CASE REPORT

REVISED Case Report: Mepolizumab in the treatment of idiopathic chronic eosinophilic pneumonia [version 3; peer review: 2 approved]

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Abstract
Idiopathic chronic eosinophilic pneumonia (ICEP) is a rare interstitial lung disease of unknown cause. It usually responds well to systemic corticosteroid therapy, but relapses are frequent. We describe two cases of 21- and 27-year-old patients, presenting with dyspnea. The diagnosis of steroid-relapsing and steroid-dependent ICEP was made respectively. Mepolizumab was prescribed to both patients. This treatment resulted in successful long-term disease management with much fewer side effects than a traditional corticosteroid therapy.

Keywords
Mepolizumab, Idiopathic chronic eosinophilic pneumonia, Corticosteroid, Treatment

Open Peer Review

Approval Status ✓ ✓

	1	2
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1. **Sevim Bavbek**, Ankara Universitesi, Ankara, Turkey

2. **Mikio Toyoshima**, Hamamatsu Rosai Hospital, Hamamatsu, Japan

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: Daboussi S: Writing – Original Draft Preparation; **Essebaa S**: Writing – Original Draft Preparation; **Mhamdi S**: Validation; **Aichaouia C**: Validation; **Hela G**: Investigation, Validation; **Ayadi A**: Resources; **Zied M**: Visualization

Competing interests: No competing interests were disclosed.

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REVISED **Amendments from Version 2**

The changes made did not concern the figures or the list of authors, but were modifications to the text in response to the reviewers' queries.

Finally We replaced the inappropriate phrase "It is traditionally diagnosed based on the chronic onset of respiratory symptoms" by It is characterized by chronic respiratory symptoms.

Any further responses from the reviewers can be found at the end of the article

Introduction

Idiopathic chronic eosinophilic pneumonia (ICEP) is a rare interstitial lung disease of unknown origin, associated with abnormal eosinophilic lung infiltration.[1–3] Clinical presentation is non-specific. It is characterized by chronic respiratory symptoms, peripheral infiltrates, blood and/or alveolar eosinophilia, and exclusion of other eosinophilic disorders.[2–5] Systemic corticosteroids are the first line recommended treatment. They are efficient, but relapses are frequent. Relapses may occur when the treatment is stopped or when the dose is reduced.[2]

Mepolizumab is a humanized monoclonal antibody that specifically targets interleukin 5 (IL-5) and neutralizes its effect. Two cases of successfully treated ICEP with mepolizumab are presented. The study was approved by the Ethics Committee Of The Military Hospital In Tunis. Written informed consent was collected from the patients. Anonymity was respected during data treatment.

Case report 1

A 21-year-old patient, high-level athlete, was admitted for dry cough and progressively worsening dyspnea for a month. He also reported 10 kg weight loss during this period. He did not have high fever or wheezing. He was a never smoker and he had no previous medical history. Laboratory findings showed an elevated leukocyte count with a high level of eosinophilia (4.57 G/L, 34.7%). Liver and kidney function tests were normal. Chest computed tomography (CT) showed bilateral and peripheral infiltrative shadows, essentially on the right side (Figure 1). Bronchoalveolar lavage fluid (BALF) showed an elevated eosinophil percentage (26%). Antineutrophil cytoplasmic antibodies (ANCA) were negative. FIP1L1-PDGFRA and JAK2 V617F mutations were absent. Video-assisted thoracoscopic lung biopsy showed pulmonary eosinophilia with appearances of organizing pneumonia (Figure 2). The diagnosis of ICEP was established. The patient was managed with high-dose of corticosteroids (20 mg dexamethasone for three days, then 1 mg/kg/day of prednisolone which was tapered over six months). Clinical, biological and radiological improvements were noted. However, the patient relapsed three days after the treatment was stopped. He responded again to steroids. But because of the side effects he experienced from chronic steroid use (muscle wasting, tendon rupture and depression), the decision to initiate an off-label anti-IL5 treatment was made. A monthly 100 mg of subcutaneous mepolizumab was started and oral

