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REVIEW

Interleukin-5, Eosinophils, and Interleukin-5 Pathway Inhibitors in Eosinophilic Granulomatosis With Polyangiitis

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Interlukin-5 (IL-5) plays a crucial role in the pathogenesis of eosinophilic granulomatosis with polyangiitis (EGPA) by promoting eosinophil differentiation, activation, and survival. We present here a typical case of EGPA in which treatment with IL-5 pathway inhibitors is prescribed, showing to be beneficial for the patient. We discuss available evidence proving the association between IL-5 and clinical activity in EGPA and review the clinical efficacy and safety of currently approved IL-5 pathway inhibitors (i.e. mepolizumab and benralizumab) that improve disease control, reduce relapse rates, and have significant glucocorticoid-sparing effects in EGPA by reducing eosinophilic inflammation.

Clinical challenge

The patient is a 51-year-old man diagnosed with late-onset asthma complicated by chronic rhinosinusitis with polyposis six years ago. When diagnosed with asthma, his blood eosinophil count (BEC) was between 800 and 1,100 × 10^6/L (eosinophilic asthma). Four years ago, he started to have more frequent and severe asthma exacerbations despite inhaled glucocorticoids and long-acting beta-agonist and was diagnosed during these flares with right brachial vein phlebitis and segmental pulmonary embolism. The work-up also revealed ground glass opacities in the left upper lung lobe on the chest computed tomography, mild bronchial wall thickening, and cardiac involvement, with hypokinesis of mid and distal anteroseptal wall with decreased ejection fraction at 37%. Eosinophil count peaked at 3,600 × 10^6/L at that time, when the diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) was established. Myeloperoxidase (MPO)–antineutrophil cytoplasmic antibodies (ANCA) serology was positive at 65 UA/mL (N < 20). Thrombophilia and primary hypereosinophilic work-up, including a bone marrow study with fluorescence in situ hybridization for FIP1L1-PDGFRA mutation, was negative. He received high-dose glucocorticoids (intravenous [IV] pulses of methylprednisolone for three days, followed by oral prednisone, with a gradual taper) and IV pulses of cyclophosphamide (1200 mg) for six months, followed by maintenance therapy with 200 mg oral azathioprine per day. He recovered, but some cardiac damage remained, with persistent asthma and ear, nose, and throat (ENT) symptoms. Over the past three years, he has been unable to taper down his prednisone below 15 mg/day without experiencing ENT or asthma symptoms, with an eosinophil count between 100 and 800 × 10^6/L during this time. Thus, one year ago, he started 300 mg subcutaneous mepolizumab every four weeks. Before examining the available evidence on the use of anti–interleukin-5 (IL-5) pathway agents in EGPA, it is essential to highlight the central role of IL-5 pathway for the homeostasis and maturation of eosinophils and their biologic functions in EGPA.

IL-5 pathway crucial for eosinophils

Eosinophils, terminally differentiated myeloid cells primarily defending the host from parasites, originate from the bone marrow, where they mature before migrating into peripheral blood. They remain in circulation for a short period (with a half-life inferior to 24 hours) before moving either to peripheral tissues under normal conditions or to sites of inflammation in response to recruitment signals, primarily through IL-5 and eotaxins.[1,2] IL-5 plays a crucial role not only in promoting eosinophil differentiation and mobilization but also in their activation and degranulation[3,4] (Figure 1, left).

IL-5 is produced in vivo by Th2 cells, innate lymphoid cells, mast cells, basophils, and dendritic cells. Even if recent evidence indicates that IL-5 impacts the immune system beyond

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eosinophils,[5,6] they remain the main effector cells responsive to IL-5 signaling.

The effects of IL-5 on eosinophils can be categorized into four key areas: differentiation, migration, activation, and survival.[3] Although IL-5 does not directly induce eosinophil lineage commitment, it is well established that IL-5 receptor alpha (IL-5Ra) expression in bone marrow cells is critical for enhancing the differentiation and proliferation of eosinophil progenitors.[3]

IL-5 accelerates eosinophil migration from the bone marrow to the bloodstream and eventually to target tissues through a process dependent on a β2-integrin known as CD11b/CD18 adhesion molecule.[7] This β2-integrin–mediated adhesion is induced by IL-5 via the MAPK pathway,[8] showing chemotactic activity by increasing eosinophil adhesion to endothelial cells.[9]

In peripheral blood, IL-5 promotes the terminal differentiation of eosinophil precursors into mature eosinophils and prolongs

