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Biologics for ANCA-Associated Vasculitis

Giuseppe Murgia*, Davide Firinu, Paolo Emilio Manconi and Stefano R. Del Giacco

Unit of Internal Medicine, Allergy and Clinical Immunology, Department of Medical Sciences "M. Aresu", University of Cagliari, Cagliari, Italy

Abstract: The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of necrotizing vasculitides with a potential fatal outcome. Conventional therapy is based on the use of glucocorticoids (GCs) and cyclophosphamide (CYC), which is associated with severe toxic effects and is unable to control the disease activity in some refractory and relapsing cases. Several authors focused their efforts on the identification of safe and more efficient drugs, primarily investigating biological agents. Rituximab (RTX) demonstrated to be an alternative to CYC as remission-induction therapy for microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) in two clinical controlled randomized trials. Contrasting data emerged regarding anti-TNF-α agents, and their use should be limited to some selected refractory or relapsing cases. Mepolizumab (MPZ) and Omalizumab (OMZ) are potentially beneficial treatments for patients with eosinophilic granulomatosis with polyangiitis (EGPA). Hereby, we perform a review focused on the use of biological drugs for AAV treatment.

Keywords: ANCA, ANCA associated vasculitis, biological agents, biological therapy, biologics, monoclonal antibodies, rituximab.

INTRODUCTION

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of necrotizing vasculitides associated with ANCA specific for myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA). AAV primarily affect small vessels with predilection for the kidneys, lungs, and peripheral nervous system. The main variants of AAV are microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, Wegener's granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome), and single-organ AAV. GPA is usually characterized by necrotizing granulomatous inflammation involving the upper and lower respiratory tract, conversely granulomatous inflammation is absent in MPA. Asthma, nasal polyps and tissue and peripheral blood eosinophilia are common characteristics of EGPA [1]. ANCA directed to proteinase 3 (PR3) have a cytoplasmic (C-ANCA) staining pattern on ethanol-fixed neutrophils in indirect immunofluorescence microscopy, while those against myeloperoxidase (MPO) have a perinuclear (P-ANCA) staining pattern [2].

According to the results of the clinical trials conducted by the European Vasculitis Study (EUVAS), patients with AAV respond to different treatment protocols depending on the disease severity (localized, early systemic, generalized, severe, refractory disease) (Table **1**). Therefore, the European League Against Rheumatism (EULAR) recommends that treatment approaches should be guided according to disease severity in the EUVAS categorization. Moreover, treatment decisions should be modified if the category of severity changes during the disease course [3].

AAV are life threatening disorders that need to be treated with aggressive immunosuppressive therapies. EULAR recommends a combination of intravenous or oral cyclophosphamide (CYC) and glucocorticoids (GC) for the remission induction of generalized and severe primary small vasculitis (GPA, MPA and EGPA) [3]. Oral and pulsed intravenous CYC have similar remission rates, but intravenous CYC associated with lower cumulative dose and less side effects such as infection and leucopenia. However, intravenous CYC has been associated with a higher relapse rate [4-6]. Given the results of the MEPEX trial, plasma exchange is recommended by EULAR for patients with rapidly progressive severe renal disease in order to improve renal survival. Methotrexate (oral or parenteral) and GC are recommended by the EULAR for the induction of remission in non-organ threatening or non-life threatening (early systemic) AAV [3]. In fact, in a randomised controlled trial, methotrexate demonstrated to be able as CYC to induce remission in these cases [7].

The EULAR recommends the use of azathioprine (AZA), methotrexate (MTX) or leflunomide (LFM) as remission-maintenance therapy [3]. In the CYCAZAREM trial, AZA demonstrated to do not increase the rate of relapse when compared to CYC for the maintenance of the remission [8]. In the WEGENET trial, MTX showed to be a good alternative to AZA for maintenance therapy, with similar rate of relapses and adverse events [9] LFM demonstrated to be more effective than MTX in remission maintenance, but it is associated with more adverse effects [10]. The IMPROVE trial showed that mycophenolate mofetil (MMF) is less effective than AZA for maintaining disease remission, but with similar adverse event rates [11].

*Address correspondence to this author at the Department of Medical Sciences "M. Aresu", Unit of Internal Medicine, Allergy and Clinical Immunology, University of Cagliari, Azienda Ospedaliero Universitaria, SS 554-Bivio Sestu, I-09042 Monserrato (CA), Italy; Tel: +39 070 51096128; Fax: +39 070 51096227; E-mail: giuse.murgia@gmail.com

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Table 1. European Vasculitis Study (EUVAS) disease categorization of ANCA-associated vasculitis.

Category	Definition
Localised	Upper and/or lower respiratory tract disease without any other systemic involvement or constitutional symptoms
Early systemic	Any, without organ-threatening or life-threatening disease
Generalised	Renal or other organ threatening disease, serum creatinine < 500 μmol/litre (5.6 mg/dl)
Severe	Renal or other vital organ failure, serum creatinine > 500 μmol/litre (5.6 mg/dl)
Refractory	Progressive disease unresponsive to glucocorticoids and cyclophosphamide

Since the use of CYC is associated to serious side effects (hemorrhagic cystitis, bladder cancer, myelodysplastic syndrome), the scientific community strives to identify alternative drugs with greater efficacy but less toxic effects. Most of recent studies are focused on monoclonal antibodies, which are emerging as promising therapeutic options, particularly for relapsing and refractory cases of AAV.