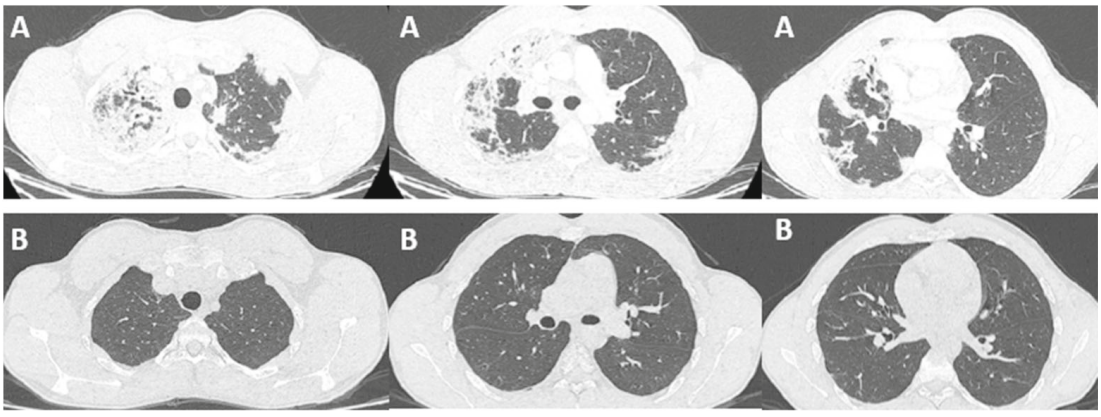

Figure 1. (A) CT chest of the first patient revealing bilateral and peripheral pulmonary infiltrates at the time of diagnosis. (B) CT chest of the first patient after 12 months of mepolizumab and tapering of corticosteroid dose, showing complete resolution of the previous infiltrates.

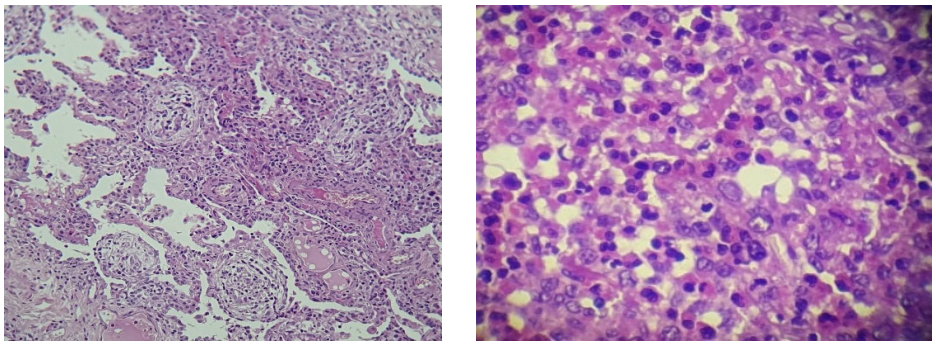

Figure 2. Video-assisted thoracoscopic lung biopsy showing pulmonary eosinophilia with appearances of organizing pneumonia.

