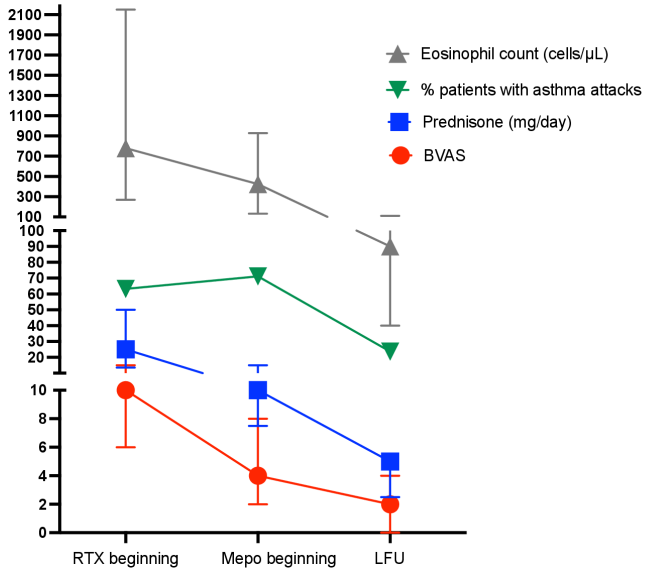
Sequential rituximab and mepolizumab in eosinophilic granulomatosis with polyangiitis (EGPA): a European multicentre observational study

Eosinophilic granulomatosis with polyangiitis (EGPA) is an anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis characterised by eosinophilic (eg, respiratory involvement, cardiomyopathy, gastroenteritis) and vasculitic manifestations (eg, neuropathy, glomerulonephritis).[1]

Rituximab is an established treatment in granulomatosis with polyangiitis and microscopic polyangiitis, and growing evidence indicates that it seems effective also in EGPA, mainly to induce and maintain remission of vasculitic involvement.[2 3] However, its efficacy on respiratory manifestations seems limited. Conversely, the anti-IL5 mepolizumab, recently licensed for relapsing-refractory EGPA, is effective on respiratory manifestations, although it may also partially control systemic ones.[3–5]

Based on the idea that combining treatments with complementary mechanisms of action might induce and maintain remission of both disease components,[6 7] we investigated the efficacy and safety of a regimen based on sequential rituximab and mepolizumab for the control of EGPA.

This multicentre, European, retrospective study included patients meeting the American College of Rheumatology classification criteria for EGPA or the eligibility criteria proposed in the MIRRA trial.[1] Only patients who received therapy with rituximab (any dosage), and subsequent treatment with mepolizumab (100–300 mg/4 weeks) within 12 months from last rituximab



	Rituximab beginning (n=38)	Mepolizumab beginning (n=38)	Last follow-up (n=38)	P-value
Time elapsed, months (median, IQR)	-	5 (3-11) from last Rituximab dose	26 (13-33) from Mepolizumab beginning	
Efficacy				
Remission (n,%)	2 (5.3%)	6 (15.8%)	11 (28.9%)	0.003
Active disease (n,%)	36 (94.7%)	32 (84.2%)	27 (71.1%)	
BVAS (median, IQR)	10 (6-15)	4 (2-8)	2 (0-4)	<0.001
Eosinophil count, cells/µL (median, IQR)	780 (270-2150)	424 (133-929)	90 (40-110)	<0.001
Asthma attacks in the last months (median, IQR)	1 (0-3)	1 (0-2)	0 (0-0)	<0.001
Patients with 1+ asthma attacks	24 (63.2%)	27 (71.1%)	9 (23.7%)	<0.001
ANCA positivity (n,%)	12/17 (70.6)	5/16 (31.3%)	2/17 (11.8%)	0.001
Concomitant treatments				
Glucocorticoids	37 (97.4%)	37 (97.4%)	31 (81.6%)	0.034
Prednisolone dosage, mg/day (median, IQR)	25.0 (13.5-50.0)	10.0 (7.5-15.0)	5.0 (2.5-5.0)	<0.001
Immunosuppressants	22 (57.9%) AZA (n=8); MTX (n=8); MMF (n=3); CSA (n=3)	12 (31.6%) AZA (n=5); MTX (n=3); MMF (n=3); CSA (n=1)	8 (21.1%) MMF (n=4); AZA (n=2); MTX (n=2)	<0.001

Figure 1 Efficacy of sequential rituximab and mepolizumab. P values for the paired comparison between data at last follow-up and at the start of rituximab. ANCA, anti-neutrophil cytoplasmic antibody; AZA, azathioprine; BVAS, Birmingham Vasculitis Activity Score; CSA, ciclosporin; MMF, mycophenolate mofetil; MTX, methotrexate.

administration, without other induction/maintenance therapies in the meanwhile, were included.

