

## Treatment of antineutrophil cytoplasmic antibody-associated vasculitis: update\*

Atualização do tratamento das vasculites associadas a anticorpo anticitoplasma de neutrófilos\*

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### Abstract

In its various forms, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterized by a systemic inflammation of the small and medium-sized arteries (especially in the upper and lower respiratory tracts, as well as in the kidneys). The forms of AAV comprise Wegener's granulomatosis (now called granulomatosis with polyangiitis), microscopic polyangiitis, renal AAV, and Churg-Strauss syndrome. In this paper, we discuss the phases of AAV treatment, including the induction phase (with cyclophosphamide or rituximab) and the maintenance phase (with azathioprine, methotrexate, or rituximab). We also discuss how to handle patients who are refractory to cyclophosphamide.

**Keywords:** Anti-neutrophil cytoplasmic antibody-associated vasculitis; Wegener granulomatosis; Antibodies, antineutrophil cytoplasmic.

### Resumo

As vasculites *antineutrophil cytoplasmic antibody* (ANCA, anticorpo anticitoplasma de neutrófilos) associadas (VAAs) são caracterizadas por uma inflamação sistêmica das artérias de pequeno e médio calibre (especialmente no trato respiratório superior e inferior, e nos rins). As VAAs compreendem a granulomatose de Wegener (agora chamada de granulomatose com poliangeíte), poliangeíte microscópica, VAA limitada ao rim e a síndrome de Churg-Strauss. Neste artigo, discutiremos as fases de tratamento dessas vasculites, como fase de indução (com ciclofosfamida ou rituximab) e fase de manutenção (com azatioprina, metotrexato ou rituximab). Além disso, discutiremos como manejar os casos refratários à ciclofosfamida.

**Descritores:** Vasculite associada a anticorpo anticitoplasma de neutrófilos; Granulomatose de Wegener; Anticorpos anticitoplasma de neutrófilos.

### Introduction

In its various forms, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterized by a systemic inflammation of the small and medium-sized arteries. The inflammation occurs mainly in the upper and lower respiratory tracts (Figure 1), as well as in the kidneys (pauci-immune necrotizing glomerulonephritis). The forms of AAV comprise Wegener's granulomatosis (WG)—now called granulomatosis with polyangiitis—microscopic polyangiitis (MPA), renal AAV, and Churg-Strauss

syndrome.<sup>(1-6)</sup> However, in the present article, we do not discuss Churg-Strauss syndrome, because it does not usually require intensive immunosuppression.<sup>(7)</sup>

In the 1980s, a relationship was found between these forms of vasculitis and the presence of ANCA in the serum. The presence of a common serum marker, as well as the good response of these pathologies to treatment with cyclophosphamide, led some authors to classify these forms of systemic vasculitis as a single

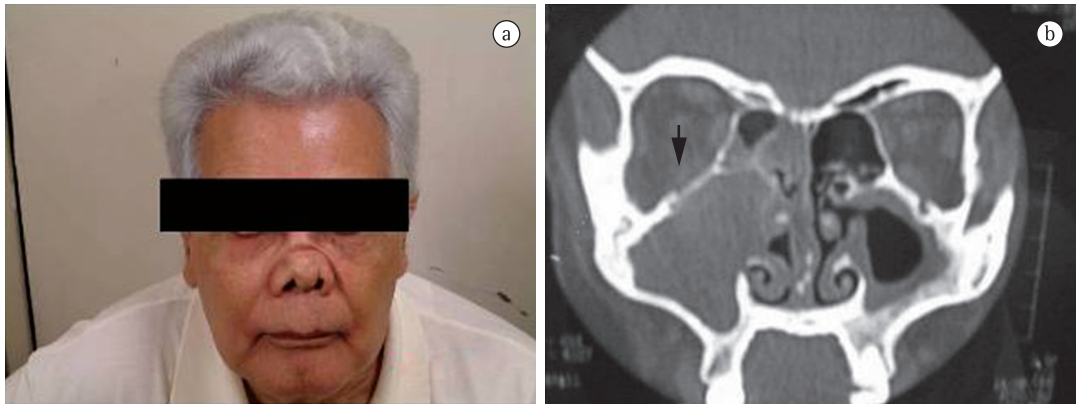
\* Study carried out at the Department of Thoracic Diseases, *Hospital Regional da Asa Norte* – HRAN, North Wing Regional Hospital – *Escola Superior de Ciências da Saúde/Secretaria de Estado da Saúde* – ESCS/SES, Graduate School of Health Sciences/State Department of Health – Brasília, Brazil.

