Newly diagnosed eosinophilic granulomatosis with polyangiitis in patients on biologics for severe asthma: A multicenter case series

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Clinical Implications

The emergence of eosinophilic granulomatosis with polyangiitis in patients with severe asthma receiving type 2 biologics is rare. In our series, it usually followed systemic steroid tapering, but there was no clear relationship between the timing and rate of steroid tapering and eosinophilic granulomatosis with polyangiitis emergence.

Biologic therapies for severe asthma (SA) target type 2 (T2) inflammatory pathways and have potent oral corticosteroid (OCS) sparing capacity, enabling patients to taper off maintenance OCS (mOCS). Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare small to medium vessel vasculitis characterized by asthma (often severe), multisystem involvement, and blood and tissue eosinophilia. There are reports of emergent EGPA in patients who have been receiving T2 biologics.[1,2] It is unclear whether this phenomenon is related to mOCS tapering unmasking preexisting EGPA and whether inflammatory biomarkers before the biologic can predict the emergence of EGPA. To address these uncertainties, we performed a multicenter retrospective study. All members of the 28 countries in the European Respiratory Society Severe Heterogeneous Asthma Research Patient-Centered Collaboration were invited to submit details of patients who developed EGPA while receiving a T2 biologic.

All patients provided signed consent. Table E1 (in this article's Online Repository at www.jaci-inpractice.org) describes the cases. Results are presented as medians (interquartile ranges [IQR]) unless otherwise specified. We performed analyses using R software (version 4.3.0, R Core Team, Vienna, Austria). Because of modest statistical power, we conducted only descriptive analyses and did not perform significance testing.

A total of 27 patients (52% female) from 11 countries were reported. Six were excluded from the current analysis owing to historical hypereosinophilia (>3,000 cells/μL) and therefore the possibility of preexisting EGPA. Of the remainder, all had adult-onset asthma and 18 of 21 (86%) had comorbid sinus disease. One patient used dupilumab (5%), one omalizumab (5%), three mepolizumab (14%), and 16 benralizumab (76%). All patients were receiving the biologic dose licensed for asthma.

The diagnosis of EGPA was made based on the American College of Rheumatology 2022[3] (17 patients) and/or the Mepolizumab in Relapsing or Refractory EGPA trial criteria[4] (13 patients) (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). The most common additional features were worsening sinonasal symptoms or abnormalities (14 of 21; 67%) and pulmonary infiltrates (14 of 21; 67%). Moreover, 10 of 21 patients were newly anti-neutrophil cytoplasmic antibody positive (48%) and nine of 21 had a biopsy suggestive of vasculitis (43%).

Of 21 patients, 16 (76%) were receiving mOCS at biologic initiation (median dose 10 mg/day; IQR, 7.5-10/day). Patients who were taking mOCS had received a higher OCS load than those not taking mOCS (who had received OCS for exacerbations) in the year before the biologic: 3,320 mg (IQR, 2208-4100 mg) versus 1,100 mg (IQR, 800-1,400 mg). Steroid tapering started 4 weeks (IQR, 4-9 weeks) after biologic initiation, and EGPA was diagnosed 24 weeks (IQR, 12-36 weeks) after tapering started. By this time, 14 of 16 patients (88%) either stopped taking mOCS (eight of 16) or were receiving 5 mg or less daily (six of 16) (Figure 1). There was no clear relationship between the timing and rate of OCS tapering and EGPA development. Eosinophilic granulomatosis with polyangiitis was diagnosed 28 weeks (IQR, 22-52 weeks) after biologic initiation, and the time from biologic initiation to EGPA diagnosis did not depend on mOCS use at baseline.

The peak pre-biologic blood eosinophil count (BEC) was high at 1,050 cells/μL (IQR, 800-1,560 cells/μL; maximum, 2,040 cells/μL) but not positively correlated with BEC at the EGPA diagnosis (900 cells/μL; IQR, 200-3,400 cells/μL). In three patients, all of whom were receiving benralizumab, BEC was 0 when EGPA was diagnosed. There was no obvious relationship between baseline FeNO (at biologic initiation) and FeNO at EGPA diagnosis. At biologic initiation, six patients had an FeNO of greater than 100 ppb; at EGPA diagnosis, six patients had an FeNO of greater than 100 ppb. Two patients had an FeNO of greater than 100 ppb at both time points.

