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Mepolizumab - a novel option for the treatment of hypereosinophilic syndrome in childhood

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Abstract

Background

Mepolizumab was originally intended as a therapeutic agent for atopic asthma in adults, and consequently little is known about its use in children. Up to now corticosteroids have formed the basis of the initial treatment of hypereosinophilic syndromes and are shown to be effective in most patients. To analyse the effect of mepolizumab in children is the aim of this study.

Methods

We are reporting the experience of the effect of mepolizumab in two paediatric patients of hypereosinophilic syndrome that was not sufficiently controlled by other drugs. In addition, the literature regarding the treatment with mepolizumab in paediatric and adult patients is reviewed for the most important studies regarding safety and efficacy.

Results

Mepolizumab therapy showed in two paediatric patients with severe hypereosinophilic syndrome a safe and efficient therapeutic approach. No significant intolerances appeared. Furthermore, treatment with systemic corticosteroids was terminated, and therefore severe side effects were avoided in our pediatric cases.

Conclusions

Anti-IL-5 antibodies, which can be applied without substantial drug intolerances, are a new, safe and effective treatment option for paediatric patients with hypereosinophilic syndrome.

Key words: anti-IL5 antibodies, hypereosinophilic syndrome, mepolizumab

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Introduction

Blood hypereosinophilia (HE) is associated with many different disorders, including parasitic infections, drug hypersensitivity and atopic as well as malignant diseases. It is defined as an elevation of blood eosinophils $> 500/\text{mm}^3$ (1).

Apart from these associations, HE marks a central pathogenic factor in a group of diseases defined as hypereosinophilic syndrome (HES). HES is defined as blood eosinophilia $\geq 1500/\text{mm}^3$ on at least two occasions or evidence of prominent tissue eosinophilia associated with symptoms and marked

peripheral blood eosinophilia(2). Organ infiltration of eosinophils with consecutive tissue damage caused by toxic granule proteins, cytokines and humoral factors most frequently involves skin, lungs, the cardiovascular system and the central nervous systems (3-5). HES shows a higher incidence in adults but has also been diagnosed in paediatric cohorts of all ages(6). Since HES remains a rare disease (1:100.000), there exist only scarce data on the clinical presentation, laboratory findings, treatment requirements and prognosis of paediatric HES patients.

Mepolizumab, a humanized monoclonal antibody binding free IL-5 with high affinity and specificity and thus inhibiting the interaction of IL-5 and the IL-5 receptor complex located on the eosinophil granulocyte cell surface, was originally intended as a therapeutic agent for atopic asthma in adults (7-9). In children it has been used in patients with eosinophilic esophagitis and has shown a reduction in esophageal mast cell accumulation and numbers of intraepithelial eosinophils (10,11).

Here we report the experience of the effect of mepolizumab in two paediatric patients of HES that was not sufficiently controlled by other drugs.

Case presentations

Case 1

A 14-year-old boy with bronchial asthma received an anti-obstructive, anti-inflammatory inhalation therapy and systemic corticosteroids. This treatment strategy did not result in sufficient symptom control. Chest X-ray indicated pulmonary bilateral infiltrates of the lung (Figure 1). CT scan revealed additionally bilateral pleural effusion and pericardial effusion (Figure 1). Bronchoscopy was performed and showed obstruction of the right main bronchus (Figure 2), which could be re-canalized with rigid forceps. Histopathological findings from the skin biopsy of the rash verified eosinophilic infiltrates (Figure 3). The finding of the fusion gene FIP1L1/PDGFR α confirmed also the clonal genetic abnormality. The eosinophilia count was very high at 45%. Even the add-on therapy with azathioprine or tyrosine kinase inhibitor imatinib did not positively influence the course of disease. Due to the dramatic clinical course, a “compassionate-use” trial of therapy with 750 mg intravenous mepolizumab was initiated. Lung function and eosinophil blood count improved during mepolizumab treatment (Figure 4). Pleural and pericardial effusions had regressed completely. Standard values of bone mineral density measured by quantitative computed tomography were reached after corticosteroid treatment was slowly decreased and finally terminated. To date, the patient has continued mepolizumab treatment and the physical work capacity is unremarkable. The patient has received the monoclonal anti-IL-5 antibody for 4 years now. Mepolizumab has been

administered in 4- to 6-week intervals with very good efficacy and without serious adverse events (Table 1).

