Invited Review Article

The roles of IL-5 and anti-IL-5 treatment in eosinophilic diseases: Asthma, eosinophilic granulomatosis with polyangiitis, and eosinophilic chronic rhinosinusitis

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A R T I C L E   I N F O

Article history:
Received 8 February 2020
Available online 2 March 2020

Keywords:
Benralizumab
Chronic rhinosinusitis with nasal polyps
Eosinophils
IL-5
Mepolizumab

A B S T R A C T

IL-5 is the most potent activator of eosinophils and is produced by Th2 cells and ILC2s. A role for IL-5 in eosinophil extracellular trap cell death, i.e., a proinflammatory cell death, has also been reported. Mepolizumab and benralizumab are humanized mAbs that target IL-5 and the IL-5 receptor α, respectively, and their therapeutic efficacy for severe asthma has been established. Although consistent differences in the efficacies of those drugs have not been proven, benralizumab extensively depleted eosinophils via Ab-dependent cell-mediated cytotoxicity. Blood eosinophil count, but not FeNO or IgE, is the best-established predictive biomarker of the efficacy of anti-IL-5 treatment. Regarding the choice of biologics, the balance between blood eosinophil count and FeNO, indication of comorbidities, longitudinal safety, and interval of injection should be considered. Mepolizumab was also effective in maintaining the remission of refractory eosinophilic granulomatous polyangiitis. Moreover, mepolizumab decreased the proportion of patients who required surgery and lowered the nasal polyp score in patients with chronic rhinosinusitis with nasal polyps; a further extensive trial is currently under way. In a phase II benralizumab study performed in Japan, no significant effect on nasal polyp score at week 12 was observed, suggesting a requirement for longer treatment. In this review, the role of IL-5 in eosinophil biology and the current status of anti-IL-5 therapy are discussed. The longitudinal safety of anti-IL-5 therapy has been increasingly established, and this strategy will be continuously indicated for eosinophilic diseases as a specific treatment for eosinophilic inflammation.

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Basic aspects of IL-5 and eosinophilic inflammation

For more than 100 years, eosinophils have been linked to allergic and parasitic diseases. Eosinophils are terminally differentiated myeloid cells derived from CD34+ hematopoietic stem cells in the bone marrow. The process is regulated by transcription factors, including the GATA-binding factor 1. Once eosinophils reach maturity, they are released into the blood stream. In normal homeostatic conditions, the half-life of blood eosinophils is approximately 25 h.1 The majority of senescent (or apoptotic) eosinophils are cleared in the liver and spleen, where they are taken-up by macrophages of the reticuloendothelial system. The remaining eosinophils are distributed across the gastrointestinal tract, thymus, lung, uterus, and adipose tissue, indicating physiological function in each organ2 (reviewed in Ref. 3). In response to type 2 reactions, eosinophils are markedly mobilized from the bone
marrow and blood pool to local sites, creating a tissue eosinophilia. The excessive accumulation and activation of eosinophils can have a deleterious effect and contribute to tissue damage.

Eosinophil differentiation is mediated by IL-5, IL-3, and the granulocyte macrophage colony-stimulating factor (GM-CSF). These cytokines are called β common cytokines, because of their shared β receptor structure. The β common cytokine receptor comprises a cytokine-specific α chain and a common β chain that is essential for receptor signaling and assembly. Among them, IL-5 has been considered to be a therapeutic target for allergic eosinophilic diseases because of the presence of exclusive IL-5 receptor (IL-5R) expression in eosinophils and basophils (in humans) and its critical role in eosinophilopoiesis.

In the allergen-induced adaptive immunity process, IL-5 is primarily produced by Th2 cells. In addition, ILC2s produce abundant IL-5 in response to IL-33 and other alarmins, thus playing a critical role in innate immunity settings. A previous study indicated that IL-5-deficient mice exhibit a slight reduction in circulating eosinophils under baseline conditions, but completely fail to induce parasite-induced eosinophilia. In contrast, IL-5 transgenic mice showed high-level eosinophilia at the baseline. Familial eosinophilia is a rare autosomal dominant inherited disorder that is characterized by prolonged peripheral eosinophilia likely secondary to IL-5 overproduction in peripheral blood mononuclear cells. To date, a considerable amount of evidence indicates that the systemic increase of IL-5 is important for promoting eosinophilia.

