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MINIREVIEWS

Classification, diagnosis and treatment of ANCA-associated vasculitis

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Abstract

Diagnosis of anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis is usually not difficult in patient with systemic disease, including lung and kidneys involvement, and laboratory signs of inflammation. The presence of ANCA and the results of histological investigation confirm diagnosis of ANCA-associated vasculitis. Cyclophosphamide/azathioprine in combination with high dose steroids are used to induce and maintain remission of systemic vasculitis. The clinical trials also showed efficacy of rituximab that induces depletion of B-cells. Our understanding and management of ANCA-associated vasculitis improved significantly over the last decades but there is still a lot of debate over its classification, diagnostic criteria, assessment of activity and optimum treatment.

Key words: Systemic vasculitis; Anti-neutrophil cytoplasmic antibodies; Granulomatosis with polyangiitis; Microscopic polyangiitis

Core tip: The diagnosis and treatment of anti-neutrophil cytoplasmic antibodies-associated vasculitis are a challenge for physicians. This article presents an updated information about these uncommon diseases.

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INTRODUCTION

Systemic vasculitides associated with anti-neutrophil cytoplasmic autoantibodies (ANCA) include granulomatosis with polyangiitis (Wegener's; GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (Churg-Strauss; EGPA). The annual incidence of ANCA-associated vasculitides is 10 to 20 cases per 1000000 of the general population[1,2]. The relative incidence depends on the geographic region, *e.g.*, in Europe GPA is more prevalent than MPA while the opposite is true in Japan[3]. The circulation of ANCA is the distinctive feature of all three ANCA-associated vasculitides though these autoantibodies are present only in part of patients, are not obligatory classification criterium and may be detected in patients with other diseases, including infective endocarditis[4]. *In vitro*

and *in vivo* studies suggest that ANCA are essential fo the development of ANCA-associated vasculitis. Interaction of autoantibodies with antigens expressed by neutrophils (and mononuclear cells) induces activation of cells and inflammatory response that ultimately leads to necrotic changes in vascular walls and surrounding tissues[5]. In these review we focused on GPA and MPA that have many common features and do not discuss EGPA.

CLASSIFICATION AND NOMENCLATURE OF ANCA-ASSOCIATED VASCULITIDES

The modern nomenclature of systemic vasculitides was developed in 2012 at the consensus conference in Chapel-Hill (United States)[6]. According to the current definition ANCA-associated vasculitis is predominantly small-vessel necrotizing vasculitis associated with autoantibodies for myeloperoxidase (MPO) or proteinase-3 (PR3)[7]. In patients with MPA inflammation involves practically exclusively vessels walls, mainly in kidneys and lungs, while in GPA (as is in EGPA) vasculitis is associated with extravascular necrotizing granulomatous inflammation of tissues, *e.g.,* of upper and/or lower respiratory tract. Necrotizing glomerulonephritis is common in patients with both ANCA-associated vasculitides, especially in MPA.

The current classification of ANCA-associated vasculitides may be revised in the future. Lionaki *et al*[7] showed in 502 patients with ANCA-associated vasculitides that ANCA-specificity predicted the risk of relapse while the clinical phenotype had lower predictive value[7]. In patients with PR3-ANCA the risk of relapse was almost twice higher than in patients with MPO-ANCA (OR = 1.89; 95%CI: 1.33-2.69) though ANCA-specificity did not predict the resistance to standard treatment or the risk of end-stage renal failure and death. These data suggest that ANCA-specificity may be a valuable classification criterium, *e.g.,* PR3-ANCA- and MPO-ANCA-associated vasculitis, though the obvious limitation of such approach is the absence of autoantibodies in significant number of patients.

The genetic studies confirmed the possible significance of ANCA-specificity for MPO and PR3 in disease recognition and prognosis. Lyons *et al*[8] in a large-scale study in 2687 patients with GPA or MPA and 7550 control patients have detected close association of PR3-ANCA with HLA-DP and genes that coded α_1-antitrypsin (SERPINA1) and PR3 (PRTN3), while MPO-ANCA were associated with HLA-DQ[8]. Meanwhile the association of clinical syndromes with genetic factors was less significant.

