Updates in Treatment of ANCA-associated Vasculitis

Albert Young and Ronald Man-Lung Yip

Abstract: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis are devastating diseases with high mortality if left untreated. Combined corticosteroid and cyclophosphamide is an effective treatment but it also carries high risks of adverse events and high relapse rates. Numerous studies endeavor to explore alternative agents. This review aims to examine the landmark studies concerning the use of different immunosuppressive agents and biologics on the ANCA-associated vasculitis.

Keywords: Anti-neutrophil cytoplasmic antibody, Churg-Strauss syndrome, Cyclophosphamide, Microscopic polyangiitis, Systemic vasculitis, Wegener's granulomatosis

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of primary systemic autoimmune diseases characterized by small vessel inflammation and ANCA production. It consists of three main types, namely Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg-Strauss syndrome (CSS). WG and MPA are related diseases and they share similar clinical presentations, pathologies and outcomes. CSS is also called allergic granulomatosis and angiitis. It is distinguished from the others by its close association with asthma and peripheral eosinophilia. If left untreated, AAV causes high mortality with less than 10% survival within two years.1,2 Patients, who present at advanced age (age >50), have renal impairment at the onset of disease and have permanent organ damage, have higher mortality risks.3 With the use of high dose corticosteroid and the development of various immunosuppressive agents, survival rates of AAV have much improved.4 This article summarizes the evidence of using distinct immunosuppressants for treating AAV with major organ involvement.

Traditional Induction Treatment

Both WG and MPA are highly responsive to therapies consisting of cyclophosphamide (CYC). The remission rates are up to 70-90%.2,5-9 CYC can be given either orally in the dose of 1.5-2 mg/kg/day or intravenously (IV) pulsed in the dose of 375 mg-1g/m²/month. CYC is continued until disease remission, which usually requires three to six months. Clinical efficacy and safety between two different regimens have been compared by different studies. A meta-analysis10 published in 2001 reviewed three randomized control trials (RCT) with a total 143 patients. It showed that pulsed IV CYC group received lower cumulative doses of CYC but was more likely to induce remission. The pulsed IV CYC group had lower risk of infection (odd ratio 0.45; CI 0.23-0.89) and leucopenia (odd ratio 0.36; CI 0.17-0.78). However, relapses were more frequent in the pulsed IV group. The CYCLOPS trial9 by the European Vasculitis Study Group (EUVAS) published in 2009 was a multicentre RCT, which consisted of 149 cases. From this study, oral CYC group received nearly twice the amount of cyclophosphamide when compared to IV group (15.9 g vs 8.2 g, p<0.001). The total remission rate from both groups was 78.9% after nine months of treatment and there was no difference in the time to induce remission between two groups. There were fewer patients in the oral group relapsed after remission but the difference was not statistically significant. Concerning the safety profiles, the oral group was more prone to leucopenia but both groups showed similar mortality and infection risks.

Another essential component of the induction therapy is the use of high dose corticosteroid. The application of pulsed IV
methylprednisolone on top of oral prednisolone for complicated cases is mainly based on experts’ opinions.\textsuperscript{11} There was, however, evidence showing that isolated application of corticosteroid without combining with CYC was associated with reduced treatment efficacy (only 56% remission rate) and higher relapse rates.\textsuperscript{12}

The use of chemoprophylaxis against pneumocystic jiroveci (carinii) (PCP) infection during the induction phase has been emphasized. Based on foreign cohorts,\textsuperscript{7,13} PCP incidence was from 6-20% for patients having AAV undergoing induction therapy. Risk factors for PCP infections include older age group, patients having Wegener's granulomatosis, low lymphocyte count before and during therapy, prolonged usage of glucocorticoid (prednisolone >15-20 mg/day for more than one month) and the usage of other immunosuppressive agents especially CYC.\textsuperscript{13-15} The usage of trimethoprim/sulfamethoxazole (usual dose: 960 mg thrice weekly) as chemoprophylaxis, although is widely accepted and suggested by both the EULAR and British Society for Rheumatology,\textsuperscript{11,16} is merely based on non-randomized trials and expert opinions. Chung and colleagues\textsuperscript{17} had tested on the cost-effectiveness and concluded that PCP prophylaxis was cost-effective in WG patients unless the annual incidence of PCP fell below 0.2%.

