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RECENT ADVANCES AND TREATMENT OPTIONS IN ANCA ASSOCIATED VASCULITIS

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ABSTRACT

This article reports on innovations in the field of current approaches to the therapy of ANCA-associated vasculitis (AAV). Randomized clinical trials and prospective open label trial of newer therapies performed in the last 15 years in Wegener's granulomatosis and microscopic polyangiitis or both (AAV) were reviewed. Although cyclophosphamide remains the favoured immunosuppressive for remission induction, the use of alternative immunosuppressives and of intravenous pulsed administration have reduced cyclophosphamide exposure and are likely to increase the safety of treatment. Mycophenolate mofetil, leflunomide and deoxyspergualin are newer immunosuppressive drugs which have been evaluated in AAV, while tumor necrosis factor, alemtuumab and rituximab are 'biologic' agents that have received attention. There is insufficient study of the dosing of glucocorticoids. Plasma exchange is indicated for severe renal vasculitis. These have led to consensus recommendations on how AAV should be treated. Many newer agents are currently under evaluation which have the potential to improve AAV outcomes in the future.

INTRODUCTION

The antineutrophil cytoplasmic antibodies (ANCA)-associated small vessel vasculitides include Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis (MPA), and the renal limited form of MPA, also known as pauci-immune or idiopathic crescentic glomerulonephritis. Classical induction and maintenance therapy of these conditions with corticosteroids and long-term cyclophosphamide is associated with occasional relapse and major toxicities. Therefore, treatment regimens being investigated especially for patients with more aggressive disease accompanied by renal insufficiency, therapies that include either pulses of methylprednisolone, rituximab and plasma exchanges.

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Evolution of advances in therapy[i] :

- About four decades ago, AAV was invariably fatal
- Introduction of cyclophosphamide changed the outcome of severe GPA and MPA.
- Remission could be successfully induced with the combination of glucocorticoids and cyclophosphamide, and the syndromes became manageable chronic conditions.
- Unfortunately, the relapsing nature of GPA and MPA often requires repeated and prolonged exposure to cyclophosphamide, thus causing significant toxicity leading on to infertility & hematological malignancies
- Moreover, some patients could not achieve stable remission with maximal tolerated cyclophosphamide doses.
- For these reasons, better tolerated alternatives were desperately needed.
- Studies showed that methotrexate could replace

cyclophosphamide in patients with limited or nonsevere disease GPA and mycophenolate mofetil might be the alternative for patients with MPA and mild renal disease.

- Biologic response modifiers allowing mechanism-based treatment approaches have become available over the last decade[ii].
- The ability to specifically target B lymphocytes with rituximab, a chimeric monoclonal antibody against the B lymphocyte specific cell surface receptor CD20, has fundamentally changed the therapy of severe AAV.
- The Rituximab Versus Cyclophosphamide for ANCA-Associated Vasculitis (RAVE) trial showed that rituximab was superior to cyclophosphamide for remission induction in severe GPA and MPA.
- FDA approved rituximab in combination with glucocorticoids for remission induction in newly diagnosed and relapsing severe GPA and MPA.
- In 2013, most patients with GPA and MPA can be managed without exposure to cyclophosphamide and its dreaded long-term toxicities.
- For EGPA, Glucocorticoids have long been the mainstay of treatment but Side effects of glucocorticoids represent the biggest challenge in the long-term management of this disease[iii].
- A role for biologic response modifiers is also emerging for EGPA. Mepolizumab, a monoclonal antibody targeting IL-5, has shown promise in EGPA.

Recent advances in pathogenesis[iv] :

Significant progress has been made over the last two decades in understanding the pathogenesis of AAV. Research conducted at Mayo Clinic and elsewhere has paved the way for novel and individually targeted therapeutic approaches. Clinical and experimental evidence supports the concept that a genetic predisposition for autoimmunity, epigenetic factors and environmental triggers are necessary for the loss of tolerance and development of an inflammatory milieu that supports the production of ANCAs. In the context of an inflammatory milieu, ANCAs can cause specific tissue inflammation and vascular injury by a variety of different mechanisms that involve direct interactions with the respective ANCAs' target antigens PR3 or MPO.

