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Review article

Recommendations of the Brazilian Society of Rheumatology for the induction therapy of ANCA-associated vasculitis

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ABSTRACT

The purpose of these recommendations is to guide the appropriate induction treatment of antineutrophil cytoplasmic antibody-associated vasculitis (AAV) patients with active disease. The recommendations proposed by the Vasculopathies Committee of the Brazilian Society Rheumatology for induction therapy of AAV, including granulomatosis with polyangiitis, microscopic polyangiitis and renal-limited vasculitis, were based on systematic literature review and expert opinion. Literature review was performed using Medline (PubMed), EMBASE and Cochrane database to retrieve articles until October 2016. PRISMA guidelines were used for the systematic review and articles were assessed according to the Oxford levels of evidence. Sixteen recommendations were made regarding different aspects of induction therapy for AAV. The purpose of these recommendations is to serve as a guide for therapeutic decisions by health care professionals in the management of AAV patients presenting active disease.

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Recomendações da Sociedade Brasileira de Reumatologia para a terapia de indução para vasculites associadas ao ANCA

Palavras-chave:
Vasculite associada a ANCA
Granulomatose com poliangiite
Poliangiite microscópica
Vasculite limitada ao rim
Diretrizes

RESUMO

O objetivo destas recomendações é orientar o tratamento apropriado de indução em pacientes com vasculites associadas a anticorpos anticitoplasma de neutrófilos (VAA) ativa. As recomendações propostas pelo Comitê de Vasculopatias da Sociedade Brasileira de Reumatologia para a terapia de indução para VAA, incluindo granulomatose com poliangiite, poliangiite microscópica e vasculite limitada ao rim, foram baseadas em uma revisão sistemática da literatura e na opinião de especialistas. A revisão da literatura foi feita com as bases de dados Medline (PubMed), Embase e Cochrane para consultar artigos até outubro de 2016. As diretrizes Prisma (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses* – Principais itens para reportar revisões sistemáticas e metanálises) foram usadas para a revisão sistemática e os artigos foram avaliados de acordo com os níveis de evidência Oxford. Dezesseis recomendações foram feitas em relação a diferentes aspectos da terapia de indução para VAA. O objetivo dessas recomendações é servir como um guia para decisões terapêuticas por profissionais da saúde no tratamento de pacientes com VAA que apresentem a doença ativa.

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of necrotizing systemic vasculitis that affects predominantly small vessels with few or no immune deposits at vessels wall, associated with ANCA as a common biomarker.[1] ANCA are antibodies against enzymes in azurophilic granules of neutrophils and lysosomes of monocytes with specificity for proteinase-3 (PR3-ANCA) and for myeloperoxidase (MPO-ANCA).[2] AAV includes granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA, previously known as Churg-Strauss syndrome) and organ-limited AAV, for example renal limited vasculitis (RLV).[1]

Before starting therapy for AAV patients at onset especially GPA and MPA, it is necessary to determine disease extension. The European Vasculitis Study (EUVAS) classification categorizes disease extension into five different subsets as follows: localized disease, early systemic disease, generalized disease, severe disease and refractory disease (Table 1).[3] However, management of a newly diagnosed AAV patient may be also planned based on the presence of organ/life threatening disease or not or whether there is rapidly progressive renal failure or pulmonary hemorrhage.[4] The main outcome measures for the assessment of AAV disease activity are the third version of the Birmingham Vasculitis Activity Score (BVAS) and the BVAS-WG which was adapted for GPA patients.[5,6]

The AAV treatment is divided in induction and maintenance therapy. Induction therapy is prescribed for patients with active disease, either at disease onset or at disease relapses during follow-up; its purpose is to attain complete remission and to avoid damage accrual. After achieving remission, maintenance therapy is started and its goal is to prevent disease relapses.[7]

Table 1 – EUVAS disease categorization for AAV according to different levels of severity.[3]

Categories	Definition
Localized	Disease restricted to upper and/or lower respiratory tract without systemic involvement or constitutional symptoms
Early systemic	Involvement of any organ or system, without organ-threatening or life-threatening disease
Generalized	Renal or other organ-threatening disease, serum creatinine <500 μmol/L or 5.6 mg/dL
Severe	Renal failure or other organ-threatening disease, serum creatinine >500 μmol/L or 5.6 mg/dL
Refractory	Progressive disease unresponsive to therapy with glucocorticoids and cyclophosphamide

AAV, antineutrophil cytoplasmic antibody associated vasculitis; EUVAS, *European Vasculitis Study*.

The purpose of these recommendations is to guide the management of AAV patients according to current evidence from literature, facilitating the access to available therapies as well as minimizing permanent damage due to uncontrolled disease activity. These recommendations addressed aspects of induction therapy in patients with AAV, including GPA, MPA and RLV.

Methods

A systematic review of the literature from 1992 to October 2016 was performed using the following databases: Medline (Pubmed), Embase and Cochrane. Search strategy was done according to each PICO (Patient, Intervention, Control and Outcome) question elaborated by ten rheumatologists with experience in the management of AAV. The PICO questions were based on the different aspects of the induction treatment

Table 2 – Categories of evidence in studies.[9]

Levels	Evidence
1a	Systematic review and meta-analysis[a] of RCT
1b	At least one RCT with narrow CI
2a	Systematic review and meta-analysis[a] of cohort studies
2b	At least one cohort study or a low quality RCT
3a	Systematic review and meta-analysis[a] of case-control series
3b	At least one case-control study
4	At least one case-series or poor quality cohort and case-control studies
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

CI, confidence interval; RCT, randomized controlled trials.
[a] Homogeneity is necessary for meta-analysis.

of patients with AAV, including GPA, MPA and RLV. Studies evaluating EGPA patients were not included in this systematic review since its pathophysiology is different from the other forms of AAV and EGPA patients are not included in clinical trials that assessed therapy in AAV.

The following terms were used for the systematic search of the literature: ANCA-Associated Vasculitis OR Pauci-Immune Vasculitis OR Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis OR Granulomatosis with Polyangiitis OR Wegener OR microscopic polyangiitis OR Subglotic estenosis AND Induction Chemotherapy OR Remission Induction OR Induction. Applying the "random" filter, the terms related to each modality of induction treatment for AAV patients were added.

Inclusion criteria for studies in this systematic review were as follows: randomized controlled clinical trials (RCTs) addressing AAV treatment, with a number of patients greater than 100 and with a minimum follow-up of 6 months, extension studies performed from RCTs with the above mentioned criteria and systematic reviews with meta-analysis of RCT. In some instances, historical cohort studies and review articles were included, as well as in the absence of RCT for specific therapy modalities, open-label studies or lower-quality cohort studies were included.

The steps of this systematic review of the literature followed PRISMA guidelines.[8] Selected studies were evaluated and the degree of recommendation for each question was based on the level of evidence from the studies (Tables 2 and 3).[9–11] Sixteen recommendations were developed to cover different aspects of the induction therapy of AAV (Table 4).

Table 3 – Grades of recommendation for each evidence.[9]

Grades	Definition
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

Results

1. Are glucocorticoids recommended for the treatment of active AAV?

The treatment protocol for every AAV patient with active disease must include systemic glucocorticoids (GC). The initial dose for prednisone or equivalent is 1 mg/kg/day (grade of recommendation C). GC therapy needs to be associated with an immunosuppressive agent or with a biological agent in patients with active AAV (grade of recommendation C).

