

A focus on chronic rhinosinusitis with nasal polyposis: leaving aside endoscopic surgery, a step towards biologic therapies

Abstract

Traditional surgical treatment of chronic rhinosinusitis with nasal polyps is not always definitive since a high rate of polyps recurrence is reported all over the world. Precision medicine, with the utilization of biological therapies, could be a new opportunity for accurately selected patients with nasal polyp's regrowth that underwent previous surgery. In this review we provide a brief historiography of the surgical treatments of chronic rhinosinusitis with/without nasal polyps and describe the first applications of biological therapies.

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Introduction

The modern concept of rhinosinusitis with or without nasal polyps has developed through several milestones that led to the reconsideration of the classical therapeutic approach. These fundamental steps include the anatomical studies and the awareness of the anatomical role of paranasal sinuses. Until the 16th century, mysterious functions were attributed to the paranasal sinuses, which were considered a sort of “cloaca cerebri” allowing the drainage to the outer world of the “bad spirits” of the brain, or a sort of container for the “grease” that permits the eyeballs movement.¹ In fact, even if the first anatomical studies on the paranasal sinuses date back to the Egyptians, their functions were still nebulous until the last century, when their physiological roles were unraveled and permitted to theorize and realize the modern surgical accesses, alternative to the classical and traditional external accesses, especially for the frontal and maxillary sinuses.

The study of their physiological impact on the upper airways and the centrality of the nasal mucosa in the development of sinonasal disorders brought specialists to hypothesize innovative intranasal accesses to paranasal sinuses and for the first time the nobility of the nasal lateral wall is recognized. In was only with Messerklinger in the 60s that the basis of the endoscopic surgery were laid, following the recognition of the ethmoid sinus, as the key of ventilation and drainage of all sinuses, and the resultant subordination of the frontal and maxillary sinuses.² Another cornerstone in this revolutionary reconsideration of the role of paranasal sinuses is the exponential push of the technological upgrading, started in the second half of the last century and still ongoing, which, basing on the novel anatomical, physiological and functional awareness of paranasal sinuses, has permitted the development of the so-called functional endoscopic sinus surgery FESS.

Permitting a lateral vision of the nasal chambers through angled optics, the endoscope permits to reach the surgical targets and use different surgical techniques. Although nasal lining mucosa is the starting point of sinonasal disorders, mucosal streaping is no longer proposed. The introduction of the microdebrider, which can gently demolish and remove tissue, has definitely enhanced the potential roles of FESS and its advantages in terms of improved visualization, precision and expedited removal of diseased tissue. In parallel, FESS can guarantee a reduction in operative time and complications and can flatten hospitalization and operative costs.³ With these innovative techniques and concepts, endoscopic sinus surgery has been recognized as the gold standard in the treatment of paranasal flogistic and tumoural disorders, and has given dignity to diseases.

Nasal polyps can be considered the prototype of nasal diseases with a novel dignity. Settupane first recognized the importance of nasal polyps in the 80s, considering them the “top of the iceberg” of nasal and paranasal sinuses chronic disorders, allergic disorders included, and not only a minor symptom.⁴ Albeit these basis and the undeniable advantages of these techniques, recurrence rate in sinus endoscopic surgery is very consistent, exposing patients to surgical reinterventions.

Leaving aside endoscopic surgery, a step towards biologic therapies

So far nasal and paranasal sinuses disorders have not been considered to be related to airways diseases but the “united airways disease” theory by Passalacqua and Canonica highlighted the anatomical, physiopathological and functional continuity of the upper and the lower airways.⁵ In other words, the lower airways must be considered as a continuum with the nose and paranasal sinuses. A critical example is chronic rhinosinusitis with or without nasal polyps (CRSw/NP),

which can be associated with conjunctivitis and/or asthma. This modern vision of the physiopathological mechanisms of chronic sinonasal disorders and the increasing interest on the immunological basis of allergic diseases, together with a novel pharmacological baggage, could lead to a new therapeutic era centered on biologic therapies, including monoclonal antibodies, in which surgery could play a boundary role. Chronic rhinosinusitis CRS has a different prevalence throughout the world and has always been classified in two distinct forms according to the presence or not of concomitant nasal polyps.⁶ Since nasal polyps can influence therapeutic management and consequently disease control, researchers' attention focused on the physiopathological basis of their development. So far, we can assume the existence of different phenotypes of CRS with CRSwNP or without CRSsNP nasal polyps with different clinical explications and different endotypes distinct each other from a pathological, functional and molecular point of view and a potentially different response to current therapies.⁷

