DRUGS IN CONTEXT
RIGOROUS • RAPID • RESPONSIVE

A continuous publication, open access, peer-reviewed journal

ACCESS ONLINE

CASE REPORT

Mepolizumab: an alternative therapy for idiopathic chronic eosinophilic pneumonia with glucocorticoid intolerance

Adam Kisling MD[1], Jason Jones MD[1], Caleb Hixson DO FCAP[2], David Hostler MD MPH FACP[3], Jordanna Hostler MD FACP[3]

[1]Department of Medicine, Tripler Army Medical Center, Honolulu, HI, USA; [2]Department of Pathology, Tripler Army Medical Center, Honolulu, HI, USA; [3]Department of Pulmonology, Tripler Army Medical Center, Honolulu, HI, USA

Abstract

A 55-year-old woman with cough-variant asthma presented for 1 month of worsening wheezing, cough, and dyspnea refractory to treatment. Initial laboratory findings revealed profound peripheral eosinophilia, and a chest computed tomography showed bi-apical consolidation. Bronchio-alveolar lavage demonstrated alveolar eosinophilia. She was diagnosed with idiopathic chronic eosinophilic pneumonia (ICEP). Her peripheral eosinophilia and respiratory symptoms improved rapidly with high-dose systemic corticosteroid therapy. However, she was intolerant to corticosteroid monotherapy due to non-compliance and psychological adverse effects. Mepolizumab was initiated as a steroid-sparing agent, resulting in successful therapy for 2 years without relapse or adverse effects. Mepolizumab is an interleukin-5 (IL-5) antagonist monoclonal antibody, which is a targeted therapy for diseases mediated by eosinophil activity and eosinophil proliferation. Mepolizumab is typically used in ICEP refractory to steroids, but this case supports its use in cases of glucocorticoid intolerance. Further study of IL-5 antagonist therapies for ICEP may identify an alternative treatment modality for patients in whom the adverse effects of corticosteroids pose a challenge.

Keywords: complementary therapies, glucocorticoids, humanized monoclonal antibodies, mepolizumab, pulmonary eosinophilia.

Citation

Kisling A, Jones J, Hixson C, Hostler D, Hostler J. Mepolizumab: an alternative therapy for idiopathic chronic eosinophilic pneumonia with glucocorticoid intolerance. Drugs in Context 2020; 9: 2020-5-3. DOI: 10.7573/dic.2020-5-3

Introduction

Idiopathic chronic eosinophilic pneumonia (ICEP) is a rare disorder typically characterized by progressive dyspnea, cough, fevers, and weight loss.[1] Common findings include middle and upper lobe peripheral opacities on imaging, elevated inflammatory markers, and eosinophilia of both the peripheral blood and bronchio-alveolar lavage fluid (BALF).[2] The disease is twice as frequent in women as in men and is often preceded by a diagnosis of asthma.[3] The majority of patients with ICEP are non-smokers, unlike those with acute eosinophilic pneumonia.[3] Spirometric findings are highly variable and not diagnostic, although the diffusing capacity is often reduced.[3]

ICEP is typically treated with high-dose systemic corticosteroids. A clinical pattern of relapse-and-remission often leads to protracted steroid courses.[1] Prolonged therapy with systemic corticosteroids may cause a host of complications, including glucose intolerance, hypertension, skin atrophy, osteopenia, infection, impaired healing, and psychiatric disturbance.[4,5] Several recent reports indicate a role for novel biologic agents in the treatment of a variety of eosinophil-driven disease processes, including ICEP.[6,7] Mepolizumab has previously been shown to reduce symptoms and relapse rate and to have corticosteroid-sparing potential in ICEP.[7,8] We present a case of ICEP in which mepolizumab was used as a steroid-sparing agent, resulting in improvement in markers of disease activity and corticosteroid requirement.

The patient described in this case has been completely de-identified such that the identity of the patient may not be ascertained in any way. This case was approved by the Tripler Army Medical Center Department of Clinical Investigation. However, this case report was not submitted to nor approved by a review board.

