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REVIEW
DERLEME

Eosinophilic granulomatosis with polyangitis: A new target for biologicals

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ABSTRACT

Eosinophilic granulomatosis with polyangitis: A new target for biologicals

Eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome) is a rare systemic necrotizing granulomatous vasculitis in the spectrum of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Nevertheless, EGPA has specific clinical, biological and histological properties different from other AAVs [microscopic polyangiitis (MPA) and granulomatous polyangiitis (GPA)]. Recently, thanks to the studies conducted to understand the pathophysiology of EGPA, unlike neutrophils in other AAVs, the main cells involved in EGPA have been observed to be eosinophils. The key role of eosinophils in EGPA and recent development of targeted agents to treat other eosinophil-related diseases have created new therapeutic opportunities for EGPA. Conventional treatment of EGPA relies mainly on agents that decrease inflammation. Cornerstone therapy is systemic glucocorticoids, used as monotherapy or in combination with immunosuppressive agents. However, new therapeutic approaches are needed especially for persistent asthma symptoms, refractory disease, relapses and problems associated with corticosteroid dependence. Recently, the first large-scale randomized controlled clinical trial on polyangiitis and eosinophilic granulomatosis has demonstrated the efficacy of eosinophil-targeted biotherapy anti-interleukin-5 (IL-5) mepolizumab, and is approved for the management of EGPA. This finding opens a new era for EGPA management. This review provides an overview of eosinophilic granulomatosis with polyangiitis in the light of new targeted biological therapies.

Key words: *Eosinophilic granulomatosis with polyangiitis; biologics; mepolizumab; benralizumab; rituximab*

ÖZ

Eozinofilik granülomatöz polianjitis: Biyolojikler için yeni bir hedef

Eozinofilik granülomatöz polianjitis (EGPA, Churg-Strauss sendromu), antinötrofil sitoplazmik antikor (ANCA) ile ilişkili vaskülit (AAV) spektrumunda nadir görülen sistemik nekrotizan granülomatöz vaskülittir. Bununla birlikte, EGPA'nın diğer AAV'lerden [mikroskopik polianjiitis (MPA) ve granülomatöz polianjit (GPA)] farklı olarak spesifik klinik, biyolojik ve histolojik özellikleri

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vardır. Son zamanlarda; EGPA'nın patofizyolojisini anlamak için yapılan çalışmalar sayesinde EGPA'da görev alan ana hücrelerin diğer AAV'lerdeki görev alan nötrofillerden farklı olarak eozinofiller olduğu gözlemlendi. Eozinofillerin EGPA'daki kilit rolü ve diğer eozinofil ile ilişkili hastalıkları tedavi etmek için hedeflenen ajanların son zamanlardaki gelişimi, EGPA için yeni terapötik fırsatlar yaratmıştır. EGPA'nın geleneksel tedavisi, esas olarak antiinflamatuvar ajanlardır. Başlıca ana tedavisi, monoterapi olarak veya immünosupresif ajanlarla kombinasyon halinde kullanılan sistemik glukokortikoidlerdir. Ancak özellikle persistan astım semptomları, refrakter hastalık, relapslar ve kortikosteroid bağımlılığı ile ilişkili problemler için yeni tedavi yaklaşımlarına ihtiyaç duyulmaktadır. Yakın zamanlı; eozinofilik granülomatöz polianjitis üzerine ilk büyük ölçekli randomize kontrollü klinik çalışma, eozinofil hedefli biyoterapi anti-interlökin-5 (IL-5) mepolizumabın etkinliğini göstermiştir ve EGPA tedavisi için onaylanmıştır. Bu çalışma sonuçları EGPA tedavisi için yeni bir çağ açmaktadır. Bu derleme, yeni hedefe yönelik biyolojik tedaviler ışığında eozinofilik granülomatozis polianjitise genel bir bakış sunmaktadır.

