Review Article

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The Efficacy of Rituximab in the Treatment of Membranous Nephropathy

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ABSTRACT

Rituximab is a chimeric monoclonal antibody directed against the CD20 expressed on B cells, originally used to treat lymphoma but is increasingly used for the treatment of autoimmune diseases. Membranous nephropathy is an autoimmune disease resulting from the deposition of IgG and complements components onto the subepithelial layer of the glomerular capillary wall and remains the leading cause of nephrotic syndrome in adults. Several prospective and retrospective studies showed rituximab induces remission and may decrease proteinuria in patients with membranous nephropathy. Considerable evidence supports the use of B-cell depletion as initial therapy in nephrotic patients with membranous nephropathy. This review focuses on the efficacy and safety of rituximab in the treatment of membranous nephropathy.

Keywords: Membranous nephropathy; rituximab; treatment

INTRODUCTION

Rituximab is a chimeric monoclonal antibody especially to B cell receptor, induces depletion of B lymphocytes. Recently, rituximab has been used widely in the treatment of membranous nephropathy (MN). Rituximab has significantly less adverse effects and complications. Rituximab treatment protocols for MN vary widely. Rituximab was initially used for the treatment of non-Hodgkin's lymphoma. Rituximab may represent a new therapeutic hope for the treatment of MN. MN is an immune-mediated disease that has a peak incidence during the fourth and fifth decades of life and affects more men than women. Progression to end-stage kidney disease is about 35% at 10 years.[1]

CLINICAL SIGNIFICANCE OF RITUXIMAB

EXTRARENAL CONDITIONS

Rituximab in non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma (NHL) is the most common hematological cancer in adults.[2] Rituximab was initially approved by the Federal Food and Drug Administration (FDA) in 1997 for the treatment of non-Hodgkin's lymphoma and then in June 1998 was approved for use in relapsed, low-grade, or follicular NHL by the European Medicines Agency, afterward in 2006 gained approval for use in combination with chemotherapies for aggressive forms of NHL.[3] The first clinical trial was performed by Maloney et al.in patients with indolent lymphoma.[4] Adding rituximab to chemotherapy can result in late-onset neutropenia. Rituximab has been safe and well-tolerated in all age groups.[2]

Rituximab in Rheumatoid Arthritis (RA)

FDA and European Medicines Agency approved rituximab to treat RA as two intravenous 1 gm infusions given two weeks apart with concomitant methotrexate (MTX) and premedication with an intravenous corticosteroid.[5] In 1998, the efficacy of rituximab in RA was first reported by a group of UK investigators in an open-label trial. The reduction of immunoglobulins, especially immunoglobulin G during repeated administration of rituximab may increase the risk of infection. Pregnancy, hypersensitivity to rituximab or other murine proteins, active serious infections, and severe heart failure are the contraindications of rituximab and lactating women should avoid rituximab treatment.[6]

Rituximab in Chronic Lymphocytic Leukemia (CLL)

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Chronic lymphocytic leukemia (CLL) is the most commonly present as adult leukemia. In vitro data show that rituximab sensitizes neoplastic cells to the effects of chemotherapeutic drugs when used in combination.[7] Rituximab in combination with fludarabine, cyclophosphamide was the first novel therapy for CLL to increase overall survival. Factors like the cost of rituximab may restrict patient access to this drug.[8]

Rituximab in Granulomatosis with Polyangiitis (Wegener'sGranulomatosis) and Microscopic Polyangiitis (MPA)

Rituximab was approved by FDA on April 19, 2011, in combination with glucocorticosteroids for the treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis.[9] Two randomized clinical trials have shown that rituximab is not inferior to cyclophosphamide in inducing remission in severe GPA and MPA.[10,11] The remission rate was about 90 % with rituximab in open-label clinical trials and case series. Rituximab was initially used for the treatment of refractory vasculitis in 2001. Rituximab is categorized as category 'C' drug due to lack of adequate data of fetal exposure to rituximab, thus effective contraception is recommended before the first infusion. Some complications and neonatal abnormalities were reported in pregnant during an assessment of the global safety database for rituximab.[12]