Hence, bearing these considerations in mind, we may hypothesize an application of precision medicine in patients with CRSw/sNP which may potentially have significant benefits from targeted therapies and a molecularly-targeted approach. Precision medicine could potentially

be resolute in patients with recurrence of CRSwNP after surgical treatment or prior to surgical treatment. For this purpose, fundamental could be finding and dosing specific, sensitive, low cost, non invasive and highly reproducible biomarkers, that could predict in advance patients' therapeutical responses to biologic therapies in order to properly target these treatments to the patients that could benefit most from them and allocate economic resources in the best way possible.⁸

Monoclonal antibodies in CRSwNP

Several clinical trials have been run investigating safety, tolerability and clinical utility of monoclonal antibodies administered to patients with CRSw/sNP and the initial results have been encouraging. This led to the approval of other phase II clinical trials that are currently still ongoing, which hopefully could bring promising data (Table 1). Since CRSwNP is usually characterized by an intense Eosinophilic inflammation and high interleukin (IL)-5 levels in nasal polyp's tissue,⁹ a potential new treatment strategy in patients with difficult-to-control nasal polyps could be antagonizing the effect of IL-5 with monoclonal antibodies. Among them, reslizumab and mepolizumab, two humanized anti-human IL-5 monoclonal antibodies, have been investigated by Gevaert and colleagues and Castro and colleagues.

Table 1 NA: Not Available Data

Monoclonal Antibody	N° Patients	Nasal Polyp Score	TC Score	Sputum Eosinophilia	Blood Eosinophilia	Total IgE	Quality of Life	FEV1	Adverse Events	
Reslizumab (Gevaert) [9]	3 Mg/Kg	53	NA	NA	-95.4% (P 0.0068)	-0.4 (P<0.0001)	NA	-0.7 (P 0.0541; Acq)	0.18 (P 0.0023)	38 (71.7%)
	Control	53	NA	NA	-38.7% (P 0.0068)	0 (P<0.0001)	NA	-0.3 (P 0.0541; Acq)	-0.08 (P 0.0023)	42 (79.2%)
Omalizumab (Gevaert) [13]	Variable Dose	15	-2.67 (P 0.001)	-4 (P 0.2; Lund-Mackay)	NA	NA	NA	+0.81 (P 0.003 Aqlq)	NA	24
	Controls	8	-0.12 (P 0.99)	+0.5 (P 0.10; Lund-Mackay)	NA	NA	NA	+0.27 (P 0.003 Aqlq)	NA	8
Mepolizumab (Gevaert P[10])	750 Mg	20	-1.3 (P 0.028)	0.68 (P Not Provided; Score Not Available)	NA	-332 (Count, P<0.001)	NA	NA	NA	21
	Control	10	0 (P 0.028)	Not Provided	NA	NA	NA	NA	NA	3
Dupilumab (Bachert C)[15]	600 Mg Load + 300 Mg/W	30	-1.9 (P<0.001)	-9.1 (P<0.001; Lund-Mackay)	NA	-7.30% (P 0.78)	-48.4 (P<0.001)	-1.2 (P<0.001; Acq)	+0.3 (P 0.07)	NA
	Control	30	-0.3 (P<0.001)	-0.2 (P<0.001; Lund-Mackay)	NA	-2.9% (P 0.78)	7.9 (P<0.001)	-0.1 (P<0.001; Acq)	0.1 (P 0.07)	NA

Gevaert et al run a phase I, single-dose, randomized, double-blind, placebo-controlled clinical trial assessing safety and pharmacokinetic profiles of reslizumab (1mg/kg or 3mg/kg) in 24 patients with massive bilateral nasal polyps. A single intravenous dose was administered. The authors demonstrated that a single injection of reslizumab (up to 3mg/kg) is well tolerated and safe and produce a significant reduction of blood Eosinophilia and Eosinophilic cationic protein ECP in serum and nasal secretions up to 8weeks after treatment. Individual nasal polyp scores and the size of nasal polyps improved only in half of the patients receiving the investigational product. A post-hoc analysis confirmed the necessity of a better selection of the eligible patients since responding patients had increased nasal IL-5 concentrations

at baseline compared to non responders and that nasal IL-5 levels decreased only in responders. Hence, a logistic regression analysis estimated a nasal IL-5 levels threshold (>40 pg/ml) that could hypothetically predict the response to anti-IL-5 treatment.¹⁰ Another double-blind, randomized, placebo-controlled clinical trial evaluated the efficacy of two intravenous injections of 750 mg of mepolizumab, another anti IL-5 humanized monoclonal antibody, in patients with severe CRSwNP.

