REVIEW

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The use of biologics in children with allergic rhinitis and chronic rhinosinusitis: Current updates

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ABSTRACT
The therapeutic goals of the treatment of allergic rhinitis (AR) and chronic rhinosinusitis (CRS) are symptom relief, avoiding complications, and improving quality of life. In the treatment of AR and CRS, several limitations of currently prescribed medicines have been identified. Antihistamine administration (both oral and topical) together with intranasal corticosteroids bring relief to the majority of patients, but their dependency on the medications and a necessity to maintain strict compliance with regular medication regimes pose a challenge. Immunotherapeutic agents are an option in some patients, but polysensitized patients, the risk of anaphylaxis, and the need for daily administration for years are limiting it from becoming the main therapy modality. Immunotherapy in any form requires commitment by the patient, which renders adherence and compliance issues particularly relevant. The procedure involved are generally time-consuming and entail an associated risk of severe adverse reactions. The use of biologics could overcome the limitations of other therapeutic modalities. They could be used as a monotherapy or combined with pre-existing medications. The benefits of targeted therapy include less adverse effects and optimal efficacy. The aim of the present review was to investigate the collective literature to date pertaining to the role of biologics in managing children with AR and CRS.

KEYWORDS
Adolescents, Allergic rhinitis, Biologics, Children, Chronic rhinosinusitis

Introduction

There are several modalities available for the treatment of allergic rhinitis (AR) and chronic rhinosinusitis (CRS) including antihistamine (systemic and topical), immunotherapy, systemic and topical corticosteroids, saline douching, immunomodulators, and endoscopic sinus surgery patients who are not responsive to other therapies.[1] These treatment strategies are limited however, because they focus on symptom relief and reduction of inflammation rather than treating the root cause. It is therefore not surprising that disease control remains elusive in many patients, especially those with comorbid asthma. Recent advances in our understanding of the pathophysiology of AR and CRS have improved management paradigms, which in turn holds the promise of better outcome in patients especially those with refractory conditions.

Newly developed targeted and specific therapies such as biologics may represent treatment strategies with the potential to conquer severe AR and recalcitrant CRS. One biologic that has undergone numerous successful clinical trials is omalizumab, an anti-IgE antibody that is specific

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for the IgE mediator.[2] Because IgE is one of the main mediators involved in allergic reactions, one approach to treating IgE-mediated allergic conditions is to target both membrane-bound and soluble IgE. As well as having been approved for treating patients with severe persistent allergic asthma, omalizumab is also approved for use in patients with recalcitrant and antihistamine-resistant chronic idiopathic urticaria.[3]

Given the link between AR and asthma by way of shared biological pathways, the use of omalizumab in patients with both conditions may yield significant benefits.[4] Omalizumab is evidently well tolerated, with no serious treatment-related adverse events leading to study discontinuation having been identified to date. Most adverse events are of a mild to moderate nature.[4] Subcutaneous injection of omalizumab is reportedly well tolerated, with infrequent and generally mild local reactions.[4] As well as exhibiting efficacy in patients with severe asthma, the use of omalizumab in patients with CRS with or without asthma has demonstrated its potential to reduce nasal and sinus nasal polyp burden and to improve typical symptoms.[5]

In a study reported by Gevaert et al[6] there was a significant decrease in total nasal endoscopic polyp scores after 16 weeks of therapy. The significant decrease in nasal polyps was associated with significant reduction in of clinical symptoms in both allergic and non-allergic patients. In addition, it had a beneficial effect on airway symptoms (nasal congestion, anterior rhinorrhea, loss of sense of smell, wheezing, and dyspnea) and on quality of life scores, irrespective of the presence of allergy. Nasal polyp disease also exhibits a type 2 inflammatory pattern with expression of interleukin (IL)-4, IL-5, and IL-13 in conjunction with increased concentrations of IgE. The degree of type 2 inflammation is reportedly associated with disease severity, asthma comorbidity, and recurrence of disease after surgery. Furthermore, IL-5 is evidently the key driver of eosinophilic differentiation and survival. In patients with nasal polyps that were refractory to corticosteroid therapy the use of the anti-IL-5 biologic mepolizumab, resulted in significant reduction of nasal polyp size as determined via nasoendoscopic examination and computed tomography.[7] At present, that method of treatment via injection and the associated high costs represent a barrier to availability for the majority of patients.

