Lung
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CHRONIC EOSINOPHILIC PNEUMONIA

Real-Life Study of Mepolizumab in Idiopathic Chronic Eosinophilic Pneumonia

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Abstract

Introduction Idiopathic chronic eosinophilic pneumonia (ICEP) is an orphan lung disease characterized by concomitant systemic and local eosinophilia, along with bilateral lung infiltrates. Symptoms include dyspnea of subacute/chronic onset, cough, and general systemic signs. Although all patients do respond to oral corticosteroids, relapse rate is very high, which highlights the need for alternative therapies in case of relapsing ICEP. Mepolizumab is a fully humanized antibody directed against interleukin 5, a key growth factor of eosinophils. In the present study, we retrospectively studied the effect of off-label use of mepolizumab for relapsing ICEP.

Materials and Methods All data from patients treated with mepolizumab for relapsing ICEP were included in our database and diagnoses were reviewed. We analyzed the effect of treatment on relapse rate, oral corticosteroids (OCS) use, and lung lesions on high-resolution computed tomography (HRCT).

Results We included ten patients in the final analysis, with a median follow-up of 9 months after initiation of mepolizumab. Beside its expected effect on circulating eosinophils, treatment with mepolizumab was associated with a significant reduction of annual rate of exacerbations and a reduced consumption of corticosteroids. We also observed a remission of lung lesions on follow-up HRCT.

Conclusions In this open-label retrospective study, treatment of ICEP with mepolizumab was associated with a reduction of relapses, OCS use, and the disappearance of lung infiltrates.

Keywords Idiopathic chronic eosinophilic pneumonia · Mepolizumab · Interstitial lung diseases

Abbreviations

ICEP	Idiopathic chronic hypereosinophilic pneumonia
HRCT	High-resolution computed tomography
OCS	Oral corticosteroids

Introduction

Idiopathic chronic eosinophilic pneumonitis (ICEP) is a rare respiratory disease characterized by the subacute occurrence of dyspnea and chest discomfort, often accompanied by general symptoms including arthralgia and fever. Although there are no guidelines for the diagnosis of ICEP, cardinal features include concomitant blood and bronchoalveolar lavage (BAL) eosinophilia: Usually accepted cut-off are 1000 eosinophils/µL or 10% in blood and a 25% eosinophilia in BAL, without elevated lymphocytes and neutrophils [1]. Lung infiltrates are constant and consist in bilateral, often apical- and subpleural-based (consolidative) opacities on high-resolution computed tomography (HRCT), in the absence of an alternative identified cause, such as an infection or allergic bronchopulmonary aspergillosis [2]. Initial workup should include a complete workup including exclusion of an underlying bacterial or parasitic infection (systematic azole treatment is advised) or another causal agent

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(especially drugs). Spontaneous improvement is described but very rare (less than 5% of patients) [3]. Oral corticosteroids (OCS) represent the standard treatment, although different regimens have been described, consisting either in long-term (3–6 months) treatment with tapered doses or short courses (4–6 weeks) [4]. Although ICEP is always responsive to OCS, relapses occur in more than half of patients: There has been a growing attention given to side effects related to long-term corticosteroid treatment, especially in the ENT and respiratory field. Recent evidence shows a deleterious effect of OCS even when low doses are prescribed [5]. Although the deleterious effects of OCS have not been specifically studied in ICEP patients, this issue highlights the need for alternative therapy in case of relapsing ICEP.

Mepolizumab is a fully humanized anti-interleukin (IL)-5 antibody approved as a biological treatment for severe eosinophilic asthma. Phase III trials with mepolizumab demonstrated that this agent is able to prevent exacerbations and has a corticosteroid-sparing effect [6, 7]. In addition, mepolizumab is also approved in the USA for the treatment of granulomatosis with polyangiitis (EGPA) [8] and has been shown to be an effective corticosteroid-sparing agent in subjects with hypereosinophilic syndrome [9]. At this point, only case reports of successful use of mepolizumab for ICEP have been published [10]. In the present study, we retrospectively studied the effect of open-label mepolizumab in patients with relapsing ICEP treated in four academic centers and one regional hospital in Belgium. We hypothesized that mepolizumab would have a significant effect on the rate of relapses and OCS consumption.

