REVIEWS

Steroid-sparing strategy for the treatment of vasculitis associated with antineutrophil cytoplasmic antibodies

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Glucocorticoids (GC) and immunosuppressants (IS) are traditional treatments for vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA), often resulting in the development of infections, diabetes mellitus and other adverse events (AEs). The development of a steroid-sparing strategy using biologic disease-modifying antirheumatic drugs (bDMARDs, including rituximab, etc.) and synthetic targeted drugs (avacopan) has radically improved the course of the disease. Currently, there are increasing number of basic and clinical trials of numerous bDMARDs that effectively reduce the number of AEs associated with GC and IS. The steroid-sparing therapeutic strategy not only shows considerable efficacy, but also opens up new perspectives for the treatment of patients with ANCA-associated systemic vasculitis.

Keywords: *vasculitis associated with antineutrophil cytoplasmic antibodies; steroid-sparing therapy; glucocorticoids; immunosuppressants; genetically engineered biological drugs; rituximab; avacopan.*

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Vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) is a complex autoimmune disease characterized by inflammation and necrosis of the wall of small and medium blood vessels, resulting in tissue disintegration and organ dysfunction. ANCA-associated vasculitides (AAVs) comprise microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic GPA (EGPA). Proteinase 3 (PR3) and myeloperoxidase (MPO) are two major antigens found in the cytoplasm of neutrophils that interact with ANCA. PR3-ANCA are commonly associated with GPA, whereas MPO-ANCA are an important diagnostic marker for MPA [1]. Approximately 30–40% of patients with EGPA test positive for ANCA [2].

The annual incidence of AAV is 1.2–2.0 cases per 100,000, with a prevalence of 4.6–18.4 cases per 100,000 [3]. The annual incidence ranges from 2 to 13 cases per million for GPA, with higher rates in Northern Europe [4], and from 1.25 to 18.2 cases per million for MPA, peaking in Japan and Southern Europe [5, 6]. The annual incidence of EGPA is much lower, ranging from 0.9 to 4 cases per million, without sex-related differences [6].

AAV can affect subjects of all ages, with 40–60 years of age more at risk, regardless of sex. GPA occurs predominantly in Caucasian men with a mean age ranging between 35 and 50 years [4, 5]. However, patients with MPA are almost 10 years older than patients with GPA at the time of the diagnosis, and the incidence rate in men and women is similar [5, 6].

GPA and MPA are characterized by necrotizing vasculitis that can affect any organ but primarily the kidneys, lungs, upper respiratory tract, skin, eyes, and peripheral nerves. Granulomas and giant multinucleated cells are key pathological features of the diseases. They occur due to the excessive activation of circulating neutrophilic granulocytes after binding to ANCA, resulting in necrotizing vasculitis with inflammatory and ischemic damage, fibrotic tissue remodeling, and organ dysfunction. EGPA is markedly different from other AAVs and is characterized by late-onset asthma, rhinosinusitis, eosinophilia in the peripheral blood, and signs of vasculitis. The pathogenesis of EGPA is poorly understood and is related to the proliferation and activation of eosinophilic granulocytes mediated by interleukin (IL) 5 and IL-13 [4].

Individualized treatment decisions are made based on the disease activity, preexisting and irreversible organ damage, risk of relapse, overall prognosis, and quality of life. The conventional approach to AAV involves induction and maintenance of remission and monitoring for possible relapses. According to the recommendations of the European League Against Rheumatism (EULAR) and the European Renal Association-European Dialysis Transplant Association (ERA-EDTA), treatment of patients with organ- or life-threatening GPA and MPA begins with a combination of high doses of glucocorticoids (GCs) with cyclophosphamide (CP) and/or rituximab (RTX; Table 1) [7, 8]. A combination of GC with azathioprine (AZA) or mycophenolate mofetil (MMF), or methotrexate (MTX) can be used in patients with mild, non-life-threatening disease (Table 1) [7, 8]. This treatment is effective but entails the risk of toxic adverse events (AEs), probably due to the non-selective effects of these agents on different tissues and cell types.

Table 1. Main regimens for GC dose reduction for remission induction according to randomized clinical trials data

Parameter	PEXIVAS20						LOVAS21	AVC 30 mg twice daily + GC 20 mg/day[47,48]	
Treatment	GC + CP pulse therapy ± 7 PE			± 7 PE		± 7 PE	GC 0.5 mg/kg/day + RTX 375 mg/m^2/week, 4 doses GC, mg/day	GC pulse therapy + RTX 375 mg/m^2/week once every 4 weeks, then AZA 2 mg/kg/day up to week 52	
	Standard-dose GC regimen, mg/day			Reduced-dose GC regimen, mg/day				GC, mg/day	
Body weight	<50 kg	50–75 kg	>75 kg	<50 kg	50–75 kg	>75 kg	—	>55 kg	<55 kg
GC treatment week	GC dose, mg/day								
1	50	60	75	50	60	75	37.5	60	45
2	25	30	40	25	30	40	37.5	45	45
3–4	20	25	30	20	25	30	18.75	30 (3 weeks) 25 (4 weeks)	30 (3 weeks) 25 (4 weeks)
5–6	15	20	25	15	20	25	7.5	25	25
7–8	12.5	15	20	12.5	15	20	5	20	20
9–10	10	12.5	15	10	12.5	15	4	15	15
11–12	7.5	10	12.5	7.5	10	12.5	3	10	10
13–14	7.5	10	12.5	6	7.5	10	2	10	10
15–16	7.5	10	12.5	5	5	7.5	2	5	5
17–18	7.5	10	12.5	5	5	7.5	1	5	5
19–20	5	5	5	5	5	5	1	5	5
21–22	5	5	5	5	5	5	0	0	0
23–52	5	5	5	5	5	5	0	0	0

Note. After week 52, local investigators determined subsequent GC dosing. PE, plasma exchange.

