Chapter

Eosinophilic Granulomatosis with Polyangiitis: The Beginning of a New Era

Carlos Melero Moreno, Marta Corral Blanco and Rocío Magdalena Díaz Campos

Abstract

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare type of anti-neutrophil cytoplasm antibody-associated vasculitis (AAV) with unique features, such as involvement of eosinophils in the pathogenesis, which requires different therapies from those used for other AAV. Conventional treatment includes glucocorticoids (GC) and immunosuppressants. GC are the cornerstone of the initial treatment of EGPA, but relapses are frequent. Cyclophosphamide is typically used in combination with GC for patients with life- and/or organ-threatening disease manifestations. Azathioprine and methotrexate are recommended to maintain remission after induction with cyclophosphamide or as a GC-sparing agent. Nowadays, a better comprehension of the physiopathology of EGPA has opened new therapeutic targets, such as interleukin-5, which has a key role in the refractory disease, relapses, and GC dependence, especially for asthma manifestations. Mepolizumab is the first anti-IL5 antibody approved to treat EGPA. Another anti-IL5 monoclonal antibody, reslizumab, and an anti-IL5 receptor monoclonal antibody, benralizumab, are now being investigated for EGPA.

Keywords: eosinophilic granulomatosis with polyangiitis, Churg-Strauss syndrome, vasculitis, eosinophilia, anti-IL5 therapy, glucocorticoids, cyclophosphamide, mepolizumab

1. Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly Churg-Strauss syndrome, is a rare necrotizing vasculitis, with an annual incidence and prevalence of 0.9–2.4 per million [1–4] and 10.7–17.8 per million [5–8], respectively, depending on geographic regions and applied criteria. The disease is now recognized as one form of anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) characterized by eosinophil-rich granulomatous inflammation and small to medium size vessel vasculitis associated with asthma and eosinophilia [9].

ANCA occur only in about 30–70% of patients with newly diagnosed untreated EGPA, and organ involvement can be different depending on the presence or not of ANCA [10], probably being different subgroups with specific characteristics. In this way, Matsumoto et al. [11] reported that AAV patients could be divided into three subgroups according to peripheral immune cell numbers: antibody production

related, cytotoxic activity related, and neutrocytosis/lymphocytopenia. These subgroups could have different prognosis and treatment.

EGPA has been excluded from most of randomized controlled trials for AAV because of its rarity and unique features, such as involvement of eosinophils in the pathogenesis. Reliable evidence of treatment for EGPA is limited, and there are no strong recommendations for treatment of EGPA at the moment [12].

Treatment has been based on the use of glucocorticoids (GC) and immunosuppressants. Cyclophosphamide is typically used in combination with GC for patients with poor prognostic factors (assessed by the Five Factor Score). Azathioprine and methotrexate are recommended to maintain remission after induction with cyclophosphamide or as a GC-sparing agent. All these medications have many and deleterious adverse effects.

Fortunately, a better comprehension of the physiopathology of EGPA has opened new therapeutic targets, such as interleukin-5, which has a key role in the disease.

2. Assessing vasculitis severity

The French Vasculitis Study Group conducted two randomized controlled clinical trials to develop a score to assess the severity of vasculitis disease: the Five Factor Score (FFS) [13].

The FFS is a prognostic tool used to quantify the extent of the disease and guide therapy. It consists of five items. Age >65 years old, cardiac insufficiency, severe gastrointestinal involvement, and renal insufficiency [stabilized peak creatinine 1.7 mg/dL {150 μmol/L}] are associated with poor prognoses, each scores +1 point, while the fifth factor (ear, nose, and throat [ENT] manifestations) is associated with better outcome and its absence is scored +1 point.

3. Conventional therapy for EGPA

3.1 Systemic glucocorticoids

Glucocorticoids are the cornerstone of the initial treatment of EGPA. They act quickly against vasculitis and normalize the value of peripheral eosinophils within few days of treatment.