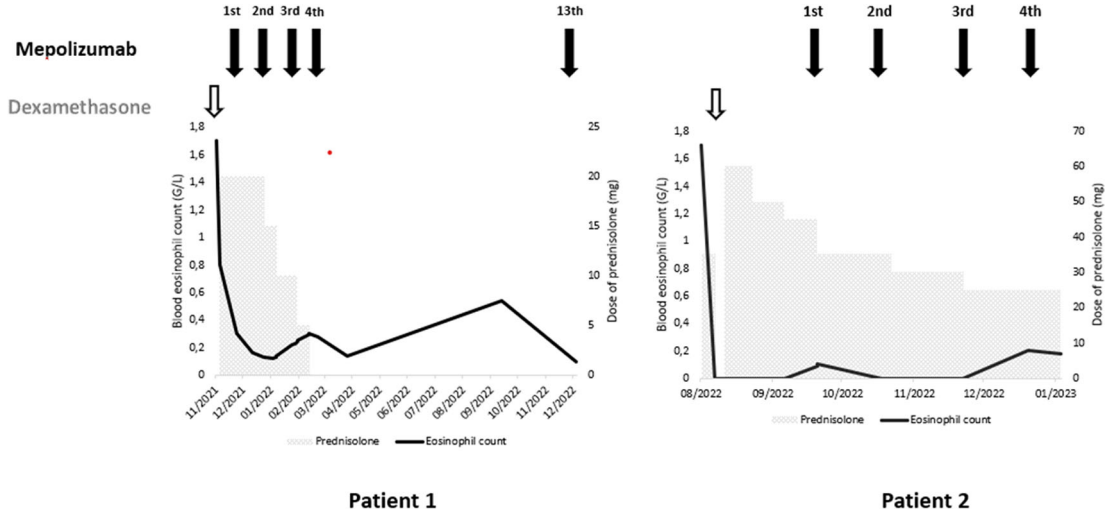

Figure 3. Treatment and evolution of the patients' eosinophil count.

corticosteroids were gradually stopped. With 12 months of hindsight, he was asymptomatic, the eosinophil counts dropped to normal range (Figure 3) with a complete radiological clearance. No adverse reaction to the therapy was noted.

Case report 2

Our second case is a-27-year-old man, active military, admitted for increasing dyspnea, cough and wheezing for a few weeks. He had been diagnosed with asthma one year earlier. He was an ex-smoker of two-five packs per year. Tests showed blood eosinophilia (2G/L, 15%). The C-reactive protein level was 10 mg/L. Chest CT revealed peripheral and diffuse ground glass opacities. The serum Immunoglobulin E level was 502 IU/mL. ANCA were negative. The BALF showed a marked percentage of eosinophils of 31%. Further investigations were unrevealing for parasitic or fungus infections, and hematologic disorders. Hence, the diagnosis of ICEP was made. Systemic corticosteroids were prescribed (4 days of 20 mg of dexamethasone, then 1 mg/kg/day of prednisone, which was tapered over 3 months). His asthma was treated with daily inhaled budesonide and formoterol. The patient responded well to the therapy: a rapid resolution of symptoms was noted, the eosinophils blood count dropped to normal range, and the pulmonary infiltrates completely disappeared. However, attempts at tapering the corticosteroids below 35 mg were met with three relapses in 16 months, which were associated with clinical worsening, reascension of eosinophil count, recurrence of pulmonary lesions and multiple hospital admissions. A high glucose level due to the chronic steroid use was noted. Subcutaneous mepolizumab 100 mg monthly was initiated. A gradual decrease of oral steroids was well tolerated (Figure 3). The patient is currently at four months of overlap of anti-IL5 and tapering doses of corticosteroids. With a current dose of 20 mg of prednisone, no relapse has occurred.

Discussion

Eosinophils play a major role in the pathogenesis of ICEP. The IL-5 is a cytokine involved in the production, maturation and release of eosinophils from the bone marrow. Therefore, using a therapy that specifically targets eosinophil activity and proliferation could help treating ICEP.[1,3]

Many reports support the use of anti-IL5/5R agents - such as mepolizumab, reslizumab or benralizumab – for the treatment of relapsing and/or corticosteroid dependent/intolerant ICEP.[2,4–7] These agents have been clinically proven to be effective for eosinophilic asthma, eosinophilic granulomatosis with polyangiitis (EGPA), and FIP1L1-PDGFRA-negative hypereosinophilic syndrome (HES).[4]

Targeting IL-5 cytokin in patients with ICEP was firstly done by To and al. in 2018. The suppression of local levels of IL-5 and infiltration of eosinophils with mepolizumab resulted in the resolution of CT findings and decreased symptoms.[5] In a recent study conducted by Delcros *et al.* - which is the largest cohort of ICEP patients treated with anti-IL5/5R-, no relapses were reported with a median follow up of 13 months. In that study, median annual rate of severe asthma exacerbations decreased from 0.15 to 0, median blood eosinophil count dropped to normal range and a complete disappearance of pulmonary infiltrates was noted in 71% of patients.[4]