Recently the researchers from the French Vasculitis Study Group (FVSG) and the European Vasculitis Society (EUVAS) have performed cluster analysis in 673 subjects with GPA (59%) and MPA (41%)[9]. Five partially redundant clusters were founed, *e.g.*, "renal vasculitis with PR3-ANCA" (40% of subjects), "renal vasculitis without PR3-ANCA" (32%), "nonrenal vasculitis" (12%), "cardiovascular vasculitis" (9%) and "gastrointestinal vasculitis" (7%). The five phenotypes had distinct relapse rates and mortality. The non-renal ANCA-associated vasculitis class (this group predominantly consisted of patients with GPA) was characterized by the lowest risk of death and the highest risk of relapse and was chosen as the reference group. Kidney disease was associated with 2 to 4-fold lower relapse risk compared to reference group while the death risk was increased significantly only in patients with renal vasculitis without PR3-ANCA. Cardiovascular disease had unfavorable prognosis and was associated with the highest risk of death and the relapse rate comparable to that in non-renal ANCA-associated vasculitis. The authors suggested that a classification based on kidney involvement and ANCA specificity, and perhaps also gastrointestinal and cardiovascular diseases, may lead to more accurate stratification of patients into homogeneous disease groups though the clinical relevance of this approach requires further validation.

DIAGNOSTIC CRITERIA

There are no accepted criteria for the diagnosis of ANCA-associated vasculitis. The criteria developed by the American College of Rheumatology (ACR) in 1990[10] can be used for classification of systemic vasculitides, while the caterories that were defined in Chapel-Hill represent the nomenclature of these systemic diseases[6]. The ACR criteria performed badly in 198 patients who have been referred to rheumatologists with probable systemic vasculitis[11]. Moreover ACR classification did not include MPA. The Diagnostic and Classification Criteria for Vasculitis (DCVAS) study is a multinational observational study that was designed to develop diagnostic criteria for primary systemic vasculitis according to the guidelines of the ACR and the European League against Rheumatism (EULAR)[12]. The researchers anticipate to recruit > 2000 patients with primary systemic vasculitis and 1500 patients with other conditions that can mimic vasculitis. The study incorporates detailed clinical data, evaluation of ANCA and other laboratory parameters, biopsy and imaging data. As of April 2014 more than 115 medical centers in Europe, North America, Russia, Asia, Australasia, and South America were contributing data to this study.

Though diagnostic criteria for systemic vasculitis are not established, ANCA-associated vasculitis can be usually suspected in patients with typical clinical manifestations, *e.g.,* fever, joint pain, disease of upper and lower respiratory tract, kidney and other organs, and laboratory signs of inflammation (high ESR and C-reactive protein)[13]. GPA and MPA have overlapping features but show certain differences, *e.g.,*

ear, nose and throat involvement is more common in GPA than in MPA. In addition, patients with GPA frequently present with extravascular granulomatous lesions that are not seen in MPA. Not all patients with ANCA-associated vasculitides will have biopsy, while the results of histological examination may be difficult to interpretate. Thus, the clinical equivalents of granulomatous inflammation should be taken into account, *e.g.*, the following ones[14,15]: (1) lower respiratory tract and lung disease: persisting infiltrates, nodules and cavities, stenosis of bronchi; (2) upper respiratory tract disease: necrotising rhinitis with nasal bleedings and crusting, saddle nose deformity, chronic sinusitis (> 3 mo) and radiological damage, otitis media and mastoiditis; subglottic stenosis of trachea; and (3) orbital inflammatory pseudotumour.

ANCA-specificity has no decisive diagnostic value though PR3-ANCA are usually detected in GPA patients while MPO-ANCA are more common in MPA. In clinical practice it may be difficult to differentiate GPA and MPA but it is worth noting that nosological form, especially at the time of diagnosis, is less important for treatment decisions than the extent and severity of target organs damage.

Diagnosis is usually more complicated in patients with localised GPA (up to 25% of cases) that involves ear, nose and throat, eyes and/or ears, especially if imaging methods show the presence of pseudotumour with destruction of orbital and nasal sinuses walls. In patients with isolated orbital mass that is not associated with systemic manifestations the diagnosis of GPA may be established only with biopsy or after resection of "tumour". The presence of ANCA that can be detected with immunofluorescence method or ELISA contributes significantly to the diagnosis of ANCA-associated vasculitis[16] though these autoantibodies can be negative or disappear during immunosuppressive treatment. Biopsy (nose, lung, kidney, *etc.*) can be used to confirm the diagnosis of systemic vasculitis but histological study is not necessary for all patients.

