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RHINOSINUSITIS (J MULLOL, SECTION EDITOR)

Precision Medicine in Rhinosinusitis

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Abstract

Purpose of Review Our scope is the presentation of research and clinical progresses in relation to precision medicine that are expected to alter our clinical practice in relation to chronic rhinosinusitis (CRS). Current knowledge on phenotypes and endotypes, biomarkers, and clinical markers for diagnosis, medical and surgical therapy, and prognosis is presented as well as the role of precision medicine in United Airway Disease and SCUAD (severe-uncontrolled chronic upper airway inflammation).

Recent Findings Current technological progresses, mostly in relation to molecular biology and information technology, have permitted more detailed pathophysiological assessments and multidimensional approaches in airways diseases. Based on the concept of united airways diseases, new classification schemes, called endotypes, have been proposed for CRS. In addition, novel biological treatments that have been introduced for the treatment of asthma show great promise as well for severe uncontrolled cases of CRS with nasal polyps. Central to this approach are new biomarkers that are being examined in relation to complex bio-clinical traits of CRS.

Summary As this narrative review of the aforementioned precision medicine initiatives in relation to CRS advances, a modification of current practice is expected not only for severe chronic upper airways diseases in tertiary centers but also for milder and more common cases that are being encountered in the community.

Keywords Precision medicine · Chronic rhinosinusitis · Biomedicine · Endotypes · Biomarkers

Introduction

Diagnosis of rhinosinusitis, either acute or chronic, is based on clinical presentation and endoscopic or radiologic findings [1]. As a result, the various types of rhinosinusitis are often treated similarly and, potentially, suboptimally [2, 3]. On the other hand, recent technological advances, mainly in the fields of genetics and engineering, increase the amount of information that enable more targeted, effective, and efficient treatment plans. Precision medicine 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" [4]. It is obvious that current data producing and analyzing technologies can enable precision medicine, thus allowing classification of individuals into subgroups and customized treatment based on their traits.

Phenotypes and Endotypes

Current treatment guidelines and state-of-the art documents suggest a tailored management of rhinosinusitis, based on clinically observable characteristics. This approach has progressively improved outcomes over the years. Initiation of the appropriate treatment protocol requires the recognition of specific clinical symptoms, atopy status, as well as the presence of nasal polyps. Chronic rhinosinusitis (CRS) can be subdivided into several phenotypes based on the presence of nasal polyposis on endoscopy or computed tomography, the co-existence of lower airway disease (e.g., NSAID-exacerbated respiratory disease or N-ERD) (Kowaslki et al.

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Allergy 2018 Epub ahead), hypersensitivity to allergens (e.g., allergic fungal rhinosinusitis), and other underlying diseases, such as cystic fibrosis, ciliary dyskinesia, autoimmune diseases, immune deficiency, and systemic illness [5••].

For decades, assigning a phenotype to a patient or, in other words, patient stratification based on clinically observable characteristics determines the best fit treatment. However, for CRS patients, a phenotype-driven treatment is not always sufficient to obtain optimal control [6, 7]. Recalcitrant cases or patients with severe chronic upper airways diseases (SCUAD), whose symptoms are inadequately controlled despite treatment following international validated guidelines [8, 9], dictate the need for a thorough investigation of the underlying pathophysiological mechanisms.

Latest advances in molecular and microscopic investigations allowed for the identification of disease variants within specific phenotypes. In asthma, a heterogeneous inflammatory disorder involving the epithelium of the lower airways, these disease variants are called endotypes [10]. Development of asthma endotypes, which relies on specific inflammatory patterns, has resulted in better disease description schemes and the application of novel targeted biologic treatments [11]. Similarities in inflammatory mechanisms between asthma and CRS have driven research towards the identification of CRS endotypes that correlate with disease phenotypes [12], thus differentiating them further into clusters with meaningful prognostic and therapeutic correlations by providing a more accurate description of the involved inflammatory mechanisms [13••].