Case 2

An 11-year-old girl was diagnosed with HES (lymphocytic type, CD3⁺CD4⁺ L-HES) with initial skin- and lung-manifestation. She received high dose corticosteroid inhalation therapy and beta2-adrenergic agonists up to her 15th birthday. Afterwards she developed a progressive dyspnea with severe impairment of lung function. Oral systemic corticosteroid and intravenous methylprednisolone pulse therapy did not positively influence the course of disease. Even a combined therapy of prednisolone, azathioprine und methotrexate did not stop disease progression. In a “compassionate-use” clinical trial, 750 mg mepolizumab was administered every 4 to 6 weeks. The clinical status of the patient improved and pulmonary symptoms decreased. Therapy with systemic corticosteroids was no longer necessary. In total, the patient has received mepolizumab for 7 years now, without any significant adverse event. The patient could travel to Australia and received the required intravenous mepolizumab applications in Australia from Australian clinicians. In 2016, she experienced an uncomplicated pregnancy and delivered a healthy newborn. The long-term follow up has been favorable with FEV1 between 65 and 90%. No systemic eosinophilia during mepolizumab therapy has been revealed. Mild exacerbation of obstructive airway disease has been the only disease manifestation during the 12 years of follow up.

Discussion

IL-5, secreted by activated CD4⁺ Th2 cells, is one of the main eosinophil chemotactic agents. It has been demonstrated that IL-5 regulates differentiation, growth, recruitment, activation and life span of eosinophil granulocytes. Furthermore, it increases the ability of eosinophil granulocytes to adhere to endothelial cells, resulting in eosinophil accumulation in solid organs such as the lung. There, eosinophil granulocytes can cause serious tissue damage following release of eosinophil-derived neurotoxin (EDN) and major basic protein (MBP) resulting in end-organ dysfunction or even failure(12).

Up to now corticosteroids form the basis of the initial treatment of hypereosinophilic syndromes and are shown to be effective in most patients. In a large multicentre study with 188 HES patients, 81% of the participants were initially treated with corticosteroids of whom 85% showed partial or complete remission within one month(3). As HES is a chronic disease, problems result from the corticosteroid-related side effects and the possibility of patients becoming refractory to medication when long-term treatment is required. To address this issue, several other drugs were introduced as second line or complementary therapies including hydroxyurea, Interferon- α , and methotrexate.

In a review of literature Katz et al. reported a high association of paediatric HES with acute lymphoblastic leukaemia (36.8% of the patients with HES) followed by a high prevalence of fever (20%), significant death rate (42%), and short mean survival (10.6 months) in their paediatric cohort(6).

Williams et. al recently postulated that this might be the result of an overrepresentation of the most severe cases in the literature and themselves performed a large retrospective cohort study, comparing clinical, diagnostic and prognostic aspects of paediatric (n=37) and adult (n=254) patients with hypereosinophilic syndromes. After exclusion of patients with associated HES, there was no significant difference regarding the distribution of clinical subtypes between the two groups. Undefined HES was the most common subtype (46% of the children vs. 47% of the adults). Children showed higher median peak absolute eosinophil counts, had more gastrointestinal symptoms and less pulmonary manifestations than adults. They largely resembled the adult cohort regarding treatment responsiveness and overall prognosis(13).

HES subgroups were established to implement a classification system that honours the broad variety of factors that can cause HES and to treat the patients with a more specific approach (Table 2).

