optimal method of steroid administration in sinonasal diseases has yet to be clarified. Intranasal corticosteroid drops reduce the need for surgery in patients previously receiving conventional intranasal steroids.[63,64] Although the optimal dose or duration has not been fully clarified, oral corticosteroids have proven to relieve CRS symptoms and shrink polyp size transiently when used over 2 to 4 weeks.[65] Mometasone furoate-releasing implants placed during ESS were shown to provide better healing outcomes in terms of synechiae formation and polyposis.[34,66] An exhalation delivery system for intranasal corticosteroids (INS) reduced symptoms, improved QOL, and polyp size but has not been tested against drop formulations.[67]

Antibiotics

Prolonged low-dose macrolide therapy has a better success rate in neutrophilic patients than in those with eosinophilic inflammation, similar to asthmatic patients.[11,68] Macrolide therapy was found to reduce IL-8 levels, with one study demonstrating a significant effect on patients with low IgE levels.[69] Head et al.[70] in a recent Cochrane review demonstrated that the clinical benefit of oral antibiotic therapy in CRS was a matter of debate according to the sparse quality of evidence. Similarly, they reported that extended macrolide therapy had a limited benefit for QOL in patients with CRS. On the other hand, antibiotic resistance in CRS has been increasing steadily.[71–73] Soler et al.[74] reported that nonmacrolide therapies administered for up to 3 weeks have been a reasonable option for CRS treatment, although further randomized controlled trials are still required.

In contrast, NPs with type 2 inflammation have been treated with long-term doxycycline with benefit.[75]

Antileukotrienes

When introduced, it was assumed that these drugs would be particularly effective in N-ERD where high levels of leukotrienes are found. In fact, this is not the case—some NSAID sensitive subjects are responders, others not.[76] There are several genes involved in responsiveness.[77] But currently, it is simpler and cheaper to test this by administration for a month with monitoring of symptoms and airways.

Currently, CRSwNP treatment is composed of topical and/or systemic corticosteroids,[78] nasal irrigations, and sometimes antileukotrienes[79] orantibiotics.[27]

Several agents and/or strategies have also been described as lacking clear benefit.[34] These include antihistamines, immunotherapy, large-volume irrigations,[80,81] methotrexate,[82] antifungal medicine,[83] phototherapy, proton-pump inhibitors,[84] capsaicin, massage of the sinus ostea with botanical essential oils, air cleaners, and diet.[85] However, as most of the trials of these involved a disparate group of CRS subjects, it may be that some of these treatments could be effective in particular endotypes, for example, allergen-specific immunotherapy in children with high IgE and allergic polyps could be trialed.

Specific Treatments

Aspirin Desensitization

Oral aspirin desensitization has been shown to reduce both upper and lower airway symptoms and reduce asthma exacerbations and the need for surgery.[86] Topical nasal desensitization is also effective, uses lower doses of aspirin conjugated with the amino acid lysine to render it soluble, and is less likely to cause side effects such as gastrointestinal bleeding.[87] Not all N-ERD patients respond, those with positive skin prick tests and a longer history appear more likely to benefit.[87]

Allergic Fungal Sinusitis

Surgical removal of all of the inciting fungal allergens can be very effective in alleviating this condition, which has low rates of revision surgery.[88] The role of antifungals, either orally or in douches, is unclear, as is that of immunotherapy.[13]

New Treatment Options

Anti-IgE

Omalizumab is a recombinant DNA-derived humanized IgG1k monoclonal antibody that binds specifically to free human IgE in the blood and interstitial fluid and to membrane-bound form of IgE (mIgE) on the surface of mIgE-expressing B lymphocytes.

As free IgE is depleted by omalizumab, the FcεRI receptors on basophils, mast cells, and dendritic cells are gradually downregulated, reducing their sensitivity to allergen stimulation. Thus, omalizumab is the beginning of a new class of mast cell stabilizer. Omalizumab does not bind to IgE that is already bound by the high affinity IgE receptor (FcεRI) on the surface of mast cells, basophils, and antigen-presenting dendritic cells and therefore does not cause degranulation of these cells.[89]

Although the initial report concluded that omalizumab was ineffective in CRSwNP,[90] it was underpowered. It was composed of CRSsNP and CRSwNP and actually showed the essential role of endotyping CRS patients in order to elucidate who will benefit from a particular treatment.[79,91] In asthmatic CRSwNP patients, omalizumab demonstrated nasal symptom relief and improved QOL with decreased nasal endoscopic polyps and Lund–Mackay scores.[92]

There are lessons to be learnt from the experience in asthma. Currently, the marketing authorization states that omalizumab treatment "should only be considered for patients with convincing IgE-mediated asthma." It also specifies that, 16 weeks after the start of omalizumab, physicians should assess how effective the treatment is and should continue omalizumab only in patients whose asthma has markedly improved.[93] The product label of omalizumab initially approved by Food and Drug Administration covers patients with serum IgE in the range of 30 to about 700 IU/mL. However, there is also evidence of omalizumab efficacy in nonallergic asthma, possibly where local IgE is involved.[94] There is evidence of efficacy in allergic bronchopulmonary aspergillosis.[95] So omalizumab may also provide benefit in allergic fungal sinusitis.