Infections are common in patients receiving high cumulative doses of GC [9], which also exert adverse effects on many organ systems, contributing to musculoskeletal disorders (osteoporosis, avascular necrosis, and myopathy) [10], endocrine dysfunction (diabetes mellitus and adrenal suppression) [11], and increased cardiovascular risk (hypertension, atherosclerosis, heart failure), eye disorders (glaucoma and cataract), gastrointestinal disorders (peptic ulcer disease and gastrointestinal bleeding), mental disorders, etc. [12, 13]. According to T.C. Yao et al. [14], short courses of high-dose GC therapy increase the risk of AEs. Moreover, mortality in some forms of vasculitis is higher than in the general population, despite a very good response to GCs [15]. O. Flossmann et al. [16] point out that most deaths are due to infections and cardiovascular complications related to GCs rather than vasculitis. In recent years, there has been a trend toward minimizing high doses of GCs, including pulse therapy with methylprednisolone, particularly in patients with low disease activity [17]. The metabolites of CP exert toxic effects on the bladder and reproductive system, with increased risks of malignancies [18] and infertility [19] during long-term treatment.

The problem of AEs induced by GCs and CP in AAV patients has facilitated the development of steroid-sparing strategies which significantly improved treatment outcomes. A rapid GC tapering regimen was introduced in the recent PEXIVAS trial (induction with GC and CP with or without plasma exchange in patients with AAV and severe renal impairment or diffuse alveolar hemorrhage) and has become widely used. Both regimens of oral GCs showed comparable efficacy (Table 2), although the frequency of AEs, primarily infections, insomnia, and new-onset diabetes mellitus, was significantly lower in the reduced-dose group [20]. In a subsequent randomized controlled trial (RCT) conducted by S. Furuta et al. [21], a reduced-dose GC plus rituximab regimen was noninferior to a high-dose GC plus rituximab regimen with regard to induction of disease remission in patients without severe glomerulonephritis or alveolar hemorrhage (Table 2). Subsequently, Y. Xiao et al. [22] confirmed that medium- to low-dose GC therapy reduces the risks of mortality and end-stage renal disease. This data had supported the conditional recommendation of the American College of Rheumatology (ACR) to use a reduced-dose GC regimen over a standard-dose GC regimen for remission induction in patients with active, severe GPA/MPA [23].

Over the past decades, biologic agents have dramatically improved the outcomes of AAV and replaced cytotoxic drugs as the cornerstone of induction and maintenance therapy. Currently, there is a growing number of fundamental and clinical studies of various therapies that not only significantly reduce the frequency of AEs related to GCs and immunosuppressants (ISs) but also demonstrate considerable efficacy (Table 2).

RTX, a chimeric mouse/human monoclonal anti-CD20 IgG1 antibody approved by the US Food and Drug Administration (FDA) in 2011, has been successfully used for the treatment of patients with AAV. In 2020, the Oxford Centre for Evidence-Based Medicine recommended extended RTX therapy (Table 1), with immediate withdrawal of ISs and complete cessation of GCs 6–12 months after RTX commencement [24]. However, in 2021, the Kidney Disease: Improving Global Outcomes (KDIGO) group recommended that GCs in combination with CP or RTX be used as initial treatment of new-onset AAV [25]. In patients presenting with serum creatinine > 354 mmol/L, CP and GCs are preferable for induction therapy, although the combination of RTX and CP can also be considered in this setting (Table 1). Either AZA plus low-dose GCs or RTX without GCs is recommended as maintenance therapy after remission induction. Patients with relapsing disease should be reinduced, preferably with RTX. Refractory disease can be treated by an increase in GCs or by the addition of RTX or CP [26–28]. The 2022 EULAR [8] and 2023

Table 2. Brief description of GPA, MPA, and EGPA treatment protocols [8,29,30,37,42,45,47,48,55,70,72,74]

AAV	Drug	Treatment phase	Dosage
GPA/MPA	GC	Remission induction and maintenance	See Table 1
	CP pulse therapy	Induction: life-threatening organ damage (kidneys, lungs, eyes, brain)	15 mg/kg IV (up to 1200 mg/pulse) at weeks 0, 2, and 4, then every 3 weeks until remission, up to 10 doses or 2 mg/kg orally daily for a total of 3–6 months
	RTX		375 mg/m^2 IV initially, at weeks 1, 2, and 3 or 1000 mg IV on days 1 and 15
	ONT		1000 mg IV on days 1 and 15 with GC taper
	AVC		30 mg twice daily
	MTX	Remission induction and maintenance: *non-life/organ-threatening* disease, any grade	15–25 mg once weekly
	MMF		2000–3000 mg/day orally
	RTX	Maintenance of remission: any severity grade	1000 mg IV every 4 months *or* 500 mg IV every 6 months for 18–36 months
	BLM		10 mg/kg after induction with RTX or CP with GC
	AVC		30 mg twice daily
	AZA		2 mg/kg/day orally, up to 200 mg/day
	LEF		20–30 mg/day orally
	TCZ		8 mg/kg every 4 weeks
	Immunoglobulins	Refractory disease	A single course (2 g/kg) is added to standard induction therapy
	Alemtuzumab		60 mg/day or 30 mg/day
EGPA	CP pulse therapy	Induction: life-threatening organ damage	600 mg/m^2 on days 1, 15, and 29, then 500 mg every 3 weeks 6 doses
	RTX		1 g on days 1 and 15 300 mg subcutaneously every 4 weeks
	Mepolizumab	Remission induction and maintenance: *non-life/organ-threatening* disease, any grade	1 mg/kg/day over 3 weeks (up to 80 mg/day), then reduction by 7.5 mg every 2 weeks to 0.25 mg/kg/day after 3 months, then by 5 mg every 2 weeks to 10 mg/day, then by 1 mg every 3 weeks to the minimum effective dose
	PS monotherapy		2 mg/kg/day, up to 200 mg/day
	AZA		15–25 mg once weekly
	MTX		2000–3000 mg/day
	MMF		

Note. IV, intravenously; LEF, leflunomide; PS, prednisolone.

