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Letter to the Editor

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Letter to the Editor (Case report)

Successful combination therapy of mepolizumab and dupilumab in a patient with EGPA: a future therapeutic option?

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Key message

- The combination therapy of dupilumab and mepolizumab is safe and effective for treating EGPA.

Dear Editor, Mepolizumab, an anti- IL-5 monoclonal antibody, is recommended as both induction and maintenance therapy for patients with eosinophilic granulomatosis with polyangiitis (EGPA) presenting with non-organ/life-threatening disease [1]. Nonetheless, there have been some concerns about the efficacy of mepolizumab in managing sinonasal symptoms in routine care [2, 3]. Dupilumab is an IL-4 receptor alpha antagonist approved for the treatment of chronic rhinosinusitis with nasal polyposis, asthma, atopic dermatitis, prurigo nodularis and eosinophilic oesophagitis. Given the favourable results of dupilumab in treating chronic rhinosinusitis and the perceived limitations of mepolizumab in this regard, a combination of these medications could hold promise for improving clinical outcomes in patients with EGPA and challenging-to-treat nasal symptoms. However, caution is needed when using dupilumab in EGPA, since there have been cases of dupilumab-induced eosinophilia and EGPA reported in the literature, which could potentially mean a higher risk for relapses of the disease [4].

We present a case of a 47-year-old woman with a diagnosis of EGPA, which was established based on late-onset asthma and nasal polyposis with pansinusitis at the age of 35, eosinophilia (maximum 0.9×10^9/l) and urticarial-like cutaneous lesions in the hands, feet and lower legs with a biopsy compatible with eosinophilic vasculitis at the age of 36, and eosinophilic oesophagitis at the age of 43. Proteinase 3- and myeloperoxidase antineutrophil cytoplasmic antibodies were negative. She was progressively started on deflazacort (up to 30 mg/day), hydroxychloroquine 400 mg/day, methotrexate 20 mg/week, azathioprine 100 mg/day and colchicine 1 mg/day at the age of 36 years. At the age of 44, she was referred to our rheumatology department still experiencing multiple exacerbations of her sinonasal symptoms, dysphonia and cough, requiring increasing glucocorticoid doses and repeated cycles of antibiotic therapy. Gradually, her medication was adjusted, leaving her on methotrexate 20 mg/week and deflazacort 6 mg/day, at which point her cutaneous lesions recurred and an increase in eosinophilia was detected (0.8×10^9/l). Therefore, mepolizumab 300 mg subcutaneously every 4 weeks was started, and subsequently methotrexate was tapered down to 15 mg/week and deflazacort discontinued. Despite notable clinical improvement in asthma control (with no exacerbations and normal lung function tests), skin manifestations and eosinophilia, her sinonasal symptoms remained challenging to manage, particularly due to persistent nasal polyposis and sinusitis. Consequently, at the age of 47, the patient was started on dupilumab 300 mg subcutaneously every 2 weeks, in addition to mepolizumab. To prevent potential drug toxicity, methotrexate was also stopped. Two months after this therapeutic change, the skin lesions resurged, prompting reintroduction of methotrexate 10 mg/week with benefit. Three months post-initiation of dupilumab, she reported significant improvement of her sinonasal symptoms. Follow-up computed tomography of her paranasal sinuses at 4 months revealed a marked reduction in polyposis and sinusitis compared with a scan performed 2 years prior. At this time, there was a slight, asymptomatic elevation in eosinophils (1.1×10^9/l), with subsequent levels ranging from 0.1 to 0.4×10^9/l. The patient remains symptom-free after 12 months of combined therapy, including the absence of sinonasal symptoms and the need for oral glucocorticoid therapy. Her Birmingham Vasculitis Activity Score stands at 0 and the Vasculitis Damage Index is 3. Importantly, the patient has tolerated this combination therapy well without any documented adverse events.

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Table 1. Case series and reports on the association of mepolizumab and dupilumab in various diseases