It is noteworthy that the systemic increase of IL-5 is not always sufficient to cause an eosinophil-mediated pathological condition. IL-5 transgenic mice remain physically normal, with the exception of the development of splenomegaly. In patients with familial eosinophilia, clinical manifestations related to the eosinophilia are uncommon. At a mechanistic level, IL-5 signaling in mature eosinophils activates several signaling molecules, such as the JAK-STAT and MAPK pathways, inducing priming (augmentation of effector functions), chemokinieschemotaxis, the activation of integrins, and the prolongation of survival by inhibiting apoptosis. Tissue-specific IL-5 production might be important in some cases, as transgenic mice that express lung-specific IL-5 can recreate the pathological conditions of asthma, such as airway hypersensitivity. In addition, nasal appreciation of recombinant IL-5 induced selective recruitment of eosinophils in the mucosa.

In a variety of allergic diseases, circulating blood eosinophils are in a resting state and do not degranulate until they have reached their target tissue. The proinflammatory chemokines, especially eotaxins (CCL11, CCL24, and CCL26), that are produced by structural cells (including bronchial epithelial cells and fibroblasts) primarily regulate the accumulation of eosinophils in the airways. The capacity to generate reactive oxygen species and the secretory function of eosinophils are important features of their role as tissue-damaging cells. Eosinophil pack approximately 200 granules that contain not only cytotoxic proteins (i.e., major basic protein, eosinophil peroxidase, eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin), but also over 30 cytokines. This cargo is an efficient system for short-lived eosinophils, as de novo protein synthesis is time consuming. Eosinophils can rapidly release selected cytokines from granular storage through piecemeal degranulation and possibly exocytosis. Moreover, eosinophils also release the total cellular content through cytolytic degranulation (cytolysis). Cytolytic degranulation in inflamed tissues has been shown to occur in 30–80% of eosinophils. Recent evidence revealed that cytolysis is an active cell death program, i.e., extra-cellular trap cell death (ETosis). Unlike apoptosis, eosinophil ETosis (ETosis) releases the total cellular content of these cells, including damage-associated molecular patterns. Thus, ETosis is considered to be a potentially proinflammatory type of cell death.

In tissues, the presence of multiple inflammatory signals (e.g., adhesion molecules, complements, lipid mediators, cytokines, and pathogens) that work synergistically with IL-5 are required for the “full” activation of eosinophils. In vitro systems, isolated human eosinophils spontaneously undergo apoptosis within 48 h; however, the survival of eosinophils is significantly prolonged in the presence of a low concentration of IL-5. Of interest, the stimulation of eosinophils with IL-5 and the platelet-activating factor in low serum/albumin conditions leads to the rapid ETosis, suggesting that activated eosinophils in tissues and/or after luminal entry can degranulate through suicidal ETosis (Fig. 1, 2). ETosis has been implicated in the pathogenesis of several eosinophilic diseases, including asthma, allergic bronchopulmonary aspergillosis, eosinophilic otitis, eosinophilic chronic rhinosinusitis (ECRS) or chronic rhinosinusitis with nasal polyps (CRSwNP), hypereosinophilic syndrome, COPD, and Wells syndrome (eosinophilic cellulitis).

The immunoregulatory capacities of eosinophils could be explained by their accomplishment of the highly selective process of granule-derived proteins, i.e., piecemeal degranulation. In response to exogenous stimulus, granule-stored cytokines are differentially sorted into vesicular-tubular compartments and mobilized to the outer plasma membrane. In addition to the selective release system, recent evidence suggests the existence of several specific subtypes of eosinophils. In situ differentiation of eosinophil-committed cells might be associated with eosinophil heterogeneity. Several studies have demonstrated that hematopoietic CD34+ progenitor cells migrate to the sites of allergic inflammation, where they undergo further proliferation and final maturation.

The role of anti-IL-5 therapy for severe asthma and eosinophilic granulomatosis with polyangiitis

Clinical evidence of the usefulness of mepolizumab for the management of severe asthma

As mentioned above, IL-5 is among the most eosinophil-selective and potent activators of various cellular functions.
Mepolizumab (SB240563), which is a humanized mAb targeting IL-5, was developed in the late 1990’s and the results of its first clinical trial were published in 2000. Although mepolizumab greatly reduced the number of eosinophils in the blood and sputum, the improvement in airway hyperresponsiveness after allergen challenge was not observed. This negative result was confirmed by a subsequent clinical study that recruited 362 patients and showed an absence of improvement in pulmonary function or symptoms. Although those results were disappointing and dampened the positioning of eosinophils in the pathology of asthma, a major drawback of those studies was that patients were not selectively recruited based on inflammatory phenotypes. In addition, regarding the study endpoint, a trend for a decrease in exacerbation was observed in the latter study.

