Effect of Mepolizumab on reducing ANCA levels in eosinophilic granulomatosis with polyangiitis: a case series and review of the literature

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Main text;

To the editor,

Eosinophilic granulomatosis with polyangiitis (EGPA) is anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis with eosinophilia[1]. Mepolizumab, an anti-IL-5 antibody, has been shown to maintain remission in EGPA patients, contribute to reduced use of oral steroids, and reduce the frequency of relapses[2]. However, the effect of mepolizumab on ANCA remains unclear, as only case reports have been published so far. Herein, we present a case series where the effect of mepolizumab on ANCA values in EGPA is evaluated and a synthesis report of the published cases.

We conducted a retrospective cohort study at Sagamihara Hospital and Shonan Kamakura General Hospital. From April 2004 to March 2022, 710 cases with EGPA disease insurance coverage at these hospitals were identified, and 166 cases diagnosed as EGPA according to the American College of Rheumatology 1990 criteria and the International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHSS) were extracted using medical records (Figure 1). Of the 61 patients treated with mepolizumab, 44 cases who were ANCA-negative at onset and 6 cases whose ANCA levels were negative due to use of systemic steroids or immunosuppressants were excluded. The remaining 11 patients (nine with Myeloperoxidase anti-neutrophil cytoplasmic antibodies (MPO-ANCA), and two with Proteinase 3 anti-neutrophil cytoplasmic antibodies) were included in the study (Tables S1, S2).

The blood eosinophil count was significantly lower after treatment, and many cases showed low values even before mepolizumab treatment (Figure 2A). On the other hand, ANCA (median and interquartile range U/mL) showed a clear decrease ($p = 0.0014$) after mepolizumab treatment (4.0 [1.0-7.1] U/mL) compared to ANCA levels before treatment (11.0 [6.3-28.7] U/mL) (Figures 2B-1 and 2B-2). Corticosteroid doses and Birmingham Vasculitis Activity Score (BVAS) decreased after mepolizumab treatment (Figure 2C, D), suggesting that mepolizumab improved EGPA activity and decreased ANCA levels, despite reduced corticosteroid levels (median and interquartile range mg/day before mepolizumab; 7.0 [4.0-10.0] U/mL, after mepolizumab; 4.0 [2.0-5.0] U/mL).

Next, we created a synthesis report of the published cases (Supplementary Material). Of the 90 relevant articles, 16 articles that used biologics preparations other than mepolizumab, 58 articles in which ANCA

was negative, and 12 articles in which ANCA was not measured before and after antibiotic treatment were excluded; 4 articles were included (Figure S1). All 12 eligible cases were MPO-ANCA-positive, and ANCA reduction was confirmed with mepolizumab in 10 patients (Table S1).

There have been no large-scale reports that mepolizumab reducing ANCA levels, and the reason why mepolizumab lowered ANCA levels is unknown. Based on reports, B cell-activating factor and a proliferation-inducing ligand produced by eosinophils act on B cells[3], and IL-5 promotes antibody production from B cells in mice[4]. It is also possible that blocking IL-5 suppressed antibody production in B cells directly. However, in the present study, serum IgG and IgE levels were not decreased by mepolizumab (Figures E and F), suggesting that the suppression of B cell function cannot explain the decrease in ANCA levels. On the other hand, neutrophil extracellular trap (NET) has been reported as an ANCA production mechanism in granulomatosis with polyangiitis and microscopic polyangiitis[5], and we recently reported the relationship between severe EGPA and eosinophil ETosis[6]. It is also possible that mepolizumab reduced ETosis, resulting in decreased ANCA production. However, further studies are required in the future. In addition, since mepolizumab simultaneously improves EGPA disease activity and reduces ANCA levels, elucidation of the mechanism of action of mepolizumab on EGPA pathology will lead to elucidation of EGPA pathology itself.

Thus, we concluded from case series and literature that mepolizumab significantly reduced ANCA in ANCA-positive EGPA.

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Figure Legends

Figure 1 . Flow chart of the inclusion of ANCA positive EGPA patients. ANCA=anti-neutrophil cytoplasmic antibody, EGPA=eosinophilic granulomatosis with polyangiitis

Figure 2 . Changes in serum eosinophils (A), ANCA (B-1 and B-2), GCs dose (C), BVAS (D), serum IgE (E), and serum IgG (F) due to treatment of GCs or mepolizumab. ANCA=anti-neutrophil cytoplasmic antibody, BVAS=Birmingham Vasculitis Activity Score, GCs=glucocorticoids treatment, Mepo=mepolizumab treatment.

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Conflicts of interest

YK received honoraria for lectures from AstraZeneca (AZ), GlaxoSmithKline (GSK) and Sanofi; KS received honoraria for lectures from AZ, GSK, Kyorin Co, Ltd, Novartis, Sanofi and Taiho Co, Ltd; MT received honoraria for lectures from AZ, GSK, Novartis and Sanofi and grant support from GSK

Authors‘ contributions

YK, KW, YN and MT conceived and designed the study. YK, KW and YN collected the data. YK wrote the article. YF, MI, MT and KS critically revised the article. YK, KW and MT involved in the literature search.

Supplementary Information

Supplementary Figure 1. Flow diagram of included study

Supplementary Table 1. Baseline characteristics of 11 individuals

Supplementary Table 2. Changes in laboratory values due to treatment.

Supplementary Table 3. Summary of analyzed case reports on the administration of Anti-IL-5 for EGPA.

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