

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

171,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Current Treatment of ANCA Vasculitis

Yosra Bouattour, Mouna Snoussi and Zouhir Bahloul

Abstract

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) constitute a group of necrotizing systemic vasculitis with preferential involvement of small- to medium-sized vessels. None treated; they are considered as a life-threatening illness by their renal, cardiac and neurologic damages. Therefore, treatment is usually aggressive, with high-dose corticosteroid therapy combined with immunosuppressive drugs in the major part of cases. New biologic drugs have been introduced such as rituximab. In this chapter, we will present the update and recent advances in the treatment of AAV.

Keywords: ANCA vasculitis, granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis, Eosinophilic granulomatous with polyangiitis, treatment

1. Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) constitute a group of necrotizing systemic vasculitis with preferential involvement of small- to medium-sized vessels. They represent serious disorders, and three clinical subtypes are involved: granulomatosis with polyangiitis (GPA; formerly Wegener's disease), microscopic polyangiitis (MPA) and eosinophilic GPA (EGPA; formerly Churg Strauss Syndrome). They share similar pathogenic mechanisms, and most patients have only one ANCA serotype detected in their serum [1, 2]. Non-treated, they were considered as fatal or life-threatening illnesses. In the last two decades, better knowledge of pathogenic mechanisms and progression in classification criteria improved therapeutic management [3–5]. Treatment is usually aggressive, with high-dose corticosteroid therapy combined with immunosuppressive drugs in the major part of cases. New biologic drugs have been introduced such as rituximab [4]. In this chapter, we will present the update and recent advances in the treatment of AAV.

2. Pathogenesis of ANCA-associated vasculitis: new paths for intervention

The etiology of AAV remains poorly understood, and research on their pathogenesis focuses on the role of ANCAs themselves [4].

2.1 Role of ANCA antibodies and neutrophils

ANCAs, which represent autoantibodies directed against neutrophil cytoplasmic proteins, recognize a range of antigens. Only two relevant protein targets are identified, called proteinase 3 (PR3) and myeloperoxidase (MPO). These proteins are found in the primary granules of neutrophils and are involved in defense against microbes [5].

During AAV and in small vessels, a pathological and sustained interaction occurs between ANCA and abnormally activated neutrophils. Thus, in the systemic form of GPA, ANCAs recognize PR3 in about 75% of cases. Whereas MPO-ANCA is more commonly associated with MPA (60%) and EGPA (50%) [5–7].

Experimental and clinical data provide evidence that ANCAs and neutrophils are the key players in pathogenesis. In response to inflammation or infection, neutrophils exposed to cytokines (interleukin 1, tumor necrosis factor α ...) or complement C5a become primed with movement of MPO and PR3 from primary granules to the cell surface. ANCAs bind to these autoantigens on the neutrophil surface. Neutrophils become activated and bind to vascular endothelium, resulting in tissue damage.

2.2 Role of the complement system, cellular and humeral immunity

The pathogenesis of AAV also involves [5–8]

- A. Activation of the alternative complement pathway responsible for the amplification of neutrophil-ANCA activation.
- B. Monocytes and macrophages: in the formation of the classic GPA granuloma.
- C. B and T lymphocytes: in the occurrence of endothelial damage and granuloma formation.
- D. Eosinophilic polynuclear cells: The blood level of eosinophils can be high in the various vasculitis. These cells have cytotoxic granules that can contribute to cardiac involvement and vascular damage as seen in EGPA [7].

2.3 Predisposing factors for ANCA-associated vasculitis

- A. Environmental factors:
 - Pesticides, asbestos, smoke and silica.
 - A number of therapeutic agents are responsible for drug-induced AAV such as propylthiouracil, benzylthio-uracil and hydralazine ... [5].
 - Chronic carriage of staphylococcus aureus which is reported to be a risk factor for relapse in GPA.
- B. Genetic predisposition: Familial cases of AAV have been reported and predisposing HLA haplotypes such as HLA DPB1 [8].