ASSESSMENT OF ACTIVITY AND PROGNOSIS

The detection of ANCA is a valuable diagnostic test but their role as a marker of activity has not been established. Birck *et al*[17] in meta-analysis of 22 studies in 950 patients with ANCA-associated vasculitides failed to confirm the value of serial ANCA titers for evaluation of activity[17]. In the cohort study PR3-ANCA levels also did not correlate with disease activity in 156 patients with GPA[18]. Nevertheless, the results of several studies suggest that detection of ANCA can predict relapse in patients with ANCA-associated vasculitis. In 87 patients with GPA or MPA and PR3-antibodies ANCA-positivity at 18 and 24 mo of immunosuppressive treatment was associated with 2.7 (95%CI: 1.1-4.3) and 4.6 (95%CI: 1.2-6.3)-fold increased risk of relapse during 5-year follow-up[19]. Tomasson *et al*[20] evaluated the predictive value of ANCA detection in meta-analysis of 18 trials that measured the levels of autoantibodies during follow-up of patients. The persistence of ANCA-positivity increased the risk of relapse 2.84-fold (95%CI: 1.65-4.90) while increase in ANCA level during treatment was associated with 1.97-fold (95%CI: 1.43-2.70) higher relapse rate. These data suggest that ANCA detection during immunosuppressive treatment may predict the relapse of ANCA-associated vasculitis though predictive power of a rise in or a persistence of ANCA is probably modest[4]. In at least 25% of patients there is no correlation between clinical signs of vasculitis and immunological parameters[21]. Thus treatment decisions cannot be based only on ANCA titers[21].

Monach *et al*[22] measured 28 serum proteins, including cytokines, soluble receptors, chemokines, markers of tissue damage and inflammation, at baseline and at 6 mo in 186 patients with active ANCA-associated vasculitis who received immunosuppressive agents in RAVE study. At 6 mo 137 patients have achieved remission of vasculitis and showed significant declines in 24 of the 28 studied biomarkers. ROC analysis suggested that CXCL13 (BCA-1), matrix metalloproteinase-3 and tissue inhibitor of metalloproteinases-1 levels best discriminated active vasculitis from remission (AUC > 0.8) and from healthy controls (AUC > 0.9). These proteins are the promising candidates for the future studies that would probably identify more reliable markers of activity and predictors of relapse of ANCA-associated vasculitis. Poor correlation of these markers with ESR or C-reactive protein (CRP) confirmed the low predictive value of the latters. Nevertheless the changes in ESR and CRP level during treatment should be taken into account especially if patients present with clinical signs of vasculitis relapse.

In 1994, Luqmani *et al*[23] in a study of 213 consecutive patients with different forms of vasculitis have devised the Birmingham Vasculitis Activity Score (BVAS) as the clinical index of activity in systemic necrotizing vasculitis[23]. BVAS is widely used in clinical studies in patients with ANCA-associated vasculitides[24]. BVAS 3.0 includes 56 clinical signs and symptoms in nine separate organ systems[25]. Disease signs and symptoms are scored only when they are attributable to active systemic vasculitis and to other causes, such as infection, hypertension, toxic effects of treatment, and when they are new or deteriorate in the previous 28 d. BVAS 3.0 was recently validated in 238 patients from 7 European countries[26]. Higher BVAS value reflects activity and severity of systemic vasculitis and indicates unfavorable prognosis[27].

Vasculitis damage index (VDI) was developed to assess the irreversible tissue damage in systemic vasculitis and to account for the consequences of

immunosuppressive treatment (*e.g.,* osteoporosis, diabetes, hypertension *etc.*) and other factors such as atherosclerosis[28]. Each feature is scored only if it persists for more than 3 mo. Patients with at least five items of damage on the VDI score had 7- to 11-fold higher risk of death, as compared with those with lower VDI score[29]. Irreversible damage develops in 80% to 90% of patients with ANCA-associated vasculitis and usually progresses with time. In 302 patients who were followed in four European Vasculitis Study group trials at 7.3 years post-diagnosis the most frequent items of vasculitis damage were proteinuria, impaired glomerular filtration rate, hypertension, nasal crusting, hearing loss and peripheral neuropathy while the most commonly reported items of treatment-related damage included hypertension (41.5%), osteoporosis (14.1%), malignancy (12.6%), and diabetes (10.4%)[30]. At long-term follow-up around one-third of patients had ⩾ 5 items of damage. VDI does not measure functional disability related to systemic vasculitis or its treatment. For example, in patient with chronic nasal discharge and mild arterial hypertension VDI will be higher (2 items) than in disabled patient with persistent palsy associated with transverse myelitis (1 item) or end stage renal failure requiring dialysis (1 item).