A genome-wide association study found major histocompatibility complex (MHC) and non-MHC associations with AAV and genetic distinctions between GPA and MPO, and even more clearly between PR3- and MPO-ANCA-associated diseases, providing support for the concept that they are genetically distinct autoimmune disorders. The documented higher relapse rate of patients with PR3-ANCAs compared with MPO-ANCAs may have a genetic basis[v].

A large body of experimental work supports that B lymphocytes are essential for the development of ANCAs and disease activity, whereas T lymphocyte abnormalities seem to persist, particularly in patients with GPA, even during remission. The presence of ANCAs alone does not inevitably cause disease, but ANCAs seem necessary for the development of disease manifestations caused by capillaritis, such as alveolar hemorrhage, glomerulonephritis, scleritis or mononeuritis multiplex.

For all of these reasons, interventions aimed at B lymphocytes, T lymphocytes and ANCA have made inroads into the therapeutic arsenal for AAV[vi].

Recent advances in therapy[vii]:

About four decades ago, the introduction of cyclophosphamide (Cytoxan) changed the invariably fatal outcome of severe GPA and MPA. Remission could be successfully induced with the combination of glucocorticoids and cyclophosphamide, and the syndromes became manageable chronic conditions. Unfortunately, the relapsing nature of GPA and MPA often requires repeated and sometimes prolonged exposure to cyclophosphamide, causing significant cumulative toxicity. Infertility in both women and men is induced after only a few months of exposure, and solid as well as hematologic malignancies are dreaded late complications of cyclophosphamide exposure. Moreover, some patients could not achieve stable remission with maximal tolerated cyclophosphamide doses[viii].

For these reasons, better tolerated alternatives were desperately needed. Randomized controlled trials and prospective observational cohort studies first showed that methotrexate could replace cyclophosphamide in patients with limited or nonsevere disease GPA. For patients with MPA and mild renal disease, mycophenolate mofetil (CellCept) might be the alternative.

Biologic response modifiers allowing mechanism-based treatment approaches have become available over the last decade. Targeting specific molecules, these agents can block immune pathways thought to cause maladaptive inflammation in autoimmune diseases by inhibiting pro-inflammatory cytokines, eliminating cells of defined lineage (B lymphocytes) or inhibiting their activation or recruitment (T lymphocytes, eosinophils) [ix].

The ability to specifically target B lymphocytes with rituximab (Rituxan), a chimeric monoclonal antibody against the B lymphocyte specific cell surface receptor CD20, has fundamentally changed the therapy of severe AAV. Following the first report of its use in AAV in 2001, experience with rituximab in AAV has rapidly expanded. The Rituximab Versus Cyclophosphamide for ANCA-Associated Vasculitis (RAVE) trial showed that rituximab was not inferior to cyclophosphamide for remission induction in severe GPA and MPA. In fact, for patients with relapsing disease, rituximab was found to be superior to cyclophosphamide. Based on the primary endpoint results of RAVE, the Food and Drug Administration (FDA) approved rituximab in combination with glucocorticoids for remission induction in newly diagnosed

and relapsing severe GPA and MPA[x].

18-month follow-up study of RAVE, led by researchers at Mayo Clinic, showed that a single course of four once-weekly infusions of rituximab is as effective for remission induction and maintenance as 18 months of continuous immunosuppressant therapy with cyclophosphamide followed by azathioprine (Imuran). Long-term single-center cohort studies indicated that rituximab is also effective and safe for remission maintenance, particularly in chronically relapsing GPA. In 2013, most patients with GPA and MPA can be managed without exposure to cyclophosphamide and its dreaded long-term toxicities[xi].

A role for biologic response modifiers is also emerging for EGPA. Glucocorticoids have long been the mainstay of treatment, and cyclophosphamide is used for disease activity that threatens the function of vital organs. Side effects of glucocorticoids represent the biggest challenge in the long-term management of this disease. The exact mechanisms of tissue injury in EGPA remain unclear, but blood and tissue eosinophilia appear to be responsible for tissue damage.

Interleukin-5 (IL-5) mediates bone marrow release, tissue survival, maturation and activation of eosinophils. Furthermore, IL-5 levels are increased in patients with EGPA and are associated with disease activity. Consequently, reducing the number of eosinophils and preventing their activation by inhibiting IL-5 appears to be a rational novel approach for EGPA. Mepolizumab, a monoclonal antibody targeting IL-5, has shown promise in EGPA. Small pilot trials demonstrated prompt and prolonged reduction of peripheral eosinophils, clinical improvement and reduction in glucocorticoid use. A large multicenter randomized controlled trial of this agent in EGPA is underway. Small case series and a pilot trial suggest that rituximab may represent an alternative to cyclophosphamide in severe EGPA, particularly if it's MPO-ANCA-associated[xii].

