Treatment of ANCA-Associated Vasculitis: New Therapies and a Look at Old Entities

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Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a small-vessel vasculitis that primarily comprises 2 clinical syndromes: granulomatosis with polyangiitis and microscopic polyangiitis. Cyclophosphamide and glucocorticoids have traditionally been used for induction of remission. However, more recent studies have shown that rituximab is as effective as cyclophosphamide for induction therapy in patients with newly diagnosed severe AAV and superior for patients with relapsing AAV. There is also accumulating evidence indicating a potential role of rituximab for maintenance therapy in AAV. In this article, we will review the evidence supporting the various treatment choices for patients with AAV.

Key Words: ANCA-associated vasculitis, Cyclophosphamide, Rituximab

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) refers to a multisystem small-vessel vasculitis that is composed of 3 heterogenous clinical syndromes including microscopic polyangiitis (MPA), granulomatosis polyangiitis (GPA, formerly Wegener's granulomatosis), and eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome).[1] AAV primarily affects the kidneys, lungs, and peripheral nervous system and is characterized by the presence of necrotizing lesions in small vessels. In most patients ANCA is present in the serum at the time of initial diagnosis.[2-4] The 2 major patterns seen by indirect immunofluo-rescence when sera of patients containing ANCA are incubated with ethanol-fixed neutrophils include cytoplasmic ANCA (C-ANCA) and perinuclear ANCA (P-ANCA) patterns.[5] The C-ANCA pattern represents diffuse granular staining in the cytoplasm that is seen mostly in patients with GPA and is caused by antibodies against proteinase-3 (PR3).[6] On the other hand, the P-ANCA pattern is most commonly seen in patients with MPA and represents perinuclear staining. In contrast to the C-ANCA pattern, the P-ANCA pattern can be caused by various different antibodies targeting cationic granule constituents that rearrange around the negatively charged nucleus under ethanol fixation conditions. Because only antibodies against myeloperoxidase (MPO) causing a P-ANCA pattern are of interest in the context of AAV, confirmation of MPO specificity by enzyme-linked immunoabsorbent assay is mandatory in the diagnostic evaluation of patients suspected of having AAV.[6]

Immunosuppressive therapy is indicated in all patients with active AAV. Without therapy, the disease follows a progressive course and results in vital organ failure with fatal outcomes once there is evidence of kidney involvement.[7] The choice of therapy may depend on disease activity, but treatment typically consists of 2 phases: (1) a remission induction phase, with the goal of therapy being the interruption of active inflammation to prevent tissue damage and allow recovery; and (2) a remission maintenance phase, in which therapy aims to prevent relapses, ideally without the use of glucocorticoids. In this article, we will review standard induction therapy as well as new therapeutic approaches with the use of rituximab. We will also review the role of rituximab for maintenance therapy.

Remission Induction Therapy

Cyclophosphamide

Before the introduction of high-dose glucocorticoids in combination with cyclophosphamide (CYC), AAV was considered to be fatal once there was evidence of kidney involvement.[7] In 1973, the first series of 15 patients who were treated with CYC (2 mg/kg per day) in combination with prednisone was published.[8] In this study, 13 of the 15 patients achieved remission. Follow-up studies of larger cohorts observed for longer periods of time provided similar data with a 75% rate of complete remission and 80% rate of survival.[9,10] The continued use of corticosteroids plus CYC changed AAV from a uniformly fatal disease to a chronic and relapsing condition. However, CYC-based therapy is associated with significant short- and long-term toxicities including

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bone marrow suppression (2%); infection (46%); malignancies, particularly bladder cancer (2.8%); and infertility (57%).[10] In an attempt to lower the exposure to the cumulative dose of CYC, intravenous (IV) CYC pulse therapy was suggested.

