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Combination Therapy With Rituximab and Cyclophosphamide for Remission Induction in ANCA Vasculitis

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Introduction: Remission induction in antineutrophil cytoplasmic autoantibody (ANCA) vasculitis may be complicated by slow response to treatment and toxicity from glucocorticoids. We describe outcomes with a novel remission induction regimen combining rituximab with a short course of low-dose, oral cyclophosphamide and an accelerated prednisone taper.

Methods: Patients were included in this retrospective study if they had newly diagnosed or relapsing ANCA vasculitis with a Birmingham Vasculitis Activity Score for Wegener Granulomatosis (BVAS-WG) ≥3 and received a standardized remission induction regimen. The primary outcome was complete remission, defined as a BVAS-WG of 0 and a prednisone dose of ≤7.5 mg/d.

Results: We identified 129 patients who met the inclusion criteria, 31% of whom also received plasma exchange (PLEX) for rapidly progressive glomerulonephritis (RPGN) or diffuse alveolar hemorrhage. Seventy percent of patients had myeloperoxidase (MPO)-ANCA and 9% had relapsing disease. Median time to complete remission was 4 months (interquartile range [IQR] 3.9–4.4), and by 5 months 84% of patients were in complete remission. Prednisone was tapered to discontinuation as tolerated, such that the median prednisone dose at 8 months was 0 mg/d (IQR 0–2.5). In patients with RPGN, proteinase 3–ANCA was associated with a greater increase in eGFR at 6 months compared with MPO-ANCA (16 vs. 5.6 ml/min per 1.73m^2; $P = 0.028$). During the year following remission, 1 major relapse occurred over 122 patient-years. Serious infections occurred more frequently in patients receiving PLEX and were associated with increasing age and diffuse alveolar hemorrhage. Four deaths occurred, 3 of which were associated with serious infections.

Conclusion: Combination therapy was efficacious, allowed for rapid tapering of high-dose glucocorticoids and was well tolerated.

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Antineutrophil cytoplasmic autoantibody (ANCA) vasculitis is a systemic autoimmune disease characterized by small vessel inflammation with a propensity to affect the kidney and respiratory tract.[1,2] Urgent treatment is required to prevent irreversible organ damage.[3] Current strategies for remission induction in severe ANCA vasculitis include either rituximab or cyclophosphamide in combination with glucocorticoids.[4,5] The success of these regimens has been limited by the sequelae of prolonged exposure to high-dose glucocorticoids and treatment failure in some patients.[2–4,6]

In an attempt to more rapidly attain remission and minimize exposure to high-dose glucocorticoids, our approach for remission induction evolved into a standardized 3-drug regimen: rituximab, a 2-month course of low-dose, oral cyclophosphamide, and an accelerated glucocorticoid taper. Other regimens combining rituximab and intravenous cyclophosphamide have Q1 been previously reported in smaller patient populations in the RITUXVAS trial and in the regimen reported by

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Mansfield *et al*. with favorable outcomes.[7,8] Our rationale for this strategy is to target autoantibody-producing plasmablasts and plasma cells with cyclophosphamide and glucocorticoids while simultaneously depleting their precursors with rituximab. In cases of severe rapidly progressive glomerulonephritis (RPGN) or pulmonary hemorrhage, plasma exchange (PLEX) and pulse intravenous glucocorticoids are added to the standardized regimen. We present a retrospective analysis of 129 patients treated with this standardized regimen with a focus on efficacy, risk of relapse, and safety.

METHODS

Patients

We performed a retrospective analysis of 129 sequential patients with newly diagnosed or relapsing active ANCA vasculitis treated with a standardized remission induction regimen at the Massachusetts General Hospital Vasculitis and Glomerulonephritis Center from June 2006 to January 2016. Included patients had a positive test for antibodies to proteinase 3 (PR3) or myeloperoxidase (MPO) together with clinical and laboratory features consistent with granulomatosis with polyangiitis, microscopic polyangiitis, or renal-limited vasculitis.[9] Active vasculitis was defined as a Birmingham Vasculitis Activity Score for Wegener Granulomatosis (BVAS-WG) of ≥ 3.[10,11] Patients in this study have also been included in other reports addressing different aspects of treatment.[10,12,13] The study was approved by the Partners HealthCare Human Research Committee and performed in accordance with the Declaration of Helsinki.