Hereby, we perform a review with the aim of summarizing and discussing the data regarding the use of biological drugs for AAV treatment. MEDLINE (PubMed) was searched for articles published up to June 2014 using combinations of the following keywords: "ANCA associated vasculitis", "microscopic polyangiitis", "granulomatosis with polyangiitis", "Wegener's granulomatosis", "eosinophilic granulomatosis with polyangiitis", "Churg-Strauss syndrome", "biological drugs", "biologics", "monoclonal antibodies", "rituximab", "infliximab", "etanercept", "adalimumab", "alemtuzumab", "intravenous immunoglobulins", "mepolizumab", "omalizumab", "adalimumab". Bibliographies were scrutinized in order to identify others relevant papers. We selected the studies with higher level of evidence for each biological drug according to internationally accepted criteria [12]. The studies included in our review are summarized in Tables **2-4**.

RITUXIMAB

Rituximab (RTX) is a chimeric murine human monoclonal IgG1 antibody directed against CD20 lymphocytes. In 2001, RTX was used for the first time to treat a case of AAV [13]. Afterwards, several case series and uncontrolled prospective or retrospective studies reported remission rates higher than 80 % in patients with refractory AAV who were treated with RTX [14-19].

Two clinical controlled randomized trials investigated the efficacy of RTX as remission-induction treatment in patients with severe AAV [20, 21]. In the RAVE trial, RTX followed by placebo was compared with oral CYC followed by AZA for remission induction in patients with newly diagnosed or relapsing ANCA-positive GPA/MPA. The primary end point was complete remission without the use of prednisone at 6 months. RTX-regimen was not inferior to daily CYC for induction of remission and demonstrated to be more efficacious in refractory and relapsing cases, with a steroid-sparing effect. The two regimens had the same effectiveness in the treatment of patients with major renal disease or alveolar hemorrhage. The rates of adverse events were not significantly different between the two regimens [20]. In the RITUXVAS trial, RTX and CYC were compared for induction of remission in 44 patients with newly diagnosed GPA/MPA and renal involvement. They were randomly assigned to two regimens: RTX associated with two intravenous CYC pulses plus GC or CYC pulses plus GC for 3 to 6 months followed by AZA. Sustained remission rates at 12 months and rates of severe adverse events were not significantly different between the two regimens [21]. The long term follow-up of the patients recruited in the RAVE trial evidenced that a single course of RTX was as effective as continuous conventional immunosuppressive therapy for the induction and maintenance of remission over a period of 18 to 24 months [22, 23]. Therefore, RTX demonstrated the potential advantage over CYC to achieve long-term remission without the requirement of remission-maintenance therapy. According to these trials, although RTX did not show a superior safety profile compared to CYC, it demonstrated to be a valid alternative to CYC for remission induction of AAV.

In both controlled clinical trials, the efficacy of RTX was demonstrated using the administration schedule that is commonly employed to treat lymphoma (four weekly infusions of 375 mg/m2 of body-surface area) [24]. However, the administration schedule that is usually employed in patients with rheumatoid arthritis (RTX 1 g on days 1 and 15) did not show obvious inferiority or any particular adverse events in AAV [16, 25-27].

The French Vasculitis Study Group (FVSG) claims that RTX may be prescribed as first-line treatment to induce remission of GPA and MPA with the same indications as CYC. Moreover, FVSG recommends the use of RTX as treatment for GPA or MPA relapses, primarily in those patients who were previously treated with at least one full intravenous CYC cycle. RTX is also recommended in case of failure or incomplete response to intravenous CYC or in women of childbearing age [24].

The use of RTX for remission maintenance therapy has been investigated in various retrospective studies. Cartin-Ceba *et al.* observed that RTX can effectively and safely be used to establish and maintain remission in patients with chronic relapsing refractory GPA, hypothesizing that relapses can be prevented retreating the patients basing on B lymphocytes counts and PR3 ANCA determinations [27]. Smith el al. showed that the use of a two years fixed-interval RTX re-treatment protocol (1 g every 6 months) can reduce relapse rates compared to the re-treatment at the time of relapse in patients with refractory or relapsing AAV [28]. In a retrospective study of Charles *et al.*, RTX seemed to achieve superior remission maintenance compared with

Table 2. Rituximab for granulomatosis with polyangiitis and microscopic polyangiitis.

