CASE SERIES

RITUXIMAB IN THE TREATMENT OF REFRACTORY IDIOPATHIC MEMBRANOUS NEPHROPATHY IN PAKISTANI POPULATION

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This is the time of paradigm shift in the treatment of primary membranous nephropathy which carries a major position in causing nephrotic syndrome in adult population and has been labelled as a cause of idiopathic primary glomerulonephropathy in about 90% of patients. It is two folds more common in male population as compared to female population. It is held responsible for about 0.7% cases of end stage kidney disease. However, unfortunately, the optimal treatment for idiopathic membranous nephropathy is still unresolved. Rituximab has been made especially to attach to CD20 receptors and therefore cause depletion of B cells. It has been found to be a potential treatment option for idiopathic membranous nephropathy. We present four cases of primary idiopathic membranous nephropathy that were successfully treated with rituximab. They were all previously treated with conservative management followed by immunosuppression therapies but none of them was fortunate enough to achieve partial or complete remission. Therefore, all of them were given two doses of rituximab (375 mg/m2), two weeks apart. Except for only one of the patients who required a second round of rituximab therapy, they all achieved complete remission of the disease without any significant side effects of the drug. This represents that those patients of idiopathic membranous nephropathy who are refractory cases with use of steroids, calcineurin inhibitors, (cyclosporine or tacrolimus) or alkylating agents (cyclophosphamide or chlorambucil) still have a hope in the form of Rituximab which has no doubt shown promising results in Pakistani population. Indeed, Rituximab may also be used early in the course of the disease to improve the outcome of the disease.

Keywords: Primary idiopathic membranous nephropathy; Proteinuria; Rituximab; Cyclophosphamide; Cyclosporine; Tacrolimus; Corticosteroids; Nephrotic syndrome

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INTRODUCTION

Primary idiopathic membranous nephropathy is a common cause nephrotic syndrome occurring in adults.[1] In about 40% of the patients, it may slowly and gradually progress to end stage kidney disease[2], while spontaneous remission may develop in 30–50% of patients[3]. This has led to the recommendation of immunosuppressive treatment for those patients whom THE disease progression risk rate is high.[4] At present the recommended first-line immunosuppressive drugs that include steroids, calcineurin inhibitors and cyclophosphamide, carry much degree of harm. Certain devastating complications including bone marrow suppression, infertility, drug induced diabetes, hypertension and cancer, can occur by their use.[5,6]

APLA2R are present on podocytes and autoantibodies against them have been discovered recently. This has made much improvement in the basic pathogenetic concepts of primary idiopathic membranous nephropathy.[7,8] These autoantibodies are present in about 70–80% of such patients.[9] This extra ordinary discovery has marked the importance of rituximab therapy in primary idiopathic membranous nephropathy. There are a number of studies that have successfully evaluated the effectiveness of rituximab therapy for idiopathic membranous nephropathy.[10,11] The management of idiopathic membranous nephropathy with rituximab has not been reported in Pakistan so far. We report four cases of membranous nephropathy showing complete remission after intravenous rituximab treatment in a dose of 375 mg/m2, two weeks apart.

CASE 1

A 32-year-old female, housewife, mother of a female child was diagnosed with IMN with initial proteinuria of 4.8 g/day. She remained on conservative management for 7 months but proteinuria increased to 9 g/d. Cyclosporine 3.5 mg/kg/day and prednisolone 5mg/day were given for six months, initially proteinuria decreased to 7 gm/day then it gradually increased to 10 gm/day, while patient was on treatment. Cyclophosphamide containing Ponticelle regimen was advised but it was refused by patient due to fertility issues. Patient was labelled as cyclosporine resistant membranous nephropathy and rituximab in a dose of 375 mg/m2, was administered in two doses, two weeks apart. Patient did not experience any drug related side effects during and

after the infusion. Monthly follow ups with urine routine examination, renal function tests and 24 hours urinary protein showed that after 10 months patient achieved complete remission with proteinuria of 267 mg/24 hours and normal serum creatinine.