The basis of the HES treatment remains corticosteroids(3,4,14) (13) in adults and children. In addition to corticosteroid therapy, tyrosine kinase inhibitor imatinib, hydroxyurea, interferon-alpha and methotrexate are commonly used in adult and paediatric patients with HES, and in rare cases other therapies, used as rescue therapies, have been described(13,15). Corticosteroids are widely used in the therapy of HES as the response rate is very high. The comparison of the response rate between adults and children is similar and shows no significant difference (children 88% versus adults 83%, p=NS). HES is an ongoing disease with need for recurrent therapies in most patients(13). Therefore, next to the response rate of HES therapy, therapy-related side effects, especially in the paediatric cohort, are of major interest. The severities of the safety concerns vary with dose duration and age(16,17). One of those are the corticosteroid-related changes in bone remodelling, which lead to stunting of growth and vertebral fractures in children and need preventive interventions (18). Other quality-of-life-influencing side effects are weight gain, cushingoid appearance, mood changes, sleep disturbances, and immune suppression. To avoid severe side effects therapeutic strategies in inflammatory bowel disease have been changed already towards use of biologicals(19). Comparable to this strategy, an alternative therapy for HES could be the implementation of antibody therapy to reduce side effects significantly.

In adult cohorts of patients with hypereosinophilic syndrome the therapeutic use of mepolizumab – an anti-IL-5-antibody – showed good efficacy and safety in long-term treatment with low side effects (20,21). Rothenberg et al. performed a study to evaluate the potential of mepolizumab as a steroid-sparing agent in adult patients with F/P-negative HES. After initial prednisone monotherapy for clinical stabilisation, the participants underwent randomization in two groups, receiving either 750 mg mepolizumab (n=46) as a monthly infusion or placebo (n=42) over 36 weeks. The primary endpoint was disease control on less than 10 mg prednisone for at least 8 weeks. Of the patients receiving mepolizumab, 84% were able to reach the endpoint, versus only 43% in the placebo group – a significant statistical difference. In addition, no major adverse events were reported that were thought to be related to administration of the study drug(21).

To further evaluate the long-term safety and efficacy of mepolizumab, 78 of the patients of the first study were included in an open-label extension study, receiving 750 mg mepolizumab with an average dosing interval of 9-12 weeks over a median exposure time of 251 weeks. The primary endpoint was the overall frequency of (severe) adverse events. The rates adjusted for exposure were like those of the placebo group in the earlier study and remained stable over the course of the trial. Four severe adverse events were reported as possibly related to the administration of mepolizumab. Among these were two patients with a clonal T-cell proliferation that had been previously documented in these patients. In terms of efficacy, mepolizumab therapy could reduce the median daily prednisone dose from 20 mg to 0 mg in those patients who previously received placebo during the earlier trial. After this increase of patients who were prednisone free after corticosteroid tapering, the percentage of patients remaining cortisone free over the course of the study was stable at over 50%. Anti-mepolizumab antibodies were found in 57% of participants but had no activity in vitro and did not affect the daily prednisone dose at the end of the study. In summary, this study could demonstrate the safety and efficacy of long-term mepolizumab therapy in adults(20). Meanwhile, only scarce data exist on the clinical presentation and treatment requirements of paediatric HES patients. But results are available that describe eosinophilic esophagitis (EoE) that was treated with mepolizumab. These data showed a reduction in esophageal mast cell accumulation and numbers of intraepithelial eosinophils(10,11). We present two cases of children that have been successfully treated with mepolizumab after first-line treatment with various other anti-inflammatory agents could neither influence the disease significantly nor control the symptoms. Because of the incredible safety and efficacy profile that could be demonstrated in our patients, who have been studied now for over 10 years, and experiences in paediatric patients with EoE, we advocate the use of mepolizumab in paediatric patients.

Conclusion

HES in childhood is a rare, impairing disorder. Anti-IL-5 antibodies are a new, safe and effective treatment option for paediatric patients with hypereosinophilic syndrome (HES) and also for EoE, which can be applied without substantial drug intolerances. Until now no major clinical trials in paediatric patients have been available. One reason might be the status of a rare disease with only a very low number of patients around the world. Paediatric treatment results with mepolizumab are only summarized in anecdotal reports. But with the anti-IL-5 antibody the first pathogenesis-oriented intervention is feasible. The promising results from the adult cohort and the new promising experience in paediatric patients call for a re-thinking of the therapeutic strategies towards a therapy with lower side effects, which is especially important in young patients.

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Table 1. Case synopsis from a 14 year old boy with hypereosinophilic syndrome.