Anahtar kelimeler: *Eozinofilik granülomatozis polianjitis; biyolojik; mepolizumab; benralizumab; rituksimab*

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic necrotizing granulomatous vasculitis, predominantly affects small to medium vessels, and is characterized by chronic rhinosinusitis, asthma, blood and tissue eosinophilia (1). The annual incidence and prevalence of EGPA does not exceed 2.3 cases/million people and 23 cases/million people, respectively, depending on the geographic regions and the applied criteria (2). EGPA belongs to the anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) spectrum despite the fact that only 30–40% of its patients are ANCA positive (3). It is the rarest among AAV (4) and has specific clinical, biological and histological features that differ from other AAV [microscopic polyangiitis (MPA) and granulomatous polyangiitis (GPA)].

The main therapy is systemic glucocorticoids, used as monotherapy or in combination with immunosuppressive agents (4). Recently, the efficacy of eosinophil-targeted biotherapy, anti-interleukin-5 (IL-5), has been proved to be effective in EGPA (5). This review provides a summary of eosinophilic granulomatosis with a review of new targeted biological agents in therapy.

Pathogenesis

Immunopathogenesis of EGPA remains largely unknown with many factors contributing to its pathophysiology. Genetic predisposition, environmental factors and immune dysregulation contribute to the development of EGPA. Its pathophysiology is considered by many authors to be an overlap between the immune mechanisms at work in AAVs and the pathological mechanisms in eosinophilic syndromes (6).

Genetic studies have found associations between EGPA and specific human leukocyte antigen (HLA) alleles. One study showed the association between the HLA-DRB4 gene and the vasculitic manifestations of EGPA (7); another genome-wide association study (GWAS) conducted on 542 EGPA patients and 6.717 healthy controls from nine European countries supported the hypothesis that it is a polygenic disease (8). A recent GWAS including 684 EGPA patients identified 11 EGPA related loci (9). Variants in GATA3, TSLP, LPP, and BACH2, that may contribute to eosinophilic inflammation were detected in all patients. On the other hand, HLA-DQ has been identified as a risk allele in MPO-ANCA-positive EGPA, while variants in IRF1/IL5 and GPA33 have been associated with MPO-ANCA-negative EGPA. While, ANCA-positive EGPA patients are sharing a MHC association with other forms of AAV (MPA), and are clinically similar to them; ANCA-negative EGPA patients are genetically closer to asthma (8,9).

Eosinophils are thought to play a key role in the pathogenesis of EGPA, with its abnormal proliferation, impaired apoptosis, and high tissue toxicity attributed to eosinophil products (10). The increase in blood and tissue eosinophils is widely thought to be the result of Th2 cytokine production by CD4 T cells, particularly IL-5, the most potent stimulator of eosinophil proliferation and functional activation (10,11). Besides, TH1 and TH17 immune cell responses and B-lymphocyte activation also play a role in the pathogenesis of EGPA (12). The presence of ANCA is another aspect of EGPA pathogenesis and appears as an indicator of B lymphocyte activation (10). Possible mechanisms in EGPA were summarized in Figure 1.

Classification

Several nomenclature and classification criteria have been developed for vasculitis. The Chapel Hill Conference consensus, Lanham criteria and the criteria of the American College of Rheumatology (ACR)