A multicenter retrospective study, done by Cottin et al. [14] in 2016, showed that treatment with systemic GC was associated to a decrease in peripheral eosinophilia (with a mean cell count $<1.0 \times 10^9\ L^{-1}$ over the long-term).

The initial management of EGPA includes high doses of GC, usually 1 mg/kg/day of prednisone or its equivalent. Methylprednisolone pulses (7.5–15 mg/kg intravenously, repeated at 24 h intervals, for 3 days) can be used in the presence of life-threatening symptoms. When clinical response is obtained and inflammation reactants return to normal values, usually within 3–4 weeks, GC can be tapered slowly to the minimal effective dose or, when possible, until withdrawal. However, most patients need to maintain GC to prevent relapses of systemic manifestations and control asthma. The optimal minimal dose should be 7.5 mg/day to limit GC-induced side effects [15, 16].

In the French Vasculitis Study Group cohort [17], which included 383 EGPA patients, approximately 85% required long-term prednisone (mean dose 12.9 ± 12.5 mg/day) to control asthma, rhinitis, and/or arthralgias.

GC as monotherapy may be suitable for most EGPA patients. In a study, which included 72 EGPA patients without poor prognosis factors, 93% achieved remission with systemic GC therapy alone [18]. However, additional immunosuppression can

be considered for patients with life- and/or organ-threatening disease, when the prednisone dose cannot be tapered to 7.5 mg/day after 3–4 months of therapy or for patients with recurrent disease [16, 19].

Samson et al. [20] assessed the outcomes of 118 EGPA patients (with or without FFS) enrolled in two prospective, randomized, open-label clinical trials from 1994 to 2005. Forty-four patients with poor prognosis (FFS ≥ 1) were assigned to receive 6 or 12 cyclophosphamide (CPh) pulses plus GC, and 74 without poor prognosis factors (FFS = 0) received GC alone (with immunosuppressant [IS] adjunction when GC failed). Follow-up was done from 2005 to 2011. Twenty-nine percent achieved long-term remission, while 41% had ≥1 relapse at 26 months after treatment onset. More than half of the relapses occurred when GC tapering reached <10 mg/day, especially in patients with anti-myeloperoxidase antibodies and baseline eosinophilia <3000/mm^3.

3.2 Immunosuppressants

3.2.1 Cyclophosphamide

Cyclophosphamide is typically used in combination with GC for patients with life- and/or organ-threatening disease manifestations (i.e., heart, gastrointestinal involvement, central nervous system, severe peripheral neuropathy, severe ocular disease, alveolar hemorrhage, and/or glomerulonephritis) [14].

In a retrospective study of 595 patients with severe necrotizing vasculitides (including EGPA), treatment had no significant impact on early death, except for patients with FFS ≥ 2 for whom GC monotherapy showed association ($p < 0.05$). The principal cause of early death was uncontrolled vasculitis (58%), followed by infection (26%) [21]. A study of 278 patients with polyarteritis nodosa, microscopic polyangiitis, and EGPA showed that survival was significantly higher in patients with FFS > 2 treated with GC and CPh rather than GC alone [22].

Cyclophosphamide can be administered as continuous oral therapy or intravenous (IV) pulses. The doses should be adjusted according to age and renal function. Cyclophosphamide pulses are usually preferred to oral administration because of the lower cumulative dosage. The frequency of relapses, however, can be higher with pulses, and it has been shown that oral CPh can be effective when pulses have failed [15]. Sodium 2-mercaptoethanesulfonate is recommended to reduce bladder toxicity.

Regarding the duration of CPh therapy, Cohen et al. [23] conducted a prospective, multicenter trial to compare first-line treatment with systemic GC and 6 or 12 pulses of adjunctive CPh for the treatment of severe EGPA. Forty-eight patients were included, 42 (87.5%) achieved complete remission, 21 (91.3%) in the 6-pulse regimen, and 21 (84%) in the 12-pulse regimen. Severe side effects were similar in both groups. However, a too-short duration of CPh administration was associated with more relapses, so the authors concluded that a 12-pulse regimen was better to control severe EGPA than a 6-pulse regimen. Other less toxic IS, as azathioprine (AZA) or methotrexate (MTX), were not tested for maintenance so further data is needed to clarify the optimal duration of therapy.