Treatment Regimen

Patients were treated with a 3-drug regimen: rituximab, a 2-month course of oral, low-dose cyclophosphamide, and an accelerated prednisone taper (Figure 1). Rituximab was administered as two 1000-mg i.v. doses separated by approximately 2 weeks. Thereafter, rituximab was administered as one 1000-mg i.v. dose every 4 months for maintenance therapy. Beginning at month 4, B-cell depletion was monitored in most patients before each rituximab dose with flow cytometry by evaluating the population of $CD19^+CD20^+$ lymphocytes. B-cell depletion was defined as a $CD19^+CD20^+$ population below the level of detection at our laboratory (<0.1% of the lymphocyte pool).

Cyclophosphamide was dosed at 2.5 mg/kg daily for 1 week, followed by 1.5 mg/kg daily for 7 weeks. The dose of cyclophosphamide was reduced for impaired renal function as follows: 10% reduction if the estimated glomerular filtration rate (eGFR) was 60 to 90 ml/min per 1.73 m^2, 25% if the eGFR was 45 to 59 ml/min per 1.73 m^2, 33% if the eGFR was 30 to 44 ml/min per 1.73 m^2, 40% if the eGFR was 15 to 29 ml/min per 1.73 m^2, and 50% if the eGFR was <15 ml/min per 1.73 m^2. In the first month of treatment, prednisone was tapered as follows: 60 mg daily for 1 week, 40 mg daily for 1 week, 30 mg daily for 1 week, and 20 mg daily for 1 week. Thereafter, prednisone was tapered by 2.5 mg monthly, starting at 15 mg daily. Small deviations in prednisone tapering were made at the discretion of the treating physician.

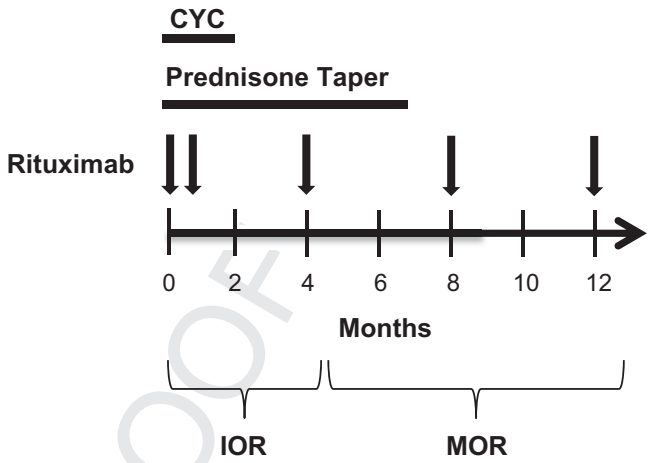

Figure 1. Treatment regimen. Cyclophosphamide was administered at 2.5 mg/kg daily for 7 days, followed by 1.5 mg/kg daily for 7 weeks. The dose of cyclophosphamide was adjusted for renal function as described in the Methods section. Prednisone was administered at 60 mg daily and tapered to 15 mg by week 5. Thereafter, prednisone was tapered by 2.5 mg monthly. Rituximab (arrows) was administered as 1000 mg i.v. doses separated by approximately 2 weeks, followed by 1 dose every 4 months. CYC, cyclophosphamide; IOR, induction of remission; MOR, maintenance of remission.

In the setting of severe pulmonary hemorrhage or RPGN, pulse i.v. glucocorticoids and PLEX were added to the standardized regimen. Pulse glucocorticoids were administered as i.v. methylprednisolone at 500 or 1000 mg daily for 3 days. Patients treated with PLEX received 7 treatments over the course of 2 weeks.

During remission induction therapy, patients received prophylaxis for *Pneumocystis* pneumonia with trimethoprim-sulfamethoxazole. Patients with an allergy to sulfonamides were administered atovaquone. *Pneumocystis* pneumonia prophylaxis was continued in patients receiving ongoing rituximab therapy until the prednisone dose was ≤5 mg daily. Patients with a positive hepatitis B core antibody were given prophylaxis to prevent hepatitis B reactivation with either entecavir or lamivudine.

Remission

The BVAS-WG was collected prospectively at each visit as part of patient care. Complete remission was

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