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VASCULITIS (LR ESPINOZA, SECTION EDITOR)

Treatment of Severe and/or Refractory ANCA-Associated Vasculitis

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Abstract Most patients presenting with systemic necrotizing vasculitides improve when they are adequately treated. The presence of life-threatening manifestations or visceral involvement modifying organ function characterizes severe vasculitis, confirmed by disease-severity scores. Sequelae cannot always be predicted and prevented but organ involvement present at disease onset requires rapid therapeutic intervention. Some patients present a persistent active disease, which does not respond to treatments and deserve other drugs or combination of drugs. The therapeutic options for severe and/or relapsing and refractory diseases are described.

Keywords Vasculitis · Severe · Refractory · ANCA · Immunosuppressants · Rituximab · Plasma exchanges · Corticosteroids · Treatment

Introduction

In the 1970s, outcomes of vasculitides were poor and survival rate was low around 10 % without treatment and reached 50 % when patients received only corticosteroids [1]. Survival improved significantly when cyclophosphamide was combined with corticosteroids [2] and, for the first time, complete remissions were obtained in patients considered refractory to corticosteroids. Over the last 3 decades, survival has continued to improve, with fewer and less severe sequelae, mainly the consequence of optimization of treatment strategies. During the last few years, a new step towards better care of vasculitis patients has been evaluated, based on new drug families, named biotherapies. These new agents are promising but therapeutic strategies remain to be determined and assessed, especially for diseases considered refractory to conventional treatments.

This article reviews treatments of severe and/or refractory vasculitides—even though therapeutic strategies sometimes differ according to the precise context being addressed—focusing on antineutrophil cytoplasm antibody (ANCA)-associated vasculitides(AAV), comprising granulomatosis with polyangiitis (Wegener's) (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (EGPA).

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Definitions of Severe and/or Refractory Vasculitis

The presence of life-threatening manifestations or visceral involvement modifying organ function characterizes severe vasculitis, as shown in many reported series [3•, 4•, 5•] and confirmed by disease-severity scores [6••]. Sequelae cannot always be predicted and prevented but organ involvement present at disease onset requires rapid therapeutic intervention.

Vasculitis refractory to treatment is an evolving concept. In 1979, when Fauci et al. [2] demonstrated cyclophosphamide efficacy to control vasculitis, the disease was considered refractory to the "gold standard" of that time. Because of progressive improvement of therapeutic strategies, decade after decade, the number of vasculitides not responding to treatments decreased but did not completely disappear. In such cases, new therapeutic approaches, like newly available drugs or combinations of drugs, deserve evaluation. Refractory AAV is not synonymous with severity. GPA patients often have chronic manifestations, especially affecting the ear, nose

and throat (ENT) and/or upper respiratory tract. Their clinical manifestations are not always severe but should be considered, based on facial tissue necrosis, for instance, as progressively destructive, chronic and refractory to conventional drugs.

Corticosteroids and Cytotoxic Drugs

Patients are treated with prednisone or prednisolone at the initial dose of 1 mg/kg/day. For severe AAV, pulse methylprednisolone, 7.5–15 mg/kg/day, can be administered for 1–3 days. Consensus on the initial corticosteroid dose has been reached but not its duration or tapering schemes. The European Vasculitis (EUVAS) Group [7••] and the Vasculitis Clinical Research Consortium (VCRC) recommend tapering steroids quickly, by 25 % every week until the 7th week, when the prednisone dose could reach one-third of the initial dose. We also demonstrated that, for elderly patients, the prednisone and cyclophosphamide doses could be reduced by at least one-third, while maintaining the clinical response and limiting the number and severity of adverse events [8].

When AAV do not respond to treatment or are severe, we usually intensify corticosteroids to the dose able to control the disease and maintain that dose for 2–3 weeks, before again starting to taper the drug. We also showed that corticosteroids alone can be sufficient to control some forms of vasculitis without poor-prognosis factors [6••, 9, 10]. In contrast, for severe AAV or disease considered refractory to treatments, at least a combination of corticosteroids and cytotoxic agents was prescribed [11, 12]. Cytotoxic drugs are mandatory for severe AAV or those not responding to corticosteroids and some vasculitides like GPA. Cyclophosphamide is the standard cytotoxic agent. In Europe and some US centers, cyclophosphamide is administered intravenously (0.5–0.7 g/m^2, every 2–3 weeks) but Americans tend to prescribe oral cyclophosphamide, at 2 mg/kg/day. Both administration routes are effective, with the major advantage for intravenous (IV) treatment being a lower total cumulative dose and, thus, fewer side effects (infections, sterility and malignancies) [13]. Before the more widespread use of rituximab, we routinely started AAV treatment with IV cyclophosphamide and switched to oral treatment to obtain remission. Since rituximab became available, we no longer recommend switching to oral cyclophosphamide but rather giving rituximab as second-line therapy [14•].