Pan-American League of Associations for Rheumatology (PANLAR) [29] guidelines also suggest using a combination of GCs and RTX to induce remission in patients with new or recurrent GPA or MDA (Table 1).

Regarding safety, the 2024 KDIGO guidelines [30] and numerous well-designed studies [31,32] point out comparable rates of infection between RTX and CP used as the first-line induction therapy. However, scientists disagree on the safety of the two treatments. A comprehensive meta-analysis showed that the cumulative incidence of serious infections during the total follow-up period was significantly higher for the combination of CP and AZA compared to the combination of RTX and AZA [33]. Chinese investigators demonstrated comparable efficacy of low-dose RTX (375 mg/m^2/week total over 4 weeks) and CP, although the incidence of serious AEs in the RTX group was significantly lower (Table 1) [34]. Japanese investigators also reported lower risks of fungal infections and Pneumocystis pneumonia in patients with severe AAV in the RTX group compared with the CP group [35]. Also, the 2024 KDIGO guidelines suggest that RTX is preferable than CP for induction therapy in frail elderly patients [30], although the specific evidence remains unclear.

Inspired by the success of RTX, a second generation of humanized, fully chimeric, type I anti-CD20 IgG1 (rituximab-like) monoclonal antibodies with deliberately modified pharmacodynamic profiles has been developed.[36] ***Obinutuzumab*** (ONT) is another anti-CD20 antibody that can significantly reduce the risk of AAV relapse.[37] In an *in vitro* study using cells from patients with GPA, ONT showed stronger effects compared to RTX on both the reduction of B cells and the activation of NK cells due to the optimized activity of Fc fragments [37, 38]. ONT appears to be a safe and effective option for patients with AAV who have refractory disease or poor tolerability to RTX (Table 2) [37]. An RCT comparing the efficacy of ONT and RTX in the treatment of patients with AAV positive for PR3-ANCA is in progress (NCT05376319) [39].

The B lymphocyte stimulator (BLyS) is a member of the tumor necrosis factor (TNF) family that plays a unique role in B cell development/differentiation in autoimmune diseases [40]. BLyS is expressed by neutrophils, which have been identified as key cells in the pathogenesis of AAV [41]. ***Belimumab*** (BLM), a human IgG1λ monoclonal antibody against BLyS, is licensed for the treatment of adults with active systemic lupus erythematosus who are receiving standard therapy. Two studies demonstrated that dual immunotherapy (AZA/BLM or RTX/BLM) targeting B cells (i.e., B cell depletion and BLyS inhibition) may be more effective than single-agent therapy (Table 2) [42, 43].

Currently, ***avacopan*** (AVC), the first selective antagonist of the complement 5a receptor (C5aR1 or CD88) for oral administration that competitively inhibits the interaction between C5aR1 and anaphylatoxin C5a, is considered the most promising steroid-sparing strategy. The specific and selective blockade of C5aR1 by AVC reduces the pro-inflammatory effects of C5a, which include neutrophil activation, migration, and adherence to sites of small blood vessel inflammation, vascular endothelial cell retraction and permeability [44].

AVC has been approved for the treatment of GPA and MPA in several countries, including the USA and Japan [45]. In November 2021, AVC, in combination with RTX or CP, was approved for the treatment of adult patients with severe, active AAV [46]. The efficacy and safety of AVC was evaluated in 331 patients with AAV in the ADVOCATE trial. Patients received AVC at a dose of 30 mg twice daily for 52 weeks and GCs on a tapering schedule for 20 weeks. In the control group (n = 164), patients received matching placebo twice daily for 52 weeks with GCs (60 mg/day tapered to discontinuation by week 21). Patients in both groups received RTX or CP according to the established protocols. At week 26, remission rates in the AVC and GC groups were similar (Table 2). There was a 54% reduction in the relative risk of relapse after 52 weeks of AVC treatment (hazard ratio (HR) 0.46; 95% confidence interval (CI) 0.25–0.84) [47]. The steroid-sparing effect of AVC (reduction in the maximum doses and duration of GC use) was evident in a 56% reduction in the cumulative GC dose after week 52 and in an improvement in GC-induced toxic effects (reduction in the Glucocorticoid Toxicity Index) [47]. Another RCT compared the efficacy of GCs alone (60 mg/day, followed by a tapering regimen until discontinuation) and a combination of GC (20 mg/day) and AVC (60 mg/day; Tables 1 and 2) administered over 20 weeks. The primary endpoint was a ≥50% reduction in the Birmingham Vasculitis Activity Score (BVAS). This study found no differences in the safety or efficacy between the two groups [48]. P.A. Merkel et al. [49] showed that AVC in addition to standard-of-care treatment with GCs and RTX or CP was well tolerated and improved the duration of AAV remission. Another study demonstrated the efficacy of a 52-week combination treatment with GC and AVC in patients with severe renal insufficiency [50]. F.B. Cortazar et al. reported 3 cases of rapidly progressing AAV requiring renal replacement therapy [51]. Patients received AVC in combination with RTX and/or CP and a rapid GC tapering regimen. Renal function significantly improved in all patients, and hemodialysis was discontinued. Interestingly, AVC reduces AAV activity without affecting ANCA levels [52, 53]. In the 2024 KDIGO guidelines, AVC is recommended as an effective alternative therapy for patients requiring high doses of GCs and patients with renal involvement and a low glomerular filtration rate (Table 1).