3. Classification and prognostic score of ANCA-associated vasculitis

3.1 Classification criteria of ANCA-associated vasculitis:

3.1.1 Granulomatosis with polyangiitis

Granulomatosis with polyangiitis (GPA), formerly named Wegner's disease, is characterized by vessel wall inflammation, peri- and extra-vascular granulomatosis. Its annual incidence is 10.2 cases per million people, and its prevalence is between 24 and 150 cases per million people [9]. Caucasians are the most affected persons according to researches conducted in Europe [10]. GPA is diagnosed at an age of 35–55 years with no gender predominance.

This disease involves mainly upper and lower airways, ear nose throat sphere and kidney. Nasosinus involvement occurs in 70–100% of patients as epistaxis, nasal septum deformation or perforation [11, 12]. Lungs manifestations affect 50–90% of the patients as lung nodules, cavitations, pleuritis and/or alveolar hemorrhages. Renal involvement affects 40–100% of patients as abnormalities in urine sediment and renal failure. Other systemic manifestations may include arthralgia, anorexia, weight loss, ocular involvement (episcleritis, uveitis, retinal thrombosis, orbital pseudotumor...) myocarditis [11]. Recently, a new criteria set has been approved and validated by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR). The aim of the classification criteria is to differentiate GPA from other types of small- or medium-vessel vasculitis (**Table 1**) [13].

A limited form of GPA is defined by the presence of upper airways and/or pulmonary involvement without alveolar hemorrhage. There is no renal involvement or life-threatening conditions.

A diffuse or severe form of GPA is known by the presence of a severe renal dysfunction and/or progressive alveolar hemorrhage and/or life-threatening organ involvement.

Clinical criteria	
Nasal involvement: bloody discharge ulcers, crusting, congestion, blockage, septal defect/perforation	+3
Cartilaginous involvement (inflammation, of ear or nose cartilage, hoarse voice or stridor, endobronchial involvement or saddle nose deformity)	+2
Conductive or sensorineural hearing loss	+1
Laboratory, imaging and biopsy criteria	
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (c ANCA) or antiproteinase 3 (anti-PR3) antibodies	+5
Pulmonary nodules, mass or cavitation on chest imaging	+2
Granuloma, extravascular granulomatous inflammation or giant cells on biopsy	+2
Pauci-immune glomerulonephritis on biopsy	+1
Positive test for perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antimyeloperoxidase (anti-MPO) antibodies	-1
Blood eosinophil count $\geq 1 \times 10^9$ /liter	-4

Table 1.
 2022 American college of rheumatology (ACR)/European alliance of associations for rheumatology [13].

3.1.2 Eosinophilic granulomatosis with polyangiitis

Eosinophilic granulomatosis with polyangiitis (EGPA) formerly known as Churg–Strauss syndrome is a rare systemic small-vessel vasculitis associated with asthma and eosinophilia. EGPA is the least common systemic vasculitis among AAV with an annual incidence of 4.2 cases per million people and a prevalence of 10.7 per million people [14]. It affects people aged between 40 and 60 years with no gender predominance or ethnic predisposition [15, 16]. In 1990, ACR defined the classification criteria for EGPA including asthma, eosinophilia >10%, neuropathy, non-fixed lung infiltrates, paranasal sinus abnormalities and extravascular eosinophils on biopsy (**Table 2**) [17]. EGPA should be suspected in a patient with an adult-onset asthma and multiple systemic manifestations (asymmetric neuropathy, purpura or skin ulcers, cardiac, pulmonary and/or renal involvement ...). Laboratory data show mainly peripheral eosinophilia (>1500 cells/ μ L) correlated with the disease activity [18]. MPO-ANCA with perinuclear Immunofluorescence (pANCA) are noted in 50% [5]. Histologic findings confirm the leukocytoclastic vasculitis with eosinophilic granulomas in different biopsy sites (lung, kidney...).