In a small follow-up study that recruited only patients with a sputum eosinophil percentage of more than 3% and set the exacerbation as a primary endpoint, a significant decrease in exacerbation was shown. This positive result was further confirmed in large-scale trials called DREAM study and MENSA study, which recruited only patients with eosinophilic inflammation. The process used for establishing the clinical efficacy of mepolizumab suggested the importance of identifying the eosinophilic asthma phenotype when applying anti-IL-5 treatment. The entry criteria for the MENSA study, which was a pivotal study for this clinical indication, were set to recruit patients who had a peripheral blood eosinophil count ≥ 150 cells/μl at screening or ≥ 300 cells/μl at some point during the previous year. These thresholds were based on the analysis of the DREAM study, in which the best responders to mepolizumab were identified. The primary endpoint in the MENSA study was the rate of exacerbation and the other outcomes included pulmonary function, health-related quality of life (HRQOL), and asthma symptoms, all of which were significantly improved by mepolizumab. In addition, a comparable effect of the intravenous and subcutaneous administration of this drug was shown, which led to the approval of subcutaneous injection. The eosinophil criteria in the MENSA study shown above were cited in the attached document for mepolizumab in Japan, the perusal of which is recommended when applying this drug to patients. In subsequent clinical studies, an improvement in HRQOL as a primary endpoint was shown in the phase 3b MUSCA study, whereas a glucocorticoid-sparing effect was demonstrated in the SIRIUS study. Mepolizumab was approved for severe asthma in November 2015 in the United States, December 2015 in European countries, and March 2016 in Japan.

Features and clinical evidence of the anti-IL-5 receptor α mAb, benralizumab

As mentioned previously, the IL-5R is composed of an IL-5-specific α subunit and a signal-transducing β subunit that is common to IL-3 and GM-CSF receptors. Benralizumab (MEDI-563) is a humanized afucosylated mAb that was developed by Kyowa Hakko Kirin in the late 2000’s and is specific for the human IL-5Ra. Afucosylation enhances the interaction between benralizumab and FcγRII/II, and heightens Ab-dependent cell-mediated cytotoxicity (ADCC) functions. The incubation of NK effector cells with benralizumab in vitro induced the apoptosis of IL-5Ra-expressing eosinophils and basophils, suggesting the ADCC activity of benralizumab. The eosinophil-depletion efficacy of the drug was rapid and single doses of benralizumab resulted in marked reduction of blood eosinophil counts within 24 h; moreover, benralizumab decreased the airway mucosal eosinophil counts by 61.9% compared with the baseline (day 28).

The clinical efficacy of benralizumab was investigated in two independent phase 3 trials (SIROCCO and CALIMA). Benralizumab significantly reduced the annual exacerbation rate in patients with blood eosinophil counts of at least 300 cells/μl as the primary endpoint and improved the forced expiratory volume in 1 s (FEV1) in both studies. A glucocorticoid-sparing effect was also reported by the ZONDA study. Benralizumab was approved for severe asthma in November 2017 in United States, and January 2018 in European countries and Japan.

Anti-IL-5 mAb, reslizumab

Reslizumab is another anti-IL-5 mAb that was approved for the treatment of severe asthma in the United States and European countries, but not in Japan. In contrast with other IL-5-targeted drugs, reslizumab is administered intravenously and the administered dose is corrected according to body weight. Among patients with obesity, because the administered dose of reslizumab increases as the body weight increases, a fraction of those patients responded better to reslizumab vs. mepolizumab, which was administered at a fixed dose. The efficacy of subcutaneous administration and the improvement in efficacy observed after switching from mepolizumab to reslizumab is under investigation. As studies such as those of the steroid-sparing effect of reslizumab are lacking because of the current commercial limitations of the drug, this review will focus of benralizumab and mepolizumab as IL-5-targeted therapies.
Predictive factors of the efficacy of anti-IL-5 treatments