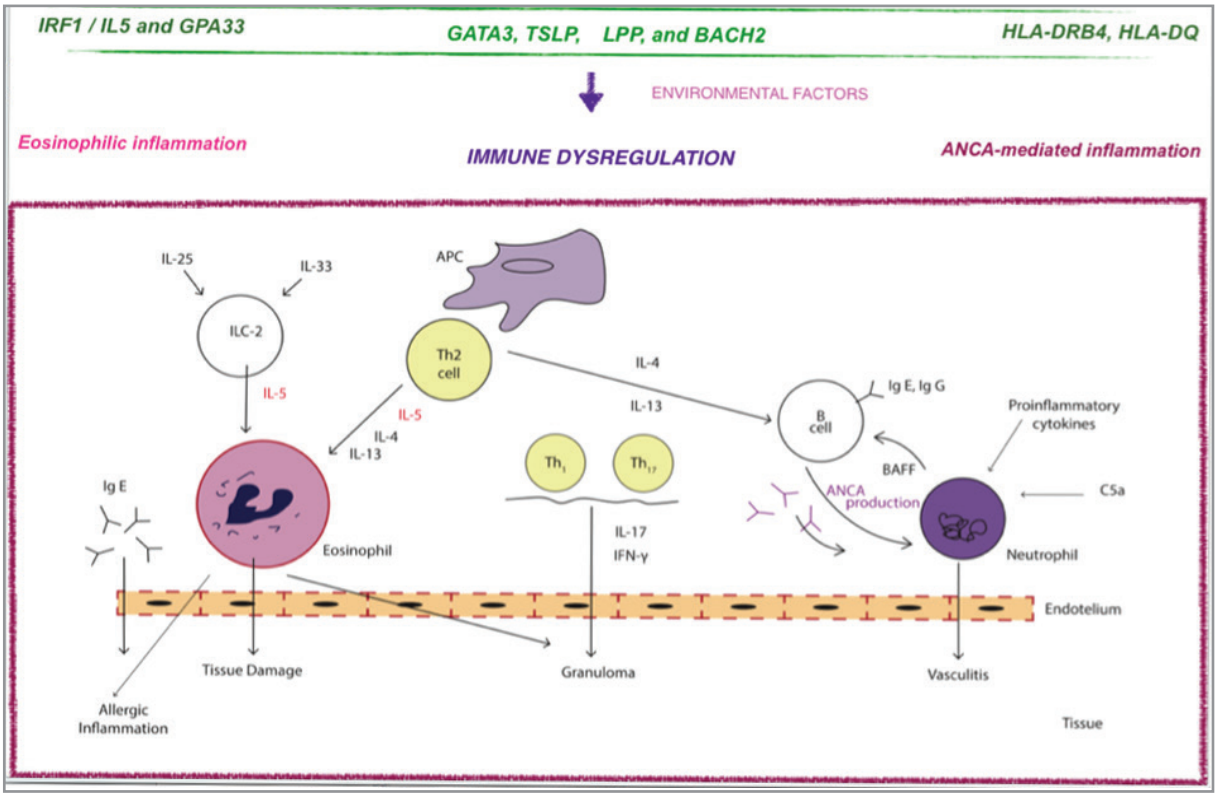

Figure 1. Genetic predisposition, environmental factors and immune dysregulation contribute to the development of EGPA. The increase in blood and tissue eosinophilia is widely thought to be the result of Th2 cytokine, particularly IL-5, the most potent stimulator of eosinophil proliferation and functional activation (10,11). Although eosinophils are the main cells that cause tissue damage, TH1 and TH17 immune cell responses and B-lymphocyte activation also play a role in the pathogenesis of EGPA (12). IL-5, interleukin-5; IL-4, interleukin-4; IL-13, interleukin-13; IL-17, interleukin-17; IL-25, interleukin-25; IL-33, interleukin-33; IgE, immunoglobulin E; IgG, immunoglobulin G; ILC2, lymphoid cells type 2; Th2 cell, T-helper type 2; Th1, T-helper type 1; Th17, T-helper type 17; IFN, interferon; C5a, active compleman 5; ANCA, antineutrophil cytoplasmic antibody; APC, antigen-presenting cell; BAFF, B cell activating factor.

have been used to define and diagnose EGPA (1,13,14), but none of these classification systems can fully distinguish EGPA from hypereosinophilic syndrome and there is overlap between AAVs. Recently, the draft of new classification criteria for EGPA has been proposed and final approval by EULAR/ACR working group is awaited (15). The new criteria are expected to be valid, more sensitive and specific to EGPA. But for now, the 1990 ACR classification criteria, are mainly based on disease clinical symptoms, such as; asthma, eosinophilia higher than 10%, neuropathy (mono or poly, including multiplex), unstable pulmonary infiltrates, paranasal sinus abnormalities and biopsy showing extravascular eosinophils have been the most popular classification criteria for EGPA with a sensitivity of 85% and a specificity of 99.7%, if at least 4 of these 6 criteria are positive (13).

