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Rituximab in Therapy of Glomerular Diseases: Single Center Experience

Azra Ribic - Mrkonja, Merima Odobasic, Aida Hamzic - Mehmedbasic, Vedad Herenda, Senad Hasanspahic, Edina Hasanagic, Majda Delic, Alma Muslimovic, Alma Mutevelic - Turkovic and Damir Rebic

Clinic of Nephrology and Renal Replacement therapy, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

Abstract

Introduction. Glomerular diseases remain challenging to treat, particularly in patients with persistent proteinuria and an inadequate response to conventional immunosuppressive therapy. Rituximab has emerged as an important therapeutic option in refractory or relapsing cases. We aimed to evaluate the early clinical response to rituximab in patients with glomerular diseases previously treated with conventional immunosuppressive therapy.

Methods. We conducted a retrospective observational case series at the Department of Nephrology and Renal Replacement Therapy, Clinical Center University of Sarajevo, over a two-year period. Twelve patients with glomerular diseases treated with rituximab were included. Demographic and clinical characteristics, underlying disease, previous immunosuppressive therapy, proteinuria, serum creatinine, and estimated glomerular filtration rate (eGFR) were analyzed. The primary outcome was the change in proteinuria three months after rituximab treatment.

Results. The cohort included 11 men and 1 woman, with a mean age of 47 years (range, 23-68). Membranous nephropathy was the most common diagnosis (58.3%), followed by ANCA-associated vasculitis (16.6%), lupus nephritis, minimal change disease, and thrombotic microangiopathy each accounted for 8.3%. All patients had previously received immunosuppressive therapy, most commonly corticosteroids, cyclophosphamide, and calcineurin inhibitors. In 11 patients, rituximab was administered at 375 mg/m² once weekly for four weeks, while one patient received 1 g twice, 14 days apart. Among six patients with paired measurements, mean proteinuria decreased from 9.53 to 0.86 g/day after three months, representing an approximately 91% reduction. Five patients achieved proteinuria <1 g/day. In membranous nephropathy, mean proteinuria decreased from 7.46 to 0.41 g/day (n=4). In lupus nephritis, proteinuria decreased from 18.12 to 0.74 g/day. Among seven patients with available creatinine measurements, mean serum creatinine decreased from 162 to 149 µmol/L. eGFR remained stable in six patients (41.8 vs. 42.4 mL/min/1.73 m²).

Conclusion. Rituximab was associated with a marked early reduction in proteinuria without deterioration of renal function in this single-center series of previously treated glomerular diseases. The most pronounced response was observed in membranous nephropathy. Larger studies with longer follow-up are needed to confirm these findings.

Keywords: rituximab, glomerular diseases, membranous nephropathy, proteinuria, lupus nephritis, immunosuppressive therapy, renal function

Introduction

Glomerular diseases represent a heterogeneous group of kidney disorders that may lead to significant proteinuria, nephrotic syndrome, progressive deterioration of kidney function and, in a proportion of patients, progression to end-stage kidney disease (ESKD). The treatment of these diseases remains challenging because of their diverse pathophysiological mechanisms, variable clinical course, and heterogeneous response to immunosuppressive therapy. Although conventional therapeutic strategies, including corticosteroids, cyclophosphamide, calcineurin inhibitors, and other immunosuppressive agents, may induce remission and preserve kidney function, a substantial proportion of patients fail to achieve an adequate response, experience disease relapse, or develop treatment-related adverse effects [1].

Increasing evidence indicates an important role of B lymphocytes and their products in the pathogenesis of several immune-mediated glomerular diseases. B cells contribute to disease activity through antibody production, antigen presentation, cytokine release, and interactions with other components of the immune

system. These findings provide a rationale for B-cell–depleting therapies in selected glomerular diseases [1-3].
Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen expressed on the surface of B lymphocytes. By inducing B-cell depletion, rituximab may reduce the production of pathogenic autoantibodies and modulate the immune response. Its use has increasingly been investigated in a variety of glomerular diseases, including membranous nephropathy, lupus nephritis, ANCA-associated vasculitis, and other immune-mediated kidney diseases [1-5].
Rituximab has demonstrated clinically meaningful reductions in proteinuria in patients with membranous nephropathy and has become an important therapeutic option, particularly in patients at risk of disease progression or with an inadequate response to conventional therapy. In the randomized MENTOR trial, rituximab was noninferior to cyclosporine in achieving complete or partial remission of proteinuria at 12 months and was superior in maintaining remission at 24 months [4].
Potential advantages of rituximab include targeted immunological activity, the possibility of reducing corticosteroid exposure, and the potential to achieve sustained remission in selected patients. However, treatment response may vary according to the underlying glomerular disease, disease severity, previous exposure to immunosuppressive therapy, and the degree of chronic kidney damage (CKD) [1,4,5].
In this context, we evaluated the early clinical response to rituximab in patients with glomerular diseases treated at a single nephrology center. The primary objective was to assess the change in proteinuria three months after rituximab administration, while secondary analyses evaluated changes in serum creatinine and estimated glomerular filtration rate (eGFR). Particular attention was given to treatment response according to the underlying glomerular disease, with the aim of presenting our center's experience with rituximab in patients who had not achieved an adequate response to previous conventional immunosuppressive therapy.