Thus, AVC represents a new treatment strategy that has a potential to change standard-of-care AAV treatment and completely replace GCs.

Cellular immunity plays a crucial role in the pathogenesis of AAV. CD4+ cells promote ANCA production, and both CD4+ and CD8+ cells recognize ANCA antigens deposited in peripheral tissues through activated neutrophils. ***Alemtuzumab*** is a humanized anti-CD52 monoclonal antibody that depletes all lymphocytes, with a particularly long-lasting effect on T cells resulting in CD4+ cell recovery approximately 60 months after cessation of treatment [54]. The ALEVIATE trial included 23 patients with refractory AAV or Behзet's disease who were randomized to receive 60 or 30 mg/day alemtuzumab (Table 2). Remission was reported in 2/3 of patients after 6 months and was maintained to 12 months in 1/3. No dose-dependent differences were found [55]. By targeting T cells, alemtuzumab has demonstrated some potential in the treatment of AAV, but further studies are needed.

Abatacept (ABC) is a fusion protein consisting of the Fc region of IgG1 and the extracellular domain of CTLA4 that binds to the costimulatory ligands CD80 and CD86 and inhibits their interaction with the costimulatory receptors CD28 and CTLA-4 expressed by T cells, thereby inhibiting T cell activation [56]. C. Mettler et al. [57] observed remission or response in less than 50% out of 6 patients with refractory and/or recurrent GPA treated with ABC. In another study, patients received dual-agent therapy with GC (30 mg/day) and ABC for 2 months, as well as AZA, MMF or MTX. Of the 20 patients, 18 (90%) had disease improvement, and 16 (80%) achieved remission after 1.9 months. Eleven of the 15 (73%) ABC-treated patients on GCs reached 0 mg. However, 7 patients experienced 9 severe AEs, including 7 infections that were successfully treated [58].

TNF-α plays a central role in the pathogenesis of AAV by inducing neutrophil activation which causes vascular endothelial damage [59]. This mechanism justifies the use of ***monoclonal antibodies against TNF-α*** (infliximab, etanercept, and adalimumab) for the treatment of AAV. However, a meta-analysis of four RCTs did not show significant efficacy of etanercept and infliximab in achieving remission or preventing relapse in patients with GPA and MPA [60, 61. Notably, the combination of CP with etanercept significantly increased the risk of solid malignancies compared to the general population [62]. In another prospective, multicenter study conducted in a small sample of AAV patients, induction therapy with infliximab permitted reducing GC doses and resulted in remission in 88% [63]. Similar data were reported by other investigators [64, 65]. In a prospective study of 14 patients with active AAV receiving adalimumab in combination with CP, 11 (78.5%) patients achieved remission within 14 weeks (mean, 12 weeks), with a reduction in the daily dose of GCs. The efficacy and safety of this regimen did not differ significantly from standard-of-care treatment; however, 1 patient died and 3 experienced infection [66].

IL-6 and chemokines may play a role in the pathogenesis of AAV [67, 68]. ***Tocilizumab*** (TCZ), an antibody against the interleukin-6 (IL-6) receptor, is the first-line treatment for patients with giant cell arteritis [69]. P.F. Tang et al. [70] reported an interesting case of a patient with refractory GPA and increased IL-6 expression. After TCZ treatment, his symptoms improved, and his inflammatory marker levels, including IL-6, returned to normal. Similar results were obtained by A. Berti et al. [71], and TCZ treatment resulted in stable remission in patients with generalized MPA. In a prospective, single-center, cohort study of TCZ monotherapy for MPA, 2 (33.3%) of 6 patients achieved complete remission at 6 months, and 3 (50.0%) at 12 months. Four (66.7%) patients stopped treatment after 1 year; no relapses of the disease were observed for 6–15 months [72]. TCZ monotherapy may be considered an acceptable treatment strategy for some patients with AAV.

IL-5, a cytokine mainly involved in chemotaxis and activation of eosinophils, plays a central role in the pathogenesis of EGPA [73]. ***Monoclonal antibodies targeting IL-5*** (mepolizumab, reslizumab) and its receptors (benralizumab) are effective for the treatment of bronchial asthma with severe eosinophilia both in the blood and lungs. The first evidence-based guidelines for the diagnosis and treatment of

EGPA were published in Europe in 2023 [74]. Mepolizumab in combination with GCs is recommended for inducing remission in patients with relapsed and refractory EGPA without organ damage or other life-threatening complications (Table 2). Meanwhile, RTX, mepolizumab, or ISs in combination with GCs are used to maintain remission in patients with severe EGPA (Table 2) [74]. Currently, GCs and/or their combination with mepolizumab are recommended for patients with mild EGPA and/or recurrent respiratory symptoms [75]. After 3 years of treatment with mepolizumab, approximately 50% of patients may achieve a GC-free status, and GCs could be discontinued even in severe cases and ANCA-positive EGPA.75 The 2023 European guidelines suggest that other IL-5 or IL-5 receptor inhibitors may be used in patients who are refractory to mepolizumab [74]. S. Nolasco et al. [76] reported comparable efficacy and safety of mepolizumab and benralizumab in patients with refractory EGPA treated over 24 months. Similar results were obtained in a multicenter, double-blind, phase III RCT in 2024 [77]. A recent retrospective study demonstrated that benralizumab itself is an effective steroid-sparing option for patients with EGPA and refractory asthma or respiratory symptoms [78], with maintenance of remission for up to 2 years [79].