Blood eosinophil count is the best-established biomarker for the prediction of the efficacy of anti-IL-5 treatments. A post-hoc analysis of phase 3 trials showed that mepolizumab and benralizumab reduced the rate of exacerbation as blood eosinophil count increased. Regarding mepolizumab, the exacerbation rate reduction afforded by this agent vs. the placebo increased progressively, from 52% in patients with a baseline blood eosinophil count $\geq 150$ cells/$\mu$L to 70% in patients with a count $\geq 500$ cells/$\mu$L. A significant effect was not observed in patients from the DREAM study with a baseline blood eosinophil count $<150$ cells/$\mu$L. The criteria “eosinophil count $\geq 150$ cells/$\mu$L at treatment start” and “eosinophil count $\geq 300$ cells/$\mu$L at some time during the previous year” were compared, and the rate of reduction in exacerbation was comparable. Thus, the selection of patients for mepolizumab therapy based on the criteria adopted in the MENSA study is recommended also in clinical settings.

Regarding benralizumab, although a significant effect was observed in patients with an eosinophil count $\geq 150$ cells/$\mu$L, the effect was also dependent on blood eosinophil count and a significant effect was not observed in patients with an eosinophil count $<150$ cells/$\mu$L. In a study that investigated the glucocorticoid-sparing effect, patients were eligible for benralizumab study if they had a blood eosinophil count $\geq 150$ cells/$\mu$L or fulfilled the criteria used in the MENSA mepolizumab study. Thus, the effect of anti-IL-5 therapy in glucocorticoid-dependent patients with an eosinophil count $<150$ cells/$\mu$L has not been established.

FeNO and the levels of serum IgE, which are regulated by IL-4 and IL-13, were not effective predictive markers of the efficacy of mepolizumab or benralizumab. Regarding the clinical background, the efficacy of mepolizumab was not different between patients with or without prior treatment with omalizumab. Oral glucocorticoid use, comorbid nasal polyps, forced vital capacity $<65\%$ of the predicted value, and more than 3 exacerbation events in the previous year were correlated with a higher efficacy of benralizumab.

Regarding the continuation rules at 16 weeks after the onset of mepolizumab therapy, there was no evidence of a reliable marker that could predict the long-term effects of the drug, suggesting the existence of late responders.

Safety of the anti-IL-5 treatment

As eosinophils have been reported to have potential anti-parasitic and anti-viral effects, there is a concern about the decrease in host defense during anti-IL-5 therapy. However, the frequency of upper-airway infection tended to be lower than that of the placebo arm in clinical studies of the 1-year use of mepolizumab and benralizumab. The longitudinal safety of mepolizumab up to 52 weeks (COSMOS study, n = 558) or 3.5 years (COLUMBA study, n = 347), and of benralizumab for 1 year (BORA study, n = 1576) or 2 years was assessed, but no serious concern about an increase in infections was raised. No parasitic infections were reported for both drugs.

Regarding malignancies, six out of 347 patients (1.7%) and 12 of 1576 patients (0.8%) reported malignancies while receiving mepolizumab and benralizumab, respectively. The types of malignancies included basal cell carcinoma (5.8 events per 1000 patient-years in mepolizumab); cancers of the nasal cavity, prostate (1.7 events per 1000 patient-years in mepolizumab), breast (0.83 events per 1000 patient-years in mepolizumab), colon, and pancreas; chronic myeloid leukemia; and B-cell lymphoma. The rate of incidence of malignancy during mepolizumab treatment was similar to rates in the placebo arms and rates in age- and sex-adjusted general population from Surveillance Epidemiology and End Results Registry for 2007–2011 in the United States.

For the assessment of systemic reactions after mepolizumab and benralizumab use showed that hypersensitivity reactions were present in 2% and 1%–3% of patients, respectively; moreover, an anaphylactic reaction was observed in one patient who received benralizumab. Pyrexia was reported in less than 1% of patients treated with mepolizumab, and in 3%–4% of those treated with benralizumab. Headache was observed in 20% of patients treated with mepolizumab (17% in the placebo group) and 7%–9% in those who received benralizumab (5%–7% in the placebo group).