CASE 2

A 28 years old female, unmarried, teacher by profession was diagnosed IMN with initial proteinuria of 8.3 gm/day, albumin of 2.7 g/dl and creatinine of 1.5 mg/dl. Initially non-immunosuppressive anti-proteinuric therapy was administered for six months but patient's proteinuria continued to rise and reached 11 gm/day. Immunosuppressive therapy including cyclosporine 3.5 mg/kg/day and prednisolone in the dose of 10 mg/day was being given. Her 24-hour urinary protein level initially improved to 7 gm/day but patient then had a relapse while on treatment. Cyclophosphamide combined with prednisolone 5 mg/day was given for 6 months but the proteinuria did not improve. After 6 months' patient was admitted for rituximab infusion in a dose of 375 mg/m2, two doses, fourteen days apart were administered. Blood complete picture, renal function tests, liver function tests were normal at base line, albumin in serum was 3.1mg/dl, urine routine examination showed +4 proteins and 24-hour urinary proteins level was 7.9 gm/day. Monthly follow ups for 9 months after rituximab therapy revealed that the patient achieved complete remission with proteinuria of 268 mg/day.

CASE 3

A 54 years old male, security officer by profession was diagnosed as a case of IMN with initial proteinuria of 5.8 g/24 hours, creatinine of 1.4 mg/dl, cholesterol of 220 mg/dl, and albumin of 3.2 mg/dl. Patient was initially treated conservatively with angiotensin converting enzyme (ACE)-Inhibitors and angiotensin receptor blockers (ARBs) for four months followed by immunosuppressive therapy including cyclosporine for six months but both therapies failed to decrease his proteinuria. Cyclophosphamide in the dose of 3.5 mg/kg /day and prednisolone in the dose of 1mg/kg/day were then advised in next five months but then discontinued as patient developed steroids induced myopathy with no significant improvement in proteinuria and his edema persisted. Rituximab was then administered in a dose of 375 mg/m2, fortnightly, total two doses with continuation of valsartan. The patient did not develop any drug associated side effects. His monthly follow up with 24-hour urinary protein, renal function tests, serum electrolytes, serum albumin and urine routine examination showed that his proteinuria initially decreased to 5.5 gm/day but then it increased to 9 gm/day associated with generalized body edema. Therefore, a second round of rituximab treatment was administered in same dosage and time duration. Eight months of follow up revealed that patient achieved complete remission with last proteinuria of 197 mg/day and normal renal function tests.

CASE 4

A 28 years old male, technician by profession was diagnosed with stage III/IV IMN. Non-immunosuppressive anti-proteinuric therapy was administered for initial six months; however nephrotic\range proteinuria persisted in a range of 6.5-7 gm/day. Cattran regimen with cyclosporine and prednisolone 10 mg/day was given for six months, but the response was not successful, therefore patient was then administered with Ponticelle regimen including cyclophosphamide and prednisolone, but unfortunately this regimen also failed to achieve the partial or complete remission. Patient was then admitted for rituximab infusion. Blood complete picture showed hemoglobin of 11.2 g/dl, normocytic normochromic anemia, white blood cells and platelets were normal, liver function tests and renal function tests were normal, total proteins were 4.4 gm/dl, albumin was 3.3 mg/dl, creatinine was 1.2 mg/dl, 24-hour urinary protein level was 11.3 gm/day. Rituximab, in a dose of 375 mg/m2 was administered according to the recommended protocol, fourteen days apart, total two doses, ACE-inhibitors and ARBs were continued despite of rituximab treatment. After ten months of follow up on monthly basis, 24-hour urinary protein level dropped to 256 mg/day and complete remission was thus achieved.

DISCUSSION

The above reported four cases represent the effectiveness of rituximab treatment for patients of primary idiopathic membranous nephropathy who initially did not show positive response to usual recommended immunosuppressive drugs regimens. Twenty-four-hour urine protein level done during monthly follow-up, tapered down after rituximab treatment and all four patients successfully achieved the complete remission. However, in one case, approximately 6 months following the initial treatment, rituximab was again required, as neither partial nor complete remission was achieved in first round.