Literature review

Although there is no data from studies comparing GC with placebo in AAV patients, GC were used in all RCTs that evaluated AAV induction therapy.[12–17] Treatment of AAV with GC alone, without immunosuppressive or associated biological therapy, is not recommended. In historical series, addition of GC to the treatment of active GPA did not yield any improvement in survival (level of evidence 4).[18,19] In addition, treatment of non-severe AAV relapses exclusively with an increase in prednisone dose was associated with a high relapse rate after tapering the drug, despite the initial favorable response observed in most cases (level of evidence 2b).[20]

2. Is there any difference between oral and intravenous GC in the induction therapy of AAV?

There is no evidence that intravenous (IV) GC are more efficient than oral GC in AAV patients with active disease. However, patients with severe manifestations (i.e. life threatening disease with the involvement of vital organs) IV pulse therapy with methylprednisolone should be prescribed at 15 mg/kg/day or 0.5–1.0 g/day for 1–3 days when starting treatment (grade of recommendation D).

Literature review

To date, no study has compared oral and IV GC use in the treatment of AAV patients. IV pulse therapy with methylprednisolone was administered before prednisone in most studies that evaluated induction and maintenance therapy in AAV. Methylprednisolone dose ranged from 0.5 to 1.0 g per day for 1–3 days or 15 mg/kg (maximum dose per pulse of 1 g) per dose for 1–3 days or (level of evidence 5).[12–17,21–23] However, the assessment of efficacy of IV pulse therapy with methylprednisolone was not one of the aims of these RCT.

3. What is the optimal dose and duration of oral GC in the induction therapy of AAV?

Treatment of patients with active AAV should be planned in an individualized basis. Prednisone or prednisolone is prescribed at an initial daily dose of 0.5–1.0 mg/kg/day (maximum 80 mg/day) for one to four weeks (grade of recommendation B) followed by tapering 10 mg every two to four weeks until 20 mg/day. Afterwards, dose reduction should be 2.5–5.0 mg every 2–4 weeks until complete withdrawal (grade of recommendation D). The duration of GC therapy should be at least 6 months and in some instances, it may be up to 1 or 2 years.

Table 4 – Recommendations for induction therapy of AAV.

PICO questions	Recommendations
1. Are glucocorticoids recommended for the treatment of active AAV?	The treatment protocol for every AAV patient with active disease must include systemic glucocorticoids. The initial dose for prednisone or equivalent is 1 mg/kg/day (grade of recommendation C). Glucocorticoid therapy needs to be associated with an immunosuppressive agent or with a biological agent in patients with active AAV (grade of recommendation C).
2. Is there any difference between oral and IV glucocorticoids in the induction therapy of AAV?	There is no evidence that IV glucocorticoids are more efficient than oral glucocorticoids in AAV patients with active disease. However, patients with severe manifestations (i.e. life threatening disease with the involvement of vital organs) IV pulse therapy with methylprednisolone should be prescribed at 15 mg/kg/day or 0.5–1.0 g/day for 1–3 days when starting treatment (grade of recommendation D).
3. What is the optimal dose and duration of oral glucocorticoids in the induction therapy of AAV?	Treatment of patients with active AAV should be planned in an individualized basis. Prednisone or prednisolone is prescribed at an initial daily dose of 0.5–1.0 mg/kg/day (maximum 80 mg/day) for one to four weeks (grade of recommendation B) followed by tapering 10 mg every two to four weeks until 20 mg/day. Afterwards, dose reduction should be 2.5–5.0 mg every 2–4 weeks until complete withdrawal (grade of recommendation D). The duration of glucocorticoid therapy should be at least 6 months and in some instances, it may be up to 1 or 2 years. Longer glucocorticoid therapy could be necessary in relapsing patients (grade of recommendation B).
4. What is the role of cyclophosphamide in the induction therapy of AAV?	Cyclophosphamide is indicated in induction therapy in AAV patients with generalized disease or in those presenting life/organ-threatening disease (grade of recommendation A). Additionally, patients with less severe forms of AAV, such as localized disease and the early systemic form may benefit from cyclophosphamide therapy, especially in patients who do not respond to methotrexate therapy (degree of recommendation D). The duration of cyclophosphamide therapy in patients with AAV should be limited to 3–6 months in order to avoid adverse events due to its cumulative dose and cyclophosphamide should be switched to a less toxic maintenance therapy as soon as remission is accomplished (grade of recommendation A).
5. Are there differences between oral and IV pulse therapy cyclophosphamide for therapy induction of AAV?	In the short term, there are no differences in induction of remission rates between oral and IV pulse therapy of cyclophosphamide. Therefore, patients with active AAV may be treated with either oral cyclophosphamide at a dose of 2 mg/kg/day (maximum 200 mg/day) or IV pulse cyclophosphamide at a dose of 15 mg/kg (maximum 1.2 g per pulse) given 3 times in the first month with 2 weeks interval, and then within every 3 weeks up to 3–6 months or until remission is achieved (grade of recommendation A). In patients with renal insufficiency, cyclophosphamide dose should be corrected according to age and renal function.
6. Is methotrexate indicated for remission induction in AAV?	Methotrexate, 20–25 mg/week, is an alternative to cyclophosphamide for remission induction in AAV patients with non-organ threatening disease, i.e. localized or early systemic disease (grade of recommendation A). Methotrexate doses should be reduced by 50% in patients with GFR between 10 and 50 mL/min and it should not be used in end-stage renal disease (i.e. GFR under 10 mL/min) (grade of recommendation D).
7. What is the role of rituximab in the induction therapy of AAV?	Rituximab is an alternative to cyclophosphamide in the induction therapy in generalized forms of AAV, especially in patients with organ/life-threatening disease (grade of recommendation A). Rituximab (375 mg/m^2 weekly for 4 weeks) is non-inferior to cyclophosphamide for induction therapy in AAV and it may be prescribed when there are contraindications for cyclophosphamide use, such as in patients with a high cumulative dose and in young patients of childbearing age without established offspring, or in AAV patients with relapsing disease (grade of recommendation A). Alternatively, rituximab can be used in two infusions at a dose of 1 g two weeks apart.
8. Which precautions should be taken when prescribing rituximab?	Before the infusion of rituximab in AAV patients, serology tests for HIV, HBV and syphilis should be checked. Patients with chronic HBV and HIV should only be treated with rituximab with concomitant prescription of antiviral therapy and the consultation from a specialist in infectious diseases (grade of recommendation C). Vaccination should be given prior to rituximab infusion whenever it is possible, especially for annual influenza, pneumococcal and HBV. Administration of other vaccines such as anti-tetanus and diphtheria or anti-meningoccocal is optional but immunization records should be updated (grade of recommendation D). Baseline serum immunoglobulin levels and B-cell count in peripheral blood are recommended to be measured before rituximab infusion and thereafter. It is important to measure serum immunoglobulins, especially serum IgG, prior to each administration of rituximab and 4–6 months after and to assess the need for replacement of IVIG (grade of recommendation C). In cases of severe hypogammaglobulinemia (IgG <500 mg/L) and infectious complications, the replacement of IVIG is required at a dose of 0.2–0.4 g/kg for 1 day, every 3–4 weeks, as required to maintain serum IgG levels above 500 mg/mL. Rituximab withdrawal should be considered if patient presents serum IgG persistently below 500 mg/dL and severe recurrent infections (grade of recommendation C). However, it should be to taken into account the balance between treatment benefits to control inflammatory activity and the risk of severe adverse events with rituximab therapy.