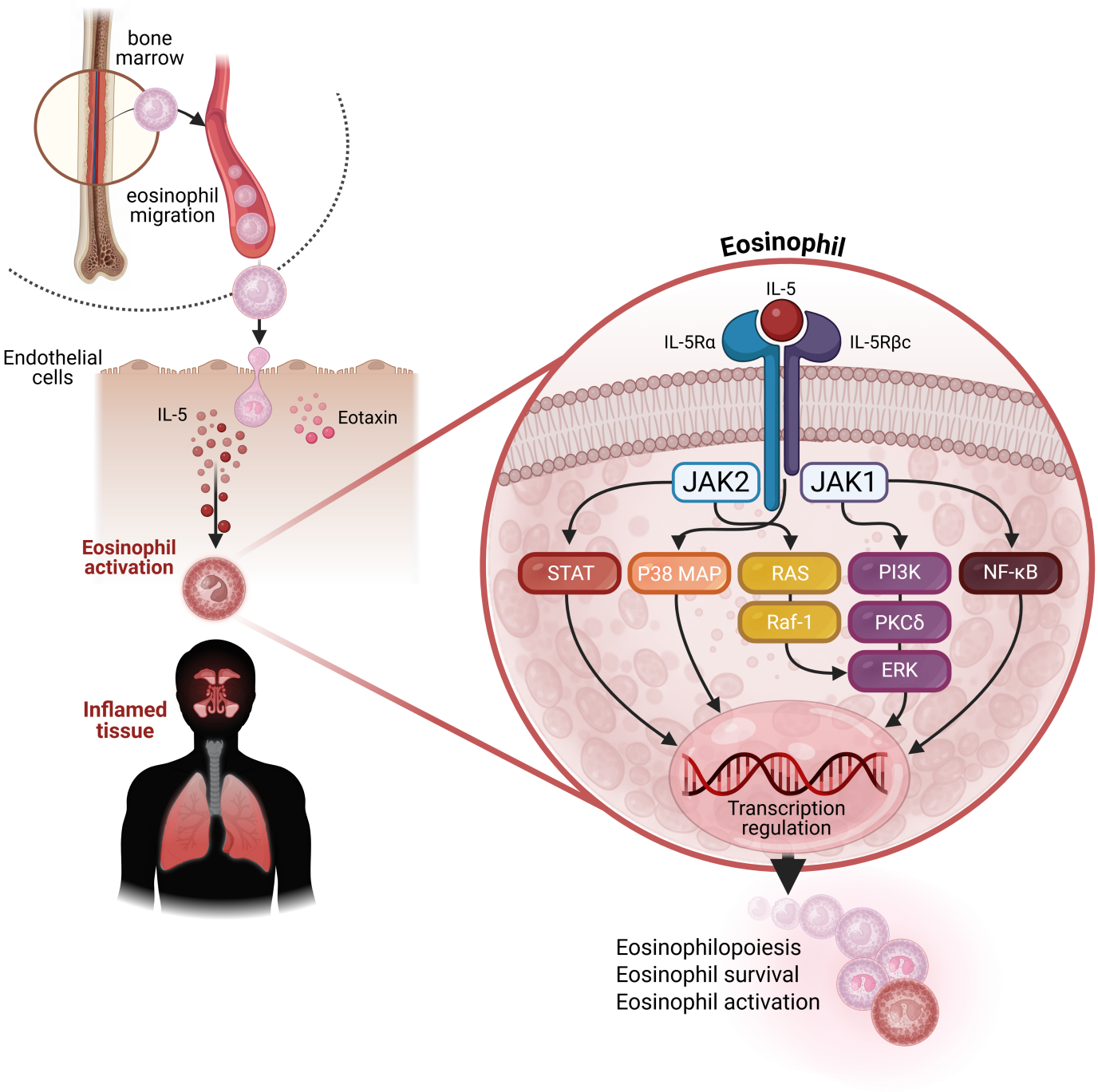

Figure 1. IL-5 is essential for the maturation, activation, and migration of eosinophils (left). Intracellular signaling through membrane IL-5 receptor regulates eosinophilopoiesis, activation, and survival of eosinophils (right). IL-5, interleukin-5; IL-5Rα, IL-5 receptor subunit alpha.

their survival by delaying apoptotic death in both humans and mice, increasing eosinophil numbers in blood and tissues.[1] Notably, IL-5 directly inhibits eosinophil apoptosis via Bid inactivation, a proapoptotic member of Bcl-2 family involved in Fas receptor signaling, because IL-5 has been shown to block Bid activation in vitro.[10]

Mechanistically, IL-5 signaling in mature eosinophils triggers the activation of multiple pathways, including JAK–STAT and MAPK (reviewed in[3,11]) (Figure 1, right). This activation enhances effector functions (priming), promotes chemokinesis and chemotaxis, activates integrins, and extends eosinophil survival by preventing apoptosis. In mice, it has been proven that the activation of JAK2 and STAT5 is essential for IL-5–driven signal transduction in both B cells and eosinophils.[12,13] In addition to the JAK–STAT pathway, other kinases like Lyn and BTK are also involved.[3] Moreover, the MAPK is critical for IL-5–dependent human eosinophil proliferation and survival.[14] Overall, IL-5 tightly regulates the expression of genes associated with eosinophil and B cell lineage proliferation, survival, maturation, and effector functions.

