

Anti-interleukin-5 antibody therapy in asthma and allergies

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Purpose of review

Interleukin 5 (IL-5) has been shown to play an instrumental role in eosinophilic inflammation in allergic diseases. The purpose of this review is to explore clinical trials of anti-IL-5 antibody therapy that have been conducted in patients with asthma, hypereosinophilic syndromes, eosinophilic esophagitis, atopic dermatitis, Churg-Strauss syndrome, and nasal polyposis.

Recent findings

Recent trials of anti-IL-5 in patients with severe asthma refractory to existing therapies and prominent sputum eosinophilia experienced significant reductions in asthma exacerbations. Studies in patients with hypereosinophilic syndromes have shown that IL-5 antagonism allows significant reductions in systemic corticosteroid doses while maintaining or improving blood eosinophil counts and symptoms. In children and adults with eosinophilic esophagitis, anti-IL-5 treatment reduced eosinophil numbers in esophageal tissue; it is uncertain whether these findings are predictive of clinical improvement. Clinical studies of individuals with atopic dermatitis do not support efficacy of anti-IL-5 in either reducing allergen patch test intensity or symptoms of chronic dermatitis. In small trials in both Churg Strauss syndrome and nasal polyposis, anti-IL-5 shows promise but larger numbers of patients with these conditions will need to be studied.

Summary

Anti-IL-5 is efficacious in treating patients with severe asthma and sputum eosinophilia and hypereosinophilic syndromes. Larger controlled trials with appropriate endpoints will be necessary to assess the role of anti-IL-5 in other eosinophilic disorders.

Keywords

asthma, eosinophilic esophagitis, hypereosinophilic syndrome, interleukin-5, monoclonal antibody

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Introduction

Tissue eosinophilia is a prominent feature of atopic diseases, including asthma, rhinitis, atopic dermatitis, eosinophilic esophagitis, hypereosinophilic syndrome, and Churg–Strauss syndrome. Interleukin-5 (IL-5) has been proposed to be a key factor in regulating the growth, differentiation, recruitment, activation, and survival of eosinophils [1,2]. Increased concentrations of IL-5 in the tissues and systemic circulation of patients with allergic diseases suggests that this factor may have important effects in these disorders [3–6]. The purpose of the present review is to examine the results of published clinical trials of anti-IL-5 therapy in patients with asthma, hypereosinophilic syndrome, atopic dermatitis, eosinophilic esophagitis, and Churg–Strauss syndrome. Although there are currently three different anti-IL-5 antibodies in development, including mepolizumab, reslizumab, and benralizumab, nearly all of the published trials have been conducted with mepolizumab. These

data will serve to both assess the potential role of anti-IL-5 as a therapeutic agent in eosinophilic diseases as well as establish the mechanistic role of IL-5 and eosinophils in allergy.

Anti-interleukin-5 therapy in asthma

Dating back to the middle of the last century, eosinophils have been implicated in the pathology of asthma and numbers of these cells have been correlated to asthma severity [7]. Evidence from recent clinical investigations also support the role of IL-5 in asthma: mRNA for IL-5 is increased in bronchial biopsies from patients with asthma [3]; mRNA for IL-5 is related to asthma severity [8]; and bronchial allergen provocation causes an increase in IL-5 mRNA [9]. These data suggest that inhibition of IL-5 activity would prevent eosinophil migration or activation in the airways and thereby reduce the severity of asthma. In the past decade, a number of clinical trials have been conducted with anti-IL-5 antibody therapy in

patients with asthma. As noted above, all of the published literature utilized mepolizumab as the therapeutic agent.

In one of the first studies of anti-IL-5 antibody therapy, Leckie *et al.* [10] sought to examine the effects of IL-5 inhibition upon allergen-induced blood and sputum eosinophilia and the late asthmatic response to inhaled allergen. In a randomized, placebo-controlled study, patients with mild asthma managed with beta-agonists alone received a single dose of mepolizumab 2.5 mg/kg ($n=8$), 10 mg/kg ($n=8$) or placebo and then underwent inhaled allergen and histamine challenges 7 and 28 days later. On day 7, prior to allergen challenge, patients who received mepolizumab 2.5 mg/kg had a mean eosinophil count of $0.24 \times 10^9/L$ ($P=NS$ vs. placebo), whereas the 10 mg/kg dose resulted in a mean count of $0.08 \times 10^9/L$ ($P=0.005$ vs. placebo). Postchallenge sputum eosinophils on day 9 revealed no significant effect with the mepolizumab 2.5 mg/kg dose (placebo 12.2%, mepolizumab 7.2%), whereas mepolizumab 10 mg/kg dose reduced sputum eosinophils to 0.9% ($P=0.0076$ vs. placebo). On day 30, very similar reductions in sputum eosinophils were seen. No significant effects on the late asthmatic response to allergen challenge or on airway hyperresponsiveness to inhaled histamine were seen. These study results indicate that anti-IL-5 reduces both baseline blood eosinophil counts as well as the increase in blood eosinophils that occurs following inhaled allergen challenge. These reductions in blood and sputum eosinophilia, however, had no significant effects on airway physiology.