Ongoing and imminent clinical trials[xiii] :

Plasma exchange has been advocated for use in patients with severe alveolar hemorrhage leading to respiratory failure and for severe renal disease. The rationale for this approach is that the rapid removal of pathogenic ANCAs might be beneficial in rapidly progressive disease. The data supporting this practice, however, are inconclusive. The FDA and multiple international agencies have joined forces to cooperatively fund an ongoing global randomized trial (PEXIVAS) to evaluate the efficacy and safety of plasma-exchange for patients with ANCA-associated renal disease or diffuse alveolar hemorrhage or both.

The biggest remaining challenge in the management of these relapsing conditions is the long-term maintenance of remission with minimum cumulative drug toxicities. The relapse risk is not the same for all patients. For these reasons, the focus of phase III randomized controlled trials has shifted from remission induction trials to remission maintenance trials[xiv].

While rituximab may be effective for remission maintenance in GPA and MPA, the best dosing and timing of re-treatment as well as efficacy and safety of long-term B lymphocyte depletion compared with traditional agents remains to be clarified by larger randomized controlled trials. Currently, an international, open-label, randomized trial comparing rituximab versus azathioprine for maintenance of remission following induction with rituximab in relapsing GPA and MPA patients (RITAZAREM) is open for enrollment[xv].

Other biologic agents may also be of interest for remission maintenance. Belimumab (Benlysta) is a human IgGΛ monoclonal antibody that neutralizes soluble B cell activating factor (BAFF), also called B lymphocyte stimulator (BLyS). BAFF is essential for B lymphocyte development and survival as well as immunoglobulin production. Targeting BAFF with belimumab is effective and safe in systemic lupus erythematosus. As B lymphocytes appear crucial for AAV disease activity, the Belimumab in Remission of Vasculitis (BREVAS) trial is designed to evaluate the efficacy and safety of belimumab in combination with azathioprine for remission maintenance in GPA or MPA following standard remission induction.

Abatacept (CTLA-4-IgG1) is a recombinant fusion protein consisting of the ligand binding portion of CTLA-4 and a modified Fc portion of human IgG1 that acts therapeutically by blocking T lymphocyte costimulation. This agent is approved for the use in rheumatoid arthritis, and a pilot trial with abatacept in nonsevere GPA has yielded promising results. A phase III study of abatacept (ABROGATE) will clarify the potential role of this agent in the treatment of relapsing, nonsevere GPA[xvi].

Treatment[xvii] :

All patients with AAV should be considered to have severe, potentially life- or organ-threatening disease. Treatment regimens are divided into induction, maintenance and long-term follow-up. Patients who relapse may require a further course of induction therapy (secondary).

[xviii]The essential principles of management are :

(i) Rapid diagnosis
(ii) Rapid initiation of treatment
(iii) Early induction of remission to prevent organ damage
(iv) Maintenance of remission with the aim of eventual drug withdrawal
(v) Prevention of drug toxicity

Primary induction of remission:

All patients with newly diagnosed AAV should be assessed for treatment with glucocorticoids (GCs) and i.v. pulse cyclophosphamide (CYC) or rituximab (RTX).

Cyclophosphamide

CYC should be given by i.v. pulses initially at 2-week intervals and then at 3-week intervals following the CYCLOPS trial regimen . The standard dose is 15 mg/kg, reduced for age and renal function. Because of the lower toxicity, the i.v. regimen is preferred .Lifetime exposure to CYC should be 425 g since the long-term toxicity of CYC is determined by cumulative dose . Patients on CYC should be monitored regularly and the dose should be reduced if there is CYC-induced leucopenia/ neutropenia . Patients intolerant to CYC can be effectively treated with RTX [xix].