References	Study	Efficacy	Safety	LoE
Stone JH *et al*., 2010 [20]	RCT (RAVE trial) RTX (4 weekly doses of 375 mg/m2) *vs* oral CYC for induction of remission 197 patients with newly diagnosed or relapsing GPA or MPA Primary endpoints at 6 mo	RTX was not inferior to CYC Remission at 6 mo: 64% in RTX arm *vs* 53 % in CYC arm RTX may be superior in relapsing disease Remission in relapsing cases at 6 mo: 67% in RTX arm *vs* 42% in CYC arm Same effectiveness in cases with major renal disease or alveolar hemorrhage	No significant differences in the numbers of total adverse events or SAE More episodes of leucopenia in CYC group 8 hospitalization for adverse events in RTX group and 2 in CYC group 6 (5%) cancers in RTX group *vs* 1 (1%) in CYC group Discontinuation of treatment for adverse events in 14% in the RTX group *vs* 17% in CYC group 7 infections in both arms	1B
Jones RB *et al*., 2010 [21]	RCT (RITUXVAS trial) RTX (4 weekly doses of 375 mg/m2) + 2 IV CYC pulses *vs* IV CYC for induction of remission 44 patients with newly diagnosed GPA or MPA with renal involvement Primary endpoints at 12 mo	No significant differences in rates of sustained remission (76% in RTX arm *vs* 76% in control arm) Remission at 2 mo: 93% in RTX group *vs* 91% in CYC group Median estimated GFR increased of 19 ml/min/1.73 m2 in RTX group *vs* 15 ml/min/1.73 m2 in CYC group No significant differences in Vasculitis Damage Index At 12 months: 15% relapses in RTX group *vs* 10% in control group	No significant differences in rates of SAE (42% for RTX *vs* 36% for CYC) 2/33 cancers in RTX group *vs* none in CYC group 19 infections in 12/33 patients in RTX group (36%) *vs* 7 in 3/11 patients in CYC group (27%) 18 % of mortality for both groups: 6/33 deaths in RTX group (3/6 for infection, 1/6 for cardiovascular disease, 2 complications of end-stage renal failure) *vs* 2/11 in CYC group (1/2 for infection, 1/2 for cardiovascular disease)	1B
De Menthon MP *et al*., 2011 [60]	RCT RTX (4 weekly doses of 375 mg/m2) *vs* IFX (3 mg/kg on day 1 and 14, then 3 mg/kg or 5 mg/kg monthly) for induction of remission 17 patients with refractory GPA (9 IFX, 8 RTX) Follow-up 30.6±15.4 mo	IFX and RTX are effective to obtain remission of refractory GPA with a favoring trend for RTX At 12 months: 6 complete remission (2 IFX, 4 RTX), 2 partial remission (1 IFX, 1 RTX), 7 failures (5 IFX, 2 RTX) Long-term follow-up: RTX was better able at obtaining and maintaining remission Over the long term follow-up (30.6 ± 15.4 months): 10/17 (59%) patients responded to RTX, 1 to IFX, 2 to other strategies, 2 died	No significant differences in SAE rates 2 deaths: 1 in the IFX group (aspergillosis), 1 in the RTX group (sudden death) 2 cancers in the RTX group *vs* none in the IFX group	1B
Guillevin L *et al*., [abstract] 2013 [30]	RCT (MAINRITSAN) RTX (500-mg RTX infusion on day 1, day 15, 5.5 mo later, then every 6 mo for a total of five infusions over 18 mo) *vs* AZA (2 mg/kg/d for 22 mo) to maintain remission 117 AAV (89 GPA, 23 MPA): 59 in AZA arm, 58 in RTX arm Follow-up: 28 mo	RTX every 6 months was superior to AZA to maintain AAV remission Major relapses:3 (5.4%) in the RTX arm, 15 (25.4%) in the AZA arm	SAE: 18 in AZA arm, 15 in RTX arm Similar infection rates in the two arms:12 in AZA arm, 11 in RTX arm Deaths: 2 in AZA arm (1 sepsis, 1 cancer)	1B
Keogh K *et al*., 2006 [15]	Prospective open-label pilot study RTX regimen: 4 weekly doses of 375 mg/m2 10 patients with refractory GPA or intolerance for CYC Follow-up: 12 mo	All patients achieved complete remission at 3 mo B-lymphocytes were undetectable in all patients at 6 mo Discontinuation of GC in all patients at 6 mo 1 relapse at 9 mo	Infusion-related adverse events: 1 rigors and chills Infections: 2 Herpes Zoster eruptions, 1 influenza, 13 upper respiratory tract infections IgM levels dropped in all patients IgG levels and subclass levels showed only a minimal decline	2B
Smith KGC *et al*., 2006 [19]	Open-label study RTX regimen: 4 weekly doses of 375 mg/m2 Refractory or active AAV (5GPA, 5 MPA, 1 EGPA) Median follow-up: 24 mo	9 CR, 1 PR, 1 NR (median time to first remission 3.5 mo) 6 relapses ANCA levels fell in all patients Successful re-treatment of relapses with RTX in 5	Common mild to moderate infusion reactions Low infection rates 1 cutaneous Herpes Zoster infection	2B

(Table 2) contd…..