At EGPA diagnosis, 18 of 21 patients (86%) presented with worsening asthma symptoms and 16 of 21 (76%) were admitted to the hospital. Figure 2 shows the prevalence of symptoms when EGPA was diagnosed. The management of EGPA included steroids in all 21 patients. The biologic was switched in seven of 21 patients (33%), all of whom switched to mepolizumab (five patients at 100 mg four times weekly and two patients at 300 mg four times weekly).

The development of EGPA during administration of a T2 biologic is rare. The presenting symptoms in the current cohort

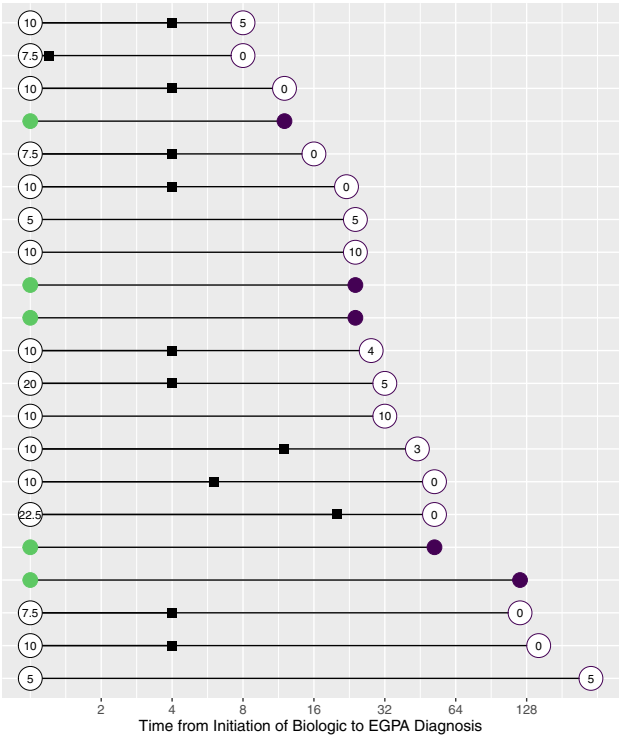

FIGURE 1. Time from biologic initiation to diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA). *White circles* show oral corticosteroid dose at biologic initiation and at EGPA diagnosis. *Green circles* indicate patients who were not receiving maintenance oral corticosteroids at biologic initiation. *Black squares* indicate when steroid tapering commenced.

were similar to those in the published literature,[5] which suggests that T2 biologic use does not alter the clinical presentation. In the European EGPA study group, 30 of 529 patients with EGPA (5.7%) developed EGPA during T2 biologic use, 13 of whom (43%) received anti-IL-5/5R biologics at baseline.[1] In our case series, of 3,720 patients with SA, 21 cases of EGPA were reported (0.6%). Although this figure is susceptible to recall bias, it indicates overall the low prevalence of this phenomenon. Almost all patients in our case series (90%) were receiving anti-IL-5/5R biologics, higher than the proportion in the European EGPA study group.

Most patients in our case series developed eosinophilia despite the use of biologics that directly reduce eosinophil numbers. The mechanisms underlying this are unclear but may involve pathways that were previously suppressed by the broader immunosuppressive effect of steroids and are activated on steroid tapering. All the patients in our case series had a high steroid burden before the biologic, and a higher proportion were receiving mOCS compared with cohorts with SA published in international registries.[6] Most of those receiving mOCS had tapered to low doses before EGPA was diagnosed. This suggests that the use of OCS may have been masking an underlying vasculitis in some patients, or the use of OCS was preventing progression to overt systemic disease. It remains unclear whether EGPA would have occurred despite the use of OCS and whether T2 biologics themselves influenced the timing or severity of EGPA onset.