Materials and Methods

Study Population

This is an open-label multicentric retrospective study in Belgium. We collected data on the off-label use of mepolizumab for relapsing ICEP. A protected eCRF was sent and filled by specialists involved in ICEP in four academic centers and one regional hospital. All files were centrally reviewed for the diagnosis of ICEP. HRCT features were compatible with the diagnosis (consolidative opacities). JAK2- and PDGFRα-FLP1-related hypereosinophilic syndrome were not considered in the present study. Patients with a significant other organ involvement (skin, heart) were excluded.

Outcomes

We collected patients' demographic data at the time of the diagnosis, as well as data on blood eosinophilia, BAL, pulmonary function tests, and HRCT. Toxic exposure and comorbidities were also analyzed.

Biological data just prior and 3 months after mepolizumab were included in the database. In the following text, the term "baseline" is used for characteristics of patients at the time of mepolizumab initiation.

We evaluated the effect of mepolizumab on the annual rate of relapses and OCS use before and after mepolizumab initiation. We defined a relapse as the recurrence of respiratory symptoms (cough, dyspnea) accompanied by increase in blood eosinophils, new lesions at the chest X-ray, or HRCT in the absence of infection. Based on the time since initial diagnosis, we estimated the annual rate of relapse for the patients prior to mepolizumab initiation and during follow-up.

We also reviewed the effect of treatment on lung lesions. The last available HRCT prior to mepolizumab treatment was compared to the first HRCT during follow-up after mepolizumab initiation.

Statistics

We used Wilcoxon matched-pairs signed-rank test for simple paired comparisons and Friedman test followed by Dunn's multiple comparisons test for multiple values. A P value < 0.05 was considered significant.

Results

Patients Characteristics

We collected data from 12 patients. One patient was excluded from the analysis, as he did not fulfill the criteria for ICEP (blood eosinophil count was lower than 1000 and BAL cell analysis demonstrated a clear excess of lymphocytes along with eosinophils). We also excluded one patient with a significant skin and heart involvement, which pointed towards a diagnosis of systemic hypereosinophilic syndrome. Two patients fulfilled all classical criteria for ICEP except for one biological value: One had only 19% eosinophils in BAL, without concomitant lymphocytosis or neutrophilia and had marked blood eosinophilia (3000/μL) and typical HRCT lesions. Another patient had only 720 eosinophils/μL in blood at the time of diagnosis and 24% of eosinophils in BAL. However, in this patient, lung biopsy confirmed the diagnosis of ICEP. Therefore, those two patients were conserved for the final analysis. For one patient, the BAL analysis protocol only specified that there was an excess of eosinophils, without mentioning the exact percentage, we also decided to include his data in the present study, provided that all other criteria were met.

In total, ten patients (five women, five men) were finally included in the study. Patients' characteristics are presented in Table 1. Median age at diagnosis was 48 (range 22–65).

Table 1 Patients' characteristics

Gender, M/F	5/5
Age, years (median, range)	48 (22–65)
Blood eosinophils at diagnosis, *N*/μL (median, range)	2035 (720–22,860)
BAL eosinophil percentage at diagnosis (median, range)	30 (19–95)[a]
Blood eosinophils at baseline (mepolizumab initiation), *N*/μL (median, range)	900 (410–2130)
FVC at baseline, % predicted (median, range)	87 (64–112)
FEV1 at baseline, % predicted (median, range)	78 (67–103)