The Course of Disease

The disease is characterized by three stages that overlap or can progress chronologically at varying intervals: prodromal period (mainly late-onset asthma and other allergic symptoms), eosinophilic phase (blood and tissue eosinophilia) and finally small vessel vasculitis (14). EGPA can affect any system, however the respiratory system is most frequently affected and asthma is seen with 90%. Other affected organ systems and dominant symptoms are; rhino-sinusitis (48-96%), general symptoms (80%), lung infiltrations (34-61%), mononeuritis multiplex (51-88%), skin (39-52%), heart (11-46%), gastrointestinal system (12-28%) and kidney involvement (18-26%) (16-19). Clinical manifestations differ between ANCA-positive and negative patients. Glomerulonephritis, alveolar hemorrhage and neuropathies are more common in

Table 1. Five factor score by French vasculitis study group

1 point/item	Age≥ 65 years
	Presence of renal insufficiency (creatinine> 150 mmoL/L)
	Presence of symptomatic cardiac insufficiency
	Presence of severe gastrointestinal involvement
	Absence of ear, nose, and throat symptoms

FFS: 0 non-severe disease, FFS≥ 1 severe disease.

ANCA-positive patients, whereas cardiac involvement are more frequent in ANCA-negative patients (18,20).

Treatments

Treatment of EGPA is guided by the type of organ involvement, and its severity as defined by the Five-Factor Score (FFS) (21) Table 1. Traditional treatment; if FFS is 0, systemic glucocorticoids is used monotherapy; in the presence of FFS≥ 1 or life/organ-threatening symptoms, immunosuppressive agents such as cyclophosphamide, methotrexate, azathioprine, mofetil mycophenolate, or rituximab are added in addition to glucocorticoids (4). For resistant disease, relapses, problems associated with corticosteroid dependence, and asthma symptoms that usually persist after the vasculitis is in remission, new therapeutic approaches are needed. Recently; the efficacy of eosinophil-targeted biotherapy, anti-interleukin-5 (IL-5), was proved to be effective in EGPA (5). Evaluation of emerging targeted biotherapies may suggest phenotype-based treatment regimens for EGPA patients (4), but additional studies are needed to determine which patients with EGPA would benefit from targeted therapies and personalized treatment.

Targeted Therapies

The key role of eosinophils in EGPA (6,9,10) and recent development of targeted agents to treat other eosinophil-related diseases have opened up new therapeutic opportunities for EGPA. After mepolizumab (anti-IL-5) was approved (22), eosinophil-targeted therapies have become the strongest scientifically based biologics in the treatment of EGPA. Below, we will talk about the biological agents used for EGPA.

Mepolizumab

Mepolizumab is a humanized IgG1 kappa monoclonal antibody that binds free IL-5, the main cytokine responsible for growth, differentiation, recruitment, activation, and survival of eosinophils (5,11). Thus, it prevents IL-5 from binding to the α-subunit of IL-5 receptor which is predominantly expressed on human eosinophils (4,23). Ultimately, mepolizumab inhibits IL-5 signaling in eosinophils, blocking eosinophilic activation, recruitment and tissue accumulation (4). Because of these features, mepolizumab has been investigated in some eosinophil-related diseases; such as eosinophilic asthma, hypereosinophilic syndrome, chronic rhinosinusitis, atopic dermatitis and EGPA. Following the good results from randomized controlled trials (RCTs), mepolizumab was approved in 2015 by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as an add on therapy in severe eosinophilic asthma at a dose of 100 mg per month (5,22,24). The centrality of eosinophils in the pathogenesis of EGPA and increased IL-5 levels, positioned this cytokine as a potential therapeutic target in EGPA patients (11,25).

In 2010, the first case of refractory ANCA-negative EGPA presented with a long history of asthma, hypereosinophilia, interstitial pneumonia (60% eosinophils in bronchoalveolar lavage fluid), myocarditis and increased level of serum IgE was reported to be successfully treated with mepolizumab. After failure to control with wide variety of treatment options such as methotrexate, interferon-alfa, cyclophosphamide, intravenous immunoglobulins, and azathioprine, in combination with corticosteroids, mepolizumab (750 mg/month intravenous) was initiated and remission was achieved (26).