Five-factor score (FFS) was developed by the French Vasculitis Study Group in 1996 as a prognostic index[31]. FFS was revised in 2009 in a study in 1108 consecutive patients with 4 systemic necrotizing vasculitides (GPA, polyarteritis nodosa, MPA and EGPA)[32]. This score is based on five factors that were associated with higher 5-year death rate, *e.g.*, age (> 65 years), heart disease, gastrointestinal involvement and renal failure (creatinine level ⩾ 150 μmol/L) and an additional criteria for GPA and EGPA-the absence of ENT symptoms. In patients with FFS of 0, 1 and ⩾ 2 the 5-year mortality was 9%, 21% and 40%, respectively.

CURRENT TREATMENT

Without treatment majority of patients with ANCA-associated vasculitis die within two years after diagnosis. Treatment with corticosteroids and cyclophosphamide significantly increased patients survival but also induced the changes in the causes of death, *e.g.*, increased the risk of cardiovascular outcomes and the complications of prolonged immunosuppression. In 535 patients with GPA and MPA who had been enrolled at the time of diagnosis to four randomised controlled trials in 1995-2002 overall survival at five years of follow-up was 75%[27]. Compared with an age- and sex-matched general population there was a mortality ratio of 2.6 (95%CI: 2.2-3.1). Within the first year of follow-up patients mainly died from infection (48%) and active vasculitis (19%) while later the death was more frequently attributed to cardiovascular disease (26%) and malignancy (22%) and more rarely to infections (20%). Multivariable analysis showed an end-stage kidney disease, advancing age and higher BVAS were negative prognostic factors for patient survival.

In spite of considerable advances in treatment there is a high need in new immunosuppressive regimens as a significant proportion of patients are refractory to current therapies and around 50% develop a relapse within 5 years while more than 90% of patients accumulate irreversible damage associated with both vasculitis and prolonged immunosuppression[33].

The aim of treatment for ANCA-associated vasculitis is to induce (usually within 3 to 6 mo) and to maintain remission. Maintenance treatment should be continued for at least 2 years or frequently life-long. The choice of the immunosuppressive regimen depends on activity, extent of damage and severity of visceral manifestations (*e.g.*, kidney or lung disease) that can be fatal or disabling. It worth noting that patients with localised GPA can also require intensive immunosuppressive treatment taking into account the risk of serious outcomes (*e.g.*, loss of vision or hearing, destruction of tissues) and/or generalization of vasculitis. In patients with active ANCA-associated vasculitis the current standard of care is cyclophosphamide oral (2 mg/kg daily) or intravenous (15 mg/kg every 2 wk for the first three doses and thereafter every 3 wk) administration in combination with high-dose glucocorticoids (0.5 to 1 mg/kg orally ± one to three intravenous pulses of up to 1000 mg). Cyclophosphamide dose should be reduced by up to 25% in the elderly and in patients with renal impairment. Following induction of remission glucocorticoids should be tapered or discontinued while cyclophosphamide can be replaced with azathioprine or other immunosuppresive agents, *e.g.,* methotrexate or more rarely leflunomide or mycophenolate mofetil. Co-trimoxazole 960 mg three times per week is frequently administered for prevention of *Pneumocystis jiroveci* infections that can induce relapse of systemic vasculitis.

The efficacy of a sequential cyclophosphamide and azathioprine (2 mg/kg per day) treatment as an alternative to prolonged cyclophosphamide administration was established in the CYCAZAREM study[34]. In this trial, 155 randomized patients received either oral cyclophosphamide for 1 year or 3 to 6 mo of oral cyclophosphamide followed by azathioprine. At 18 mo the relapse rates was not significantly different between the two regimens. The randomised CYCLOPS study showed similar efficacy (the time to remission and the rate of remission at 9 mo) of intravenous or oral cyclophosphamide in 149 patients with generalised ANCA-associated vasculitis. However, long-term follow-up (median 4.3 years) showed higher relapse rate in patients who were treated with pulsed intravenous cyclophosphamide[35,36]. The potential advantages of intravenous cyclophosphamide included reduced exposure (8.2 g compared to 15.9 g with

oral administration) and the lower rate of leucopenia though the latter was not associated with reduced risk of infectious complications.

