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LETTER TO THE EDITORS

Low- versus high-dose rituximab for antibody-mediated rejection after kidney transplantation

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Dear Sir

The treatment of antibody-mediated rejection (AMR) after kidney transplantation is based on the association of plasma exchange (PE) with or without rituximab, with or without intravenous immunoglobulins (Iv-Ig) [1–3]. However, if used, the optimal dose of rituximab is still unknown. Furthermore, an increased risk of infection has been reported in kidney-transplant patients receiving rituximab, mainly when combined with polyclonal antibodies [4]. Here, we compared the efficacy and safety of low-dose (375 mg/m²/week for 2 weeks) to high-dose (375 mg/m²/week for 3–5 weeks, median 4) rituximab given for AMR after kidney transplantation.

Between 03/2004 and 01/2011, 39 kidney-transplant patients experienced an AMR, defined by a decreased glomerular filtration rate (GFR), histological features of humoral rejection, positive C4d staining, and the presence of donor-specific antibodies. AMR occurred 46 (1–417) days after transplantation. Initially, high doses of rituximab were given to 22 patients (group I) whereas 17 other patients received later and lower doses of rituximab (group II). Results for 22 of the 39 patients have been previously reported [2]. The patients' characteristics are presented in Table 1. All patients received steroid pulses (10 mg/kg/day for 3 days), PE, rituximab, as well as *Pneumocystis jiroveci* and cytomegalovirus prophylaxis for 12 months. Rabbit anti-thymocyte globulins (Thymoglobulin®; Genzyme-Sanofi Lyon, France, 1.25 mg/kg/day for 5 days) or OKT3 (5 mg/day for 5 days) was given to patients who had steroid-resistant cellular and humoral rejection. Before AMR, the proportion of patients receiving tacrolimus was higher in group II; however, after AMR, all patients received tacrolimus, mycophenolic acid, and steroids.

The time since the AMR to the last follow-up was significantly longer for patients in group I. At last follow-up, patient- and graft-survival rates were similar in both groups, respectively, at 91% and 59% for group I, and 82.3% and 58.8% for group II. Death-censored graft survivals were 68.2% in group I and 70.6% in group II. At the AMR episode, 19% of patients from group I and 56% from group II required dialysis ($P = 0.03$). In patients not requiring dialysis at diagnosis of AMR, estimated MDRD GFR was 28 (15–56) ml/min in group I and 34 (14–107) ml/min in group II. At last follow-up, eGFR was 35 (21–58) ml/min in group I and 44 (21–90) ml/min in group II, P = ns. The incidence of a bacterial or viral infection did not differ between groups during the follow-up period, although the incidence of fungal infection was lower in the low-dose rituximab group. Receiving low-dose rituximab (versus receiving high-dose rituximab) was the sole independent protective factor for fungal infection (OR: 0.11, $CI_{95\%}$ 0.012–0.986, $P = 0.05$).

Whether rituximab has a beneficial role on treating AMR is still unknown [5], although small series suggest it may have [6]. Here, despite the differences in length of follow-up and the small number of patients, the outcomes were similar regardless of whether rituximab was used at high- or low-dose. However, in the absence of histological data, their impact on chronic AMR is unknown. Less fungal infections occurred in patients receiving low-doses of rituximab.

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Conflict of interest

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Table 1. High- versus low-doses of rituximab for antibody-mediated rejection.

Factor	High-dose rituximab (group I) $n = 22$	Low-dose rituximab (group II) $n = 17$	*P*-value
Age (years)	46	50	ns
Gender (male/female)	14/8	10/7	ns
Previous transplantation (%)	36%	41%	ns
Previous pregnancies (%)	75%	71%	ns
Median number of HLA A/B/DR/DQ mismatches	5 (2–8)	3 (0–4)	ns
Median number of HLA A/B mismatches	2.5 (0–4)	2 (1–4)	ns
Median number of HLA DR/DQ mismatches	3 (1–4)	5 (1–8)	ns
Median PRA at transplantation (%)	0 (0–80)	0 (0–90)	ns
DSA at transplantation (%)	0%	0%	ns
Induction therapy	81.8%	94.1%	ns
RATG	31.8%	35.3%	ns
Anti-IL2R	50%	58.8%	ns
Immunosuppression at AMR			
Cyclosporine A	45.4%	17.6%	ns
Tacrolimus	45.4%	82.4%	0.02
mTOR inhibitors	4.5%	0%	ns
MPA	81.8%	100%	ns
Steroids	100%	100%	ns
Median time since transplantation to AMR (days)	58.5 (5–417)	21 (1–359)	ns
Median time since AMR to last follow-up (months)	44 (6–86)	17 (4–79)	0.01
Number of PE sessions	6 (2–17)	6 (1–12)	ns
T-cell depleting agents for AMR	27.2%	23.5%	ns
RATG	50%	75%	ns
OKT3	50%	25%	ns
Iv-Ig	19%	17.6%	ns
Patients' survival	90.9%	82.3	ns
Cause of death			
Infection	50%	66%	ns
Cardiovascular event	0%	0%	ns
Others	50%	33%	ns
Graft survival (%)	59%	58.8%	ns
Death-censured graft survival (%)	68.2%	70.6%	ns
Dialysis at AMR episode (%)	18.2%	52.9%	ns
eGFR at AMR episode (ml/min)	28 (15–56) ($n = 17$)	34 (14–107) ($n = 8$)	ns
eGFR at M3 after AMR (ml/min)	35 (9–66) ($n = 22$)	39 (16–79) ($n = 16$)	ns
eGFR at M6 after AMR (ml/min)	31.5 (13–61) ($n = 20$)	42 (15–96) ($n = 13$)	ns
eGFR at M12 after AMR (ml/min)	35 (15–54) ($n = 17$)	42 (24–79) ($n = 9$)	ns
eGFR at last follow-up (ml/min)	35 (21–58) ($n = 15$)	44 (21–90) ($n = 11$)	ns
Infection rate (%)	72.3%	58.8%	ns
Bacterial infection (%)	54.5%	52.9%	ns
Viral infection (%)	40.9%	29.4%	ns
Fungal infection (%)	36.4%	5.9%	0.052
CD4 cell count at month 6 after AMR (/mm^3)	332 (15–1241)	133 (8–727)	ns
CD8 cell count at month 6 after AMR (/mm^3)	229 (38–725)	286 (18–498)	ns
CD4/CD8 cell ratio at month 6 after AMR	1.35 (0.07–3.95)	0.72 (0.11–1.74)	ns
CD19 cell count at month 6 after AMR (/mm^3)	0 (0–183)	0 (0–5)	ns

HLA, human leukocyte antigen; PRA, panel-reactive antibodies; DSA, donor-specific antibodies; RATG, rabbit anti-thymocyte globulins; Anti-IL2R, anti-interleukin2 receptor; AMR, antibody-mediated rejection; CNI, calcineurin inhibitors; mTOR, mammalian target for rapamycin; MPA, mycophenolic acid; PE, plasma exchange; Iv-Ig, intravenous immunoglobulins; eGFR, estimated glomerular filtration rate.

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