Blood and tissue eosinophils and EGPA

In the general population, the levels of circulating eosinophils are between 100 and 400 cells × 10^6/L. The circulating levels of total eosinophils are consistent with hypereosinophilia when eosinophil count is persistently elevated above 1,000–1,500 × 10^6/L.[15]

In healthy subjects, >90% of eosinophils reside in the tissues, where they can be found in the gastrointestinal tract, spleen, lymph nodes, thymus, mammary glands, and uterus and are collectively called resident eosinophils (rEOS).[2] In contrast, inflammatory eosinophils (iEOS) can be induced by IL-5 signaling, resulting in eosinophilic tissue infiltration upon stimulation. In preliminary studies, it is emerging that iEOS and rEOS subpopulations can be distinguished based on CD62 ligand (CD62L) surface expression, with Siglec8$^+$CD16$^-$CD62L^{low} identifying iEOS and with Siglec8$^+$CD16$^-$CD62L^{high} identifying rEOS, respectively,[16] with iEOS levels correlating with inflammatory manifestations due to eosinophilic tissue infiltration such as asthma and chronic sinusitis.[16] In vitro, IL-5 induces CD62L^{low} eosinophils expansion, whereas the treatment with anti–IL-5 pathway inhibitors in asthmatic subjects reduces the proportion of CD62L^{low} eosinophils, restoring the balance among eosinophils subphenotypes.[16] However, from a clinical perspective, blood subpopulations of eosinophils are not yet routinely measured.

It is known that significantly elevated total blood eosinophils may reflect eosinophilic tissue infiltration, especially in the context of a systemic disorder such as EGPA, leading to tissue inflammation and damage, particularly affecting the respiratory system, heart, nerves, and gastrointestinal tract.[17] The tight relationship between eosinophilic inflammation, systemic and organ eosinophilic infiltration, and vasculitis led to the conceptualization of EGPA natural history as three partially overlapping stages. The first is a prodromal phase, which can last for years and is marked by respiratory symptoms such as asthma and rhinosinusitis. The second phase involves blood eosinophilia, infiltration of eosinophils into tissues, and organ damage caused by eosinophilic inflammation. The final phase is characterized by systemic necrotizing vasculitis.[17] Once EGPA is diagnosed, the clinical course may vary from a short-lived, self-limiting condition to a more severe progression with multiorgan dysfunction (reviewed in[18]), leading to considerable morbidity.[19,20]

Hypereosinophilia in EGPA represents a hallmark feature, bearing clinically and biologically meaningful information. For instance, the new 2022 American College of Rheumatology (ACR)/EULAR criteria to classify EGPA, delineating the salient clinical features that differentiate EGPA from other forms of vasculitis, used a BEC of 1,000 × 10^6/L as a laboratory cut-off to identify hypereosinophilia for this condition.[21] In addition to IL-5, eotaxin-3, produced by epithelial and endothelial cells, promotes the recruitment and tissue infiltration of eosinophils.[22]

From a biologic standpoint, eosinophilic inflammation directly induces tissue cytotoxicity and activates coagulation pathways through the release of tissue factor, ultimately resulting in organ damage. Eosinophil-mediated inflammation causes tissue injury through the release of granule proteins and proinflammatory mediators, such as major basic protein (MCP), eosinophil peroxidase (EPO), and eosinophil cationic protein (ECP).[2] In addition, in the presence of additional stimuli, IL-5 seems to induces eosinophil ETosis, a process of active cell death causing eosinophils to release filamentous chromatin structures, called eosinophil extracellular traps, which possibly contribute to tissue damage in EGPA.[23] Activated eosinophils undergo ETosis and lose cytoplasmatic content, including galectin-10, a marker of Th2 inflammation and eosinophil lysis, that is found in the extracellular traps in the form of slender bipyramidal hexagonal crystals, called Charcot-Leyden crystals, considered an hallmark of eosinophilic inflammation.[24] Finally, the direct accumulation by eosinophils of the tissue and/or ischemic damage due to the occlusion of small arteries by cell infiltration and/or clotting can be the cause of organ-specific damage.[22,25]

It needs to be remembered here that the pathophysiology of EGPA goes beyond eosinophils and involves other immune cells, in particular neutrophils and lymphocytes. B cells contribute to EGPA autoimmunity—stimulated by T cells—through the production of ANCA, typically targeting MPO, in subjects with genetic predisposition (particularly, but not limited to, HLA-DQ). [25] In fact, whereas ANCA-positive EGPA is strongly linked to HLA genes, suggesting a prominent role for adaptive immune response, ANCA-negative EGPA shows strong associations with polymorphism in genes regulating mucosal immunity and eosinophilic inflammation, such as IL-5, IRF1, and GATA3, reflecting barrier dysfunction mechanisms and eosinophil activation rather than autoantibody-mediated inflammation.[25,26]

From the pathologist's perspective, in ANCA-positive EGPA, both eosinophil- and ANCA-mediated inflammation are present. ANCA-mediated inflammation activates neutrophils and contributes to inflammation in the walls of small blood vessels. In ANCA-negative EGPA instead, eosinophil-driven tissue damage appears to be the dominant mechanism, with evidence of eosinophilic-rich, granulomatous, necrotizing vasculitis.[4,23]

