

# Switching from omalizumab to mepolizumab therapy improved extra-pulmonary abdominal and cutaneous vasculitis symptoms in a patient with eosinophilic granulomatosis with polyangiitis

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## Abstract

Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic vasculitis of small-to-medium-sized vessels. Both eosinophilic infiltration and vasculitis are thought to contribute to multi-organ damage. Some biologics have been used to reduce the required dose of corticosteroids in EGPA, but no single agent can ensure a complete control of this disease. Here, we describe a patient with anti-neutrophil cytoplasmic antibodies-negative relapsing EGPA whose asthma control was improved by omalizumab, but she continued to develop flares of abdominal and cutaneous vasculitis symptoms. After switching to mepolizumab therapy, her blood hypereosinophilia and extra-pulmonary symptoms were significantly improved. Moreover, the dose of daily maintenance corticosteroid could be tapered off. The experience from our case suggests that biologics targeting interleukin-5 may be more effective than omalizumab in the management of extra-thoracic manifestations in EGPA.

## KEYWORDS

eosinophilic granulomatosis with polyangiitis, extra-pulmonary, mepolizumab, omalizumab, switching

## INTRODUCTION

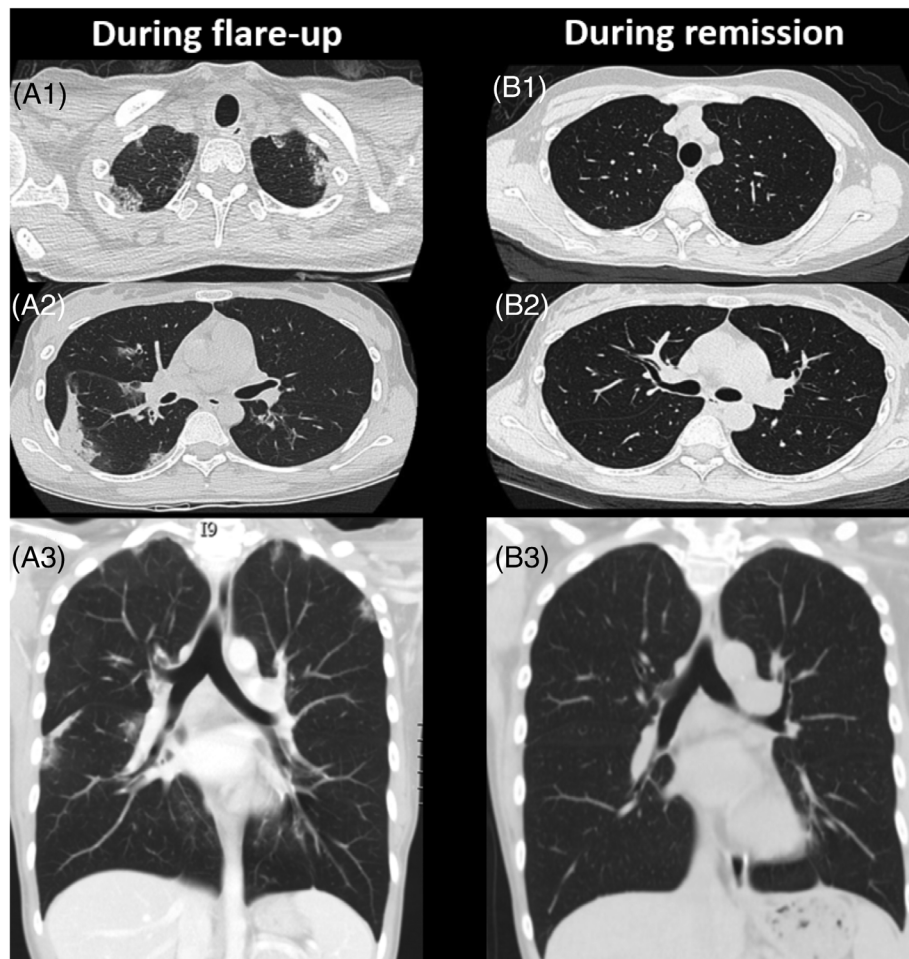
Eosinophilic granulomatosis with polyangiitis (EGPA) is an autoimmune disease characterized by small-to-medium-sized vessel necrotizing vasculitis, asthma and blood and tissue eosinophilia.<sup>1–4</sup> Anti-neutrophil cytoplasmic antibodies (ANCA) are positive in approximately 30%–40% of these patients.<sup>4–6</sup> Patients positive for ANCA more commonly had neurological and renal involvement compared with patients negative for ANCA, who had more cardiac and lung manifestations.<sup>4–6</sup> The treatment of relapsing EGPA is challenging due to the lack of a consensus on its optimal management.<sup>7</sup> The efficacy of some biologics, such as omalizumab, mepolizumab, benralizumab and rituximab, has been evaluated in these patients,<sup>8–11</sup> but no single agent can ensure a complete control of this disease and the comparative efficacy remains unclear. Here, we report the clinical benefits after switching from omalizumab to mepolizumab in an ANCA-negative EGPA patient on her abdominal and cutaneous manifestations.