Rituximab

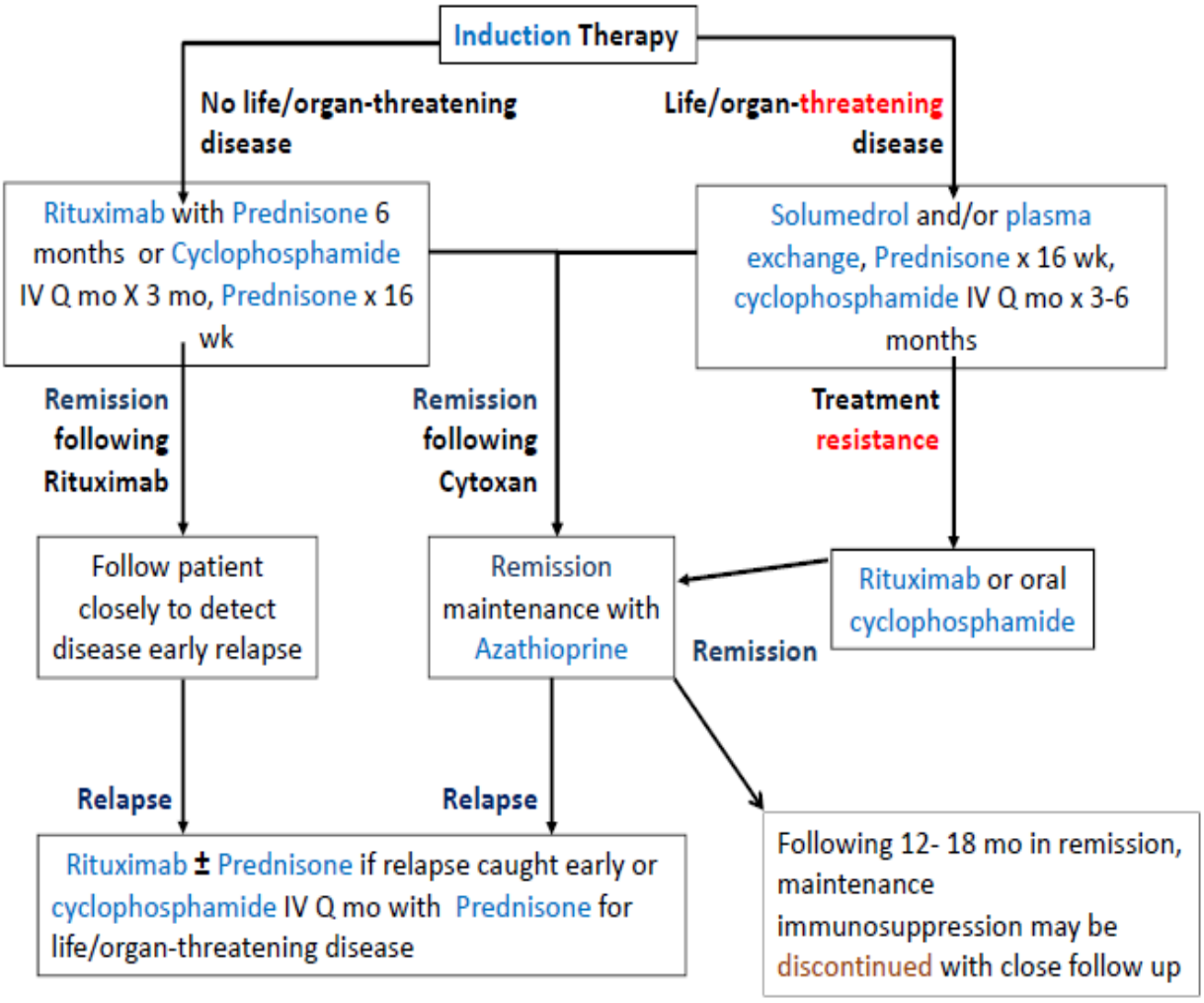
RTX is as effective as CYC for remission induction of previously untreated patients and is preferable when CYC avoidance is desirable, such as in young people at risk of infertility and those at high risk of infection . The licensed RTX dosing protocol is 375 mg/m2/week for 4 weeks , however, 1 g repeated after 2 weeks is equally effective[xx] .