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**Figure 1** - In a, photograph of a patient with saddle nose deformity (due to destruction of the nasal septum by Wegener's granulomatosis). In b, CT scan showing bilateral maxillary sinusitis with partial destruction of the bony wall of the right maxillary sinus due to Wegener's granulomatosis.

group. Nevertheless, it should be emphasized that not every form of AAV shows this marker and not every ANCA-positive patient has vasculitis.<sup>(8)</sup>

Immunofluorescence is the primary technique for the study of ANCA. With this method, it is possible to observe two patterns closely related to the presence of clinically evident vasculitis: cytoplasmic ANCA (c-ANCA), present in 80% of cases of WG and in 30% of cases of MPA, and perinuclear ANCA (p-ANCA), present in 10% of cases of WG and in 60% of cases of MPA. The cytoplasmic pattern usually corresponds to the existence of antibodies against proteinase 3 that can be detected with greater sensitivity by ELISA. This association is highly specific for this type of vasculitis, especially WG. In contrast, p-ANCA immunofluorescence is nonspecific, typically showing anti-myeloperoxidase antibodies on ELISA, and can occur in many situations not related to systemic vasculitis, potentially representing the existence of antibodies against different intracellular antigens. The presence of antibodies against myeloperoxidase, which can also be detected by ELISA, is closely related to AAV, especially MPA. The ELISA test (specific for antiproteinase 3 or antimyeloperoxidase) is more sensitive than is immunofluorescence, the former being particularly useful in cases of inconclusive immunofluorescence results, in cases of atypical immunofluorescence patterns, or in cases of p-ANCA in which one wishes to determine the relationship with the presence of antimyeloperoxidase antibodies (especially in situations of clinical uncertainty). However, unlike

immunofluorescence, the ELISA technique to be used has yet to be internationally standardized. Therefore, screening for the presence of these antibodies should always be performed by immunofluorescence, ELISA being reserved for special cases.<sup>(8)</sup>

In AAV, pulmonary manifestations occur especially in WG. A study conducted in Brazil and involving 98 patients (mean age,  $48 \pm 15$  years) with WG who were recruited from a department of pulmonology, which represents a bias, revealed that 98% of the cases had pulmonary involvement, characterized by (cavitary or noncavitary) pulmonary nodules, (cavitary or noncavitary) masses, pulmonary consolidations, ground-glass areas (commonly associated with alveolar hemorrhage), and lower airway injury (subglottic stenosis, tracheal stenosis, bronchial stenosis, etc).<sup>(9)</sup> In addition, 95% of the patients had sinus involvement, and 90% of those patients were ANCA-positive. Pulmonary involvement is much less common in MPA than in WG and is usually characterized by ground-glass areas (which is consistent with alveolar hemorrhage) or interstitial involvement (which is consistent with pulmonary fibrosis; Table 1, Figure 2).<sup>(9)</sup>

The second most common form of AAV is renal AAV, which presents as necrotizing glomerulonephritis with crescent formation and a lack of immunoglobulin expression (pauci-immune). In addition, there is fibrin deposition and thrombus formation in the glomerulus, and, in the 1970s, there were sporadic reports of reversion of renal failure in AAV with the use

**Table 1** - Chest CT findings in 98 patients with Wegener's granulomatosis who were treated at a pulmonology clinic in Brazil.<sup>a</sup>

Chest CT findings	Frequency, %
Nodules	25.2
Cavitary nodules	18.6
Masses	4.3
Cavitary masses	17.5
Infiltrates	37.3
Lower airway injury	9.8

<sup>a</sup>Data taken from Barbas et al.<sup>(9)</sup>

of anticoagulation therapy.<sup>(10)</sup> A finding of acute tubular necrosis is also quite common.