Other cytotoxic drugs can be prescribed to control AAV refractory to combined corticosteroids and cyclophosphamide. These drugs, which are necessarily more powerful than cyclophosphamide or rituximab to induce remission, can be effective against chronic refractory AAV. In a prospective trial [15], mycophenolate mofetil non-inferiority could not be demonstrated at 6 months, compared to cyclophosphamide, as therapy for newly diagnosed AAV. It is therefore improbable that mycophenolate mofetil could be a drug sufficiently potent to induce remission of severe or refractory AAV. Methotrexate is a cytotoxic agent that could be a useful alternative when prescribed to treat some predominantly granulomatous, non-renal forms of GPA [16]. Indeed, in conjunction with corticosteroids, it induced remission as effectively as cyclophosphamide in a prospective study [16]. Despite a higher relapse rate in the methotrexate arm, this drug has shown some efficacy, making it a valid option for induction or maintenance therapy for patients with non-renal AAV [17].

Modulators of Immunity and Biotherapies

These treatments include agents that are not cytotoxic drugs, and their therapeutic effects are obtained through different specific mechanisms: neutralization or removal of autoantibodies, cytokines, cell-receptor blockade or others, which are not yet fully elucidated. Plasma exchanges, IV immunoglobulins (IVIg), anti-TNF–blocking agents, abatacept and anti-CD20 meet this definition.

Plasma Exchanges

Plasma exchanges have been proposed to treat vasculitis since the 1970s. The benefit for patients with rapidly progressive crescentic glomerulonephritis was shown in two small series [18, 19•]. The first controlled trials [20, 21], designed to treat all vasculitis forms, did not show any improved survival advantage. Similar results were obtained when plasma exchanges, added to corticosteroids and cyclophosphamide, were prescribed to treat severe vasculitis [21]. However, their efficacy was proven more recently when their use focused on patients with severe renal insufficiency (creatininemia >500 μmol/l). The results of a prospective, randomized trial [22] showed that adding plasma exchanges to oral cyclophosphamide and corticosteroids was superior to the arm comprising pulse methylprednisolone to reduce the severity of renal impairment. But that trial failed to show a survival benefit. The new ongoing PEXIVAS trial aims to evaluate plasma exchanges together with a lower steroid dose to treat AAV with creatininemia clearance <50 ml/min.

Anti-Tumor Necrosis Factor Biotherapies

A monoclonal antibody directed against TNFα (infliximab) or an analogue of its receptor (etanercept) has been used to treat systemic necrotizing vasculitides (SNV) [23, 24]. Infliximab, a humanized anti-TNFα monoclonal antibody, in combination with conventional therapy, achieved clinical remissions in 88 % of the patients with acute or persistently active AAV enrolled in an open, prospective trial [24]. In 2002, we reported our experience with infliximab to treat severe refractory

SNV, including 7 patients with GPA, all of whom entered complete or partial remission [23].

More recently, we reported on our long-term experience with 15 patients with refractory or relapsed SNV that confirmed infliximab efficacy in the short term but also revealed that its beneficial effect was temporary [25]. Etanercept, another TNF blocker, which is comprised of a soluble protein of the p75 TNF-receptor-derived epitope fused to the Fc portion of IgG, was prescribed to treat AAV, also in conjunction with conventional therapy, but with a different aim—to lower the relapse rate. Indeed, compared to placebo (the WGET trial) and in combination with induction therapy (cyclophosphamide or methotrexate for limited disease), etanercept did not prevent relapses [26]. Etanercept and perhaps other TNF blockers should probably not be considered for maintenance therapy, but rather as potential rescue therapies for some patients with refractory AAV.