Table 4 – (*Continued*)

PICO questions	Recommendations
9. Is plasma exchange indicated in the treatment of patients with active AAV?	Plasma exchange is indicated in AAV patients with rapidly progressive glomerulonephritis with serum creatinine >5.8 mg/dL, since it leads to improvement in renal survival when associated with glucocorticoids and cyclophosphamide (grade of recommendation A). Plasma exchange is prescribed in a 7-session schedule on alternate days at a 60 mL/kg volume exchange on each occasion, volume replacement needs to be done with 5% albumin and occasionally with fresh frozen plasma at the end of the procedure to replenish coagulation factors (grade of recommendation A). There is still insufficient evidence to support plasma exchange to treat patients with AAV presenting alveolar hemorrhage, possibly these patients may benefit from plasma exchange (grade of recommendation D).
10. Is IVIG as an alternative therapy for the induction therapy of AAV?	IVIG is an alternative for the induction therapy of AAV patients with active disease at an immunomodulatory dose (i.e. 2 g/kg divided in 2–5 days), in specific scenarios such as in infected AAV patients with persistent disease activity and in patients refractory to standard treatment with glucocorticoids and cyclophosphamide (grade of recommendation B). Additionally, AAV patients with persistent and active disease who present contraindications to cyclophosphamide or rituximab may also benefit from IVIG therapy (grade of recommendation D).
11. Is mycophenolate mofetil (MMF) indicated for the induction therapy of AAV?	To date, there is not enough evidence to recommend the use of MMF in AAV induction therapy, it should be reserved as an alternative to cyclophosphamide, rituximab or methotrexate, since small studies have shown some benefits over cyclophosphamide in AAV patients with active disease (grade of recommendation C).
12. Is there any place for anti-TNFα agents in the induction therapy of AAV patients?	The TNF receptor blocker agent etanercept is not recommended in the induction therapy of AAV patients (grade of recommendation A). Other anti-TNFα agents have not been studied properly in AAV.
13. Is azathioprine indicated for the induction therapy of AAV patients?	Azathioprine is not indicated for induction therapy of AAV patients with active disease (grade of recommendation D).
14. How subglottic stenosis should be approached in GPA patients?	GPA patients presenting SGS in the presence of systemic disease activity should be treated with glucocorticoids and immunosuppressive agents according to disease severity in association with local treatment. In case of SGS in GPA patients in remission, we recommend only local treatment (grade of recommendation D). As first line local therapy, mechanical intratracheal dilation associated with intralesional injection of a long-acting glucocorticoid (e.g. methylprednisolone acetate or triamcinolone) is recommended, sometimes requiring repeated procedures (grade of recommendation C). In refractory cases and in patients presenting severe manifestations of SGS, open surgery with laryngotracheal reconstruction or permanent tracheostomy should be performed. Indeed, tracheostomy should be reserved only as an urgent intervention for life-threatening situations (grade of recommendation D).
15. Is prophylaxis for pneumocystis pneumonia indicated in AAV patients during induction therapy?	Prophylaxis for PCP with 400 mg/80 mg dose/day or 800 mg/160 mg three times a week of SMT-TMP is indicated to AAV patient undergoing induction therapy with glucocorticoids and cyclophosphamide or rituximab (grade of recommendation A). Patients with a total lymphocyte count below 300 cells/mm^3 must also receive prophylactic treatment for PCP regardless of the immunosuppressive therapy prescribed (grade of recommendation B). If GFR is between 15 and 30 mL/minute, SMT-TMP dose should be reduced to 400 mg/80 mg three times a week. In AAV patients presenting terminal renal failure, during methotrexate therapy or in sulfa allergy, inhaled pentamidine at 300 mg/month should be preferred (grade of recommendation C).
16. What should be considered regarding vaccination in patients with AAV receiving induction therapy?	Whenever it is possible, patients with AAV should be vaccinated prior to starting immunosuppressive treatment, ideally three weeks before. Influenza vaccine seems to be safe and effective for AAV patients in remission and it should be given annually (grade of recommendation B). Considering the high frequency of pulmonary infections in AAV patients, pneumococcal vaccine should also be administered (grade of recommendation D). Immunization schedule in AAV patients should follow the Immunization Guide published by the Brazilian Society of Immunization/Brazilian Society of Rheumatology.

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibodies; GFR, glomerular filtration rate; GPA, granulomatosis with polyangiitis; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IV, intravenous; IVIG, intravenous immunoglobulin; PCP, *Pneumocystis jirovecii* pneumonia; SGS, subglottic stenosis; SMT-TMP, sulfamethoxazole and trimethoprim; TNF, tumor necrosis factor.

Longer GC therapy could be necessary in relapsing patients (grade of recommendation B).

Literature review

In all RCTs that included AAV patients, prednisone or prednisolone was given at an initial dose of 1.0 mg/kg/day,[12–17,21–24] with a daily dose limited to 60–80 mg/day in some studies.[15,16,22] Only one RCT, started prednisone at 0.5–1.0 mg/kg/day as initial dose (level of evidence 2b).[17] Different prednisone tapering and duration regimens were prescribed in RCT that evaluated therapy in AAV. The initial prednisone dose was kept from 1 week to 28 days with subsequent tapering weekly or every 2 weeks up to 15 mg/day, followed by more gradual dose reduction every 1–2 months

(level of evidence 2b).[12–17,21–24] In only two RCTs, prednisone was completely withdrawn within 5–6 months,[15,17] whereas in most RCTs, the total duration of prednisone therapy ranged from 12 to 24 months (level of evidence 2b) (Supplementary Table S1).[12–14,16,21–24] In a cohort study, the median time to total oral GC withdrawal was 8 months (level of evidence 2b).[25] A meta-analysis of RCT and cohort studies observed that the relapse rate is lower in AAV patients who have maintained long-term GC use even at low dose compared with patients who discontinued GC therapy within less than 12 months 14% [95% confidence interval (95%CI: 10–19%)] versus 48% (95%CI: 39–58%), respectively (level of evidence 5).[26] However, this issue still remains open since this meta-analysis had a high heterogeneity and no study has assessed whether long-term GC has any impact on outcomes of AAV patients.

4. *What is the role of cyclophosphamide in the induction therapy of AAV?*

Cyclophosphamide is indicated in induction therapy in AAV patients with generalized disease or in those presenting life/organ-threatening disease (Table 1) (grade of recommendation A). Additionally, patients with less severe forms of AAV, such as localized disease and the early systemic form may benefit from cyclophosphamide therapy, especially in patients who do not respond to methotrexate therapy (degree of recommendation D). The duration of cyclophosphamide therapy in patients with AAV should be limited to 3–6 months in order to avoid adverse events due to its cumulative dose and cyclophosphamide should be switched to a less toxic maintenance therapy as soon as remission is accomplished (grade of recommendation A).