For four of the 21 patients in the current cohort, there had been a clinical suspicion of EGPA before biologic initiation. In these patients, EGPA was diagnosed earlier than for the rest of the cohort, at 20 weeks (IQR, 14-24 weeks) versus 32 weeks (IQR, 24-69 weeks) after biologic initiation. Almost all patients had sinonasal disease (86%), higher than reported that within national and international SA registries,[7] and the peak historical BEC (1,050 cells/μL; IQR, 800-1,560 cells/μL) was also higher than that observed in straightforward T2-high SA. For example, within the UK SA registry, peak pre-biologic BEC is 700 cells/μL (IQR, 460-1,100 cells/μL).[8] These clinical features likely raised clinical suspicion.

Almost 50% of the patients newly received the diagnosis of being ANCA positive. This is similar to the European EGPA study group cohort of patients who developed EGPA while receiving biologics for SA.[1] Real-world cohorts of SA patients with comorbid EGPA report less than 30% ANCA positivity.[9] Although ANCA negativity is more closely associated with eosinophil biology, the higher prevalence of ANCA positivity in this cohort leads us to speculate that these patients may have been more predisposed to a vasculitic phenotype that was able to manifest despite T2 biologic therapy. Alternatively, the underlying disease severity may have been refractory to suppression by T2 biologic therapy. Whether the use of T2 biologics, especially anti-IL-5/5R biologics (used by 19 of 21 patients), prevents the development of ANCA-negative EGPA needs further investigation.

In our case series, baseline biomarkers and peak pre-mOCS eosinophil count bore no relationship to biomarkers at EGPA onset. Because of the small numbers, we were unable to evaluate the statistical correlation between biologic type and EGPA development. Pharmacovigilance data indicate that EGPA cases have been reported with all T2 biologics,[2] suggesting the involvement of factors other than biologic-specific mechanisms.

This case series has several limitations related to its being retrospective and susceptible to recall bias. Owing to its multicenter nature, heterogeneity in clinical management between countries cannot be excluded. Although no patients had received the diagnosis of EGPA when they began taking T2 biologics, the diagnosis of EGPA is challenging, and some patients might have had undiagnosed disease from the outset. Finally, in view of the limited numbers, the absence of an obvious relationship between the timing and rate of steroid tapering and EGPA onset deserves further exploration.

We have collated a case series of patients who received the diagnosis of EGPA while taking a T2 biologic for SA. All patients had a high peak BEC and significant steroid burden before the biologic, and most had comorbid sinonasal disease. Most developed symptoms once OCS were tapered, but there was no clear relationship between the timing and rate of tapering and the