FVC forced vital capacity, *FEV1* forced expiratory volume in 1 s

[a]One missing data

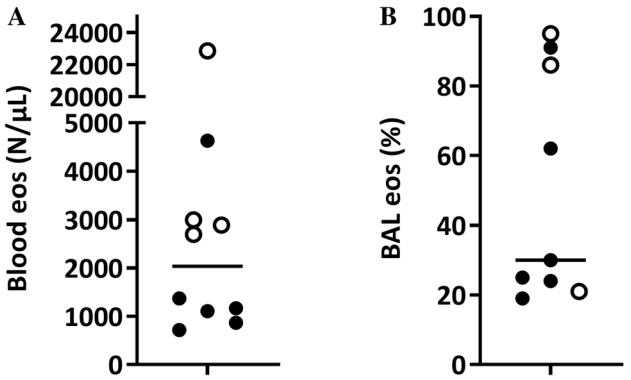

Fig. 1 Blood eosinophils (*N* cell/μL) (**a**) and BAL eosinophil percentage (**b**) at the time of diagnosis. Black dots represent patients treated with mepolizumab 100 mg/4 weeks; white dots represent those treated with mepolizumab 300 mg/4 weeks

Eight patients were non-smokers; two were former smokers (7.5 and 10 pack-years, respectively).

At the diagnosis, median (range) blood eosinophil was 2035 (720–22,860)/μL and median BAL eosinophil percentage was 30% (19–95) (Fig. 1). Four patients had a history of asthma, while two patients developed asthma and airway hyper responsiveness concomitantly to ICEP. All patients had undergone a complete workup in order to confirm the diagnosis and had received antiparasitic treatment with mebendazole. Underlying hematologic condition (presence of a CD3 CD4 T clone or detection of factor interacting with PAP-platelet-derived growth factor receptor alpha (FIP1L1-PDGFR alpha) fusion clone) had also been excluded.

Median follow-up period from ICEP diagnosis to mepolizumab initiation was 36.5 months (range 12–129). All patients had presented at least one relapse requiring OCS prescription after initial treatment (range 1–6) and the annual rate of relapse was 0.83 before the initiation of mepolizumab treatment. None of the patients had beneficiated from immunosuppressive drug other than corticosteroids. We did not find any drug potentially responsible for systemic eosinophilia (one patient was treated with acenocoumarol, a K vitamin antagonist, for atrial fibrillation and another with amlodipine for hypertension).

Seven out of ten patients were still treated with OCS at the time of initiation of mepolizumab: The median OCS dose, expressed as prednisone equivalent, was 5 mg/day. Five patients with concomitant asthma received low to median dose of inhaled corticosteroids (median 400 μg equivalent beclomethasone, range 200–800). Median baseline blood eosinophil count was 900/μL (range 410–2130). Subcutaneous mepolizumab was initiated at a dose of 100 mg every 4 weeks in six patients (the dose approved in severe asthma), whereas four patients received 300 mg every 4 weeks (similarly to the dose used in studies in EGPA and hypereosinophilic syndromes). The referring physician had chosen the dose regimen. The four patients that were treated with 300 mg SC had access to this higher dose though an early access program of high-dose Mepolizumab (currently not reimbursed for this dose). There were no baseline differences between patients receiving 100 and 300 mg.

Baseline Lung Function and HRCT Features

Baseline lung function (just prior to mepolizumab initiation) was close to normal with a median forced expiratory volume in 1 s of 2.68 L (77.7% predicted) and a median forced vital capacity of 3.45 L (93.5%).

Lung lesions at baseline as assessed by high-resolution computed tomography consisted of subpleural condensations with septal lines in seven patients, "pure" ground-glass opacities in two patients and a mixed pattern including condensations and nodules in one patient.