Literature review

The introduction of cyclophosphamide in GPA treatment modified the natural history of the disease, improving treatment response and survival (level of evidence 4). Despite the benefits of cyclophosphamide in the treatment of GPA, several adverse events were observed, such as hemorrhagic cystitis, bone marrow toxicity, severe infections, including *Pneumocystis jirovecii* pneumonia and an increased risk of cancer, mainly bladder cancer. The long-term toxicity of cyclophosphamide is associated with its cumulative dose and a high frequency of adverse events attributed to cyclophosphamide was observed in a large cohort study of GPA patients due to the its extended use for at least 1 year after achieving remission.[27] Then, attempts were tried to minimize cyclophosphamide exposure and toxicity. Firstly, a cohort study showed that complete remission of GPA with GC and cyclophosphamide was achieved at a median of 3 months of treatment (level of evidence 2b)[25] and subsequently a RCT demonstrated that oral cyclophosphamide use for 3–6 months with the replacement by azathioprine did not increase the risk of relapses when compared with continuous use of cyclophosphamide for 12 months (level of evidence 1b).[24] Currently, GC associated with 3–6 months cyclophosphamide therapy is the main modality of induction therapy for AAV, especially in generalized forms of the disease and it is used as the gold standard treatment in RCT evaluating efficacy of other agents in AAV.[13,15,16,28]

Table 5 – Dose reduction of pulsed cyclophosphamide based on age and serum creatinine.[12]

Variables	Cyclophosphamide dose
IV pulse cyclophosphamide	
Age between 60 and 70 years	Reduce 2.5 mg/kg per pulse
Age >70 years	Reduce 5.0 mg/kg per pulse
Serum creatinine between 300–500 μmol/L or 3.4–5.7 mg/dL	Reduce 2.5 mg/kg per pulse
Oral cyclophosphamide	
Age between 60 and 70 years	Reduce 25% of daily dose
Age >70 years	Reduce 50% of daily dose

IV, intravenous.

5. *Are there differences between oral and IV pulse therapy cyclophosphamide for therapy induction of AAV?*

In the short term, there are no differences in induction of remission rates between oral and IV pulse therapy of cyclophosphamide. Therefore, patients with active AAV may be treated with either oral cyclophosphamide at a dose of 2 mg/kg/day (maximum 200 mg/day) or IV pulse cyclophosphamide at a dose of 15 mg/kg (maximum 1.2 g per pulse) given 3 times in the first month with 2 weeks interval, and then within every 3 weeks up to 3–6 months or until remission is achieved (grade of recommendation A). In patients with renal insufficiency, cyclophosphamide dose should be corrected according to age and renal function (Table 5).[12]

Literature review

In an effort to reduce the exposure to cyclophosphamide in the treatment of AAV, small studies evaluated the efficacy of oral and IV pulse therapy with cyclophosphamide in the induction of remission in AAV patients, and no difference was found between both treatment regimens.[29–31] However, this issue was definitely solved by the EUVAS trial *Cyclophosphamide Oral versus Pulsed* (CYCLOPS), the largest RCT performed comparing oral and IV pulse of cyclophosphamide in newly diagnosed GPA, MPA and RLV with active glomerulonephritis. In this study, IV pulse therapy and oral cyclophosphamide had similar efficacy regarding time to remission (mean of 3 months for both groups) and the proportion of patients who achieved complete remission. However, more episodes of leukopenia and a higher cumulative dose of cyclophosphamide (almost twice when compared to pulse therapy group) was found in patients on oral cyclophosphamide (level of evidence 1b).[12] In the long-term follow-up of the CYCLOPS study, patients were evaluated in an average of 4.3 years and a higher risk of relapses was observed in patients treated with IV cyclophosphamide pulse therapy, especially in those with PR3-ANCA. The increase in the frequency of disease flares did not result in an increase in mortality or renal failure compared with the group without relapses (level of evidence 2b).[32]

6. *Is methotrexate indicated for remission induction in AAV?*

Methotrexate, 20–25 mg/week, is an alternative to cyclophosphamide for remission induction in AAV patients with

non-organ threatening disease, i.e. localized or early systemic disease (grade of recommendation A). Methotrexate doses should be reduced by 50% in patients with glomerular filtration rate (GFR) between 10 and 50 mL/min and it should not be used in end-stage renal disease (i.e. GFR under 10 mL/min) (grade of recommendation D).

Literature review

Although cyclophosphamide changed disease course of AAV, there was a growing interest in minimizing toxicity caused by long-term therapy and a case series had already demonstrated the benefit of methotrexate use in less severely ill patients with AAV (level of evidence 4).[7,33] In the RCT *Nonrenal Wegener's Granulomatosis Treated Alternatively with Methotrexate* (NORAM), no differences were observed in terms of remission induction between methotrexate (20–25 mg/week) and oral cyclophosphamide (2 mg/kg/day) at 6 months of therapy. Patients presenting severe disease manifestations such as serum creatinine levels >1.7 mg/dL, urinary red cell casts, proteinuria >1 g/day, severe hemoptysis associated with bilateral infiltrates, cerebral vasculitis, orbital pseudotumor, massive gastrointestinal bleeding, heart failure due to pericarditis or myocarditis and rapidly progressive neuropathy were excluded. It should be noted that in both groups immunosuppressive agents were tapered and discontinued by month 12. Relapse rate at 18 months was higher in the methotrexate group, but these mostly occurred after discontinuation of therapy (level of evidence 1b).[13] After a mean follow-up time of 6 years, in AAV patients originally evaluated at NORAM study, there was no significant difference regarding the relapse rate between patients treated with methotrexate and cyclophosphamide.[34] It is important to emphasize that immunosuppressive therapy should not be discontinued in AAV patients at 12 months in order to prevent relapses (level of evidence 4).[13]

7. What is the role of rituximab in the induction therapy of AAV?

Rituximab is an alternative to cyclophosphamide in the induction therapy in generalized forms of AAV, especially in patients with organ/life-threatening disease (grade of recommendation A). Rituximab (375 mg/m^2 weekly for 4 weeks) is non-inferior to cyclophosphamide for induction therapy in AAV and it may be prescribed when there are contraindications for cyclophosphamide use, such as in patients with a high cumulative dose and in young patients of childbearing age without established offspring, or in AAV patients with relapsing disease (grade of recommendation A). Alternatively, rituximab can be used in two infusions at a dose of 1 g two weeks apart.

Literature review

Two RCT evaluated the efficacy of rituximab in AAV induction therapy compared to cyclophosphamide, both at 375 mg/m^2 of body surface area, weekly for 4 consecutive weeks (level of evidence 1b).[15,16] The RAVE study (Rituximab for ANCA-associated vasculitis) included 197 patients with active AAV. Rituximab and conventional therapy groups comprised 99 and 98 patients respectively. In the group treated with a conventional protocol, cyclophosphamide was prescribed at 2 mg/kg/day for 3–6 months, followed by azathioprine. Unless a relapse occurred, GC had to be tapered and withdrawn at 6 months of treatment. Rituximab was non-inferior to cyclophosphamide and complete remission was achieved in 64% of the patients in the rituximab group and 53% of the patients in the cyclophosphamide group at 6 months of treatment (level of evidence 1b). However, in the subgroup of relapsing patients, rituximab was superior to cyclophosphamide (67% vs. 42%, $p = 0.01$) (level of evidence 1b).[15] In the long-term follow-up of the RAVE study, sustained remission rates remained similar in both groups at 6, 12 and 18 months and no differences in adverse events were observed (level of evidence 2b).[35]

The RITUXVAS (*Rituximab Versus Cyclophosphamide in ANCA-Associated Vasculitis*) study protocol was somewhat different from the RAVE study and its primary end points were sustained remission at 12 months and severe adverse events. Forty-four patients with newly diagnosed AAV with renal involvement were randomly included in a 3:1 ratio in two groups as follows rituximab (375 mg/m^2 four weekly infusions) with two infusions of cyclophosphamide and the other group received IV cyclophosphamide pulses for 3–6 months, followed by azathioprine. Patients on dialysis were not excluded, although they were a small subgroup, some of these patients underwent plasma exchange. Sustained remission at 12 months was similar between rituximab and cyclophosphamide AAV patients with severe disease manifestations (76% vs. 82%, $p = 0.68$, respectively). Severe adverse events, death rate and the improvement in GFR were also similar in both groups (level of evidence 1b).[16] At 24 months, relapse rate remained similar between rituximab and cyclophosphamide groups, but in the former relapses were associated with B cell normalization in peripheral blood (level of evidence 2b).[36]