Several distinct but overlapping classification models exist that define the various endotypes. A cytokine-based approach seems meaningful based on currently developed targeted biologic treatments as it is going to be explained in this text. It is well known since many years that CRS with (CRSwNP) or without (CRSsNP) nasal polyps can be differentiated by distinct inflammatory cytokine profiles, namely a skewed type 2 or type 1 inflammation respectively. The typical CRS patients in North America and Europe follow a type 2 inflammatory response characterized by a high presence of eosinophils, mast cells, basophils, and T-helper 2 (Th2) cells, and comorbid associations with asthma and atopy [14]. Type 2 inflammatory patterns seem to be driven by various interleukins (IL) such as IL-5, IL-4, and IL-13, whereas type 1 inflammation, classically seen in Asian patients, is characterized by the presence of neutrophils and T-helper 1 cells as well as elevated interferon-γ (IFN-γ) [10].

In this respect, several phenotypes of CRSwNS, such as allergic fungal rhinosinusitis (AFRS) and N-ERD, may be counted as a type 2 response, whereas other CRS distinct phenotypes, such as cilia motility defects, cystic fibrosis, and infectious sinus diseases are characterized by a skewed type 1 response. Further differentiation of the aforementioned difficult to treat cases has been proposed on the basis of alternative molecular/endotyping approaches. This is mostly evident for CRS with type 2 responses. For example, increased levels of IL-4 can been seen in AFRS and N-ERD, whereas not otherwise-categorized eosinophilic rhinosinusitis has been defined by significant elevated levels of IL-5 and IL-13 [10]. In addition, AFRS is characterized by elevated levels of the proinflammatory mediator periostin, whereas the proinflammatory CysLT, produced from the 5-lipoxygenase and leukotriene C4 synthase pathways, is marked elevated in N-ERD [15]. However, CRS is not a dichotomous disease. A mixed cytokine profile, which can be classified as a Th0 profile, has also been demonstrated [16]. It has been hypothesized that the plasticity of type 2 innate lymphoid cells may contribute to disease heterogeneity, which might lead to recalcitrance and exacerbation of inflammatory diseases [5••].

It is obvious that the improved understandings of the various pathophysiologic mechanisms in CRS allows for the identification of disease clusters as endotypes. Clustering or network analyses of CRS have been performed previously based on symptoms and quality of life questionnaires [16]. These are valid and useful approaches that still guide appropriate disease management. However, these approaches do not rely on immune-histologic biomarkers involved in disease pathophysiology. From the initial clustering of CRS based on IL-5, Eosinophilic cationic protein (ECP), *S. aureus* enterotoxin (SE-IgE), and albumin concentrations [12] to current impressive increase in knowledge about immune pathomechanisms of CRS, appreciation of biomarkers is the first step prior to the application of novel treatment options.

Biomarkers and Clinical Markers for Diagnosis, Medical and Surgical Therapy, and Prognosis

Current patient stratification as an essential management step and prognosis indicator relies mostly on computer tomography or nasal endoscopy findings, severity and recurrence of symptoms and asthma comorbidity. These clinical markers of disease are well known for several years, and there is a continuous effort for the creation of simplified diagnosis and treatment algorithms based upon clinical factors and simple outcome measure tools such as visual analog scale (VAS) and Sino-nasal outcome test (SNOT-22) score [17, 18]. Nevertheless, as our understanding of CRS pathophysiology is progressing in the microscopic and molecular level, several biomarkers of disease are being examined in relation to diagnosis, treatment success, and prognosis.

A first step is towards prediction of clinical phenotypes and treatment responsiveness that directly leads to improvements in the management. Eosinophilic mucin, eosinophilia, and increased IgE levels that are associated with a type 2 immune response have been associated with treatment response and

recurrence. More specifically, glucocorticosteroids work better in an eosinophilic environment [16], since eosinophilic polyps seems to react better to local steroids compared to neutrophilic adult polyps [19–21].

In addition, there is evidence that low-dose clarithromycin long-term treatment will be successful in patients with neutrophilic rather than eosinophilic inflammation; in contrast, long-term doxycycline is considered suitable for type 2 eosinophilic inflammation [13••, 22]. Even predictions for recurrence after surgery could be made with eosinophil and neutrophil counts. However, unlike asthma, in approximately 50% of CRSwNP cases, eosinophilia is not evident [16]. This means that the number of peripheral eosinophils is not increased above normal values and the diagnosis of eosinophilic CRSwNP in these cases is hardly performed in routine clinical setting since it is either based directly on tissue eosinophilia or indirectly on ECP/myeloperoxidase (MPO) ratio determined on nasal biopsies [6].