Mepolizumab Treatment was Associated with a Decrease in Relapses and a Resolution of HRCT Lesions

Median follow-up after mepolizumab initiation was 9 months (range 6–12). As shown in Fig. 2, mepolizumab was associated with a significant reduction in the annual rate of relapse from 0.8 to 0.0, $P = 0.002$). As expected, blood

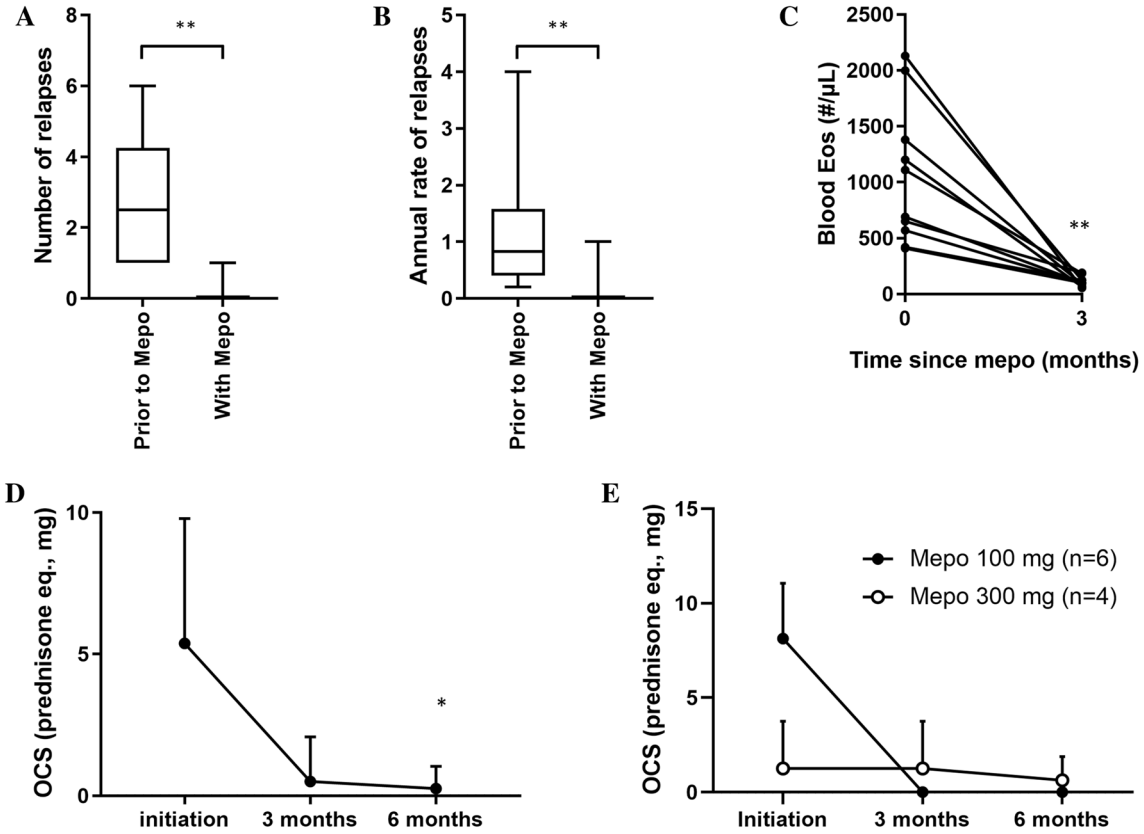

Fig. 2 Effect of mepolizumab on total exacerbations (**a**) and annual rate of exacerbations (**b**) (statistics: Wilcoxon's matched-pairs ranked test). **c** Mepolizumab treatment resulted in a significantly lower blood eosinophils count. **d** Reduction in OCS use during follow-up on mepolizumab (statistics: Friedman test followed by Dunn's multiple comparisons test). **e** Reduction in PCS use during follow-up on mepolizumab (black dots represent patients treated with mepolizumab 100 mg/4 weeks; white dots represent those treated with mepolizumab 300 mg/4 weeks)

eosinophil count significantly dropped at 3 months treatment (median count 100/µL, range 55–190).

Eight patients underwent a lung high-resolution computed tomography (HRCT) after 6 months of treatment with mepolizumab. Comparison with baseline HRCT demonstrated a complete disappearance of lung lesions in seven patients and a significant improvement with mild residual ground-glass opacities in one patient. Two patients underwent a chest X-ray that did not demonstrate any lung lesion. HRCT was available 12 months after treatment initiation for four patients and did not show any residual lesion. Two examples of resolutive lesions are shown in Fig. 3.