Thus, a steroid-sparing strategy helps to reduce relapse rate, morbidity, and mortality associated with AAV treatment. Biologic agents increase treatment efficacy and significantly reduce immune-related AEs, improving compliance and offering hope to patients with AAV. An optimized strategy of using biologic agents in AAV will be the main focus of future fundamental studies aimed at confirming their safety and efficacy, especially during long-term treatment.

REFERENCES

1. Van Beers JJBC, Vanderlocht J, Roozendaal C, Damoiseaux J. Detection of anti-neutrophil cytoplasmic antibodies (ANCA) by indirect immunofluorescence. *Methods Mol Biol.* 2019: 1901:47-62. doi: 10.1007/978-1-4939-8949-2_4.
2. White J, Dubey S. Eosinophilic granulomatosis with polyangiitis: A review. *Autoimmun Rev.* 2023 Jan;22(1):103219. doi: 10.1016/j.autrev.2022.103219. Epub 2022 Oct 22.
3. Watts RA, Mahr A, Mohammad AJ et al. Classification, epidemiology and clinical subgrouping of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. *Nephrol Dial Transplant.* 2015 Apr:30 Suppl 1:i14-22. doi: 10.1093/ndt/gfv022.
4. Kitching AR, Anders HJ, Basu N, et al. ANCA-associated vasculitis. *Nat Rev Dis Primers.* 2020 Aug 27;6(1):71. doi: 10.1038/s41572-020-0204-y
5. Mohammad AJ. An update on the epidemiology of ANCA-associated vasculitis. *Rheumatology (Oxford).* 2020 May 1;59(Suppl 3):iii42-iii50. doi: 10.1093/rheumatology/keaa089.
6. Terrier B, Darbon R, Durel CA, et al. French recommendations for the management of systemic necrotizing vasculitides (polyarteritis nodosa and ANCA-associated vasculitides). *Orphanet J Rare Dis.* 2020 Dec 29; 15(Suppl 2):351. doi: 10.1186/s13023-020-01621-3.
7. Yates M, Watts AR, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis.* 2016 Sep;75(9):1583-94. doi: 10.1136/annrheumdis-2016-209133.
8. Hellmich B, Sanchez-Alamo B, Schirmer JH, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. *Ann Rheum Dis.* 2024 Jan 2;83(1): 30-47. doi: 10.1136/ard-2022-223764.
9. Cutolo M, Seriolo B, Pizzorni C, et al. Use of glucocorticoids and risk of infections. *Autoimmun Rev.* 2008 Dec;8(2):153-5. doi: 10.1016/j.autrev.2008.07.010. Epub 2008 Aug 12.
10. Chotiyarnwong P, McCloskey EV. Pathogenesis of glucocorticoid-induced osteoporosis and options for treatment. *Nat Rev Endocrinol.* 2020 Aug;16(8):437-447. doi: 10.1038/s41574-020-0341-0. Epub 2020 Apr 14.
11. Patel NJ, Jayne DRW, Merkel PA, et al. The Glucocorticoid Toxicity Index-Metabolic Domains, an abridged version of the Glucocorticoid Toxicity Index: post-hoc analysis of data from the ADVOCATE trial. *Lancet Rheumatol.* 2023 Jul;5(7):e413-e421. doi: 10.1016/S2665-9913(23)00131-5.
12. Koshi EJ, Young K, Mostales JC, et al. Complications of corticosteroid therapy: a Comprehensive literature review. *J Pharm Technol.* 2022 Dec; 38 (6):360-367. doi:10.1177/87551225221116266.
13. Rice JB, White AG, Scarpati LM, et al. Long-term systemic corticosteroid exposure: a systematic literature review. *Clin Therapeut.* 2017 Nov;39(11):2216-2229. doi: 10.1016/j.clinthera.2017.09.011.
14. Yao TC, Huang YW, Chang SM, et al. Association between oral corticosteroid bursts and severe adverse events: a Nationwide population-based cohort study. *Ann Intern Med.* 2020 Sep 1;173(5):325-330. doi: 10.7326/M20-0432
15. Tan JA, Dehghan N, Chen W, et al. Mortality in ANCA-associated vasculitis: ameta-analysis of observational studies. *Ann Rheum Dis.* 2017 Sep;76 (9):1566-1574. doi: 10.1136/annrheumdis-2016-210942.
16. Flossmann O, Berden A, de Groot K, et al. Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis.* 2011 Mar;70(3):488-494. doi: 10.1136/ard.2010.137778.
17. McGovern D, Williams SP, Parsons K, et al. Long-term outcomes in elderly patients with ANCA-associated vasculitis. *Rheumatology (Oxford).* 2020 May 1;59(5):1076-1083. doi: 10.1093/rheumatology/kez388.
18. Rahmattulla C, Berden AE, Wakker SC, et al. Incidence of malignancies in patients with antineutrophil cytoplasmic antibody-associated vasculitis diagnosed between 1991 and 2013. *Arthritis Rheumatol.* 2015 Dec; 67(12):3270-8. doi: 10.1002/art.39317.
19. Bermas BL. Paternal safety of antirheumatic medications. *Best Pract Res Clin Obstet Gynaecol.* 2020 Apr:64:77-84. doi: 10.1016/j.bpobgyn.2019.09.004. Epub 2019 Oct 8.
20. Walsh M, Merkel PA, Peh CA, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med.* 2020 Feb 13;382 (7):622-631. doi: 10.1056/NEJMoa1803537.
21. Furuta S, Nakagomi D, Kobayashi Y, et al. Effect of reduced-dose vs high-dose glucocorticoids added to rituximab on remission induction in ANCA-associated vasculitis: a randomized clinical trial. *JAMA.* 2021 Jun 1; 325(21):2178-2187. doi: 10.1001/jama.2021.6615.
22. Xiao Y, Guyatt G, Zeng L, et al. Comparative efficacy and safety of alternative glucocorticoids regimens in patients with ANCA-associated vasculitis: a systematic review. *BMJ Open.* 2022 Feb 25;12 2):e050507. doi: 10.1136/bmjopen-2021-050507.
23. Chung SA, Langford CA, Maz M, et al. 2021 American College of Rheumatology/vasculitis Foundation guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheumatol.* 2021 Aug;73(8):1366-1383. doi: 10.1002/art.41773. Epub 2021 Jul 8.
24. Tieu J, Smith R, Basu N, et al. Rituximab for maintenance of remission in ANCA-associated vasculitis: expert consensus guidelines. *Rheumatology (Oxford).* 2020 Apr 1;59(4): e24-e32. doi: 10.1093/rheumatology/kez640.
25. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guide-