Similar findings regarding mismatch between plasma levels and local concentrations may be found for IgE. Although elevated levels of IgE may be seen in all forms of CRSwNP except N-ERD and is considered a useful biomarker of early monitoring of immunotherapy [6], local IgE may be more strongly related to disease pathophysiology [6, 23]. A solution to this mismatch may be possibly offered by SE-IgE, which has been found to be correlated with some of the highest local concentrations of IgE. This is interesting since the functionality of local IgE in the upper and lower airways has been demonstrated by patients' response to anti-IgE therapy in a proof-of-concept study [16]. Omalizumab, an anti-IL5 monoclonal antibody, has been shown to reduce nasal symptoms and endoscopic nasal polyp score improving smell and quality of life in a study which included asthmatic patients with nasal polyps [24]. However, its effectiveness was not universal in CRSwNP patients and could not be reliably predicted by blood eosinophil counts and serum IgE values. On the other hand, periostin that was mentioned previously as a potential biomarker of AFRS has been demonstrated also as a marker for omalizumab responsiveness in patients with moderate to severe allergic asthma [25]. Nevertheless, periostin as well as SE-IgEs need to be validated further in larger cohorts. Thus, a clear indication of omalizumab remains undetermined in nasal polyps [5••].

Currently, the same applies for all new pharmacologic treatments that are focused on highly pathway-specific molecules. Although the effectiveness on CRSwNP of mepolizumab (anti–IL-5), dupilumab (anti–IL-4 receptor α, covering both the IL-4 and IL-13 pathways), and benralizumab (anti–IL-5 receptor α) has been shown in asthmatic patients, no indication approval for any of these drugs has been achieved so far for nasal polyposis [13••]. It is obvious that the application of these treatments should concern only patients with a type 2 disease. Despite the fact that, in contrast to steroids, these medications seem to be well tolerated with minimal adverse events in the middle term, further individualization is needed due to financial cost and relatively unknown long-term consequences. Biomarkers which will allow a more precise stratification are expected to revolutionize the treatment of CRS, since more patients will be eligible for biologicals treatment [16].

Other type 2 directed therapeutical options exist and are under investigation either in asthma trials or in animal experiments. Targets against sialic acid-binding Ig-like lectin 8 and thymic stromal lipoprotein (anti–Siglec-8 and anti-TSLP) are already been investigated in clinical trials. Siglec-8 is a receptor found predominately on the surface of type 2 immune cells, whereas TSLP is an epithelial cell-derived innate cytokine. In addition, two G-protein-coupled prostaglandin (PGD_2) receptor antagonists are under clinical investigation especially in N-ERD [26••]. Other examples are the antagonists of oral prostaglandin D_2/chemoattractant receptor-homologous molecule expressed on Th2 cells that maybe beneficial in type 2 immune reactions in CRS [27], whereas the blockade of IL-25 has been shown to reduce the burden of nasal polyps in a mouse model [28].

The 24-h urinary measurement of LTC_4, a metabolite of cysteinyl leukotriene, has been suggested as a biomarker of N-ERD variant of CRSwNP [29]. Medications that are being utilized for other diseases may be beneficial for the N-ERD variant. This is an example of the potential role of biomarkers on drug repositioning. More specifically, leukotriene receptor antagonists (i.e., montelukast and zafirlukast) and a 5-lipoxygenase inhibitor (i.e., zileuton), in addition to selective purinergic receptors P2Y12 (prasugrel) and T prostanoid receptors (ifetroban), are currently under investigation for N-ERD.

It is obvious that development and utilization of biomarkers in airway disease will aid clinicians in recognizing and managing the heterogeneity of CRS [30] or even differentiate this from other diseases with similar symptoms. For instance, evaluation of substance P in nasal secretions has been proposed as a potential diagnostic biomarker for idiopathic rhinitis, while overexpression of transient receptor potential (TRP) channels for nasal hyperreactivity (NHR) [6].

