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Review Article

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Review on the Role of Therapeutic Rituximab in Idiopathic Membranous Nephropathy

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ABSTRACT

An autoimmune disease called the idiopathic membranous nephropathy is a glomerular disease which affects the adult population and leads to nephrotic syndrome. Although one-third of affected patients have spontaneous remission and proteinuria resolution with only supportive management, almost one-third evolved to end-stage renal disease and required hemodialysis. Several agents have been used to treat membranous nephropathy in addition to corticosteroids; some cases developed serious adverse events and required omission of therapy. A monoclonal antibody which is Rituximab works by deleting certain cells i,e CD20 B cells, which are the main pathogenic factors in this condition, and have been used to treat this disease. This narrative review aims to review the idiopathic membranous nephropathy and the role of rituximab in this condition in terms of efficacy and safety. A relevant article to the topic was selected through the PubMed database. We used the following Mesh terms: Membranous nephropathy, nephrotic syndrome, rituximab. Rituximab therapy proved its significant efficacy and safety in idiopathic membranous nephropathy patients. It induced and maintained partial or complete remission variably, with minimal and infusion-related adverse outcomes. Nonetheless, few serious adverse events have been reported secondary to rituximab therapy, which may need further randomized clinical trials to assess the safety profile of rituximab.

Key words: *Idiopathic membranous nephropathy, Membranous nephropathy, Nephrotic syndrome, Rituximab, Anticd20, Monoclonal antibody*

INTRODUCTION

The most common cause of nephrotic syndrome (NS) found in Caucasian individuals is related to an autoimmune-mediate glomerular disease called the Idiopathic membranous nephropathy (IMN) [1, 2]. While the disease

progresses slowly in nature, end-stage renal disease (ESRD can be seen in almost 40% of affected individuals) [1, 2]. Because of the high frequency of the disease, primary glomerulopathy is considered to be 2nd or 3rd most common condition which leads to, end-stage renal disease in in adults, though it is not frequent in children (biopsie of 1-7% s) [2, 3]. Besides, IMN is a common cause of NS in adults with a variety of course [4]. The incidence of IMN in the United States is projected at about 12 million per-anum with age range between 50 and 60 and 2:1 male predominance. IMN is commonly affected by white's people, then by Asians, black race, and Hispanics [3]. The current available immunosuppressive therapies include inhibitors of calcineurin and corticosteroids in addition to cytotoxic agents (e.g., cyclophosphamide - CYC). However, the above agents are partially successful in achieving decrease of proteinuria, and use of these agents can be related with serious adverse outcomes (toxicity of the bone marrow, pronounced infections, dysfunctions of gonads, malignancy-related risk of CYC in a long-term), which carries a high rate of failure [1, 2]. Therefore, several United States academic centers have recognized CYC as very toxic and considered it only in patients who showed a failure to less toxic immunosuppressive therapy [2].

Notably, remarkable remission of proteinuria and long-term renal survival was seen in almost up to 30% of patients with IMN with only supportive management, which usually occurs in the first two years after onset [1, 4]. dietary protein together with sodium intake is the initial supportive management, managing BP, hyperlipidemia, and edema. Additionally, IMN patients who continue to be nephrotic are at high risk for cardiovascular events and thromboembolic [2]. Cyclosporin has also been used successfully for IMN treatment and NS resistance to corticosteroids due to its different adverse effect profiles. Nonetheless, cyclosporin is a strong immunosuppressant agent which is related with substantial short and long-term toxicity. Common adverse effects of cyclosporin are, hirsutism, increased blood pressure, gingival enlargement, mild tremor, infections, raised levels of bilirubin, and mild nausea. Cyclosporin-associated hypertension may require anti-hypertensive medications and/or dose reduction [2].

IMN is most commonly facilitated by antibodies against the thrombospondin type 1 domain-containing 7A (THSD7A) (3-5%) in adults, M-type phospholipase A2 receptor (anti-PLA2R) (85%), the cationic bovine serum albumin, aryl sulfatase in childhood, and neutral endopeptidase(NEP) in newborns, an [3, 5]. The PLA2R antibodies are of certain clinical significance because they are common in IMN adult cases without obvious secondary causes, especially in men. The antibodies of THSD7A can be detected in not more than 2% of adult people with IMN, with a greater frequency in females. Presence of both PLA2R and THSD7A antibodies is reported to be seen in almost 1% of IMN. PLA2R and THSD7A antibodies have been proposed as biomarkers of IMN autoimmune activity; Furthermore, a dependable prognostic factor have been recently reported as high anti-PLA2R levels which may futher modify the treatment indications and increase the long-term outcomes of IMN in the future [5].