A significant reduction in total polyps symptoms score was demonstrated in 12 of the 20 treated patients and these effects were confirmed by CT scan and endoscopic evaluations. Similarly to reslizumab, mepolizumab also produced statistically significant

reductions in blood Eosinophilia, blood and nasal IL-5R alpha, blood ECP and nasal myeloperoxidase MPO.¹¹ Another biologic agent against the IL-5 pathway is benralizumab, a humanized afucosylated monoclonal antibody targeting the IL-5 receptor expressed on eosinophils and basophils surface; benralizumab competitively inhibits IL-5 interaction with its receptor and induces antibody-dependent, cell-mediated Cytotoxicity.¹²

A single phase II, double-blind, randomized, placebo-controlled trial evaluating benralizumab for eosinophilic rhinosinusitis is currently ongoing without, as far as now, any known primary results.¹³ Together with anti IL-5 strategies, omalizumab, an anti-IgE monoclonal antibody, has been investigated in a randomized, double-blind, placebo-controlled clinical trial on a total of 24 allergic and nonallergic patients with nasal polyps and comorbid asthma. Researchers found a statistically significant reduction in total nasal endoscopic polyp scores after 16 weeks of treatment in responders, confirmed by a reduction in nasal and asthma symptoms, quality-of-life scores, nasal and serum biomarkers and computed tomography scans (Lund-Mackay score). Since CRSwNP and difficult-to-control severe asthma often coexist in the same subjects and interfere each other to attain and maintain a good control of both the diseases, all these findings suggest a potential utilization of anti-IgE strategies in patients with CRSwNP and concomitant asthma with high IgE circulating levels.¹⁴

A previous double-blind, randomized, placebo-controlled trial by Pinto et al.,¹⁵ studied omalizumab in a cohort of subjects with CRS with prior sinus surgery, most presenting with polyps; the trial resulted in a statistically significant decrease in sinus CT scan involvement (accompanied by a reduced need for steroid therapy) that was not confirmed when the magnitude of change was compared across groups. Moreover, none of the other secondary outcomes were not successfully reached.

Therefore, as far as now, there are promising but still conflicting results on anti-IgE treatment of nasal polyposis. Another investigated biological strategy to treat CRSwNP is blocking the IL-13/IL-4 pathways: they are important drivers of Th2 differentiation activating type 2 inflammatory responses via IgE synthesis and related cell types. Dupilumab is a fully human monoclonal antibody directed against IL-4 receptor alpha (IL-4R α), the common receptor for both IL-13 and IL-4; a phase II multinational, multicenter, randomized, double-blind, placebo-controlled study, evaluated dupilumab in patients with CRSwNP refractory to intranasal corticosteroids: treated patients obtained significant reduction in polyp burden in a four-week treatment period, significant improvements in SNOT-22 symptom score, Lund-McKay (CT) scores, olfaction (by means of the University of Pennsylvania Smell Identification Test) and nasal peak inspiratory flow.¹⁶

Moreover, the study put in evidence a significant decrease in IgE and eotaxin in dupilumab treated patients. Finally, the safety and tolerability of a novel monoclonal antibody inhibiting the binding of IL-33 to the ST2 receptor (AMG 282) in patients with CRSwNP were recently reported. AMG 282 is a novel mAb that inhibits binding of IL-33 to the ST2 receptor. Although there are currently no results available, a study is complete assessing the safety and tolerability of AMG 282 in “healthy volunteers” with CRSwNP.¹⁷ The primary outcome measures of the study are to assess the safety and immunogenicity of the drug; however, if the therapy shows promise, there will likely be continued investigation for use as therapy in CRSwNP.

Conclusion

From the era of the “one size fits all” therapy, precision medicine and biologic therapies, including monoclonal antibodies, will change the way of treating patients in favor of more specific treatments.⁸ This innovation will be relevant for surgical specialties above all and could be an opportunity for patients with difficult-to-control CRSwNP, especially those patients with nasal polyps recurrences after previous surgical intervention. Sinonasal surgery could be spared to such patients. Even surgery costs could be lowered and waiting lists could be shortened in favor of patients with other ENT disorders. On the other hand, biologic therapies are very expensive and research still needs more data to enlarge our knowledge on the application of biological therapies to conditions that have been and are traditionally treated with surgical interventions such as CRSwNP. This new treatment approach should prompt research to define distinct CRSwNP patients eligibility to single biologic tools.

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Conflicts of interest

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