8. Which precautions should be taken when prescribing rituximab?

Before the infusion of rituximab in AAV patients, serology tests for HIV, HBV and syphilis should be checked. Patients with chronic HBV and HIV should only be treated with rituximab with concomitant prescription of antiviral therapy and the consultation from a specialist in infectious diseases (grade of recommendation C).[37] Vaccination should be given prior to rituximab infusion whenever it is possible, especially for annual influenza, pneumococcal and HBV. Administration of other vaccines such as anti-tetanus and anti-diphtheria or anti-meningoccocal is optional but immunization records should be updated (grade of recommendation D).[37] Baseline serum immunoglobulin levels and B-cell count in peripheral blood are recommended to be measured before rituximab infusion and thereafter. It is important to measure serum immunoglobulins, especially serum IgG, prior to each administration of rituximab and 4–6 months after and to assess the need for replacement of IV immunoglobulin (IVIG) (grade of recommendation C).[37–39] In cases of severe hypogammaglobulinemia (IgG <500 mg/L) and infectious complications, the replacement of IVIG is required at a dose of 0.2–0.4 g/kg for 1 day, every 3–4 weeks, as required to maintain serum IgG levels above 500 mg/mL. Rituximab withdrawal should be considered

if patient presents serum IgG persistently below 500 mg/dL and severe recurrent infections (grade of recommendation C).[37,39,40] However, it should be taken into account the balance between treatment benefits to control inflammatory activity and the risk of severe adverse events with rituximab therapy.

Literature review

Low IgG levels is observed in up to 34% of patients with multisystem autoimmune diseases after rituximab therapy and higher GC doses as well as total dose of rituximab ≥6 g are associated with IgG fall (level of evidence 3b).[41] In addition, in AAV patients the use of cyclophosphamide is associated with a decrease in immunoglobulin levels that are further decreased with subsequent rituximab therapy (level of evidence 3b).[42] Up to 24 months of follow-up, severe infections were not different between AAV patients treated with rituximab and patients treated with conventional therapy for AAV in RCT.[15,16,35,36]

9. *Is plasma exchange indicated in the treatment of patients with active AAV?*

Plasma exchange is indicated in AAV patients with rapidly progressive glomerulonephritis with serum creatinine >5.8 mg/dL, since it leads to improvement in renal survival when associated with GC and cyclophosphamide (grade of recommendation A). Plasma exchange is prescribed in a 7-session schedule on alternate days at a 60 mL/kg volume exchange on each occasion, volume replacement needs to be done with 5% albumin and occasionally with fresh frozen plasma at the end of the procedure to replenish coagulation factors (grade of recommendation A). There is still insufficient evidence to support plasma exchange to treat patients with AAV presenting alveolar hemorrhage, possibly these patients may benefit from plasma exchange (grade of recommendation D).

Literature review

Plasma exchange was introduced in the treatment of pauci-immune vasculitis with renal involvement after its successful use in anti-glomerular basement membrane antibody (anti-GBM) disease.[43] Initially, two small RCT evaluated the addition of plasma exchange to conventional treatment in AAV patients with renal impairment and observed a better recovery of renal function, especially in patients with elevated creatinine and those on hemodialysis. However, no impact was observed on mortality (level of evidence 2b).[44,45]

The largest RTC that evaluated plasma exchange in AAV was the *Plasma Exchange versus Methylprednisolone for severe renal vasculitis* (MEPEX) study. In this study, 137 patients with AAV and rapidly progressive glomerulonephritis with creatinine above 5.8 mg/dL were treated with sessions of plasma exchange or with IV monthly pulses of methylprednisolone. Both groups received oral prednisone and cyclophosphamide. After 3 months, 69% of patients who underwent plasma exchange were free from dialysis, compared to 49% of those receiving methylprednisolone pulses ($p = 0.02$) (level of evidence 1b). Plasma exchange was associated with a reduction in the risk of progression to end-stage renal disease by 24% at 12 months (95% CI: 6.1–41.0%). However, survival and adverse events were similar between both groups after 1 year of follow-up (level of evidence 1b).[14] The benefit of plasma exchange on survival and on the risk of developing end-stage renal disease are not evident at 3.95 years of follow-up (level of evidence 2b).[46] Regarding alveolar hemorrhage in AAV, there is no evidence of benefit from plasma exchange yet. The *Plasma Exchange and GC dosing in the treatment of anti-neutrophil cytoplasm associated vasculitis* (PEXIVAS) study is an ongoing RCT that evaluates the efficacy of plasma exchange in patients with GPA and MPA with renal involvement and decreased renal function and/or alveolar hemorrhage.[47]

10. *Is IVIG as an alternative therapy for the induction therapy of AAV?*

IVIG is an alternative for the induction therapy of AAV patients with active disease at an immunomodulatory dose (i.e. 2 g/kg divided in 2–5 days), in specific scenarios such as in infected AAV patients with persistent disease activity and in patients refractory to standard treatment with GC and cyclophosphamide (grade of recommendation B). Additionally, AAV patients with persistent and active disease who present contraindications to cyclophosphamide or rituximab may also benefit from IVIG therapy (grade of recommendation D).

Literature review

A satisfactory response was observed in most AAV patients treated with IVIG in small open-label studies that included patients with active AAV refractory to GC and immunosuppressive agents, or in patients with rapidly progressive glomerulonephritis associated with MPO-ANCA (level of evidence 4).[48–50] A multicenter RCT evaluated the efficacy of a single dose of IVIG in 34 patients with active GPA or MPA despite treatment. Seventeen AAV patients were treated with IVIG and 17 with placebo. The primary outcome was reduction of more than 50% in the BVAS in three months and it was achieved by 14 patients. However, after three months no significant differences were found in serum CRP levels or in disease activity between groups (level of evidence 2b). Adverse events were more frequent in IVIG group.[51] A French multicentric retrospective study evaluated 92 AAV patients who had received different IVIG dose regimens and observed complete remission in only 56% at six months (level of evidence 4).[52]

11. *Is mycophenolate mofetil (MMF) indicated for the induction therapy of AAV?*

To date, there is not enough evidence to recommend the use of MMF in AAV induction therapy, it should be reserved as an alternative to cyclophosphamide, rituximab or methotrexate, since small studies have shown some benefits over cyclophosphamide in AAV patients with active disease (grade of recommendation C).

Literature review

Only two small open-label studies performed in China have compared the use of MMF to IV monthly pulse therapy with cyclophosphamide for 6 months in AAV induction therapy. In one study, MMF resulted in a lower BVAS value at 6 months compared with cyclophosphamide and the other study found

no difference between the two therapeutic modalities in MPA (level of evidence 3b).[53,54]

12. *Is there any place for anti-TNFα agents in the induction therapy of AAV patients?*

The TNF receptor blocker agent etanercept is not recommended in the induction therapy of AAV patients (grade of recommendation A). Other anti-TNFα agents have not been studied properly in AAV.