Subsequently, a small open label pilot study in which mepolizumab was administered intravenously to 7 EGPA patients at 750 mg/month for 4 months evaluated disease activity and systemic corticosteroid dose were reliably reduced (27). Although the significant reduction in eosinophil count and asthma exacerbations seen with mepolizumab returned to pretreatment levels after discontinuation of the treatment, overall, the study revealed that mepolizumab allowed for significant corticosteroid reduction while maintaining clinical stability.

Another single center open label study supporting these trials showed that, use of mepolizumab 750 mg every 4 weeks not only produced a steroid sparing effect (28), but also provided effective induction and maintenance of remission in the absence of further conventional immunosuppressants.

Potential benefit from mepolizumab in EGPA treatment derived from these case reports and open label studies supported to conduct phase studies. In a multicenter double-blind, randomized placebo-controlled trial (MIRRA) (5), 136 patients with relapsed or refractory EGPA receiving 7.5 mg/day or more of prednisolone were randomly assigned 1:1 to receive either mepolizumab 300 mg or placebo subcutaneously every four weeks in addition to standard care for 52 weeks period. Remission was defined in MIRRA trial as: reduction in the glucocorticoid dose according to a standardized programme, zero score from Birmingham Vasculitis Activity Score (BVAS) and prednisone ≤4 mg/day. Mepolizumab led to significantly more weeks of accrued remission than placebo (28% vs. 3%); a higher percentage of participants in the mepolizumab arm were in remission (32% vs. 3%) at weeks 36 and 48, and the rate of reduction of prednisone or equivalent to 4 mg/day or less per day was 44% in mepolizumab and 7% in placebo. Mepolizumab was approved for EGPA after the MIRRA trial reported in 2017 that it was effective in approximately 50% of the patients (22). Although, 47 percent of those in the mepolizumab group could not achieve remission according to the remission criteria accepted in the MIRRA study; post hoc analysis found a significantly higher remission rate in the mepolizumab group than in the placebo group (87% vs. 53%) after taking a prednisolone cut-off point of 7.5 mg/day or less, which is more appropriate to the real-life target dose (29).

After mepolizumab was approved for use in EGPA at a dose of 300 mg/month, the efficacy of 100 mg/month in EGPA patients was evaluated in 18 subjects with real-life data over 12 months. It was questioned whether asthma symptoms could be controlled, the dose of oral corticosteroids (OCS) and/or immunosuppressants could be tapered and whether clinical remission could be maintained at a dose of 100 mg/month (30). Accordingly, 66.6% of the patients did not experience any asthma exacerbation during mepolizumab treatment, the daily dose of OCS could be reduced by at least 50% in 77.7% of the subjects, and cyclosporine-A was discontinued in 4 patients during the study period. There was no EGPA recurrence and the majority of patients achieved clinical remission (94.3%). In this real-life study, low-dose mepolizumab was shown to contribute to the reduction of asthma exacerbations and OCS dose in EGPA patients. However, before saying that 100 mg/dose is sufficient in the treatment of EGPA, a vasculitis with eosinophilic infiltration in the tissue, it would be appropriate to evaluate it with RCT in larger series. New studies are needed to answer questions such as why it is not effective in all patients, in which disease features the possibility of remission is higher with mepolizumab, and how long the treatment should be continued. These studies are summarized in Table 2.

Benralizumab

Benralizumab is a humanized monoclonal antibody targeting the IL-5 receptor α subunit (IL-5Rα) on eosinophils and basophils, with enhanced ADCC function that potently induces eosinophil apoptosis and preventing IL-5 from binding. Thus, it provides both neutralizing and cytotoxic effects (31,32).