The long-term effects of anti-TNF blockers on AAV have not been evaluated but, like other diseases for which it is prescribed, the infectious risk should be considered. Moreover, in the etanercept trial, six cancers were diagnosed, all in the experimental arm, and three additional cancers were diagnosed later, two of them in the placebo group [26]. We compared infliximab versus rituximab in addition to conventional cytotoxic drugs and corticosteroids to control severe or refractory AAV [27]. That study's results showed some responders in each arm, and rituximab superiority to infliximab to induce remission and control the disease over the long term. It now seems clear that anti-TNFα–blocking agents are not sufficiently effective to maintain remission and that their ability to induce remission is very limited. However, for selected patients whose vasculitides do not respond to conventional treatments, infliximab (more than etanercept, which is not active against granuloma) could be prescribed in combination with other therapeutics.

IVIg

IVIg are powerful drugs already used for decades to treat vasculitis, especially Kawasaki disease [28]. ANCA neutralization is one of their mechanisms of action against AAV. Other complex mechanisms have been identified, more cellular than humoral, which justify IVIg use. They have been prescribed in conjunction with other treatments [29] and are ineffective when prescribed alone [30], but can be indicated in combination with a conventional regimen for severe or refractory AAV [31, 32]. IVIg cannot be prescribed to all patients with severe disease, since they are contraindicated for those with renal insufficiency (creatininemia <30 ml/min). For refractory AAV, IVIg can be indicated as adjunctive therapy for patients already taking corticosteroids and cytotoxic or other immunomodulating drug(s). In a prospective open study, we showed their effectiveness against AAV that did not respond to conventional therapy and relapsed despite a regimen considered optimal [33]. IVIg certainly have a place in the therapeutic strategies for patients with severe and refractory AAV. They should not be prescribed alone but can be associated with other treatments.

Abatacept

Abatacept blocks CD28 binding to its ligand, thereby inhibiting T-cell activation. Based on the pathophysiological mechanisms implicated in AAV, this biotherapy could be effective against them. At present, abatacept has only been evaluated on a small series of patients with non-severe relapsing AAV [34]. We are not aware of any experience with its use to treat severe or refractory AAV.

Anti-CD20

Rituximab, a chimeric murine–human monoclonal IgG1 antibody directed against CD20 expressed on B lymphocytes, has been prescribed to treat AAV. Rituximab has been given to increasing numbers of patients, especially after the publication of the two randomized–controlled trials showing that it was as effective as cyclophosphamide at inducing AAV remission [35, 36•••]. The results of both trials demonstrated that rituximab was not inferior to cyclophosphamide to induce remission. Moreover, they demonstrated that rituximab was superior to cyclophosphamide when given to treat relapses. Rituximab is now approved as first-line treatment, in the USA and Europe. Before publication of those findings, rituximab was mainly prescribed as a second- or third-line therapy.

Our experience in France [37, 38] showed rituximab effectiveness as second-line treatment. Ninety-eight of our patients were previously treated with corticosteroids and cytotoxic drugs to induce remission, and then received rituximab for a flare. An 85 % response rate was obtained but, when patients had granulomatous manifestations, the response rate was different: none of the 5 patients with orbital masses achieved complete remissions, but 77 % of patients with pulmonary nodules and 55.2 % with ENT involvement and upper airway stenoses obtained complete remission.

Those outcomes highlight that there is no standard treatment for refractory vasculitis and that the clinician should choose the most appropriate regimen based on previous treatments and organ involvement. Based on several findings, it also seems that clinical responses to rituximab vary according to the organ and types of lesions involved: very good against active vasculitis (e.g., glomerulonephritis and alveolar hemorrhage) and less efficacy against granulomatous forms (e.g., orbital tumor) [39] and, intriguingly, generally good responses against lung nodules, despite the fact that they are granulomatous.

What is the Optimal Strategy?

In Patients with Severe AAV

The therapeutic strategy is to obtain remission quickly, to prevent organ-function deterioration and disease progression. For this purpose, a combination of rapidly acting medications is needed. They will be relayed by others effective over the long term. Pulse methylprednisolone initially, IVIg and plasma exchanges satisfy this definition. They are particularly well adapted to treating acute renal insufficiency and alveolar hemorrhage. The optimal treatment of mononeuritis multiplex has not yet been defined. Although that symptom is not life-threatening [6], it is associated with a high relapse rate [40, 41], which could require combined corticosteroids and cytotoxic agents.

Pertinently, AAV is not the only factor to be taken into account; each patient's comorbidities, preexisting diseases and general condition should also be considered, as they can compromise the overall outcome.