In another early study of anti-IL-5 published by Buttner *et al.* [11] again focused upon blood eosinophil counts, eosinophil cationic protein levels, and T-cell function in patients with mild to moderate asthma receiving inhaled corticosteroid (ICS). In a randomized, double-blind study, mepolizumab, 250 mg ($n=7$) or 750 mg ($n=5$) or placebo ($n=7$) were administered intravenously every 4 weeks for 12 weeks and followed for an additional 12 weeks. Blood eosinophils fell rapidly from 300 to 45 cells/microliter ($P<0.05$) and ECP was reduced from 15 to 5 mcg/L ($P=0.05$); no change was noted in peripheral blood T-cell subset counts or T-cell cytokine production. This study confirmed the ability of anti-IL-5 antibody therapy to significantly reduce circulating blood eosinophil numbers and eosinophil-derived mediators but did not affect lymphocyte numbers or function.

In the first large study [12] of anti-IL-5 therapy in asthma, 362 patients with moderate asthma receiving ICS were treated with mepolizumab 250 mg or 750 mg i.v. or placebo every 4 weeks for 12 weeks. Blood eosinophil counts decreased by 80% from baseline whereas sputum eosinophils were reduced markedly in the 250 mg and

Key points

- Interleukin-5 (IL-5) appears to contribute significantly to the pathogenesis of asthma and several other eosinophilic diseases.
- In patients with severe, corticosteroid-requiring asthma who have increased sputum eosinophils, anti-IL-5 antibody therapy has been demonstrated to reduce asthma exacerbations.
- In patients with hypereosinophilic syndrome treated with systemic corticosteroids, anti-IL-5 has been shown to maintain control of symptoms while allowing doses of corticosteroids to be tapered.

750 mg treatment groups, both of which were statistically significant. Clinical endpoints, including morning domiciliary peak expiratory flow rate, forced expiratory volume in 1 second (FEV₁), daily β_2 -agonist use, asthma symptom scores, asthma-related quality of life measures, or asthma exacerbation rates demonstrated few statistically significant differences between mepolizumab and placebo. In this study, in patients receiving moderate doses of ICS, IL-5 inhibition did not improve asthma symptoms, pulmonary function or exacerbations of asthma, suggesting that neither IL-5 nor eosinophils are important in patients with mild-moderate asthma.

As eosinophils increase during exacerbations, it was speculated that the drug might provide benefit to patients with more severe disease and clear evidence of eosinophilia. Nair *et al.* [13] investigated mepolizumab in a small group of patients with severe, oral-steroid dependent asthma, and elevated levels of sputum eosinophils. Patients were assigned to receive mepolizumab 750 mg i.v. ($n=9$) or placebo ($n=11$) every 4 weeks for 16 weeks and prednisone was tapered as tolerated after the second dose. Mepolizumab caused a greater than 90% reduction in blood eosinophils that persisted for 4 weeks after the last dose compared with placebo as well as a significant reduction in sputum eosinophils. There was a significant reduction in number of patients with exacerbations during prednisone tapering with mepolizumab (1 exacerbation) vs. placebo (12 exacerbations in 10 patients; $P<0.01$) and the median time to exacerbation was 20 weeks with mepolizumab vs. 12 weeks with placebo ($P=0.003$). There was also a significant reduction in prednisone dose with mepolizumab (mean $\pm$ SD, $83.8 \pm 33.4\%$) vs. placebo ($47.7 \pm 40.5\%$; $P=0.04$). Other important outcomes, including FEV₁ and Asthma Control Questionnaire were both significantly improved from baseline while asthma symptoms were not.