Mepolizumab Treatment was Associated with a Lower Corticosteroid Consumption and was Well Tolerated

When possible, OCS were tapered from 2.5 mg prednisone every 4 or 8 weeks, depending on centers. Median daily OCS dose dropped from 5 mg prednisone (range 0–10) at baseline to 0 (range 0–5) after 3 months (Fig. 2), and only one patient was still taking OCS. After 6 months, the only remaining patient on OCS was only taking 2.5 mg prednisone/day.

We recorded no side effects related to mepolizumab treatment (local reaction at the site of injection, headache, arthralgia) in any patient.

Discussion

To the best of our knowledge, this is the first study to describe the effect of mepolizumab in a series of patients with ICEP. Altogether, this retrospective study integrating ten patients with relapsing ICEP strongly suggests that mepolizumab is a valuable treatment option for recurrent ICEP that leads to a significant reduction of relapses and OCS use, together with disappearance of HRCT lesions. Our findings are in line with a previously published case report [10] and with data from a study evaluating the effect of mepolizumab in systemic hypereosinophilic syndrome [11], further indicating that eosinophils represent a cardinal driver of the disease. All patients included in the present

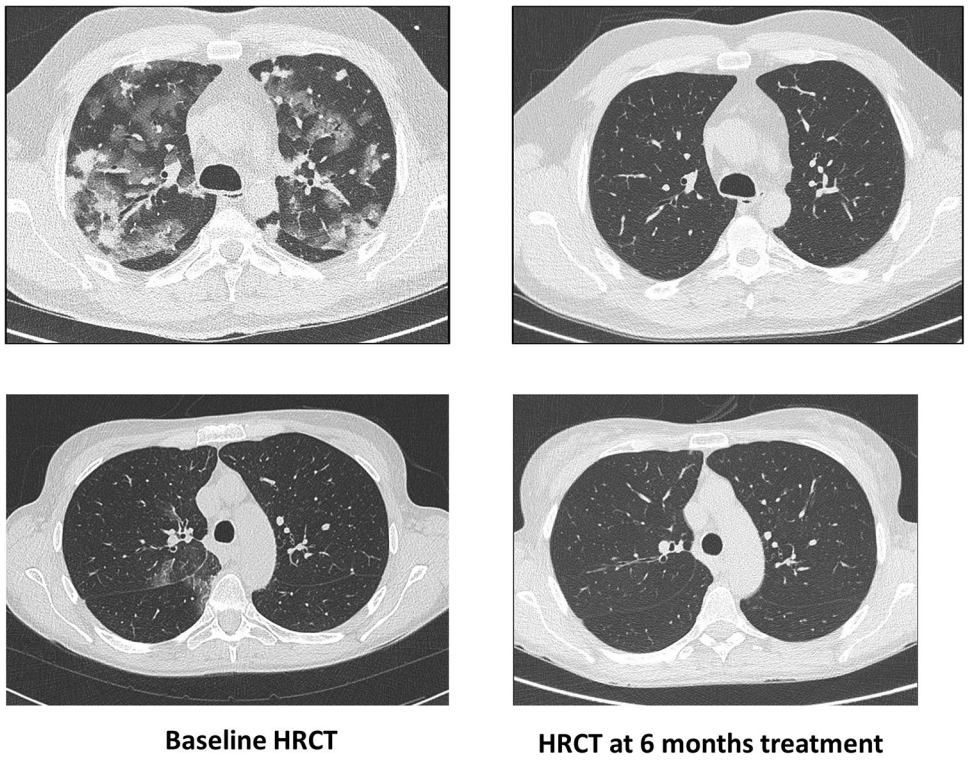

Fig. 3 Two representative examples of HRCT lesions at baseline (left) as compared to control HRCT after 6 months treatment with mepolizumab, where ground-glass opacities and consolidations have disappeared

cohort suffered from relapsing ICEP. Their characteristics at the onset of the disease are similar to what was previously described in published cohorts (recently reviewed in [12]), with a median blood eosinophilia > 1000/µL and a median BAL eosinophilia > 15%. All patients presented with HRCT lesions were compatible with the diagnosis.