EGPA among other eosinophilic disorders

The circulating levels of total eosinophils are consistent with hypereosinophilia when eosinophil count is persistently elevated above 1,000–1,500 × 10^6/L, a condition which can be associated with different causes other than EGPA, such as reactive, neoplastic, or idiopathic hypereosinophilic syndrome (HES). The work-up can be challenging in light of the broad spectrum of these differential, including respiratory allergies, medication hypersensitivity, parasitic or fungal infections, primary HES, malignancies, and autoimmune disorders.[15] Among all the other eosinophilic disorders, the differential diagnosis between ANCA-negative EGPA and HES may represent the most difficult one because of several overlapping clinical and immunopathological features. Both conditions are characterized by peripheral hypereosinophilia (≥1,500 × 10^6/L) and eosinophil-mediated organ damage, with ANCA-negative EGPA often presenting with chronic rhinosinusitis and nasal polyps (CRSwNP), asthma, pulmonary infiltrates, peripheral neurologic involvement (most frequently mononeuritis multiplex), and palpable purpura, whereas HES is associated more often with eosinophilic myocarditis, eosinophilic gastroenteritis, and a broad spectrum of skin involvement different from purpura (psoriasiform dermatitis, urticaria, angioedema, atopic dermatitis, and erythroderma).[4,27] From a pathology perspective, vasculitis is a hallmark of EGPA, although it may be histologically subtle or absent in ANCA-negative cases, and eosinophil-rich necrotizing granulomatous inflammation supports a diagnosis of EGPA, in contrast with HES, which typically lacks granulomas and vasculitis.[4,27]

In addition to ANCA testing, vitamin B_{12} (frequently raised in myeloproliferative HES) and screening for FIP1L1-PDGFRA gene fusion, and other tyrosine kinase fusions (myeloid variants of HES), should be routinely checked, at least when facing ANCA-negative patients with chronic hypereosinophilia and no definitive histologically proven vasculitis, as well as testing for chronic parasitic infections such as *Strongyloides stercoralis* and *Toxocara canis*.[4,27] Notably, EGPA and HES may coexist or evolve over time, further blurring diagnostic boundaries, such as those cases initially diagnosed with HES and treated with glucocorticoids and anti–IL-5 therapies, further developing vasculitis' features, unmasking EGPA, or those cases defined as poorly controlled ANCA-negative EGPA and later diagnosed as HES and requiring cytoreductive or molecular targeted therapies (e.g., imatinib). These infrequent but exciting observations underscore the importance of follow-up and of reconsideration of the diagnosis, in case of new and/or unusual clinical development under treatment.[28]

Targeting the IL-5 pathway in EGPA

Serum IL-5 levels correlate with EGPA clinical activity, being elevated during active untreated disease and decreasing with clinical remission.[24,30] The central role of the IL-5 pathway in the maturation, activation, and mobilization of eosinophils and its correlation with disease activity provided a strong rationale for targeting the IL-5 pathway in EGPA, as for other eosinophilic disorders. The development of therapeutic monoclonal antibodies targeting IL-5 or its receptor has opened new treatment options for EGPA by addressing a key regulator of eosinophil maturation and mobilization.

Mepolizumab, reslizumab, and depemokimab are monoclonal antibodies that specifically target IL-5, whereas benralizumab is designed to bind to the α-subunit of the IL-5 receptor (Table 1).[31–34] These treatments vary in their ability to deplete eosinophils, with benralizumab demonstrating a more profound reduction in both circulation and tissues. This difference is attributed to their distinct mechanisms of action; by binding to the IL-5Ra, benralizumab not only blocks IL-5 receptor activation but also triggers Natural Killer (NK) cell–mediated eosinophil destruction, instead of neutralizing IL-5 as done by mepolizumab, depemokimab, and reslizumab.[52,59] Consistently, eosinophil tissue depletion seems to be higher for benralizumab, with IV benralizumab for severe asthma (at doses of 100 mg or 200 mg) reducing 95.8% airway eosinophils, 89.9% sputum eosinophils, and 100% bone marrow eosinophils,[52] as compared with approximately 50% depletion of tissue eosinophils shown by IV mepolizumab for eosinophilic esophagitis (at the dose of 750 mg).[60] It remains unknown to which extent a higher level of eosinophilic tissue depletion is clinically relevant and the consequence of this depletion on rEOS.

To date, only two phase 3 clinical trials evaluating an IL-5 inhibitor in patients with relapsing or refractory EGPA added onto the standard of care (glucocorticoid with or without conventional immunosuppressive therapies) have been published: the MIRRA trial, comparing mepolizumab to placebo,[36] and the MANDARA trial, comparing benralizumab to mepolizumab,[39] detailed below. Depemokimab, a long-acting anti–IL-5 therapy that binds the same epitope as mepolizumab but with greater affinity and an extended half-life, is currently under investigation (OCEAN NCT05263934; assessing depemokimab versus mepolizumab).