Case Report

A 55-year-old woman with a history of adjustment disorder with anxiety, eczema, seasonal rhinitis, and cough variant asthma was referred to pulmonology for 1 month of worsening wheezing, cough, and dyspnea. Her asthma had been diagnosed 2 years prior, and her moderate persistent symptoms remained uncontrolled despite twice-daily usage of the long-acting beta$_2$ agonist, salmeterol, and the inhaled corticosteroid, fluticasone, which had both recently been increased. She had no clinically significant history of smoking or occupational exposures. Her spirometry had recently been normal. Physical exam initially revealed mild crackles in bilateral lower lung fields and was otherwise unremarkable. Initial laboratory evaluation revealed an immunoglobulin E (IgE) of 1850 IU/mL, peripheral eosinophilia (31.2% and absolute count 2.45×10^9/L), and elevated acute phase reactants. Normal laboratory findings included Aspergillus antibodies, a tuberculosis interferon-gamma release assay, hemoglobin, platelet count, and calcium. A chest computed tomography demonstrated bi-apical patchy consolidation with left upper lobe mass-like consolidation and with enlarged mediastinal and perihilar lymph nodes.

These findings led to a differential diagnosis, which included ICEP, eosinophilic granulomatosis with polyangiitis, lymphoma, sarcoidosis, parasitic infection, or tuberculosis. Her symptoms continued to progress despite adjustment of pharmacotherapy. A bronchoscopy was performed, and a BALF and an endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) were obtained. The BALF revealed profound alveolar eosinophilia (86%), and the cytology of the BALF revealed abundant eosinophils without atypical cells (Figure 1). Anaerobic, fungal, and acid fast bacilli cultures of the BALF were negative. The EBUS-TBNA of a lymph node revealed a heterogeneous lymphoid population and eosinophils consistent with a reactive lymph node (Figure 2). Flow cytometry was normal. Tissue exam of alveolated lung parenchyma revealed reactive pneumocytes and eosinophils. Laboratory evaluation revealed an antinuclear antibody of 1:1280 and normal cytoplasmic antineutrophil cytoplasmic antibodies, perinuclear antineutrophil cytoplasmic antibodies, myeloperoxidase, proteinase 3 antibodies, and serum complement C3 and C4. A viral respiratory panel was negative.

Following bronchoscopy, the patient developed worsening cough, dyspnea, and new hypoxemia requiring supplemental oxygen at 2 LPM via nasal cannula. A chest x-ray revealed a small left apical pneumothorax, and she was admitted for treatment and monitoring. Empiric treatment of ICEP was initiated with methylprednisolone, 125 mg, every 6 hours for 1 day, and then transitioned to oral prednisone. As expected, this resulted in resolution of her respiratory symptoms, supplemental oxygen requirement, peripheral eosinophilia (0.2% and absolute count 0.02×10^9/L), and radiographic

Figure 1. Cytology of the bronchio-alveolar lavage fluid demonstrates abundant eosinophils, which appear as a light shade of pink in this stain.

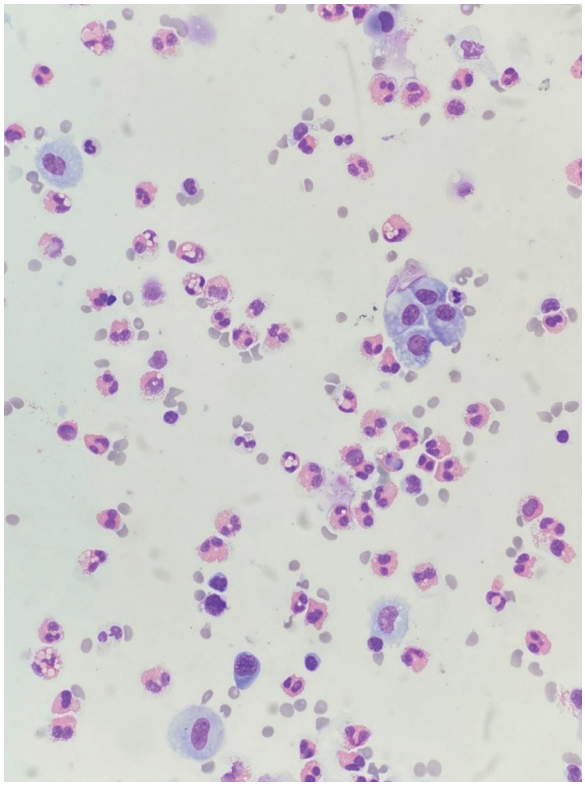
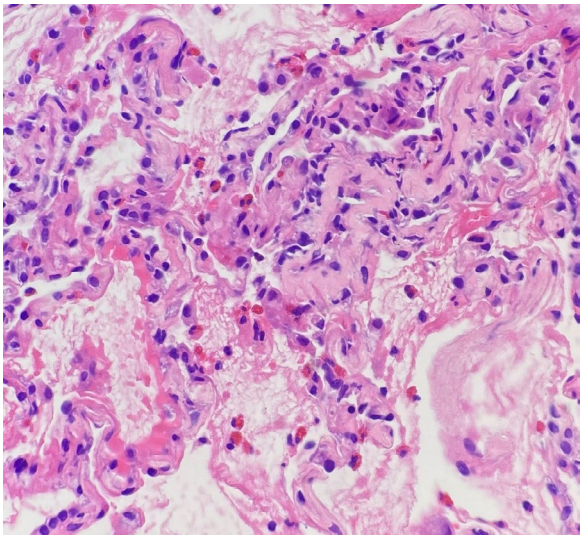