3.1.3 Microscopic polyangiitis

MPA is a systemic necrotizing vasculitis with a pneumo-renal tropism. Capillaritis is the cause of its main feature including alveolar hemorrhage and rapidly progressive glomerulonephritis. The annual incidence of MPA is about 5.8 cases per million people [14]. MPA affects older patients compared to other AAV (between 50 and 60 years) [19]. Some studies suggest that increased life expectancy may contribute to the increased incidence of this disease [20]. Men are more frequently affected than women [14]. Other clinical manifestations may include general signs (fever, weight loss) in 70% of patients, skin lesions as vascular purpura, peripheral neuropathy, liver dysfunction and gastrointestinal manifestations. MPO-ANCA are detected in about 50% of cases, but its absence does not exclude its diagnosis [5]. Histological data allow the differentiation of MPA from other AAV. This entity is characterized by the absence of eosinophilic tissue infiltration found in EGPA and granulomas found mainly in GPA but also in EGPA.

3.1.4 Five-factor score: a prognosis score of ANCA-vasculitis

The five-factor score (FFS) for AAV is used to evaluate prognosis at diagnosis of the vasculitis. The following factors were significantly combined with higher five-year mortality: age > 65 years, cardiac involvement, renal insufficiency (creatinine \geq 150 μ mol/L) and gastrointestinal symptoms. The presence of each was scored +1

-
1. Asthma
 2. Eosinophilia >10%
 3. Neuropathy (mono- or poly-neuropathy)
 4. Non-fixed pulmonary infiltrates
 5. Paranasal sinus abnormalities
 6. Extravascular eosinophil infiltration on biopsy
- At least four of the six ACR criteria are required.
-

Table 2.
ACR classification of EGPA [17].

Age > 65 years
Cardiac insufficiency
Renal insufficiency (Creatinemia > 150 µmol/L)
Gastrointestinal involvement
Absence of ear, nose and throat manifestation for GPA and EGPA.
One point for each of these five items when present.

Table 3.
Revised 2011 Five-Factor score in AAV [21].

point. Whereas ear, nose and throat (ENT) involvement, affecting patients with GPA and EGPA, were associated with a lower risk of death. Their absence was accorded +1 point (**Table 3**) [21].

4. Treatment of granulomatosis with polyangiitis

The choice of treatments in GPA depends on several forms of the disease (limited vs. diffuse), patient's age, his overall physiological state and in particular his renal function. At present, the choice of treatment according to the immunological profile (ANCA-PR3, ANCA-MPO or ANCA-negative) remains a subject of controversy [22].

4.1 Remission induction therapy

Regardless the clinical form of GPA, the treatment is based on a combination of corticosteroids with immunosuppressant drug or rituximab. Corticosteroids are used at a dose of 1 mg/kg/day, preceded by methylprednisolone pulses (7.5 to 15 mg/kg/day) in severe or active cases. The choice of the immunosuppressant drug depends on the clinical form and extent of the disease [22, 23].

4.2 Non-severe or limited forms of granulomatosis with polyangiitis

Methotrexate, rituximab and cyclophosphamide are effective at inducing remission the limited form of GPA. Although, methotrexate is currently recommended in this patient group [24]. The weekly dose is 0.3 mg/kg. According to the NORAM study, its efficacy is comparable to that of cyclophosphamide with a lower risk of infection. Also, mycophenolate mofetil (MMF) is effective as an induction therapy for the limited form of GPA with satisfactory results. Rituximab may be used for patients with recurrent relapses while receiving methotrexate or concerns regarding compliance [24].