The analysis of anti-drug Ab (ADA) in patients treated with mepolizumab and benralizumab revealed that 8% or 15%–17% of the subjects had positive ADA, respectively. Neutralizing drug Abs were not detected in patients who received mepolizumab, whereas 9%–13% of patients were treated with benralizumab were positive for these Abs. Regarding benralizumab, although a slight decrease in eosinophil-depleting activity was observed in patients with high titers of ADA, positivity for ADA was not clearly associated with drug efficacy or hypersensitivity.

A review article published by Gleich commented that no specific complications were observed in patients who lost eosinophils because of autoimmune diseases. The safety of anti-IL-5 treatment seems to be increasingly established, although a close monitoring of its long-term safety is desirable.

Comparison of the clinical efficacy of anti-IL-5 Abs

The efficacy of benralizumab in decreasing the number of eosinophils in blood and lung tissues seems to be more prominent compared with that of mepolizumab. In addition, as basophils express IL-5Rα, apoptosis of basophils was induced by the ADCC activity of benralizumab in an in vitro experiment, and the decrease in blood basophil counts was also suggested. Although, no head-to-head comparison of clinical efficacy is available, and it is impossible to compare the results of different trials, because the baseline number of eosinophils and exacerbation events differ among studies.

As an approach to this type of comparison, the efficacy of mepolizumab, benralizumab, and reslizumab was compared via an indirect treatment comparison by analyzing the data from clinical studies using the drugs at licensed dose and the route of administration. The analysis matched the number of eosinophils among studies and showed that mepolizumab was associated with significantly greater improvements in exacerbations and asthma control compared with other anti-IL-5 drugs in patients with a blood eosinophil count $\geq 300$ cells/$\mu$L. In contrast, another matching-adjusted indirect comparison analysis that matched the various parameters including number of eosinophils, IgE levels, and previous exacerbations by estimating a propensity score did not show significant differences between mepolizumab and benralizumab.

These contradictory results might stem from the different analytical method used in the various studies. Although the better efficacy of benralizumab after mepolizumab treatment was reported in case reports, a clear difference in efficacy between these drugs has not been established.

Although the specific reason for the discrepancy observed between the efficacy of the elimination of eosinophils and clinical improvement is unclear, the following are potential explanations. In animal experiments, the existence of a subset of “good eosinophils”, which are termed resident eosinophils (rEOS), has been suggested. As rEOS reportedly suppress airway inflammation and
their survival is IL-5-independent, mepolizumab might not eliminate those cells and the number of residual eosinophils might not be related to asthma exacerbation. However, as the existence of rEOS has not been established in human tissues, further human studies should clarify the potential existence of this subset of good eosinophils and the nature of the residual eosinophils after mepolizumab treatment. From another perspective, compared with the circulating eosinophils, the expression of IL-5Rα appears to be functionally downregulated in lung tissues.77 Although another study also reported that expression of the IL-3 receptor and GM-CSF receptor, but not IL-5Rα, was observed in tissue eosinophils after an allergen challenge.78 Those observations suggest that the additional efficacy of benralizumab afforded by ADCC activity might be limited to complete elimination of tissue eosinophils.

**Positioning of anti-IL-5 treatment for severe asthma (Table 1)**

In our analysis, approximately 25% of patients with severe asthma were indicated for all biologics, including omalizumab, mepolizumab, benralizumab, and dupilumab, if the threshold values of blood eosinophils and FeNO were set at 150 cells/µl and 25 ppb, respectively.79 Although a definitive biomarker for the choice of biologics has not been established, the following information should be considered in this context.

The efficacy of anti-IL-5 therapy and dupilumab strengthens as the blood eosinophil count increases (Table 1). As the level of FeNO is regulated by IL-4/IL-13, this parameter is a good marker for predicting the efficacy of dupilumab.80 However, the utility of FeNO was not shown for mepolizumab.

We classified the patients with severe asthma (n = 102) into four phenotypes based on eosinophil count and FeNO (Fig. 3). The FeNO single-high phenotype (C) was the smallest group in our analysis (4.9%) and in a recent phase 3 QUEST study of dupilumab (8.5%)80 and this phenotype will be indicated for dupilumab or omalizumab therapy. The eosinophil single-high phenotype (B) and the dual-high phenotype (D) encompassed the largest proportion of patients, both in our analysis (B, 39.2%; D, 31.4%) and in the QUEST study (B, 29.9%; D, 41.7%)80, and the all biologics may be indicated for those phenotypes. In the QUEST study, the exacerbation rate reduction afforded by dupilumab vs. the placebo was significant in both phenotypes, however, numerically lower in the eosinophil single-high phenotype (B) compared with the dual-high phenotype (D) (B, -47% vs. D, -65%).80 Thus, anti-IL-5 therapies might be relatively more effective than is dupilumab for the eosinophil single-high phenotype (B), although further investigation is required to confirm this notion.