In Patients with Refractory AAV

By definition, patients have already received corticosteroids and one or several cytotoxic drugs at their optimal doses. However, the optimal dose is partly arbitrary and has been established based on a compromise between efficacy and potential side effects. Tables 1 and 2 list the doses used to induce remission in several prospective trials, clearly demonstrating that "optimal" is in fact "relative". When AAV do not respond to corticosteroids and cyclophosphamide (IV or oral), we now recommend rituximab [14•]. This therapeutic option has the major advantage of being active by targeting other immune mechanisms. It has also been shown to be effective more frequently than readministration of a cytotoxic agent previously used to treat a flare. Although what has been found to treat relapses is not necessarily applicable to refractory AAV, it seems reasonable to follow the same therapeutic scheme and prescribe an agent that targets other pathogenic mechanisms, rather than those given initially and unsuccessfully.

For patients whose disease does not respond to rituximab, other strategies are needed. When patients' first flares are unsuccessfully treated with corticosteroids and cytotoxic drugs, followed by rituximab, it is recommended that agents be combined: corticosteroids, cytotoxic drugs, IVIg, for example. An immunosuppressant different than that used for the first flare should be chosen to be used alone or in combination. Plasma exchanges are rarely useful in this setting. A polychemotherapy approach, as commonly administered to patients with malignant diseases, should be evaluated.

Table 1 Steroid doses used in some prospective therapeutic trials on necrotizing vasculitides

Week	EUVAS mg/kg [44, 45]	WEGENT mg/kg [17]	CORTAGE mg/day [8]
0	1	1	60
1	0.75	1	60
2	0.5	1	60
4	0.4	0.75	50
6	0.33	0.5	40
8	0.28	0.4	30
10	0.25	0.33	27.5
12	0.25	0.33	22.5

Table 2 Cyclophosphamide doses used in some prospective therapeutic trials on necrotizing vasculitides

WEEK	EUVAS mg/kg [44, 45]	WEGENT mg/session [17]	CORTAGE mg/session [8]
0	2	0.6 g/m^2	500
1	2		
2	2	0.6 g/m^2	500
4	2	0.6 g/m^2	500
6	2	0.7 g/m^2 (at wk 7)	500 (at wk 7)
8	2		
10	2	0.7 g/m^2	500
12	1.5	0.7 g/m^2 (at wk 13)	500 (at wk 13)

Is it Possible to Prevent Flares and/or Refractory AAV?

Undoubtedly, AAV outcomes have improved and, in recent years, fewer patients have died from these diseases, thereby demonstrating the efficacy of therapeutic strategies devised for severe vasculitis. However, it is more difficult to prevent relapses and lower the number of patients with grumbling disease that is refractory to several treatment lines. Because 40–50 % of AAV patients relapse 4–5 years post-remission, several therapeutic options can be proposed to contain this relapse rate. We showed that rituximab was able to do so up to 28 months [42], but that finding does not preclude what will happen in the long term. Another option could be to maintain patients indefinitely on a cytotoxic drug, like azathioprine [43]. In fact, long-term AAV treatment has not yet been evaluated in prospective trials and is certainly a task for the future.