Literature review

The study *Wegener's Granulomatosis Etanercept Trial* (WGET) was the only randomized controlled trial that evaluated the use of anti-TNFα agents in GPA. In this study, 180 GPA patients received standard therapy with GC and cyclophosphamide or methotrexate plus etanercept or placebo. No differences were found between etanercept and placebo regarding the frequency of disease relapses, sustained remission, irreversible damage, quality of life or side effects. However, six cases of solid tumors were identified in patients from the etanercept group who were also under cyclophosphamide therapy, whereas no solid tumors were observed in the placebo group (level of evidence 1b).[17] The occurrence of solid tumors remained increased during long-term follow-up (level of evidence 2b).[55]

13. *Is azathioprine indicated for the induction therapy of AAV patients?*

Azathioprine is not indicated for induction therapy of AAV patients with active disease (grade of recommendation D).

Literature review

To date, no RCT has evaluated azathioprine in the induction therapy of AAV patients (level of evidence 5). Azathioprine prevents disease relapses in AAV patients who attained remission (level of evidence 1b).[21,22,24]

14. *How subglottic stenosis should be approached in GPA patients?*

GPA patients presenting subglottic stenosis (SGS) in the presence of systemic disease activity should be treated with GC and immunosuppressive agents according to disease severity in association with local treatment. In case of SGS in GPA patients in remission, we recommend only local treatment (grade of recommendation D). As first line local therapy, mechanical intratracheal dilation associated with intralesional injection of a long-acting GC (e.g. methylprednisolone acetate or triamcinolone) is recommended, sometimes requiring repeated procedures (grade of recommendation C). In refractory cases and in patients presenting severe manifestations of SGS, open surgery with laryngotracheal reconstruction or permanent tracheostomy should be performed. Indeed, tracheostomy should be reserved only as an urgent intervention for life-threatening situations (grade of recommendation D).

Literature review

SGS is a potentially life-threatening complication of GPA and it affect more frequently patients with disease onset in younger ages.[56] SGS have been described in a state of disease remission despite immunosuppressive therapy. There are no RCT assessing therapeutic options for this disease manifestation but numerous case reports and case series including from 2 to 36 patients have been published. Approximately 25% of patients with SGS respond to oral GC with or without an immunosuppressive agent.[56,57] The remainder will need local therapy. One of the most well described local intervention is mechanical intratracheal dilation associated with intralesional injection of a long-acting GC.[56,58–60] In the two largest case series with 20 and 21 GPA patients with SGS who underwent this procedure, no new tracheostomy was necessary and decannulation was possible in almost all previously tracheostomized patients. An average of 2.4–3.0 procedures was necessary per patient.[56,58] Intralesional injection is performed with a long-acting GC (e.g. methylprednisolone 40–120 mg or triamcinolone 40 mg) in a 4-quadrant submucosal pattern of the stenotic ring before mechanical dilation. Some authors suggest to perform the lysis of stenotic ring with radial incisions before manual dilation.[58–60] IV GC was administered during the procedure in some papers. Regarding its antifibrotic effects, topical mitomycin C was proposed to prevent restenosis, but contradictory results were observed in different case series.[59,61,62] Local laser therapy (CO2 or NG:YAG) has been described as an alternative for SGS, but results were divergent, including cases of stenosis exacerbation after this procedure.[57,58,63] Open surgical interventions such as laryngotracheoplasty are described in patients who failed endoscopic procedures.[57] In view of new endoscopic techniques, tracheostomy have been reserved for emergency situations.[64,65] Intratracheal stents have been contraindicated by some authors in GPA patients due to the high frequency of complications.[66]

15. *Is prophylaxis for pneumocystis pneumonia indicated in AAV patients during induction therapy?*

Prophylaxis for *Pneumocystis jirovecii* pneumonia (PCP) with 400 mg/80 mg dose/day or 800 mg/160 mg three times a week of sulfamethoxazole and trimethoprim (SMT-TMP) is indicated to AAV patient undergoing induction therapy with GC and cyclophosphamide or rituximab (grade of recommendation A). Patients with a total lymphocyte count below 300 cells/mm^3 must also receive prophylactic treatment for PCP regardless of the immunosuppressive therapy prescribed (grade of recommendation B). If GFR is between 15 and 30 mL/minute, SMT-TMP dose should be reduced to 400 mg/80 mg three times a week. In AAV patients presenting terminal renal failure, during methotrexate therapy or in sulfa allergy, inhaled pentamidine at 300 mg/month should be preferred (grade of recommendation C).

Literature review

Severe infections are observed in up to 39% of the GPA patients and PCP affects a third of them (level of evidence 2b).[67] Most cases of PCP occur during induction therapy and in the absence of appropriate prophylaxis (level of evidence 3b).[68] A

systematic review evaluated the efficacy of prophylaxis for PCP in immunocompromised patients who were not HIV-infected and found that SMT-TMP use resulted in 85% reduction of PCP (relative risk: 0.15; 95%CI: 0.04–0.62) (level of evidence 1a).[69]

In a small RCT that compared oral and IV pulse cyclophosphamide to treat GPA, up to 20% of patients developed PCP. Amongst patients who did not receive prophylaxis with SMT-TMP, the incidence of PCP was higher in those treated with oral cyclophosphamide (30.4%) compared with those treated with IV pulse cyclophosphamide (11.1%) (level of evidence 2b).[29] In the trial *Japanese patients with MPO-ANCA-associated vasculitis* (JMAAV) that evaluated the AAV treatment based on disease severity, 31 out of 48 patients received SMT-TMP prophylaxis for PCP. During the study, three PCP events were observed, two in patients without PCP prophylaxis and a third event two months after PCP prophylaxis withdrawal due to liver toxicity. Indeed, no patients under prophylaxis developed PCP (level of evidence 2b).[70]

In two review articles that approached infections observed in observational and interventional studies that included AAV patients, the authors state: (1) SMT-TMP or pentamidine (in case of intolerance or contraindication) should be prescribed routinely, during the initial phase of induction therapy, and this prophylaxis should be maintained in the presence of risk factors such as age above 55 years, lymphocyte count below 300/mm^3, long-term treatment with GC at doses above 15–20 mg/day, and treatment with other immunosuppressive agents, particularly cyclophosphamide (level of evidence 2a); (2) SMT-TMP should be prescribed during induction therapy with other agents, especially rituximab, until GC daily dose is reduced to 10 mg/day (level of evidence 3b); (3) In patients using methotrexate as induction therapy, the use of pentamidine should be considered, in view of drug interactions with SMT-TMP (level of evidence 3b).[71,68]

16. What should be considered regarding vaccination in patients with AAV receiving induction therapy?

Whenever it is possible, patients with AAV should be vaccinated prior to starting immunosuppressive treatment, ideally three weeks before. Influenza vaccine seems to be safe and effective for AAV patients in remission and it should be given annually (grade of recommendation B). Considering the high frequency of pulmonary infections in AAV patients, pneumococcal vaccine should also be administered (grade of recommendation D). Immunization schedule in AAV patients should follow the Immunization Guide published by the Brazilian Society of Immunization/Brazilian Society of Rheumatology.[72]

Literature review

Influenza vaccination in AAV patients in remission leads to high antibody titers and protection similarly to that of controls, with no impact on disease activity (level of evidence 2b).[73–75] Additionally, a retrospective study has demonstrated a reduction in the risk of disease relapse in AAV patients who were given influenza vaccine compared with non-vaccinated patients (level of evidence 3b).[74] In fact, it is recommended to immunize AAV patients with inactivated vaccines such as hepatitis B vaccine and anti-pneumococcal vaccine, particularly in AAV patients prior to rituximab therapy (level of evidence 5).[37]

In the *Pneumovas* Pilot 1 study, 19 AAV patients were divided into two groups (e.g. induction and maintenance therapy), and were given the anti-pneumoccocal vaccine 13 valent, 23 valent or both. Preliminary data have demonstrated that the anti-pneumococcal vaccine, even when both 13 and 23 valent were associated, were ineffective when administered during induction therapy for AAV.[76]

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Conflicts of interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.rbre.2017.06.003.