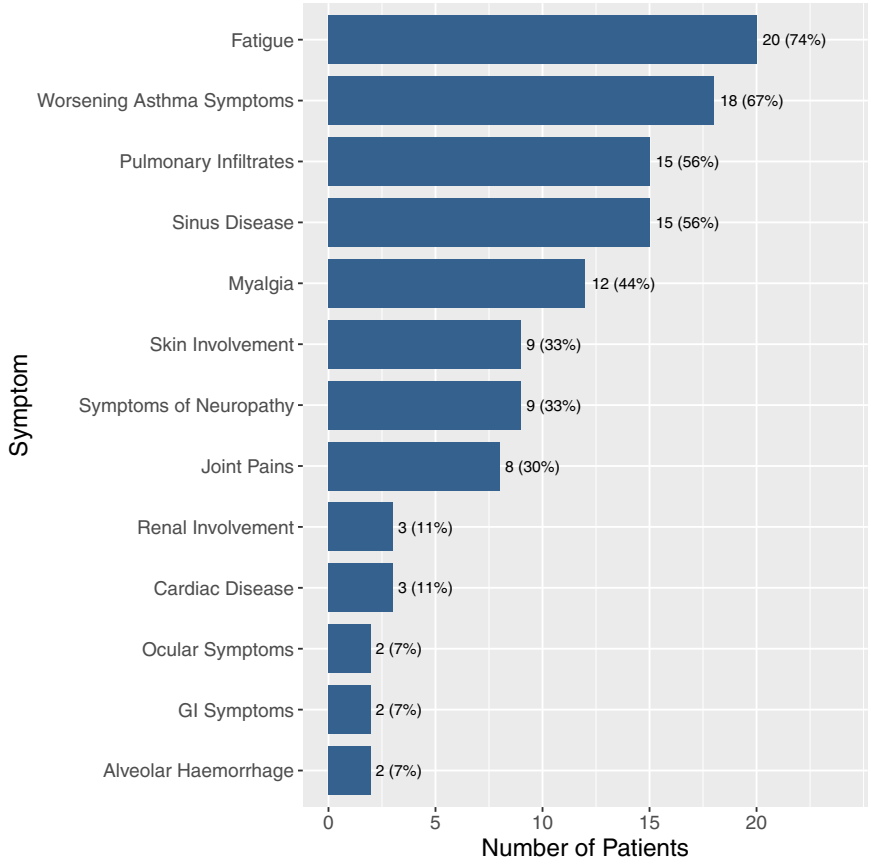

FIGURE 2. Symptoms when eosinophilic granulomatosis with polyangiitis was considered, with number of patients and overall prevalence shown. *GI*, gastrointestinal.

EGPA diagnosis. We hypothesize that removing the broad immunosuppressive effects of OCS may have unmasked preexisting EGPA or allowed disease progression, and therefore clinicians should remain vigilant.

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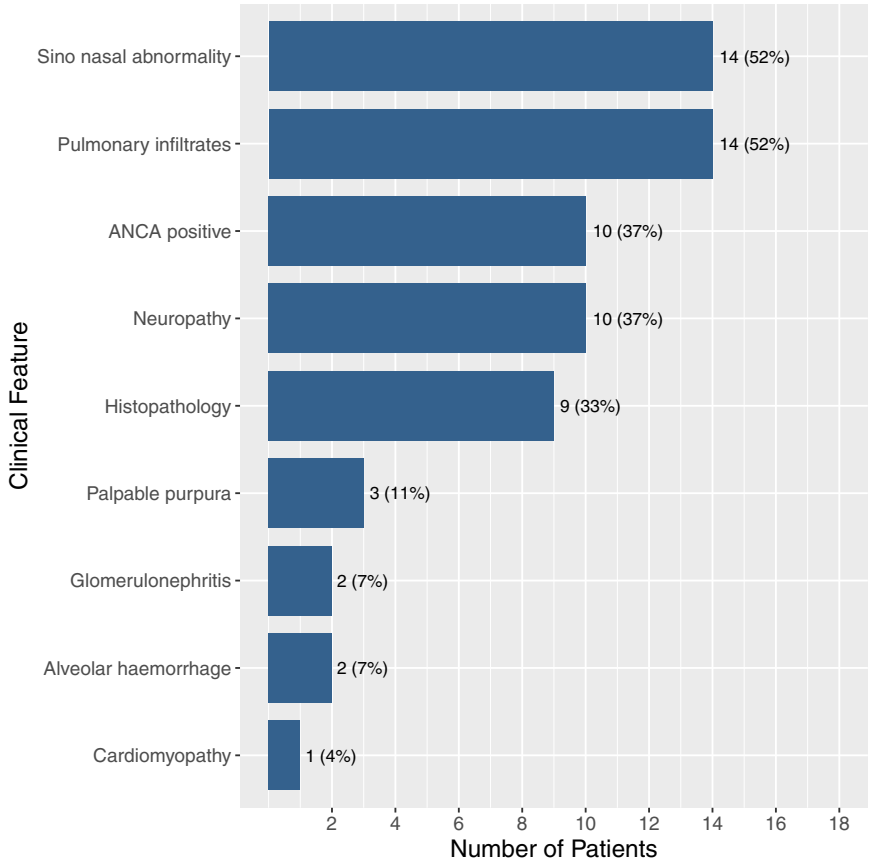

FIGURE E1. Number of patients with each additional feature according to Mepolizumab in Relapsing or Refractory EGPA trial diagnostic criteria. *ANCA*, anti-neutrophil cytoplasmic antibody.