## CASE REPORT

A 24-year-old woman presented to our outpatient clinic with a recurrent cough, wheezing, skin rash, abdominal pain and diarrhoea. During the 3 years before her first visit to our hospital, she had been admitted to another local hospital several times due to these symptoms, but no definite diagnosis was established there. Also, her asthma became uncontrolled despite treatment with a fixed high-dose inhaled corticosteroid and long-acting beta2 agonists. In that hospital, hypereosinophilia was also observed, with the highest blood eosinophil count of 8480/ $\mu$ l, and the pathology of her skin biopsy showed vasculitis with infiltration of eosinophils. During one episode of hospitalization, she developed cough and dyspnoea again and the high-resolution computed tomography (HRCT) of the chest revealed peripheral ground-glass opacification and consolidations at bilateral upper lobes and more at the right upper lobe (Figure 1A1–A3), which were refractory to antibiotic therapy but finally resolved on the chest

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**FIGURE 1** Axial and coronal views of the chest computed tomography during flare-up (A1–A3) and remission (B1–B3) of eosinophilic granulomatosis with polyangiitis

radiograph after administration of intravenous methylprednisolone at 40 mg every 8 h for 5 days with gradual tapering. After hospital discharge, a maintenance prednisolone at 5–10 mg per day was required to control her asthma and extra-pulmonary symptoms. Her past history was notable for a diagnosis of allergic asthma at a local clinic since early childhood.

In our hospital, all autoimmune profiles were negative. The allergen panel was positive for dust mites. The level of serum total immunoglobulin-E (IgE) was 247 IU/ml. Results of the pulmonary function test were normal when her asthma was stable, but wide variations of her peak expiratory flow rate (PEFR) were observed during follow-up (Figure 2). ANCA-negative EGPA was diagnosed and the initial Birmingham Vasculitis Activity Score (BVAS) was 14. Despite add-on therapies including montelukast and inhaled tiotropium, her Asthma Control Test (ACT) scores were still below 20. Subcutaneous omalizumab 300 mg was administered every 4 weeks initially, because no other biologics were available for severe asthma at that time. Her asthma control became better thereafter, with reduced frequency of coughing and chest tightness, and

significant improvements in ACT scores and PEFR (Figure 2). Unfortunately, she developed another relapse of her abdominal and skin manifestations, requiring hospitalization to her previous hospital where the abdominal CT revealed diffuse wall thickening over the colon and small amount of ascites. The dose of her maintenance prednisolone increased to 10–20 mg per day after discharge. In addition, her biologic was switched to mepolizumab at an initial dose of 100 mg per month, when this agent was available for the treatment of severe eosinophilic asthma in our hospital (Table 1). Her hyper-eosinophilia and extra-pulmonary symptoms significantly improved thereafter, and the dose of her maintenance corticosteroid could be reduced (Figure 2). The monthly dose of mepolizumab was increased to 300 mg 10 months later, when this agent was approved for EGPA in our country. At this higher dose of mepolizumab, her extra-pulmonary symptoms nearly disappeared, and the dose of daily prednisolone could be gradually tapered off (Table 1 and Figure 2). The chest HRCT performed when she was in remission revealed total resolution of previous lung infiltrates (Figure 1B1–B3).