REFERENCES

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65:1–11.
2. Silva de Souza AW. Autoantibodies in systemic vasculitis. Front Immunol. 2015;6:184.
3. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al., European Vasculitis Study Group. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009;68:310–7.
4. 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. Ann Rheum Dis. 2016;75:1583–94.
5. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis. 2009;68:1827–32.
6. Stone JH, Hoffman GS, Merkel PA, Min YI, Uhlfelder ML, Hellmann DB, et al. International Network for the Study of the Systemic Vasculitides (INSSYS). A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. Arthritis Rheum. 2001;44:912–20.
7. Kallenberg CG. Key advances in the clinical approach to ANCA-associated vasculitis. Nat Rev Rheumatol. 2014;10:484–93.
8. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting

systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
9. Oxford Centre for Evidence-based Medicine. Levels of Evidence (March 2009). CEBM; 2009.
10. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al., GRADE Working Group. Going from evidence to recommendations. BMJ. 2008;336:1049–51.
11. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al., GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924–6.
12. de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al., EUVAS (European Vasculitis Study Group). Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med. 2009;150:670–80.
13. De Groot K, Rasmussen N, Bacon PA, Tervaert JW, 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 Rheum. 2005;52:2461–9.
14. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al., European Vasculitis Study Group. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol. 2007;18:2180–8.
15. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al., RAVE-ITN Research Group. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363:221–32.
16. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al., European Vasculitis Study Group. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010;363:211–20.
17. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med. 2005;352:351–61.
18. Walton EW. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). Br Med J. 1958;2:265–70.
19. Hollander D, Manning RT. The use of alkylating agents in the treatment of Wegener's granulomatosis. Ann Intern Med. 1967;67:393–8.
20. Miloslavsky EM, Specks U, Merkel PA, Seo P, Spiera R, Langford CA, et al., Rituximab in ANCA-Associated Vasculitis-Immune Tolerance Network Research Group. Outcomes of nonsevere relapses in antineutrophil cytoplasmic antibody-associated vasculitis treated with glucocorticoids. Arthritis Rheumatol. 2015;67:1629–36.
21. Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, et al., French Vasculitis Study Group. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med. 2008;359:2790–803.
22. Hiemstra TF, Walsh M, Mahr A, Savage CO, de Groot K, Harper L, et al., European Vasculitis Study Group (EUVAS). Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. JAMA. 2010;304:2381–8.
23. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaître O, Cohen P, et al., French Vasculitis Study Group. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014;371:1771–80.
24. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniené J, et al., European Vasculitis Study Group. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med. 2003;349:36–44.
25. Langford CA, Talar-Williams C, Barron KS, Sneller MC. Use of a cyclophosphamide-induction methotrexate-maintenance regimen for the treatment of Wegener's granulomatosis: extended follow-up and rate of relapse. Am J Med. 2003;114:463–9.
26. Walsh M, Merkel PA, Mahr A, Jayne D. Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody-associated vasculitis: a meta-analysis. Arthritis Care Res (Hoboken). 2010;62:1166–73.
27. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med. 1992;116:488–98.
28. Holle JU, Gross WL. Treatment of ANCA-associated vasculitides (AAV). Autoimmun Rev. 2013;12:483–6.
29. Guillevin L, Cordier JF, Lhote F, Cohen P, Jarrousse B, Royer I, et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. Arthritis Rheum. 1997;40:2187–98.
30. Haubitz M, Schellong S, Göbel U, Schurek HJ, Schaumann D, Koch KM, et al. Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement: a prospective, randomized study. Arthritis Rheum. 1998;41:1835–44.
31. Adu D, Pall A, Luqmani RA, Richards NT, Howie AJ, Emery P, et al. Controlled trial of pulse versus continuous prednisolone and cyclophosphamide in the treatment of systemic vasculitis. QJM. 1997;90:401–9.
32. Harper L, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O, et al., EUVAS Investigators. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. Ann Rheum Dis. 2012;71:955–60.
33. Hoffman GS, Leavitt RY, Kerr GS, Fauci AS. The treatment of Wegener's granulomatosis with glucocorticoids and methotrexate. Arthritis Rheum. 1992;35:1322–9.
34. Faurschou M, Westman K, Rasmussen N, de Groot K, Flossmann O, Höglund P, et al., European Vasculitis Study Group. Brief Report: long-term outcome of a randomized clinical trial comparing methotrexate to cyclophosphamide for remission induction in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2012;64:3472–7.
35. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al., RAVE-ITN Research Group. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med. 2013;369:417–27.
36. Jones RB, Furuta S, Tervaert JW, Hauser T, Luqmani R, Morgan MD, et al., European Vasculitis Society (EUVAS). Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial. Ann Rheum Dis. 2015;74:1178–82.
37. Charles P, Bienvenu B, Bonnotte B, Gobert P, Godmer P, Hachulla É, et al., French Vasculitis Study Group. Rituximab. Recommendations of the French Vasculitis Study Group (FVSG) for induction and maintenance treatments of adult, antineutrophil cytoplasm antibody-associated necrotizing vasculitides. Presse Med. 2013;42:1317–30.
38. Guerry MJ, Brogan P, Bruce IN, D'Cruz DP, Harper L, Luqmani R, et al. Recommendations for the use of rituximab in anti-neutrophil cytoplasm antibody-associated vasculitis. Rheumatology (Oxford). 2012;51:634–43.
39. Bukhari M, Abernethy R, Deighton C, Ding T, Hyrich K, Lunt M, et al., BSR and BHPR Standards, Guidelines and Audit Working