Complications of rituximab therapy in the postoperative period

Patients under treatment of immunosuppressive therapy have decreased in immunity, thus increasing the risk of infection and impairment of postoperative tissue healing. Godot et al. mentioned that spine surgery may have more risk of postoperative complications after rituximab therapy. The rate of short-term postoperative complications in RA patients receiving a few cycles of rituximab is 8.5%. The American College of Rheumatology (ACR) 2017 guidelines, recommended a 6-months wait period after the last rituximab dose, to schedule elective hip or knee surgery.[13]

In a retrospective study, Scemla et al. compared between 38 patients who underwent renal transplant with rituximab therapy with 26 patients who underwent renal transplant with other forms of treatment, where 55.3% of patients in the rituximab group developed severe bacterial infections compared to 60% of the patients without rituximab group.[14] To perform elective surgery, monitoring immunoglobulin levels, specifically IgG levels is suggested for at least 100 days after rituximab treatment. If IgG levels are abnormal, then administration of intravenous immunoglobulin (IVIG) is advised before surgery.[15]

RENAL CONDITIONS

Rituximab has been used widely in patients with and without kidney diseases. In kidney disease population, rituximab has been used in the treatment of membranous nephropathy, focal segmental glomerulosclerosis (FSGS), systemic lupus erythematosus (SLE), and minimal change disease (MCD).[16-19]

Role of rituximab on membranous nephropathy

Ronco and Nawaz et al. mentioned that about 80% of patients with MN have primary MN while nearly 20-25% of patients are secondary to autoimmune disease, infection, malignancy, drugs (e.g. penicillamine, non-steroidal anti-inflammatory drugs), or other non-identified autoantibodies.[20,21]

Rituximab induces the depletion of B lymphocytes through apoptosis via antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.[22] The studies done in Heymann nephritis showed subepithelial immune-mediated complement activation plays a significant role in the pathogenesis of MN.[23] Complement activation promotes podocyte apoptosis and shedding from the glomerular basement membrane in MN.[24] Most of the circulating B lymphocyte express CD20 markers and B lymphocyte depletion affects antibody production, B-cell–mediated antigen presentation, and activation of T cells and macrophages. (B Cell Depletion with Rituximab in Relapsing-Remitting Multiple Sclerosis Stephen). Thus, Rituximab, a monoclonal anti-CD20 antibody specifically targets CD20-expressing B lymphocytes.[25] Rituximab has been used successfully for the treatment of membranous nephropathy in adults since 2002.[26] Rituximab is used off-label in the treatment of membranous nephropathy. It has been significantly used in the treatment of autoimmune diseases due to its broad immunoregulatory effect and reduced side-effects as compared with other immunosuppressants. Several studies in recent years showed the efficacy of rituximab in improving the outcome of renal diseases of an underlying autoimmune cause, but the mechanism of action of this drug is still not clear.[27]

Since 2002 multiple studies were done among the western population using rituximab as first-line therapy as well as in patients resistant to other immunosuppressive regimens.[28] However, there is a lack of data in the Asian population.[29] Even though the available data about rituximab in idiopathic membranous nephropathy

is encouraging, there is no consensus regarding the optimum dose.[30] Ruggenenti et al. mentioned that a dose of rituximab 375mg/m2 once a week for 4 weeks is the most frequently used protocol, but eight-dose 'prolonged protocols', or 'extended protocols' with monthly infusions for 2 or 3 months following the standard four-dose regimen have also been used.[31,32] In a study done by Remmuzi, rituximab (375mg/m2) was infused every 4 weeks in 8 patients with idiopathic membranous nephropathy to evaluate the effect of rituximab. At weeks 4 and 20, urinary protein decreased from mean (SE) 8.6 g/24 h (1.4) to 3.8 (0.8) and 3.7 (0.9), respectively ($p<0.0001$). At week 20, there was a decrease in albuminuria and albumin fractional clearance by 70% and 65%, serum albumin increased by 31% and CD20 B lymphocytes fell below normal ranges.[28]