It was first reported in 2019 that benralizumab achieved clinical remission and MPO-ANCA negativity in an MPO-ANCA positive EGPA case (33). In another case, a significant decrease in peripheral eosinophil count and increase in ACT score after the first dose were reported as rapid onset of action of benralizumab. In addition, improvement in symptoms and lung functions, regression of CT scan abnormalities and reduction in OCS dose have been documented after three months of subcutaneous injection of benralizumab (34). In a recently published study conducted in a small group of EGPA patients (n= 5), 3 of whom were resistant to mepolizumab treatment and 1 was positive for ANCA-MPO; it has been reported that clinical improvement was seen and steroid intake was significantly reduced in all patients. Moreover, steroids can be completely discontinued in 3 of them after 24 weeks of benralizumab treatment (31).

Following these two case reports and a five patient study in 2020, benralizumab was administered for the first time as an induction agent in an EGPA patient with myocarditis and central nervous system involvement complicated by *Staphylococcus aureus* sepsis, and clinical and laboratory parameters were improved (35).

Finally, in a 40-week prospective open label pilot study including 10 EGPA patients; benralizumab is well tolerated and has been shown to reduce the median corticosteroid dose from 15 mg at baseline to 2 mg at the end of treatment and reduce attacks (32). All of these results indicate that larger controlled studies are needed to further evaluate the role of benralizumab in EGPA. These studies are summarized in Table 2.

Table 2. IL-5 & IL-5R targeted therapies in patients with EGPA

Author, Year, (Reference number)	Number of patients	Drug dose	Follow-up time	Results
Mepolizumab treatment in patients with EGPA				
Kahn J-E, 2010 (26)	1	750 mg/m/iv	28 m	-Decreased dose of OCS -Decrease in ECP -Decreased eosinophil count -Clinical remission -Reduction in exacerbations
Kim S, 2010 (27)	7	750 mg/m/iv	40 wk	-Decreased dose of OCS -Decreased eosinophil count -Clinical remission -Reduction in exacerbations -No change in FeNO, PEF, BVAS
Moosig F, 2011 (28)	10	750 mg/m/iv	32 wk	-Decreased dose of OCS -Decreased eosinophil count -Clinical remission -BVAS reduction -Potential for use as an induction agent -maintains remission
Wechsler ME, 2017 (5)	136	300 mg/m/sc	60 wk	-Decreased dose of OCS -Increase in remission time -Fewer relapses
Vultaggio A, 2020 (30)	18	100 mg/m/sc	12 m	-Decreased dose of OCS -Decrease in ECP -Decreased eosinophil count -Clinical remission -Reduction in exacerbations
Benralizumab treatment in patients with EGPA				
Takenaka K,2019 (33)	1	30 mg*/sc	16 wk	-Clinical remission -Decreased eosinophil count -Makes ANCA negative
A. Coppola, 2020 (34)	1	30 mg*/sc	3 m	-Decreased dose of OCS -Decreased eosinophil count -Increase in ACT -Clinical remission -Reduction in exacerbations
R. Padoan, 2020 (31)	5	30 mg*/sc	24 wk	-Clinical remission -Decreased dose of OCS -Reduction in exacerbations
Guntur V. P.,2021 (32)	10	30 mg*/sc	40 wk	-Decreased dose of OCS -Reduction in exacerbations -Clinical remission
Reslizumab treatment in patients with EGPA				
Kent, B. D., 2020 (36)	9	3 mg/kg/m/iv	48 wk	-Decreased dose of OCS -Decreased eosinophil count -Clinical remission -No change in BVAS

IL-5: Interleukin-5, IL-5-R: Interleukin-5 receptor, *every 8 weeks after initial 3 doses given every 4 weeks, mg: Milligram, m: Months, iv: Intravenous, wk: Weeks, OCS: Oral corticosteroids, ECP: Eosinophilic cationic protein, sc: Subcutaneous, BVAS: Birmingham vasculitis activity score, FeNO: Fractionated exhaled nitric oxide, PEF: Peak expiratory flow rate, ACT: Asthma control test.