Material and methods

A retrospective observational case series was conducted at the Department of Nephrology and Renal Replacement Therapy, Clinical Center University of Sarajevo, over a two-year period. Twelve patients with glomerular diseases who were treated with rituximab were included in the study.
All patients had biopsy-proven kidney disease. The cohort consisted of seven patients with membranous nephropathy, two patients with ANCA-associated vasculitis, and one patient each with minimal change disease, systemic lupus erythematosus (SLE)–associated lupus nephritis, and thrombotic microangiopathy (TMA).
Before rituximab administration, all patients had received previous immunosuppressive treatment and were initiated on rituximab because they had either achieved complete remission followed by relapse, or failed to achieve remission despite previous treatment.
We analyzed demographic and clinical characteristics, underlying glomerular disease, previous immunesuppressive therapy, proteinuria, serum creatinine, and eGFR. The primary outcome was the change in proteinuria three months after rituximab treatment. Secondary outcomes included changes in serum creatinine and eGFR. Treatment response was evaluated according to the underlying glomerular disease.

Results

The cohort consisted of 11 men and one woman, with a mean age of 47 years (range, 23-68 years). Seven patients (58.3%) had membranous nephropathy, two patients (16.6%) had ANCA-associated vasculitis, and one patient each (8.3%) had lupus nephritis, TMA, and minimal change disease.
Eleven patients received rituximab at a dose of 375 mg/m² once weekly for four consecutive weeks, whereas one patient received 1 g twice, 14 days apart.

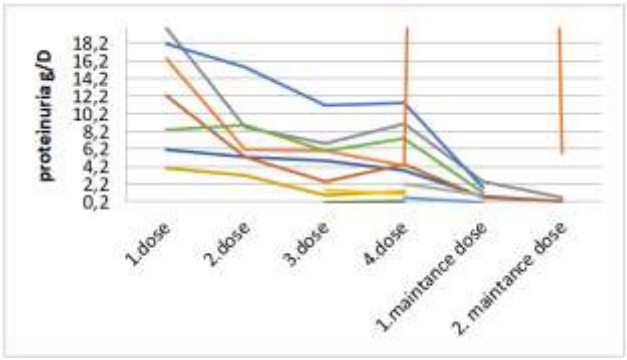


Fig. 1. Changes in proteinuria from baseline to three months after rituximab treatment

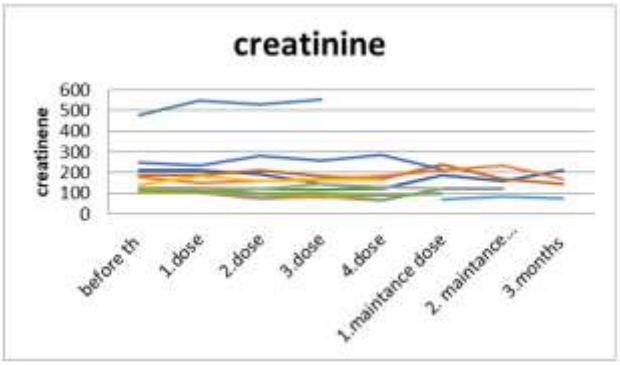


Fig. 2. Changes in serum creatinine before and after rituximab treatment

Among six patients with available paired measurements, mean proteinuria decreased from 9.53 g/day at baseline to 0.86 g/day three months after rituximab administration, representing an approximately 91%

reduction. Proteinuria below 1 g/day was achieved in five patients.

The most pronounced response was observed among patients with membranous nephropathy, in whom mean proteinuria among four patients decreased from 7.46 g/day at baseline to 0.41 g/day three months after rituximab treatment. In the patient with lupus nephritis,proteinuria decreased from 18.12 g/day to 0.74 g/day.

Among seven patients with available serum creatinine measurements, mean serum creatinine decreased from 162 to 149 µmol/L. Eleven patients had some degree of chronic kidney disease, whereas one patient had normal nitrogenous waste parameters.

Among six patients with available paired measure–ments, eGFR remained essentially stable, with mean values of 41.8 and 42.4 mL/min/1.73 m² before and three months after rituximab treatment, respectively.