Apart from the new aforementioned highly specific drugs, application of more established treatment options, such as allergic immunotherapy (AIT) or surgical approaches are also expected to be determined by biomarkers. For example, among the various biomarkers that have been evaluated for the identification of AIT-responsive endotypes, serum IgG_4 levels seem to be related with clinical improvement [6]. Still a satisfactory biomarker for earlier and more aggressive surgical treatment, e.g., the reboot approach, has not been identified

although this approach seems more appropriate for some patients with severe type 2 CRSwNP [6, 31, 32].

Moreover, research on biomarkers in non-type 2 inflammatory diseases lags well behind the type 2 inflammatory diseases, and so far, no endotype-driven treatment has been proven to be effective [6]. Novel therapies targeting non-type 2 inflammation, such as CXC chemokine 2 receptor (CXCR2) antagonists and anti-IL17A antibodies, have shown little or unsatisfactory efficacy in asthma cases that have been studied [26••]. Nevertheless, the possibility of existence of mixed pathologic subgroups in recalcitrant subgroups has been proposed [5••], e.g., upon the identification of Th22 and Th17 cells as novel subsets [13••]. Thus, these or similar kinds of pharmaceuticals could have a role in SCUAD cases testing the hypothesis of defective pathways involved in the regulation of Th1 vs Th2 responses [8].

In general, biomarkers should enable diagnosis, by differentiating phenotypes and endotypes, indicate treatment responsiveness, and monitor disease control [30]. Biomarkers that have been investigated recently for this purpose are briefly presented in Table 1. Identification and adequate validation of biomarkers for the various types of CRS, as well as current and new treatment options, are neither practical nor cost-effective within commonly applied methods and protocols. New trial designs should be applied that could enable the extraction of useful information either from asthma studies, based on the concept of united airways diseases or from the simultaneous evaluation of several treatment modalities in various CRS types and chronic upper airway diseases in general.

Role of Precision Medicine in United Airway Disease and SCUAD

The concept of precision medicine in chronic nasal diseases is not new. Allergen-specific immunotherapy may be considered as an individualized treatment that is based on the sensitization patient profile [33]. As it is shown below, AIT offers neither a multidimensional approach nor a detailed pathophysiological assessment. Precision medicine has been implemented and has transformed the landscape in diseases like cancer [30], by enabling predictive cues and the active participation of patients, whereas at the same time, allows for the collection and creative use of detailed data mostly at the molecular level.

Nevertheless, current implementation of precision medicine in national as well as private level has brought up several financial, legal, and ethical issues and revealed various obstacles in personalized medicine evolution. The most important concerns exist for the various genetic tests that have been developed recently. It is commonly reported that these tests deliver uncertain information and create patient expectations that may align poorly with evidence, clinical priorities, or in some cases, the patient's best interests [34]. Uncertain information and limited ability to interpret the significance of all detected parameters are different aspects of the same thing, namely the need of practical integration of genetic and related data within the various clinical aspects of the disease. So far, high-throughput transcriptomic technologies, such as genome-wide gene expression microarrays and next generation RNA sequencing and integrative analyses of large-scale transcriptomics and epigenomics datasets with protein expression levels, have resulted in an exhaustive portfolio of significant and statistically validated genes, molecular interactions, and pathways [35]. These concern mostly physiological processes and diseases other than CRS.

However, the existence of very powerful computational models, based mostly on deep learning technology, is expected to permit the large-scale integration of existing knowledge from the various airway diseases with newly acquired multidimensional data. This approach involves the identification of biomarkers both in relation to various disease components and in part of a multidimensional assessment [30]. In other words,

Table 1 Potential biomarkers in CRS and their reported relationship with specific phenotypes, endotypes, and treatment options