4.3 Severe or diffuse forms of granulomatosis with polyangiitis

Both rituximab and cyclophosphamide, in combination with glucocorticoids, have been used for remission induction in GPA [24]. Corticosteroids with cyclophosphamide have always represented the gold standard in the treatment of diffuse forms of GPA. Cyclophosphamide can be administered per os (2mg/kg/day) or by intravenous pulses (15mg/kg every 2 weeks for the first 3 pulses then every 3 weeks) for an initial duration of 3 to 6 months. According to the studies, they have comparable results in terms of efficiency and average survival. However, due to the high cumulative dose of the oral route, this modality is associated with a high risk of infectious

events [25, 26]. Rituximab or anti-CD20 is now preferred over cyclophosphamide for many reasons. Its efficiency in inducing remission has been proven by numerous studies, especially for relapsed diffuse forms [22, 27, 28]. It is a better-tolerated treatment and is considered less toxic than cyclophosphamide. It has lower risks of malignancy and/or infertility. Also, the risk of infectious complications is almost the same between these two drugs [29]. Rituximab has been approved for use in GPA as a weekly infusion of 375 mg/m² for 4 consecutive weeks or as two 1-gram infusions spaced two weeks apart. Currently, it is prescribed for relapsed patients, those of childbearing age and/or those who have already received high cumulative doses of cyclophosphamide. A duration of 3 months may be required to achieve maximum therapeutic benefit.

As in all AAVs and by extrapolation to their efficiency in Goodpasture's syndrome, plasma exchange is indicated in severe forms of GPA with alveolar hemorrhage and/or glomerulonephritis. The MEPEX study showed their efficacy in patients with severe renal impairment (creatinine level over 500 $\mu\text{mol/l}$), but this action is not maintained over the long term [30]. The benefit was most pronounced in patients with the highest risk of end-stage renal disease [24]. Polyvalent immunoglobulins are recommended for relapsing or severe disease. The total dose of infusions is 2 g/kg over 2 or 5 days.

4.4 Remission maintenance therapy

To reduce its iatrogenicity, gradual tapering of corticosteroids is preferable after inducing remission.

- Remission maintenance treatments for non-severe or limited forms of GPA are based on the same immunosuppressant used in the induction phase (methotrexate, MMF) [22]. Methotrexate should be taken for a long-term period (several years). According to the NORAM study, stopping methotrexate at one year of progression increases the risk of relapse of GPA [23]. For diffuse forms of GPA, methotrexate and azathioprine represented the conventional remission maintenance drugs in the last years. The WEGENT study concluded that they have comparable results in terms of efficiency, safety and relapse frequency [31]. Rituximab is mentioned in the latest European EULAR/ERA-EDTA guidelines as a remission maintenance drug. Several prospective and retrospective studies have compared rituximab with other molecules such as azathioprine. The results of these studies were in favor of a greater reduction in the relapse rate of GPA by rituximab [22]. Therefore, rituximab is now favored and highly recommended over methotrexate or azathioprine for maintaining remission of severe GPA, but cost and other factors may limit rituximab use [24]. Upon remission of GPA, this biomedicine is started within 1 month of the last cyclophosphamide infusion or 4 to 6 months after the start of rituximab induction therapy. It is administered in 5 infusions of 500 mg over 18 months (at D1 and D15 then every 6 months for 18 months) (FDA-approved) [22].

5. Treatment of eosinophilic granulomatosis with polyangiitis

5.1 Conventional therapeutic regimen

Like other AAV, corticosteroids are the treatment's cornerstone for GEPA. Depending on the severity of the presentation, high-dose corticosteroids are oftenly

initiated with pulses of methylprednisolone (15 mg/kg). It is recommended for a minimum period of 4 weeks followed by a taper. This helps to control asthma, general signs and hypereosinophilia [32]. Corticosteroids are prescribed alone or combined with an immunosuppressant after evaluation of the clinical presentation by the FFS.

- If the FFS is equal to 0: These patients have no poor prognostic factors. Corticosteroids are sufficient to achieve remission in more than 70% of cases [32]. Cyclophosphamide is used in case of relapse or resistance to corticosteroids [33]. Survival rates in this group are important even in case of relapse.
- If the FFS is equal to or more than 1: Intravenous pulse cyclophosphamide should be combined. Treatment strategy recommends 6 pulses in less than 4 months (15 mg/kg every two weeks for three doses and then every three weeks for three doses). For remission maintenance, azathioprine at a dose of 2 mg/kg/day or methotrexate at a dose of 0.3 mg/Kg/week will be used for 12 to 18 months depending on the evolution [34].