Determining its effectiveness and safety may have important implications for the management paradigm of some children with severe AR and CRS who do not respond to more established prescribed treatments.

Types of biologics

Most biologics are used to treat moderate to severe allergic asthma (Table 1) and other indications include chronic idiopathic urticaria. No biologic is currently approved for the treatment of AR.[1] It is only used as salvage therapy in patients with AR and CRS when other medical treatments and surgical options have failed. Only omalizumab is used in children under 12 years of age whereas other biologics are used in older children. There are several types of biologic agents and they differ with regard to their targeted mechanisms of action. The most well-known anti-IgE monoclonal antibody is omalizumab, recombinant humanized antibody.[7] It selectively binds to free IgE, and thus decreases the expression of IgE receptors on mast cells/basophils, and dendritic cells.[2,4,8] Anti-IL-5 biologics include mepolizumab, and benralizumab which binds to IL-5 receptor leading to the induction of eosinophil and basophil apoptosis.[9] Reslizumab is another anti-IL‐5 monoclonal antibody and it is indicated in patients whose asthma is not adequately controlled via standard therapy. It is reportedly efficacious, well tolerated, and safe.[10]

Pascolizumab is a monoclonal antibody that selectively binds and competitively inhibits free IL-4, and dupilumab, anrukinzumab, and lebrikizumab are monoclonal antibodies targeting IL-13 in patients with atopic

TABLE 1 Type of available biologics and their indications

Name	Mechanism of action	Age (years)	Indications
Omalizumab	Anti-IgE	≥ 6	1. Moderate-to-severe persistent allergic asthma 2. Chronic idiopathic urticaria
Reslizumab	Anti-IL-5	≥ 18	Severe asthma with an eosinophilic phenotype
Mepolizumab	Anti-IL-5	≥ 12	1. Severe asthma and with an eosinophilic phenotype 2. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome)
Dupilumab	Anti-IL-4	≥ 12	1. Moderate-to-severe asthma with eosinophilic phenotype or corticosteroid dependent asthma 2. Moderate-to-severe atopic dermatitis 3. Chronic rhinosinusitis 4. Eosinophilic esophagitis
Benralizumab	Anti-IL-5	≥ 12	1. Severe asthma with an eosinophilic phenotype 2. Hypereosinophilic syndrome 3. Eosinophilic granulomatosis with polyangitis

dermatitis and asthma.[11] In patients with CRS, the addition of subcutaneous dupilumab with nasal mometasone furoate for a 16-week period was shown to reduce nasal polyp burden, as determined via both clinical and radiological examinations.[12] In that same study it also improved both olfactory and disease-specific quality of life questionnaire scores, more so than mometasone spray alone.[12] Siglec-8, a new biologic agent which acts on a receptor found in mature eosinophils is under investigations.[13,14] The binding of antibody by siglec-8 will induce apoptosis cytokine-activated eosinophils and prevention of release of mediators from mast cell.[13]

Mechanism of action

Different biologics function via a variety of different mechanisms (Figure 1). The anti-IgE monoclonal antibody omalizumab binds to high-affinity IgE Fc receptor in interstitial fluid and blood, thus blocking the IgE-mediated inflammatory cascade and eventually reducing the concentration of free IgE in serum which in turn results in reduced binding of IgE to mast cells and basophils.[11,13] The IL-5 pathway functions by activating Th2 cells, leading to the release of IL-5, which in turn leads to increased IgE, eosinophilia, chemotaxis, differentiation, activation, and eosinophil survival.[13,14] In the IL-4/IL-13 pathways inhibitors activate cytokines that lead to Th2 cell differentiation and activate a type 2 inflammatory response via IgE synthesis and eosinophils, basophils, and mast cell production.[13,15] Lastly, the epithelial cell-derived cytokine pathway is a mechanism promotes important upstream mechanisms that drive the type 2 inflammation mechanical barrier to the external environment, and also actively stimulates innate and acquired immune responses via cytokine production.[14,15]