Biomarkers	Diagnosis (phenotypes/endotypes)	Treatment/ prognosis
Eosinophils	Type 2 immune reaction	Reboot surgery? GATA3 DNAzyme spray? Clarithromycin
IgE, SE-IgE	CRSwNP except AERD	Early monitoring of AIT (allergen immunotherapy) Omalizumab (anti-IgE)
Urine LTC_4 (cysteinyl leukotriene)	AERD	PGD_2 receptors antagonists, leukotriene receptor antagonists (i.e., montelukast and zafirlukast), 5-lipoxygenase inhibitor (i.e., zileuton), selective purinergic receptors P2Y12 (prasugrel), and T prostanoid receptors (ifetroban) antagonists.
IgG_4		AIT
Cytokines (IL-4, IL-5)		Monoclonal antibodies (biological, biosimilars) Long-term antibiotics

the four pillars of precision medicine, namely personalized care with the tailored diagnostic and therapeutic approaches, prediction of disease progression and success of treatment, prevention of disease and participation of the patient [6], require the assessment of additional disease components beyond the narrow framework of the topical sinus inflammation. Comorbid diseases, psychological factors, environmental issues, and other modifiable factors have long been recognized as important aspects of the individualization of treatment and there is a continuous effort for their integration in patient care. Real-time continuing computation of these components and quantification of their impact remains an important issue for their appropriate handling. Nevertheless, current technological advances are very promising. For example, behavioral aspects such as self-management skills may be recorded and promoted through specially designed applications in CRS, e.g., *mySinusitisCoach* [36], as well as in other airway diseases [11].

Convergence of innovative health information technology and -omics will aid in the formulation of integrated care pathways that are structured multidisciplinary care plans detailing essential patient management steps [13••]. In a primary effort for the effective application of a multidimensional assessment prior to an individualized management based on current knowledge, biomarkers, and innovative drugs, new trial designs have been utilized in patients with chronic airway diseases [37]. Master protocols and similar trials based on response-adaptive randomization techniques allow for the simultaneous study of multiple interventions, each targeting a particular biomarker-defined population or disease subtype [37]. The 'Rational Patient Experiment' that is currently applicable in CRS [7] or similar algorithms that include progressive addition or replacement of medications individualized to the patient's symptoms in various airway diseases may be incorporated in new trials dealing with the multilevel complexity created by the exponentially increased data on exposome, genome, endotypes, and phenotypes.

Conclusions

Currently, the united airways concept is of use by research efforts that attempt to unravel the pathophysiology of CRS. As in case of endotypes research in relation to novel biologic treatment with antibodies, the approach of complex bio-clinical traits with new information technology tools is expected to optimize the effect of treatment and the use of resources not only in asthma and COPD cases but also in upper airway diseases. Since SCUAD carries a significant burden [8, 38], there is a continuous effort so that precision medicine initiatives are not limited in patients with asthma and COPD. In addition, it is expected that new technological advancements will allow for rapid, on-site ("point of care") assessment of multiple biomarkers derived from high-throughput "-omic" platforms even in patients with milder disease treated in the community [39]. The integration of these data by dynamic knowledge repositories is expected to advance precision medicine from a more tailored approach based on biomarkers to the assessment and management of human health at an unprecedented level of resolution, namely high definition medicine [40].

Compliance with Ethical Standards

Conflict of Interest Dr. Kalliopi Gkouskou is the founder of Embiodiagnostics, a research company in the field of precision medicine. More specifically, it owns Genosophy-Discover Yourself, a genotyping test that is mostly related to Nutrigenetics field. Nevertheless, it does not sell/promote any of the medications or the biomarkers reported in the manuscript. The other authors declare no conflicts of interest relevant to this manuscript.

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References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Fokkens WJ, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl. 2012;23:3 preceding table of contents, 1–298.
2. Hellings PW, Akdis CA, Bachert C, Bousquet J, Pugin B, Adriaensen G, et al. EUFOREA Rhinology Research Forum 2016: report of the brainstorming sessions on needs and priorities in rhinitis and rhinosinusitis. Rhinology. 2017;55(3):202–10.
3. Fokkens WJ, Pugin B, Bachert C, Bousquet J, Joos G, Louis R, et al. Rhinology Future Debates 2017 by EUFOREA: novel treatments and surgical solutions in rhinology. Clin Otolaryngol. 2018;43:1429–38.
4. Timmerman L. What's in a Name? A Lot, When It Comes to 'Precision Medicine. Xconomy, 4 February 2013.
5.•• De Greve G, et al. Endotype-driven treatment in chronic upper airway diseases. Clin Transl Allergy. 2017;7:22 **A very interesting and useful review that concerns not only chronic rhinosinusitis but other chronic upper airways diseases that are commonly misdiagnosted for CRS**.
6. Kim DW, Cho SH. Emerging endotypes of chronic rhinosinusitis and its application to precision medicine. Allergy Asthma Immunol Res. 2017;9(4):299–306.
7. Prokopakis E, Vlastos I, Pant H, Ferguson BJ. Chronic rhinosinusitis: observation or treatment. Curr Opin Allergy Clin Immunol. 2013;13(1):31–6.
8. Prokopakis EP, Vlastos IM, Ferguson BJ, Scadding G, Kawauchi H, Georgalas C, et al. SCUAD and chronic rhinosinusitis. Reinforcing hypothesis driven research in difficult cases. Rhinology. 2014;52(1):3–8.