A new classification of glomerular involvement in AAV has recently been proposed. This classification can predict renal survival and is subdivided into four classes:

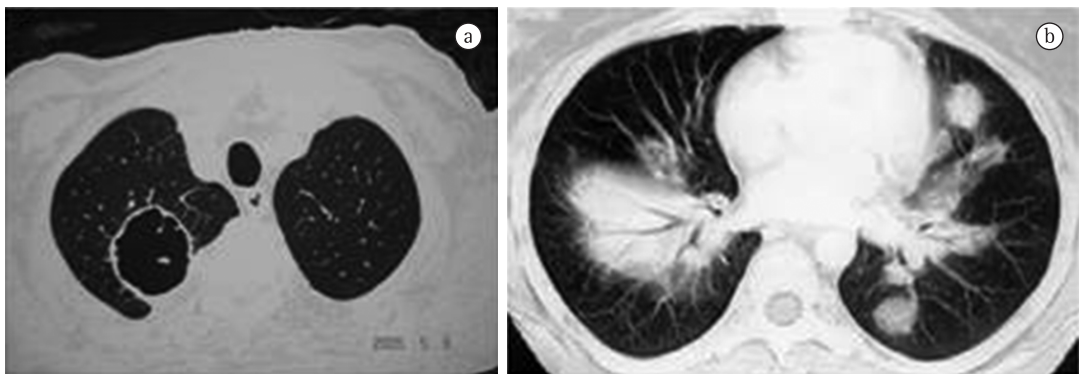
- Class 1 - Focal glomerulonephritis: 50% or more of the glomeruli are normal (that is, without vasculitic lesions, without global sclerosis, although mild ischemic changes or minimal inflammatory infiltration can occur)
- Class 2 - Crecentic glomerulonephritis: 50% or more of the glomeruli have (cellular or fibrotic) crescents
- Class 3 - Mixed glomerulonephritis: fewer than 50% of the glomeruli are normal; fewer than 50% of the glomeruli have crescents; fewer than 50% of the glomeruli are completely sclerosed
- Class 4 - Sclerosing glomerulonephritis: 50% or more of the glomeruli are completely sclerosed

This classification was validated in renal biopsies from 100 patients who had had at least one year of clinical follow-up and revealed that end-stage chronic renal failure was more common in classes 3 and 4 than in classes 1 and 2. It should be borne in mind that classes 2, 3, and 4 did not differ regarding baseline renal function, although class 2 showed greater function gain over the course of the cases. It should also be borne in mind that in the first year of follow-up, the last three of the four classes resulted in high mortality (25-39%).<sup>(11)</sup>

## Treatment overview

### History

When Wegener described AAV in 1936, this new disease was characterized by high mortality, with a one-year survival of only 10%. However, in the 1970s, cyclophosphamide began to be used, which resulted in a drastic change in survival from this disease.<sup>(12)</sup> Currently, five-year survival is 70-90%, including in a study conducted in Brazil.<sup>(9)</sup> However, the extended use of cyclophosphamide (for at least 18 months) is associated with an increased risk of hemorrhagic cystitis, bladder cancer, leukemia, and lymphoma. Therefore, treatment of vasculitis has been defined as consisting of an induction phase (the patient is freed of the inflammation), with the use of cyclophosphamide, and a maintenance phase (the patient is kept free of the inflammation), ideally with the use of a less toxic drug than cyclophosphamide.<sup>(13-20)</sup>



**Figure 2** - In a, CT scan showing a cavitary lung mass in a patient with Wegener's granulomatosis. In b, CT scan showing right pulmonary consolidation and left pulmonary nodules in a patient with Wegener's granulomatosis.

In addition to the problem of the maintenance phase, there is the risk of disease recurrence (reinstitution of cyclophosphamide is indicated to treat the inflammation, with consequent increased risks inherent in its use, because of repeated use of the drug) and the risk of developing disease that is refractory to cyclophosphamide (the inflammation persists despite treatment with the drug).<sup>(15)</sup>

Below, we specifically discuss the phases of AAV treatment: induction; maintenance; treatment of AAV recurrence; and treatment of AAV that is refractory to cyclophosphamide.

### **Induction phase**

The principal remedies used in the induction phase are cyclophosphamide, methotrexate, rituximab, plasmapheresis, and pulse therapy with methylprednisolone. Mycophenolate mofetil (MMF) can also be used in the induction phase; however, it has lower efficacy than do cyclophosphamide and rituximab, and is therefore considered a second-line drug.<sup>(13)</sup>

In the induction phase, the combination of cyclophosphamide ( $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ ) and prednisone ( $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ ) is used. Cyclophosphamide should be used for up to 1-2 months after remission of AAV is achieved, which usually equates to approximately 3-9 months of treatment. Absence of inflammation in AAV is defined as urinalysis results (sediments and abnormal elements) without glomerular hematuria and absence of active lung injury.<sup>(21)</sup>

Regarding prednisone, the patient begins to show signs that the inflammation is subsiding usually after 1 month of treatment at a dose of  $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ , and, thereafter, the dose can be tapered at a rate of 2.5 mg/week. Some authors recommend discontinuing prednisone at month 6 of treatment if control of vasculitis is achieved, whereas others suggest using prednisone at a dose of 5-10 mg/day continuously, because it might reduce the risk of AAV recurrence.<sup>(13,14)</sup> We opted to maintain the dose of 5-10 mg/day continuously.