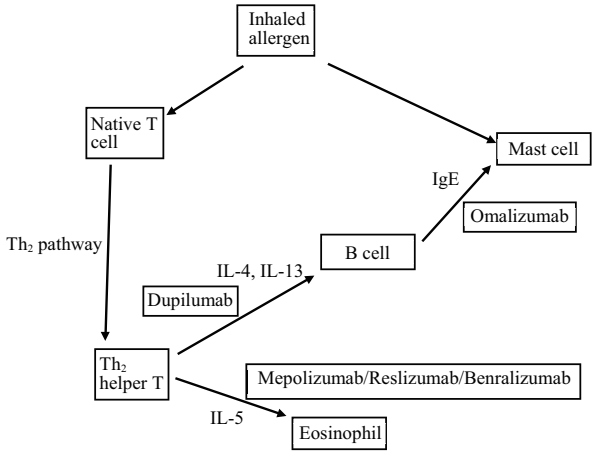

FIGURE 1 Mechanism of action of the biologics

Adverse effects

The most common adverse effects of biologics are anaphylaxis, oropharyngeal pain, increased blood creatine phosphokinase, myalgia, and localized injection site reactions.[16]

Challenges with biologics

There are significant costs associated with the use of biologics. Direct costs have been estimated to range from approximately $10 000 to $40 000 annually.[14,17,18] The use of biologics may be justified in patients with life-threatening conditions such as severe allergic asthma with frequent intensive care unit admissions and frequent visits to the emergency room requiring nebulizer therapy. Conversely, their use in AR and CRS which that are not such critical conditions is controversial. Strong justification is required for the long-term use of biologics in cases of hard to treat AR and to avoid revision surgery in cases of severe recurrent CRS. In cases of CRS, that justification might be the provision of a cost-effective alternative to repeated multiple surgeries. Because inhibition of the allergic reaction does not lead to specific immune tolerance in this context, it is not a curative approach.[19] This leads to the question of whether to use it permanently or repeatedly, depending on symptom severity and frequency. When using it on a long-term basis the issue of cost compared to the benefit should be considered, as is the availability and/or applicability of other options.

As the approach is relatively new, the safety profile of biologics is not fully understood. Apart from common adverse effects such as localized injection site reactions (8%–45%) and headaches (6%–19%) as well as associations with herpes simplex reactivation, conjunctivitis, and a risk of serum sickness, more serious complications have been reported.[14,20] Anaphylaxis and hypersensitivity reactions have been reported in 1% of patients.[20] It is recommended that patients undergo an observation period in the clinic after administration, and patients should be informed about the signs and symptoms of anaphylaxis and issued with an epinephrine auto-injector.[13,15,21,22] Current recommendations include monitoring patients for 2 hours after each of the first 3 three doses, and a 30-minute observation period after the administration of every subsequent doses.[1,21,23] Omalizumab administration has also been associated with cardiovascular complications such as pulmonary embolism, deep vein thrombosis, myocardial infarction, and unstable angina, as well as malignancy.[14,20,24] In addition to the need to be vigilantly aware of the potential complications and monitor the patient accordingly, there is a requirement for frequent monitoring of body weight and IgE levels, and appropriate adjustment of dosage and frequency based on those parameters. Frequent monitoring of IgE levels requires frequent blood taking, which may not be an easy task in children.