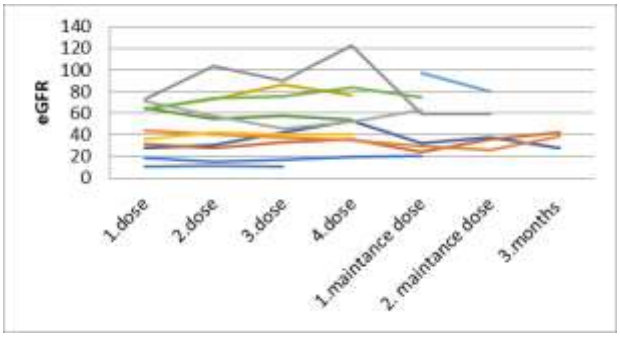


Fig. 3. Changes in estimated glomerular filtration rate (eGFR) from baseline to three months after rituximab treatment

Discussion

The results of our study demonstrated that rituximab treatment was associated with a marked reduction in proteinuria in patients with membranous nephropathy and was also associated with a reduction in proteinuria in patients with ANCA-associated vasculitis and lupus nephritis. Although the number of patients was small, this finding is clinically relevant because proteinuria is an important marker of glomerular injury and an es–tablished prognostic factor for the progression of CKD. Our findings are consistent with previous evidence in–dicating an important role of B lymphocytes and auto–antibody production in the pathogenesis of several immu–ne-mediated glomerular diseases and suggesting that B-cell depletion with rituximab may result in reduced proteinuria and improved renal outcomes [1-5].

The most pronounced reduction in proteinuria in our cohort was observed among patients with membranous nephropathy. This finding is consistent with randomized clinical trials demonstrating the efficacy of rituximab in reducing proteinuria and inducing partial or complete remission in primary membranous nephropathy. In the MENTOR trial, which included 130 patients with membranous nephropathy and proteinuria ≥5 g/day, rituximab was noninferior to cyclosporine in achieving complete or partial remission at 12 months. At 24 months, remission was maintained in 60% of patients treated with rituximab compared with only 20% of those treated with cyclosporine [4].

The evidence for the antiproteinuric effect of rituximab is particularly strong in membranous nephropathy. In the GEMRITUX trial, rituximab was administered in addi–tion to non- immunosuppressive antiproteinuric treat–ment and compared with antiproteinuric treatment alone. Although the difference in remission rates was not statistically significant at six months, extended follow-up demonstrated a significantly higher rate of complete or partial remission in the rituximab group. After a median follow-up of approximately 17 months, remission was achieved in 64.9% of patients treated with rituximab compared with 34.2% of patients re–ceiving supportive therapy alone [6,7].

These findings are particularly relevant to the inter–pretation of our results because they indicate that the clinical effect of rituximab on proteinuria may develop gradually and that the reduction in proteinuria may not occur immediately after treatment. The relatively short three-month follow-up in our study therefore repre–sents an assessment of an early treatment response rather than the final therapeutic effect.

The biological basis for this delayed clinical response is also supported by the relationship between B-cell depletion, anti-phospholipase A2 receptor (PLA2R) antibody levels, and proteinuria. In membranous neph–ropathy, immunological remission, reflected by a re–duction or disappearance of anti-PLA2R antibodies, may precede clinical remission by several months. Con–sequently, patients without a substantial reduction in proteinuria at three months should not necessarily be considered treatment failures, particularly if an immu–nological response has occurred [6,7].

The RI-CYCLO trial provides additional evidence re–garding the time course of response. In this rando–mi–zed trial, complete or partial remission at 12 months was achieved in 62% of patients treated with ritu–ximab, compared with 73% of those receiving cyclic corticosteroid-cyclophosphamide therapy. At 24 months, complete or partial remission was observed in 83% and 82% of patients, respectively. These findings de–monstrate that the clinical response to rituximab may continue to increase during longer-term follow-up [4].

In our cohort, the marked reduction in proteinuria among patients with membranous nephropathy from 7.46 to 0.41 g/day among the four patients with paired measurements appears greater than the average re–duction reported in many clinical studies. However, this observation should be interpreted cautiously be–cause of the very small sample size and the potential influence of spontaneous fluctuations in proteinuria, concomitant antiproteinuric therapy, and differences in baseline disease severity. Nevertheless, the finding is

consistent with the established efficacy of rituximab in membranous nephropathy.

The interpretation of proteinuria reduction in patients with ANCA-associated vasculitis is more complex. The primary therapeutic goals in ANCA-associated vasculitis are induction and maintenance of remission, control of systemic and renal disease activity, and preservation of kidney function. Proteinuria alone is therefore insufficient to define renal response. In the RAVE trial, rituximab was noninferior to cyclophosphamide for induction of remission in severe ANCA-associated vasculitis and was superior in patients with relapsing disease. Rituximab was also effective in patients with major renal disease [4].