References	Study	Efficacy	Safety	LoE
Keogh K *et al*., 2005 [14]	Case series RTX regimen: 4 weekly infusions of 375 mg/m2 11 patients with refractory AAV (10 GPA and 1 MPA) or contraindication for CYC Mean follow-up: 16 mo	10 CR, 1 PR at 6 mo Discontinuation of GC in all patients 2 relapses after GC discontinuation (respectively after 7 and 12 mo RTX therapy)	Infusion-related adverse events: 4 mild Infections: 2 bacterial bronchitis, 1 viral upper respiratory tract infection, multiple exacerbations of respiratory infection in 1 patient Others: thrombocytemia, lower extremity petechiae	4
Jones RB *et al*., 2009 [16]	Case series RTX regimen: 4 weekly doses of 375 mg/m2 or 2 weekly doses of 1g or other regimens 65 patients with AAV (46 GPA, 10 MPA, 5 EGPA, 4 unclassified) 60 were receiving others immunosuppressive drugs Median follow-up: 20 mo	CR in 75 %; PR in 23%, NR in 2% Relapses occurred in 57% of CR (median 11.5 mo) Rates of relapse were not higher in patients in whom concomitant treatments were withdrawn ANCA and B cell levels lacked sufficient sensitivity to guide the timing of re-treatment No difference in efficacy between the 2 main treatment regimens	45 SAE in 25 patients (17 related to disease activity) No severe infusion reactions 16 serious infections Transient neutropenia in 2 patients Significant fall in IgM levels occurred by 6 mo IgG levels were maintained within the normal range	4
Stasi R *et al*., 2006 [17]	Case series RTX regimen: 4 weekly doses of 375 mg/m2 Refractory or relapsing AAV (8 GPA, 2 MPA) Median follow-up: 33.5 mo	9 CR and 1 PR at 6 mo 3 relapses in median follow-up of 33.5 mo ANCA titres decreased significantly in all patients Peripheral B-cell depletion in all patients	1 mild infusion-related adverse event (fever, chills and nausea)	4
Eriksson P 2005 [18]	Case series RTX regimen: 4 weekly doses of 375 mg/m2 or 4 weekly doses of 500 mg or 2 weekly doses of 1g Refractory AAV (7 GPA, 2 MPA) Concomitant immunosuppressive drugs Follow-up: 6-24 mo	8 CR and 1 PR at 6 mo 2 minor nasal relapses after 12 and 13 mo respectively	No SAE 2 respiratory tract infections	4
Cartin-Ceba RJ *et al*., 2012 [27]	Retrospective cohort study RTX regimen: ≥ 2 RTX courses of 4 weekly doses of 375 mg/m2 53 relapsing GPA Median follow-up: 4.4 years	All patients achieved CR 32 relapses (all after reconstitution of B cells or increase of ANCA levels)	No SAE 16 infusion-related adverse events 30 infections 2 deaths (1 acute myelogenous leukemia, 1 Pneumocystis jiroveci pneumonia)	4
Smith RM *et al*., 2012 [28]	Retrospective observational study RTX regimen: 4 weekly doses of 375 mg/m2 73 refractory or relapsing AAV (61 GPA, 12 MPA) Median follow-up 44 mo	Group A (28) RTX induction therapy and RTX at relapses: 80% CR, 11% PR, 7% TF, relapses in 73% at 24 mo, 81 at 48 mo Group B (45) routine RTX re-treatment for 2 years (1 gm every 6 months): 85% CR, 11 % PR, 4% TF, relapses in 12% at 24 mo, relapses in 26 % at 48 mo Group C (19) patients that relapsed in group A and began routine re-treatment for 2 years 90% CR, 5% PR, 5% TF Reduction of relapse rates with fixed-interval RTX re-treatment GC were decreased and immunosuppressive therapy was withdrawn in most of patients	No significant differences in rate of SAE: 32% group A, 47% group B, 37% group C No significant differences in rate of infections: 21% group A, 27% group B, 26% group C Deaths: 1 in group A and 3 in group B	4
Charles P *et al*., 2013 [29]	Retrospective multicentre study RTX regimen: 4 weekly doses of 375 mg/m2 or 2 weekly doses of 1g 80 AAV (mostly refractory or relapsing AAV) (70 GPA, 9 MPA, 1 EGPA) Median follow-up 18 mo	Respective 1-, 2-, and 3-year relapse-free survival rates after the first RTX infusion were 80%, 63% and 52% Relapse-free survival was longer for patients receiving RTX maintenance therapy	Adverse events in 28% RTX-treated patients Infectious complications in 15% patients (4 deaths)	4

RCT = randomized controlled trial; RTX = Rituximab; CYC = cyclophosphamide; IV = intravenous; AZA = azathioprine; mo = monts; CR = complete remission; PR = partial remission; TF = treatment failure; SAE = severe adverse event; LoE = level of evidence; GC = glucocorticoids.

Table 3. Rituximab for eosinophilic granulomatosis with polyangiitis.

References	Study	Efficacy	Safety	LoE
Cartin-Ceba R *et al.,* 2011 [38]	Open label pilot study RTX for induction of remission in 3ANCA-positive EGPA with renal involvement RTX regimen: 4 weekly doses of 375 mg/m2 Follow-up: 12 mo	At 3 mo: 3 CR of renal involvement At 12 mo: no renal relapses, 1 non-renal relapse	No SAE reported	2B
Thiel J *et al.,* 2013 [31]	Case series 9 relapsing or refractory EGPA Mean follow-up: 9 mo	At 3 mo: 1 CR, 8 PR At 9 mo: no relapses	5 minor infections	4
Kaushik VV *et al.,* 2006 [34]	Case report RTX regimen: 3 weekly doses of 375 mg/m2 1 refractory EGPA	CR	No SAE reported	4
Koukoulaki *et al.,* 2006 [32]	Case report RTX regimen: 2 weekly doses of 1g 2 refracory EGPA	2 CR	No SAE reported	4
Pepper RJ *et al.,* 2008 [33]	Case report RTX regimen: 2 weekly doses of 1g 2 refracory EGPA	2 CR Decrease of IL-5 production	No SAE reported	4
Saech J *et al.,* 2010 [36]	Case report RTX regimen: 2 weekly doses of 1g 1 refractory EGPA with central nervous system involvement	CR	No SAE reported	4
Donvic KK *et al.,* 2011 [37]	Case report RTX regimen: 2 weekly doses of 1g 2 refractory EGPA	2 CR	No SAE reported	4

RTX = Rituximab; mo = months; CR = complete remission; PR = partial remission; TF = treatment failure; SAE = severe adverse event; LoE = level of evidence; GC = glucocorticoids.

standard therapy, but the authors recommend a particular caution due to the occurrence of severe infections [29]. The preliminary results of a prospective randomized–controlled clinical trial (MAINRITSAN) that compared RTX with AZA for the maintenance of remission, were exposed at the 16th International Vasculitis & ANCA Workshop. Major relapses were fewer in the RTX-arm compared to AZA-arm, while infection rates and severe adverse events were comparable in the two arms [30].

Various case reports and small retrospective series have reported positive results of the use of RTX in patients with EGPA refractory to standard therapy [28, 31-38]. The FVSG agreed that the data derived from these studies are insufficient to recommend the use of RTX for EGPA. However, it could be considered as an option for refractory cases, particularly when characterized by predominant vasculitic manifestations and MPO-ANCA positivity [24].