5.2 Therapeutic alternatives

There have been very few randomized controlled trials conducted to date in EGPA. Rituximab is not yet validated as an alternative to cyclophosphamide in GEPA. Due to the rarity of this disease compared to other AAV, a small number of therapeutic trials have been reported in the literature with conflicting results. Some studies confirm the efficiency of this biomedicine especially in case of relapse [35–38] and particularly in patients with a positive vasculitis/anti-MPO profile [39]. Nevertheless, in addition to infectious complications, rituximab has been incriminated in the occurrence of severe bronchospasm secondary to a hypersensitivity reaction [39].

Recently, interleukin-5 inhibitors have been introduced into the GEPA therapeutic regimen. Mepolizumab is a humanized monoclonal antibody against interleukin-5. It has been approved for use in severe eosinophilic asthma. In refractory forms of GEPA, it was effective in remission induction and maintenance due to its immunosuppressive properties [40, 41]. A recent international randomized, controlled and double-blind study compared the effect of mepolizumab versus placebo in refractory GEPA treated with corticosteroids combined or not with immunosuppressive treatment. Long-term remission of GEPA was noted in the group using mepolizumab [42].

Anti-IgE drugs such as omalizumab have been used during severe allergic asthma. For GEPA, the results of the use of this biomedicine are variable and contradictory. As previously described, omalizumab has been incriminated as an unmasking factor for underlying vasculitis [43]. Other studies suggest its efficacy during GEPA especially for pulmonary relapses but also as a cortisone-sparing agent [44, 45]. In conclusion, further data are needed before omalizumab can be recommended or contraindicated in the treatment of GEPA [36].

6. Treatment of microscopic polyangiitis

Management of MPA is based on remission induction therapy and remission maintenance therapy. For non-renal forms with an FFS equal to zero, corticosteroids are used alone as a first-line treatment to induce remission. An immunosuppressant will be associated in case of non-response, relapse or dependence on corticosteroids

but also in case of extension to a systemic form with involvement of other organs (cardiac, renal, CNS ...). However, high-dose corticosteroids associated with rituximab or cyclophosphamide are recommended for severe forms of MPA with a life-threatening outcome [22]. Azathioprine and methotrexate have been validated as remission maintenance treatments [31]. By extrapolation of their efficacy in good pasture's syndrome, plasma exchange is indicated in fulminant forms of MPA with severe renal involvement and/or alveolar hemorrhage. Currently, rituximab is also recommended for remission induction in case of refractory disease [28].

7. Associated treatments in ANCA-associated vasculitis

Management of AAV includes other therapeutic measures such as local and/or surgical treatment of ENT manifestations in GPA and EGPA (nasal irrigations,

Type of vasculitis	Phase of treatment	Form of vasculitis	Recommendation/ statement	Level of evidence	Associated treatment
GPA/MPA	Remission induction therapy	Active non-severe/limited form of GPA	High dose of GCs + MTX (over CYC, RTX, AZA or MMF)	Very low to moderate	-Cotrimoxazole -Local or surgical treatment of ENT manifestations -Kinesitherapy and symptomatic treatments for neuropathic manifestations
		Active severe form of GPA/MPA	High dose of GCs + RTX (over CYC)		
	Remission maintenance therapy	Non-severe/limited form of GPA	GCs + MTX, AZA or MMF (continue the same medication)	-	
		severe form of GPA/MPA	Patients whose disease has entered remission after treatment with CYC or RTX: GCs + RTX (over MTX or AZA)	Very low to moderate	
EGPA	Remission induction therapy	Active non-severe form of EGPA	GCs alone or with MEP (over MTX, AZA or MMF)	Very low to low	
		Active severe form of EGPA	High dose of GCs + either CYC or RTX (over MEP)	Very low	
	Remission maintenance therapy	Non-severe limited form of EGPA	CGs	-	
		severe form of EGPA	Patients whose disease has entered remission after treatment with CYC: GCs + MTX, AZA or MMF (over RTX or MEP)	Very low	