Possible side effects include anaphylaxis (a life-threatening systemic allergic reaction), with a rate of occurrence of 1 to 2 patients per 1000,[96] a slight increase in heart attacks and strokes and possible unmasking of EGPA by reduction of corticosteroid.[97]

Omalizumab therapy should be initiated only by those competent in treating anaphylaxis and identifying EGPA. New anti-IgE agents, for example, ligelizumab, have greater affinity for and increased suppression of free IgE when compared to omalizumab. They may improve anti-IgE treatment.[98,99]

Anti-IL-5

IL-5 derived from T cells and ILC2 is a key mediator of tissue eosinophilia in the majority of patients with CRSwNP.[100] IL-5 also contributes to eosinophil activation, maturation, and survival; therefore, anti-IL-5 therapy may have a suppressive effect on eosinophil-related inflammation and polyp size.[101] In a small study on reslizumab, NP scores improved in half of the treated patients. Logistic regression analysis revealed that increased nasal IL-5 levels (>40 pg/mL) predicted the response to anti-IL-5 treatment.[102]

In a larger multicenter randomized, double-blind, and placebo-controlled study, the humanized anti-IL5 monoclonal antibody (mAb) mepolizumab showed a significant improvement in NP severity and symptom scores with a decreased need for surgery in CRSwNP patients, with a safety profile similar to that of placebo.[103]

Anti-IL-4/IL-13

IL-4 and IL-13 have mutual and vital functions in type 2 inflammation due to their action on the same receptors, called type 1 and type 2 receptors. A type 1 receptor has an IL-4Rα subunit, whereas a type 2 receptor has IL-4Rα and IL-13Rα1 subunits.[79] Dupilumab is a human mAb acting against the IL-4Rα subunit. It gave improvement in NP score, SNOT-22, and sense of smell in CRSwNP patients resistant to topical steroid therapy.[104]

Siglec-8

Sialic acid immunoglobulin-like lectins (siglecs) are surface proteins on cells of the immune system.[105] Among the several types, Siglec-8 is typically located on human eosinophils, mast cells, and basophils, thus constituting a possible target in the treatment of asthma and CRSwNP. A therapeutic antibody against Siglec-8 in CRSwNP patients is under test in a phase II trial.[79]

New Anti-Type-2 Pharmacotherapy

Type 2 immune reactions can also be targeted by chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) or oral prostaglandin D2 antagonists.[106] Tests are under organization in CRSwNPs.

The Future

In a very recent opinion piece,[107] the authors state that "clinical researchers should design and mount pragmatic head-to-head trials of these 4 new asthma-treatment biologics." This is certainly true, but such trials should include the assessment of the upper, as well as the lower, respiratory tract, because it is often the upper airway which very significantly impairs QOL. In fact, research in real life is more practical, and all those

treated with the new biologics should be characterized as extensively as possible, followed up, and the results analyzed in order to determine what characterizes responders and which therapy is the most effective in the real world.

Similarly, large-scale prospective studies of both surgical and medical therapies in highly investigated CRS subjects should prove enlightening. The days of individual case series are over, and collaboration and cooperation between centers is needed. The establishment of EUFOREA (http://www.euforea.eu/) is to be welcomed, as is MACRO, a National Health Service-sponsored multicenter study of medical and surgical CRS treatment in 600 patients in the UK.

With careful research, not only should CRS patients benefit, but in time, the etiopathology of various forms may be elucidated and prevention instituted.

Conclusion

Currently, CRS is usually phenotyped as being with (CRSwNP) or without (CRSsNP) NPs. Endotypes of CRS can be (1) nontype Th2, (2) moderate type Th2, and (3) severe type Th2 immune reactions, based on cytokines and mediators such as IL4, 5, 13. CRS endotyping can also include (1) type 2 cytokine-based approach, (2) eosinophil-mediated approach, (3) IgE-based approach, and (4) cysteinyl leukotriene (CysLT)-based approach. Endotypes may differ according to geographical location.

Endotyping can allow for the identification of groups of patients with CRS with a high likelihood of successful treatment, such as patients with a moderate type 2 immune reaction or those with acquired immune deficiency.

Analysis of the response to treatment in the whole airway is needed in the future, especially when expensive new drugs are employed.

Author Contributions

Nuray Bayar Muluk: planning, literature survey, writing the manuscript, and submission. Cemal Cingi: planning and literature survey. Glenis K. Scadding: planning, literature survey, drew the figure, critical review of the manuscript, and revision following review. Guy Scadding: planning, helped with the figure, and literature survey.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Glenis K. Scadding has taken part in the trials of CRS treatment with surgery, corticosteroids, antibiotics, douching, and mepolizumab. Guy Scadding has taken part in the trials of CRS treatment with mepolizumab. All other authors have no conflicting interests.

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