Symptoms	Cough, sputum production, dyspnea, reduction in exercise, fever, tachycardia, chest pain, exanthema of the skin, erythema nodosa, hepatosplenomegaly
Diagnostic results	Ultrasound: Pericardial effusion X-Ray: diffuse infiltrates Lung function test: vital capacity 40 % predicted, FEV 1: 35 % predicted, MEF 50: 8 % predicted. Blood test: leucocytes 29/nl, 45% eosinophils, uric acid 1.6 mg/dl, urea 6 mg/dl, CRP 42 mg/l, IgE 910 kU/l, ECP 200 yg/l, IL-2R 1768 kU/l, IgG 22.41 g/l. Bronchoscopy: bronchial stenosis due to fibrine clots Skin biopsy (histology): eosinophilic cellulitis, no vasculitis Molecular biology diagnostic: fusion gene FIP1L1/PDGFRA
Therapy	Corticosteroids: no significant improvement. Side effects with growth arrest, adipositas and osteoporosis. Imatinib: no significant improvement. Azathioprin: no significant improvement. Omalizumab: significant improvement: Exercise increased, no dyspnea, no cough, eosiniphiles <1%, no osteoporosis, normal BMI, normal FEV1: 103 % predicted and vital capacity: 105 % predicted. No cotrticosteroids.

Table 2 Subtypes of hypereosinophilic syndromes (adapted from (4))

Myeloproliferative HES	Chronic Eosinophilic Leukemia (CEL) Different entities characterised by eosinophil myeloproliferation following clonal or non-clonal proliferation of eosinophil precursor cells. For a group of patients that presents clonal eosinophil proliferation, the gene fusion of Fip1-like 1 (FIP1L1) and platelet-derived growth factor receptor alpha (PDGFRA) (F/P) could be identified as the causing molecular defect. This aberration results in the activation of a tyrosine kinase, leading to an expansion of the eosinophil population (Chronic Eosinophilic Leukemia/CEL). M-HES If screening for the F/P-fusion gene or other causing molecular defects is negative, patients must meet four of the following criteria to be classified as M-HES: dysplastic eosinophils on peripheral smear serum vitamin B₁₂-level > 1000 pg/ml, serum tryptase > 12 ng/ml, anemia and/or thrombocytopenia, hepatosplenomegaly, bone marrow cellularity > 80%, myelofibrosis or spindle-shaped mast cells in the bone marrow.
Lymphocytic HES	Clonal T cells Eosinophilia is caused by an increased production of the eosinophil hematopoietins IL5 by populations of abnormal activated T-Cells. Episodic angioedema with Eosinophilia Often presented with clonal T cells.
Undefined HES	Eosinophilia of undetermined significance Symptomatic eosinophilia without fulfilling the criteria of M-HES or L-HES or benign eosinophilia without symptoms or organ involvement. Or presenting with symptoms but without features of L-HES/M-HES.
Overlap Disorders	Organ restricted eosinophilia Organ restricted eosinophilia, e.g. in the context of eosinophilic gastrointestinal disorders (EGID) like eosinophilic colitis or esophagitis in combination with a possible association of blood eosinophilia.
Associated HES	Eosinophilia with known diagnoses (EGPA) Eosinophilia in the context of diseases known to cause peripher eosinophilia like HIV, mastocytosis, inflammatory bowel disease or sarcoidosis.
Familial HES	Inherited eosinophilia with unknown mechanism Presentation of marked eosinophilia in successive generations of the same family. These rare cases often present with asymptomatic eosinophilia and the underlying pathogenesis is still unknown.



Figure 1. On the left: chest X-ray indicating pulmonary bilateral infiltrates of the lung. On the right: CT scan with bilateral pleural effusion and pericardial effusion indicating thoracic involvement in hypereosinophilic syndrome.