In the NORAM study methotrexate 25 mg weekly was not inferior to oral cyclophosphamide at inducing remission in 100 patients with early GPA (*e.g.*, without serious visceral manifestations) but showed slower effect in patients with pulmonary disease[37]. Methotrexate administration was associated with lower risk of leucopenia, but higher rate of liver impairment and relapse of systemic vasculitis. In the long-term first-line treatment with methotrexate was associated with less effective disease control than cyclophoshamide induction therapy[38].

In the WEGENT study maintenance treatment with methotrexate was at least as effective as azathioprine in 126 patients with remission of ANCA-associated vasculitis that was induced by cyclophosphamide[39]. Thus, methotrexate can be used as an alternative to azathioprine in patients with normal kidney function who do not tolerate the latter. The IMPROVE randomised study showed increased risk of relapses and shorter time to relapse in patients treated with mycophenolate mofetil after cyclophosphamide induction compared to those with azathioprine[40], while efficacy of leflunomide for maintenance treatment remains uncertain. In the multicentre, randomized controlled clinical trial, 54 patients with generalized GPA were treated either with oral leflunomide 30 mg/d or oral methotrexate (7.5 to 20 mg/wk) for 2 years following induction of remission with cyclophosphamide[41]. The rate of major relapses was significantly higher in the methotrexate group (P = 0.037), and the study was terminated prematurely. However, treatment with leflunomide was associated with an increased frequency of adverse events. Mycophenolate mofetil and leflunomide should not be used as a first-line treatment.

Rituximab was first studied in relapsing and refractory ANCA-associated vasculitis. It's efficacy for induction of remission in patients with GPA and MPA was shown in two randomised trials (RITUXVAS and RAVE)[42,43] and numerous case series and uncontrolled studies[44-46]. In the RITUXVAS study 44 patients with ANCA-associated renal vasculitis were randomised to a standard glucocorticoid regimen plus either rituximab at a dose of 375 mg/m^2 per week for 4 wk, with two intravenous cyclophosphamide pulses, or 3 to 6 mo intravenous cyclophosphamide[42]. Following induction of remission at 3 to 6 mo patients in the conrol group continued treatment with azathioprine, while in the rituximab group patients recieved only glucocorticoids for maintenance treatment. Sustained remission at 12 mo was achieved in 76% and 82% of patients in rituximab and control groups, respectively. The safety of two regimens was also comparable. Thus, a rituximab-based regimen was not inferior to intravenous cyclophosphamide in patients with severe ANCA-associated vasculitis. The use of rituximab permitted to avoid of maintenance immunosuppression but was not associated with reduced rate of infectious complications.

In a multicenter, randomized, double-blind, noninferiority RAVE study rituximab (375 mg/m^2 once a week for 4 wk) followed by placebo was compared to cyclophosphamide for 3 to 6 mo followed by azathioprine for 12 to 15 mo in 197 patients with severe ANCA-associated vasculitis[47]. Severe disease was defined as vital organ involvement that posed an immediate threat to the function of that organ or the patient's life. By 5 mo all patients who had a remission without disease flares had discontinued glucocorticoids. The primary end point was remission of disease without the use of prednisone at 6 mo. Primary end point was reached in 63 patients in the rituximab group (64%) and 52 patients in the control group (53%). Non-Inferiority was confirmed in this study (P < 0.001). Rituximab was more efficacious than cyclophosphamide for inducing remission in relapse of vasculitis: the primary end point was reached in 67% of patients in the rituximab group and in 42% of patients in the control group (P = 0.01). Rituximab was also as effective as cyclophosphamide in the treatment of patients with renal involvement or alveolar hemorrhage and in patients with both GPA and MPA. The rate of adverse events was not different between the two groups. The long-term follow-up of patients confirmed the comparable efficacy of the rituximab- and cyclophosphamide-based regimens[47]. At 12 and 18 mo, the complete remissions was maintained in 48% and 39% of patients, respectively, in the rituximab group and 39% and 33% of patients in the control group. The duration of complete remission and the frequency or severity of relapses did not differ significantly between the two groups. In patients with relapsing disease, rituximab was superior to cyclophosphamide-based treatment at 12 mo (P = 0.009) but not at 18 mo (P = 0.06). At the latter point the majority of patients in the rituximab group had reconstituted B cells. The overall incidence of adverse events was not different between the two groups, with the exception of leukopaenia and pneumonia that were less common in the rituximab group. Thus, at 18 mo a single course of rituximab was as effective as a standard immunosuppressive therapy for the induction and maintenance of remissions in patients with severe ANCA-associated vasculitis. Rituximab may be superior to conventional immunosuppresive regimen in relapsing disease.