Infusion-related adverse effects are commonly mild (headache, hypotension, chills, rhinitis, pruritus, rash) and usually occur during the first infusion [20, 21, 27, 39]. Premedication with antihistamines or corticosteroids may prevent or attenuate these events.

Late-onset neutropenia has been reported to occur in about 5% of patients treated with RTX for autoimmune diseases, with a higher incidence among those with GPA and systemic lupus erythematosus [40]. In the RAVE trial the incidence of leucopenia was higher in the CYC arm than in the RTX arm [20].

The decrease of serum immunoglobulin levels is common in patients receiving RTX for rheumatic diseases, particularly of IgM levels. The specific role of RTX in this event is difficult to establish since these patients are usually receiving other immunosuppressive drugs in most of clinical studies [20, 41]. It is unclear if RTX-related hypogammaglobulinemia is associated with an increased risk of infections [41-43].

Infection rates in AAV patients treated with RTX vary across studies (7-36%) and are higher when RTX is combined with other immunosuppressants [20, 21, 28, 29].

Since various cases of Pneumocystis jiroveci pneumonia (PJP) have been reported during RTX treatment for AAV, the FVSG recommends prophylactic therapy with co–trimoxazole [24, 27, 28].

The risk of reactivation of hepatitis B in patients treated with RTX is high, thus patients should be screened for HBsAg and anti-HBc prior to initiation of treatment and if seronegative they should be vaccined. Pre-emptive therapy is recommended for HBsAg-positive patients and HBsAg-negative patients with high HBV DNA levels, while close follow-up is recommended for HBsAg-negative, anti-HBc positive patients with undetectable serum HBV DNA [44-46].

The occurrence of progressive multifocal leucoence-phalopathy (PML) has been reported in patients treated with RTX for lymphoproliferative or autoimmune disorders, but not in those treated for AAV. Therefore, patients should be monitored for any neurological disease-suggestive symptoms or signs [47-49].

Table 4. Biologics other than Rituximab for ANCA-associated vasculitis.

Drug	References	Study	Efficacy	Safety	LoE
IFX *vs* RTX	De Menthon MP *et al.,* 2011 [60]	Described in Table **2**	Described in Table **2**	Described in Table **2**	1B
IFX	Booth A *et al.,* 2004 [55]	Open-label trial IFX (5 mg/kg at 0, 2, 6, and 10 wk) as adjuvant therapy 32 AAV (19 GPA, 13 MPA) with acute flares or persistent activity Mean follow-up: 16.8 mo	Remission in 28 (88%) patients 5 (20%) relapses after a mean of 27 wk Reduction of mean GC dose	1 moderate infusion-related adverse event 7 (21%) serious infections 2 deaths: 1 pulmonary hemorrhage, 1 broncopneumonia	2B
IFX	Bartolucci P *et al.,* 2002 [57]	Open pilot study IFX dose: 5 mg/kg on days 1, 14, 42 and then every 8 wk 7 refractory GPA Follow-up: 6 mo	At 6 mo: 4 CR, 3 PR Reduction of GC dose in all patients 1 patient relapsed twice (3 mo and 4 mo)	No SAE No infections 2 mild cutaneous infusion-related adverse events	2B
IFX	Morgan *et al.,* 2011 [59]	Open-label cohort trial IFX as additional therapy in 33 AAV 17 AAV standard therapy alone 16 AAV standard therapy + IFX IFX dose: 5 mg/kg day 1, wk 2, 6 and 10 Follow-up: 12 mo	The addition of IFX did not confer benefits for remission rates, damage index scores, relapse rates or biomarker levels	19 infections (6 severe) in IFX group *vs* 8 (all severe) in standard group 1 thrombosis in IFX group Leukopenia in 4 patients of IFX group	2B
IFX	Booth AD *et al.,* 2002 [54]	Case series IFX dose: 200 mg monthly for 3 months 6 refractory AAV (3 GPA, 3 MPA)	5 CR	1 infusion-related adverse event	4
IFX	Lamprecht P *et al.,* 2002 [56]	Case series IFX dose: 3 mg/kg or 5 mg/kg on day 1, after 2 wk and then every 4 wk until remission 6 refractory GPA Addition of IFX to standard therapy Follow-up: 6-24 mo	Remission in 5 patients Reduction of GC dose in all patients No relapses during follow up	No SAE reported	4
ETN	WGET research group 2005 [51]	RCT ETN (25 mg sc twice weekly) *vs* placebo plus standard therapy for maintainance of remission in 174 GPA Mean follow-up: 27 mo	No significant differences in rates of sustained remission between the ETN group and control group (69.7% *vs* 75.3%) No significant differences in sustained periods of low-level disease activity No significant differences in the time required to achieve sustained remission or low-level disease activity Common disease flares: 118 in the ETN arm and 134 in the control arm No significant difference in the relative risk of disease flares per 100 person-years of follow-up	Similar rates of SAE, life-threat- ening events, and deaths in the two groups (56.2 % in ETN arm *vs* 57.1 % in placebo arm) Deaths: 4 in ETN group, 2 in control group Cancers: 6 solid cancers in ETN group, none in control group	1B
ETN	Stone J *et al.,* 2001 [50]	Open-label trial ETN (25 mg sc twice weekly) in combination with standard therapy 20 patients with persistently active or new flares of GPA Follow-up:6 mo	Mean BVAS/WG decreased from 3.6 to 0.6 at 6 mo BVAS/WG = 0 at some point during the 6 mo in 16 (80%) patents Intermittently active disease in 15 (75%) patients Decrease of the mean daily prednisone dose from 12.9 mg at entry to 6.4 at 6 mo	Injection site reactions: 8 mild in 5 patients Hospitalizations: 5, but none solely related to a ETN averse event Neutropenia in 5 patients Infections: 2 in the same patient No deaths	2B

(Table 4) contd…..

