Keywords
Asthma control, eosinophilic inflammation, mepolizumab, severe asthma, severe eosinophilic asthma.

Correspondence
Simran Chhatwal, Medical Affairs – India, Emerging Markets & Asia Pac, GlaxoSmithKline Pharmaceuticals Ltd, Bharat Yuvak Bhawan, 1 Jai Singh Road, New Delhi 110001, India. E-mail: simranxchhatwal@gsk.com

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Abstract
Severe asthma can be associated with eosinophilic or allergic phenotypes or both. Eosinophilic inflammation is associated with exacerbations and disease severity due to biological activity of interleukin-5 (IL-5). Patients with severe asthma have reported reduced lung function and poor health-related quality of life (HRQoL) and may require systemic corticosteroids for its management. Thus, treatment targeting IL-5 can help improve quality of life and reduce the use of systemic corticosteroids in severe asthma. Mepolizumab is approved for treating severe eosinophilic asthma as it helps reduce exacerbations, improve lung function and asthma control, and reduce the use of systemic glucocorticoids. This further helps in enhancing HRQoL of these patients. This case series includes four adult patients suffering from severe eosinophilic asthma who were treated with mepolizumab.

Introduction
Asthma affects 339 million individuals across the globe [1]. Majority of patients receiving standard care and treatment are able to keep asthma under control; however, a subset of patients viz. 5–10% of patients suffer from severe asthma. These patients may usually require high-dose inhaled corticosteroids (ICS) along with other controller medications. Despite these measures, patients may continue to have uncontrolled disease typified by recurrent exacerbations, reduced lung function, and a poor health-related quality of life (HRQoL). Severe asthma may present with characteristics of eosinophilic and allergic phenotypes [2]. The common phenotype of severe asthma is eosinophilic asthma [3]. Eosinophilic inflammation is majorly linked to increased asthma exacerbations, and is sustained due to biological activity of interleukin-5 (IL-5). Thus, IL-5 is an imperative treatment target in the management of severe eosinophilic asthma [4].

Mepolizumab is a humanized monoclonal antibody approved for the treatment of severe eosinophilic asthma. It selectively inhibits IL-5 and prevents eosinophilic inflammation, which reduces exacerbation and the requirement of oral corticosteroids (OCS), further improving the lung function, asthma control, and HRQoL [1,5,6]. In this article, we aim to discuss four adult case reports of severe eosinophilic asthma successfully treated with mepolizumab.

Case Series
Case 1
A 56-year-old male patient with asthma presented with intermittent complaints of wheezing and breathlessness. He had been treated with inhaled medication (salmeterol and fluticasone) for the past 10–12 years. He reported seven to eight exacerbations in the year preceding his visit, for which he required OCS bursts as well as ephedrine and theophylline injections. He had received six-month trial of omalizumab
without significant relief. He was hospitalized a year before and required treatment with intravenous (IV) corticosteroids and inhaled long-acting beta-agonist (LABA) with ICS. Clinical investigations revealed serum immunoglobulin E (IgE) levels of 1720 IU/mL and absolute eosinophilic count (AEC) of 171 cells/μL. Also, specific allergen test showed elevated specific IgE levels to Dermatophagoides farinae, Dermatophagoides pteronyssinus, and dog dander. His Asthma Control Test (ACT) score was 9. This patient was diagnosed with uncontrolled severe eosinophilic atopic asthma.

The patient was initially treated with ciprofloxacin for 10 days (sputum isolated Klebsiella pneumoniae sensitive to quinolones) and inhaled formoterol-budesonide along with tiotropium and leukotriene receptor antagonists (LTRAs). After one week of follow-up, he reported symptomatic improvement in cough, but complained of breathlessness. The pulmonary function test revealed forced expiratory volume in 1 sec (FEV₁) of 26% of predicted value with a reversibility of 200 mL. Mepolizumab treatment was initiated and he had been given 13 doses. The patient showed improvement in ACT score (ACT score: 20; Table 1). However, the patient was diagnosed with coronavirus disease 2019 (COVID-19). He was discharged after 10 days of treatment, and he was followed up for continuation of mepolizumab therapy. His current medications included inhaled formoterol-budesonide, tiotropium, and LTRA along with mepolizumab. The patient showed good response to mepolizumab after poor response to omalizumab treatment.