3.2.2 Azathioprine and methotrexate

AZA and MTX are recommended to maintain remission after induction with CPh or as a GC-sparing agent in patients requiring long-term therapy with prednisone at doses >10 mg/day. Maintenance therapy with an IS usually begins 2–3 weeks after the last CPh pulse, or a few days after oral CPh, and continues for 12–18 months [16].

Pagnoux et al. [24] conducted a prospective, open-label, multicenter trial to evaluate the safety and efficacy of AZA and MTX in ANCA-associated vasculitis. One hundred twenty-six patients in remission with IV CPh and GC were randomly assigned to receive AZA (at a dose of 2.0 mg/kg/day) or MTX (at a dose of 0.3 mg/kg/week, progressively increased to 25 mg per week) as maintenance therapy for 12 months. Adverse events occurred in 29 AZA recipients and 35 MTX recipients. There was one death in the MTX group. Twenty-three patients who received AZA and twenty-one patients who received MTX had a relapse. The results suggested that none of the drugs were more effective at maintaining remission, but severe adverse events were more frequent in the MTX group.

4. New therapeutic strategies

4.1 Role of IL-5 in EGPA

EGPA is characterized by elevated peripheral eosinophilia with different degrees of activation. Eosinophilia is secondary to more synthesis, enhanced extravasation, and its prolonged survival in target tissues. Histological features of EGPA are small-vessel angiitis and extravascular necrotizing granulomas, usually containing eosinophilic infiltrate [25, 26].

An initial Th2-mediated immune response provokes the migration of eosinophils to tissues. IL-5, produced by TH-2 lymphocytes, plays an active role in chemotaxis, activation, degranulation, and survival of eosinophils [26]. IL-5 is not the only mediator of eosinophilic tissue infiltration; IL-4 and IL-13 are two other cytokines of Th2-mediated immune response that play an important role in tissue infiltration and degranulation of eosinophils [27, 28]. Epithelial and endothelial cells, when activated by Th2 cytokines, secrete eosinophil-specific chemokines like eotaxin 3 (CCL26), CCL17, and CCL22 that facilitate recruitment of eosinophils and effector Th2 cells in target organs, amplifying the immune response [29, 30].

A better comprehension of the physiopathology of EGPA highlights the role of eosinophils and IL-5. It has been observed that serum level of IL-5 correlates with disease activity and that it decreases with the initiation of immunosuppressive therapy [30–32].

4.2 Anti-IL-5 antibodies in EGPA

Interleukin-5 is well known as a key mediator in eosinophil activation. Thus, the efficacy of mepolizumab, a humanized monoclonal antibody against interleukin-5, was evaluated in EGPA patients.

Kahn et al. [33] published the first case of refractory EGPA treated with mepolizumab. The patient had many relapses despite treatment with GC, MTX, interferon alpha, CPh, IV immunoglobulin, AZA, and etoposide. Mepolizumab 750 mg IV monthly was started. After the first dose, asthma significantly improved, the eosinophil count decreased (reaching normal values), and the chest computed tomography (CT) showed complete regression of parenchymal findings. After 6 months of treatment, asthma symptoms disappeared, and chest CT did not show infiltrates, so an attempt to increase the intervals between mepolizumab infusions to 2 months was done which resulted in relapse with reappearance of asthma symptoms, interstitial lung infiltrates, and increase of peripheral eosinophilia. All parameters normalized with transient increase of prednisone and reintroduction of mepolizumab monthly infusions.