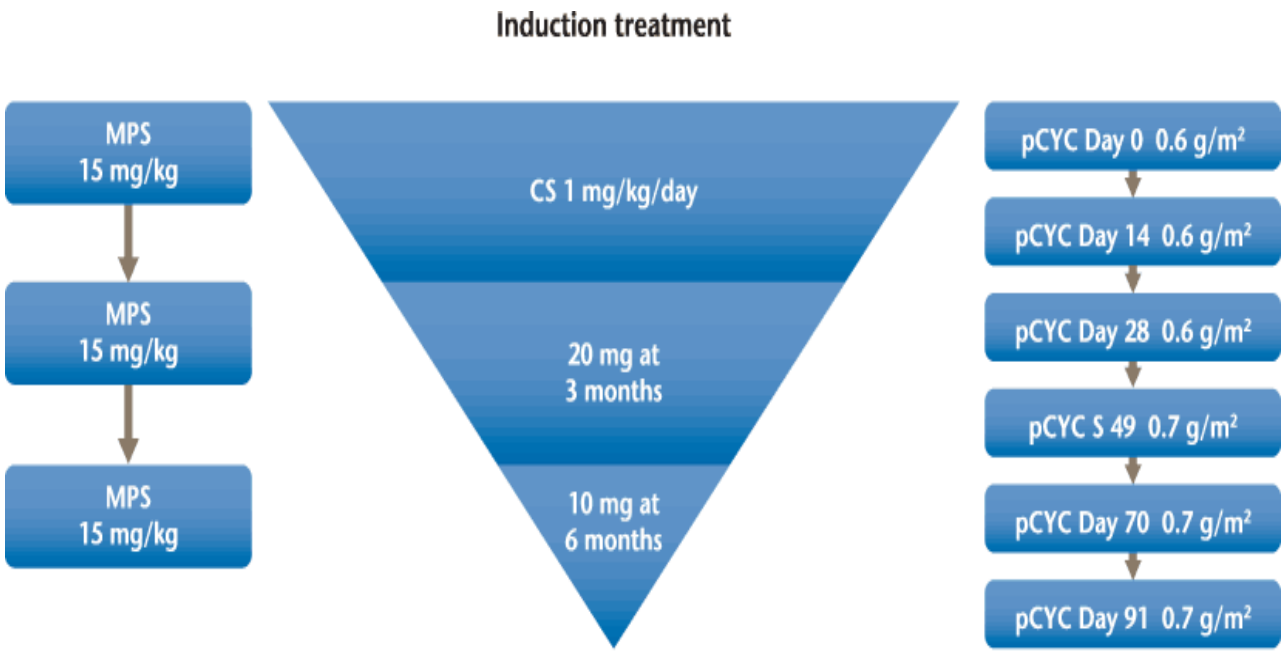
MTX and MMF

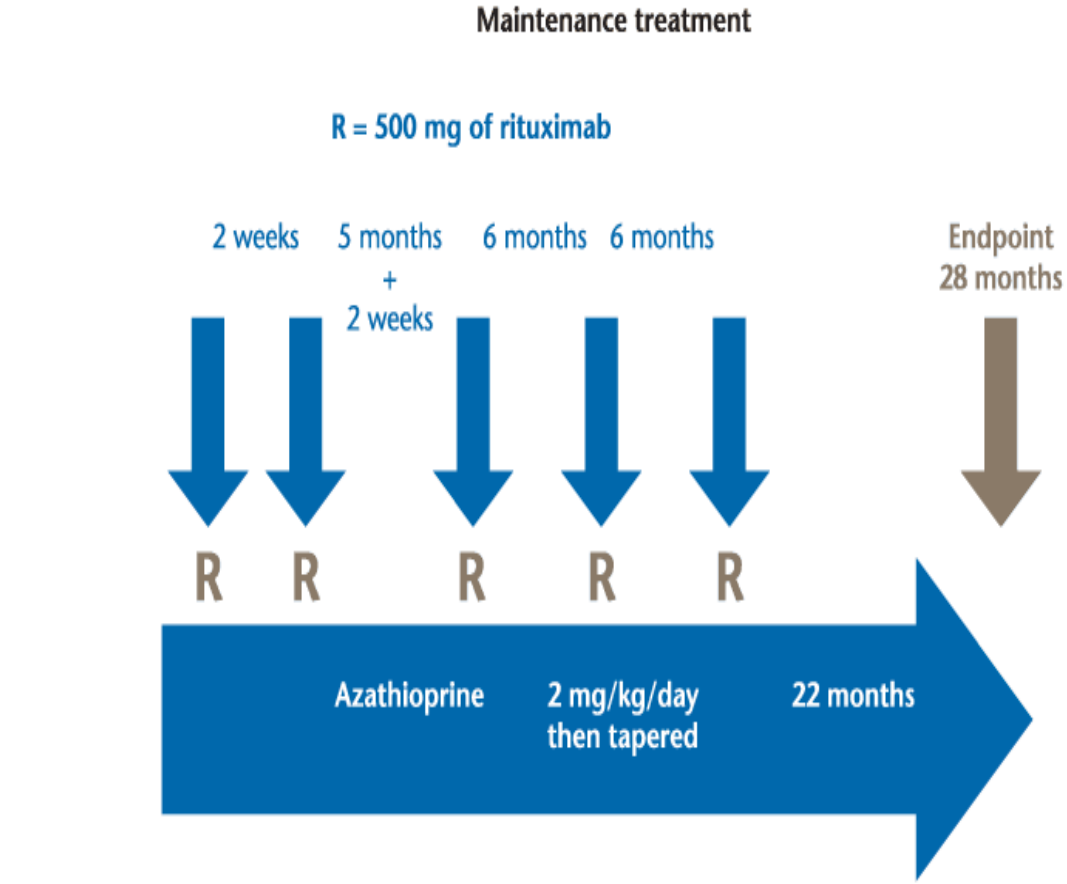
MTX (up to 25_30 mg/week) and MMF (up to 3 g/day) are alternative remission induction agents for patients with evidence of low disease activity and not at risk of suffering organ damage as assessed by the BVAS . MTX should not be used in patients with moderate or severe renal impairment . MMF may be an alternative to MTX [xxi].