Conclusion

If most vasculitides can be successfully treated, some patients have a poor outcome due to life-threatening manifestations and/or relapses which are responsible for sequelaes and a poor outcome. New drugs and therapeutic strategies are able, in most cases, to control these severe vasculitis and to reduce mortality, morbidity and sequelaes.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Leib ES, Restivo C, Paulus HE. Immunosuppressive and corticosteroid therapy of polyarteritis nodosa. Am J Med. 1979;67(6):941–7.
2. Fauci AS, Katz P, Haynes BF, Wolff SM. Cyclophosphamide therapy of severe systemic necrotizing vasculitis. N Engl J Med. 1979;301(5):235–8.
3.• Comarmond C, Pagnoux C, Khellaf M, Cordier JF, Hamidou M, Viallard JF, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. Arthritis Rheum. 2013;65(1):270–81. *The largest series of patients affected with eosinophilic granulomatosis with polyangiitis, describing clinical characteristics, management and outcome.*
4.• Holle JU, Gross WL, Latza U, Nolle B, Ambrosch P, Heller M, et al. Improved outcome in 445 patients with Wegener's granulomatosis in a German vasculitis center over four decades. Arthritis Rheum. 2011;63(1):257–66. *This large series of patients with granulomatosis with polyangiitis describes clinical manifestations and outcomes. This paper describes disease evolution over several decades.*
5.• Pagnoux C, Seror R, Henegar C, Mahr A, Cohen P, Le Guern V, et al. Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. Arthritis Rheum. 2010;62(2): 616–26. *The largest series of patients with polyarteritis nodosa describing HBV-positive as well as HBV-negative patients, their clinical characteristics and outcomes.*
6.•• Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine (Baltimore). 2011;90(1):19–27. *This score, when measured at disease onset, predicts prognosis, independently of treatments. It is the first score to predict prognosis of some vasculitides.*
7.•• Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009;68(3): 310–7. *These recommendations are a tool for clinicians in charge of patients affected with systemic vasculiites.*
8. Pagnoux C, Quéméneur T, Ninet J, Perrodeau E, Diot E, Kyndt X, et al. Treatment of systemic necrotizing vasculitides in patients ≥65 years old: results of the multicenter randomized CORTAGE trial (Abstract). Presse Med. 2013;42:679–80.
9. Ribi C, Cohen P, Pagnoux C, Mahr A, Arene JP, Puechal X, et al. Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: A prospective randomized study of one hundred twenty-four patients. Arthritis Rheum. 2010;62(4): 1186–97.
10. Ribi C, Cohen P, Pagnoux C, Mahr A, Arene JP, Lauque D, et al. Treatment of Churg-Strauss syndrome without poor-prognosis factors: a multicenter, prospective, randomized, open-label study of seventy-two patients. Arthritis Rheum. 2008;58(2):586–94.
11. Cohen P, Pagnoux C, Mahr A, Arene JP, Mouthon L, Le Guern V, et al. Churg-Strauss syndrome with poor-prognosis factors: A prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. Arthritis Rheum. 2007;57(4):686–93.
12. Guillevin L, Cohen P, Mahr A, Arene JP, Mouthon L, Puechal X, et al. Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients. Arthritis Rheum. 2003;49(1):93–100.
13. Le Guenno G, Mahr A, Pagnoux C, Dhote R, Guillevin L. Incidence and predictors of urotoxic adverse events in cyclophosphamide-treated patients with systemic necrotizing vasculitides. Arthritis Rheum. 2011;63(5):1435–45.
14.• Charles P, Bienvenu B, Bonnotte B, Gobert P, Godmer P, Hachulla E, et al. Rituximab: Recommendations of the French Vasculitis Study Group (FVSG) for induction and maintenance treatments of adult, antineutrophil cytoplasm antibodyassociated necrotizing vasculitides. Presse Med. 2013;42:1317–30. *The most recent recommendations to help clinicians to prescribe rituximab in ANCA-associated vasculitis, established by the members of the French Vasculitis Study Group.*
15. Jones R, Harper L, Ballarin J, Blockmans D, Brogan K, Bruchfeld A, et al. A randomized trial of mycophenolate mofetil versus cyclophosphamide for remission induction of ANCA-associated vasculitis: "MYCIC". On behalf of the European Vasculitis Study Group. Presse Med. 2013;42:678. *A65.*
16. De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2005;52(8):2461–9.
17. Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med. 2008;359(26):2790–803.
18. Rifle G, Dechelette E. Treatment of rapidly progressive glomerulonephritis by plasma exchange and methylprednisolone pulses. A prospective randomized trial of cyclophosphamide. Interim analysis. The French Cooperative Group. Prog Clin Biol Res. 1980;337: 263–7.
19.• Pusey CD, Rees AJ, Evans DJ, Peters DK, Lockwood CM. Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. Kidney Int. 1991;40(4):757–63. *This study describes, for the first time, the short-term efficacy of plasma exchanges in patients with severe renal insufficiency and their superiority to pulse methylprednisolone.*
20. Guillevin L, Fain O, Lhote F, Jarrousse B, Le Thi HD, Bussel A, et al. Lack of superiority of steroids plus plasma exchange to steroids alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome. A prospective, randomized trial in 78 patients. Arthritis Rheum. 1992;35(2):208–15.
21. Guillevin L, Lhote F, Cohen P, Jarrousse B, Lortholary O, Genereau T, et al. Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss

syndrome patients with factors predicting poor prognosis. A prospective, randomized trial in sixty-two patients. Arthritis Rheum. 1995;38(11):1638–45.
22. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol. 2007;18(7):2180–8.
23. Bartolucci P, Ramanoelina J, Cohen P, Mahr A, Godmer P, Le Hello C, et al. Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. Rheumatology (Oxford). 2002;41(10):1126–32.
24. Booth A, Harper L, Hammad T, Bacon P, Griffith M, Levy J, et al. Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. J Am Soc Nephrol. 2004;15(3):717–21.
25. Josselin L, Mahr A, Cohen P, Pagnoux C, Guaydier-Souquieres G, Hayem G, et al. Infliximab efficacy and safety against refractory systemic necrotising vasculitides: long-term follow-up of 15 patients. Ann Rheum Dis. 2008;67(9):1343–6.
26. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med. 2005;352(4):351-61.
27. de Menthon M, Cohen P, Pagnoux C, Buchler M, Sibilia J, Detree F, et al. Infliximab or rituximab for refractory Wegener's granulomatosis: long-term follow up. A prospective randomised multicentre study on 17 patients. Clin Exp Rheumatol. 2011;29(1 Suppl 64):S63–71.
28. Newburger JW, Takahashi M, Beiser AS, Burns JC, Bastian J, Chung KJ, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N Engl J Med. 1991;324(23):1633–9.
29. Jayne DR, Davies MJ, Fox CJ, Black CM, Lockwood CM. Treatment of systemic vasculitis with pooled intravenous immunoglobulin. Lancet. 1991;337(8750):1137–9.
30. Jayne DR, Lockwood CM. Intravenous immunoglobulin as sole therapy for systemic vasculitis. Br J Rheumatol. 1996;35(11):1150–3.
31. Richter C, Schnabel A, Csernok E, Reinhold-Keller E, Gross WL. Treatment of Wegener's granulomatosis with intravenous immunoglobulin. Adv Exp Med Biol. 1993;336:487–9.
32. Ito-Ihara T, Ono T, Nogaki F, Suyama K, Tanaka M, Yonemoto S, et al. Clinical efficacy of intravenous immunoglobulin for patients with MPO-ANCA-associated rapidly progressive glomerulonephritis. Nephron Clin Pract. 2006;102(1):c35–42.
33. Martinez V, Cohen P, Pagnoux C, Vinzio S, Mahr A, Mouthon L, et al. Intravenous immunoglobulins for relapses of systemic vasculitides associated with antineutrophil cytoplasmic autoantibodies: results of a multicenter, prospective, open-label study of twenty-two patients. Arthritis Rheum. 2008;58(1):308–17.
34. Langford CA, Monach PA, Specks U, Seo P, Cuthbertson D, McAlear CA, et al. An open-label trial of abatacept (CTLA4-IG) in non-severe relapsing granulomatosis with polyangiitis (Wegener's). Ann Rheum Dis. Online First: December 9, 2013 doi:10.1136/annrheumdis-2013-204164.
35. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010;363(3):211–20.
36.••Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363(3):221–32. *The first well-designed prospective trial demonstrating than rituximab is not inferior to cyclophosphamide to induce a remission of ANCA-associated vasculitis*.
37. Charles P, Néel A, Tieulié N, Hot A, Pugnet G, Decaux O, et al. Rituximab for Induction and Maintenance Treatment of ANCA-Associated Vasculitides. A Multicenter Retrospective Study on 80 Patients. Rheumatology (Oxford). 2014;53:532–9.
38. Charles P, Guillevin L. Rituximab for ANCA-associated vasculitides: the French experience. Presse Med. 2013;42(4 Pt 2):534–6.
39. Holle JU, Dubrau C, Herlyn K, Heller M, Ambrosch P, Noelle B, et al. Rituximab for refractory granulomatosis with polyangiitis (Wegener's granulomatosis): comparison of efficacy in granulomatous versus vasculitic manifestations. Ann Rheum Dis. 2012;71(3):327–33.
40. Samson M, Puéchal X, Devilliers H, Ribi C, Cohen P, Bienvenu B, et al. Long-term follow-up of a randomized trial on 118 patients with polyarteritis nodosa or microscopic polyangiitis without…,. Autoimmun Rev. 2013:on line first: doi. 10.1016/j.autrev.2013.10.001
41. Samson M, Puechal X, Devilliers H, Ribi C, Cohen P, Stern M, et al. Long-term outcomes of 118 patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) enrolled in two prospective trials. J Autoimmun. 2013;43:60–9.
42. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al. Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis. Presse Med Q Med Rev. 2013;42:679. *Abstract*.
43. Hoffman GS. Vasculitis treatment: is it time to change the standard of care for ANCA-associated vasculitis? Presse Med. 2013;42(4 Pt 2):643–50.
44. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med. 2003;349(1):36–44.
45. de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med. 2009;150(10):670–80.