During that same year another trial was published which studied the effects of mepolizumab in a similar population of severe, treatment refractory asthmatics

with persistent sputum eosinophilia [14]. Patients were randomized to receive mepolizumab 750 mg i.v. ($n=29$) or placebo ($n=32$) every 4 weeks for 12 months. The mean number of exacerbations during the study was reduced by 43% with mepolizumab compared with placebo (2.0 exacerbations per patient with vs. 3.4 with placebo, $P=0.02$). Asthma-related quality of life was also significantly improved in patients receiving active therapy (0.55 with mepolizumab vs. 0.19 with placebo, $P=0.02$) but there were no significant differences between groups in symptoms, FEV1 after bronchodilator use, or airway hyperresponsiveness. The initial small study by Nair *et al.* [13] and larger study by Haldar *et al.* [14] suggested that IL-5 inhibition was most effective in preventing symptomatic exacerbations occurring in patients with severe asthma and airway eosinophilia.

Anti-interleukin-5 therapy in hypereosinophilic syndromes

The hypereosinophilic syndromes represent a group of rare blood disorders in which patients have marked, persistent elevation of the blood eosinophil count ($>1500/\mu\text{l}$ for >6 months), signs and symptoms of organ involvement, and absence of any primary cause (e.g. parasitic infection) [15]. The organs most frequently affected by eosinophil infiltration are the heart, lungs, liver, nervous system, skin, and digestive tract [15].

Hypereosinophilic syndrome (HES) is most often characterized as either a lymphocytic-variant or myeloproliferative-variant HES [16]. Lymphocytic-variant HES has been attributed to a high expression of IL-5 from a clonal T-cell population [17]. The myeloproliferative-variant HES represent myeloid clonal disorders that may be associated with a specific chromosomal mutation [16], including the *FIP1L1-PDGFR*A mutation.

Therapy of HES is directed at reducing end-organ damage caused by eosinophils. A number of effective therapies have been developed for symptomatic patients with evidence of organ dysfunction. Specific therapy is chosen based upon clinical presentation, which organs are involved, and the presence of the *FIP1L1-PDGFR*A mutation.

Systemic corticosteroids are the mainstay of therapy for symptomatic HES patients who do not have the *FIP1L1-PDGFR*A mutation [15]. It has been estimated that up to one-third of HES patients are unresponsive to corticosteroids and a significant group do not tolerate corticosteroids over long periods of time due to significant adverse effects. These patients are candidates for other treatments, including hydroxyurea and IFN- α [18]. Unfortunately, some patients also develop resistance to

these second-line agents or develop adverse effects that limit long-term tolerability. In patients who are *FIP1L1-PDGFR*A positive, systemic corticosteroids are usually not effective and imatinib mesylate, a tyrosine kinase inhibitor, is used as first-line therapy [19]. Imatinib is not usually effective in *FIP1L1-PDGFR*A negative patients and therefore not a therapeutic option in these patients who prove to be corticosteroid resistant.

The recognition of IL-5 as an important regulator of eosinophil proliferation and terminal differentiation has led to the use of IL-5 inhibitors in treating HES. One of the first case reports in which mepolizumab was used to treat HES involved a 51-year-old man with a 4-year history of HES with eosinophil counts as high as 8000 cells/mm and marked elevation of serum IL-5 [20]. Administration of three doses of mepolizumab 750 mg i.v. over 6 weeks caused large reductions in the eosinophil count and level of IL-5, partial improvement in pulmonary symptoms, and resolution of skin lesions. Following this and other encouraging reports using both mepolizumab and reslizumab, an open label trial of mepolizumab was tried in three patients with HES [21]. Each patient received three doses of mepolizumab 10 mg/kg i.v. (maximum, 750 mg) every 4 weeks. Follow-up assessments were conducted at 4 and 12 weeks after the final dose. All three of the patients had HES for at least 2 years, had various combinations of skin, pulmonary, cardiac, and gastrointestinal manifestations, and were receiving chronic therapy with prednisone with or without an additional agent. Following treatment, marked reductions in peripheral eosinophil counts and improvements in skin lesions, constitutional symptoms, exercise capacity, FEV1, and constitutional symptoms were observed in all of the patients.

These positive data led to the organization of a randomized, placebo-controlled, double-blind trial of mepolizumab in 85 patients with steroid-dependent HES [22]. Following 36 weeks of treatment with mepolizumab 750 mg i.v. ($n=43$) or placebo ($n=42$) given monthly, patients receiving active therapy maintained clinical stability while tapering their prednisone to significantly lower doses than patients receiving placebo and nearly half of mepolizumab-treated patients were able to taper off of prednisone completely. Despite using lower doses of prednisone, use of mepolizumab more effectively lowered peripheral blood eosinophil counts and eosinophil-derived mediators, such as eosinophil-derived neurotoxin.