9. Georgalas C, Cornet M, Adriaensen G, Reinartz S, Holland C, Prokopakis E, et al. Evidence-based surgery for chronic rhinosinusitis with and without nasal polyps. Curr Allergy Asthma Rep. 2014;14(4):427.
10. Dennis SK, Lam K, Luong A. A review of classification schemes for chronic rhinosinusitis with nasal polyposis endotypes. Laryngoscope Investig Otolaryngol. 2016;1(5):130–4.
11. Bousquet J, et al. ARIA Phase 4 (2018): change management in allergic rhinitis and asthma multimorbidity using mobile technology. J Allergy Clin Immunol. 2018.
12. Tomassen P, Vandeplas G, van Zele T, Cardell LO, Arebro J, Olze H, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. J Allergy Clin Immunol. 2016;137(5):1449–1456 e4.
13.•• Bachert C, et al. Endotype-driven care pathways in patients with chronic rhinosinusitis. J Allergy Clin Immunol. 2018;141(5):1543–51 **A very informative and dense review on current precision medicine initiatives in relation to chronic rhinosinusitis.**
14. Bachert C, Zhang L, Gevaert P. Current and future treatment options for adult chronic rhinosinusitis: focus on nasal polyposis. J Allergy Clin Immunol. 2015;136(6):1431–40.
15. Sommer DD, Rotenberg BW, Sowerby LJ, Lee JM, Janjua A, Witterick IJ, et al. A novel treatment adjunct for aspirin exacerbated respiratory disease: the low-salicylate diet: a multicenter randomized control crossover trial. Int Forum Allergy Rhinol. 2016;6(4):385–91.
16. Bachert C, Akdis CA. Phenotypes and emerging endotypes of chronic rhinosinusitis. J Allergy Clin Immunol Pract. 2016;4(4):621–8.
17. Soler ZM, Hyer JM, Ramakrishnan V, Smith TL, Mace J, Rudmik L, et al. Identification of chronic rhinosinusitis phenotypes using cluster analysis. Int Forum Allergy Rhinol. 2015;5(5):399–407.
18. Doulaptsi M, Prokopakis E, Seys S, Pugin B, Steelant B, Hellings P. Visual analogue scale for sino-nasal symptoms severity correlates with sino-nasal outcome test 22: paving the way for a simple outcome tool of CRS burden. Clin Transl Allergy. 2018;8:32.
19. Wang C, Lou H, Wang X, Wang Y, Fan E, Li Y, et al. Effect of budesonide transnasal nebulization in patients with eosinophilic chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol. 2015;135(4):922–29 e6.
20. Wen W, Liu W, Zhang L, Bai J, Fan Y, Xia W, et al. Increased neutrophilia in nasal polyps reduces the response to oral corticosteroid therapy. J Allergy Clin Immunol. 2012;129(6):1522–8 e5.
21. Karatzanis A, Chatzidakis A, Milioni A, Vlaminck S, Kawauchi H, Velegrakis S, et al. Contemporary use of corticosteroids in rhinology. Curr Allergy Asthma Rep. 2017;17(2):11.
22. Bachert C, Hamilos DL. Are antibiotics useful for chronic rhinosinusitis? J Allergy Clin Immunol Pract. 2016;4(4):629–38.
23. Kim JW, Hong SL, Kim YK, Lee CH, Min YG, Rhee CS. Histological and immunological features of non-eosinophilic nasal polyps. Otolaryngol Head Neck Surg. 2007;137(6):925–30.
24. Gevaert P, Calus L, van Zele T, Blomme K, de Ruyck N, Bauters W, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol. 2013;131(1):110–6 e1.