Ponticelli regimen and calcineurin inhibitors (CNI)

Randomized studies demonstrated that the modified Ponticelli regimen (mPR) has remained the standard treatment for decades, however, newer therapy rituximab has promising results. Ponticelli et al. used immunosuppression which is generally a combination of alkylating agents and steroids in his studies.[33-36] The regimen of rotating high-dose intravenous steroids and immunosuppression was first described in 1984 and has been the mainstay of treatment ever since.[33] At first methylprednisolone and chlorambucil were used in the Ponticelli regimen, later was modified to methylprednisolone and cyclophosphamide.[33-36] KDIGO's 2012 Clinical Practice Guideline for MN recommended using CNIs (Cyclosporine A or tacrolimus) as the alternative option for the ponticelli regimen.[37]

Comparison of efficacy of rituximab with Ponticelli regimen and CNIs

Despite treatment success, the modified Ponticelli regimen bears significant side-effects.[34,38] The recommended first-line immunosuppressive drugs carry many degrees of harm. Certain devastating complications include bone marrow suppression, infertility, drug-induced diabetes, hypertension, and cancer.[39-41] Unfortunately, these regimens generally result in the complete remission of < 35%.[41-43]

The modified Ponticelli regimen has low cost but needs frequent admission for steroid infusions. A matched cohort study showed that rituximab persistently reduced proteinuria in untreated patients and those not responding to immunosuppressive therapy or in those relapsed after transient remission.[31,43] These drugs though effective has high-relapse rates. In this context, rituximab is an attractive treatment option, considering its ease of administration and minimal risk of noncompliance.[30,44-46] Cyclophosphamide has a profound but unselective B-cell depleting effect, leading to reduced production of nephrotoxic antibodies. Whereas a more selective B-cell depleting effect of rituximab appears to be a promising approach.[32,47] It is well documented that there is an increased risk of malignancy many years after receiving cyclophosphamide therapy.

Rituximab, in contrast, has fewer complications and no risk of malignancy.[38,48] An important benefit of rituximab is its major impact on a patient's quality of life. Patients receiving rituximab benefit from the improvement in symptoms associated with remission of proteinuria and discontinuation of other immunosuppressive medications. While steroids, alkylating agents or CNIs, detrimentally affects the quality of life by toxicities of these medications, even after the remission is achieved.[31,49] Despite, the relative safety profile of rituximab, common infusion-related side effects, such as fever, chills, and rigors are reported to be 87%. Caution during the use of rituximab is advised by FDA in patients with a history of cardiovascular disease due to cases of angina, acute coronary syndrome (ACS), and arrhythmias related to rituximab infusion.[50] Rituximab reactions ranging from simple flushing and dyspnea to anaphylaxis usually occurs with the first infusion. These reactions occur due to a cytokine release potentially triggered by the murine element of the antibody.[51,52]

An important clinical benefit of rituximab associated with improvement or regression of the histologic lesion of MN was never reported with the use of other medications.[53] Remuzzi et al. used rituximab successfully in eight patients diagnosed as idiopathic membranous nephropathy with persistent nephrotic syndrome.[28,54] Marco et al confirmed that treatment of MN with rituximab (13 patients as first-line therapy and remaining 25 after conventional immuno-suppressive therapy) was remarkably safe and had a significantly higher rate of complete or partial remissions. Patients were given four weekly intravenous infusions dose of rituximab 375 mg/m2, where 39.5% (15 patients), 36.8% (14 patients), and 76.3% (29 patients) achieved complete remission, partial remission and the composite endpoint (complete or partial remission), respectively. There was a significant reduction in 24-hrs proteinuria level, while albuminemia increased constantly. Renal function wasn't significantly affected during the observation period. Circulating CD19+ B-cells were reduced significantly from the baseline value to the 24-month value (P <

0.01).[55] Till date only one published RCT(Gemritux) has investigated conservative therapy (nonimmune suppressive antiproteinuric therapy) in comparison with rituximab (375 mg/m2 at days 1 and 8 in patients with nephrotic proteinuria, normal range creatinine).[56,57]