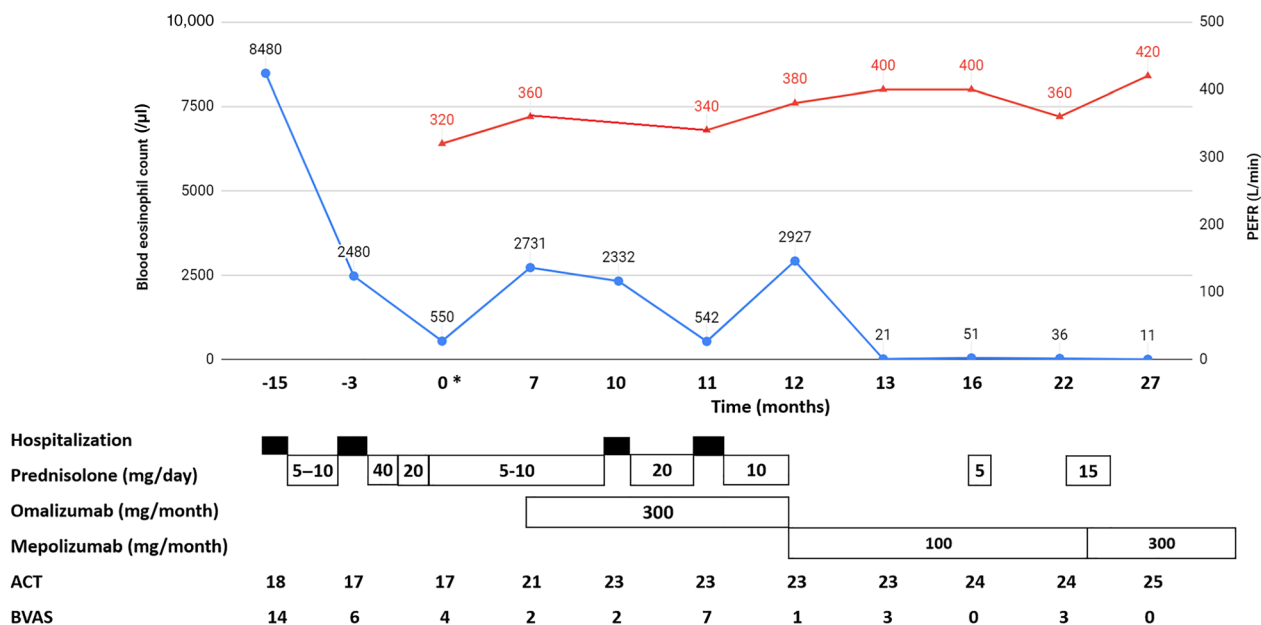


FIGURE 2 Time course of blood eosinophil counts, treatments and clinical parameters. \*Month 0: Initial visit to our hospital. ACT, Asthma Control Test; BVAS, Birmingham Vasculitis Activity Score; PEFR, peak expiratory flow rate

TABLE 1 Summary of blood eosinophil counts, events and treatment highlights

Time (months)	Eosinophil percentage (%)	Eosinophil count (/µl)	Event/setting	Treatment highlights
-15	53	8480	Hospitalization (diarrhoea, skin rash, asthma exacerbation)	IV methylprednisolone
-3	41.3	2480	Hospitalization (asthma exacerbation, pulmonary infiltrates)	IV methylprednisolone
0	7.6	550	Initial visit to our hospital (outpatient clinic)	Add montelukast and inhaled tiotropium
7	35.9	2731	Outpatient clinic	Initiation of SC omalizumab 300 mg/month
10	22.3	2332	Hospitalization (generalized painful skin rash)	IV methylprednisolone
11	10.7	542	Hospitalization (abdominal pain, diarrhoea)	IV methylprednisolone
12	17.1	2927	Outpatient clinic	Switching to SC mepolizumab 100 mg/month
16	0.9	51	Outpatient clinic	SC mepolizumab 100 mg/month
23	NA	NA	Outpatient clinic	Increasing SC mepolizumab dose to 300 mg/month
27	0.3	11	Outpatient clinic	SC mepolizumab 300 mg/month

Abbreviations: IV, intravenous; NA, not available; SC, subcutaneous.

## DISCUSSION

In this report, we describe a case of relapsing EGPA, where the use of mepolizumab demonstrated superior efficacy over omalizumab in her abdominal and cutaneous vasculitis symptoms. To our knowledge, few previous studies have addressed the relative therapeutic benefits between anti-IgE and anti-interleukin (IL)-5 biologics in EGPA.<sup>12</sup>

In our case, the use of omalizumab improved her asthma control but was ineffective for the extra-pulmonary symptoms. In EGPA patients, omalizumab was reported to reduce the daily corticosteroid requirement and the frequency of asthma exacerbation.<sup>8,13</sup> Clinical studies of omalizumab in EGPA, however, are still limited and its benefits are

controversial.<sup>14-17</sup> Furthermore, some case reports even implied an increased risk for the development of EGPA among asthmatic patients treated with omalizumab, probably related to the reduction in steroid dosage.<sup>17-19</sup> Therefore, clinical use of this agent remains a concern in these patients.

