Mepolizumab 100 mg in severe asthmatic patients with EGPA in remission phase

Mepolizumab 100 mg in severe asthmatic patients with EGPA in remission phase

MarcoCaminati [a], ErnestoCrisafulli [b], ClaudioLunardi[a], ClaudioMicheletto [c], GiulianaFesti [c], MatteoMaule [d], AlessandroGiollo [e], GiovanniOrsolini [e], GianenricoSenna [a,f]

J Allergy Clin Immunol Pract. 2021 Mar;9(3):1386-1388.
doi: 10.1016/j.jaip.2020.09.025. Epub 2020 Oct 1.

Mepolizumab 100 mg in severe asthmatic patients with EGPA in remission phase

MarcoCaminati [a], ErnestoCrisafulli [b], ClaudioLunardi[a], ClaudioMicheletto [c], GiulianaFesti [c], MatteoMaule [d], AlessandroGiollo [e], GiovanniOrsolini [e], GianenricoSenna [a,f]

[a] Department of Medicine, University of Verona and Verona University Hospital, Verona, Italy
[b] Department of Medicine, Respiratory Medicine Unit and Section of Internal Medicine, University of Verona and Verona University Hospital, Verona, Italy
[c] Cardio-Thoracic Department, Respiratory Unit, Integrated University Hospital, Verona, Italy
[d] Department of Medicine, Specialization Course in Allergy and Clinical Immunology, University of Verona, Verona, Italy
[e] Division of Rheumatology, Department of Medicine, University of Verona and Verona University Hospital, Verona, Italy
[f] Allergy Unit and Asthma Center, Verona University Hospital, Verona, Italy

Clinical Implications

• In patients with eosinophilic granulomatosis with polyangiitis in remission phase and persisting severe steroid-dependent asthma, mepolizumab 100 mg/4 wk prevents vasculitis relapse and maintains asthma control. An “asthma-tailored” dose may be considered in the maintenance phase of eosinophilic granulomatosis with polyangiitis as a steroid/immunosuppressive-sparing agent.

Eosinophilic granulomatosis with polyangiitis (EGPA) and severe eosinophilic asthma share some pathophysiological key features related to the vascular and tissue eosinophilic infiltration and the cytokine cascade it mediates.[1,2] Given the consistent reduction in blood eosinophils and their pathogenic effects in patients with severe asthma treated with mepolizumab at the dose of 100 mg/4 wk, the same drug has been explored in patients with EGPA.[1] The US Food and Drug Administration recently approved mepolizumab 300 mg/4 wk for EGPA.[3] However, no recommendations are currently available on the dose and timing of the anti–IL-5 mAb in the management of vasculitis.[1]

The database of patients with EGPA referring to our center was analyzed to identify subjects with persisting severe eosinophilic steroid-dependent asthma and systemic vasculitis in remission phase. Mepolizumab 100 mg/4 wk was investigated as a maintenance therapy in that subpopulation.

Severe steroid-dependent asthma was defined as asthma requiring systemic corticosteroid for 50% or more of the previous year to prevent it from becoming uncontrolled, according to European Respiratory Society/American Thoracic Society guidelines.[4] EGPA diagnosis was established on

verification of history and presence of asthma, blood eosinophilia of 10%, or absolute eosinophil count greater than 1000 cells/mm^3, and evidence of systemic involvement besides the lung, according to the American College of Rheumatology criteria.[5] Allergic bronchopulmonary aspergillosis and *Strongyloides stercoralis* infection were ruled out.