Figure 2. This tissue obtained via transbronchial ultrasound-guided fine needle aspiration of a lymph node demonstrates fibrotic changes along the alveolar lining and eosinophils, which appear red in this stain.



abnormalities. She was discharged on oral prednisone, 20 mg, daily.

Following hospital discharge, the patient repeatedly self-discontinued prednisone therapy due to concern for possible complications related to her adjustment disorder with anxiety, as well as possible steroid-induced paranoia, anxiety, irritability, and insomnia. This intolerance and non-compliance to her corticosteroid treatment was likely the reason that her ICEP was not responsive to a short course as would otherwise be expected. She experienced a resurgence of respiratory symptoms and peripheral eosinophilia with each discontinuation of steroids. Frequent discontinuation led to repeat administration of higher prednisone doses than would likely have otherwise been necessary, inadequate symptom control, and a high number of healthcare visits, which includes emergency room visits and physician appointments related to the diagnosis of ICEP. In the first two and a half months after diagnosis when steroid monotherapy was employed, the patient had 22 healthcare encounters that were directly related to ICEP (Figure 3).

Given her inability to tolerate standard therapy, alternatives were explored. Mepolizumab was selected as a disease-specific alternative therapy with physiologic and clinical evidence supporting its potential for disease control and its corticosteroid-sparing potential. Additionally, mepolizumab would have a long-acting effect with the goal of minimizing the impact of therapy non-compliance. Mepolizumab, 300 mg, every 4 weeks subcutaneously, allowed successful treatment of ICEP. Her daily prednisone dose was subsequently halved to 20 mg by mouth every other day. The patient's serum immunoglobulin E (IgE) was periodically measured over the course of her treatment. It decreased drastically with treatment, but never reached normal levels. Without an increase in compliance, she had dramatically decreased symptoms, serum IgE, peripheral eosinophilia, and healthcare utilization since starting mepolizumab (Figures 3–5).

Prednisone, 20 mg, by mouth every other day was continued for 15 months. During this period, compliance continued to be limited by her anxiety with specific patient concerns being the risk of infection, weight gain, and glucose intolerance. However, during that time, she was consistently compliant with mepolizumab and had no significant relapses of ICEP symptoms or mepolizumab adverse effects. She is currently being tapered to prednisone, 5 mg, by mouth daily with the goal of tapering off of corticosteroids completely.

Discussion

ICEP is an idiopathic pulmonary disease characterized by severe pulmonary eosinophilia. Similar to other pulmonary eosinophilic processes, it is traditionally treated with corticosteroids with corresponding reduction of eosinophilia and overall disease activity.[9] Treatment is targeted at inducing remission. However, relapse is common. These patients often experience repeated prolonged treatment with oral corticosteroids.[2] While the benefit of treating ICEP and preventing progression to pulmonary fibrosis is generally considered to outweigh the risks of side effects from corticosteroids, those side effects carry very real morbidity. The presence or threat of these complications can have a profound effect on a patient's compliance with corticosteroids.