Learning from trials and studies about efficacy and safety of IL-5 pathway inhibitors in EGPA

In the placebo-controlled MIRRA trial, mepolizumab (administered subcutaneously at 300 mg every 4 weeks for 52 weeks)

Table 1. Monoclonal antibodies directly targeting the IL-5 pathway*

Monoclonal Antibody	Molecular Target	Specifics	Approved Dose(s)	Approved Indication(s)
Mepolizumab	IL-5	Humanized IgG1, given subcutaneously	Adults (≥12 years old): 100 mg every 4 weeks Children (6–11 years old): 40 mg every 4 weeks Adults (≥12 years old): 300 mg every 4 weeks Children 6–11 years old: 100 mg for <40 kg or 200 mg for ≥40 kg, every 4 weeks	Asthma (children and adults, ≥12 years old) CRSwNP (≥18 years old) HES (≥12 years old) EGPA (≥6 years old)
Reslizumab	IL-5	Humanized IgG4, given intravenously	3 mg/kg every 4 weeks	Asthma (≥18 years old)
Benralizumab	IL-5Rα	Humanized afucosylated IgG1, given subcutaneously	30 mg every 4 weeks for three doses, then every 8 weeks 30 mg every 4 weeks	Asthma (≥12 years old) EGPA (≥18 years old)
Depemokimab	IL-5	Humanized IgG1, given subcutaneously	Adults (≥12 years old): 100 mg every 26 weeks	Asthma (≥12 years old)

* CRSwNP, chronic rhinosinusitis with nasal polyps; EGPA, eosinophilic granulomatosis with polyangiitis; HES, hypereosinophilic syndrome; IL-5, interleukin-5; IL-5Rα, IL-5 receptor subunit alpha.

demonstrated efficacy for subjects with EGPA who had been diagnosed for over 6 months and were experiencing glucocorticoid-dependent, relapsing and/or refractory disease despite receiving standard of care (Table 1).[36] The trial found that mepolizumab resulted in more accrued weeks of remission compared with placebo (28% vs 3% had ≥24 weeks of accrued remission) and reduced the frequency of disease relapses of more than 40%, enabling a substantial reduction in glucocorticoid dose (Table 2). Further, a post hoc analysis of the trial showed that the clinical benefit of adding mepolizumab to standard of care (using a comprehensive outcome encompassing remission, oral glucocorticoid dose reduction, and relapse reduction) can be achieved in the great majority of patients.[35] It is important to highlight that at randomization in MIRRA, participants with EGPA had predominantly eosinophilic-asthmatic symptoms rather than vasculitic ones and a low rate of ANCA positivity (only 10%), likely due to a disease duration of approximately 5 years in both studies and prior glucocorticoid and immunosuppressive treatment.[36] Safety reported in the trial at 52 weeks was comparable to placebo. In addition, a recent prospective clinical study assessing long-term (≥144 weeks) mepolizumab 300 mg every four weeks in EGPA and the long-term extension of the MIRRA trial (follow-up median 27.0 months, min–max 1.0–89.0 months) showed excellent safety profile, allowing oral glucocorticoid dose reduction while improving disease control, as compared with pretreatment period.[37,38]

The dose of 300 mg every 4 weeks used in the trial was found by a dose-response meta-analysis of blood eosinophil data collected from 16 mepolizumab studies conducted on eosinophilic disorders, including asthma of varying severity, HES, and eosinophilic esophagitis.[46] Dose prediction from the modeling showed that subcutaneous mepolizumab dose of 300 mg every four weeks is appropriate for eosinophilic diseases that present with significantly higher blood eosinophil levels at diagnosis (>1,000 cells x 10^6/L) to maximize the pharmacological effect of the drug. Large, retrospective, multicenter real-life studies have further supported the use of mepolizumab in EGPA, with doses of either 300 mg or 100 mg every four weeks (the latter being the approved dose for eosinophilic asthma and chronic rhinosinusitis with nasal polyposis).[45,50] These studies showed that mepolizumab effectively reduced disease activity and led to a significant decrease in prednisone use. No high-quality trial directly comparing the two doses of mepolizumab are available, and only the higher dose is currently approved for EGPA by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA).

More recently, the results of the placebo-controlled MANDARA trial were published, a randomized noninferiority trial comparing benralizumab 30 mg every 4 weeks to mepolizumab 300 mg every 4 weeks for 52 weeks, in patients with relapsing and refractory EGPA (Table 1).[39] Benralizumab resulted in similar weeks of accrued remission compared with mepolizumab (58% and 56%, respectively, at 26 and 48 weeks), proving the noninferiority but not the superiority of benralizumab to mepolizumab (Table 2). In both benralizumab and mepolizumab arms, approximately 30% of patients experienced a relapse during follow-up, and 70% received daily oral glucocorticoid doses of ≤4 mg during the final four weeks of the trial, with a higher proportion of subjects in the benralizumab group being able to completely withdraw from glucocorticoid therapy.[39] Safety profiles of the two tested drugs were similar over the 52 weeks of observation. Like the MIRRA trial, participants with EGPA had predominantly eosinophilic-asthmatic symptoms rather than vasculitis symptoms and approximately

Table 2. Phase 3 clinical trials reporting data of subcutaneous mepolizumab 300mg/month and benralizumab 30mg/month in eosinophilic granulomatosis with polyangiitis on the main clinical outcomes, glucocorticoid-sparing activity, and blood eosinophil counts