Regarding histological findings in IMN, it is characterized by the creation immune deposits at the subepithelial (extramembranous) which is associated with different levels of modifications in the morphology of the glomerular basement membrane (spikes). Immunofluorescence is an essential diagnostic technique because it presents the type and subtypes of immunoglobulin G within the deposits. Importantly, all IgG subclasses have been observed in immune deposits, while IgG1, IgG2, and IgG3 deposits are reported more frequently in secondary IMN (lupus, graft-versus-host disease, malignancies. In addition, the IgG4 subclass is commonly observed in IMN and absent in MN related to malignancy [5].

RESULTS AND DISCUSSION

Rituximab is a chimeric monoclonal antibody against the protein CD20 that deletes B cells through binding to the CD20 antigens via multiple mechanisms [4, 6]. With the presence of complementarity determining regions of the murine anti-CD20 antibody 2B8 in communication with human kappa and IgG1 heavy-chain constant region sequences [7, 8]. Initially RTX efficacy was tested in IMN patients by Remuzzi *et al*. more than 15 years ago [4]. As the IMN induced by B cells activation resulted in Ig deposition within the glomerular basement membrane and causing glomerular filtering barrier injury and subsequent proteinuria, targeting selective B cells halting the production of the pathogenic antibodies [9, 10]. Consequently, even though IMN autoantigens are still unknown, role of B cells is not yet clearly described. Improvement of the glomerular pathology in IMN is as result of agents that uniquely interfere with selective B cell antibodies production [9, 10].

The role of rituximab in IMN

Intravenous infusion of RTX was given every 4 weeks in a study for 3 male and 4 female patients that have IMN and persistent proteinuria for the last six months. As a result, proteins of the urine expressively and inconsistently decreased in all patients; 62% proteinuria reduced, 70% albuminuria reduced, fractional albumin 65% depletion increase in serum albumin by 31% vs. minimum starting point, linked with serum cholesterol reduction. Moreover, (proteinuria <1g/24 h) in two people who have attained full remission. Besides, through fluorescence-assisted cell-sorter analysis CD20 B lymphocytes declined to untraceable numbers following the first RTX prescription and stayed well under normal ranges until the end of the study [10]. Another study included 34 IMN patients with nephrotic proteinuria to receive RTX once in eighteen participants or twice in sixteen participants, where the first line for 19 patients was RTX and another 15 patients for the second line. 5 participants (14.7%) attained complete remission After 12 months of follow-up.10 (29.4%) partial and 19 (55.8%) did not presented any response. The clinical condition remains unchanged at 24 months of follow-up: two non-responders attained incomplete remission and two responders failed. Importantly, significant higher baseline glomerular filtration rate (GFR) was seen in responders and lowered anti-PLA2R antibodies compared with non-responders [11]. The latter study concluded that a higher RTX dose and longer treatment duration might be required to induce and maintain remission [11]. Likewise, the effect of RTX was reported in a prospective observational study where eight IMN patients received four weekly doses of RTX. The outcome includes a significant decrease in proteinuria, fractional albumin clearance, and increased serum albumin levels. Additionally, diastolic blood, serum cholesterol level, body weight, and pressure were gradually reduced along with improved edema in all patients [12].