Authors	Type of manuscript (No. of patients on mepolizumab and dupilumab)	Age/sex	Disease(s)	Therapeutic regimen	Follow-up time on dual therapy	Response	Adverse events
Pitlick and Pongdee, 2022 [5]	Case series (4 patients)	54/M	HEP + atopic dermatitis	Mepolizumab 300 mg q4w + Dupilumab 300 mg q2w	24 months	Improvement in eosinophilia; the rest not reported	No
		41/F	EGPA + CRSwNP	Mepolizumab 300 mg q4w + Dupilumab 300 mg q2w	1 month	Improvement in eosinophilia; the rest not reported	No
		40/M	Severe asthma + CRSwNP	Mepolizumab 100 mg q4w + Dupilumab 300 mg q2w	15 months	Not reported	No
		55/M	Non-specific inflammatory lung disease	Mepolizumab 100 mg q4w + Dupilumab 300 mg q2w + Omalizumab 375 mg q4w	24 months	No improvement	No
Lommatzsch *et al*. 2022 [6]	Case series (3 patients)	49/M	Severe asthma + CRSwNP	Combination therapy (regimen not reported)	6 months	In all patients: improved asthma control (no asthma exacerbations, no need for oral GC) and improvement in ACT and FEV1	No
		52/F	Severe asthma + CRSwNP + NERD		3 months		
		44/M	Severe asthma + atopic dermatitis		36 months		
Otten *et al*. 2023 [7]	Case series (2 patients)	Not reported	Severe asthma + CRSwNP	Combination therapy (regimen not reported)	≤ 12 months Not reported	Disease control Not reported	Not reported
Serajeddini *et al*. 2023 [8]	Case series (2 patients)	60/M	Severe asthma + CRSwNP	Combination therapy (regimen not reported)	Not reported	Symptom control on ACQ, stopped disease exacerbations, improved sinus disease with no mucus observed on CT, no need for oral GC, no eosinophilia, improvement in FEV1 and FeNO	No
		16/F	Severe asthma	Combination therapy (regimen not reported)	Not reported	ACQ improvement (without symptom control), stopped disease exacerbations, reduced oral GC dose, decreased the mucus observed on CT, no eosinophilia, improvement in FEV1 and FeNO	No
Matsumoto *et al*. 2023 [9]	Case series (1 patient)	52/M	Severe asthma + atopic dermatitis + chronic spontaneous urticaria	Combination therapy (regimen not reported)	Not reported	Improved skin manifestations; suboptimal asthma management, motivating switch in therapy	No
Numata *et al*. 2021 [10]	Case series (1 patient)	Not reported	Severe asthma	Combination therapy (regimen not reported)	Not reported	Moderate improvement in GETE score	Not reported

(continued)

Table 1. (continued)

Authors	Type of manuscript (No. of patients on mepolizumab and dupilumab)	Age/sex	Disease(s)	Therapeutic regimen	Follow-up time on dual therapy	Response	Adverse events
Curtiss *et al*. 2023 [11] (abstract only)	Case series (1 patient)	42/M	Severe asthma + ABPA	Combination therapy (regimen not reported)	Not reported	Improved asthma control (tapered down oral GC dose; reduced IgE serum levels); one disease exacerbation	Not reported
Iwadate *et al*. 2023 [12]	Case report	60/M	EGPA + atopic dermatitis	Mepolizumab 300 mg q4w + Dupilumab 300 mg q2w	12 months	Rapid improvement in skin manifestations (within a month), decrease in serum IgE levels, without EGPA exacerbation and GC dose reduction.	No
Anai *et al*. 2022 [13]	Case report	42/M	Severe asthma + EGPA (diagnosed after introduction of dupilumab in monotherapy)	Mepolizumab 300 mg q4w + Dupilumab 300 mg q2w	4 months	Improvement of dyspnea and FEV1 (improved from 3.84 l to 4.43 l in three months), decreased FeNO, no eosinophilic count elevation, improvement in ACT	No
Hamada *et al*. 2022 [14]	Case report	47/M	Severe asthma + CRSwNP	Cycling therapy: Mepolizumab 300 mg q8w alternated with Dupilumab 300 mg q2w (for one month) every other month	12 months	Improved asthma control (no asthma exacerbations, no need for oral GCs or SABA), no eosinophilic count elevation, resolution of nasal polyps (on CT scan by the Lund-Mackay score), no decrease in ACT	No
Philipenko *et al*. 2020 [15] (abstract only)	Case report	28/M	Severe asthma + atopic dermatitis + dupilumab-induced conjunctivitis	Combination therapy (regimen not reported)	Not reported	Improved asthma control (no asthma exacerbations, marked improvement in ACQ), rapid resolution of blood eosinophilia and of dupilumab-induced conjunctivitis	Not reported

ABPA: allergic bronchopulmonary aspergillosis; ACQ: asthma control questionnaire; ACT: asthma control test; CRSwNP: chronic rhinosinusitis with nasal polyps; EGPA: eosinophilic granulomatosis with polyangiitis; FeNO: fractional exhaled nitric oxide; FEV1: forced expiratory volume in 1 s; GC: glucocorticoids; GETE: global evaluation of treatment effectiveness; HEP: hypereosinophilic syndrome; NERD: non-steroidal anti-inflammatory drug exacerbated respiratory disease; q2w: every 2 weeks; q4w: every 4 weeks; q8w: every 8 weeks; SABA: short acting beta agonists.