Outcomes	MIRRA (placebo vs Mepolizumab)		MANDARA (Mepolizumab vs Benralizumab)	
	Placebo (*n*=68)	Mepolizumab (*n*=68)	Mepolizumab (*n*=70)	Benralizumab (*n*=70)
Main clinical outcomes				
Remission at weeks 36 and 48, % of patients				
Trial definition (BVAS = 0 and ≤4 mg)[a]	3%[36]	32%[36]	56%[39]	58%[39]
EULAR definition (BVAS = 0 and ≤7.5 mg)[a]	10%[36]	41%[36]	74%[39]	79%[39]
Accrued duration of remission (trial definition), % (n)				
≥24 weeks of accrued remission[a]	3%[36]	28%[36]	N/A	N/A
0 weeks	81% (55)[36]	47% (32)[36]	21% (15)[39]	13%9[39]
0 to <12 weeks	12% (8)	12% (8)	14% (0)	19% (3)
12 to <24 weeks	4% (3)	13% (9)	11% (8)	11% (8)
24 to <36 weeks	0% (0)	15% (10)	27% (0)	29% (0)
≥36 weeks	3% (2)	13% (9)	26% (18)	29% (0)
Relapse-free survival, % of patients	18%[35]	44%[35]	70%[39]	70%[39]
Glucocorticoid-sparing activity				
Daily PDN ≤4 mg in the final 4 weeks, % of patients	7%[36]	44%[36]	70%[39]	68%[39]
Daily PDN ≤7.5 mg in the final 4 weeks, % of patients	34%[36]	59%[36]	90[39]	89%[39]
Daily dose of PDN in the final 4 weeks, mean ± SD, mg	12.9 ± 9.5[40]	8.7 ± 14.9[40]	3.4 ± 4.1[39]	3.0 ± 3.8[39]
Median (min–max)	10.0 (0–46.3)[40]	5.0 (0–113.4)[40]	3.0 (0-25.7)[39]	1.2 (0-16.6)[39]
≥50% reduction in PDN in mg during the last 4 weeks, % of patients	22%[36]	56%[36]	74%[39]	84%[39]
Patient off PDN during the last 4 weeks, % of patients	3%[36]	18%[36]	26%[39]	41%[39]
Cumulative dose of PDN over 52-week period, mg	4,710.0[40]	3,286.9[b40]	N/A	N/A
Blood eosinophil counts				
Eosinophils reduction				
Least-squares mean ratios				
At week 1	–	–	0.39[39]	0.15[39]
At week 4	1.21[36]	0.21[36]	–	–
At week 52	–	–	0.26[39]	0.10[39]
Eosinophils reduction, %				
At week 1	–		61%[39]	85%[39]
At week 4	83% less vs placebo[36]		–	–
At week 52	–		74%[39]	90%[39]

* Benra, benralizumab; BVAS, Birmingham Vasculitis Activity Score; Mepo, mepolizumab; PDN, prednisolone or prednisone equivalent.
[a] In both MIRRA and MANDARA trials, remission is defined as a BVAS of 0 and an oral glucocorticoid dose of ≤4 mg per day.
[b] Equal to 1,423.1 mg less in the mepolizumab arm as compared to placebo.

10% of ANCA positivity at randomization.[39] A post hoc analysis of the MANDARA trial, published in an abstract form, showed that more benralizumab- than mepolizumab-treated patients achieved the four-component remission of asthma (28.0% vs 12.4%), which included no relapse, prednisone 0 mg/day, Asthma Control Questionnaire score of <1.5, and no worsening in forced expiratory volume 1 (change from baseline to week 52, more than –10%).[41]

Retrospective, multicenter real-life studies confirmed the efficacy, safety, and steroid-sparing activity of benralizumab in EGPA[42–44], even at the dose approved for asthma (ie, 30 mg every other month after the first 3 months), allowing an oral glucocorticoid-free remission in more than 65% of patients in one study[44] and showing lower efficacy after prior failure of mepolizumab in another.[43] Of note, in a real-life study comparing benralizumab versus mepolizumab at asthma dose in EGPA, the proportion of patients discontinuing benralizumab was numerically higher than the proportion of patients discontinuing mepolizumab (18% vs 10%, respectively).[47] Overall, many real-life studies reported that lower doses (the "asthma dose") of mepolizumab (100 mg every month) and benralizumab (30 mg every other month) can maintain remission of EGPA-related asthma and, to a lesser extent, CRSwNP (reviewed here[48]). However, there is currently no consensus on whether dosing of IL-5 pathway inhibitors should be adjusted based on BEC or clinical

symptoms or after a few years of good disease control with the higher EGPA dosing.

Overall, the 2021 ACR/Vasculitis Foundation guidelines recommend 300 mg mepolizumab every 4 weeks as the induction treatment, directly with glucocorticoid, in patients with active, nonsevere EGPA over glucocorticoid alone for maintenance in these patients.[49] Strong data to support this recommendation are yet lacking because no prospective trial has yet investigated the role of mepolizumab (or other anti–IL-5 therapies) as a first-line treatment for newly diagnosed EGPA, either with or without glucocorticoids. The 2022 EULAR updates and the recent European EGPA Study Group (EESG) recommendations suggest the use of mepolizumab for induction of remission in patients with relapsing or refractory EGPA without active organ-threatening EGPA and for maintenance of remission in patients with or without life-threatening EGPA.[50,51] Since the MANDARA trial was published at the beginning of 2024, benralizumab was not included in any of the guidelines and recommendations available for EGPA, all published before that date.