In an open-label, randomized, multicenter clinical trial conducted by Fervenza *et al*., 130 IMN patients with nephrotic proteinuria were assigned for RTX (65 patients received two infusions, 1000mg each, prescribed 14 days apart; and again at 6 months if they showed incomplete response) or oral cyclosporin (65 patients received dose starting from 3.5 mg/kg/day for 12 months). After 12 months of follow-up, 39/65 (60%) of the RTX group and 34/65 (52%) of the cyclosporin group attained complete or incomplete remission. While after 24 months of follow-up, 39 patients (60%) of the RTX group and 13 (20%) of cyclosporin group had attained complete or incomplete remission. In addition, among patients who tested positive for PLA2R antibodies, the decrease in this antibodies level was faster and of greater magnitude and duration in the RTX group compared with the cyclosporin group. Notably, serious adverse outcomes were reported in 11 (17%) of the RTX group compared with 20 (31%) of the cyclosporin group [13]. This trial concluded that RTX is non-inferior to cyclosporin in inducing complete or partial remission of proteinuria at 12 months and superior in maintaining remission of proteinuria up to 24 months [13]. A similar result was reported in a prospective study of 20 IMN patients with nephrotic proteinuria, where four doses of RTX effectively achieved complete or partial remission in a significant number of patients [14]. Also, RTX use significantly reduced circulating CD19 B cell autoantibodies from baseline [14, 15].

A meta-analysis by Zou *et al*. had investigated the efficacy and safety of RTX use in biopsy-proven IMN adults and targeting complete or partial remission. After analyzing seven studies with 120 patients, RTX treatment showed excellent efficacy and tolerability in achieving complete or partial remission in >60% at 24 months. Adverse effects are rare and mostly infusion-related reaction which is generally mild [16]. Furthermore, another meta-analysis by Huang *et al*. for 21 studies (602 IMN patients) investigated RTX remission rates' efficacy for proteinuria. As a result, RTX therapy provides up to a 67% remission rate (Complete or partial) with a more significant reduction in patients with higher baseline proteinuria, lower baseline serum albumin levels, and lower estimated GFR levels. Nevertheless, the remission rates were not significantly associated with the anti-PLA2R antibodies level or previous immunosuppressant therapy [17]. In addition, a systematic review conducted by Bomback *et al*. concluded that RTX (375 mg/m2 once weekly for 4 weeks or 1 g every 14 days) achieves up to 15-20% complete remission and 35-40% partial remission with good tolerability and minimal side effects [18].

Rituximab adverse events

RTX therapy is well tolerated and often associated with side effects that are mainly mild infusion-related reactions [19, 20]. Serious adverse effects that require hospitalization or are proposed as life-threatening include interval infections, severe nausea, vomiting, and sweating [19]. Besides, RTX was reported to induce cutaneous rash in one patient, which was fully relieved after hydrocortisone injection. Another patient had an episode of hypotension that fully recovered with plasma expanders and intravenous hydrocortisone [21]. In addition, prophylactic medications are preferred to be given prior to RTX infusion, including 100mg intravenous methylprednisolone, 650mg acetaminophen, and 4 mg chlorpheniramine [22].

Nonetheless, two patients were reported to have serious adverse effects after RTX infusion; The first one suffered septic shock two months after RTX pulse therapy due to *Enterococcus spp*. with multiple pneumoniae reported

by chest radiography, for which a bronchoalveolar lavage revealed a culture of *Candida albicans.* Unfortunately, medical and supportive therapy was unsuccessful, and the patient ultimately expired. The second patient developed acute pulmonary insufficiency with septic shock one month after RTX pulse therapy, for which pulmonary aspergillosis was detected, and subsequent medical pulse therapy which reassuring was commenced. Luckily, in few weeks the patients' health was improved, but later the development of irreversible kidney damage was seen in the patient and ended up with hemodialysis dependent three times per week [22].

CONCLUSION

The most common immune-mediated glomerular disease which represents the leading cause of nephrotic syndrome in adult population is called idiopathic membranous nephropathy and may also result in end-stage renal disease. Although various medical agents have been used for treating this disease, including corticosteroids, alkylating and cytotoxic agents, these agents are well known for their serious adverse outcomes. Rituximab, a monoclonal antibody targeting CD20 B cells, has been gained attention in the last years to induce and maintain complete or partial remission in idiopathic membranous nephropathy. The use of rituximab among patients with membranous glomerular nephropathy resulted in successful complete or partial remission in the form of significant reduction of proteinuria, B cells autoantibodies, and increased serum albumin level. In addition, rituximab therapy reported improved serum cholesterol level and improved blood pressure and edema. Although rituximab is considered safe with excellent tolerability and mild infusion-related adverse effects, few serious adverse events have been reported in response to rituximab infusion, which may question the safety profile of this agent in the future.

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