Discussion

Optimal management and treatment of AR and CRS

is aimed at safe and effective symptom relief and the prevention of complications and disease progression. The use of evidence-based guidelines helps to improve outcomes. The use of intranasal corticosteroid sprays and oral second-generation antihistamines remains the most common first-line therapy.[25] In selecting patients, immunotherapy is also used. The use of immunotherapy and/or pharmacological medications provides symptom relief, but it often does not totally control the disease, and it can be associated with significant side effects. Thus, the search for an effective and safe treatment is warranted.

The coexistence of AR and asthma is explained by the involvement of similar inflammatory pathophysiology pathways in the two conditions, particularly elevated serum IgE.[4,26,27] The coexistence of AR and asthma affects the outcome of each and imposes a burden with regard to health care costs.[28] Therapeutic approaches that target factors that are common to both conditions will be beneficial in patients experiencing these two mechanistically associated conditions. Allergic Rhinitis and its Impact on Asthma (ARIA)[29] recommends strategies to treat both upper and lower airways and achieve better outcomes. Patients with asthma who received treatment for AR were at a lower risk of asthma attacks, emergency department visits, and hospitalization than those with untreated AR.[30] The biologics that are currently on the market for the treatment of severe allergic asthma and as salvage therapy in severe AR and CRS are omalizumab, mepolizumab, dupilumab, benralizumab, and reslizumab.[4,31-33]

Allergic rhinitis

Patients who have asthma with concomitant AR are suitable candidates for omalizumab treatment, which is often effective in preventing asthma exacerbation, controlling AR symptoms, and improving quality of life.[19] Patients treated with omalizumab reportedly exhibited significant improvements in both asthma and rhinitis quality of life questionnaire scores.[4] The administration of omalizumab in patients with seasonal AR (SAR) and perennial AR (PAR) has been shown to improve daily nasal symptoms, and quality of life, and reduce IgE levels and the use of rescue antihistamines.[13,34,35] In clinical practice, omalizumab has been shown to reduce asthma exacerbations and steroid requirement in allergic asthmatics.[19,36-39] Treatment of mild- to severe allergic asthma in association with high IgE levels via intravenous or subcutaneous omalizumab has resulted in significant reduction in free IgE compared to placebo.[36]

The use of omalizumab has additional benefits in the treatment of patients with comorbid AR and asthma and it is suitable for use in polysensitized allergic patients, unlike immunotherapy that depends on allergen specificity. Omalizumab is indicated as an add-on therapy in patients aged more than 6 years with severe persistent allergic asthma, with a positive skin prick test or in vitro reactivity to permanently present aeroallergens.[19] The indications include the presence of symptoms during the day or night, and several serious asthma exacerbations despite daily high-dose inhalation of steroids in combination with a long-acting inhaled β2-agonist.[19]

Several studies have reported good outcomes associated with omalizumab used as a single modality or as part of combined therapy, in both SAR and PAR.[1] Its use as a single modality in AR reduces nasal symptom severity, and the use of rescue antihistamines, and improves quality of life.[34,35,40] In addition, there was no significant difference in the occurrence of adverse events between omalizumab and placebo groups. Omalizumab therapy was well tolerated. Omalizumab treatment reduces free IgE in serum and responses to nasal allergen challenge.[41]

Immunotherapy that modifies the natural course of allergic airway disease is the only causal treatment for AR. Subcutaneous immunotherapy (SCIT) is widely used but it is time-consuming and is associated with a risk of severe adverse reactions.[31,42] An alternative, sublingual immunotherapy (SLIT), is administered via drops or tablets and has been found to be effective and safe.[42] The success of immunotherapy depends on patient selection, the type of allergen involved, and choosing the right product for treatment. Combined treatment using omalizumab and immunotherapy is aimed at improving AR symptom control and reducing immunotherapy-derived systemic allergic reactions.[1,43-48] Via the targeting of different mechanisms in the allergic pathway, immunotherapy desensitizes the host to specific antigens by modifying the Th1/Th2 balance, while omalizumab targets the humoral effectors of allergic inflammation.[49] Omalizumab pretreatment in patients receiving rush immunotherapy (RIT) has been shown to reduce systemic and respiratory-related reactions, and is thus potentially a good strategy for preventing immunotherapy-derived anaphylaxis.[45,48]

