

Rituximab in the Frail and Elderly with Severe ANCA-Associated GN

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Introduction

ANCA-associated vasculitides are multisystem disorders that often affect the kidneys with an aggressive inflammation, leaving irreversible damage. The introduction of cyclophosphamide transformed the disease from a fatal to a chronic relapsing one, but an unsatisfactorily high morbidity and mortality remain from treatment side effects and chronic organ dysfunction. Clinical trials of rituximab, a monoclonal chimeric CD20 antibody, have resulted in an attempt to avoid this toxicity. Upon binding, rituximab induces apoptosis of pre-B and mature B lymphocytes *via* antibody- and complement-dependent cytotoxicity, and the CD20 antibody established itself as a noninferior induction alternative to cyclophosphamide. Here, we discuss the use of rituximab in severe ANCA-associated GN, with a focus on the frail and elderly population, highlighting benefits, special requirements, and pitfalls to improve individualized medicine and outcomes in ANCA GN.

Patient Presentation

Mrs. N.M., 77 years old, presented to the emergency department after a fall. She had recently lost 10 kg of weight, could hardly walk due to generalized pain, and had noticed a rash on her lower limbs. In the past, she had suffered from recurrent sinusitis. She was an ex-smoker, with 30 pack-years. On examination, she was frail, 51 kg, with a collapsed saddle nose, a purpura, and significant edema on her lower limbs. Her BP was 147/88 mm Hg. Her laboratory markers were as follows: creatinine, 368 $\mu\text{mol/L}$; eGFR, 10 ml/min per 1.73 m²; C-reactive protein, 85 mg/dl; anti-myeloperoxidase antibodies (anti-MPO), >80 AI/L; urine cytometry, >100 red blood cells; and urine protein-creatinine ratio, 228 mg/mmol. A computed tomography scan detected moderate emphysema, no fibrosis, and a ground glass opacity in the right upper lobe. The kidney biopsy specimen demonstrated the following: 11 glomeruli, two of which were globally sclerosed, four showed fibrinoid necrosis and cellular crescents, one had a fibrocellular crescent, two had segmental sclerosis, and two appeared normal; there was mild-to-moderate patchy interstitial fibrosis;

little to no positivity in immunofluorescence; and no deposits on electron microscopy, being classed as mixed class and scored in the high-risk group with nine points (G1=3, N1=4, T1=2).

Discussion

Mrs. N.M. was diagnosed with multiorgan granulomatosis with polyangiitis (GPA) with a high mortality risk due to frailty and severe kidney failure. Patients with MPO-positive GPA are more often female, of older age, suffer more frequently from kidney involvement, and show a lower overall survival than patients with PR3-positive GPA. Kidney involvement greatly affects morbidity and mortality, it varies in its presentation, and the renal risk score has been shown to accurately predict kidney failure (1). In this case, the 36-month kidney survival estimate was 50%, highlighting the precarious situation the patient was in.

Rituximab has demonstrated its noninferiority compared with cyclophosphamide in patients with non-severe kidney involvement. However, the combination of rituximab with glucocorticoids has demonstrated similar infection rates. Recently published data from the Plasma Exchange and Glucocorticoids for treatment of Anti-Neutrophil Cytoplasm (ANCA) - Associated Vasculitis (PEXIVAS) trial provided evidence that a reduction in glucocorticoid treatment is safe, showing equal efficacy and less serious infections (2). There is limited experience of rituximab in patients with advanced ANCA-associated kidney disease (3). On the basis of data from the Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis trial (4), rituximab is often administered with two initial doses of cyclophosphamide. This approach promises rapid disease control, prolonged remission, and the ability to minimize glucocorticoids (5).

The initial trial dosage calculated per body surface used a weekly infusion for 4 weeks, according to the “lymphoma” regimen. The “rheumatoid arthritis” regimen was established in clinical practice using two infusions of 1 g 2 weeks apart. Patients who are elderly and frail benefit from immunosuppressive treatment, although they suffer more frequently from

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adverse events of treatment. The cell depletion after rituximab usually lasts 4–6 months but is variable, and prolonged cell depletion has been observed in those who are elderly and frail. As a maintenance immunosuppression, rituximab has demonstrated that higher rates of relapse-free survival and dosing on demand, instead of fixed 6-monthly dosages, reduces the cumulative dose (6,7).

Rituximab usage requires screening for hepatitis B and *Pneumocystis jirovecii* prophylaxis. The most common adverse event is the infusion reaction (20%–25%), other side effects differ depending on concomitant immunosuppression. Monitoring is required for late-onset neutropenia (10%), hypogammaglobulinemia (20%–30%), and progressive multifocal leukoencephalopathy (one to two cases per 10,000). IgG levels are routinely checked before treatment as predictive of future hypogammaglobulinemia. Other reported events (*e.g.*, serum sickness) are very rare (8).

Patient Follow-Up

Mrs. N.M. received three 250-mg methylprednisolone pulses, followed by 40 mg oral prednisolone, tapered to 5 mg maintenance treatment by week 6. In week 1, she received a combination of 500 mg cyclophosphamide and 500 mg rituximab, followed by a second cyclophosphamide pulse of 500 mg in week 3. With physiotherapy, she mobilized to walking into clinic by month 6. Her systemic inflammation resolved within 3 weeks (C-reactive protein <1 mg/dl). Her creatinine improved to 257 $\mu\text{mol/L}$ and her eGFR was 15 ml/min per 1.73 m^2 by week 8. Hematuria resolved by week 10, and proteinuria resolved by month 4. She received 500 mg rituximab maintenance treatment by month 12 when her CD20 B cells repopulated to

5 cells/ μl , and her IgG remained at 5 g/L. By month 24, her MPO antibody was 5.5 AI/L, her eGFR was 14 ml/min per 1.73 m^2 , and her B cells were fully depleted.