Drug	References	Study	Efficacy	Safety	LoE
ADA	Laurino S *et al.,* 2010 [61]	Phase II, open-label trial ADA (40 mg sc every 2 wk for 3 mo) in combination with standard therapy 14 patients with AAV acute flares (relapse or new diagnosis) Kidney involvement in all patients	Remission in 11 (78.5%) patients within 14 wk (mean, 12 wk) Decrease of mean BVAS from 11.9 to 2.0 at 14 wk Decrease of mean daily prednisolone dose from 37.1 mg to 8.1 at 14 wk Increase of estimated glomerular filtration rate increased from 17.1 ml/min/1.73 m2 to 30.1 ml/min/1.73 m2 at 12 wk	Deaths: 1 Infections: 3 (2 severe)	2B
IVIG	Jayne D *et al.,* 2000 [68]	RCT Standard therapy + IVIG (total dose 2 g/kg) or placebo in 34 GPA with persistent activity 17 in IVIG group (one single course) 17 in placebo group Follow-up: 12 mo	IVIG reduced disease activity up to 3 mo: 14/17 treatment responses in IVIG group and 6/17 in placebo group After 3 mo: no differences in vasculitis activity and frequency of relapse	17 adverse effects in IVIG group *vs* 6 in placebo group Reversible rise of creatinine levels in 4 patients in IVIG group 1 case of aseptic meningitis in IVIG group	1B
IVIG	Martinez V *et al.,* 2008 [69]	Prospective open-label study IVIG (0.5 g/kg/day for 4 days monthly for 6 months) as additional therapy for relapses in 22 AAV (19 GPA, 3 MPA) Follow-up: 24 mo	Between 1-5 mo: 21 CR, 1 TF At 9 mo: 13 CR, 1 PR, 7 relapsed, 1 TF At 24 mo: persistent remission in 8/14 patients	SAE: 1 renal insufficiency Moderate or transient AE in 7 (33%) patients	2B
IVIG	Jayne DR *et al.,* 1991 [63]	Prospective study One course of IVIG (0.4 g/kg/day for 5 days) as additional therapy 7 AAV: 5 resistant to standard therapy, 2 without previous therapy Mean follow-up: 12 mo	Clinical improvement in all patients 6 CR, 1 transient PR 3 relapses during the follow-up	No SAE reported	4
IVIG	Jayne DR *et al.,* 1993 [66]	Prospective study One course of IVIG (0.4 g/kg/day for 5 days) as additional therapy 26 patients with systemic vasculitis (14 GPA, 11 MPA, 1 rheumatoid arthritis): 16 refractory, 9 untreated Mean follow-up: 12 mo	13 CR, 13 PR at 8 wk 6 transient flares between 10 days and 4 wk after IVIG infusion At 12 mo: 19 CR, 6 PR, 1 died	1 death for septic complication	4
IVIG	Richter C *et al.,* 1993 [65]	Prospective study One course of IVIG (30 g daily for 5 days) 9 AAV (8 GPA, 1 MPA) poor responders to standard therapy 4 with localized disease, 5 with generalized disease	Clinical improvement of solitary organ manifestations (primarily ear, nose, throat) in 5 patients at 4 wk No effects on ophthalmologic, renal an pulmonary manifestations	No SAE reported	4
IVIG	Jayne DR *et al*., 1996 [64]	Prospective study Single IVIG (0.5 g/kg/day for 4 days) course for 6 newly diagnosed AAV without threatened vital organ function No previous immunosuppression Follow-up: 16-48 mo	At 6 wk: 4 CR, 2 transient PR Among 4 CR: 2 relapses respectively at 12 mo and 14 mo	6 cases of diffuse erythematous rash (spontaneously resolved)	4
IVIG	Richter C *et al.,* 1995 [67]	Prospective study One or multiple IVIG (30 g daily for 5 days) course in 15 active AAV	At 4 wk: no CR, 9 had some limited benefit (confined to single organ involvement)	No SAE reported	4

(Table 4) contd…..