In a randomized controlled trial in 221 children aged 6 to 17 years with moderate to severe AR comparing the use of immunotherapy with and without concurrent omalizumab, combination therapies were reportedly superior to immunotherapy alone. Combination therapies were associated with symptom reduction of 48% and an 80% reduction in rescue medication score beyond that of immunotherapy alone.[1,43] In another study there was reduced leukotriene release in 92 children receiving combination therapies.[47]

The efficacy of omalizumab in patients with concomitant moderate to severe asthma and persistent AR has been evaluated in a double-blind trial, and another study has evaluated omalizumab as an adjunct to SCIT.[1,4,50] In both studies there were reductions in symptoms improvements in quality of life measures. The ARIA

guidelines recommend the use of a monoclonal anti-IgE antibody such as omalizumab for the treatment of asthma in patients with concomitant AR if there is a clear IgE-dependent allergic component and failure of other maximal therapy.[1,29] Other biologics, such as anti-IL-5, have yielded positive results in the treatment of asthma and other atopic diseases, and the ARIA guidelines include similar recommendations with reference to them.[29]

Four trials have investigated combinations of omalizumab and immunotherapy with the aim of achieving better efficacy and fewer adverse events than immunotherapy alone.[1] In younger children and adolescents, combination therapy significantly diminished rescue medication use, reduced the number of symptomatic days, and reduced symptoms load more so than immunotherapy alone, independent of the allergen involved.[43] Combined treatment with immunotherapy and anti-IgE has also exhibited superior efficacy to anti-IgE alone.[44] The results of that study clearly indicated that combination therapy was useful for the treatment of AR, particularly in polysensitized patients.

There is consistent evidence that omalizumab monotherapy is superior to placebo, and that the combination of omalizumab and immunotherapy is superior to immunotherapy alone with regard to controlling AR symptoms, improving quality of life, and reducing the risk of anaphylaxis associated with immunotherapy, but the financial cost of the treatment precludes its widespread use.[1]

The accelerated dosing schedule used in RIT raised fear of anaphylactic shock due to a sudden increase in total and specific IgE levels.[19] In one study omalizumab in combination with RIT, was associated with fewer adverse events than RIT alone.[45] In that study the risk of adverse events associated with RIT alone was 15-fold greater than that associated with placebo, whereas the risk of adverse events associated with omalizumab plus RIT versus placebo was of 2 fold risk. The efficacy of omalizumab plus RIT was also reportedly higher than that of RIT alone. No biologic is currently approved for the treatment of AR.[1] While it has been demonstrated that they can reduce symptoms, reduce rescue medication use, and improve quality of life, they are very costly.[51]

Chronic rhinosinusitis

CRS is defined as greater than 12 weeks of nasal obstruction, nasal discharge, facial pain and/or pressure, and hyposmia/anosmia in conjunction with endoscopic or computed tomographic evidence of inflammation, polyps, or purulence.[1] Conversely, AR is driven by IgE-mediated hypersensitivity to environmental allergens and is characterized by sneezing, rhinorrhea, and nasal blockage or itching after exposure to allergens to which the patient is sensitized.[1] Biologics are used as a salvage therapy in patients with CRS that is recalcitrant to other medical treatments and surgery.[52]

Gevaert et al [6] reported that treatment with biologics was associated with significant reductions in endoscopic nasal polyp size, and the degree of nasal obstruction in conjunction with improvements in other nasal symptoms in patients with nasal polyps and asthma, irrespective of their allergy status.[6] Notably however, other studies have yielded inconclusive results evidently as due to limited numbers of participants enrolled and higher baseline eosinophilic inflammation in placebo-treated patients.[1,6,16] Corticosteroid administration is the most common treatment for CRS, and both topical and systemic agents have been used as part of the treatment regimen.[14] Topical intranasal corticosteroids are considered safe, but their long-term use may not be desirable in patients with comorbid medical conditions. While the dose of systemic corticosteroids required to put patients at risk is not clear, the use of long-term or high-dose systemic corticosteroids is associated with multiple complications including adverse changes in bone mineral density, adrenal suppression, avascular necrosis, cataracts, and psychosis.[53]