The use of pulse therapy with methylprednisolone (500-1,000 mg/day for 3 days) in the induction phase is indicated in cases of AAV associated with acute renal failure or with diffuse alveolar hemorrhage (DAH), which is characterized by the triad consisting of new

pulmonary infiltrates, worsening of  $\text{SpO}_2$ , and decreased hemoglobin levels.<sup>(13)</sup>

In addition, plasmapheresis can be used in the AAV induction phase. Its use was evaluated in a prospective randomized study involving 137 patients with serum creatinine levels  $\geq 5.8 \text{ mg/dL}$ . All patients received oral cyclophosphamide plus prednisone. Some of the patients also underwent plasmapheresis (seven sessions of plasmapheresis in 14 days), whereas others did not. The study results showed that plasmapheresis reduced the risk of dialysis-dependent chronic renal failure in 3 months (from 51% to 31%), with no increase in adverse events. Plasmapheresis is also used in combination with cyclophosphamide + prednisone in cases of severe DAH ( $\text{PaO}_2/\text{FiO}_2 < 200\text{-}300$ ). Plasma replacement at the end of plasmapheresis must not be forgotten in cases of severe DAH or in cases of biopsy or recent surgical manipulation.<sup>(22)</sup>

In summary, in cases of AAV associated with severe DAH or with acute renal failure (serum creatinine levels  $\geq 5.8 \text{ mg/dL}$ ), the combination of cyclophosphamide, prednisone, pulse therapy with methylprednisolone, and plasmapheresis should be used.

Another important drug in the induction phase is rituximab, which can replace cyclophosphamide. In a prospective randomized study of 197 patients with AAV, of whom 49% had recently been diagnosed with AAV (treatment-naïve patients) and 51% had experienced AAV recurrence (patients with a history of treatment), rituximab ( $375 \text{ mg/m}^2$  of body surface area, once a week, for 4 weeks) was administered in combination with pulse therapy with methylprednisolone (1 dose) and prednisone ( $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ ) to a group of patients, which was compared with another group receiving the combination of cyclophosphamide ( $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ ) and prednisone ( $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ ).<sup>(23)</sup> The study results showed that treatment with rituximab was as successful as was treatment with cyclophosphamide in the patients with recently diagnosed AAV, and that the former was more successful than the latter in the patients with AAV recurrence. The adverse events were similar in the two groups.<sup>(23)</sup> Therefore, if these results are confirmed in future studies, rituximab becomes an excellent surrogate for cyclophosphamide in the induction phase in patients with recently diagnosed AAV,

and it can be the first choice in the induction phase in patients with AAV recurrence.

Rituximab is an anti-CD20 B lymphocyte monoclonal chimeric antibody, that is, it eliminates CD20+ B lymphocytes, with the potential effect of controlling the inflammation of AAV. Treatment with rituximab can cause some adverse events, such as fever, chills, allergic reactions, and anaphylactic shock. In order to minimize them, patients should be pretreated with paracetamol (750 mg), ranitidine (50 mg), diphenhydramine (one ampoule), and methylprednisolone (100 mg). Rituximab should be diluted in 0.9% saline in order to obtain a concentration < 4 mg of rituximab/mL of 0.9% saline. Rituximab infusion should begin at a rate of 50 mg/h, and this rate should be increased by 50 mg/h every 30 min until it reaches 400 mg/h. During the one-month treatment period, prophylaxis for pneumocystis pneumonia should be performed. The contraindications to the use of rituximab are being allergic to this drug, having leukocyte counts < 1,000-3,000 mm<sup>3</sup>, having active infection, and being pregnant. The most severe adverse events associated with rituximab are mild hypotension, fever, leukopenia, thrombocytopenia, severe arrhythmia, severe congestion, and Stevens-Johnson syndrome.<sup>(23)</sup>