Current treatments for IMN include steroids and immunosuppressant drugs including alkylating agents (cyclophosphamide or chlorambucil) or calcineurin inhibitors (cyclosporine or tacrolimus). None of them is disease-specific and they are associated with serious risks of toxicity.[12] In spite of

these powerful immunomodulating drug combinations, there have been worldwide published cases of refractory membranous nephropathy. Therefore, treatment of these refractory membranous nephropathies, with mycophenolate mofetil, ACTH, and intravenous immunoglobulin has been tried[13] but none has provided promising results so far. Among all newly explored agents, rituximab has risen as the most reliable candidate drug to be added in the already present treatment guidelines.

Presently most of what we know about the use of rituximab for treating primary idiopathic membranous nephropathy has been achieved from observational studies and only single randomized control trial, (GEMRITUX trial). Different treatment protocols have been applied, without any significant difference in the response rate.

In 2002, Remuzzi *et al*, chose eight patients of primary idiopathic membranous nephropathy who failed to respond to conservative therapy for six months. Their proteinuria still remained in high nephrotic range. Throughout the treatment period. He gave rituximab in the dose of 375mg/m2, four weekly doses and results showed that two patients got complete remission and three achieved partial remission.[14,15]

It was in 2008, when rituximab was used in a prospective observational study by Fervenza *et al*, in 15 refractory cases of idiopathic membranous nephropathy, who were having nephrotic range proteinuria. These patients were given two infusions of 1-gram rituximab, two weeks apart and regular follow-up was done. Even at the end of 6 months ten out fifteen patients remained significantly proteinuric (>3 g/24 hr) Rituximab was once again administered to them in the same dose and regular monthly follow up was done for next 12 months. Complete and partial remission was achieved in 60% of the cases.[16]

GEMRITUX trial, published in June, 2016, was the only prospective and multicenter trial done at 31 French hospitals for rituximab in the management of refractory cases idiopathic membranous nephropathy (IMN). Seventy-even refractory cases of primary idiopathic membranous nephropathy were randomized to either continue conservative therapy alone or the addition of rituximab 375 mg/m2, one week apart. Seventeen months regular follow -up showed 64.9% patients of the non-immunosuppressive conservative therapy and rituximab group was successful and gained remission while only 34.2% patients of non-immunosuppressive antiproteinuric treatment group gained remission of the disease. Neither group developed any side effects of the treatment.[17] Secondly, this trial also revealed that those patients who after b3 months of treatment with rituximab showed depletion of APLA2R antibodies, showed much good chance of achieving remission. This represents that depletion of APLA2R antibodies can be a sign of positive response to rituximab therapy.

It is therefore concluded that rituximab has proven to be an effective alternative in the treatment of idiopathic membranous nephropathy. However, more randomized control trials with longer follow-up are still required in order to establish the efficacy and safety of rituximab in comparison to already existing treatment modalities.

In our all four cases, we administered rituximab in a dose of 375 mg/m2, two doses, two weeks apart and found that this regimen was not only complied with but was also effective in achieving partial or complete remission with median of 7.5 months. Keeping in view the possible side effects of rituximab (20–40% of cases)[18], our patients were prophylactically given 100 mg methylprednisolone, 650 mg acetaminophen, and 4 mg chlorpheniramine before rituximab infusion, we did not observe any side effects.

CONCLUSION

As illustrated in our four cases, patients of idiopathic membranous nephropathy who were previously given treatment with corticosteroids, alkylating agents (cyclophosphamide and chlorambucil) and calcineurin inhibitors (cyclosporine or tacrolimus) and failed to achieve remission, still have hope in the form of rituximab which has shown positive effects in Pakistani population. Perhaps, rituximab may be introduced earlier in the course of disease to improve outcome.

Infect we still need further RCT to establish and confirm the timing, duration, long term tolerability and overall survival benefit of rituximab in comparison to already existing treatment modalities.

AUTHORS' CONTRIBUTION

NA: Data Collection, analysis, interpretation, write-up. ZN: Supervision. AA: Write-up. proof reading

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