The high efficacy of rituximab was also shown in retrospective studies in patients with ANCA-associated vasculitis refractory to standard treatment. Rituximab may be less effective for induction of remission in patients with predominant granulomatous lesions, *e.g.*, orbital pseudotumour. In one uncontrolled study in 59 patients with refractory GPA complete remission or improvement following rituximab treatment were achieved in 89.2% of patients with kidney disease and

Table 1 Randomized controlled trials in patients with antineutrophil cytoplasmic antibody-associated vasculitis[53]

Trial (*n*)	Inclusion criteria	Treatment groups (dose)	Primary end-points	Outcome
Induction of remission				
NORAM (100)	New diagnosis of GPA or MPA, and creatinine < 150 μmol/L	Methotrexate (0.3 mg/kg once weekly) *vs* daily oral cyclophosphamide	Remission Time to relapse	Methotrexate not inferior to cyclophosphamide Time to relapse shorter with methotrexate
CYCLOPS (149)	New diagnosis of GPA, MPA, or relapse with renal involvement, creatinine 150-500 μmol/L	Intravenous pulse cyclophosphamide (15 mg/kg) *vs* daily oral cyclophosphamide (2 mg/kg)	Remission Time to relapse	Pulse cyclophosphamide not inferior to oral cyclophosphamide Less leucopenia and trend towards more relapses with pulse cyclophosphamide
RITUXVAS (44)	New diagnosis of AAV and severe renal involvement	Rituximab (four 375 mg/m² infusions) plus two intravenous pulses of cyclophosphamide, *vs* intravenous pulse cyclophosphamide only	Sustained remission	Rituximab not inferior to pulse cyclophosphamide
RAVE (198)	New or relapsing GPA or MPA	Rituximab (4 × 375 mg/m² infusions) *vs* daily oral cyclophosphamide	Complete remission and cessation of glucocorticoids at 6 mo	Rituximab not inferior to oral cyclophosphamide Rituximab better in patients with relapse than after first diagnosis
MEPEX (137)	New diagnosis of GPA or MPA and creatinine > 500 μmol/L	Plasma exchange and oral cyclophosphamide *vs* 3 × intravenous methylprednisolone pulse and oral cyclophosphamide	Renal survival at 3 mo	Better renal survival with plasma exchange 24% risk reduction for ESRD with plasma exchange
MYCYC (140)	New diagnosis of GPA, MPA and major organ involvement	Mycophenolate mofetil (2-3 g daily) *vs* intravenous pulse cyclophosphamide (15 mg/kg)	Remission at 6 mo Relapse	Preliminary data: noninferiority not proven for mycophenolate mofetil *vs* pulse cyclophosphamide
CORTAGE (104)	New diagnosis of MPA, GPA, EGPA, PAN and age > 65 yr	Rapid glucocorticoid tapering and reduced-dose intravenous pulse cyclophosphamide (500 mg) *vs* standard intravenous pulse cyclophosphamide (500 mg/m²)	Severe adverse events	Preliminary data: less severe adverse events with reduced immunosuppression, no difference in remission and relapse rates
Maintenance of remission				
CYCAZAREM (144)	GPA, MPA or relapse and renal or vital organ involvement	Oral azathioprine (2 mg/kg) *vs* oral cyclophosphamide (1.5 mg/kg daily)	Relapse Adverse events	No difference in relapse
IMPROVE (165)	New diagnosis of GPA or MPA	Oral mycophenolate mofetil (2 g daily) *vs* oral azathioprine (2 mg/kg)	Time without relapse Adverse events	More relapses with mycophenolate mofetil than azathioprine, trend towards more adverse events with azathioprine
WEGENT (126)	GPA or MPA and renal or multiorgan involvement	Methotrexate (0.3 mg/kg once weekly) *vs* azathioprine (2 mg/kg)	Adverse events with consecutive treatment cessation or death	No difference between groups in primary end point and relapses
LEM (54)	Generalized GPA and creatinine < 1.3 mg/dL	Leflunomide (30 mg daily) *vs* methotrexate (up to 20 mg per week)	Relapse	More relapses with methotrexate than leflunomide, trend towards more adverse events with leflunomide
WGET (174)	GPA and BVAS > 3	Etanercept and methotrexate or cyclophosphamide *vs* placebo and methotrexate or cyclophosphamide	Sustained remission for > 6 mo	No benefit with etanercept, more cancers in etanercept group