A single-center, phase 2, uncontrolled, investigator-initiated trial [34] included 10 consecutive patients with refractory or relapsing EGPA. Relapse was defined by a Birmingham Vasculitis Activity Score (BVAS) >3 despite treatment with IS plus GC at a dosage of 12.5 mg/day or higher. After stopping previous IS, the patients received nine infusions of mepolizumab, 750 mg monthly. Then it was switched to MTX maintenance therapy and a tapered dosage of GC as tolerated. Eight patients reached remission (BVAS = 0 and GC dosage <7.5 mg/day) after two or three mepolizumab infusions. One patient had a partial response (BVAS = 0 but did not achieve a GC dosage <7.5 mg/day), and another patient reached remission but was excluded owing to nonadherence. During mepolizumab treatment, no relapse occurred, the daily GC dose was reduced in all patients, and eosinophil count decreased after the first infusion. After switching mepolizumab to MTX, seven relapses occurred, over a median follow-up of 10 months. The same authors, in a later work [35], followed up these nine patients during a median of 22 months. Only three of them were still in remission at the end of the study. So, a high relapse rate after stopping mepolizumab was observed, which suggests that patients with EGPA could need a continuous treatment with mepolizumab.

An open-label pilot study [36] treated seven patients with four monthly doses of mepolizumab 750 mg IV to assess its steroid-sparing effect in GC-dependent EGPA patients. Mepolizumab allowed for safe GC reduction in all patients. The GC mean dose at baseline was 12.9 mg/day and after 12 weeks of therapy was 4.6 mg/day (64% reduction). On cessation of mepolizumab, EGPA manifestations recurred, needing steroid bursts. Mepolizumab was well tolerated, and the most frequent adverse events were headache, pruritus, and loose stools.

In 2017, a multicenter, double-blind, parallel-group, phase three trial was published [37]. It included 136 patients with relapsing or refractory EGPA, who had received treatment for at least 4 weeks and were taking a stable prednisolone or prednisone dose. They were randomized to receive 300 mg of mepolizumab (n = 68) or placebo (n = 68), administered subcutaneously (SC) every 4 weeks, plus standard care, for 52 weeks. Mepolizumab treatment led to significantly more accrued weeks of remission (defined as BVAS = 0 and prednisolone or prednisone ≤4 mg/day) than placebo (28 vs. 3% of the participants had ≥24 weeks of accrued remission) and a higher percentage of participants in remission at both weeks 36 and 48 (32 vs. 3%). Remission did not occur in 47% of the participants in the mepolizumab group vs. 81% of those in the placebo group. A total of 44% of the participants in the mepolizumab group, as compared with 7% of those in the placebo group, had an average daily dose of prednisolone or prednisone of ≤4 mg/day during weeks 48 through 52. Eighteen percent of the patients receiving mepolizumab were able to discontinue prednisolone or prednisone completely, as compared with 3% receiving placebo. Also, time to first relapse was longer, and annualized relapse rate was lower in the participants in the mepolizumab group. The most commonly adverse events with mepolizumab were headache, nasopharyngitis, arthralgia, sinusitis, and upper respiratory tract infection. A post hoc analysis [38] of the results according to peripheral eosinophilia (<150 cells/μl), GC dosage (>20 mg/day), and weight (>85 kg) was done. It showed that those patients treated with mepolizumab, with peripheral eosinophilia <150 cell/μl and weight >85 kg, had greater clinical benefit (BVAS = 0 and GC dosage ≤4 mg/day) than placebo. Although no significant differences were found in patients treated with GC dosage >20 mg/day, results favored mepolizumab treatment, but it must be considered that the study include few cases (n = 21).

Recently, Shiroshita et al. [39] published a case report of a 61-year-old man with refractory EGPA despite treatment with GC, CPh, and plasmapheresis who developed a diffuse alveolar hemorrhage. Rituximab and methylprednisolone

pulses were administered, and remission was obtained. Then mepolizumab 100 mg SC monthly was started that kept remission until now. To our knowledge, this is the first published paper where the authors used, in an EGPA patient, the same dosage and way of administration of mepolizumab used in severe asthma.