Figure 3. This graph demonstrates the reduction in the level of serum IgE after the initiation of treatment for ICEP.

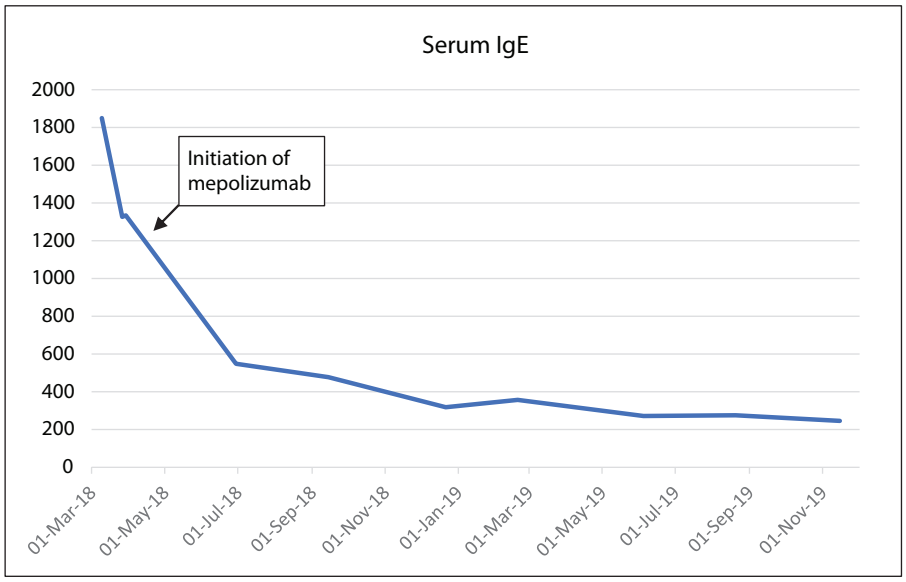
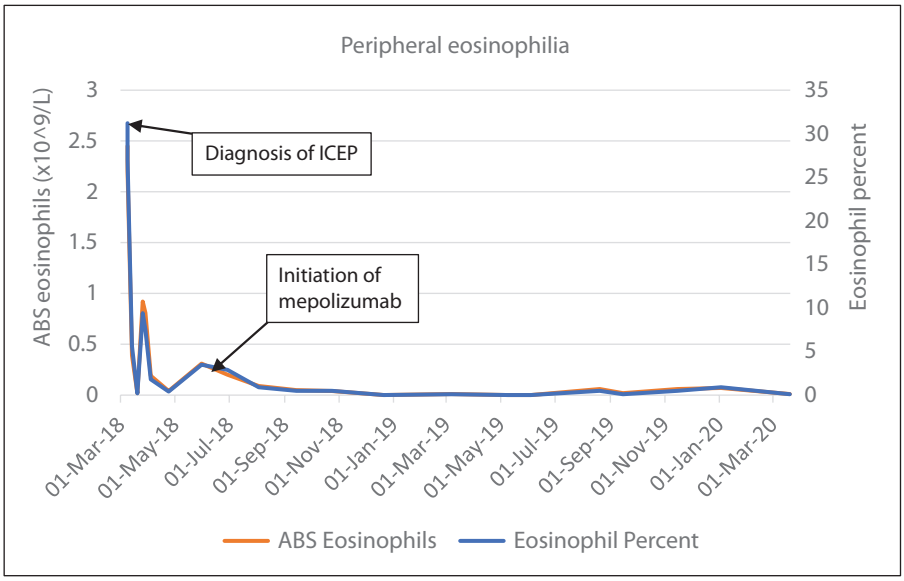
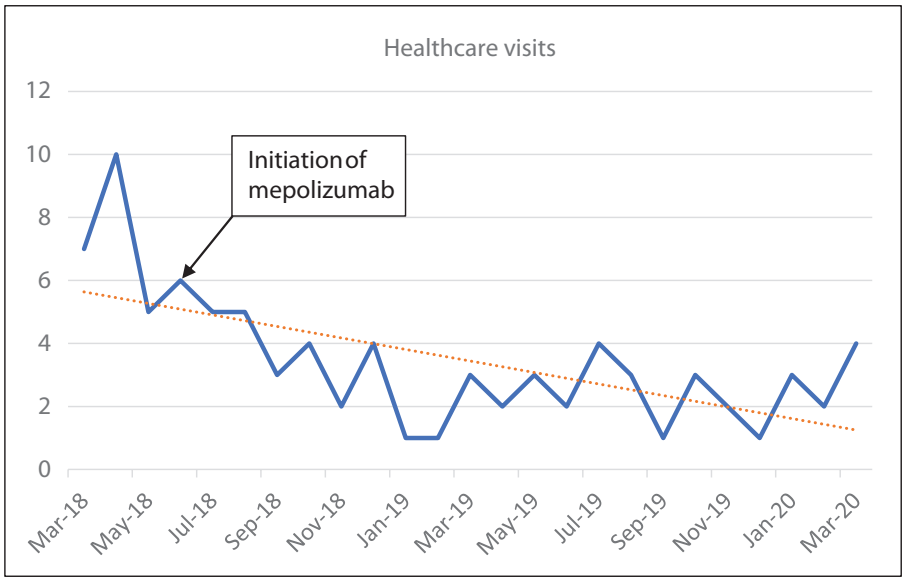