This relatively large collection of patients with a rare disease does confirm the beneficial role of anti-IL-5 treatment as a steroid-sparing agent in patients with HES and supports the role of eosinophils as direct mediators of tissue damage in HES.

Anti-interleukin-5 therapy and eosinophilic esophagitis

Eosinophilic esophagitis is a condition in which patients present with symptoms of esophageal reflux and esophageal obstruction, which is frequently refractory to acid suppressive therapy [23]. Esophageal tissue biopsies from these patients demonstrate high numbers of eosinophils and epithelial hyperplasia [23]. In order to determine whether anti-IL-5 treatment might be effective in patients with this disease, an open-label study [24] of mepolizumab was conducted in four adult patients with eosinophilic esophagitis with esophageal strictures. Patients received three infusions of mepolizumab 750 mg i.v. in addition to their current therapy. Peripheral blood eosinophils and percentage of CCR3⁺ cells decreased by 6.4-fold and 7.9-fold ($P < 0.05$), respectively, and the mean number of esophageal eosinophils decreased from 46 to 6 eosinophils/high-power field ($P < 0.05$). Patients reported improved clinical status and improved quality of life ($P = 0.03$).

These positive results from an unblinded trial led to the completion of a small, placebo-controlled study [25^{••}] of mepolizumab in adults with eosinophilic esophagitis. Eleven adults with active eosinophilic esophagitis [>20 peak eosinophil number/high power field (hpf) and dysphagia] were randomised to receive two infusions of mepolizumab 750 mg i.v. ($n = 5$) or placebo ($n = 6$) given 1 week apart. Patients who did not achieve a complete remission (<5 peak eosinophil number/hpf) after 8 weeks received two doses of mepolizumab, 1500 mg i.v., 4 weeks apart, or placebo. Four weeks after starting treatment, there was a marked reduction of mean esophageal eosinophils (-54%) in patients receiving active therapy compared with the placebo group (-5%) ($P < 0.05$). Mepolizumab also reduced tenascin C ($P = 0.033$) and transforming growth factor beta1 ($P = 0.05$) expression in the esophageal epithelial layer 13 weeks after initiation of treatment. There was a trend toward clinical improvement observed between 4 and 13 weeks after initiation of mepolizumab treatment. These data indicate that in patients with eosinophilic esophagitis, mepolizumab significantly reduced eosinophil numbers in esophageal tissues and expression of molecules associated with esophageal remodelling.

In a larger randomized study of mepolizumab in children with eosinophilic esophagitis (esophageal intraepithelial eosinophils of ≥ 20 in at least 1 high-power field), Assa'ad *et al.* [26[•]] examined the effect of mepolizumab upon esophageal histology. In a randomized and blinded fashion, patients received a monthly infusion of mepolizumab every 4 weeks (a total of three infusions) at doses of 0.55, 2.5, or 10 mg/kg with no placebo group. Four weeks after the third infusion, peak and mean esophageal

intraepithelial eosinophil counts decreased significantly, from 122.5 ± 67.5 to 40.2 ± 5.17 ($P < 0.0001$) and from 39.1 ± 27.9 to 9.3 ± 1.25 per hpf, respectively ($P < 0.0001$). In addition, 4 weeks after completing therapy, peak eosinophil counts were less than 5 per hpf in 5/57 children and peak and mean eosinophil count reductions to less than 20 per hpf were observed in 18/57 and 51/57 of children, respectively. Overall, there were moderate reductions in esophageal eosinophils following IL-5 therapy. Clinical outcomes were not reported in this study so that correlations between histologic and symptom parameters were not possible.

Anti-interleukin-5 therapy and atopic dermatitis

Eosinophils are identified in biopsies taken from patients with atopic dermatitis and may play an important role in the pathogenesis of this condition. In order to determine whether abrogation of eosinophils might benefit patients with atopic dermatitis, mepolizumab 750 mg i.v. was administered twice in a randomized placebo controlled parallel group design [27]. In patients who received mepolizumab ($n = 18$), peripheral blood eosinophil numbers were significantly reduced in the treatment group compared with placebo ($n = 22$) ($P < 0.05$). Although there was modest improvement ($<50\%$) assessed by the physician's global assessment in patients treated with mepolizumab, other validated measures of dermatitis and pruritis were not significantly different between active treatment and placebo. The authors concluded that two single doses of mepolizumab 750 mg i.v. did not result in clinical success in patients with atopic dermatitis despite a significant decrease in peripheral blood eosinophils.

