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Case Report

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The First Case of Mepolizumab for the Treatment of the Prednisone Dependent Asthma in China

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Abstract

Asthma is a chronic disease characterized by inflammation and narrowing of the airways in the lungs that lead to symptoms such as wheezing, cough, tightness of breath, and chest tightness. It is treated with inhaled corticosteroids (ICS), bronchodilators, and oral corticosteroids (OCS). Severe refractory asthma is treated with biological therapeutics. Long-term treatment with OCS is associated with systemic adverse effects, including easy bruising and increased risk of osteoporosis. The local adverse effects of ICS include oral thrush and dysphonia. Mepolizumab is a monoclonal antibody that blocks the interaction of the interleukin 5 (IL-5) pro-inflammatory cytokine with its receptor, thereby reducing the eosinophil counts in blood and inhibiting eosinophilic inflammation in the airways of patients with asthma. In this case study, a middle-aged male Chinese patient with a history of severe asthma was diagnosed with severe prednisone-dependent eosinophilic asthma with persistent symptoms despite OCS treatment. The patient was diagnosed with type 2 airway inflammation with high blood eosinophil counts (>150/µl), higher proportion of eosinophils in the induced sputum (>2%) and high fractional exhaled nitric oxide (FeNO) levels (>20 ppb). We initiated treatment with mepolizumab and showed that the absolute eosinophil counts (AECs) and serum IL-5 levels returned to normal. Moreover, mepolizumab treatment allowed lowering of prednisone dosage without affecting symptoms and the serum and induced sputum eosinophil counts returned to normal. However, the patient had to discontinue treatment with mepolizumab because of financial constraints. This resulted in the recurrence of some asthma indicators such as increased AECs and high serum IL-5 levels. In conclusion, our data showed that mepolizumab treatment resulted in significant improvement in symptoms associated with severe prednisone-dependent eosinophilic asthma in this patient. This is the first case study from China for treatment of a severe asthma patient with mepolizumab.

Keywords: Mepolizumab; Eosinophils; Prednisone-dependent severe asthma; Corticosteroids

Abbreviations: CT: Computed Tomography; ICS: Inhaled Corticosteroids; OCS: Oral Corticosteroids; IL-5: Interleukin 5; FENO: Fractional Exhaled Nitric Oxide; LABA: Long-Acting Beta- Agonist; ACT: Asthma Control Test; BALF: Bronchoalveolar Lavage Fluid; AEC: Absolute Eosinophil Counts; EGPA: Eosinophilic Granulomatosis with Polyangiitis; ABPA: Allergic Bronchopulmonary Aspergillosis

Introduction

Asthma is a heterogeneous disease that is characterized by chronic airway inflammation and variable expiratory airflow limitation. The symptoms of asthma include wheezing, shortness of breath, chest tightness, and cough. These symptoms vary over time. Severe asthma is defined as uncontrolled asthma despite high dose ICS/Long-Acting Beta- Agonist (LABA) treatment and clinical management of associated factors, or worsening of asthma when the treatment dose is reduced [1]. Patients with severe asthma can be treated with specific biological agents if the specific cause of inflammation is determined. For example, drugs targeting the IL-5 signaling pathway are used for the treatment of uncontrolled severe eosinophilic asthma. Mepolizumab is a monoclonal antibody against IL-5 that is approved for the treatment of adult patients (≥18 years) with severe, uncontrolled, and persistent eosinophilic asthma [2]. This study describes the case report of a Chinese patient with severe prednisone-dependent eosinophilic asthma being successfully treated by mepolizumab.

Patient Information

A 54-year-old male patient with a 20-year history of asthma was hospitalized with cough and expectoration for 1 year. The patient was being treated with the combination ICS/LABA (320 µg/9 µg) inhaler twice daily. However, within one year, the patient developed wheezing and was repeatedly hospitalized at an average of 1-2 times a month, and was administered intravenous injections of 20~40 mg methylprednisolone. The patient was discharged from the hospital once the symptoms were under control and was prescribed treatment with the combination ICS/LABA/ long-acting muscarine anticholinergic (LAMA) (160 µg/7.2 µg/4.8 µg) inhaler 2 times daily and Oral Corticosteroid (OCS) (methylprednisolone tablets, 20 mg/day, reduce 4 mg after two weeks). However, the symptoms recurred immediately after OCS with 3 tablets (12 mg; 1 tablet=4 mg).