GPA: granulomatosis with polyangiitis, MPA: microscopic polyangiitis, EGPA: eosinophilic granulomatosis with polyangiitis, GCs: glucocorticoids MTX: methotrexate, AZA: azathioprine, MMF: mycophenolate mofetil, CYC: cyclophosphamide, MEP: mepolizumab, ENT: ear nose throat.

Table 4. Recommendations/statements for the management of ANCA vasculitis [24].

nebulizations, polyposis resection ...), kinesitherapy and symptomatic treatments for neuropathic symptoms and hemodialysis in end-stage renal disease. In addition, complications related to the long-term use of corticosteroids should be managed (hypertension, diabetes ...) [28].

Cotrimoxazole (trimethoprim/sulfamethoxazole) is highly recommended in AAV and should be discussed in case of lymphopenia. Especially in GPA, it prevents from pneumocystis and has a role in remission maintenance of this vasculitis (**Table 4**).

8. Conclusion

Significant advancements in pathogenic knowledge helped to improve the management and the prognosis of patients suffering from AAV. This group of rare systemic vasculitis has now earlier remissions and lower relapse rates but needs urgent and aggressive treatment based on corticosteroids and immunosuppressant agents most of the time. Nowadays, rituximab has gained popularity because of his efficiency and less toxic properties. It is now preferred in severe cases of GPA and MPA. It was even more potent than cyclophosphamide in relapsing forms of the diseases. Our understanding of the pathogenesis continues to expand, and targeting specific pathogenic pathways is needed to improve the outcome.

Author details

Yosra Bouattour, Mouna Snoussi* and Zouhir Bahloul
Department of Internal Medicine, Hedi Chaker Hospital, Medical School of Sfax,
Tunisia

*Address all correspondence to: mounasnoussi23@gmail.com

IntechOpen

© 2023 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Meddeb Z, Larbi T, El Ouni A, Toujani S, Abdelkafi C, Hamzaoui S, et al. ANCA-associated vasculitis: About a Tunisian cohort. *Review Internal Medicine*. 2017;**38**:A116-A117
- [2] Cohen Tervaert JW. Trimethoprim-sulfamethoxazole and antineutrophil cytoplasmic antibodies-associated vasculitis. *Current Opinion in Rheumatology*. 2018;**30**(4):388-394
- [3] The European Vasculitis Study Group. French Vasculitis Study Group. Disponible en: [http:// www.vascularites.org/index.php](http://www.vascularites.org/index.php)
- [4] Ilva F, Cisternas M. Vasculitis asociadas a anticuerpos anti-citoplasma de neutrófilos: avances en patogenia y tratamiento [anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis: Advances in pathogenesis and treatment]. *Revista Médica de Chile*. 2013;**141**(6):765-773
- [5] Geetha D, Jefferson JA. ANCA-associated Vasculitis: Core curriculum 2020. *American Journal of Kidney Diseases*. 2020;**75**(1):124-137
- [6] Lionaki S, Blyth ER, Hogan SL, et al. Classification of antineutrophil cytoplasmic autoantibody vasculitides: The role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. *Arthritis and Rheumatism*. 2012;**64**(10):3452-3462
- [7] Mouthon L, Millet A, Regent A, Pederzoli-Ribeil M, Witko-Sarsat V. Pathophysiology of ANCA-positive vasculitides. *Presse Médicale*. 2012;**41**(10):996-1003
- [8] Li W, Huang H, Cai M, Yuan T, Sheng Y. Antineutrophil cytoplasmic antibody-associated Vasculitis update: Genetic pathogenesis. *Frontiers in Immunology*. 2021;**26**:624848
- [9] Watts RA, Mahr A, Mohammad AJ, Gatenby P, Basu N, Flores-Suarez LF. Classification, epidemiology and clinical subgrouping of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. *Nephrology Dialysis Transplantation*. 2015;**30**(suppl_1):i14-i22
- [10] Watts RA, Lane SE, Scott DG, Koldingsnes W, Nossent H, Gonzalez-Gay MA, et al. Epidemiology of vasculitis in Europe. *Annals of the Rheumatic Diseases*. 2001;**60**(12):1156-1157
- [11] de Guevara DL, Cerda F, Carreño MA, Piottante A, Bitar P. Update in the study of granulomatosis with polyangiitis (Wegener's granulomatosis). *Revista Chilena de Radiología*. 2019;**25**(1):26-34
- [12] Salah RB, Frikha F, Snoussi M, Abderrahmen M, Hentati Y, Mnif Z, et al. Limited form of Wegener's granulomatosis in a patient with Crohn's disease. A case report. *The Turkish Journal of Gastroenterology*. 2014;**25**(Suppl.-1):191-195
- [13] Robson JC, Grayson P, Ponte C, Suppiah R, Craven A, Judge A, et al. 2022 American College of Rheumatology/ European Alliance of associations for rheumatology classification criteria for granulomatosis with polyangiitis. *Arthritis and Rheumatology*. 2022;**74**(3):393-399
- [14] Watts RA, Lane S, Scott DGI. What is known about the epidemiology of the vasculitides? *Best Practice*