The management of extra-thoracic manifestations of EGPA is challenging due to its complex immunopathogenesis involving both eosinophilic proliferation and ANCA-associated vasculitis, which are the main effectors of organ damage and the hallmarks of the disease.<sup>6,20,21</sup> IL-5, IL-4 and IL-13, which are responsible for eosinophil activation and tissue recruitment, are overexpressed and contribute to Th2-mediated response.<sup>20-22</sup> On the other hand, the association between eosinophilic inflammation and ANCA

positivity remains unclear, and biomarkers capable of monitoring disease activity or predicting treatment response in these patients are still lacking.<sup>8,23</sup>

The efficacy of mepolizumab for relapsing or refractory EGPA has been demonstrated by its phase 3 trial (MIRRA).<sup>9</sup> The study population in that trial, however, was mainly ANCA-negative and 43% of participants in the mepolizumab arm still developed vasculitis relapses, despite a remarkable reduction in blood eosinophil count.<sup>9</sup> Furthermore, 47% of those in the mepolizumab group did not have protocol-defined remission.<sup>9</sup> The superior benefits of mepolizumab over omalizumab in our case were not surprising and compatible with the results reported by Canzian et al., but differences between these two biologics on extrapulmonary manifestations of EGPA were not described in that study.<sup>12</sup>

The approved dose of mepolizumab for EGPA is 300 mg every 4 weeks.<sup>9</sup> In our patient, mepolizumab was initially administered at a lower dose approved for severe eosinophilic asthma due to regulatory issue in our country. In a study of 18 EGPA patients with severe asthma but without active vasculitis, Vultaggio et al. reported that mepolizumab administered at 100 mg per month provided clinically relevant benefits in asthma control and the requirements of corticosteroids and other immunosuppressants.<sup>24</sup> Another study conducted by Canzian et al. revealed similar remission rates at 12 months among patients receiving monthly mepolizumab at 100 and 300 mg (76% and 82%, respectively), which was also consistent with the results from an European multicentre observational cohort.<sup>12,25</sup> Nonetheless, it is concerning that a low-dose mepolizumab may increase the relapse of asthma in EGPA patients.<sup>26</sup> The better steroid-sparing effect observed in our case also supports the use of a high-dose mepolizumab in these patients.

The benefits of mepolizumab in our patient reported here may be fragile, since the long-term outcomes are yet unclear. No previous studies have been conducted to compare the relative efficacy of different biologics targeting IL-5 in EGPA. Recently, Menzella et al. described remarkable improvements in asthma and ear–nose–throat symptoms in an EGPA patient after switching from mepolizumab to benralizumab, which was also consistent with the results reported by Bormioli et al.<sup>27,28</sup> These might result from a better ability of benralizumab to reduce the number of eosinophils in various tissues by 90%–100%.<sup>10,27</sup> Moreover, some studies suggest that concurrent use of mepolizumab and rituximab may be more beneficial for the treatment of ANCA-positive EGPA patients.<sup>11,29,30</sup> Therefore, the relative efficacy of biologics in each patient may be influenced by the multiple and different mechanisms involved.<sup>30</sup>

In conclusion, EGPA is a heterogeneous disease involving different mechanisms, and the optimal treatment strategies for these patients remain unclear. Experience from our case suggests that switching to an anti-IL-5 biologic may be considered in EGPA patients having an incomplete or poor response to omalizumab. Our results may also provide insights into the complex interaction between eosinophilic inflammation and vasculitis in these patients. Further

studies are required to investigate the relative therapeutic benefits between different biologics and the role of precision medicine in EGPA.

## CONFLICT OF INTEREST

None declared.

## AUTHOR CONTRIBUTION

Ping-Hung Kuo provided conception and design of the article. Yu-Hsuan Chen drafted the first version of the manuscript. Ping-Hung Kuo provided professional advice and revised the manuscript, and both authors agreed for the final version of the manuscript.

## ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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