Clinical Findings

On June 8, 2022, prednisone withdrawal caused wheezing, but rales were not heard during auscultation. Chest CT scan after admission showed exudate shadow in the middle lobe of the right lung **(Figure 1)**. The lung functional parameters before inhalation of bronchodilators were as follows: FEV1=1.32 L; FEV1/FVC=42.4%; DLCO-SB=61.7 mmol/min/kpa; after inhalation of bronchodilators─ FEV1=1.83 L and FEV1/FVC=55%. This indicated severe mixed ventilatory disorder with increased residual air/total lung volume, decreased diffusion volume, and positive Bronchodilator (BD) responsiveness. The blood gas analysis indicated type II respiratory failure because of the following results (under atmospheric pressure): pH=7.39; PaO2=59 mmHg; PaCO2=53.9 mmHg. The blood test showed mild elevation of the absolute eosinophilic count (AEC=0.58 x 109/L). The total serum IgE levels were not high (145 IU/ml), but the Fractional Exhaled Nitric Oxide (FeNO) levels were significantly high (91 ppb). Asthma Control Test (ACT) score was 15. The patient showed normal renal function. There was no evidence of blood infection. The patient was intravenously administered with 20 mg methylprednisolone for 3 days, and used an aerosol inhaler with a combination of budesonide (2 ml) and terbutaline (2 ml) twice a day. The lung function parameters of the patient were checked after treatment and were as follows: before inhalation of bronchodilators─ FEV1=1.79L; FEV1/FVC=72%; DLCO-SB=78.9 mmol/min/kpa; after inhalation of bronchodilators: FEV1=1.83 L; FEV1/FVC=78%. Therefore, COPD was ruled out. After discharge, OCS takes 20mg orally every day, reducing 4mg every 2 weeks. The symptoms of the patient relieved rapidly after the use of OCS, but recurred when OCS was reduced to 12 mg. On July 12, 2022, the patient experienced chest tightness and wheezing due to OCS withdrawal. Auscultation of both lungs generated wheezing sounds. The paranasal sinus CT scan showed sinusitis. The blood tests were normal (AEC=0.34 x 109/L). Blood gas analysis indicated hypoxemia. The Bronchoalveolar Lavage Fluid (BALF) showed lymphocytes and increased proportion of neutrophils (26.1%) and eosinophils (19.5%). The differential counts of induced sputum cells indicated eosinophilic inflammation of the airway (eosinophils=14%). We also observed increased serum levels of IL-5 (171.62 pg/ml) and IL-6 (11.5 pg/ml) (Ruisikaier, 20180013, Shandong, China). No obvious abnormality was found under bronchoscope. The total serum IgE level was 128 IU/ml. The serum was negative for Aspergillus-specific IgE and IgG antibodies. These results confirmed positive diagnosis of severe asthma and the patient was administered with mepolizumab (pen-type; provided by GSK). The IL-5 cytokine levels dropped to normal (3.36 pg/ml) when the patient received a single subcutaneous injection of 100 mg mepolizumab. Then, 40 mg/day methylprednisolone was administered intravenously for 4 days. The patient was discharged as the symptoms improved. After discharge, the patient was prescribed treatment with OCS and

aerosol inhalation of the bronchodilator. During the first week, the patient was given seven tablets of OCS once a day. During the second week, the patient received six tablets of OCS once a day. Every two weeks, one tablet of OCS was reduced.