AAV: Antineutrophil cytoplasmic antibody-associated vasculitis; BVAS: Birmingham vasculitis activity score; EGPA: Eosinophilic granulomatosis with polyangiitis; ESRD: End-stage renal disease; GPA: Granulomatosis with polyangiitis; MPA: Microscopic polyangiitis; PAN: Polyarteriitis nodosa.

in only 44.4% of patients with orbital pseudotumor (P = 0.003)[48]. The efficacy of rituximab for maintenance therapy was established in the retrospective studies[46]. It is currently being evaluated in prospective, randomized MAINRITSAN trial, comparing 500 mg of rituximab every 6 mo for 18 mo *vs* azathioprine for 22 mo. Preliminary results indicate significantly fewer relapses in the rituximab arm[49].

Recently the Recommendations Committee of the FVSG developed guidelines for rituximab use to induce and maintain remission of ANCA-associated vasculitis[50]. The main statements of these guidelines are summarised below: (1) rituximab is not inferior to conventional treatment and may be used to induce remission of GPA and MPA for the same indications as cyclophosphamide; (2) rituximab should preferentially be prescribed to women of childbearing age, especially when they are over 30 years old, taking into account

the risk of infertility with cyclophosphamide; (3) rituximab should not be administered as a first-line treatment in patients with predominant granulomatous lesions, *e.g.*, orbital pseudotumors, ENT manifestations, tracheal and bronchial stenosis; (4) rituximab should preferentially be chosen for patients with relapsing GPA or MPA who have received previously at least one full cyclophosphamide cycle; (5) rituximab is recommended to prescribe for failure or incomplete response to intravenous cyclophosphamide and in patients intolerant of cyclophosphamide or who developed complication(s) resulting from prior cyclophosphamide exposure (*e.g.*, hemorrhagic cystitis); (6) rituximab should not be combined with conventional immunosuppressive treatments (except glucocorticoids) though such option is possible in patients not responding or responding incompletely to immunosuppressant(s) or rituximab alone; and (7) rituximab can be prescribed for maintenance treatment.

The other promising biologic agents for the treatment of ANCA-associated vasculitis include ocrelizumab, afatumumab, epratumumab, belimumab, abatacept, C5a complement inhibitor. The efficacy of belimumab for maintenance treatment is currently being studied in the placebo-controlled BREVAS study (NCT01663623) that plans to enroll around 300 patients with GPA and MPA who have achieved remission with oral or intravenous cyclophosphamide.

The results of main randomized controlled trials in patients with ANCA-associated vasculitides are summarized in Table 1[51].

CONCLUSION

The diagnosis and treatment of ANCA-associated vasculitis were always the challenge for physicians. The criteria of activity and approaches to classification also remain the subject for discussion. The conventional immunosuppressive treatment allows to achieve and to maintain remission in the majority of patients with ANCA-associated vasculitis. Nevertheless, there is a need for more effective therapies for patients who are refractory or intolerant to current immunosuppressive regimens, and for those who have a relapsing systemic vasculitis. Biologic agents may have advantages over conventional immunosuppressive agents for efficacy and/or safety. The controlled and uncontrolled studies showed that rituximab can be used for induction of remission in patients with GPA and MPA and is the treatment of choice in patients with refractory ANCA-associated vasculitis and in those who had incomplete response to or were intolerant of cyclophosphamide.

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