The European Vasculitis Study Group (EUVAS) conducted a randomized controlled trial (CYCLOPS Trial—Randomized Trial of Daily Oral vs Pulse Cyclophosphamide as Therapy for AAV) to evaluate the efficacy of IV CYC given as 3 IV pulses of CYC, 15 mg/kg, given 2 weeks apart, followed by pulses at 3-week intervals (15 mg/kg IV or 5 mg/kg orally on 3 consecutive days, at the physician's discretion) until remission, and then for another 3 months vs oral CYC given at a dose of 2 mg/kg per day, until remission, followed by 1.5 mg/kg per day for another 3 months.[11] There were no differences in the rate or time to remission between the 2 treatment arms (88.1% in the IV group vs 87.7% in the oral group). There was a higher reported rate of leukopenia in the oral CYC arm compared with the IV CYC arm. However, there was no difference in the rate of serious infections or any other adverse events between the 2 arms.[11] The relapse rate was numerically higher in the IV CYC group (19%) compared with the oral CYC group (9%). This difference did not reach statistical significance, and the study was not powered to evaluate the effect of the intervention on relapse. However, the long-term follow-up of the CYCLOPS trial did show a significantly higher rate of relapse in the IV arm (39.5%) compared with the oral arm (20.8%) ($P = .029$).[12] There were no differences in kidney function, survival, or adverse events between the 2 treatment arms.[12]

CYCLOPS showed that oral and IV CYC are possible options for induction therapy. However, providers should be aware that IV CYC is not superior to the oral formulation, and, when used for the same duration of therapy, it may be associated with a higher rate of relapse. In our practice, we prefer the oral formulation because necessary dose adjustments can be implemented promptly in the event of leukopenia or severe infection. In comparison, the bone marrow effects of IV CYC pulses are longer lasting, and, once administered, their effect cannot be easily reversed. However, we do consider IV CYC in patients in whom fertility is a concern, in those who may have issues with compliance, or in those who experience severe nausea with the use of oral CYC.

CLINICAL SUMMARY

- Rituximab is as effective as Cyclophosphamide in inducing remission in severe AAV.
- Rituximab is the preferred agent when treating patients with relapsing AAV and in patients where fertility is a concern.
- Rituximab monotherapy is effective as maintenance therapy in AAV.
- MMF and high-dose corticosteroids may be a treatment option for patients who are MPO-ANCA positive and have mild renal impairment.

Although treatment with CYC induced remission in most patients, the optimal duration of therapy was unclear. In an open-label trial by Langford and colleagues, in which patients were switched to methotrexate therapy after induction was achieved by CYC, the median duration to remission was 3 months,[13] indicating that duration of therapy with CYC could be shortened. Similar results were obtained from the trial by EUVAS in which patients were treated with 3 months of CYC (2 mg/kg per day) and prednisolone, and then, once remission was achieved, they were randomized to either azathioprine (2 mg/kg per day) or continuation of CYC at a lower dose of CYC (1.5 mg/kg per day) for a total of 12 months. The relapse rate was no different between the azathioprine and the CYC arm (15.7% vs 13.7%).[14] This confirmed that CYC use could be limited to the duration required to induce remission, which is typically 3 to 6 months and does not need to be extended beyond 6 months. Consequently, after remission has been achieved, CYC should be discontinued and replaced with a less toxic alternative such as azathioprine.

Side-Effect Profile of CYC

Bone Marrow Suppression and Infection

CYC is associated with significant short- and long-term side effects, and strategies to lower the associated morbidity and mortality should be implemented. One of the most common side effects of CYC is bone marrow suppression, leukopenia, and subsequently an increased risk of infection.[14] Therefore, it is recommended that all patients on daily oral CYC therapy have a complete blood count (CBC) performed at least every 2 weeks (ideally weekly) while on CYC. Dose adjustments should be made to maintain a total white blood cell count above 3500/mm^3 and an absolute neutrophil count above 1500/mm^3. If patient is receiving IV CYC, then CBC should be performed before each dose (on average once every 2 weeks). In addition, to prevent infection with *Pneumocystis jiroveci*, all patients should receive prophylaxis with either sulfamethoxazole/trimethoprim or an alternative agent.[15] We recommend that the oral dose of CYC be reduced by 25% in patients over the age of 60 years or creatinine more than 2.5 mg/dL to 1.5 mg/kg per day for induction therapy. For example, a 62-year-old male patient with a serum creatinine of 3 mg/dL who weighs 80 kg should receive no more than 125 mg of oral CYC per day (1.5 mg/kg per day).