line for the management of glomerular diseases. *Kidney Int*. 2021 Oct;100(4S):S1-S276. doi: 10.1016/j.kint.2021.05.021.
26. Jones RB, Furuta S, Tervaert JW, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial. *Ann Rheum Dis*. 2015 Jun;74(6):1178-82. doi: 10.1136/annrheumdis-2014-206404. Epub 2015 Mar 4.
27. Charles P, Perrodeau E, Samson M, et al. Long-term rituximab use to maintain remission of antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med*. 2020 Aug 4;173(3):179-187. doi: 10.7326/M19-3827. Epub 2020 Jun 2.
28. Smith RM, Jones RB, Specks U, et al. Rituximab versus azathioprine for maintenance of remission for patients with ANCA-associated vasculitis and relapsing disease: an international randomised controlled trial. *Ann Rheum Dis*. 2023 Jul;82(7):937-944. doi: 10.1136/ard-2022-223559. Epub 2023 Mar 23.
29. Magri SJ, Ugarte-Gil MF, Brance ML, et al. Pan American League of Associations for Rheumatology guidelines for the treatment of ANCA-associated vasculitis. *Lancet Rheumatol*. 2023 Aug;5(8):e483-e494. doi: 10.1016/S2665-9913(23)00128-5. Epub 2023 Jul 6.
30. Levin A, Ahmed SB, Carrero JJ, et al. Executive summary of the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease: known knowns and known unknowns. *Kidney Int*. 2024 Apr;105(4):684-701. doi: 10.1016/j.kint.2023.10.016.
31. Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med*. 2010 Jul 15;363(3):211-20. doi: 10.1056/NEJMoa0909169.
32. Gerard M, de Boysson H, Morello R, et al. Early infectious risk in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis according to remission-induction therapy. *Scand J Rheumatol*. 2023 Mar; 52(2):161-173. doi: 10.1080/03009742.2021.2001929. Epub 2022 Jan 20.
33. Vassilopoulos A, Vassilopoulos S, Kalligeros M, et al. Incidence of serious infections in patients with ANCA-associated vasculitis receiving immunosuppressive therapy: a systematic review and meta-analysis. *Front Med (Lausanne)*. 2023 Mar 1:10:1110548. doi: 10.3389/fmed.2023.1110548. eCollection 2023.
34. Liu L, Lu H, Zou G, et al. Efficacy and safety of low-dose rituximab as induction therapy for antineutrophil cytoplasmic antibody-associated vasculitis with renal involvement: a Chinese case series. *BMC Nephrol*. 2023 Feb 8;24(1):28. doi: 10.1186/s12882-023-03075-8.
35. Ishikawa Y, Tokutsu K, Nakayamada S, et al. Short-term effectiveness and safety of rituximab versus cyclophosphamide for life-threatening ANCA-associated vasculitis: a propensity score analysis of the real-world nationwide database. *Ann Rheum Dis*. 2024 Jan 2;83(1):103-111. doi: 10.1136/ard-2023-224472.
36. Robak T, Robak E. New anti-CD20 monoclonal antibodies for the treatment of b-cell lymphoid malignancies. *BioDrugs*. 2011 Feb 1;25(1):13-25. doi: 10.2165/11539590-000000000-00000.
37. Amudala NA, Boukhlal S, Sheridan B, et al. Obinutuzumab as treatment for ANCA-associated vasculitis. *Rheumatology (Oxford)*. 2022 Aug 30;61(9):3814-3817. doi: 10.1093/rheumatology/keab916.
38. Urlaub D, Zhao S, Blank N, et al. Activation of natural killer cells by rituximab in granulomatosis with polyangiitis. *Arthritis Res Ther*. 2019 Dec 11;21(1):277. doi: 10.1186/s13075-019-2054-0
39. McGovern DP, McClure ME, Coates M, et al; ObiVas Investigators. Study protocol for a randomised, phase II, double-blind, experimental medicine study of obinutuzumab versus rituximab in ANCA associated vasculitis: ObiVas. *BMJ Open*. 2024 Jul 17;14(7):e083277. doi: 10.1136/bmjopen-2023-083277.
40. Do RK, Chen-Kiang S. Mechanism of BLyS action in B cell immunity. *Cytokine Growth Factor Rev*. 2002 Feb;13(1):19-25. doi: 10.1016/s1359-6101(01)00025-9.
41. Carter LM, Isenberg DA, Ehrenstein MR. Elevated serum BAFF levels are associated with rising anti-double-stranded DNA antibody levels and disease flare following B cell depletion therapy in systemic lupus erythematosus. *Arthritis Rheum*. 2013 Oct;65(10):2672-9. doi: 10.1002/art.38074.