This case reports a successful combination therapy involving mepolizumab and dupilumab in a patient with EGPA, which yielded notable improvement in clinical manifestations, particularly in sinonasal symptoms, without associated adverse events. In our literature review, we identified 18 cases of patients who underwent this dual therapy for different diseases, and notably, no adverse events were reported (Table 1). However, only in three cases, this treatment was used for patients with EGPA. Similar to our case, Pitlick and Pongdee [5] reported adding dupilumab to the treatment regimen with mepolizumab in a patient with EGPA and chronic rhinosinusitis with nasal polyposis, prompted by difficult-to-control nasal symptoms. However, this combined therapy was only given for 1 month, whereas in our case, the follow-up duration of the dual treatment extended for 12 months. Iwadate *et al.* [12] also reported a case of a patient diagnosed with EGPA treated with mepolizumab in whom dupilumab was started, with success, but to control atopic dermatitis, not chronic rhinosinusitis. Lastly, Anai *et al.* [13] described a case of severe eosinophilic asthma with insufficient response to mepolizumab, which motivated a switch to dupilumab. This alteration induced symptoms of active vasculitis, such as fever, sinusitis and lung infiltrates, and the patient was diagnosed with EGPA, requiring the addition of mepolizumab for control of the asthma and systemic manifestations of EGPA. To the best of our knowledge, this is the first report of a patient with EGPA and chronic rhinosinusitis, who has been successfully treated with dual inhibition of IL-4 and IL-5, with a follow-up duration of 1 year. We believe this is a safe and promising strategy to improve difficult-to-treat sinonasal symptoms in patients with EGPA under mepolizumab; however, further research is needed to validate the long-term efficacy and safety of this dual therapy in EGPA.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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References

1. Hellmich B, Sanchez-Alamo B, Schirmer JH *et al.* EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Ann Rheum Dis 2024;83:30–47.
2. Wechsler ME, Akuthota P, Jayne D *et al.*; EGPA Mepolizumab Study Team. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. New Engl J Med 2017;376:1921–32.
3. Molina B, Padoan R, Urban ML *et al.* Dupilumab for relapsing or refractory sinonasal and/or asthma manifestations in eosinophilic granulomatosis with polyangiitis: a European retrospective study. Ann Rheum Dis 2023;82:1587–93.
4. Persaud P, Karmali R, Sankar P, Majid M. Dupilumab-associated eosinophilic granulomatosis with polyangiitis. Cureus 2022; 14:e27670.
5. Pitlick M, Pongdee T. Combining biologic therapies involving anti-IgE, anti-IL5, anti-IL5R and anti IL-4/IL-13: experience from a large academic health system. J Allergy Clin Immunol 2022; 149:AB193.
6. Lommatzsch M, Suhling H, Korn S *et al.* Safety of combining biologics in severe asthma: asthma-related and unrelated combinations. Allergy 2022;77:2839–43.
7. Otten J, Van Der Lans R, De Corso E *et al.* Evaluation of switching or simultaneous use of biologic treatment in patients with severe chronic rhinosinusitis with nasal polyps and severe asthma. Considerations in clinical decision making. Expert Rev Clin Immunol 2023;19:1041–9.
8. Serajeddini H, Garrido CV, Bhalla A *et al.* A case series of dual biologics therapy for severe asthma. J Allergy Clin Immunol Pract 2023;11:335–40.e2.
9. Matsumoto T, Sakurai Y, Tashima N *et al.* Dual biologics for severe asthma and atopic dermatitis: synopsis of two cases and literature review. Respirol Case Rep 2024;12:e01266.
10. Numata T, Araya J, Miyagawa H *et al.* Effectiveness of switching biologics for severe asthma patients in japan: a single-center retrospective study. JAA 2021;14:609–18.
11. Curtiss ML, Smith WB, Trevor J. Steroid-sparing effects of dual biologic therapy in refractory ABPA. Am J Respir Crit Care Med 2023;207:A3077.
12. Iwadate Y, Arinuma Y, Matsueda Y *et al.* A case of dupilumab combination therapy for exacerbation of atopic dermatitis in a patient with eosinophilic granulomatosis with polyangiitis treated with mepolizumab. Modern Rheumatol Case Rep 2024; 8:159–62.
13. Anai M, Yoshida C, Ozono K *et al.* Successful concomitant therapy with mepolizumab and dupilumab for atypical eosinophilic granulomatosis with polyangiitis. Allergol Int 2022;71:259–61.
14. Hamada S, Ogino E, Yasuba H. Cycling biologic therapy for severe asthma. Pulmonology 2022;28:65–7.
15. Philipenko B, Walker B, Mitchell P, Ramsahai M. Dual biologic therapy with mepolizumab a novel solution to dupilumab-induced conjunctivitis. Eur Respir J 2020;56:2255.

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