Plasma exchange

Patients with AAV presenting with severe renal failure (creatinine >500 mmol/l) should be treated with pulsed CYC and GCs, with adjuvant plasma exchange in a centre experienced in its use . Treatment with plasma exchange should also be considered in those with other life-threatening manifestations of disease, such as pulmonary haemorrhage [xxii].

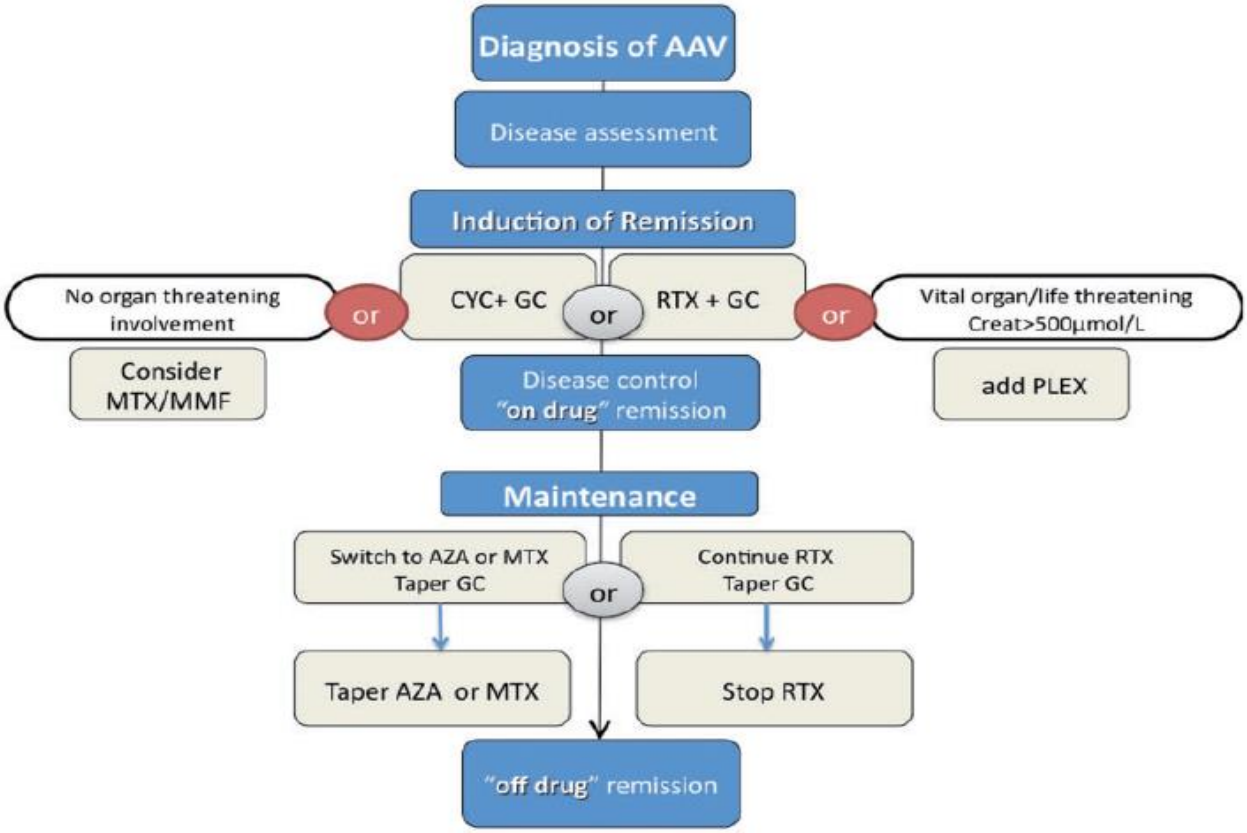






CS = corticosteroids; MPS = methylprednisolone; R = rituximab; pCYC = pulse cyclophosphamide

Recent guidelines based on British Society of Rheumatology, April 2014 :



Future scopes in therapy :

Principle	Mechanism	Agent	Evidence
Depletion of effector T cells	Antibodies directed against CD25 deplete activated T cells	Basiliximab Daclizumab	Experimental + clinical evidence (RA+Tx) Ongoing RCT in AAV
Regulation of effector T cells	Blockade of CD28/CD80 dependent T cell activation	Abatacept, Belatacept (both CTLA-4 fusion proteins)	Experimental + clinical evidence (RA+Tx) Ongoing trial in AAV
Block adhesion of neutrophils	Blockade of CD11b/ICAM-1 mediated adhesion to endothelium		Experimental evidence
Limit activation/ recruitment of neutrophils	Inhibition of C5 cleavage. Blockade of C5a receptor on neutrophils	Eculizumab, Pexelizumab (both anti-C5)	Experimental evidence
Enhance vascular repair	Promote EPC mobilization and function	EPO Statins	Experimental + clinical evidence
Inhibition of migration	Blockade of a4-integrins on T cells	Natalizumab	Experimental + clinical evidence in MS
Interfere with granuloma formation	Blockade of TNF-α	Infliximab Adalimumab	Experimental + clinical evidence in AAV
Depletion of B cells	B-cell depletion by antibodies recognizing CD20/CD22	Rituximab, Epratuzumab (both anti-CD20)	Experimental + clinical evidence in AAV