Eligibility to mepolizumab following the European Regulatory Agency requirements for severe asthma[6] was verified; remission phase of systemic vasculitis was defined as absence of laboratory and clinical signs suggesting extra respiratory organ involvement, and negative anti-neutrophil cytoplasmic antibodies in patients with anti-neutrophil cytoplasmic antibody positivity in the acute phase. Blood eosinophils, FEV_1% of predicted, fractional exhaled nitric oxide (Feno), Asthma Control Test score, and steroid and immunosuppressive treatment were assessed before and 3 and 6 months after mepolizumab initiation. At the same time points, exacerbations and hospitalizations per month were evaluated. Dose tapering of oral steroids first and second immunosuppressive drug was evaluated starting from the second mepolizumab injection, and performed following a careful step-by-step approach in the absence of laboratory and clinical signs suggesting systemic inflammation and organ involvement and in the presence of maintained asthma control, according to the standard of care practice. The study was approved by the local Ethic Committee. Overall, 16 consenting patients (males, 75.0%; mean age, 56.1 years; range, 32-77 years) were enrolled. Atopy was detected in 31.3%. The mean age of asthma onset was 35.3 ± 12.8 years, whereas EGPA occurred at the age of 49.7 ± 12.4 years. At EGPA onset, 37.5% of patients presented anti-neutrophil cytoplasmic antibody positivity and the mean Birmingham Vasculitis Activity Score was 16.1 ± 5.7. Exacerbation of asthma symptoms was present in all the patients, in association with extrarespiratory systemic involvement (Figure 1). The treatment of EGPA acute phase included prednisone (or equivalent; mean daily intake, 46.2 ± 21 mg) and other immunosuppressive agents in 11 patients (68.7%). Severe asthma duration following EGPA acute-phase remission before mepolizumab initiation was on average 4.5 years (range, 11-0.5 years).

As presented in Table I, at the 3- and 6-month follow-up, a significant improvement in blood eosinophils, Asthma Control Test score, FEV_1 %, and exacerbations rate was observed. Oral steroids were completely discontinued in 9 of 16 patients (56.2%), and overall a significant decrease in the average oral corticosteroid daily intake was observed at any time point. At the 6-month follow-up, 2 of the 11 patients under immunosuppressive drug treatment withdrew from that treatment and 4 of them reduced the drug dose without any relapse. No adverse events were recorded.

Our real-life observational study suggests that mepolizumab at the dose of 100 mg/4 wk may have a role as a steroid/immunosuppressive-sparing agent in patients affected by EGPA with systemic vasculitis in remission phase and persisting severe steroid-dependent eosinophilic asthma. Over the study time frame it prevented EGPA relapse and maintained asthma control. Unsurprisingly, Feno did not show a statistically significant change during the study course. Besides eosinophilia, tissue inflammation, IL-13 more than IL-5 as well as infectious and environmental triggers may have an impact on Feno production,[7] and its drivers may be even more complex in EGPA.

Mepolizumab at the dose of 300 mg/4 wk in patients with EGPA was explored by Wechsler et al[8] in a trial, demonstrating its superiority versus standard treatment in terms of the number of patients in remission, time to first relapse, reduction of daily glucocorticoid dose, and circulating eosinophil counts.

In our study, despite the dose of 100 mg/4 wk being investigated, the proportion of patients who were able to discontinue oral steroids was much higher than in the MIRRA trial[8] (56% vs 18%). The different baseline patients' characteristics could provide a potential explanation. In fact in the MIRRA trial, at the time of mepolizumab initiation, the study population was quite heterogeneous in terms of vasculitis activity and organ involvement, whereas in our study we selectively included patients affected by EGPA with systemic vasculitis in remission phase and persisting severe steroid-dependent eosinophilic asthma.

However, despite Food and Drug Administration–approved mepolizumab 300 mg/4 wk for the treatment of EGPA,[3] some aspects, including dose and the best target patients, are still controversial.[1]

In fact, the dose of 300 mg/4 wk versus 100 mg/4 wk approved for severe asthma was not identified through dose-findings studies but it has been proposed to target more consistent and “aggressive” blood eosinophilia commonly characterizing patients with EGPA in comparison with patients with severe asthma. After all, although controversial, a dose-dependent effect has been hypothesized in severe asthma too[9] and the effect of a higher dose of the drug could be explored in nonresponder patients with severe asthma.