42. Jayne D, Blockmans D, Luqmani R, et al. Efficacy and safety of belimumab and azathioprine for maintenance of remission in anti-neutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled study. *Arthritis Rheumatol*. 2019 Jun;71(6):952-963. doi: 10.1002/art.40802. Epub 2019 Apr 16.
43. McClure ME, Gopaluni S, Wason J, et al. A randomised study of rituximab and belimumab sequential therapy in PR3 ANCA-associated vasculitis (COMBIVAS): design of the study protocol. *Trials*. 2023 Mar 11;24(1):180. doi: 10.1186/s13063-023-07218-y.
44. Trivioli G, Vaglio A. The rise of complement in ANCA-associated vasculitis: from marginal player to target of modern therapy. *Clin Exp Immunol*. 2020 Dec;202(3):403–6. doi: 10.1111/cei.13515. Epub 2020 Oct 5.
45. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=432014
46. https://www.ema.europa.eu/en/documents/product-information/tavneos-epar-product-information_en.pdf.
47. Jayne D, Merkel PA, Schall TJ, Bekker P. ADVOCATE Study Group. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med*. 2021 Feb 18;384(7):599-609. doi: 10.1056/NEJMoa2023386.
48. Jayne D, Bruchfeld AN, Harper L, et al. Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis. *J Am Soc Nephrol*. 2017 Sep;28(9):2756-2767. doi: 10.1681/ASN.2016111179. Epub 2017 Apr 11.
49. Merkel PA, Niles J, Jimenez R, et al. Adjunctive treatment with avacopan, an oral C5a receptor inhibitor, in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis. *ACR Open Rheumatol*. 2020 Nov; 2(11):662-671. doi: 10.1002/acr2.11185. Epub 2020 Oct 31.
50. Cortazar FB, Niles JL, Jayne D, et al. Renal recovery for patients with ANCA-associated vasculitis and low eGFR in the ADVOCATE trial of avacopan. *Kidney Int Rep*. 2023 Feb 3; 8(4):860-870. doi: 10.1016/j.ekir.2023.01.039. eCollection 2023 Apr.
51. Cortazar FB, Cerda J, Dhanani R, et al. Avacopan in patients with rapidly progressive glomerulonephritis requiring dialysis. *Kidney Int Rep*. 2023 May 29;8(8):1687-1691. doi: 10.1016/j.ekir.2023.05.017. eCollection 2023 Aug.
52. Abe Y, Minowa K, Kogami M et al. Avacopan is possibly associated with the improvement of ANCA-associated vasculitis activity without decreasing ANCA titres: a four-case series. *Rheumatology (Oxford)*. 2023 Nov 2; 62(11):e317-e318. doi: 10.1093/rheumatology/kead191.
53. Van Leeuwen JR, Bredewold OW, van Dam LS, et al. Compassionate use of avacopan in difficult-to-treat antineutrophil cytoplasmic antibody-associated vasculitis. *Kidney Int Rep*. 2021 Dec 8;7(3):624-628. doi: 10.1016/j.ekir.2021.11.036. eCollection 2022 Mar.
54. Coles AJ, Cox A, Le Page E, et al. The window of therapeutic opportunity in multiple sclerosis: evidence from monoclonal antibody therapy. *J Neurol*. 2006 Jan;253(1):98-108. doi: 10.1007/s00415-005-0934-5. Epub 2005 Jul 27.
55. Gopaluni S, Smith R, Goymer D, et al. Alemtuzumab for refractory primary systemic vasculitis-a randomised controlled dose ranging clinical trial of efficacy and safety (ALEVIATE). *Arthritis Res Ther*. 2022 Apr 1; 24(1):81. doi: 10.1186/s13075-022-02761-6.
56. Ortiz-Fernandez L, Carmona EG, Kerick M, et al. Identification of new risk loci shared across systemic vasculitides points towards potential target genes for drug repurposing. *Ann Rheum Dis*. 2023 Jun;82(6):837-847. doi: 10.1136/ard-2022-223697. Epub 2023 Feb 16.
57. Mettler C, Durel CA, Guilpain P, et al. Off-label use of biologics for the treatment of refractory and/or relapsing granulomatosis with polyangiitis. *Eur J Intern Med*. 2022 Feb: 96:97-101. doi: 10.1016/j.ejim.2021.10.028. Epub 2021 Oct 27.
58. Langford CA, Monach PA, Specks U, et al. An open-label trial of abatacept (CTLA4-IG) in non-severe relapsing granulo-