The Food and Drug Administration (FDA) approved the use of mepolizumab in adult patients with EGPA in the United States (USA), in December 2017, based on Wechsler [5] results, being the first biological treatment approved with this indication in data sheet [40–42]. The dosage of 300 mg, three times the recommended dose in severe eosinophilic asthma, is based on observations done in asthma, but no specific dose evaluation has been done in EGPA [42].

Another anti-IL5 monoclonal antibody, reslizumab, and an anti-IL5 receptor monoclonal antibody, benralizumab, are now being investigated for EGPA (NCT02947945 and NCT03010436, respectively) [43, 44].

5. Conclusions

The pathogenesis and role of ANCA in EGPA are mostly unknown, although it has been reported that patients with positive ANCA usually present renal involvement (glomerulonephritis), while those with negative ANCA usually have cardiac involvement (heart failure), possibly corresponding to two different subgroups with different characteristics still to be determined which will provide information and facilitate specific treatments. GC and IS are effective in EGPA, but relapses are frequent, and there is no standard therapy based on the results of randomized clinical trials. However, there is new data that shows mepolizumab as a good treatment option due to its clinical benefit, and its use in EGPA has recently been approved in the United States.

Advances in the knowledge of EGPA pathophysiology together with the appearance of new drugs, such as mepolizumab, seems to be a solution to the unmet needs in this disease.

Author details

Carlos Melero Moreno[1*], Marta Corral Blanco[2] and Rocío Magdalena Díaz Campos[2]

1 Institute for Health Research (i+12), Hospital Universitario 12 de Octubre, Madrid, Spain

2 Pneumology Service, Hospital Universitario 12 de Octubre, Madrid, Spain

*Address all correspondence to: cmelero@separ.es

References

[1] Fujimoto S, Watts RA, Kobayashi S, Suzuki K, Jayne DR, Scott DG, et al. Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the UK. Rheumatology. 2011;**50**:1916-1920

[2] Gonzalez-Gay MA, Garcia-Porrua C, Guerrero J, Rodriguez-Ledo P, Llorca J. The epidemiology of the primary systemic vasculitides in Northwest Spain: Implications of the Chapel Hill consensus conference definitions. Arthritis and Rheumatism. 2003;**49**:388-393

[3] Reinhold-Keller E, Herlyn K, Wagner-Bastmeyer R, Gross WL. Stable incidence of primary systemic vasculitides over five years: Results from the German vasculitis register. Arthritis and Rheumatism. 2005;**53**:93-99

[4] Mohammad AJ, Jacobsson LT, Westman KW, Sturfelt G, Segelmark M. Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa. Rheumatology. 2009;**48**:1560-1565

[5] Watts RA, Lane SE, Bentham G, Scott DG. Epidemiology of systemic vasculitis: A ten-year study in the United Kingdom. Arthritis and Rheumatism; 2000;**43**:414-419

[6] Martin RM, Wilton LV, Mann RD. Prevalence of Churg-Strauss syndrome, vasculitis, eosinophilia and associated conditions: Retrospective analysis of 58 prescription-event monitoring cohort studies. Pharmacoepidemiology and Drug Safety. 1999;**8**:179-189

[7] Mahr A, Guillevin L, Poissonnet M, Ayme S. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: A capture-recapture estimate. Arthritis and Rheumatism. 2004;**51**:92-99

[8] Sada KE, Amano K, Uehara R, Yamamura M, Arimura Y, Nakamura Y, et al. A nationwide survey on the epidemiology and clinical features of eosinophilic granulomatosis with polyangiitis (Churg-Strauss) in Japan. Modern Rheumatology. 2014;**24**:640-644

[9] Furuta S, Iwamoto T, Nakajima H. Update on eosinophilic granulomatosis with polyangiitis. Allergology International. 2019; pii: S1323-8930(19)30081-4. DOI: 10.1016/j.alit.2019.06.004. [Epub ahead of print]