Ongoing clinical trials of rituximab on membranous nephropathy

The ongoing STARMEN (Sequential Therapy With Tacrolimus and Rituximab in Primary Membranous Nephropathy) trial is comparing corticosteroids and cyclophosphamide for 6 months with 6 months of tacrolimus followed by a single dose of rituximab (1 g at days 1 and 15, repeated at 6 months independent of CD19 count).[56,58] Furthermore, REBOOT (Belimumab With Rituximab for Primary Membranous Nephropathy) trial is ongoing which will evaluate the effectiveness of a combination of belimumab and rituximab versus rituximab alone at inducing a complete remission.[59]

A pilot study is also ongoing where a combination of rituximab and cyclosporine are used, with tapering off cyclosporine after 6 months while giving repeated rituximab infusion at that point.[56] In multiple uncontrolled studies, rituximab showed a reduction in proteinuria of 60 to 80 % in the majority of patients for as long as 24 months after the initiation of immunosuppressive treatment.[28,32,60-62]

Fervenza et al. demonstrated the results of a prospective, randomized trial with adequate follow-up and statistical analysis in patients with membranous nephropathy and nephrotic-range proteinuria (Membranous Nephropathy Trial of Rituximab [MENTOR].[32] They addressed the question if an anti-CD20 monoclonal antibody was at least non-inferior to cyclosporine in inducing and maintaining remission of proteinuria. At 24 months of follow-up, 39 out of 65 patients (60%) in the rituximab group had complete or partial remission, as compared with 13 out of 65 patients (20%) in the cyclosporine group ($p<0.001$ for both non-inferiority and superiority). The progressive decline of renal function was slower with rituximab than with cyclosporine over the whole trial period, due to the chronic nephrotoxic effects associated with cyclosporine.[63] Membranous nephropathy recurs in approximately 42% of patients after renal transplantation and rituximab have been used successfully in these patients.[64-70]

Recent studies show that depletion of B lymphocyte with Rituximab seems an effective and safe treatment approach for first-line therapy of membranous nephropathy, with less adverse effects and relapse.[71-73] Moroni et al. used low-dose rituximab in his study. The result shows the partial response in a small number of patients and complete remission in a minority of patients, which means perhaps higher doses and longer treatments are necessary to treat MN, particularly in patients with high titers of anti-PLA2R antibodies.[57,71,74]

A French multicenter, randomized controlled trial [The Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy (GEMRITUX) study] evaluated the efficacy of rituximab in inducing remission in patients diagnosed with idiopathic membranous nephropathy of medium to high risk.[58,75] In this study 37 patients received rituximab (375 mg/m2 on days 1 and 8) as well as conservative therapy while 38 patients received conservative therapy only. Remission rates did not vary much at 6 months (35.1% in the rituximab group compared to 21.1% in the control group, $p = 0.21$). Although during extended follow up (median 17.0 months), remission rates were significantly higher in the rituximab group (64.9 vs. 34.2%, $p < 0.01$).[75]

In another randomized controlled trial, rituximab was added to non-immunosuppressive anti-proteinuric therapy which leads to significant improvements in immunologic and clinical outcomes, at 6 months period as well as till 24-months observational period. The remission rate and time to occur remission were similar in both groups at month 6, but the rates of remission were significantly higher in the rituximab group during the observation period. Here the titer of anti-PLA2R affected the remission rate as rituximab showed a dramatic effect on the anti-PLA2R titer.[58,71] B cell-targeted therapy like rituximab is effective as steroids and alkylating agents in achieving remission in membranous nephropathy, and available evidence suggests that it is safer and well-tolerated.[31]

CONCLUSIONS

In conclusion, rituximab can be used as first-line therapy in the treatment of membranous nephropathy, as rituximab significantly decreases proteinuria, has a less adverse effect, and a high rate of remission. Further studies might determine the efficacy and optimum dose of rituximab. Currently, ongoing clinical trials such as STARMEN and REBOOT trial can further evaluate the efficacy of rituximab in membranous nephropathy.

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