Similarly, the RITUXVAS trial evaluated rituximab in patients with ANCA-associated vasculitis and renal involvement. At 12 months, sustained remission was achieved in 91% of patients in both treatment groups, with no significant difference between rituximab and cyclophosphamide-based therapy. Renal function also improved substantially in the rituximab group, with median eGFR increasing from approximately 20 to 39 mL/min/1.73 m² at 12 months [10].

Therefore, the reduction in proteinuria observed in our patients with ANCA-associated vasculitis may represent one component of an early renal response to control of vasculitis activity. However, changes in proteinuria should be interpreted together with serum creatinine, eGFR, urinary sediment, and other indicators of disease activity. It is particularly important to distinguish active glomerular inflammation from residual proteinuria caused by chronic structural kidney damage.

The available evidence for rituximab in lupus nephritis is more heterogeneous. In the LUNAR randomized controlled trial, rituximab was added to mycophenolate mofetil and corticosteroids in patients with active proliferative lupus nephritis. Although the overall renal response rate was numerically higher with rituximab than with placebo (56.9% versus 45.8%), the difference did not reach statistical significance. Nevertheless, rituximab produced profound peripheral B-cell depletion and significant improvements in complement levels and anti-double-stranded DNA antibodies. Greater reductions in anti-dsDNA levels were associated with reductions in proteinuria [11].

Observational data have suggested a more favorable response in patients with refractory lupus nephritis. In the prospective Rituxilup cohort, rituximab combined with mycophenolate mofetil without maintenance oral corticosteroids resulted in complete remission in 52% and partial remission in 34% of patients at 52 weeks [12]. These findings suggest that rituximab may have clinically meaningful activity in lupus nephritis, particularly in selected or refractory patients, despite the neutral results of the LUNAR randomized trial.

In our study, the patient with lupus nephritis demonstrated a marked reduction in proteinuria, from 18.12 to 0.74 g/day after three months. Although this represents a substantial early response, this finding cannot be generalized because it is based on a single patient finding. Furthermore, the patient had previously received immunosuppressive therapy, and the observed improvement may reflect the combined effect of rituximab, previous treatment, supportive therapy, and the natural fluctuation of lupus nephritis activity.

Another important consideration is the stability of kidney function observed in our cohort. Mean serum creatinine decreased from 162 to 149 µmol/L among seven patients with available measurements, while mean eGFR remained essentially unchanged, from 41.8 to 42.4 mL/min/1.73 m². The absence of deterioration in kidney function is clinically relevant, particularly because most patients had pre-existing CKD. However, the short follow-up period and the small number of patients with paired measurements prevent conclusions regarding the long-term renoprotective effect of rituximab.

Our findings should be interpreted in light of several limitations. First, the study included only 12 patients, and paired proteinuria measurements were available in only six patients. Second, the cohort was heterogeneous, comprising several different glomerular diseases with distinct pathophysiological mechanisms. Third, this was a retrospective single-center study without a control group, making it impossible to determine the extent to which the observed changes were attributable specifically to rituximab. Fourth, patients had received different immunosuppressive regimens before rituximab, and concomitant supportive treatment may have influenced proteinuria. Finally, the three-month follow-up may have been too short to capture the full clinical effect of rituximab, particularly in membranous nephropathy.

Despite these limitations, our results provide useful real-world data regarding the early response to rituximab in patients with difficult-to-treat glomerular diseases. The pronounced reduction in proteinuria observed in the membranous nephropathy subgroup is consistent with the evidence from randomized trials supporting rituximab as an effective therapy for primary membranous nephropathy. The findings in ANCA-associated vasculitis and lupus nephritis are more difficult to interpret because proteinuria is only one component of renal disease activity and because the evidence supporting rituximab differs between these diseases.

Overall, our results support the hypothesis that rituximab may induce an early reduction in proteinuria in selected patients with immune-mediated glomerular diseases. The strongest evidence for an antiproteinuric effect exists in membranous nephropathy, whereas data in ANCA-associated vasculitis and lupus nephritis are more heterogeneous. Longer follow-up and larger prospective studies are required to determine whether the early reduction in proteinuria observed in our cohort is sustained and translates into durable renal remission and preservation of kidney function.

Conclusion

In this single-center case series of patients with previously treated glomerular diseases, rituximab treatment was associated with a marked early reduction in proteinuria without deterioration in kidney function. The most pronounced response was observed in patients with membranous nephropathy, with proteinuria below 1 g/day achieved in most patients with available follow-up measurements.

Although these findings support the potential role of rituximab in patients with difficult-to-control glomerular diseases, they should be interpreted cautiously because of the small sample size, heterogeneous disease spectrum, absence of a control group, and short follow-up period. Larger prospective studies with longer follow-up are needed to confirm these findings and to better define the role of rituximab in refractory glomerular diseases.

Conflict of interest statement. None declared.

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