Finally, methotrexate can also be used in the induction phase. Its initial dose is 0.2 mg/kg per week (the maximum dose is 15 mg/week), and it is increased by 2.5 mg/week up to the maximum dose of 25 mg/week if the patient can tolerate it (transaminase/bilirubin levels < 3 times higher than normal and leukocyte counts > 3,000-4,000 mm<sup>3</sup>). However, methotrexate can only be used in the induction phase in cases of AAV with mild activity/inflammation (without DAH and without glomerulonephritis), with creatinine clearance > 50 mg/dL. In addition, special attention should be given to its combination with sulfamethoxazole/trimethoprim (because of the risk of anemia, leukopenia, and thrombocytopenia). Folate (1 mg/day) should be administered to all patients receiving methotrexate.<sup>(13,24,25)</sup>

### **Maintenance phase**

The maintenance phase begins 1-2 months after remission of the inflammation of AAV. The principal drug used in this phase is azathioprine (2 mg • kg<sup>-1</sup> • day<sup>-1</sup>, usually for

12 months), replacing the cyclophosphamide used in the induction phase. Its use is based on a prospective randomized study of 155 patients with AAV in which the use of azathioprine after remission of vasculitis was compared with that of cyclophosphamide. In that study, recurrence of the inflammation of AAV was similar with the use of azathioprine and with that of cyclophosphamide, and the adverse events were acceptable.<sup>(21)</sup>

Another point that has recently been discussed was the duration of the maintenance phase, which until then had been established at 1 year. Since the risk of AAV recurrence can be as high as 4.3% per month, and since recurrence implies the reinstitution of cyclophosphamide (with its possible severe adverse events), some authors suggest the use of azathioprine for 2 years, for 3 years, or even indefinitely. The factors associated with AAV recurrence include PR3-ANCA positivity, upper airway injury, pulmonary involvement, and a history of AAV recurrence. A greater number of risk factors translate to a greater propensity to use azathioprine for an indefinite length of time, as follows: 2 mg • kg<sup>-1</sup> • day<sup>-1</sup> in the first year; 1.5 mg • kg<sup>-1</sup> • day<sup>-1</sup> in the second year; and 1 mg • kg<sup>-1</sup> • day<sup>-1</sup> indefinitely.<sup>(13,14)</sup>

Another drug that is also used in the maintenance phase is methotrexate (the maximum dose is 20-25 mg/week). The minimum duration of treatment with methotrexate in the maintenance phase is 24 months (in contrast to the minimum duration of 12 months for azathioprine). In addition, creatinine clearance should be > 50 mg/dL and there must be no history of glomerulonephritis. Methotrexate should be used in combination with folate (1 mg/day).<sup>(13,14,26)</sup>

In patients who do not respond well to azathioprine or to methotrexate in the maintenance phase, MMF (1,000-3,000 mg/day) or rituximab ((375 mg/m<sup>2</sup> of body surface area, once a week, for 4 weeks, every 6 months) should be attempted.<sup>(14)</sup>

#### **Phase of treatment of AAV recurrence**

Recurrence is characterized by the onset of glomerular hematuria, pulmonary or ocular involvement, sinusitis, neuritis, skin lesion, etc. In cases of mild recurrence (Table 2) in the maintenance phase, the maintenance dose (corticosteroid + immunosuppressant:



**Table 2** – Definitions of mild and severe recurrence in antineutrophil cytoplasmic antibody-associated vasculitis.

Type of recurrence	Glomerular hematuria	Lung injury	Diffuse alveolar hemorrhage
Mild	No increase in creatinine	Small	No
Severe	Increase in creatinine	Extensive	Yes

azathioprine or methotrexate) should be increased. In cases of mild recurrence after discontinuation of the maintenance phase, the maintenance phase should be reinstated, there being no need for another induction phase.<sup>(13,14)</sup>

Conversely, in cases of severe recurrence, another induction phase is always necessary. If severe recurrence occurs in the maintenance phase, there must be another induction phase (cyclophosphamide or rituximab, the latter being preferable if the patient has already used two cycles of cyclophosphamide), and, after remission of vasculitis is achieved, there is a maintenance phase with a different drug than that used in the previous maintenance phase (if azathioprine was used before, consider methotrexate, MMF, or rituximab). In cases of severe recurrence after discontinuation of the maintenance phase, there must be another induction phase (cyclophosphamide or rituximab, the latter being

preferable if there has been two previous cycles of cyclophosphamide), and, after remission of vasculitis is achieved, there is a maintenance phase with the same drug used in the previous maintenance phase (however, keep the maintenance phase for at least 24 months or even indefinitely: see “Maintenance phase”).<sup>(13,14)</sup>