Outlook

The combination of rituximab and cyclophosphamide in reduced doses with rapidly tapered glucocorticoids achieved remission in this frail, elderly patient with GPA and severe kidney involvement. An improvement of kidney function enabled her to remain independent of dialysis for 2 years after her diagnosis, a significant predictor of mortality.

Rituximab is chosen to ensure longer term relapse-free survival. The initial combination with cyclophosphamide is selected to accelerate the resolution of inflammation, to reduce damage, and to facilitate a reduced cumulative glucocorticoid dose. A future option might be the replacement of glucocorticoids with complement component 5a receptor inhibition (9).

Rituximab is acknowledged as the best maintenance treatment and is preferred in patients who are frail and elderly (3), but the optimal dosing intervals and overall length of treatment remain uncertain. Patients at high risk of relapse benefit from prolonged maintenance treatment (8). To avoid overimmunosuppression, length and intensity of therapy is ideally adjusted to the individual risk and might be shortened in selected patients with anti-MPO vasculitis and low risk of relapse. Rituximab may be administered on demand when B cells recover, as was decided for this patient. Dosing rituximab per repopulating B cells reduces the cumulative dose and is expected to reduce secondary hypogammaglobulinemia and vaccination failure

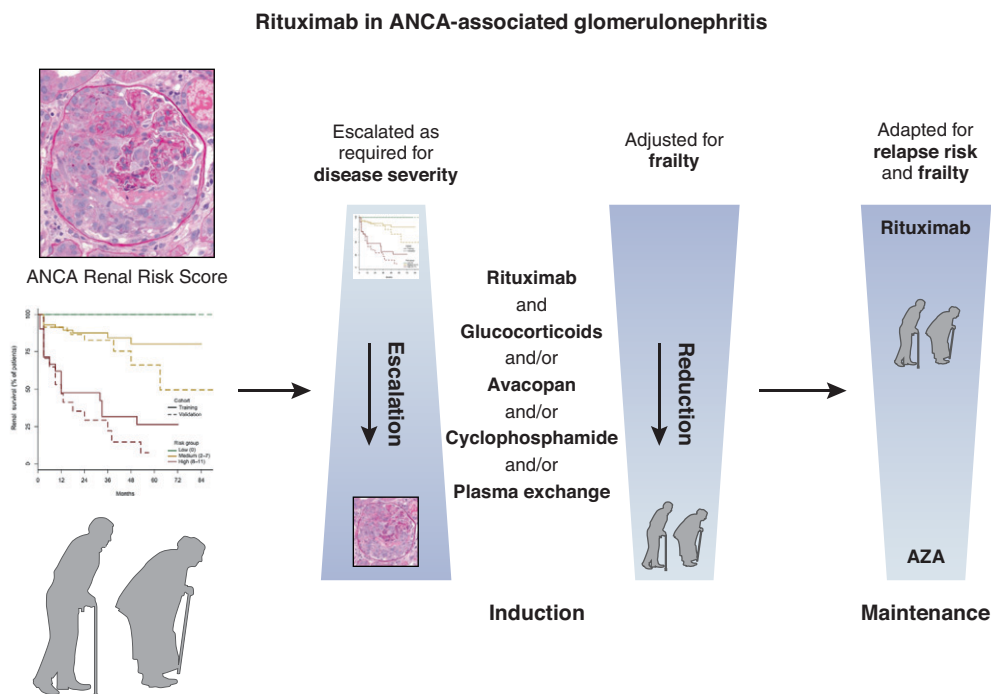


Figure 1. | Management of ANCA-associated GN stratified for disease severity, relapse risk, and frailty. AZA, azathioprine.

(7). Maintenance doses of 500–1000 mg may be used, but a 500-mg dosage is preferred in patients who are frail and elderly. Following the coronavirus disease 2019 (COVID-19) pandemic, maintenance treatment requires timing of COVID-19 booster vaccinations with rituximab redosing to allow a vaccine response and the development of COVID-19 antibodies.

Stratifying therapy to the individual demands of the patient (Figure 1) will improve kidney and patient outcomes until novel and less toxic treatment options become available. Precision medicine has become a focus, an exemplar of which is the recently proposed prediction modeling for the use of plasma exchange in vasculitis (10). Prospective trials investigating length and intensity of treatments, not in a one-fits-all approach, but according to risk stratification, are needed. The long-term outcome of Mrs. N.M. remains uncertain. Rituximab should protect her from persistent low-activity disease and relapsing disease. A high risk of mortality remains due to infectious complications and a potential progression to kidney failure, with its accompanying cardiovascular risk, despite vasculitis remission.

Disclosures

S.R. Brix reports receiving honoraria and advisory fees from Roche and Vifor. V. Tesar reports having consultancy and advisory agreements with, and honoraria from, Alexion, AstraZeneca, Baxter, Bayer, Boehringer-Ingelheim, B. Braun, Calliditas, Eli Lilly, Fresenius Medical Care, Novartis, Omeros, Otsuka, Pfizer, Sanofi, and Swixx BioPharma.

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Author Contributions

S.R. Brix and V. Tesar wrote the original draft and reviewed and edited the manuscript.

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