Drug	References	Study	Efficacy	Safety	LoE
ALZ	Walsh M *et al.,* 2008 [62]	Open long-term follow-up study ALZ dose: 4, 10, 40, 40 and 40 mg IV on consecutive days 71 relapsing/refractory AAV (63 GPA, 8 MPA; 42% with renal involvement, 18% requiring intensive care unit) Mean follow up: 5 years	Remission in 60 (85%) patients (24 greater than 1 year, of which 10 at least of 3 years) Relapses in 43 patients (median 9.2 mo)	Infections: 31 (21 severe)in 28 patients Cancer: 3 patients 8 cases of Graves' disease	2B
MPZ	Kim S *et al.,* 2010 [73]	Open-label pilot study MPZ dose: 750 mg IV monthly for 4 months 7 steroid-dependent EGPA patients Follow-up: 40 wk	Corticosteroid-sparing effect: the mean daily prednisone dose decreased from 12.9 mg to 4.6 mg at 16 study wk, to 5 mg at 24 study wk (decrease of 61%) Mean prednisone daily dose was 15.7 mg at the end of the study (wk 40) Patients were clinically stable during the treatment phase EGPA manifestations recurred on cessation of MPZ 20 EGPA exacerbations (18 during the non treatment phase)	No SAE reported Rare mild transient infusion-related adverse events	2B
MPZ	Moosig F *et al.,* 2011 [74]	Phase 2, uncontrolled, trial MPZ (9 infusions of 750 mg once every 4 wk) for induction of remission followed by MTX for maintenance of remission 10 refractory or relapsing EGPA patients Follow-up: 32 wk	Remission (BVAS = 0 and GC ≤ 7.5 mg) in 8 patients Decrease of mean daily GC dose from 19 mg to 4 mg at 32 wk No relapses during MPZ therapy 2 major relapses and 5 minor relapses over a median follow-up of 10 mo	4 SAE in 2 patients (probably unrelated to MPZ) 11 non severe adverse reactions	2B
OMZ	Giavina Bianchi *et al.,* 2007 [76]	Case report OMZ dose: six doses of 300 mg for 3 months 1 EGPA patient with difficult-to-treat asthma Follow-up: 3 mo	Improvement of asthma activity and lung function test Improvement of eosinophilia	No SAE reported	4
OMZ	Iglesias *et al.,* 2013 [80]	Case report OMZ dose: 300mg sc every 2 wk 1 pediatric case of refractory EGPA Follow-up: 9 mo	Control of respiratory and gastrointestinal symptoms	No SAE reported	4
OMZ	Pabst S *et al.,* 2008 [79]	Case report OMZ dose: 150 mg every 4 wk 2 refractory "forme fruste" EGPA Follow-up: 18 mo	Marked clinical improvement Improvement of eosinophilia	No SAE reported	4

RCT = randomized clinical trial; IFX = infliximab; RTX = rituximab; ETN = etanercept; ADA = adalimumab; IVIG = intravenous immunoglobulins; mo = months; wk = weeks; sc = subcutaneously; CR = complete remission; PR = partial remission; TF = treatment failure; SAE = severe adverse event; LoE = level of evidence; GC = glucocorticoids.

ANTI-TNF-ALPHA AGENTS

Etanercept

Etanercept (ETN) is an anti-tumor necrosis factor alpha (TNF-α) agent consisting of two extracellular p75 TNF-α receptor domains linked to the Fc portion of human IgG1. In a open-label trial, ETN in combination to standard therapy demonstrated to improve BVAS at 6 months and to be well tolerated in patients with GPA, but intermittent disease activity was common [50]. The Wegener's Granulomatosis Etanercept Trial (WGET) Research Group performed a randomized controlled trial comparing ETN *vs* placebo in addition to standard therapy for maintenance of remission in patients with GPA. No significant differences in rates of sustained remission, in sustained periods of low-level disease activity or in the relative risk of disease flares were found between the ETN-group and the placebo-group. The frequency of adverse events was similar in the ETN and the control groups, but ETN-group presented a higher incidence of solid malignancies compared to general population [51-53].

Infliximab

Infliximab (IFX) is a chimeric murine/human monoclonal antibody directed against TNF-α. Mukhtyar and Luqmani summarized the results emerged from the first case series in which IFX was used in patients with GPA and MPA observing that the remission was achieved in most cases (about 81%) and that the relapse rate was at least 12% [54-58]. On the other hand, the results of an open cohort study showed that the addition of IFX to standard therapy in patients with active AAV did not confer clinical benefits [59]. In a prospective randomized multicentre study, Menthon *et al.* compared efficacy and tolerance of IFX versus RTX in patients with refractory GPA demonstrating the usefulness of both drugs to obtain remission with a trend at 12 months favoring RTX. Patients non-responders to IFX were switched to RTX. Over the long term follow-up, 10/17 patients responded to RTX, 1 to IFX, 2 to other strategies, and 2 died [60].

Adalimumab

Adalimumab (ADA) is a humanised anti-TNF-a monoclonal antibody. In a phase II, open-label, prospective study, subcutaneous ADA was associated to intravenous CYC to treat patients with acute flares of AAV and renal involvement. Response rates and adverse events observed with the addition of ADA were similar to standard therapy alone, but with a reduced GC exposure [61]. Further randomized controlled trials are necessary to demonstrate whether the addition of ADA may improve the speed of remission, the degree of renal recovery and safety.

ALEMTUZUMAB

Alemtuzumab is a humanised monoclonal anti-CD52 antibody (CAMPATH-1H) that selectively deplete circulating lymphocytes, macrophages and monocytes. In an uncontrolled trial, 71 patients with refractory or relapsing AAV were treated with alemtuzumab (intravenously on consecutive days at doses of 4, 10, 40, 40 and 40 mg) after discontinuation of other immunosuppressive medications except prednisolone (tapered to 10 mg/day). During the follow up (mean of 5 years), 60 (85%) patients obtained the remission, but 43 relapsed (72%) (median 9.2 months). Twenty four had a remission period greater than 1 year, of which 10 had a remission period of at least 3 years. Severe infections were common (21 patients), 3 patients were diagnosed with a malignancy within 1 year of treatment and 8 patients developed Graves' disease after a median of 3.5 years after treatment [62]. Further controlled studies are necessary to confirm the efficacy and safety of alemtuzumab for the treatment of relapsing/refractory AAV.

INTRAVENOUS IMMUNOGLOBULINS

Intravenous immunoglobulins (IVIG) preparations consist in human polyspecific IgG immunoglobulins derived from the plasma of blood donors. Before 2000, various case series and small prospective clinical studies reported positive results using IVIG alone or with concurrent immunosuppression in AAV [63-66]. Conversely, Richter *et al.* treated 15 AAV patients, who were poor responders to conventional therapy, with single or multiple courses of IVIG obtaining improvement of organ involvement in 6 patients, but none experienced complete remission [67].

