Rituximab use in late antibody-mediated rejection

Antibody-mediated rejection (AMR) is an important cause of graft loss after the 1st year of transplant.[1] The standard treatment of AMR consists of steroid pulses, plasmapheresis (PP), and intravenous immunoglobulin (IV IG), however many patients show poor response to treatment and lose their graft. Rituximab has been used as a rescue treatment after resistant rejection or along with standard treatment in case reports and small studies.[1,2] Rituximab is a chimeric murine/human monoclonal antibody directed against B cell surface molecule CD20. The CD20 molecule is found on mature B cells but not on pro-B cells or plasma cells, thus administration of anti-CD20 antibody rituximab leads to elimination of peripheral B cells from the circulation but have no effect on mature plasma cells or B cells in lymphoid organs. There is prolonged depletion of CD20 B cells from peripheral circulation subsequent to use of rituximab.[3] There are reports of reduction in donor-specific antibody (DSA) titers with use of rituximab and also the presence of CD20 positive lymphoid aggregate in patients with steroid-resistant rejection and benefit of using rituximab in these patients. However, there are also reports of increased risks of infection after rituximab use including progressive multifocal leukoencephalopathy.[2] In renal transplantation, rituximab is also used in ABO-incompatible transplant and for desensitization in human leukocyte antigen-incompatible transplant.[2,3]

There is little data for use of rituximab in treatment of resistant rejection - especially in treatment of late AMR - and most data is retrospective. Becker *et al*. used rituximab for the treatment of 27 patients with rejection resistant to high-dose steroids or ATG with PP. Most patients responded to treatment and 2 year death-censored graft survival was 85% in this study. However, C4d staining and DSA was not done and patients did not receive IV IG.[4]

In another study, Kaposztas *et al*. compared patients who received rituximab with PP and only PP. This study also found that patients who received rituximab had better graft survival at the end of 2 years. Graft survival was 90% in rituximab group versus 60% in patients without rituximab, however these patients were not classified as resistant rejection, and most of these patients had early AMR and patients in rituximab group received more PP.[5] There are other smaller studies, which have used rituximab either along with standard treatment or used it after standard treatment and have shown variable response.[2]

Recently, Immenschuh *et al*.[6] analyzed 20 patients who received rituximab for the treatment of acute AMR, half of them responded and half did not, they found that patients who had more tubulitis, inflammation, lower glomerular filtration rate, and higher proteinuria are the one who do not respond to treatment.

The only randomized controlled trial on the treatment of AMR is the effects of rituximab on acute antibody-mediated rejection in renal transplantation (RITUX ERAH) trial, which compared rituximab with placebo in 38 patients along with standard treatment with PP and IV IG. This treatment did not detect any significant difference in outcome between the groups at the end of 1 year. However, the study was not powered to detect the difference, and all patients had early acute AMR.[7]

In this issue of *Indian Journal of Nephrology*,[8] Surendra *et al*. have treated nine patients with resistant late AMR with four doses of rituximab and did not find any beneficial effect of rituximab in these patients. The strength of study is that all patients fulfilled all three criteria of AMR, i.e., DSA and C4d positivity along with histological evidence of AMR. The patients were adequately treated with a regimen of steroid pulses, seven sessions of PP and post-PP, IV IG. After poor response to this treatment, they received rituximab. Authors also did post-rituximab DSA and found that DSA decreased significantly in only one patient, and all other patients had gradual deterioration of kidney function over 12 months of follow-up. The study highlights two things - first, the treatment of late AMR is disappointing and second adding rituximab does not help in these patients. There is only one study on treatment of late AMR by Gupta *et al*., who treated 23 patients and demonstrated that after initial response to treatment with rituximab in 18 patients, (creatinine decreased from 2.9 to 2.5 mg/dl), the response was not sustained in the long term. In addition, in about half (11/23) of these patients who did not respond to treatment, bortezomib was used, making interpretation regarding response to rituximab difficult.[9]

There are some limitations in the study by Surendra *et al*.; first, it was a retrospective study, and there were

only nine patients. Authors did not do a repeat kidney biopsy before rituximab, which might have given clues about chronicity of lesions. Nonetheless, this is the first report of use of rituximab for the treatment of resistant AMR in Indian patients, and DSA have been done in all patients before and after treatment with rituximab, making this study relevant. Future studies with more number of patients in a randomized manner are required to clarify this issue, till then it is probably wise to avoid use of rituximab in late AMR.

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