[10] Thompson GE, Specks U. Update on the management of respiratory manifestations of the antineutrophil cytoplasmic antibodies-associated vasculitides. Clinics in Chest Medicine. 2019;**40**:573-582

[11] Matsumoto K, Suzuki K, Yoshimoto K, Seki N, Tsujimoto H, Chiba K, et al. Significant association between clinical characteristics and immune-phenotypes in patients with ANCA-associated vasculitis. Rheumatology. 2019. pii: kez327. DOI: 10.1093/rheumatology/kez327. [Epub ahead of print]

[12] Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Annals of the Rheumatic Diseases. 2016;**75**:1583-1594

[13] Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Toumelin PL. The five-factor score revisited. Medicine. 2011;**90**:19-27

[14] Cottin V, Bel E, Bottero P, Dalhoff K, Humbert M, Lazor R. Respiratory

manifestations of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). The European Respiratory Journal. 2016;**48**:1429-1441

[15] Sinico RA, Bottero P. Churg-Strauss angiitis. Best Practice & Research. Clinical Rheumatology. 2009;**23**:355-366

[16] Groh M, Pagnoux C, Baldini C, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) consensus task force recommendations for evaluation and management. European Journal of Internal Medicine. 2015;**26**:545-553

[17] Comarmond C, Pagnoux C, Khellaf M, Cordier JF, Hamidou M, Viallard JF, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): Clinical characteristics and long-term followup of the 383 patients enrolled in the French vasculitis study group cohort. Arthritis and Rheumatism. 2013;**65**:270-281

[18] Ribi C, Cohen P, Pagnoux C. Treatment of Churg-Strauss syndrome without poor-prognosis factors: A multicenter, prospective, randomized, open-label study of seventy-two patients. Arthritis and Rheumatism. 2008;**58**:586-594

[19] Bosch X, Guilabert A, Espinosa G, et al. Treatment of antineutrophil cytoplasmic antibody associated vasculitis: A systematic review. JAMA. 2007;**298**:655-659

[20] Samson M, Puéchal X, Devilliers H, Ribi C, Cohen P, Stern M. Long-term outcomes of 118 patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) enrolled in two prospective trials. Journal of Autoimmunity. 2013;**43**:60-69

[21] Bourgarit A, Le Toumelin P, Pagnoux C, Cohen P, Mahr A, Le Guern V, et al. Deaths occurring during the first year after treatment onset for polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: A retrospective analysis of causes and factors predictive of mortality based on 595 patients. Medicine. 2005;**84**:323-330

[22] Gayraud M, Guillevin L, le Toumelin P, et al. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: Analysis of four prospective trials including 278 patients. Arthritis and Rheumatism. 2001;**44**:666-675

[23] Cohen P, Pagnoux C, Mahr A, Aréne JP, Mouthon L, Le Guern V, et al. Churg-Strauss syndrome with poor-prognosis factors: A prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. Arthritis and Rheumatism. 2007;**57**:686-693

[24] Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. The New England Journal of Medicine. 2008;**359**:2790-2803

[25] Pagnoux C, Guilpain P, Guillevin L. Churg-Strauss syndrome. Current Opinion in Rheumatology. 2007;**19**:25-32

[26] Chakraborty RK, Aeddula NR. Churg Strauss Syndrome (Allergic Granulomatosis). Treasure Island: StatPearls Publishing; 2019. StatPearls [Internet]

[27] Martínez-Moczygemba M, Huston DP. Biology of common beta receptor-signaling cytokines: IL-3, IL-5 and GM-CSF. The Journal of Allergy and Clinical Immunology. 2003;**112**:653-665

[28] Jakiela B, Szczeklik W, Sokolowska B, Mastalerz L, Sanak M,

Plutecka H, et al. Intrinsic pathway of apoptosis in peripheral blood eosinophils of Churg-Strauss syndrome. Rheumatology. 2009;**48**:1202-1207