Figure 4. **This graph demonstrates the improvement in peripheral eosinophilia after treatment with mepolizumab. Although peripheral eosinophilia improved after initiation of prednisone, normalization of laboratory findings did not occur with prednisone monotherapy due to drug intolerance. The initiation of mepolizumab resulted in the sustained normalization of the patient's laboratory findings.**



ICEP, idiopathic chronic eosinophilic pneumonia

Figure 5. **This graph demonstrates the reduced requirement for healthcare visits that the patient experienced as a result of her symptom improvement after treatment with mepolizumab. All healthcare visits included in this graph occurred after the initiation of prednisone and were directly related to chronic eosinophilic pneumonia.**



The pathophysiology of ICEP is one of eosinophil-mediated inflammation. The phenomenon of hypereosinophilia demonstrates a direct histopathological infiltration and damage of the pulmonary interstitium.[10] Additionally, eosinophil-induced release of interferon-gamma appears to cause collagen deposition and fibrosis completely independent of lymphocytic proliferation of classical tissue remodeling.[11] Interleukins mediate the proliferation and maturation of eosinophils, which are the underlying pathological entity in ICEP and other eosinophilic diseases.[12,13] The cytokine interleukin-5 (IL-5) is the main promoter of production, maturation, and release of eosinophils from bone marrow, and is also responsible for the increase in eosinophil levels in the blood.[14] Thus, an IL-5 antagonist monoclonal antibody that limits the proliferation of eosinophils lends itself to the treatment of ICEP.[12]

As with other diseases with similar pathophysiology, targeted alternative treatment of eosinophil activity and eosinophil proliferation is effective in controlling overall disease activity in ICEP.[12] Biologic therapy with monoclonal antibodies offers highly specific therapy and is useful as an alternative therapy to corticosteroids in cases with recurrent flares, high corticosteroid doses, or corticosteroid intolerance, as with this case. Mepolizumab has previously been shown to reduce the need for corticosteroids in hypereosinophilic syndromes by blocking the binding of IL-5 to eosinophils.[15,16] Due to this mechanism of action, mepolizumab has been effectively used to treat eosinophilic asthma and eosinophilic phenotypes of chronic obstructive pulmonary disease. ICEP shares similar pathophysiology with these conditions and mepolizumab has demonstrated efficacy in inducing sustained corticosteroid-free remission.[7] The physiologic mechanism of action of mepolizumab directly guided our therapy selection for this ICEP patient with relative steroid intolerance. In addition to mepolizumab, there are other monoclonal antibodies, such as reslizumab and benralizumab, which reduce the production and survival of eosinophils by inhibiting IL-5. Mepolizumab was chosen in this case due to its availability, the larger body of evidence to support its use, and superior side effect profile compared to some other medications with a similar mechanism of action. Mepolizumab is already known to be safe and effective for long-term treatment of asthma[17,18] and has a more favorable side effect profile than systemic corticosteroids. No clear clinical markers have been identified to guide discontinuation of mepolizumab.[19] Mepolizumab will be continued in this patient with close clinical monitoring due to its clear clinical benefit.