Other points that should be taken into consideration regarding the choice of biologics are comorbidities, longitudinal safety, and interval of injection (Table 1). Mepolizumab is indicated for eosinophilic granulomatosis with polyangiitis (EGPA), and dupilumab is indicated for CRSwNP (in western countries) and for atopic dermatitis, whereas omalizumab is indicated for seasonal rhinitis in Japan, as well as for urticaria. Safety data covering 2 years for benralizumab, 4 years for mepolizumab, and 10 years for omalizumab have been generated. The interval of injection in the maintenance phase is 8 weeks for benralizumab, 4 weeks for mepolizumab, and 2 weeks for dupilumab.

As shown in Figure 3, omalizumab is indicated for 40%–60% of patients with all phenotypes stratified according to blood eosinophil counts and FeNO level. As the global evaluation of treatment effectiveness at 4 months predicted the longitudinal effect as a continuation rule, trial of omalizumab treatment for 4 months was recommended in the “care pathway” when multiple biologics are indicated.81

**Table 1**

Different characteristics of the biologics indicated for severe asthma.

<table>
<thead>
<tr>
<th>Biomarker for prediction of efficacy</th>
<th>Omalizumab</th>
<th>Mepolizumab</th>
<th>Benralizumab</th>
<th>Dupilumab</th>
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<td>○</td>
<td>X</td>
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<tr>
<td>Anti-IL-5 Ab</td>
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<td>△</td>
<td>∆ - ○</td>
<td>ND</td>
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<tr>
<td>Continuation rule established</td>
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<td>X</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>Prognosis after discontinuation</td>
<td>△</td>
<td>Study ongoing</td>
<td>ND</td>
<td>ND</td>
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<td>Blood eosinophils</td>
<td>Blood eosinophils</td>
<td>FeNO Blood eosinophils</td>
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<td>EGPA</td>
<td>None</td>
<td>Serum IgE</td>
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<tr>
<td>Longitudinal safety data</td>
<td>2 or 4 weeks</td>
<td>4 weeks</td>
<td>8 weeks (maintenance)</td>
<td>2 weeks</td>
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</table>

![Fig. 3. Distribution of severe asthma phenotypes and potential indication for biologics. Four phenotypes were defined based on a threshold value of blood eosinophil count of 150 cells/µl and a FeNO level of 25 ppb. Patients with severe asthma under inhaler corticosteroid treatment and not using biologics were recruited from an outpatient clinic at the Teikyo University Hospital (n = 102). Patients were categorized into four phenotypes (A–D); the proportion of patients belonging to each phenotype is shown. The potential indication for biologics is also shown for each phenotype. The percent-ages of patients in each category who fulfilled the indication for omalizumab are shown in parentheses. Fifteen patients (14.7% of total patients) were treated with regular oral glucocorticoids (A, 6.7%; B, 53.3%; C, 6.7%; D, 33.3%). The diagnosis of severe asthma was based on the Japanese guidelines for adult asthma and the indication for omalizumab was defined as a total serum IgE level of 30–1500 IU/ml and positive specific IgE Ab for perennial aeroallergen.](image-url)
Effect of mepolizumab on eosinophilic granulomatosis with polyangiitis

EGPA, formerly known as Churg–Strauss syndrome, is an eosinophilic vasculitis characterized by asthma, peripheral neuropathy, and eosinophilic vasculitis of various organs. Most of these patients are dependent on systemic glucocorticoid therapy, and relapses are common. The efficacy of mepolizumab was investigated as an add-on therapy in patients with refractory EGPA. Mepolizumab treatment led to a significant increase in remission time, and remission occurred in 53% of participants in the mepolizumab group vs. 19% in the placebo group. Forty-four percent of the members of the mepolizumab group, compared with 7% of those of the placebo group, received an average daily dose of prednisolone of ≤4 mg at the end of the study. This study showed for the first time the efficacy of mepolizumab for maintaining remission in EGPA. Mepolizumab was approved for EGPA in December 2017 in the United States and May 2018 in Japan. Further studies of the efficacy of the drug at the acute phase, the positioning in the initial treatment, and treatment sequence should be performed in the future.