Case 2

A 55-year-old male patient with a history of asthma was referred to the specialist with complaints of disturbed sleep due to nocturnal cough and nasal congestion. He did not report hospitalization due to exacerbation in the past six months. Initially, he was diagnosed with asthma and allergic rhinitis, which was treated with high-dose ICS plus LABA. His ACT score was 17. His spirometry findings showed severe obstruction. Laboratory investigation showed total IgE count of 1369 UI/mL without any sensitization to aeroallergens and absolute eosinophilic count of 39,000 cells/μL. Upper airway obstruction, haematological causes of eosinophilia, and allergic bronchopulmonary aspergillosis were ruled out, and the patient was diagnosed to have severe eosinophilic asthma. Considering high eosinophil counts, treatment with mepolizumab 100 mg every four weeks was initiated rather than omalizumab, along with 500 twice daily (BID) salmeterol plus fluticasone, intranasal fluticasone, oral montelukast plus fexofenadine, indacaterol and glycopyrronium dry powder inhaler (DPI), and seratrodast 80 mg/day. After the 11th dose of mepolizumab, the AEC significantly reduced to 806 cells/μL and ACT score improved to 22. Overall, treatment was effective, and significant improvement in the lung function, ACT score, and eosinophilic counts was noted. He did not report any exacerbations, hospitalization, and additional use of systemic corticosteroids after mepolizumab treatment.

Table 1. Treatment with mepolizumab in a 55-year-old male patient with severe eosinophilic asthma (case 2).

|                          | May 2019 (after the first dose) | August 2019 (after the fourth dose) | December 2019 (after the eighth dose) | March 2020 (after the 11th dose) |
|--------------------------|---------------------------------|-------------------------------------|----------------------------------------|----------------------------------|
| AEC (cells/μL)           | 39,000                          | 31,262                              | 4964                                   | 806                              |
| PEF (L/sec) (pre-test)   | 6.87                            | 8.40                                | 7.98                                   | 8.70                             |
| PEF (L/sec) (post-test)  | 7.22                            | 8.44                                | 7.91                                   | 8.67                             |
| FEV₁ (L; pre-bronchodilator) | 1.41                           | 1.54                                | 1.26                                   | 1.54                             |
| FVC (L; pre-bronchodilator) | 1.72                           | 1.78                                | 1.68                                   | 1.71                             |
| FEV₁ (L; post-bronchodilator) | 1.42                           | 1.71                                | 1.38                                   | 1.60                             |
| FVC (L; post-bronchodilator) | 1.79                           | 2.02                                | 1.77                                   | 2.02                             |
| IgE (UI/mL)*             | 1369                            | —                                   | —                                      | —                                |
| ACT score                | 17/25                           | 19/25                               | 20/25                                  | 22/25                            |

*IgE levels were not required to be evaluated after the fourth dose.

ACT, Asthma Control Test; AEC, absolute eosinophilic count; FEV₁, forced expiratory volume in 1 sec; FVC, forced vital capacity; IgE, immunoglobulin E; PEF, peak expiratory flow.
Case 3
A 36-year-old female patient came to the hospital with complaints of progressively worsening dyspnoea, persistent dry cough at night, wheezing, along with symptoms of runny nose and sneezing. She had a 14-year history of asthma, and about a year before, she reported 12 exacerbation episodes, out of which two episodes required intensive care unit (ICU) admission. Her current medications included ICS plus LABA, long-acting muscarinic antagonist (LAMA), LTRA, thromboxane A2 antagonist, and oral prednisolone (30 mg/day). Laboratory investigations revealed IgE levels of 265 IU/L, AEC of 330 cells/mm³, and fractional exhaled nitric oxide (FeNO) levels of 50 ppb. Her pulmonary function tests revealed FEV₁ 40% of predicted value and FEV₁/forced vital capacity (FVC) ratio was 65%. She had impaired quality of life and poor asthma control. Her ACT score was 12, Global Initiative for Asthma (GINA) asthma severity score was 4, Asthma Control Questionnaire score was 5.3, and Asthma Quality of Life Questionnaire score was 1.28.

She was diagnosed as a case of uncontrolled severe asthma, for which treatment with omalizumab 300 mg/month was initiated. She received five doses of omalizumab; however, she did not report any significant improvement. She required additional OCS to control her symptoms and reported a poor quality of life. Due to inadequate response to omalizumab, she underwent bronchial thermoplasty; however, she reported only a partial response after the procedure and continued to require OCS at lower dose (20 mg/day). Treatment with mepolizumab 100 mg for every four weeks was then initiated. She received 12 doses without occurrence of adverse events. Post mepolizumab, her asthma control improved significantly, OCS dose was reduced to 2.5 mg/day, and she became exacerbation free (Fig. 1).