Effects of IL-5 pathway inhibitors on blood eosinophils and glucocorticoid-sparing activity

IL-5 pathway inhibitors showed glucocorticoid-sparing effect in the trials conducted in EGPA, reducing glucocorticoid dependence by controlling eosinophilic inflammation, leading to sustained disease remission with lower steroid doses.[31–33,36,39] This glucocorticoid-sparing effect minimizes long-term steroid-related complications.

Focusing on glucocorticoids, in the MIRRA trial, the reduction of glucocorticoid exposure was significant, increasing the proportion of patients with daily prednisolone equivalent (PDN) dose of ≤4 mg to 44% in the mepolizumab group as compared with 7% in the placebo group (meeting the trial definition of remission) and daily prednisolone dose of ≤7.5 mg in 59% as compared with 34% (meeting the EULAR definition of remission), respectively (Table 2).[36] The trial and *post hoc* analyses showed substantial reduction in glucocorticoid daily dose and cumulative dose.[36,35,40]

The effect on glucocorticoid of benralizumab was higher than mepolizumab in the MANDARA trial, allowing a complete withdrawal of oral glucocorticoids in a higher proportion of patients (41% of patients in benralizumab as compared with 26% of those receiving mepolizumab during weeks 48–52).[39] This might reflect the different mechanisms of action of benralizumab and mepolizumab, with a striking depleting capacity of benralizumab known from prior studies in asthma,[52] leading to a lower glucocorticoid use. Notably, the data on glucocorticoid-sparing activity of mepolizumab are significantly better in the MANDARA trial as compared with the MIRRA trial, probably reflecting the different study designs. For instance, daily dose of PDN of ≤4 mg and of ≤7.5 mg are achieved in 70% and 89%, respectively, in the mepolizumab arm of the MANDARA trial,[39] versus 44% and 59% in the mepolizumab arm of the MIRRA trial, respectively.[36]

Regarding the BEC, in the MIRRA trial, the reduction of BEC was evident already at week 4 (83% less in mepolizumab as compared with placebo), maintaining this level of BEC abatement through all the 52 weeks of follow-up.[36,35,40] The data provided for the MANDARA trial are not directly comparable to those of MIRRA but overall suggested a numerically higher BEC depletion rate for benralizumab as compared with mepolizumab, which could be appreciated already after the first week after administration.[39]

Predictors of response to IL-5 pathway inhibitors in EGPA

Research has been conducted to identify clinical predictors of response to anti–IL-5 inhibitors in EGPA, aiming to determine which patients may benefit the most. Various factors have been explored, including baseline disease characteristics, laboratory parameters, and prior exposure to different treatments (glucocorticoids and immunosuppressive therapies).

Post hoc analyses of the MIRRA trial demonstrated that the accrued remission duration and the proportion of patients in remission at weeks 36 and 48 were greater with mepolizumab compared with placebo regardless of the stratification for baseline Birmingham Vasculitis Activity Score > 0,[53] Vasculitis Damage Index ≥ 5,[53] ANCA positivity,[53] baseline refractory disease,[40] PDN use ≤ 20 mg/day,[40] immunosuppressant use,[40] EGPA duration > 4 years,[40] or relapse number before trial enrollment.[40] In contrast to subjects that had BEC <150 cells/mm^3 at baseline (no difference between mepolizumab and placebo), those 79 subjects with a BEC ≥150 cells/mm^3 achieved remission for ≥24 weeks in 33% with mepolizumab vs 0% with placebo.[36] In addition, the subgroup with a weight >85 kg at baseline was associated with clinical benefit (defined as the trial definition of remission or being relapse free or ≥50% reduction in PDN dose) from mepolizumab as compared with placebo.[35]

Clinical predictors for benralizumab response in EGPA have not been tested or reported yet in the context of clinical trials, but real-life data showed no significant difference between ANCA-positive and ANCA-negative subgroups.[44] Overall, except for BEC and weight at diagnosis for mepolizumab, factors clearly predicting IL-5 pathway inhibitor response in EGPA have not yet been identified.