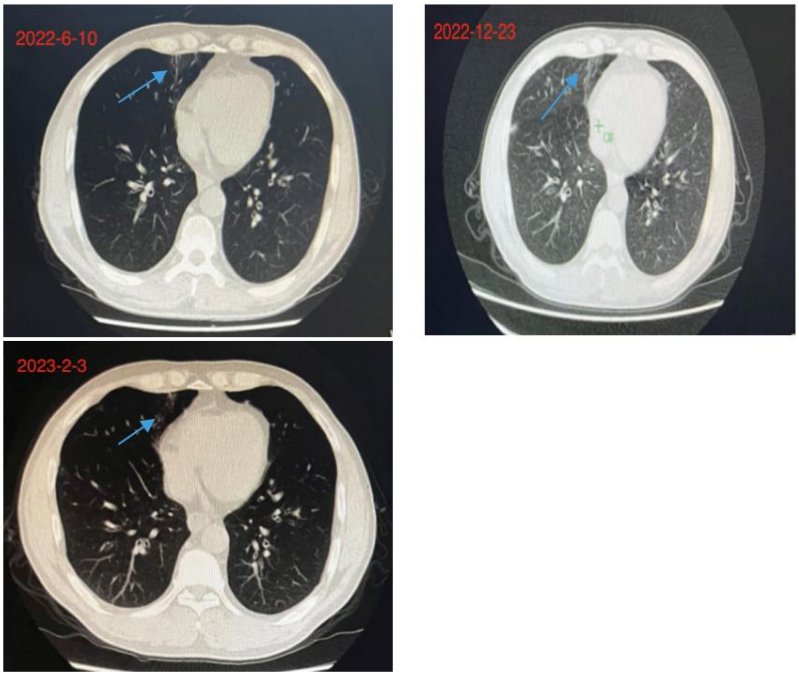

Figure 1: Representative chest scan images at different time points. The inflammation is indicated by the blue arrow in the medical segment of the middle lobe of the right lung.

Timeline

The patient was administered five times with a subcutaneous injection of 100 mg mepolizumab **(Figure 2)**. This resulted in a significant reduction of AECs. The serum IgE levels were within the normal range and mildly decreased during the treatment. However, the patient had to discontinue the regular injection (every 4 weeks) because of economic burden. This resulted in the recurrence of the above indicators **(Figure 3 and 4)** in that moment. OCS was also constantly adjusted at that time. The patient continued mepolizumab treatment and was recovering well.

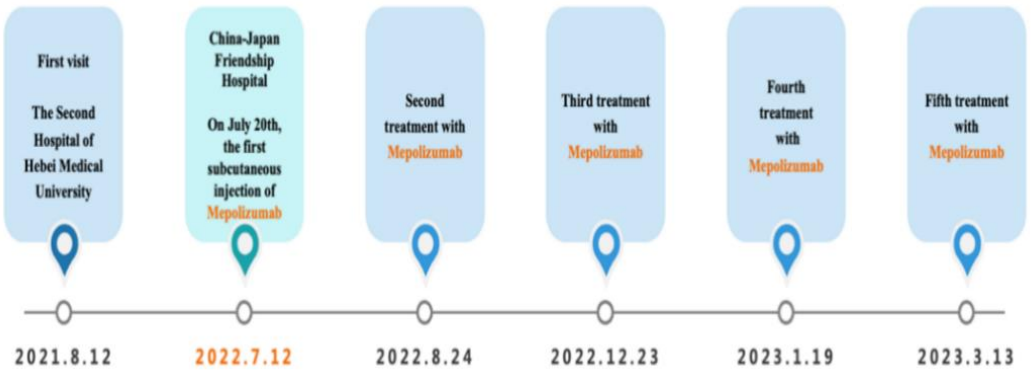

Figure 2: Timeline of subcutaneous injection of mepolizumab.