Inhibition of B-cell maturation	Neutralization of BLys. Blockade of BLys-receptors on B cells	Belimumab (anti-BLys) Atacicept (anti-TACI)	Experimental evidence
Anti-microbial treatment	Reduction of microbial flora that might trigger disease flares	Cotrimoxazol	Experimental + clinical evidence in AAV

Glucocorticoids

Induction therapy for AAV includes treatment with highdose GCs in combination with another immunosuppressive agent (CYC, RTX) . GCs are usually given as daily oral prednisolone, initially at relatively high doses (1 mg/kg up to 60 mg) with the dose rapidly reduced to 15mg prednisolone at 12 weeks . Longer courses of GCs may cause increased risk of infection, but may be associated with fewer relapses . GC i.v. infusions (250_500mg methyl-prednisolone) are sometimes given just prior to or with the first two pulses of CYC[xxiii].

Maintenance therapy [xxiv]:

Following successful remission, CYC should be withdrawn and substituted with either AZA or MTX. MMF or LEF may be used as alternatives for intolerance to or lack of efficacy of AZA or MTX. Patients should continue Maintenance therapy for at least 24 months following successful disease remission. Patients with GPA or patients who remain PR3-ANCA positive should continue immunosuppression for up to 5 years . RTX may also be used as maintenance therapy, and re-treatment can be decided based on fixed-interval regimensor evidence of relapse . The recommended RTXregimen uses 1 g every 4_6 months for 2 years.

Conclusion :

- Rituximab has emerged as an alternative to cyclophosphamide for most patients and is the preferred agent for severe disease & relapses[xxv].
- Plasma exchange and biologic agents targeting B lymphocytes and T lymphocyte activation are under investigation for GPA and MPA[xxvi].
- Anti-IL-5 therapy targeting eosinophils with mepolizumab is under investigation for EGPA[xxvii].

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