Research Clinical Rheumatology.
2005;**19**(2):191-207

[15] Zwerina J, Eger G, Englbrecht M, Manger B, Schett G. Churg–Strauss syndrome in childhood: A systematic literature review and clinical comparison with adult patients. *Seminars in Arthritis and Rheumatism*. 2009;**39**:108-115

[16] Piram M, Maldini C, Mahr A. Effect of race/ethnicity on risk, presentation and course of connective tissue diseases and primary systemic vasculitides. *Current Opinion in Rheumatology*. 2012;**24**:193-200

[17] Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology criteria for the classification of Churg–Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis & Rheumatology*. 1990;**33**:1094-1100

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

[19] Pagnoux C, Guilpain P, Guillevin L. Polyangéite microscopique. *Presse Médicale*. 2007;**36**(5):895-901

[20] Puéchal X, Pagnoux C, Baron G, Quémeneur T, Néel A, Agard C, et al. Adding azathioprine to remission-induction glucocorticoids for eosinophilic granulomatosis with polyangiitis (Churg-Strauss), microscopic polyangiitis, or polyarteritis nodosa without poor prognosis factors: A randomized, controlled trial. *Arthritis Rheumatology*. 2017;**69**(11):2175-2186

[21] Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Toumelin PL. French Vasculitis Study Group (FVSG). The Five-Factor Score revisited: assessment of prognoses of systemic

necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine (Baltimore)*. Jan 2011;**90**(1)

[22] Makhzoum J-P, Pagnoux C. Actualités thérapeutiques de la granulomatose avec polyangéite (Wegener) et de la polyangéite microscopique. Review in *Rheumatic Monograph*. 2017;**84**(3):242-248

[23] De Groot K, Rasmussen N, Bacon PA, Tervaert JWC, Feighery C, Gregorini G, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheumatology*. 2005;**52**(8):2461-2469

[24] Chung SA, Langford CA, Maz M, Abril A, Gorelik M, Guyatt G, et al. 2021 American College of Rheumatology/ Vasculitis Foundation guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. *Arthritis & Rheumatology*. 2021;**73**(8):1366-1383

[25] de Groot K, Adu D, Savage CO, EUVAS (European vasculitis study group). The value of pulse cyclophosphamide in ANCA-associated vasculitis: meta-analysis and critical review. *Nephrology Dialysis Transplantation Off Publ Eur Dial Transpl Assoc*. 2001;**16**(10):2018-2027