Other Induction Treatments

Methotrexate (MTX) is one of the most studied alternatives. The best data on the efficacy was from the NORAM trial\textsuperscript{18} by EUVAS in 2005. It was a non-inferiority randomized study comparing MTX (20-25 mg/week) to oral CYC (2 mg/kg/day) as the induction therapy for those patients who had newly diagnosed AAV with relatively mild disease profiles, serum creatinine level (sCr) \( \leq 150 \mu\text{mol/L} \) and no evidence of life or organ threatening events. The results suggested similar clinical remission rates in both treatment limbs but methotrexate group had relatively higher relapse rate (69.5% in MTX compared to 46.5% in CYC group). The safety profiles were comparable. Therefore, methotrexate can be considered as an alternative induction therapy for early AAV.

Mycophenolate mofetil (MMF) has also been studied for its efficacy but data is limited. A pilot study\textsuperscript{19} by Joy et al in 2005 showed that MMF could significantly improve Birmingham Vasculitis Activity Score (BVAS) (see Appendix) at week 24 for twelve patients having non-life threatening AAV. Another single centre open-label controlled trial\textsuperscript{20} performed by Hu et al. showed superior performance of MMF compared to classical CYC treatment for patients with severe renal impairment.

Plasma exchange (PE) has been evaluated for its application as an additional treatment for AAV with severe renal vasculitis. One of it was the large scale MEPEX study\textsuperscript{21} by EUVAS published in 2007 which enrolled 137 patients with newly diagnosed AAV complicated with severe renal failure (sCr >500 \( \mu\text{mol/L} \)). These patients were randomly assigned to receive either seven sessions of PE over the initial two weeks or IV pulsed methylprednisolone 1 g/day for three days. The outcomes suggested that there was significantly higher likelihood for patients to survive and become dialysis independent after PE. The risk reduction for patients progressing into end stage renal failure was 24% (CI: 6.1%-41%) at one-year time after PE. However, this study failed to show any survival benefits brought by PE.

Apart from renal vasculitis, PE is generally adopted for treating alveolar hemorrhage caused by pulmonary vasculitis. A retrospective review\textsuperscript{22} of 20 patients with diffuse alveolar hemorrhage received daily PE showed complete resolution of the pulmonary hemorrhage in all cases. A large international RCT (PEXIVAS trial) is currently being performed by the EUVAS group to evaluate the efficacy of PE for treating severe AAV.

Maintenance of Remission

There are two major drawbacks from the classical cyclophosphamide induction treatment. One of the major concerns is the toxicity profile (leucopenia, infertility, infection, malignancy risks, etc.), which is related to the cumulative consumption of CYC. Another problem is the high relapse rates after the cessation of CYC that can be up to 50%.\textsuperscript{10} Therefore, the need of maintenance therapy is essential.

From the CYCAZAREM study,\textsuperscript{23} a total of 144 patients with renal impairment (sCr \( \leq 500 \mu\text{mol/L} \)) achieved remissions after standard oral CYC induction therapy. They were separated into two groups to receive either a reduced dose of CYC (1.5 mg/kg/day) or azathioprine (AZA) (2 mg/kg/day). It was noted that both AZA and CYC treatment had comparable relapse rates (15.5% vs 13.7%, \( p=0.65 \)) at 18 months. Both groups showed similar renal function
improvement (in term of glomerular filtration rate), serious adverse events and life-threatening events. It was concluded that AZA could replace prolonged CYC treatment to maintain disease remission.

As aforementioned, methotrexate has proven efficacy to induce remission in patients with non-organ/ life threatening AAV. French Vasculitis Study group had investigated whether MTX could maintain remission by a well-organized clinical study – the WEGENT trial. A total of 126 patients who achieved disease remission after IV pulsed CYC were separated to receive AZA 2 mg/kg/day or MTX (started with 0.3 mg/kg/week and titrated up to 25 mg/week over three months) for up to one year. The primary end point of the study was the therapy discontinuation rates related to adverse events or mortality. The results showed that AZA caused cessation of medication in seven (11%) patients (four patients had hepatotoxicity) whereas MTX caused 12 patients (19%) to cease the medication (related to sepsis, hepatotoxicity; one patient died of sepsis). However, the difference was not statistically significant (hazard ratio 1.65, p=0.21). This study also showed no difference in terms of relapse rates and relapse-free survival rates in both groups. It was concluded that methotrexate had similar tolerability and was as effective as azathioprine in maintaining disease remission of AAV.

**Alternative Maintenance Treatments**

MMF has been reviewed in some case series as maintenance therapy but the results are variable. EUVAS has already completed the multicentre RCT (IMPROVE) to review the MMF capacity but the results are still awaited.