Table 3. IgE & CD20 targeted therapies in patients with EGPA

Omalizumab treatment in patients with EGPA				
Author, Year, (Reference number)	**Number of patients**	**Drug dose**	**Follow-up time**	**Results**
Jachiet M, 2016 (38)	17	Dose patient specific	-	-No change in Eosinophil count
Celebi Sozener Z, 2018 (39)	18	Dose patient specific	>18 m	-Decreased dose of OCS -Increase in AQLQ -No change in Eosinophil count
Rituksimab treatment in patients with EGPA				
Mohammad AJ, 2016 (40)	41	-	12m	-Decreased dose of OCS -Clinical remission

m: Months, OCS: Oral corticosteroids, AQLQ: Asthma quality of life questionnaire, IgE: Immunoglobulin E.

Reslizumab

Reslizumab is a humanized monoclonal antibody that targets IL-5, reducing eosinophil proliferation and airway inflammation levels (36).

In a cohort of nine EGPA patients with severe eosinophilic asthma who required sustained glucocorticoids to maintain disease control, a reduction in glucocorticoid use and peripheral eosinophil count was observed after 48 weeks of treatment with intravenous reslizumab (3 mg/kg every four weeks) (36). A 50% reduction in maintenance OCS dose was seen in all patients and remission achieved (<7.5 mg/day prednisolone) at OCS doses in 7 patients (78%), while OCS was completely stopped in two patients. No significant change was observed in BVAS. Finally, authors concluded that reslizumab was associated with a significant reduction in OCS dose as well as improvements in patient-reported outcomes. Afterwards an open-label pilot study was designed to evaluate the safety and efficacy of intravenous reslizumab in 10 EGPA patients with positive results similar to the other anti IL-5 biologic therapies (37). These studies are summarized in Table 2.

Omalizumab

Omalizumab is a humanized monoclonal IgG antibody blocking the allergic cascade by binding the Fc part of the circulated IgE and preventing the interaction between IgE and its receptor on basophils and mast cells. Alongside with these impacts, omalizumab diminishes eosinophil tissue infiltration. The effect of omalizumab on allergic asthma and eosinophilia suggested that it may be also effective in patients with EGPA particularly with uncontrolled asthma symptoms and sinonasal manifestations (38,39). Experience with omalizumab in the treatment of EGPA is limited to cases and case series only.

In a retrospective series of 17 patients with steroid dependent asthma and refractory or relapsed EGPA, methylprednisolone dose was reduced to ≤7.5 mg/day in six patients without asthma or sinonasal exacerbation, five patients had the same effect with prednisone dose>7.5 mg, but omalizumab was found to be ineffective in the remaining six patients. Mean eosinophil counts were not decreased during omalizumab treatment (38).

In another retrospective case series, improvement in asthma control and steroid sparing effects were observed in 18 patients with EGPA given omalizumab. However, no improvement in eosinophil count was found in this study either (39). As no RCTs have been conducted to support these case reports it is difficult to locate omalizumab therapy in EGPA patients. These studies are summarized in Table 3.

Rituximab

Rituximab, an anti-CD20 IgG1 chimeric monoclonal antibody directed against CD20-expressing B lymphocytes, has already been established as part of standard treatment for both MPA and GPA (4). In a 12-month retrospective series evaluating the efficacy of rituximab in EGPA (40); 36/41 (88%) patients showed clinical improvement in asthma/ENT symptoms and vasculitis-related organ failure. OCS dose reduction was achieved in all patients and complete weaning was achieved in two patients. 80% of ANCA-positive patients and 38% of ANCA-negative patients achieved remission. They suggested that rit-

uximab was more effective in ANCA-positive patients, but did not exclude its potential benefit in ANCA-negative patients. Currently, two prospective studies [the REOVAS (NCT02807103) and MAINRITSEG trials (NCT03164473)] conducted by the French Vasculitis Study Group are evaluating the efficacy of rituximab for EGPA. These studies are summarized in Table 3.

CONCLUSION

Although significant advances have been made for the understanding of underlying patho mechanisms of EGPA, systemic glucocorticoids, as monotherapy or in combination with immunosuppressive agents are still cornerstone of therapy. Biologicals seem to be valid alternatives for problematic EGPA patients. At present, no single biologic will be effective for all EGPA patients but ongoing studies and planned studies with careful patient selection based on predominant immune mechanisms will provide more data for optimal therapeutic approaches.

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