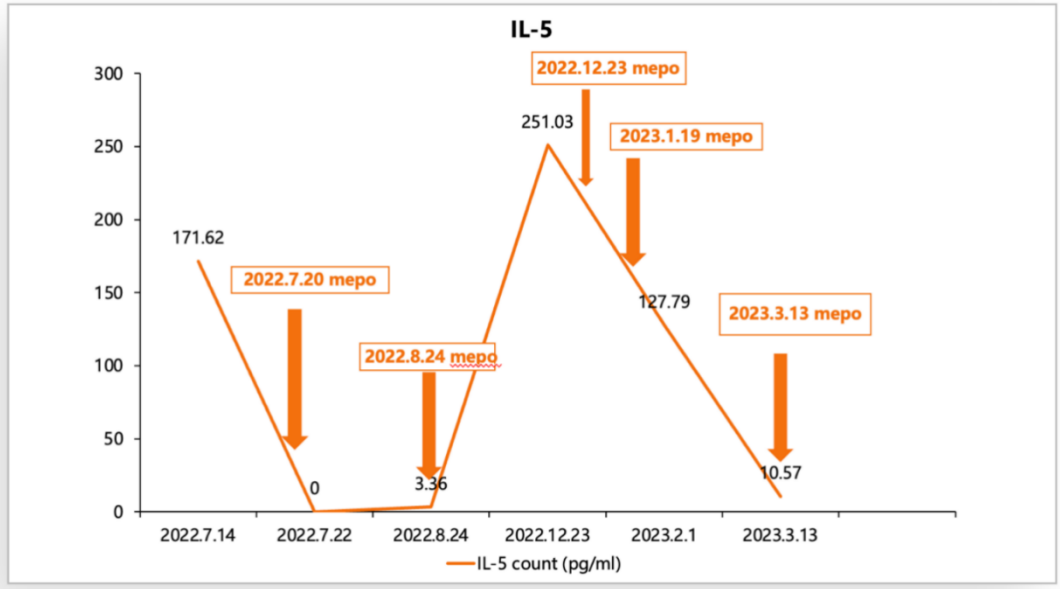

Figure 3: Changes in the serum IL-5 levels before and after mepolizumab treatment. Note: mepo= mepolizumab.

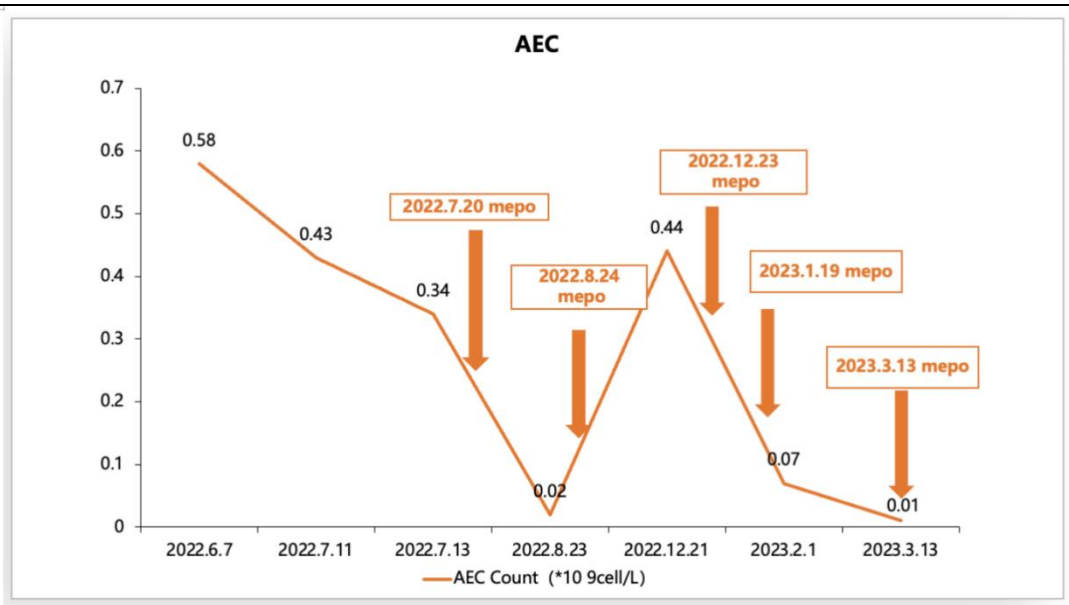

Figure 4: Changes in the AEC levels before and after administration of mepolizumab (mepo).