[26] Harper L, Morgan MD, Walsh M, Høglund P, Westman K, Flossmann O, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: Long-term follow-up. *Annals of Rheumatic Diseases*. 2012;**71**(6):955-960

[27] Keogh KA, Wylam ME, Stone JH, Specks U. Induction of remission by B lymphocyte depletion in eleven

patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheumatic*. 2005;**52**(1):262-268

[28] Jones RB, Ferraro AJ, Chaudhry AN, Brogan P, Salama AD, Smith KGC, et al. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheumatic*. 2009;**60**(7):2156-2168

[29] Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated Vasculitis. *The New England Journal of Medicine*. 2010;**363**(3):221-232

[30] Jayne DRW, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *Journal of American Society Nephrology JASN*. 2007;**18**(7):2180-2188

[31] Long-Term Outcomes Among Participants in the WEGENT Trial of Remission. Maintenance Therapy for Granulomatosis With Polyangiitis (Wegener's) or Microscopic Polyangiitis. *Arthritis Rheumatology*. 2016;**68**(3):690-701

[32] Charles P, Terrier B, Perrodeau É, Cohen P, Faguer S, Huart A, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: Results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). *Annals of Rheumatic Diseases*. 2018;**77**(8):1143-1149

[33] La GL. granulomatose éosinophilique avec polyangéite (syndrome de Churg et Strauss). *Presse Médicale*. 2012;**41**(10):1004-1013

[34] Ribi C, Cohen P, Pagnoux C, Mahr A, Arène J-P, Lauque D, et al. Treatment of Churg-Strauss syndrome without poor-prognosis factors: A multicenter, prospective, randomized, open-label study of seventy-two patients. *Arthritis Rheumatic*. 2008;**58**(2):586-594

[35] Moosig F, Holle J. Aktuelle Therapie der eosinophilen Granulomatose mit polyangiitis (Churg-Strauss-Syndrom). *Z Für Rheumatol*. 2019;**78**:333-338

[36] Raffray L, Guillevin L. Updates for the treatment of EGPA. *Presse Med*. 2020;**49**(3):104036

[37] Fanouriakis A, Kougkas N, Vassilopoulos D, Fragouli E, Repa A, Sidiropoulos P. Rituximab for eosinophilic granulomatosis with polyangiitis with severe vasculitic neuropathy: Case report and review of current clinical evidence. *Seminars in Arthritis Rheumatology*. 2015;**45**(1):60-66

[38] Charles P, Bienvenu B, Bonnotte B, Gobert P, Godmer P, Hachulla É, et al. Rituximab: Recommendations of the French Vasculitis study group (FVSG) for induction and maintenance treatments of adult, antineutrophil cytoplasm antibody-associated necrotizing vasculitides. *Presse Médicale*. 2013;**42**(10):1317-1330

[39] Bouldouyre M-A, Cohen P, Guillevin L. Severe bronchospasm associated with rituximab for refractory Churg-Strauss syndrome. *Annals of the Rheumatic Diseases*. 2009;**68**(4):606-606

[40] Kim S, Marigowda G, Oren E, Israel E, Wechsler ME. Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome. *Journal of Allergy Clinical Immunology*. 2010;**125**(6):1336-1343

[41] 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**(5):341

[42] 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**(20):1921-1932

[43] Bekçibaşı M, Barutçu S, Çelen MK, Dayan S, Hoşoğlu S. Churg-Strauss syndrome occurring during omalizumab treatment. *European Journal of Rheumatology*. 2015;**2**(3):129-130

[44] Naudion P, Méaux-Ruault N, Gil H, Humbert S, Bouiller K, Magy-Bertrand N. Le traitement de la granulomatose éosinophilique avec polyangéite réfractaire par omalizumab : à propos de 4 cas. *Rev Médecine Interne*. déc. 2016;**37**:A263

[45] Koukoulaki M. Rituximab in Churg-Strauss syndrome. *Annals of Rheumatic Diseases*. 2006;**65**(4):557-559