TABLE E1. Summary of 27 patient cases

Patient	Biologic	Peak historic BEC, cells/μL	BEC at biologic start, cells/μL	BEC when EGPA diagnosed, cells/μL	FeNO at biologic start, ppb	mOCS dose at biologic start, mg	mOCS dose when EGPA diagnosed, mg	Estimated amount of oral corticosteroid in previous 12 mo, mg	Time between biologic initiation and clinical consideration of EGPA, wk	Management
1	Benralizumab	1,450	<1,500	300	50-100	10	5	4,200	8	Oral steroids
2	Benralizumab	1,700	<1,500	950	<50	7.5	0	2,700	8	Oral steroids and methotrexate
3	Benralizumab	797	<1,500	5,250	50-100	10	0	300	12	IV steroids and IV cyclophosphamide
4	Benralizumab	780	<1,500	40	>100	N/A	N/A	800	12	Oral steroids, IV steroids, and IV cyclophosphamide
5	Mepolizumab	900	<1,500	900	50-100	7.5	0	3,300	16	Oral steroids and methotrexate
6	Benralizumab	750	<1,500	0	50-100	10	0	4,500	22	Oral steroids, IV steroids, and IV cyclophosphamide Biologic switched to mepolizumab 100 mg monthly
7	Mepolizumab	1,700	<1,500	500	<50	5	0	1,915	24	Oral steroids
8	Mepolizumab	2,000	<1,500	800	<50	10	10	800	24	IV steroids and rituximab
9	Benralizumab	2,040	<1,500	2,040	>100	N/A	N/A	2,260	24	Oral steroids and IV cyclophosphamide. Biologic switched to mepolizumab 300 mg monthly
10	Benralizumab	700	<1,500	1,400	>100	N/A	N/A	1,100	24	Oral steroids and azathioprine. Biologic switched to mepolizumab 100 mg monthly
11	Benralizumab	800	<1,500	3,500	<50	10	4	4,250	28	IV steroids and rituximab
12	Benralizumab	500	<1,500	3,400	<50	20	5	4,300	32	Oral steroids. Biologic switched to mepolizumab 100 mg monthly
13	Benralizumab	1,560	<1,500	170	>100	10	10	1,800	32	Oral steroids, IV steroids, and IV cyclophosphamide

14	Benralizumab	1,500	1,500-5,000	3,200	>100	10	3	3,650	44	Oral steroids, IV steroids, and IV cyclophosphamide
15	Dupilumab	1,060	<1,500	820	50-100	10	0	3,320	52	Oral steroids and IV steroids. Biologic switched to mepolizumab 300 mg monthly
16	Benralizumab (had previously been taking mepolizumab)	840	<1,500	4,800	<50	22.5	0	8,212	52	Oral steroids and azathioprine. Biologic switched to mepolizumab 300 mg monthly
17	Benralizumab	1,500	<1,500	0	>100	N/A	N/A	1,400	52	Oral steroids
18	Benralizumab (had previously been taking mepolizumab)	1,200	<1,500	200	<50	N/A	N/A	800	120	IV steroids
19	Benralizumab	1,000	1,500-5,000	0	50-100	7.5	0	3,800	120	IV steroids and IV cyclophosphamide
20	Omalizumab	2,000	<1,500	21,742	50-100	10	0	4,000	144	IV steroids and IV cyclophosphamide. Biologic switched to mepolizumab 100 mg monthly
21	Benralizumab	1,000	1,500-5,000	15,000	50-100	5	5	2,500	240	Oral steroids, IV steroids, and IV cyclophosphamide. Biologic switched to mepolizumab 100 mg monthly

BEC, blood eosinophil count; *EGPA*, eosinophilic granulomatosis with polyangiitis; *IV*, intravenous; *mOCS*, maintenance oral corticosteroid; *N/A*, not applicable because these patients were not receiving mOCS at biologic initiation. Cases are listed in the order that they appear in Figure 1.