One possible explanation for the lack of success with anti-IL-5 in atopic dermatitis may relate to ineffectiveness in blocking eosinophil migration into the skin of these patients. In the same group of patients described above, the investigators utilized the atopy patch test as an in-vivo model to study the effects of mepolizumab on allergen-induced eczema [28]. The atopy patch test was applied 2 days before the first dose of mepolizumab and 7 and 14 days after the second dose. The test site reactions were measured and skin biopsies were performed 48 h after the first and second atopy patch test applications. Neither the size of the reactions nor numbers of tissue eosinophils were significantly different between the two groups of patients.

The data from these studies suggest that anti-IL-5 may not be effective in atopic dermatitis because eosinophils in the skin are not significantly reduced by the therapy. It remains to be determined whether a longer period of treatment or higher dose of the drug

may reduce signs and symptoms of atopic dermatitis more effectively.

Anti-interleukin-5 therapy in Churg–Strauss syndrome

Churg–Strauss syndrome is a rare form of vasculitis characterized by asthma, sinusitis, peripheral eosinophilia, and pulmonary infiltrates. Universally, patients with this disorder require systemic corticosteroids to control the disease process. As eosinophils appear to play an important role in Churg–Strauss syndrome and levels of IL-5 may be increased in these patients, it has been suggested that anti-IL-5 may be a potential corticosteroid-sparing therapy. In order to determine whether anti-IL-5 is beneficial in Churg–Strauss syndrome, seven patients received 4 monthly doses of mepolizumab 750 mg i.v. [29**]. Mepolizumab reduced mean eosinophil counts by approximately 75% and allowed safe corticosteroid reduction (from mean dose of 18.8 mg to 4.6 mg) in all seven patients. On cessation of mepolizumab, manifestations of the syndrome recurred, necessitating an increase in corticosteroid dose. Mepolizumab was well tolerated in this small group of patients.

These positive results in patients with Churg–Strauss syndrome will need to be confirmed in an adequately powered, randomized, and placebo-controlled trial.

Nasal polyposis

Chronic rhinosinusitis with nasal polyps has been characterized by intense eosinophilic inflammation and high IL-5 levels in the nasal tissue [30]. This disorder poses a therapeutic challenge to physicians, as a significant subset of patients is refractory to both medical and surgical therapy. In addition, many patients with polyposis suffer from concomitant bronchial asthma, which often is very difficult to manage effectively. Given the nature of the inflammatory infiltrate and cytokine profile in this disease, anti-IL-5 treatment presented a logical option for treatment. In a double-blind, placebo-controlled, randomized, safety and pharmacokinetic study [30], 24 patients with bilateral nasal polyps were randomized to receive a single intravenous infusion of reslizumab at doses of 3 or 1 mg/kg or placebo. Following the one injection, blood eosinophil numbers and concentrations of eosinophil cationic protein were reduced in serum and nasal secretions. Individual nasal polyp scores improved in half of the treated patients for 4 weeks. Patient who responded most significantly to anti-IL-5 had increased IL-5 concentrations in nasal secretions at baseline compared with nonresponders. These data are promising and will require follow-up in large studies. Ultimately, this drug may be most useful in

patients who have both nasal polyp disease as well as difficult-to-control asthma.

Conclusion

To date, there have been few large clinical trials of anti-IL-5 in eosinophilic diseases. Clinical studies in asthma, the most common of the allergic disorders, have yielded mixed results. In patients with moderate asthma, anti-IL-5 was not significantly more effective than placebo. In trials which selected patients based upon sputum eosinophilia, recurrent asthma exacerbations, and refractoriness to standard therapy, anti-IL-5 significantly reduced blood and sputum eosinophils and exacerbations. These data indicate that the most important effects of eosinophils in asthma are exerted during acute attacks in patients with more severe disease. HES is a rare disorder, which has historically required systemic corticosteroids and cytotoxic agents for control of symptoms. In patients with the nonmyelodysplastic variant of HES, anti-IL-5 effectively reduced the need for oral corticosteroid drugs while significantly suppressing blood eosinophils and clinical manifestations of the disease. The use of anti-IL-5 in other conditions, including eosinophilic esophagitis, Churg–Strauss syndrome, and atopic dermatitis, will require further study before firm conclusions can be drawn.

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Conflicts of interest

J.C. receives research funding from companies including Merck, Genentech, Novartis, Actelion, Boehringer-Ingelheim and Astra-Zeneca. Merck and Genentech are also corporate sponsors of lectures. He is currently working on clinical trials with Astra-Zeneca, who have an anti-IL-5 antibody that is being tested in phase 2 clinical trials. He owns no stock in any pharmaceutical company and is not currently working as a consultant with any pharmaceutical companies.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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