[29] Zwerina J, Bach C, Martorana D, Jatzwauk M, Hegasy G, Moosig F, et al. Eotaxin-3 in Churg-Strauss syndrome: A clinical and immunogenetic study. Rheumatology. 2011;**50**:1823-1827

[30] Polzer K, Karonitsch T, Neumann T, Eger G, Haberler C, Soleiman A, et al. Eotaxin-3 is involved in Churg-Strauss syndrome—A serum marker closely correlating with disease activity. Rheumatology. 2008;**47**:804-808

[31] Jakiela B, Sanak M, Szczeklik W, Sokolowska B, Plutecka H, Mastalerz L, et al. Both Th2 and Th17 responses are involved in the pathogenesis of Churg-Strauss syndrome. Clinical and Experimental Rheumatology. 2011;**29**:S23-S34

[32] Dallos T, Heiland GR, Strehl J, Karonitsch T, Gross WL, Moosig F, et al. CCL17/thymus and activation-related chemokine in Churg-Strauss syndrome. Arthritis and Rheumatism. 2010;**62**:3496-3503

[33] Kahn JE, Grandpeix-Guyodo C, Marroun I, Catherinot E, Mellot F, Roufosse F, et al. Sustained response to mepolizumab in refractory Churg-Strauss syndrome. The Journal of Allergy and Clinical Immunology. 2010;**125**:267-270

[34] Moosig F, Gross WL, Herrmann K, Bremer JP, Hellmich B. Targeting interleukin-5 in refractory and relapsing Churg-Strauss syndrome. Annals of Internal Medicine. 2011;**155**:341-343

[35] Herrmann K, Gross WL, Moosig F. Extended follow-up after stopping mepolizmab in relapsing/refractory Churg-Strauss syndrome. Clinical and Experimental Rheumatology. 2012;**30**(Suppl. 70): S62-S65

[36] Kim S, Marigowda G, Oren E, Israel E, Wechsler ME. Mepolizumab as a steroid-sparing treatment option with Churg-Strauss syndrome. The Journal of Allergy and Clinical Immunology. 2010;**125**:1336-1343

[37] Wechsler ME, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. The New England Journal of Medicine. 2017;**376**:1921-1932

[38] Steinfeld J, Bradford ES, Brown J, Mallet S, Yancey SW, Akuthota P, et al. Evaluation of clinical benefit from treatment with mepolizumab for patients with eosinophilic granulomatosis with polyangiitis. The Journal of Allergy and Clinical Immunology. 2019;**143**:2170-2177

[39] Shiroshita A, Nakashima K, Motojima S, Aoshima M. Refractory diffuse alveolar hemorrhage caused by eosinophilic granulomatosis with polyangiitis in the absence of elevated biomarkers treated successfully by rituximab and mepolizumab: A case report. Respiratory Medicine Case Reports. 2019;**26**:112-114

[40] Faverio P, Bonaiti G, Bini F, Vaghi A, Pesci A. Mepolizumab as the first targeted treatment for eosinophilic granulomatosis with polyangiitis: A review of current evidence and potential place in therapy. Therapeutics and Clinical Risk Management. 2018;**14**:2385-2396

[41] GSK achieves approval for Nucala (mepolizumab) for the treatment of eosinophilic granulomatosis with polyangiitis (EGPA) for adults in the U.S. [news release]. GlaxoSmithKline plc. 12 December 2017

[42] Raffray L, Guillevin L. Treatment of eosinophilic granulomatosis with polyangiitis: A review. Drugs. 2018;**78**:809-821

[43] U.S. National Library of Medicine. Reslizumab in the treatment of eosinophilic granulomatosis with polyangiitis (EGPA) study. [Internet]. ClinicalTrials.gov identifier: NCT02947945. Available from: https://clinicaltrials.gov/ct2/show/NCT02947945

[44] U.S. National Library of Medicine. Benralizumab in the treatment of eosinophilic granulomatosis with polyangiitis (EGPA) study. [Internet]. ClinicalTrials.gov identifier: NCT03010436. [cited 2019 Aug 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT03010436