Diagnostic Assessment

The asthma patient in this case study was receiving medium doses of ICS+LABA+LAMA and OCS treatment for maintenance. However, the patient experienced persistent asthma-related symptoms and frequent acute attacks. Therefore, he was diagnosed with difficult-to-treat asthma. Furthermore, after excluding modifiable factors, including incorrect inhaler technique, poor adherence, smoking, and/or comorbidities, the diagnosis was clarified as severe asthma. The patient was diagnosed with type 2 airway inflammation because of high blood eosinophil counts (>150/µl), higher proportion of eosinophils in the induced sputum (>2%) and high FeNO levels (>20 ppb). Furthermore, the patient was considered to be eligible for add-on biological treatment for asthma patients with type 2 inflammation. The patient was eligible for receiving treatment with mepolizumab according to the Global Initiative for Asthma (GINA) 2022 guidelines [2]. The patient showed wheezing-like symptoms, increased airway eosinophil counts, and sinusitis according to sinus CT data. We also checked for manifestation of other diseases with asthma. The chest CT scan of the patient did not show any transient lesions. Electromyography did not show any abnormal nerve conduction. Furthermore, Eosinophilic Granulomatosis with Polyangiitis (EGPA) was not considered because there was no evidence of increased eosinophil counts (≥ 10% or absolute value ≥ 1.5 ×109/L) in the blood [3]. Although the patient showed symptoms of asthma, total serum IgE and Aspergillus-specific IgE antibodies were absent. The Absolute Eosinophil Counts (AEC) was not significantly high. The imaging data did not show any signs of consolidation, nodules, "toothpaste sign" or "finger sheath sign", wandering shadows, or bronchiectasis. Therefore, the patient did not meet the diagnostic criteria of Allergic Bronchopulmonary Aspergillosis (ABPA) [4]. The patient had a history of repeated coughing and expectoration, lower respiratory tract infection, smoking, and pulmonary functional parameters that were consistent with the acute exacerbation of COPD. However, the bronchodilation test was positive and FeNO levels were significantly high. The history of the patient also showed poorly controlled symptoms despite high dose ICS/LABA inhalation. Therefore, asthma could not be ruled out. So, initial diagnosis suggested an asthma-

COPD overlap [2]. Subsequent re-examination of the lung function showed that the FEV1/FVC value was greater than 0.7. Therefore, COPD was ruled out.

Follow-Up and Outcomes

After receiving the first injection (July 22, 2022), the patient's symptoms and laboratory tests significantly decreased, and successfully received the second injection (August 24, 2022). Later, due to the good symptom recovery and economic burden at that time, the patient refused to be admitted to the hospital for treatment with the third injection. During the 3rd month telephone follow-up of first injection (October 20, 2022), the patient complained of recurrent symptoms and inability to completely release the OCS. At that time, it was instructed to take the minimum amount of OCS with the goal of controlling symptoms. At the 5th month of receiving first injection, the patient complained of further worsening of symptoms, so they came to the hospital for the 3rd injection (December 22, 2022) treatment. After the symptoms improved and laboratory tests decreased, they were discharged and successfully completed the treatment of the 4th injection (January 19, 2023) and the 5th injection (March 13, 2023). After receiving the 5th injection, the patient has completely withdrawn from OCS. The patient's symptoms improved during medication, leading to a misconception that he did not need to take medication again, which resulted poor medication compliance and repeated fluctuations in his condition. The patient's tolerance was good throughout the entire medication period, and there were no adverse events or unanticipated events occurrence.

Discussion

We considered the optimal dosage of mepolizumab for this patient. A RCT study by Nair et al. [5] showed that five monthly infusions of 750 mg mepolizumab significantly reduced the blood and sputum eosinophil counts and allowed prednisone sparing in asthma patients with sputum eosinophilia despite prednisone treatment. HGO et al. [7] reported that subcutaneous injections of 100 mg mepolizumab were more effective in reducing the acute attacks and the emergency or readmission rates of asthma patients compared to those receiving intravenous injections of 75 mg mepolizumab. Since the sample size of the first study was small, we opted for subcutaneous injections of 100 mg mepolizumab for our case study patient. Although the absolute eosinophil counts of this patient exceeded 150/μl multiple times, they were within the normal range because of prednisone treatment. Prednisone does not significantly reduce IL-5 levels with severe asthma [8-11]. Mepolizumab (anti-IL-5 antibody) can further reduce the AECs by blocking the interaction between IL-5 and the IL-5 receptor. Our data showed that serum IL-5 and IL-6 levels of this patient were high before administration of mepolizumab. However, the serum IL-5 levels of the patient normalized within a day after subcutaneous injection of 100 mg mepolizumab. Eosinophils are produced in the bone marrow, and their differentiation, survival, and activation is significantly regulated by IL-5 [12]. Mepolizumab binds directly to IL-5 and blocks the interaction between IL-5 and its receptor, thereby reducing the eosinophil counts in blood and the airways and alleviating the clinical symptoms of asthma [13]. In patients with prednisone-dependent asthma, treatment with mepolizumab reduces the dosage of OCS and allows prednisone sparing. In a randomized, double-blind trial of 135 patients [14] with severe eosinophilic asthma, the likelihood of a reduction in the prednisone-dose stratum was 2.39 times higher in the mepolizumab group than in the placebo group. In the mepolizumab group, prednisone dose was reduced by 50% compared with the placebo group. However, mepolizumab treatment reduced the annual acute attack