For our first patient, the diagnosis of ICEP was made based on compatible radio-clinical and histopathological presentation. But for our second patient who had asthma, the possibility of EGPA was discussed even in the absence of systemic manifestations and of ANCA. Although a few cases of histologically proven ANCA-negative lung-limited EGPA were reported, we did not approve the use of lung biopsy for our patient due to the rarity of this entity and the invasive nature of the procedure.[8]

In our patients, the search for alternative therapies was due to an attempt to minimize corticosteroid use. Mepolizumab was chosen due to its availability and the body of evidence to support its use. We prescribed mepolizumab at a monthly dose of 100 mg subcutaneously, which is the dosage used to treat eosinophilic asthma. This dose is three times lower than that used for EGPA and HES.[2,9] Both our patients had a rapid decrease of the blood eosinophil count along a significant clinical and radiologic improvement. Corticosteroid tapering without relapse was also allowed. In the study of Brenard *et al.*, the median daily corticosteroid dose dropped from 5 mg prednisone (range 0–10) at baseline to 0 (range 0–5) after three months of mepolizumab use.[7]

The overall safety profile of long-term use of mepolizumab has been reported by numerous studies.[4,7,10] This medication has far fewer toxicities than systemic corticosteroids and can possibly be used in the long term to prevent relapses of ICEP.

Conclusion

Mepolizumab and other anti-IL5/5R agents seems to be a both safe and effective option as a primary steroid-sparing therapy for corticosteroid dependent or relapsing ICEP. Further investigations and clinical trials are necessary to establish recommendations and clear protocols.

Consent for publication

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patients.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Figshare. CARE flow diagram and CARE checklist. DOI: https://doi.org/10.6084/m9.figshare.22236772.v1

Acknowledgments

CEREO – Reference center for hypereosinophilic syndromes Affiliated to the MaRIH immuno-haematological rare diseases healthcare sector.

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PubMed Abstract | Publisher Full Text

Open Peer Review

Current Peer Review Status: ✔ ✔

Version 3

Reviewer Report 06 September 2023

https://doi.org/10.5256/f1000research.155328.r204136

✔ **Mikio Toyoshima**
Hamamatsu Rosai Hospital, Hamamatsu, Japan

The authors responded and revised the manuscript adequately.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Interstitial pneumonia, eosinophilic pulmonary diseases, asthma

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 29 August 2023

https://doi.org/10.5256/f1000research.151431.r199918

? **Mikio Toyoshima**
Hamamatsu Rosai Hospital, Hamamatsu, Japan

General comments

Daboussi et al. reported two cases of CEP which was successfully treated with mepolizumab.

Major comments

However, there are similar case reports regarding anti-IL-5 and anti-IL-5Rα antibody treatment in CEP.

Minor comments

1. Onset of CEP is not necessarily chronic, and acute or subacute onset of CEP sometimes seen (Hayakawa H, et al. Chest. 1994;105(5):1462-6.). The description "chronic onset of respiratory symptoms" is inappropriate.

2. The degree of BALF eosinophilia in two patients is mild and biopsy specimen in the first patient dose not show numerous eosinophils. Was lung biopsy performed in the second case? Is diagnosis of CEP in 2 patients correct?

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Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Interstitial pneumonia, eosinophilic pulmonary diseases, asthma

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 29 Aug 2023

DABOUSSI SELSABIL

Major comments:

These cases published remain exceptional and rare cases of a treatment that is proving its

efficacy for the treatment of CEP. sharing our positive experience could be benefic.
In the literature there are about 22 similar cases published.

Minor comments:
IAEP differs from ICEP in its acute onset, severity,and the absence of relapse. The presentation is that of acute pneumopathy in an individual with no previous history, with the potential for acute respiratory distress. The first diagnosis is often that of infectious pneumopathy, all the more so when fever and elevated C-reactive protein. Symptoms usually set in within1 week, and always within 1 month.In our two patients, the chronic nature of eosinophilic lung disease is due to symptomatology lasting more than 30 days and to frequent relapses, which meet the definition (ref table 4 Cottin V. Eosinophilic lung. EMC - Pneumologie 2020;0(0):1-11 [Article 6-039-K-10].)