In a randomized placebo-controlled trial, 34 AAV patients with persistent disease activity despite conventional therapy were randomized to receive a single course of IVIG (total dose 2 g/kg) or placebo. Partial or complete remission was achieved in 82% of the IVIG group and 35% of the placebo group, but this effect was not maintained beyond 3 months [68]. To evaluate the efficacy of IVIG as additional therapy to standard immunosuppressant drugs, Martinez *et al*. conducted a multicentric prospective open-label study recruiting 22 patients with a relapse of GPA or MPA. Complete remission was maintained in 13 patients at 9 months and in 7 at 24 months [69].

According to these studies, IVIG associated to conventional immunosuppressive therapy may have a role in the therapeutic approach to relapsing or refractory AAV. The use of IVIG may be considered primarily for patients with contraindications to immunosuppression, such as pregnant women [70, 71]. Moreover, IVIG were generally safe and well tolerated with mainly mild adverse events. However, further randomized, controlled trials are necessary to better assess their efficacy in the induction and/or maintenance therapy alone or in association.

MEPOLIZUMAB

Mepolizumab (MPZ) is a humanised anti-interleukin-5 (IL5) monoclonal antibody. In 2010, Kahn *et al*. reported for the first time a successful use of MPZ in a case of EGPA [72]. In two open-label trials, MPZ was used to treat EGPA patients showing to be able to induce remission in most cases and to be well tolerated, with a corticosteroid-sparing effect. In both studies patients suffered relapses at cessation of MPZ, suggesting that patients with EGPA may require long term treatment [73-75].

OMALIZUMAB

Omalizumab (OMZ) is a humanized anti-IgE monoclonal antibody. In 2007, Giavina-Bianchi *et al.* reported for the first time the efficacious use of OMZ in a case of EGPA with difficult-to-control asthma, maintaining the disease control during 2 years of treatment [76-78]. Afterwards, OMZ was used to treat two patients with refractory ''forme fruste'' of EGPA, obtaining clinical benefit and decrease of peripheral eosinophils [79]. Iglesias *et al.* described a pediatric case of refractory EGPA in which the control of respiratory symptoms was obtained with OMZ [80]. All these reports suggest that OMZ may be beneficial in patients with EGPA and persistent asthma.

CONCLUSION

AAV are a group of life threatening disorders with potentially fatal outcome, where an aggressive and prompt immunosuppressive treatment is needed. Conventional therapy for induction of remission is based on GCs and cytotoxic drugs such as CYC, which could cause severe adverse effects [3]. Moreover, CYC-based protocols are unable to control the disease activity in some refractory and

relapsing cases. Therefore, in the last years various studies investigated new drugs in order to find new less toxic and more effective treatments, primarily biological agents such as monoclonal antibodies.

RTX is the most used biological agent for AAV, demonstrating its efficacy for remission induction in two controlled randomized trials [20, 21]. According to these data, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved RTX, in combination with GCs, to treat AAV. RTX may be used as first-line treatment to induce remission instead of CYC in patients with GPA and MPA, especially in young patients to preserve fertility or elderly patients who may not tolerate cytotoxic agents [24]. Promising data emerged from the MAINRITSAN trial and retrospective studies that investigated RTX for maintenance of remission in AAV patients, but further studies are necessary to clarify safety and efficacy in the long-term treatment [27-30].

There is no recommendation to use anti-TNF-α agents for AAV as first-line treatment in association to conventional therapy or alone, but their use may be considered for some selected refractory or relapsing cases [51, 58-61].

MPZ and OMZ demonstrated to be potentially beneficial treatments for patients with EGPA, especially for their steroid-sparing effect [76, 79, 80]. Further controlled studies are needed to properly assess their safety and efficacy.

FUTURE DIRECTIONS

Given the results obtained with RTX, other biological agents that target B-cells may be of interest for the treatment of AAV. Ocrelizumab (humanized anti-CD20 monoclonal antibody), ofatumumab (human anti-CD20 monoclonal antibody) and epratuzumab (humanized anti-CD22 monoclonal antibody) are currently under investigation in patients with autoimmune disorders other than AAV. B-lymphocyte stimulator (BLyS or B-cell activating factor or BAFF) is a cytokine that plays a central role for the differentiation, selection and homeostasis of B cell lineage. The overexpression of this cytokine may promote the survival of autoreactive B cells, representing another possible target for the treatment of AAV [81, 82]. Elevated BLyS levels are found in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Moreover, the concentrations of this cytokine correlate with antibody levels and clinical disease activity in both disorders [83-86]. Significantly increased levels of BLyS are observed in patients with AAV, primarily in those with GPA [87-89]. Belimumab (BLM), a monoclonal antibody directed against BLyS, demonstrated to be an effective treatment for patients with SLE without significant renal involvement in two phase III controlled randomized trials, and for patients with RA in a phase II controlled randomized trial [90-92]. BLM is currently under investigation for maintenance of remission for patients with GPA or MPA in an ongoing randomized clinical trial (BREVAS).

The inhibition of T-cell costimulation may be another promising therapeutical approach in patients with AAV. Abatacept (ABT), a fusion protein that consists in the extracellular domain of CTLA-4 combined with the Fc portion of the human IgG1, demonstrated its efficacy in patients with RA and to have biologic activity with good tolerability in patients with lupus nephritis [93-95]. In an open-label trial, ABT was used to treat 20 patients with mild relapsing GPA, demonstrating to be well tolerated and to induce remission in most of them (80%) [96]. Further randomized controlled trials are necessary to evaluate the efficacy and safety of ABT in AAV.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

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