rate by 32% and showed similar safety profile as the placebo. A randomized, double-blind, parallel-group trial by Nair et al. [5] showed that mepolizumab reduced the blood and sputum eosinophil counts and allowed prednisone sparing in asthma patients with sputum eosinophilia despite prednisone treatment. The improvements in eosinophil numbers, asthma control, and FEV1 were maintained for 8 weeks after the last infusion of mepolizumab. Harvey et al. [15] reported that the median eosinophil counts in the blood of asthma patients decreased from 590/ μL to 100/μL at the 3rd month assessment during mepolizumab treatment and this level was maintained at the 12th month follow-up. The patient's OCS decreased from 20mg to 0, which is a manifestation of prednisone sparing. So far, mepolizumab's large-scale landmark clinical trials of GSK [7,9,10] have mainly involved Europe, North America, South America, Australia, and Asia. Indeed, we cannot deny the level of evidence for large RCT. However, there are two main differences between our case and the above research. Firstly, in this case report, we focus more on details, such as the continuous changes in IL-5, peripheral blood eosinophil count, and chest CT before and after medication, which have not been addressed in all major clinical trials so far. Previous studies have used induced sputum eosinophilic counts to measure the effects of reducing the prednisone dose [8]. In this case, we see significant changes in IL-5 before and after mepolizumab. However, there are many factors that affect the level of IL-5 (such as detection methods and factors that affect IL-5 are not very clear), and it is precisely these influencing factors that have led to the failure of IL-5 to become a biomarker used by mepolizumab. So, the clinical indicators for follow-up of discontinuation of mepolizumab are not clear. How to better distinguish these influencing factors and whether IL-5 can become a biomarker for monitoring changes in mepolizumab will also be our thinking question and direction. If it exists, what should its cut-off value be? The large-scale studies are required to establish the clinical value of monitoring progression of severe asthma after discontinuing mepolizumab. Secondly, mepolizumab's large-scale landmark clinical trials of GSK mainly involve severe asthma. Severe asthma is milder than prednisone-dependent asthma, both in terms of medication and symptoms. Only two high-quality articles in the New England Journal Medicine [5] and American Journal of Respiratory and Critical Care Medicine [6] are related to prednisone-dependent asthma from Canada. These articles respectively recommend the treatment of prednisone-dependent asthma with mepolizumab and reslizumab, indicating that in the field of prednisone-dependent asthma, more clinical evidence is needed to support the selection of biological agents. Therefore, our case can provide real-world data for the treatment of prednisone-dependent asthma with mepolizumab. Chang et al. [16] reported that Tai Chi Chuan, a traditional Chinese exercise, improved the lung function and reduced symptoms in children with asthma, but these effects have not been reported in adult patients with asthma. Zhao et al. [17] showed that acupuncture reduced the number of eosinophils and neutrophils in the BALF of the ovalbumin- induced asthma model mice by decreasing the levels of IL-4, IL-17, and TGF-β. Tang et al. [18] showed that acupuncture reduced the IgE levels in the BALF and the serum IL-5 levels in the ovalbumin-induced asthma model mice. These data suggested that combined or sequential treatment with mepolizumab, acupuncture, Tai Chi and/or other TCM treatment methods may be more effective in reducing the acute asthma attacks in patients with prednisone-dependent asthma. However, high-quality large-scale prospective studies are required to test the clinical application of these methods.

Patient Perspective Informed Consent

The case report has been approved by the patient himself and an informed consent form has been signed. The patient believes that the drug has played a crucial role in the treatment of the disease, but due to the patient's heavy economic burden and the tendency to take chances in the recovery of the disease, irregular medication has led to recurrence of the disease and reduced quality of life.

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