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Clinical Study Protocol

The Efficacy of Rituximab in High-risk Renal Transplant Recipients

Motoo Araki[a]*, Koichiro Wada[a], Yosuke Mitsui[a], Risa Kubota[a], Takashi Yoshioka[a], Yuichi Ariyoshi[a], Yasuyuki Kobayashi[a], Masashi Kitagawa[b], Katsuyuki Tanabe[b], Hiroshi Sugiyama[b], Jun Wada[b], Masami Watanabe[c], Toyohiko Watanabe[a], Katsuyuki Hotta[c], and Yasutomo Nasu[a]

Departments of [a]Urology, [b]Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, [c]Center for Innovative Clinical Medicine, Okayama University Hospital, Okayama 700–8558, Japan

Although graft survival following renal transplantation (RTx) has improved, outcomes following high-risk RTx are variable. Preexisting antibodies, including donor-specific antibodies (DSA), play an important role in graft dysfunction and survival. We have designed a study to investigate the safety and efficacy of anti-CD20 monoclonal antibodies (rituximab) in high-risk RTx recipients. Major eligibility criteria include: 1) major and minor ABO blood group mismatch, 2) positive DSA. Thirty-five patients will receive 200 mg/body of rituximab. The primary endpoint is the incidence of B cell depletion. This study will clarify whether rituximab is efficacious in improving graft survival in high-risk RTx recipients.

Key words: end-stage renal disease, immunosuppression, kidney transplantation

The incidence of end-stage renal disease has been increasing throughout the world. Renal transplantation (RTx) is the most effective and economical method of renal replacement therapy. RTx results in better quality of life and patient survival compared with hemodialysis or continuous ambulatory peritoneal dialysis [1]. Although graft survival following RTx has improved, graft survival following high-risk RTx remains poor. Preexisting and *de novo* antibodies, including donor-specific antibodies (DSA), play an important role in graft dysfunction, longevity, and loss [2]. Hence, treatment must focus on B cell suppression, as B cells are the source of donor-specific antibody production. Rituximab is an anti-CD20 monoclonal antibody that depletes circulating CD20+ B cells and plasma cells. Rituximab is used to treat non-Hodgkin's lymphoma and the lymphocyte predominant subtype of Hodgkin's lymphoma [3]. Recently, it has been used to prevent or treat antibody-mediated RTx rejection (AMR) [4–6] and antibody-mediated glomerulonephritis, including focal glomerular sclerosis (FGS) [7]. However, with the exception of ABO blood group major mismatch, rituximab has not been approved by the Japanese health care system for use in RTx. We postulate that rituximab may reduce the incidence of AMR and antibody-mediated glomerulonephritis in Japanese RTx recipients.

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*Corresponding author. Phone:+81–86–235–7287; Fax:+81–86–231–3986
E-mail:motoosh@md.okayama-u.ac.jp (M. Araki)

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Endpoints

The aim of this study is to evaluate the efficacy and safety of rituximab in Japanese RTx recipients. The primary outcome is the incidence of B cell depletion, AMR and recurrent glomerulonephritis. Secondary outcome measures include medication-related toxicity.

Study Design

The study is a single-arm, prospective, non-randomized, open label, single center investigation to evaluate the safety and efficacy of rituximab in high-risk RTx recipients. Fig. 1 shows an overview of the study design. The study periods are from Sep/17th/2014 to Mar/31st/2018.

Eligibility Criteria

All patients who meet the main inclusion and exclusion criteria will be invited for screening. The main inclusion and exclusion criteria are listed in Table 1. Of note, rituximab was approved by the Japanese national health care system for ABO blood group major mismatch RTx in February, 2016. However, the inclusion criteria remained unchanged because very little effectiveness data have been made available. Written informed consent will be obtained before any screening or inclusion procedure. The study was designed in compliance with the principles of the Declaration of Helsinki, and the protocol was approved by the institutional review boards of our hospital (approval no. m14013). The study was registered with the UMIN Clinical Trials Registry (UMIN-CTR), Japan (UMIN 000018769). The participants reviewed the informed consent document and received individual counseling with a thorough discussion of alternative treatment, including nonparticipation.