Currently the success rate of medical management of CRS is approximately 50%.[11,54] The risk of failure is higher in patients with certain conditions such as nasal polyposis, comorbid asthma, acute exacerbation of respiratory disease (AERD), and allergic fungal rhinosinusitis.[55] Biologics may constitute a strategy to overcome these issues. Biologics targeting IgE and Th2 pathways involved in both CRS and asthma have been shown to improve outcomes determined via both subjective and objective measures.[54] Patients who require multiple doses of systemic corticosteroids for CRS control or are dependent on systemic corticosteroids, as well as patients with recalcitrant CRS, are the most obvious candidates for the use of biologics. The targeted mode of therapy reduces inflammation, and provides symptom control with less adverse effects,[14] and thus, there is a reduced need for systemic corticosteroid administration and its associated risks.

Biologics such as omalizumab, reslizumab, mepolizumab, dupilumab, and benralizumab have yielded favorable outcomes in patients with CRS. Omalizumab acts in two ways. One is by binding to free IgE and preventing it from attaching to receptors on mast cells and basophils, and the other is by downregulating IgE receptor expression on effector cells.[13,56] It can be used in CRS as a salvage therapy when other medical treatments and surgical treatment have failed. Significant reduction of nasal polyps by 16 weeks in conjunction with concurrent reduction of corticosteroid use of approximately 50 % at the end of therapy have been reported.[13] In another study in patients with asthma and CRS there was a 60% reduction in antibiotic use and a 42 % reduction in systemic steroid

use.[13,57]

IL-5 has been found to be elevated in nasal polyp tissue compared to normal controls, and the highest concentrations were detected in patients with comorbid nonallergic asthma or AERD.[58,59] Anti-IL-5 antibodies such as reslizumab and mepolizumab, which have been used to treat severe eosinophilic asthma, have also been considered for the treatment of CRS.[13] Reslizumab has been used in CRS patients with bilateral grade 3 or 4 nasal polyps or recurrent nasal polyps after surgery.[13] In that study the use of reslizumab, was associated with a 50% reduction in polyp size at 4 weeks. It was well tolerated and there were no major complications. It was determined that those who responded well to the treatment had higher baseline nasal IL-5 levels, suggesting that nasal IL-5 levels may be useful for predicting responders. Mepolizumab was investigated in another study in CRS patients with grade 3 or 4 nasal polyps or recurrent nasal polyps after surgery.[7,13] At 8 weeks there was a 60% improvement in the treated group but only a 10% improvement in the placebo group. The improvements were correlated with improvements in radiologically severity and immunological markers at 8 weeks.

Benralizumab is a less known anti-IL-5 agent that is indicated for use in refractory eosinophilic asthma patients.[13,60] As well as acting on IL-5, directly it acts on the effector cells including eosinophils and basophils, which suggests a potential for use in the treatment of CRS.[61,62] Dupilumab is an anti-IL-4/anti-13 α receptor antibody, that is approved for the treatment of atopic dermatitis, and it has been tested in CRS patients.[13] In that study 70% of the treated patients exhibited reductions in nasal polyp size at 16 weeks, compared to 20% in the placebo group. Polyp reduction was correlated with improvements in radiological scores, symptom scores, and quality of life.[12]

Conclusions

The role of biologics in children with AR and CRS is still not well defined. Currently the use of biologics is confined to patients with uncontrolled severe asthma and salvage therapy for recalcitrant severe AR and CRS in cases where other medications, immunotherapy, and surgery have failed. Biologics may play a major role in AR and CRS treatment, but their high cost is their main limitation.

CONFLICT OF INTEREST

All authors declare no conflicts of interest

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