Roles of anti-IL-5 treatment in chronic rhinosinusitis with nasal polyps

CRSwNP is a severe persistent airway disease. In Europe and the United States, CRSwNP has been thought to be mainly characterized by a type-2–mediated inflammatory reaction with marked infiltration of eosinophils and mast cells in the nasal mucosa and NP. Japanese CRSwNP was recognized as a neutrophilic inflammatory disease 30 years ago. However, the infiltrated cell type in recent reports of Japanese CRSwNP cases was changed from neutrophils to eosinophils. Patients with this type of CRSwNP complain mainly of loss of smell, and strong eosinophil infiltration is observed in nasal polyp tissues. This CRSwNP type is resistant to macrolide therapy and easily recurs after endoscopic sinus surgery (ESS), suggesting the presence of intractable/refractory CRSwNP. Therefore, this intractable type of CRSwNP is termed eosinophilic chronic rhinosinusitis (ECRS).

IL-5 might be a major target in the therapeutic strategy for CRSwNP. Bachert’s group from Ghent University presented 10 clusters of CRSwNP, six of which had high concentrations of IL-5, ECP, and IgE, and four of which had low or undetectable levels of these markers. IL-4–stimulated Th2 cells and TSLP/IL-33–stimulated ILC2s are major IL-5–producing cells in nasal mucosa and nasal polyps (Fig. 4). Mast cells in ECRS also produce IL-5 by stimulation of TSLP and IL-1β.

The first randomized, double-blinded, placebo-controlled study of mepolizumab in patients with CRSwNP was reported in 2011. Objective patients exhibited failure of standard therapy for CRSwNP before the study. Twenty patients with severe CRSwNP were administrated mepolizumab (750 mg) intravenously twice with an interval of 4 weeks, while 10 patients with CRSwNP were treated with placebo using the same protocol. The nasal polyp scores in the mepolizumab group were significantly reduced from the baseline (−1.30) compared with the placebo group (0.00). Blood eosinophil counts and serum ECP and IL-5Rα levels were also significantly reduced in the mepolizumab group. However, reductions in the Lund–Mackay CT score, SNOT-22, loss-of-smell symptom score, and rhinorhoea scores were not significantly different between the groups. To obtain a significant reduction of those scores, a greater number of patients and more frequent times of mepolizumab administration might be required.

The next randomized, double-blinded, placebo-controlled study of mepolizumab in patients with CRSwNP was reported in 2017. A total of 107 patients were randomized to receive mepolizumab (n = 54) or placebo (n = 53) in three countries (Belgium, Netherlands, and the United Kingdom). Patients had a nasal polyp score of 3 or more in one nostril (and a minimum score of 2 on the other side) and a visual analog scale (VAS) nasal symptom score > 7. Patients were also required to be eligible for surgery as a result of being refractory to standard steroid therapy (typical corticosteroid and short course of systemic corticosteroids). Patients with severe CRSwNP received intravenous injection of mepolizumab (750 mg) every 4 weeks (Weeks 1, 5, 9, 13, 17, and 21), for a total of 6 doses. A significantly greater proportion of patients in the mepolizumab group (10%) compared with the placebo group (30%) no longer required surgery at Week 25 (P = 0.006). The nasal polyp score decreased significantly at Week 25 in the mepolizumab group (−1.8 from the baseline, Fig. 5) compared with the placebo group (−0.6, P = 0.001). The nasal polyp score was improved by 1 or more points in 27 (50%) patients in the mepolizumab group and in 14 (27%) patients in the placebo group. The symptom VAS scores, and SNOT-22 questionnaire score were significantly decreased in the mepolizumab group compared with the placebo group. Headache, nasopharyngitis, oropharyngeal pain, and back pain were major adverse events in both groups. Mepolizumab was tolerated well. Blood eosinophil counts decreased from a geometric mean of 500 cells/μl at the baseline to 50 cells/μl at Week 25 in the mepolizumab group; in contrast, such a decrease was not observed in the placebo group. These results suggest that mepolizumab treatment has the potential to improve QOL and reduce the surgery-associated burden in patients with severe CRSwNP. An extensive randomized, double-blinded, placebo-controlled international

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**Fig. 4.** IL-5 plays an important role in the pathogenesis of nasal polyps. TSLP, IL-33, and IL-1β are released from nasal epithelial cells after infection with microorganism (virus and bacteria). TSLP induces IL-5 production by Th2 cells and ILC2s. TSLP and IL-1β induce IL-5 release from mast cells.