Treatment Methods

Treatment will be composed of 2 sequential phases: the induction phase and the renal transplantation phase. In the induction phase, 200 mg/body of rituximab will be administered over 5 h, 1 to 2 weeks prior to RTx. We chose a dose of 200 mg/body despite the fact that 375 mg/m^2 has been approved, due to a recent study that demonstrated moderate toxicity with the 375 mg/m^2 dose [3]. The prior study indicated that lower doses of rituximab are effective at depleting B cells in the spleen and in the peripheral blood [8]. As the evaluation of the primary endpoint, The B cells in the peripheral blood will be counted 3 days prior to RTx using flow cytometry. If we find that the B cell count is not 0 at this time point, an additional dose of 200 mg/body of rituximab will be

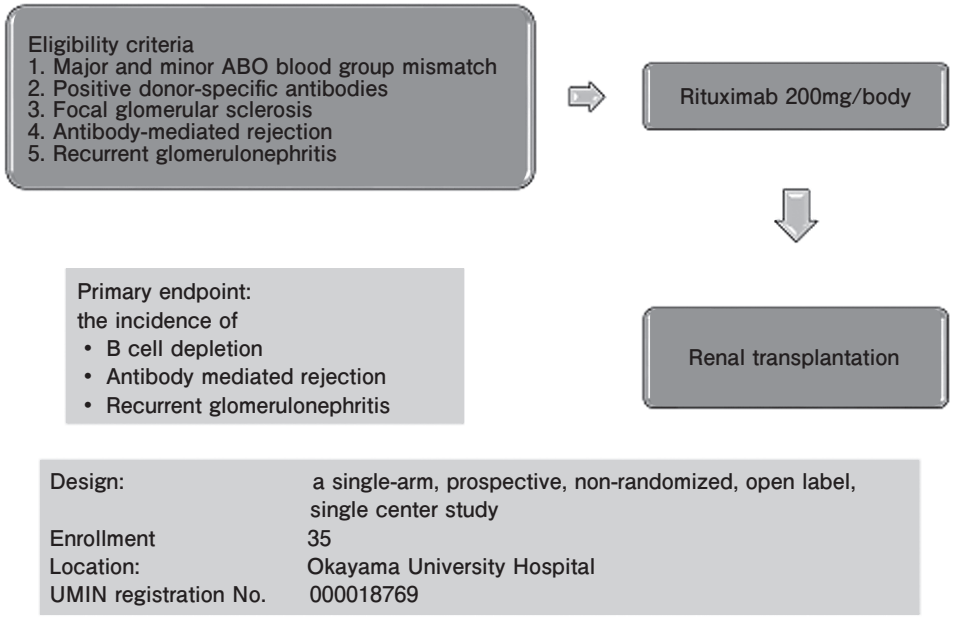

Fig. 1 Study design. Rituximab will be administered 1 to 2 weeks prior to RTx. The absence of B cells in the peripheral blood will be confirmed 1 week after the administration. If the B cell count is not 0, an additional dose of 200 mg/body of rituximab will be administered.

Table 1 Patient eligibility

Inclusion criteria
All ages
Patients with any of the following high-risk factors:
1. ABO incompatible (major mismatch)
2. ABO minor mismatch
3. donor specific antibody positive
4. original disease of focal glomerular sclerosis
5. original disease of recurrent glomerulonephritis
6. antibody-mediated rejection
Written informed consent
Exclusion criteria
A patient who does not meet inclusion criteria
A patient who meets inclusion criteria, but whom the authors judge to be inappropriate for the study

administered. In the renal transplantation phase, RTx will be performed within 2 weeks following the first dose of induction rituximab therapy. In case of post transplantation setting, the B cells in the peripheral blood will be counted one week following the administration. Vital signs, laboratory tests including complete blood count, the comprehensive metabolic panel, and urine analysis will be checked by 1 day after the administration. The incidence of any infection will be documented within one year of the administration.

Statistical Consideration

The primary end points are defined as:
1. the absence of B cells after the initial administration
2. the presence of antibody- mediated rejection
3. the presence of recurrent glomerulonephritis including focal segmental glomerulosclerosis
4. nadir serum creatinine levels after the administration

Antibody-mediated rejection and/or recurrent focal segmental glomerulosclerosis were diagnosed by elevated serum creatinine and clinical course. Biopsy is performed whenever possible. Those are followed for 1 year.

The secondary end point is defined as safety, including any possible adverse events. On average, 12 patients undergo RTx at our institution each year. We anticipate that 10 patients will require rituximab each year. A total of 35 patients will be included in the trial. All statistical analyses will be conducted using JMP software (ver. 11; SAS, Cary, NC, USA).

Discussion

We have designed a clinical study to determine the effects of rituximab in the pre- and/or post- transplantation setting. The study will clarify whether rituximab is safe and efficacious in high-risk Japanese RTx recipients. It will provide new and important data on the effectiveness of rituximab, specifically in Japanese RTx recipients.

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