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INVITED COMMENTARY

Current perspectives to overcome a positive crossmatch in living donor renal transplantation*

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Transplantation of a living donor kidney is in general the best treatment option for patients with end-stage renal disease. Two major advantages as compared to transplantation with a deceased donor kidney are the avoidance of waiting time and the superior results in terms of renal function and graft survival. In some patients who are lucky enough to have a person in their neighborhood who are willing to donate a kidney, the transplantation cannot be performed directly because there is ABO blood type incompatibility between donor and recipient, or because of a positive lymphocyte crossmatch, based on the presence of donor-specific antibodies. During recent years, several strategies have been developed to enable transplantation in these cases. A first approach is to use a living donor kidney exchange program, which can result in successful matches in more than half of the crossmatch-positive couples [1]. With the incorporation of kidneys from nondirected, anonymous donors in such an exchange program, domino-paired chains of transplantations can be set up, which end with the transplantation of a living donor kidney to a recipient from the waiting list [2]. However, for a substantial number of recipients, these exchange programs do not result in a successful donor–recipient match. In these cases, desensitization strategies to reduce the titer of ABO blood group antibodies or anti-HLA antibodies can be employed. Desensitization techniques are based on the extracorporeal removal of antibodies, treatment with intravenous immunoglobulins, and on immunosuppressive therapy. Since these procedures carry additional risks for the transplant recipient, desensitization treatment should ideally be reserved for recipients who cannot be served with a donor kidney after several rounds of matching in a (multicenter) exchange program. Unfortunately, kidney exchange programs are not allowed by legislation in every country.

In this issue of Transplant International, Morath *et al.* present the results of living donor kidney transplantation in nine crossmatch-positive patients with peritransplant immunoadsorption (IA) and induction therapy with the anti-CD20 antibody rituximab [3]. Three patients also underwent pretransplant plasmapheresis. In one additional patient with a negative crossmatch but high titers

of donor-specific antibodies, the same strategy was applied. The patients required a median of 10 IA treatments before transplantation, and a median of 7 thereafter. After a median duration of follow-up of 19 months, 9 out of 10 patients had a functioning graft, and there were only three episodes of reversible antibody-mediated acute rejection. Moreover, the side effects of the protocol appeared minimal. The main drawbacks of this uncontrolled study were its small size, the fact that the study protocol underwent some changes over time, and the relatively short follow-up. Nevertheless, the data are promising and ask for comparison with the results from other desensitization strategies in highly sensitized recipients of living donor kidneys.

One of the main questions concerning this type of studies is whether it was really necessary to apply a desensitization protocol in each patient included in the study. There appears to be quite some variation between transplant centers in the criteria that are used to preclude straightforward execution of a living donor transplantation in the presence of anti-HLA antibodies. In this regard, it should be noticed that with highly sensitive solid-phase antibody assays, like Luminex bead technology, donor-specific antibodies can be detected that have no detrimental effect on graft survival [4]. Therefore, the complement-dependent cytotoxicity crossmatch, with the addition of dithiothreitol to remove IgM antibodies, still remains the gold standard for the assessment of the functional relevance of anti-HLA antibodies in many centers. Accordingly, it can be disputed whether desensitization techniques are necessary in case of a negative CDC crossmatch, even when donor-specific antibodies are detectable. To account for this issue when comparing the results of various studies, Table 1 contains a column that gives the number of patients with a positive CDC crossmatch for each study. From the overview in Table 1, it is clear that the results obtained by Morath *et al.* are favorable as compared to those observed by others. While desensitization has usually been accomplished by plasmapheresis and administration of intravenous immunoglobulins, the current study was based on IA, which appears highly effective in removing immunoglobulins from the circulation and was already applied to render a positive crossmatch negative immediately before deceased donor kidney transplantation [12]. All patients also received rituximab, but the added value thereof cannot be judged at this moment. Potential advantages of IA as compared to plasmapheresis are a better tolerability and circumvention of the need for substitution with fresh frozen plasma. Remarkably, despite the nearly complete removal of IgG from the circulation after the pretransplant course of IA, there was no obvious increase in the frequency of infections. After the transplantation, the titer of donor-specific antibodies remained low in the majority of patients, even after discontinuation of IA treatment. It is suggested that the treatment with rituximab contributed to this finding. Notably, in all patients with persistently elevated or *de novo* Luminex detected donor specific antibodies, there were signs of antibody mediated rejection. The median costs of the columns and disposables used for the IA

Table 1. Studies on living donor transplantion after desensitization of sensitized recipients.

First author	Number of patients	Positive CDC test results prior to desensitization	Desensitization strategy	Mean follow up (years)	Graft survival	Antibody-mediated rejection
Montgomery [5]	4	1 T cell +* and B cell +	PP + IVIG	0.8	100%	100%
Schweitzer [6]	11	11 T cell +*	PP + IVIG	1.1	100%	27%
Gloor [7]	14	14 T cell +*	PP + IVIG + RTX + splenectomy	1.2	79%	43%
Magee [8]	28	21 T cell +* 26 B cell + 16 T cell + and B cell +	PP + IVIG	NA	90% at 2 years	39%
Thielke [9]	49	7 T cell +* 13 B cell +*	PP + IVIG (n = 28) PP + IVIG + RTX (n = 21)	1.0	93% at 1 years	20%
Haririan [10]	41	NA, not required for inclusion	PP + IVIG	3.9	90% at 1 years	12%
Vo [11]	31	NA, not required for inclusion	IVIG + RTX	1.6	90% at 2 years	35%
Morath [3]	10	5 T cell + 8 B cell + 4 T cell + and B cell +	IA + RTX (n = 7) IA + RTX + PP (n = 3)	1.6	100% at 2 years	30%

*Crossmatch test was enhanced by antihuman immunoglobulin.
CDC, complement-dependent cytotoxicity; IA, immunoadsorption IVIG, intravenous immunoglobulin; NA, not available; PP, plasmapheresis; RTX, rtixuximab.

treatment amounted to about €22.500 per patient. Even when personnel costs are included, performing a successful transplantation after desensitization is a money-saving procedure as compared with prolonged continuation of dialysis treatment. On the other hand, the potential complications and costs of desensitization urge for caution to use these techniques in cases where the benefits are more questionable.

In summary, desensitization by means of IA and anti-CD20 antibodies seems an attractive approach. The long term results and confirmation of the beneficial outcome in other patient cohorts are awaited with interest. Meanwhile, the promising data on the efficacy of the complement inhibitor eculizumab in the prevention and treatment of antibody-mediated rejection in sensitized patients may be extended [13,14]. Altogether, recent developments have gradually improved the perspectives for living donor kidney transplant candidates who have donor-specific antibodies resulting in a positive crossmatch.

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