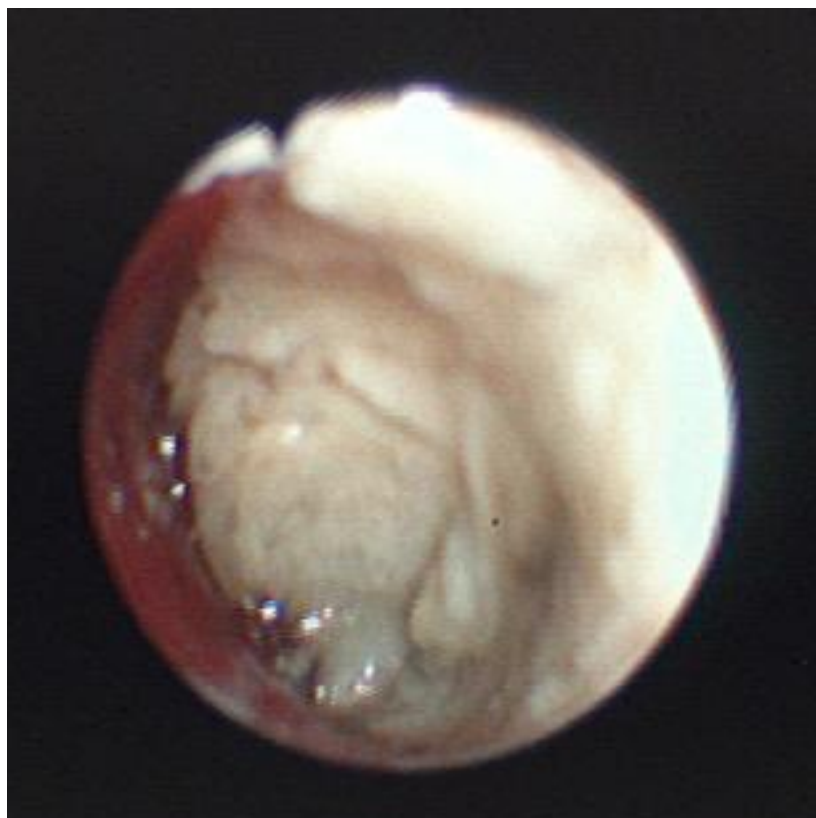


Figure 2. Bronchoscopy revealed an obstruction of the right main bronchus.



Figure 3. Histopathological findings from skin biopsy of this rash verified eosinophilic infiltrates.

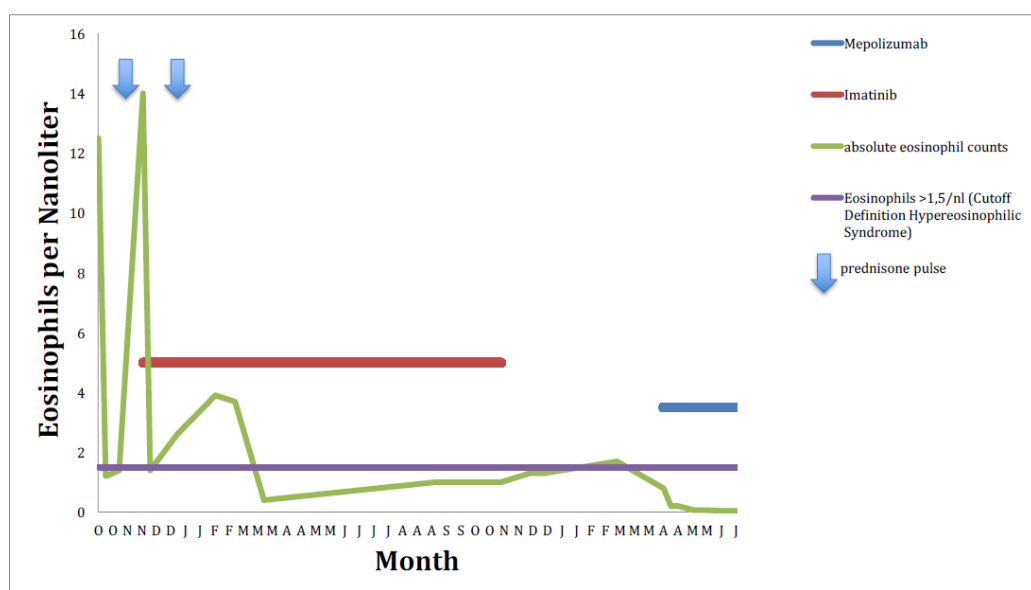


Figure 4. Treatment course and eosinophil blood count of case I.