25. Hanania NA, Wenzel S, Rosén K, Hsieh HJ, Mosesova S, Choy DF, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med. 2013;187(8):804–11.
26.•• Avdeeva K, Fokkens W. Precision Medicine in Chronic Rhinosinusitis with Nasal Polyps. Curr Allergy Asthma Rep. 2018;18(4):25 **This review provides a tabulated but thorough overview of clinical trials that concern the use of highly specific biologicals and CRS.**
27. Pettipher R, Hunter MG, Perkins CM, Collins LP, Lewis T, Baillet M, et al. Heightened response of eosinophilic asthmatic patients to the CRTH2 antagonist OC000459. Allergy. 2014;69(9):1223–32.
28. Shin HW, Kim DK, Park MH, Eun KM, Lee M, So D, et al. IL-25 as a novel therapeutic target in nasal polyps of patients with chronic rhinosinusitis. J Allergy Clin Immunol. 2015;135(6):1476–85 **e7**.
29. Divekar R, Hagan J, Rank M, Park M, Volcheck G, O'Brien E, et al. Diagnostic utility of urinary LTE4 in asthma, allergic rhinitis, chronic rhinosinusitis, nasal polyps, and aspirin sensitivity. J Allergy Clin Immunol Pract. 2016;4(4):665–70.
30. Baines KJ, Pavord ID, Gibson PG. The role of biomarkers in the management of airways disease. Int J Tuberc Lung Dis. 2014;18(11):1264–8.
31. Benninger MS, Sindwani R, Holy CE, Hopkins C. Early versus delayed endoscopic sinus surgery in patients with chronic rhinosinusitis: impact on health care utilization. Otolaryngol Head Neck Surg. 2015;152(3):546–52.
32. Hopkins C, Rimmer J, Lund VJ. Does time to endoscopic sinus surgery impact outcomes in chronic Rhinosinusitis? Prospective findings from the National Comparative Audit of Surgery for Nasal Polyposis and Chronic Rhinosinusitis. Rhinology. 2015;53(1):10–7.
33. Canonica GW, Bachert C, Hellings P, Ryan D, Valovirta E, Wickman M, et al. Allergen immunotherapy (AIT): a prototype of precision medicine. World Allergy Organ J. 2015;8(1):31.
34. Burke W, Trinidad SB. The deceptive appeal of direct-to-consumer genetics. Ann Intern Med. 2016;164(8):564–5.
35. Bousquet J, Anto JM, Akdis M, Auffray C, Keil T, Momas I, et al. Paving the way of systems biology and precision medicine in allergic diseases: the MeDALL success story: Mechanisms of the Development of ALLergy; EU FP7-CP-IP; project no: 261357; 2010-2015. Allergy. 2016;71(11):1513–25.
36. Seys SF, Bousquet J, Bachert C, Fokkens WJ, Agache I, Bernal-Sprekelsen M, et al. mySinusitisCoach: patient empowerment in chronic rhinosinusitis using mobile technology. Rhinology. 2018;56(3):209–15.
37. Agusti A, et al. Precision medicine in airway diseases: moving to clinical practice. Eur Respir J. 2017;50(4).
38. Bousquet J, Bachert C, Canonica GW, Casale TB, Cruz AA, Lockey RJ, et al. Unmet needs in severe chronic upper airway disease (SCUAD). J Allergy Clin Immunol. 2009;124(3):428–33.
39. Hellings PW, Fokkens WJ, Bachert C, Akdis CA, Bieber T, Agache I, et al. Positioning the principles of precision medicine in care pathways for allergic rhinitis and chronic rhinosinusitis - a EUFOREA-ARIA-EPOS-AIRWAYS ICP statement. Allergy. 2017;72(9):1297–305.
40. Torkamani A, Andersen KG, Steinhubl SR, Topol EJ. High-definition medicine. Cell. 2017;170(5):828–43.