Clinical trials of mepolizumab have included a wide range of doses. A dosage of 100 mg subcutaneously every four weeks is typically used for asthma and 300 mg subcutaneously every 4 weeks is typically used for eosinophilic granulomatosis with polyangiitis. The 100 mg regimen is typically more cost effective than the 300 mg one, but in this case the cost to the patient was equivalent. The 100 mg regimen has been previously described in the treatment of ICEP,[20] but the 300 mg regimen was selected in this case to trial its comparative efficacy.

The primary limitation of this case is that the corticosteroids were not able to be completely tapered off. Mepolizumab has been demonstrated to have the potential to control ICEP as monotherapy, but monotherapy was not yet achieved in this case.[7]

This case demonstrates the use of mepolizumab as a primary steroid-sparing therapy in cases of corticosteroid intolerance and non-compliance, and should encourage investigators to perform clinical trials to investigate this clinical approach. In addition to the previously described indication in cases of disease refractory to typical steroid use, this case demonstrates the use of mepolizumab may be a valuable adjunct to corticosteroid therapy and suggests the potential for further clinical investigation. Mepolizumab therapy may be beneficial in treating ICEP due to its low side effect profile, low dosing frequency, and steroid-sparing potential. Further study of IL-5 antagonist therapies for ICEP may reveal an alternative treatment modality for patients in whom the adverse effects of corticosteroids pose a challenge.

Contributions: Study conception and design: Jordanna Hostler and Adam Kisling. Acquisition of data: Adam Kisling and Jason Jones. Analysis and interpretation of data: Adam Kisling, Jason Jones, David Hostler, and Jordanna Hostler. Drafting of manuscript: Adam Kisling, Jason Jones, Caleb Hixson, David Hostler, and Jordanna Hostler. Critical revision: Adam Kisling, Jason Jones, Caleb Hixson, David Hostler, and Jordanna Hostler MD. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: The authors declare that they have no conflicts of interest. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2020/06/dic.2020-5-3-COI.pdf

Acknowledgements: The primary author is a military service member or employee of the US Government. This work was prepared as part of official duties. Title 17, USC §105 provides that copyright protection under this title is not available for any work of the US Government. Title 17, USC §101 defines a US Government work as work prepared by a military service member or employee of the US Government as part of that person's official duties. The views expressed are solely those of the authors and do not necessarily reflect the official policy or position of Tripler Army Medical Center, the Department of the Army, the Department of Defense, nor the US Government.

Funding declaration: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. There was no funding associated with the preparation of this article.

Article URL: https://www.drugsincontext.com/mepolizumab:-an-alternative-therapy-for-idiopathic-chronic-eosinophilic-pneumonia-with-glucocorticoid-intolerance

Correspondence: Adam Kisling, Department of Medicine, Tripler Army Medical Center, 1 Jarrett White Road, Honolulu, Hawaii, 96859, USA. adam.j.kisling.mil@mail.mil

Provenance: submitted; externally peer reviewed.

Submitted: 6 May 2020; **Peer review comments to author:** 26 May 2020; **Revised manuscript received:** 17 June 2020; **Accepted:** 17 June 2020; **Publication date:** 18 August 2020.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

For all manuscript and submissions enquiries, contact the Editorial office editorial@drugsincontext.com

For all permissions, rights and reprints, contact David Hughes david.hughes@bioexcelpublishing.com