Future perspective and therapies for EGPA

In the management of EGPA, anti–IL-5 therapies have significantly advanced treatment by targeting and normalizing BEC. However, this normalization presents a challenge in monitoring disease activity as traditional biomarkers like BEC become less informative. Consequently, there is a pressing need to identify

alternative biomarkers that can accurately reflect disease status in the context of suppressed eosinophil counts. Promising candidates might be searched among circulating and urinary eosinophil granule proteins, released during eosinophil activation and degranulation.[54] Recently, the levels of urine eosinophil-derived neurotoxin (uEDN), but not plasma EDN, proved its potential as a noninvasive marker of eosinophilic activity in selected eosinophilic disorders.[54] Elevated uEDN levels correlated with active disease phases regardless of benralizumab and mepolizumab treatment in a group of eosinophilic disorders (ie, EGPA, HES, and asthma), suggesting its use in monitoring disease activity undergoing anti–IL-5 therapy.[54]

Beyond biomarkers, exploring additional therapeutic avenues is crucial, especially for patients who exhibit partial or inadequate responses to anti–IL-5 treatments. JAK inhibitors have emerged as potential candidates due to their ability to interfere with multiple cytokine signaling pathways, including IL-5 (Figure 1B).[11] By inhibiting the JAK–STAT pathway, these agents can modulate immune responses and reduce inflammation associated with EGPA. An ongoing phase 2, double-blind, randomized, placebo-controlled trial is investigating the role of a potent JAK1 inhibitor in EGPA management (NS-229 trial, NCT06046222).

Another therapeutic prospect is tezepelumab, a monoclonal antibody targeting thymic stromal lymphopoietin (TSLP)[55]. TSLP is an upstream cytokine that influences the activity of multiple downstream effectors, including IL-5. By inhibiting TSLP, tezepelumab may offer a broader suppression of the inflammatory cascade, addressing both IL-5–dependent and IL-5–independent pathways, whose efficacy has already been shown for severe asthma[55]. This broad-spectrum approach could be particularly beneficial for patients with EGPA with complex disease mechanisms. A phase 2b, double-blind, randomized, placebo-controlled trial to explore the efficacy and mechanism of action of Tezepelumab in EGPA is currently underway (RACEMATE trial, NCT06230354).

Sequential biologic approaches, in which one agent targeting a broader immune dysregulation (such as JAK inhibitor, tezepelumab, or other biologics such as rituximab) is followed or associated by another one targeting eosinophilic inflammation, could be explored in patients with refractory disease or mixed phenotypes.[56] Furthermore, combination biologics—although largely untested—might offer additive or synergistic benefits, particularly in glucocorticoid-dependent patients with both eosinophilic and vasculitic manifestations. New and old biomarkers, such as BEC, ANCA, and eosinophil granules proteins, may guide such therapeutic decisions, helping to stratify patients and personalize biologic selection and sequencing.

Despite these therapeutic advancements, the management of sinonasal disease remains a major unmet need. Nasal polyps and persistent nasal obstruction are often refractory to both conventional and biologic agents. Mepolizumab and benralizumab, although effective in reducing systemic eosinophilic inflammation and asthma exacerbations, often fail to fully control sinonasal manifestations.[36,39] This therapeutic gap seems to suggest that local inflammation in the sinonasal mucosa may be driven by alternative Th2-cytokines, epithelial alarmins, or tissue-specific immune pathways insufficiently counteracted by IL-5 blockade. Preliminary retrospective data from small, uncontrolled studies on IL-4/IL-13 inhibitors (ie, dupilumab) have shown improvement in CRSwNP associated with EGPA, but efficacy has been offset by systemic disease flares in approximately one-third of these patients, currently limiting their use in this context.[57, 58] Therefore, addressing sinonasal disease control in EGPA remains an urgent need, requiring well-designed controlled trials to evaluate more effective therapies.

Another critical unresolved question remains about whether anti–IL-5 therapies can adequately control the "vasculitic" component of EGPA, such as peripheral neuropathy due to vasa nervorum vasculitis, gastrointestinal vasculitis, and cardiac vascular involvement (e.g., coronaritis).[18] The differential response of eosinophilic versus vasculitic inflammation to anti–IL-5 therapy raises concerns that biologics may alleviate respiratory symptoms and PDN dependency without fully controlling the vasculitic component. Future clinical trials and real-world data will be essential to determine the efficacy of biologics across the full range of EGPA manifestations and to clarify the role of combination and sequential strategies in this complex disease. Finally, whether the incidence of cardiovascular and thrombotic complications, often linked to eosinophilic activation and associated with systemic disease activity, could be reduced by the use of IL-5 pathway inhibitors as compared with standard PDN and immunosuppressive therapy remains to be proved.

While the currently available anti–IL-5 therapies have transformed EGPA treatment by effectively controlling eosinophilia, expanding therapeutic options through agents such as JAK inhibitors and tezepelumab holds promise for addressing the diverse pathogenic pathways of EGPA, potentially leading to more personalized and effective management strategies.

Conclusions

The patient was able to wean himself off the prednisone totally within 8 months, without a flare, and after one year from remission, azathioprine was withdrawn. Mepolizumab has been well tolerated, and he had no significant adverse events. He still has some minimal nasal congestion, and his pulmonary functions tests have remained stable after one year of mepolizumab, with clinically well-controlled asthma. He is still on inhaled glucocorticoids and long-acting beta-agonists and has not felt the need to resume prednisone. Sixteen months after having started mepolizumab, he is satisfied with his current breathing status. Mepolizumab subcutaneous injections are being continued at the same dosing (300 mg every four weeks). Evidence from future studies

should help determine whether and when mepolizumab dosing can be safely altered.

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AUTHOR CONTRIBUTIONS

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