### ***Phase of treatment of AAV that is refractory to cyclophosphamide***

This phase occurs if vasculitis remains active after 1-2 months of treatment with cyclophosphamide, that is, when there is persistent glomerular hematuria with increased creatinine levels, as well as persistent pulmonary, ocular, and cutaneous activity. It is important not to confuse refractoriness to cyclophosphamide with infection (especially in the sinuses and lungs), poor adherence to treatment (especially

**Table 3** – Summary of treatment choices in antineutrophil cytoplasmic antibody-associated vasculitis.

Phase of treatment	First choice	Alternative
Induction	CPH or RTX or MTX <sup>a</sup> Add pulse therapy with methylprednisolone plus plasmapheresis when there is severe glomerulonephritis (creatinine > 5.8 mg/dL) or severe alveolar hemorrhage (PaO <sub>2</sub> /FiO <sub>2</sub> < 200-300)	MMF Add pulse therapy with methylprednisolone plus plasmapheresis when there is severe glomerulonephritis (creatinine > 5.8 mg/dL) or severe alveolar hemorrhage (PaO <sub>2</sub> /FiO <sub>2</sub> < 200-300)
Maintenance	AZA or MTX	MMF or RTX <sup>b</sup>
Treatment of mild recurrence of vasculitis	Increase the dose of prednisone and immunosuppressant; or reinstitute the maintenance drug successfully used previously	
Treatment of severe recurrence of vasculitis	Perform another induction (CPH, RTX, <sup>c</sup> or MTX <sup>a</sup> ) Add pulse therapy with methylprednisolone plus plasmapheresis when there is severe glomerulonephritis (creatinine > 5.8 mg/dL) or severe alveolar hemorrhage (PaO <sub>2</sub> /FiO <sub>2</sub> < 200-300)	MMF Add pulse therapy with methylprednisolone plus plasmapheresis when there is severe glomerulonephritis (creatinine > 5.8 mg/dL) or severe alveolar hemorrhage (PaO <sub>2</sub> /FiO <sub>2</sub> < 200-300)
Treatment of vasculitis that is refractory to CPH	RTX	MMF

CPH: cyclophosphamide. RTX: rituximab. MTX: methotrexate. MMF: mycophenolate mofetil. AZA: azathioprine. <sup>a</sup>Do not use MTX in the induction/maintenance treatment if there is glomerulonephritis, creatinine clearance < 50 mg/dL, or alveolar hemorrhage. <sup>b</sup>Use RTX when treatment with AZA and MTX fails in the maintenance phase. <sup>c</sup>Prefer RTX in this situation when the patient has previously received two induction treatments with CPH.

in those receiving oral cyclophosphamide), or drug toxicity. The risk factors for refractoriness to cyclophosphamide include being female, being over 65 years of age, and having baseline creatinine levels > 5 mg/dL.<sup>(15)</sup>

In refractory cases, the first choice is rituximab (375 mg/m<sup>2</sup>, once a week, for 4 weeks) and the second choice is MMF ((500-1,500 mg, twice a day). The benefits of rituximab in patients who are refractory to cyclophosphamide was reported in a retrospective study involving four centers in the United Kingdom and 65 patients with AAV who ranged in age from 7 to 77 years. In that study, rituximab was used (usually at a dose of 375 mg/m<sup>2</sup>, once a week, for 4 weeks), and clinical follow-up lasted 6-55 months. The rate of remission of AAV was 98%, remission occurring 1-5 months after infusion of rituximab. Recurrence of AAV occurred in 57% of the patients (usually 4-37 months after infusion). In the patients with recurrence, remission of vasculitis was again achieved by another infusion of rituximab in 84% of the cases. It should be mentioned that, at one of the centers, 15 patients with AAV that was refractory to cyclophosphamide were treated with routine infusion of rituximab every 6 months, and there was no recurrence, which offers excellent prospects for the use of rituximab in the induction and maintenance phase even in such patients (Table 3).<sup>(27)</sup>

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