References

1. Marchand E, Reynaud-Gaubert M, Lauque D, Durieu J, Tonnel AB, Cordier JF. Idiopathic chronic eosinophilic pneumonia. A clinical and follow-up study of 62 cases. The Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). *Medicine (Baltimore)*. 1998;77(5):299–312. https://doi.org/10.1097/00005792-199809000-00001
2. Cottin V. Eosinophilic lung diseases. *Clin Chest Med*. 2016;37(3):535–556. https://doi.org/10.1016/j.ccm.2016.04.015
3. Marchand E, Cordier JF. Idiopathic chronic eosinophilic pneumonia. *Orphanet J Rare Dis*. 2006;1:11. https://doi.org/10.1186/1750-1172-1-11
4. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. *Osteoporos Int*. 2007;18(10):1319–1328. https://doi.org/10.1007/s00198-007-0394-0
5. Dubovsky AN, Arvikar S, Stern TA, Axelrod L. The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited. *Psychosomatics*. 2012;53(2):103–115. https://doi.org/10.1016/j.psym.2011.12.007
6. Lin RY, Santiago TP, Patel NM. Favorable response to asthma-dosed subcutaneous mepolizumab in eosinophilic pneumonia. *J Asthma*. 2019;56(11):1193–1197. https://doi.org/10.1080/02770903.2018.1534966
7. To M, Kono Y, Yamawaki S, et al. A case of chronic eosinophilic pneumonia successfully treated with mepolizumab. *J Allergy Clin Immunol Pract*. 2018;6(5):1746–1748.e1. https://doi.org/10.1016/j.jaip.2018.06.017
8. Brenard E, Pilette C, Dahlqvist C, et al. Real-life study of mepolizumab in idiopathic chronic eosinophilic pneumonia. *Lung*. 2020;198(2):355–360. https://doi.org/10.1007/s00408-020-00336-3
9. Kaya H, Gümüş S, Uçar E, et al. Omalizumab as a steroid-sparing agent in chronic eosinophilic pneumonia. *Chest*. 2012;142(2): 513–516. https://doi.org/10.1378/chest.11-1881
10. Crowe M, Robinson D, Sagar M, Chen L, Ghamande S. Chronic eosinophilic pneumonia: clinical perspectives. *Ther Clin Risk Manag*. 2019;15:397–403. https://doi.org/10.2147/TCRM.S157882
11. Kanda A, Driss V, Hornez N, et al. Eosinophil-derived IFN-gamma induces airway hyperresponsiveness and lung inflammation in the absence of lymphocytes. *J Allergy Clin Immunol*. 2009;124(3):573–582.e5829. https://doi.org/10.1016/j.jaci.2009.04.031
12. Domingo C. Overlapping effects of new monoclonal antibodies for severe asthma. *Drugs*. 2017;77(16):1769–1787. https://doi.org/10.1007/s40265-017-0810-5
13. Mukherjee M, Sehmi R, Nair P. Anti-IL5 therapy for asthma and beyond. *World Allergy Organ J*. 2014;7(1):32. https://doi.org/10.1186/1939-4551-7-32
14. Debrosse CW, Rothenberg ME. Eosinophilia: clinical manifestations and therapeutic options. In: Holgate ST, Church MK, Broide DH, Martinez FD, eds. *Allergy*. Philadelphia: WB Saunders; 2012:361–368. https://doi.org/10.1016/B978-0-7234-3658-4.00023-8
15. Rothenberg ME, Klion AD, Roufosse FE, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab [published correction appears in N Engl J Med. 2008 Jun 5;358(23): 2530]. *N Engl J Med*. 2008;358(12):1215–1228. https://doi.org/10.1056/NEJMoa070812
16. Garrett JK, Jameson SC, Thomson B, et al. Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. *J Allergy Clin Immunol*. 2004;113(1):115–119. https://doi.org/10.1016/j.jaci.2003.10.049

17. Roufosse FE, Kahn JE, Gleich GJ, et al. Long-term safety of mepolizumab for the treatment of hypereosinophilic syndromes. *J Allergy Clin Immunol*. 2013;131(2):461–467.e75. https://doi.org/10.1016/j.jaci.2012.07.055
18. Khatri S, Moore W, Gibson PG, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. *J Allergy Clin Immunol*. 2019;143(5):1742–1751.e7. https://doi.org/10.1016/j.jaci.2018.09.033
19. Gunsoy NB, Cockle SM, Yancey SW, et al. Evaluation of potential continuation rules for mepolizumab treatment of severe eosinophilic asthma. *J Allergy Clin Immunol Pract*. 2018;6(3):874–882.e4. https://doi.org/10.1016/j.jaip.2017.11.026
20. Lin RY, Santiago TP, Patel NM. Favorable response to asthma-dosed subcutaneous mepolizumab in eosinophilic pneumonia. *J Asthma*. 2019;56(11):1193–1197. https://doi.org/10.1080/02770903.2018.1534966