Treatment efficacy was assessed considering disease activity (by the Birmingham Vasculitis Activity Score, BVAS), eosinophil count and glucocorticoid dose.[1] Asthma attacks and adverse events (AEs) were also assessed.

The study received ethical approval (University of Florence IRB; ref.16821_OSS); as this is a retrospective study, patient representatives were not involved in designing the study.

We included 38 patients (53% female), whose median age at diagnosis was 52 years (IQR 42–61). Eighteen (47%) were ANCA positive, mostly with an anti-myeloperoxidase specificity (17/18). Rituximab (1 g every 2 weeks (q2w) in 26/38; 375 mg/m^2/week for 4 weeks in 11/38; 500 mg q2w in 1/38) was mostly initiated for the control of active disease (36/38, median BVAS of 10 (IQR 6–15), median eosinophil count of 780 (270–2150) cells/µL), particularly of systemic (±respiratory) manifestations (33/38; 87%) (figure 1). Sixty-three per cent of patients had experienced one or more asthma attacks in the preceding month. At rituximab initiation, 97% of patients were receiving glucocorticoids (median prednisone dose of 25 mg/day (13.5–50)), and 58% immunosuppressants.

Mepolizumab (100 mg every 4 weeks (q4w) in 36/38) was started after a median of 5 months (3–11) from last rituximab dose, usually for the presence of active manifestations (32/38, 84%; median BVAS of 4 (2–8)), mostly respiratory (28/32). All except one patient were still receiving glucocorticoids (97%; median dose of 10 mg/day (7.5–15), mostly for respiratory manifestations), and 32% immunosuppressants.

After a median of 26 months (13–33) from mepolizumab initiation, the median BVAS significantly decreased to 2 (0–4), as well as the median eosinophil count (90 cells/µL (40–110)), and the use of glucocorticoids and immunosuppressants (median prednisone dose of 5 mg/day (2.5–5); 21% of patients on immunosuppressants). Only 24% of patients reported asthma attacks in the previous month. Notably, following sequential rituximab and mepolizumab treatment, ANCA negativisation occurred in a relevant proportion of patients. Indeed, at the start of rituximab, 17 out of the 18 ANCA+ patients at EGPA diagnosis had available data on ANCA status, and 12 of them still tested positive

(70.6%). At the start of mepolizumab, 5 out of 16 patients with available data were positive (31.3%). At last available follow-up, only 2 out of 17 patients with available results tested ANCA+, the remaining displaying ANCA negativisation (p=0.001 as compared with the time of rituximab beginning).

Both rituximab and mepolizumab were well tolerated. Six patients had non-serious AEs on rituximab, while five patients had AEs on mepolizumab, including one serious (COVID-19 pneumonia).

Taken together, our findings confirmed previous literature evidence on the efficacy of rituximab for the control of systemic EGPA manifestations,[2] while proving limited efficacy on respiratory symptoms. Conversely, the introduction of mepolizumab allowed reducing asthma attacks, while also contributing to the sustained remission of systemic features and glucocorticoid sparing.

Notably, we confirmed[5] that in real clinical practice, mepolizumab was mostly used at the dosage for eosinophilic asthma (100 mg/4 weeks), rather than at the dosage approved for EGPA (300 mg/4 weeks).[4]

The tolerability of the sequential rituximab-mepolizumab treatment was good.

Our study has some limitations, mostly related to this retrospective nature. First, data on quality of life and on specific scores of ear-nose-throat involvement could not be retrieved, as they are not routinely collected in medical charts. Second, given the wide time window elapsed between last rituximab administration and start of mepolizumab (up to 12 months), disease flares due to an 'end-of-dose' effect cannot be fully excluded. Third, the small sample size did not allow to conduct separate analysis according to the ANCA status.

Despite these limitations, our findings suggest that a regimen based on sequential rituximab and mepolizumab might be effective to induce and maintain remission of both systemic and respiratory EGPA manifestations.

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