The lack of a placebo arm and of direct comparison between 300-mg and 100-mg regimen represent major limitations of our study. Also, the small sample size and short follow-up limit the strength of our findings. However, to our knowledge, our observations suggest for the first time that an “asthma-tailored” dose of mepolizumab may be considered in the long-term management of EGPA,

especially as a steroid/immunosuppressive-sparing agent in the maintenance phase when systemic vasculitis is in remission and severe asthma persists.

Further investigation and larger studies are needed to confirm our results and support specific recommendations.

References

1. Harish, S.A. Schwartz. **Targeted anti-IL-5 therapies and future therapeutics for hypereosinophilic syndrome and rare eosinophilic conditions.** Clin Rev Allergy Immunol, 59 (2020), pp. 231-247
2. V. Cottin, E. Bel, P. Bottero, K. Dalhoff, M. Humbert, R. Lazor, *et al.*, Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires (GERM"O"P). **Revisiting the systemic vasculitis in eosinophilic granulomatosis with polyangiitis (Churg-Strauss): a study of 157 patients by the Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires and the European Respiratory Society Taskforce on eosinophilic granulomatosis with polyangiitis (Churg-Strauss).** Autoimmun Rev, 16 (2017), pp. 1-9
3. U.S. Food and Drug Administration. **Nucala Prescribing information.** Available from: www.accessdata.fda.gov, Accessed 25th Apr 2020
4. K.F. Chung, S.E. Wenzel, J.L. Brozek, A. Bush, M. Castro, P.J. Sterk, *et al.* **International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma.** Eur Respir J, 43 (2014), pp. 343-373
5. A.T. Masi, G.G. Hunder, J.T. Lie, B.A. Michel, D.A. Bloch, W.P. Arend, *et al.* **The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis).** Arthritis Rheum, 33 (1990), pp. 1094-1100
6. European Medicines Agency. **European public assessment report (EPAR) for Nucala** Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/nucala, Accessed 25th Apr 2020
7. M. Caminati, D.L. Pham, D. Bagnasco, G.W. Canonica. **Type 2 immunity in asthma.** World Allergy Organ J, 11 (2018), p. 13

8. M.E. Wechsler, P. Akuthota, D. Jayne, P. Khoury, A. Klion, C.A. Langford, *et al.*, EGPA Mepolizumab Study Team. **Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis.** N Engl J Med, 376 (2017), pp. 1921-1932

9. M. Mukherjee, F.A. Paramo, M. Kjarsgaard, B. Salter, G. Nair, N. LaVigne, *et al.* **Weight-adjusted intravenous reslizumab in severe asthma with inadequate response to fixed-dose subcutaneous mepolizumab.** Am J Respir Crit Care Med, 197 (2018), pp. 38-46

Table I. Trends of asthma-related parameters over study time frame

Variables	T0	T3	T6	*P* value (T0 *vs* T3)	*P* value (T3 *vs* T6)	*P* value (T0 *vs* T6)
Prednisone (mg/die)	8.3 ± 5.7	4.2 ± 5.9	2.3 ± 6.1	**<.001**	**<.001**	**<.001**
Eosinophils (counts/μL)	1015.6 ± 904.6	136.2 ± 119	283.1 ± 702.8	**.001**	.364	**.003**
Asthma Control Test score	19.7 ± 2.4	22.1 ± 1.8	23.4 ± 1.7	**<.001**	**.003**	**<.001**
FEV_1, % predicted	77.4 ± 19.4	83.4 ± 17.6	81.9 ± 17.3	**.007**	.434	.075
Feno value	68.6 ± 59	53.2 ± 40.3	39.8 ± 41.9	.237	.061	.086
Exacerbations (number/mo)	0.33 ± 0.24	0.06 ± 0.13	0.04 ± 0.16	**<.001**	.580	**<.001**
Hospitalizations (number/mo)	0.05 ± 0.08	0.02 ± 0.08	0.00 ± 0.00	.188	.333	**.020**

Values are mean ± SD.

Bold indicates statistical significance ($P < .05$).

Figure 1. Organ involvement at EGPA onset.