Group. BSR and BHPR guidelines on the use of rituximab in rheumatoid arthritis. Rheumatology (Oxford). 2011;50:2311–3.
40. Carvalho B, Solé D, Condino-Neto A, Rosário Filho N, Ouricuri AL, Silva Segundo GR, et al. I Consenso brasileiro sobre o uso de imunoglobulina humana em pacientes com imunodeficiências primárias. Rev Bras Alerg Imunopatol. 2010;33:104–16.
41. Marco H, Smith RM, Jones RB, Guerry MJ, Catapano F, Burns S, et al. The effect of rituximab therapy on immunoglobulin levels in patients with multisystem autoimmune disease. BMC Musculoskelet Disord. 2014;15:178.
42. Venhoff N, Effelsberg NM, Salzer U, Warnatz K, Peter HH, Lebrecht D, et al. Impact of rituximab on immunoglobulin concentrations and B cell numbers after cyclophosphamide treatment in patients with ANCA-associated vasculitides. PLoS ONE. 2012;7:e37626.
43. Lockwood CM, Rees AJ, Pearson TA, Evans DJ, Peters DK, Wilson CB. Immunosuppression and plasma-exchange in the treatment of Goodpasture's syndrome. Lancet. 1976;1:711–5.
44. Pusey CD, Rees AJ, Evans DJ, Peters DK, Lockwood CM. Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. Kidney Int. 1991;40:757–63.
45. Szpirt WM, Heaf JG, Petersen J. Plasma exchange for induction and cyclosporine A for maintenance of remission in Wegener's granulomatosis – a clinical randomized controlled trial. Nephrol Dial Transplant. 2011;26:206–13.
46. Walsh M, Casian A, Flossmann O, Westman K, Höglund P, Pusey C, et al., European Vasculitis Study Group (EUVAS). Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. Kidney Int. 2013;84:397–402.
47. Walsh M, Merkel PA, Peh CA, Szpirt W, Guillevin L, Pusey CD, et al., PEXIVAS Investigators. Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial. Trials. 2013;14:73.
48. Richter C, Schnabel A, Csernok E, De Groot K, Reinhold-Keller E, Gross WL. Treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis with high-dose intravenous immunoglobulin. Clin Exp Immunol. 1995;101:2–7.
49. Muso E, Ito-Ihara T, Ono T, Imai E, Yamagata K, Akamatsu A, et al. Intravenous immunoglobulin (IVIg) therapy in MPO-ANCA related polyangiitis with rapidly progressive glomerulonephritis in Japan. Jpn J Infect Dis. 2004;57:S17–8.
50. Martinez V, Cohen P, Pagnoux C, Vinzio S, Mahr A, Mouthon L, et al., French Vasculitis Study Group. Intravenous immunoglobulins for relapses of systemic vasculitides associated with antineutrophil cytoplasmic autoantibodies: results of a multicenter, prospective, open-label study of twenty-two patients. Arthritis Rheum. 2008;58:308–17.
51. Jayne DR, Chapel H, Adu D, Misbah S, O'Donoghue D, Scott D, et al. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. QJM. 2000;93:433–9.
52. Crickx E, Machelart I, Lazaro E, Kahn JE, Cohen-Aubart F, Martin T, et al., French Vasculitis Study Group. Intravenous immunoglobulin as an immunomodulating agent in antineutrophil cytoplasmic antibody-associated vasculitides: a French nationwide study of ninety-two patients. Arthritis Rheumatol. 2016;68:702–12.
53. Hu W, Liu C, Xie H, Chen H, Liu Z, Li L. Mycophenolate mofetil versus cyclophosphamide for inducing remission of ANCA vasculitis with moderate renal involvement. Nephrol Dial Transplant. 2008;23:1307–12.
54. Han F, Liu G, Zhang X, Li X, He Q, He X, et al. Effects of mycophenolate mofetil combined with corticosteroids for induction therapy of microscopic polyangiitis. Am J Nephrol. 2011;33:185–92.
55. Silva F, Seo P, Schroeder DR, Stone JH, Merkel PA, Hoffman GS, et al., Wegener's Granulomatosis Etanercept Trial Research Group. Solid malignancies among etanercept-treated patients with granulomatosis with polyangiitis (Wegener's): long-term followup of a multicenter longitudinal cohort. Arthritis Rheum. 2011;63:2495–503.
56. Langford CA, Sneller MC, Hallahan CW, Hoffman GS, Kammerer WA, Talar-Williams C, et al. Clinical features and therapeutic management of subglottic stenosis in patients with Wegener's granulomatosis. Arthritis Rheum. 1996;39:1754–60.
57. Lebovics RS, Hoffman GS, Leavitt RY, Kerr GS, Travis WD, Kammerer W, et al. The management of subglottic stenosis in patients with Wegener's granulomatosis. Laryngoscope. 1992;102 12 Pt 1:1341–5.
58. Hoffman GS, Thomas-Golbanov CK, Chan J, Akst LM, Eliachar I. Treatment of subglottic stenosis, due to Wegener's granulomatosis, with intralesional corticosteroids and dilation. J Rheumatol. 2003;30:1017–21.
59. Nouraei SA, Obholzer R, Ind PW, Salama AD, Pusey CD, Porter F, et al. Results of endoscopic surgery and intralesional steroid therapy for airway compromise due to tracheobronchial Wegener's granulomatosis. Thorax. 2008;63:49–52.
60. Wolter NE, Ooi EH, Witterick IJ. Intralesional corticosteroid injection and dilatation provides effective management of subglottic stenosis in Wegener's granulomatosis. Laryngoscope. 2010;120:2452–5.
61. Gouveris H, Karaiskaki N, Koutsimpelas D, Chongolwatana C, Mann W. Treatment for adult idiopathic and Wegener-associated subglottic stenosis. Eur Arch Otorhinolaryngol. 2013;270:989–93.
62. Martinez Del Pero M, Jayne D, Chaudhry A, Sivasothy P, Jani P. Long-term outcome of airway stenosis in granulomatosis with polyangiitis (Wegener granulomatosis): an observational study. JAMA Otolaryngol Head Neck Surg. 2014;140:1038–44.
63. Gluth MB, Shinners PA, Kasperbauer JL. Subglottic stenosis associated with Wegener's granulomatosis. Laryngoscope. 2003;113:1304–7.
64. Alam DS, Seth R, Sindwani R, Woodson EA, Rajasekaran K. Upper airway manifestations of granulomatosis with polyangiitis. Cleve Clin J Med. 2012;79 Suppl 3: S16–21.
65. Rasmussen N. L24. Local treatments of subglottic and tracheal stenoses in granulomatosis with polyangiitis (Wegener's). Presse Med. 2013;42 4 Pt 2:571–4.
66. Mair EA. Caution in using subglottic stents for Wegener's granulomatosis. Laryngoscope. 2004;114:2060–1.
67. Mahr A, Girard T, Agher R, Guillevin L. Analysis of factors predictive of survival based on 49 patients with systemic Wegener's granulomatosis and prospective follow-up. Rheumatology (Oxford). 2001;40:492–8.
68. Bligny D, Mahr A, Toumelin PL, Mouthon L, Guillevin L. Predicting mortality in systemic Wegener's granulomatosis: a survival analysis based on 93 patients. Arthritis Rheum. 2004;51:83–91.
69. Stern A, Green H, Paul M, Vidal L, Leibovici L. Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients. Cochrane Database Syst Rev. 2014:CD005590.
70. Ozaki S, Atsumi T, Hayashi T, Ishizu A, Kobayashi S, Kumagai S, et al. Severity-based treatment for Japanese patients with MPO-ANCA-associated vasculitis: the JMAAV study. Mod Rheumatol. 2012;22:394–404.
71. Kronbichler A, Jayne DR, Mayer G. Frequency, risk factors and prophylaxis of infection in ANCA-associated vasculitis. Eur J Clin Invest. 2015;45:346–68.

72. Sociedade Brasileira de Reumatologia & Sociedade Brasileira de Imunologia. Reumatologia: Guia de Imunização SBIm/SBR; Magic/RM; 2014/2015.
73. Zycinska K, Romanowska M, Nowak I, Rybicka K, Wardyn KA, Brydak LB. Antibody response to inactivated subunit influenza vaccine in patients with Wegener's granulomatosis. J Physiol Pharmacol. 2007;58 Suppl 5 Pt 2:819–928.
74. Stassen PM, Sanders JS, Kallenberg CG, Stegeman CA. Influenza vaccination does not result in an increase in relapses in patients with ANCA-associated vasculitis. Nephrol Dial Transplant. 2008;23:654–8.
75. Holvast A, Stegeman CA, Benne CA, Huckriede A, Wilschut JC, Palache AM, et al. Wegener's granulomatosis patients show an adequate antibody response to influenza vaccination. Ann Rheum Dis. 2009;68:873–8.
76. Groh M, Puéchal X, Terrier B, Le Jeunne C, Batteux F, Launay O. Failure of pneumococcal immunization during remission induction treatment of ANCA-associated vasculitis: the Pneumovas Pilot 1 study. Joint Bone Spine. 2016. pii:S1297-319X(16)30174-9.