**Fig. 5.** Changes in the nasal polyp score from the baseline. Mepolizumab significantly reduced the nasal polyp score at Week 25 compared with the baseline. P*** <0.001. BL, baseline; LS, least squares; SE, standard error.
clinical trial is currently under way, to assess the effect of mepolizumab on severe CRSwNP in with a combined cohort stemming from many countries of Europe and the United states.

We conducted a phase II, multicenter, randomized, double-blinded, placebo-controlled study of ECRS for benralizumab in Japan. Fifty-six patients were enrolled (placebo, n = 11; benralizumab single shot, n = 22; benralizumab three times every 4 weeks, n = 23). Blood eosinophil count reached zero by benralizumab. Several cases in the active group exhibited a decrease in the nasal polyp score (more than 2 points) after the administration of benralizumab. However, there were no significant differences in the nasal polyp score at Week 12 between the benralizumab and placebo groups regarding changes from the baseline (data not shown). We speculated that the duration of benralizumab administration was too short and the sample size was too small to investigate this further. The design of future studies should include larger sample sizes, a longer treatment duration, and the collection of nasal tissue samples, to allow the evaluation of the potential effects of benralizumab in greater detail.

Systemic corticosteroids and ESS are effective for the treatment of CRSwNP. ECRS requires long-term administration of oral corticosteroids and repeated ESS. Long-term administration of oral corticosteroids leads to serious adverse events and repeated ESS distresses patients with ECRS. IL-5 is a critical cytokine in the pathogenesis of nasal polyps. The anti-IL-5 mAb, mepolizumab, would be an option for the treatment of intractable/refractory CRSwNP (or severe ECRS). The administration of mepolizumab may be available. As anti-IL-5 therapy is specifically targeting alarmins, including IL-33 or TSLP, which are more up-regulated in CRSwNP (or severe ECRS). The administration of mepolizumab may also lead to a substantial reduction in the need for systemic corticosteroids and repeated ESS.

Conclusion

In this review, the role of IL-5 and the current status of anti-IL-5 therapy in eosinophilic diseases, including severe asthma, EGPA, and ECRS or CRSwNP, was discussed. In the near future, biologics targeting alarmins, including IL-33 or TSLP, which are more up-stream molecules that broadly suppress the downstream pathways, may be available. As anti-IL-5 therapy is specific to eosinophilic inflammation, this strategy will be continuously indicated for eosinophilic diseases once its longitudinal safety and efficacy is better established.

Acknowledgments

This review was supported in part by a research grant from Environmental Restoration and Conservation Agency (HN), the Japan Agency for Medical Research and Development (AMED; SU: JP19ek0410055, SF: JP17ek0410040, JP16ek0109062), the Mochida Memorial Foundation for Medical and Pharmaceutical Research (SU), Japanese Society of Laboratory Medicine Fund for Promotion of Scientific Research (SU), Japan Society for the Promotion of Science KAKENHI (SU: 15K0329, 16K08926, 17K09993, FS: 17H04344), and a Health Labour Sciences Research Grant (H30-Nanitou(nan)-Ippan-016). The authors are grateful to Ms. Satomi Misawa for outstanding assistance in drawing the figure and Ms. Noriko Tan and Dr. Yui Miyabe for excellent technical assistance. Thanks are also extended to Ms. Asako Tsukamoto and Ms. Eriko Endo for their outstanding secretarial assistance. The author would like to thank Enago (www.enago.jp) for the English language review.

Conflict of interest

HN received speaker fees from AstraZeneca, GlaxoSmithKline, Novartis and Sanofi, and has been an advisory board member for GlaxoSmithKline, Kyowa Kirin and Sanofi, and received research grants from Boehringer Ingelheim. SU received speaker fees from AstraZeneca and research grants from Maruho. SF received speaker fees from Kyorin, Taiho and Mitsubishi Tanabe Pharma and has been an advisory board member for GlaxoSmithKline, Kyowa Kirin and Sanofi, and received research grants from Maruho, Tsumura, Mitsubishi Tanabe Pharma and Sanofi.

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