Leflunomide (LEF) has also been investigated as an alternative choice for remission maintenance. A RCT by Metzler et al recruited 54 patients with WG to receive MTX (20 mg/week) or LEF (step up to 30 mg/day over four weeks). However, this trial had been prematurely withdrawn because of the high relapse rate in the methotrexate limb.

**Alternative Treatments and Biologics**

For patients having persistent disease activities to standard CYC induction, like frequent relapses of disease or intolerance to CYC, other immunosuppressive treatments may be required.

There are limited and small case reviews in favor of the use of intravenous immunoglobulin (IVIG). Single RCT performed by Jayne et al in 2000 focusing on those patients having persistent diseases failed to show the efficacy of IVIG beyond three months. Similarly, another commonly use immunosuppressive agent, cyclosporine A, has limited case reports supporting its efficacy.

Concerning biologics, antibody against tumor necrosis factor α (Anti-TNF-α) has essential therapeutic role in different inflammatory conditions. Etanercept, a soluble TNF-α inhibitor, had been investigated by a RCT as an adjunct therapy on top of AZA or MTX compared to placebo in order to sustain disease remission. There were 181 patients who achieve disease remission through either CYC or MTX induction therapies. All these 181 patients received MTX (for those with sCr ≤ 176.8 µmol/L) or AZA (for those with sCr > 176.8 µmol/L) as the standard maintenance treatment. On top of the treatment, patients would either receive placebo or etanercept 25 mg twice per week. Nevertheless, the results from this study were nullified. There were no statistical differences between the treatment and placebo in the rates of sustained remission (69.7% vs 75.3%, p=0.39), sustained periods of low-level disease activity (86.5% vs 90.6%, p=0.32) or risk of disease flares (p=0.54). It was thus concluded that etanercept had no additional benefit to maintain disease remission in AAV. On the contrary, this study identified six solid tumors from the etanercept group compared to none from the placebo (p=0.01).

Alemtuzumab, the anti-CD52, a humanized monoclonal antibody that depletes peripheral T-lymphocytes and macrophages, is also found to have potential therapeutic effects against AAV. Based on a five-year single center review by Walsh et al using anti-CD52 to 71 patients with refractory AAV, 65% and 14% patients achieved complete and partial remissions respectively after the first five-day course of anti-CD52. Although there were up to 60.5% relapses over a median of 9.2 months, patients who received more than one course were more likely to remain in remissions. Apart from infection risks, there were eight patients (11%) developed Graves’ disease after a median of 3.5 years. More studies are required to ascertain the efficacy and side effect profiles related to this drug.

Rituximab, a chimeric anti-CD20 monoclonal antibody, is perhaps one of the most imperative biological agents that has proven efficacy against AAV. Former cohorts had shown
that rituximab could achieve sustained disease remission rates up to 80-90% in those with refractory AAV. The two most updated multi-centre randomized trials are the RITUXVAS trial\textsuperscript{32} by EUVAS and the RAVE trial\textsuperscript{33} by the Rituximab in ANCA-Associated Vasculitis – Immune Tolerance Network (RAVE-ITN) Research Group.

In the RITUXVAS, 44 patients with newly diagnosed AAV with renal vasculitis were separated into two groups. All patients were allowed to receive plasma exchange or a maximum of two grams pulsed IV methylprednisolone if the diseases were severe before enrollment into the study. The treatment group received four weekly rituximab (375 mg/body surface area (m\textsuperscript{2})) and two doses of pulsed IV CYC (15 mg/kg) at the first and third weeks. This group of patients did not receive AZA afterwards. On the other hand, the control group received monthly pulse CYC for three to six months and AZA given as remission maintenance therapy. This study aimed to compare the sustained remission rates at twelve months (defined as BVAS=0 for at least six months), mortality rates and adverse events. The results showed that the treatment group had comparable sustained remission rates (76% vs 82%, p=0.68) as traditional IV pulsed CYC regimen. Both adverse events and serious adverse events were similar from both groups. There were total six out of 33 patients (18%) from the rituximab group died and two out of 11 patients (18%) from the control died (p=0.11). This RCT concluded that rituximab shared comparable efficacy with IV pulsed CYC regimen and the use of rituximab, however, was not associated with the reduction of adverse events or mortality.