matosis with polyangiitis (Wegener's). *Ann Rheum Dis.* 2014 Jul;73(7):1376-9. doi: 10.1136/annrheumdis-2013-204164. Epub 2013 Dec 9.
59. Kamesh L, Harper L, Savage CO. ANCA-positive vasculitis. *J Am Soc Nephrol.* 2002 Jul;13(7):1953-60. doi: 10.1097/01.asn.0000016442.33680.3e.
60. Bala MM, Malecka-Massalska TJ, Koperny M, et al. Anti-cytokine targeted therapies for ANCA-associated vasculitis. *Cochrane Database Syst Rev.* 2020 Sep 29; 9(9):CD008333. doi: 10.1002/14651858.CD008333.pub2.
61. Morgan MD, Drayson MT, Savage CO, Harper L. Addition of infliximab to standard therapy for ANCA-associated vasculitis. *Nephron Clin Pract.* 2011;117(2):c89-97. doi: 10.1159/000319655. Epub 2010 Aug 6.
62. Silva F, Seo P, Schroeder DR, et al. Solid malignancies among etanercept-treated patients with granulomatosis with polyangiitis (Wegener's): long-term followup of a multicenter longitudinal cohort. *Arthritis Rheum.* 2011 Aug;63(8):2495-503. doi: 10.1002/art.30394.
63. Booth A, Harper L, Hammad T, et al. Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. *J Am Soc Nephrol.* 2004 Mar;15(3):717-21. doi: 10.1097/01.asn.0000114554.67106.28.
64. Lamprecht P, Voswinkel J, Lilienthal T, et al. Effectiveness of TNF-alpha blockade with infliximab in refractory Wegener's granulomatosis. *Rheumatology (Oxford).* 2002 Nov; 41(11):1303-7. doi: 10.1093/rheumatology/41.11.1303.
65. Kleinert J, Lorenz M, Köstler W, et al. Refractory Wegener's granulomatosis responds to tumor necrosis factor blockade. *Wien Klin Wochenschr.* 2004 May 31;116(9-10):334-8. doi: 10.1007/BF03040906.
66. Laurino S, Chaudhry A, Booth A, et al. Prospective study of TNFalpha blockade with adalimumab in ANCA-associated systemic vasculitis with renal involvement. *Nephrol Dial Transplant.* 2010 Oct;25(10):3307–3314. doi:10.1093/ndt/gfq187. Epub 2010 Apr 5.
67. Chen M, Kallenberg CG. ANCA-associated vasculitides – advances in pathogenesis and treatment. *Nat Rev Rheumatol.* 2010 Nov; 6(11):653-64. doi: 10.1038/nrrheum.2010.158. Epub 2010 Oct 5.
68. Krajewska Wojciechowska J, Koscielska-Kasprzak K, Krajewski W, Morawski K. Serum levels of interleukin-32 and interleukin-6 in granulomatosis with polyangiitis and microscopic polyangiitis: association with clinical and biochemical findings. *Eur Cytokine Netw.* 2019 Dec 1;30(4):151-159. doi: 10.1684/ecn.2019.0439.
69. Antonio AA, Santos RN, Abariga SA. Tocilizumab for giant cell arteritis. *Cochrane Database Syst Rev.* 2022 May 13;5(5): CD013484. doi: 10.1002/14651858.CD013484.pub3.
70. Tang PF, Xu LC, Hong WT, Shi HY. Successful treatment of granulomatosis with polyangiitis using tocilizumab combined with glucocorticoids: a case report. *World J Clin Cases.* 2023 Feb 16;11(5):1144-1151. doi: 10.12998/wjcc.v11.i5.1144.
71. Berti A, Cavalli G, Campochiaro C, et al. Interleukin-6 in ANCA-associated vasculitis: rationale for successful treatment with tocilizumab. *Semin Arthritis Rheum.* 2015 Aug;45(1):48-54. doi: 10.1016/j.semarthrit.2015.02.002. Epub 2015 Feb 20.
72. Sakai R, Kondo T, Kikuchi J, et al. Corticosteroid-free treatment of tocilizumab monotherapy for microscopic polyangiitis: a single-arm, single-center, clinical trial. *Mod Rheumatol.* 2016 Nov;26(6):900-907. doi: 10.3109/14397595.2016.1160968. Epub 2016 Apr 21.
73. Vega Villanueva KL, Espinoza LR. Eosinophilic vasculitis. *Curr Rheumatol Rep.* 2020 Jan 11;22(1):5. doi: 10.1007/s11926-020-0881-2.
74. Emmi G, Bettiol A, Gelain E, et al. Evidence-Based Guideline for the diagnosis and management of eosinophilic granulomatosis with polyangiitis. *Nat Rev Rheumatol.* 2023 Jun;19(6):378-393. doi: 10.1038/s41584-023-00958-w. Epub 2023 May 9.
75. Yamane T, Hashiramoto A. Mepolizumab exerts crucial effects on glucocorticoid discontinuation in patients with eosinophilic granulomatosis with polyangiitis: a retrospective study of 27 cases at a single center in Japan. *Arthritis Res Ther.* 2023 Jun 26; 25(1):110. doi: 10.1186/s13075-023-03097-5.
76. Nolasco S, Portacci A, Campisi R, et al. Effectiveness and safety of anti-IL-5/R biologics in eosinophilic granulomatosis with polyangiitis: a two-year multicenter observational study. *Front Immunol.* 2023 Jun 30:14: 1204444. doi: 10.3389/fimmu.2023.1204444. eCollection 2023.
77. Wechsler ME, Nair P, Terrier B, et al. Benralizumab versus mepolizumab for eosinophilic granulomatosis with polyangiitis. *N Engl J Med.* 2024 Mar 7;390(10):911-921. doi: 10.1056/NEJMoa2311155. Epub 2024 Feb 23.
78. Cottu A, Groh M, Desaintjean C, et al. Benralizumab for eosinophilic granulomatosis with polyangiitis. *Ann Rheum Dis.* 2023 Dec; 82(12):1580-1586. doi: 10.1136/ard-2023-224624. Epub 2023 Aug 7.
79. Nanzer AM, Maynard-Paquette AC, Alam V, et al. Long-term effectiveness of benralizumab in eosinophilic granulomatosis with polyangiitis. *J Allergy Clin Immunol Pract.* 2024 Mar;12(3):724-732. doi: 10.1016/j.jaip.2024.01.006. Epub 2024 Jan 9.

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