Although ICEP is usually responsive to a single course of corticosteroids (classical regimen consists in a 6–weeks treatment with tapering doses, starting from 0.5 mg/kg/day of prednisone), recurrence is frequent, implying a resumption of the treatment. In a Japanese cohort published in 1994, 44% of patients, with a median follow-up of 4 years, experienced relapses of their disease [3]. In a French cohort, relapse rate was 69% for a median follow-up of 6 years [4]. In the recent review by Suzuki and colleagues, relapse rate ranged from 37 to 58.3% [12]. As a consequence, a significant proportion of patients (up to 75% in Hayakama's study [3]) require long-term OCS treatment. Adverse events related to long-term corticosteroids consumption have been largely explored in various respiratory diseases including asthma, COPD, and sarcoidosis: In asthma, Sullivan and colleagues recently demonstrated that significant adverse events, such as osteoporosis, infections, or coronary disease occurred for a cumulative exposure to OCS as low as 2 g per year [5]. Similar conclusion were drawn in sarcoidosis, where a study showed a clear increase of adverse events and a decrease in quality of life when a cumulative dose of 500 mg prednisone per year was exceeded [13]. The lack of studies directly related to eosinophilic diseases could be explained by the rarity of these entities, but currently available data supporting that long-term use of OCS, regardless of the underlying disease, are harmful.

Apart from its corticosteroid-sparing effect, mepolizumab targets the main driver of the disease: Mechanisms underlying eosinophil proliferation and activation remain only partly elucidated in ICEP but involve the IL-5 pathway and other chemokines [14]. The recent demonstration that benralizumab, a monoclonal antibody directed against the IL-5 receptor, successfully controlled disease in patients with hypereosinophilic syndrome further confirms the role of the IL-5/IL-5R pathway in hypereosinophilic diseases [15]. In our cohort, six patients received 100 mg mepolizumab every 4 weeks and four patients received 300 mg every 4 weeks. We did not find any difference between those two subgroups regarding characteristics at diagnosis, at baseline, and during follow-up regarding the number of circulating eosinophils.

The major limitation of this study results from its retrospective design which implied that some data were missing (i.e., not all patients underwent an HRCT scan during follow-up) and that patients received different treatment regimens. The low number of patients is related to the fact that ICEP is a rare disease and that only relapsing patients were administered mepolizumab. The design of the study (open-label, retrospective) did not allow comparing our cohort to a control group.

Finally, open questions remain, such as the duration of treatment. This latter point is also crucial in severe asthma, while recent data show relapse of the disease following withdrawal [16]. Another concern is the cost-effectiveness of this treatment, which is difficult to evaluate in such a rare disease. In asthma, existing data suggest that biologicals are cost-effective when used in a properly selected population [17]. In the present cohort, mepolizumab was only considered as a therapeutic option in relapsing patients and never as a first-line treatment.

In conclusion, our results suggest that mepolizumab treatment for relapsing ICEP is associated with a significant reduction of relapses. We also observed a corticosteroid-sparing effect, as well as a disappearance of lung lesions on HRCT. Altogether, even taking into account its limitations, we feel that this proof-of-concept study paves the way for future prospective registries as well as large scale randomized controlled trials evaluating efficacy of anti-IL-5(R) therapies in ICEP.

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Compliance with Ethical Standards

Conflict of interest The authors have no conflict of interest related to this manuscript.

Ethical Approval The retrospective analysis of data from of patients who received mepolizumab for relapsing ICEP was approved by our ethical committee (study PNEU-ILD-02, approval number 2018/15MAR/116).

Informed Consent As this was a retrospective study, signed informed consent from patients was waived, according to local regulation.

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