The RAVE trial was, on the other hand, a double-blinded, double-dummy non-inferiority study compared rituximab to oral CYC regimen as induction therapy for patients with ANCA-positive WG or MPA. A total of 197 patients were enrolled. The study included those having newly diagnosed AAV or refractory diseases. Nevertheless, those patients having severe pulmonary involvement required mechanical ventilations or having advanced renal impairment (sCr $\geq$354 $\mu$mol/L) were excluded. The treatment group would receive a four weekly-based rituximab with oral placebo-CYC and the control would receive daily oral CYC 2 mg/kg plus placebo-rituximab. After three to six months, patients in the control would switch to daily AZA as maintenance whereas the rituximab group would receive placebo-AZA. Both groups were put on high dose prednisolone initially and were gradually tapered off if patient remained in remissions within six months. The primary end point was the number of patients that achieved complete remission (BVAS/WG=0) and successful tapering of the prednisolone at six months. The study also performed different subgroup analysis to evaluate the efficacy of different conditions including different types of vasculitis (MPA/WG), renal protection ability, pulmonary hemorrhage control and refractory AAV control, etc. The results showed that 64% in the treatment group achieved primary end point (that is disease remission with steroid tapered off at the sixth month) compared to control group in which only 53% achieved primary end point. The difference of 11% met the criterion for non-inferiority but was not statistically significant (p=0.09). The study also showed that rituximab was particularly effective to those who had relapsing diseases with up to 67% reaching the primary end point, compared to only 42% in the oral CYC group (p=0.01). For other subgroup analysis, the study failed to show any therapeutic advantages (in terms of improvement of renal impairment, pulmonary hemorrhage or prevention of burst of severe diseases). There were no differences between rituximab group and oral CYC group for total adverse events, serious adverse events or non-disease related adverse events. An unusually high rate of malignancy was noted in this study (two solid cancers in initial six months and five additional cases in the following six months), but there was no statistically difference in the malignancy rate between two groups. Based on this double-blind RCT, it was concluded that rituximab was not inferior to traditional oral CYC but both had similar side effect profiles. Moreover, rituximab was more effective on those patients with relapsing diseases.

**Churg-Strauss Syndrome**

Compared to WG and MPA, most of the supporting evidence of CSS treatment is from case reviews and cohorts. Glucocorticoid therapy is the mainstay treatment for CSS. A meta-analysis\textsuperscript{5} in 2001 suggested that for patients having more severe CSS (Five factor Score $>2$) (see Appendix), the application of CYC treatment could significantly prolong patient survivals (p=0.041). Alternatively, methotrexate had been evaluated in a RCT\textsuperscript{18} of 100 patients with early diseases. MTX group had 89.8% remission rate which was comparable to 93.5% in CYC group (p=0.041) and this suggested that MTX was not inferior to CYC as induction treatment. AZA is another immunosuppressive treatment commonly adopted as steroid sparing agent or as the maintenance treatment after the usage of CYC in the induction. Plenty of alternative immunosuppressive drugs, such as MMF, rituximab, and
hydroxyurea have been evaluated in small case reports. More studies are certainly required to evaluate the usefulness of
these agents.

Conclusions

Although there are plenty of immunosuppressive agents proposed for the treatments of AAV, no alternative has been
found to be more effective than the standard CYC treatment. The latest RAVE trial suggested that rituximab was not
inferior to CYC treatment and perhaps could achieve higher disease remission rates especially for those having relapsing
diseases. However, the use of rituximab seems not to be able to bring us better safety profiles and the high malignancy rates
from the RAVE trial certainly need further studies for clarification.

On the other hand, because of the development of different immunosuppressive agents, clinicians nowadays enjoy a
variety of treatment options so treatments can be tailored to different patients according to their responses and adverse
events. Hopefully this can further improve the patients’ morbidities and mortalities.

References


Appendix. Disease activity and outcome assessment.

Five Factor Score (FSS) – the earliest proposed assessment tool for systemic vasculitis since 1998; by the use of five clinical aspects (proteinuria, renal impairment, cardiac involvement, gastrointestinal involvement and neurological involvement) to reflect disease activity, it is simple and can assist clinical judgment. FSS is proved to have prognostic value as well.5

Birmingham vasculitis activity score (BVAS) – regarded as the current standard assessment tool for disease activity in clinical researches. Both the European Vasculitis Study Group (EUVAS) and International Network for the Study of Systemic Vasculitis (INSSYS) use BVAS as the assessment tool. BVAS has been modified/simplified to newer versions to suit various clinical researches, like the BVAS/WG score for Wegener's granulomatosis. By the use of BVAS, complete remission is usually defined as the score of zero and such definition has been utilized in recent large randomized control trials.