The degree of BALF eosinophilia in two patients is respectively 26% and 31% and it respond to the definition of eosinophilic alvéolitis.

Cordially

Competing Interests: No competing interests were disclosed.

Author Response 29 Aug 2023

DABOUSSI SELSABIL

We thank Reviewer2 for his positive feedback

Idiopathic chronic eosinophilic pneumonia (ICEP) is a rare disease of unknown origin characterized by chronic respiratory symptoms, pulmonary alveolar opacities (typically of peripheral distribution) and blood and/or alveolar eosinophilia. These criteria were well verified in our two patients, enabling us to retain the diagnosis after an exhaustive etiological investigation that ruled out all other etiologies.

Video-assisted thoracoscopic lung biopsy (middle and lower right lobes) for the first patient was carried out with this in mind and confirmed the diagnosis by showing pulmonary eosinophilia with appearances of organizing pneumonia (fig2), (inflammatory infiltrate icn in eosinophilis) leaving no doubt to the diagnosis.

Idiopathic chronic eosinophilic pneumonia (ICEP) is a chronic orphan disease that has no real treatment alternatives to systemic corticosteroids. Accordingly, anti-eosinophil biologics, such as benralizumab and mepolizumab, which do not have glucocorticoid toxicity, are of potential utility in this disease.

This manuscript uses an analysis of two clinical cases, to examine clinical responses in ICEP patients treated off-label with anti-eosinophil biologics.

1. We replaced the inappropriate phrase "It is traditionally diagnosed based on the chronic onset of respiratory symptoms" by It is characterized by chronic respiratory

symptoms.
We hope to have answered your pertinent comments and thank you for your interest in our article

Competing Interests: No competing interests were disclosed.

Reviewer Report 21 August 2023

https://doi.org/10.5256/f1000research.151431.r182980

Sevim Bavbek
Division of Immunology and Allergy, Department of Chest Diseases, Ankara Universitesi, Ankara, Ankara, Turkey

I am fine with the new revised version. I approve the article for indexing.

Is the background of the case's history and progression described in sufficient detail?
Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Partly

Is the case presented with sufficient detail to be useful for other practitioners?
Partly

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 04 April 2023

https://doi.org/10.5256/f1000research.143737.r168068

?

Sevim Bavbek
Division of Immunology and Allergy, Department of Chest Diseases, Ankara Universitesi, Ankara, Ankara, Turkey

I would like to thank you for the opportunity to review this article.

Idiopathic chronic eosinophilic pneumonia (ICEP) is a rare interstitial lung disease of unknown cause and responds well to systemic corticosteroid therapy, although frequent relapses are reported. Here two cases of CEP patients have been reported.

The paper might have potential to be indexed but the point below needs to be clarified:

Cases with CEP in the case report, have been well evaluated and presented but for case 2, presence of EGPA may be an alternative diagnosis. In this case, there is not data about ANCA but anyway ANCA may be negative in cases with eosinophilic dominant without presence of vasculitis yet. This possibility should be discussed. Mepolizumab has also been approved in EGPA

Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Partly

Is the case presented with sufficient detail to be useful for other practitioners?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Asthma, severe asthma, biologicals, drug allergy, desensitization to drugs

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 16 May 2023

DABOUSSI SELSABIL

We would like to thank you for reviewing this article and for providing pertinent comments. For the case 2, the ANCA were negative.

Indeed, ANCA-negative EGPA is an alternative diagnosis for this patient.

But he did not present with paranasal abnormalities, cutaneous, neurological, gastrointestinal or cardiovascular symptoms, and did not meet the ACR criteria for the disease.

Therefore, we retained the diagnosis of ICEP.

This possibility will be discussed in the revised version of the article.

Competing Interests: No competing interests were disclosed.