Case 4
A 56-year-old female patient reported to the clinic for the first time with complaints of uncontrolled wheezing, chest tightness, and night-time awakening. She had a history of asthma for 32 years and had been on inhalation therapy for 20 years. The patient also required OCS therapy for symptom control, several times in the past. Clinical investigations revealed pulmonary function test finding of 45% FEV₁, AEC of 4430/mm³ (eosinophil count: 44.7%), IgE level of 1294 IU/mL, and ACT score of 17. A diagnosis of uncontrolled severe asthma was ascertained, and the patient was treated with ICS plus LABA DPI (budesonide 800 μg/day plus formoterol 160 μg/day), tiotropium 9 μg with montelukast plus levocetirizine plus etofylline plus theophylline plus methyl prednisolone 8 mg orally daily. However, after a month, she showed no improvement in ACT score. Based on her evaluation, mepolizumab 100 mg was administered subcutaneously every four weeks along with aforementioned medications. After the first dose, she did not report any adverse event. Furthermore, the dose of methyl-prednisone was gradually tapered off, and mepolizumab treatment was continued. She did not require OCS after a month of mepolizumab treatment. Thus, mepolizumab was continued for three months. Unfortunately, because of the nationwide lockdown due to COVID-19, she could not receive two doses and had two episodes of exacerbation, for which she required short courses of OCS with methyl-prednisolone 8 mg for five days. After two months, treatment with mepolizumab was re-initiated. On follow-up, laboratory investigations showed reduction in AEC up to 100/mm³ and her ACT score showed marginal improvement. She did not require OCS in the past six months before follow-up, and treatment with tiotropium, etofylline plus theophylline, and montelukast-levocetirizine was discontinued. Overall treatment response to mepolizumab was good and she had significantly improved quality of life.

Discussion
In this case series, all the four patients with severe eosinophilic asthma treated with mepolizumab showed good
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response. Patients either required OCS burst and/or maintenance corticosteroids for managing their asthma. Two patients had received initial treatment with omalizumab, which did not provide any significant improvement. After switching to mepolizumab, both the patients had favourable treatment outcomes. All the patients had reduced or no exacerbation episodes with mepolizumab. Only one patient had asthma exacerbation due to interruption in the treatment due to the nationwide COVID-19 lockdown; but, after re-initiating the treatment, the patient had shown significant improvement.

Findings from the Dose Ranging Efficacy and Safety with Mepolizumab (DREAM) study in 621 patients with severe eosinophilic asthma showed that mepolizumab significantly improved exacerbations and is deemed to be well tolerated and an effective therapeutic option [7]. Also, a total of 576 patients from the Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) study showed that subcutaneous mepolizumab reduced exacerbation rates by 53% compared to placebo ($P < 0.001$). Mepolizumab treatment was also associated with significant improvement in lung function, asthma control score, and quality of life [5]. Another double-blind, placebo-controlled, dose-ranging study of mepolizumab in 616 patients with severe eosinophilic asthma stated 50% reduction in exacerbation rates versus placebo [8]. In addition, mepolizumab treatment significantly reduced the use of OCS [6]. Similarly, all the four patients reported reduction in exacerbation, improvement in lung function, and reduction in the use of OCS after mepolizumab treatment, suggesting it as a valuable therapeutic choice in patients with severe eosinophilic asthma.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

Conflict of Interest

Neeraj Markandeywar is a GSK employee. He reports no other conflicts of interest in this work. Bhavesh Kotak is a GSK employee and holds GSK shares. He reports no other conflicts of interest in this work. Simran Chhatwal is a GSK employee. She reports no other conflict of interest in this work.

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Author Contribution Statement

Conceptualization: Simran Chhatwal, Neeraj Markandeywar, Bhavesh Kotak. Supervision: Simran Chhatwal, Neeraj Markandeywar, Bhavesh Kotak. Data collection: Venkata Nagarjuna Maturu, Preeti Meshram, Soumya Das, Ashok Kumar Rajput Arun Chowdary Kotaru. Literature search: Simran Chhatwal. Writing manuscript: Venkata Nagarjuna Maturu, Preeti Meshram, Soumya Das, Ashok Kumar Rajput, Arun Chowdary Kotaru. Final review and editing of manuscript: Neeraj Markandeywar, Simran Chhatwal.

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