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LETTER TO THE EDITORS

Maintaining immunosuppressive treatment after early allograft nephrectomy does not reduce the risk of anti-HLA allosensitization

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Dear Sir,

Early loss of a kidney allograft within the first days or weeks after transplantation occurs in 3–5% of kidney transplant patients [1,2]. It is mainly caused by artery and/or vein allograft thrombosis [2] and requires a rapid allograft nephrectomy. We have previously shown that, even after a short transplant period, donor-specific antibodies (DSAs) and non-DSA anti-HLA antibodies develop in up to 50% of patients who stop immunosuppressive treatments immediately after an early allograft nephrectomy [3]. Mechanisms leading to sensitization are incompletely explained, but could involve the persistence of the donor's antigens after allograft removal, particularly in the vascular patches. The presence of preformed anti-HLA DSAs is associated with a poor kidney allograft outcome [4]. Hence, avoiding the development of anti-HLA antibodies is mandatory to allow rapid access to kidney transplantation without DSAs. Therefore, we have speculated that maintaining immunosuppressive therapy for 3 months after kidney allograft nephrectomy might reduce the occurrence of anti-HLA immunization.

Between July 2007 and December 2013, 925 kidney transplantations were performed in our institution. Among these, 43 (4.6%) experienced an early allograft loss, defined by graft loss within the first week after transplantation and that required rapid allograft nephrectomy. Only patients who were eligible for retransplantation and were screened for anti-HLA antibodies after an allograft nephrectomy were included in this study ($n = 33$). Arterial and/or venous thromboses were the main causes of graft loss.

Between July 2007 and November 2012, 21 early graft losses occurred. At that time, the policy in our institution was to stop all immunosuppressive drugs immediately after a kidney allograft nephrectomy. At transplantation, all patients had received mycophenolate mofetil (1 g) and a steroid pulse (10 mg/kg). Fifteen of the 21 patients had also received an induction therapy with polyclonal antibodies ($n = 3$) or anti-CD25 monoclonal antibodies ($n = 12$). After transplantation, all patients were given calcineurin inhibitors, mycophenolic acid, and steroids.

Between November 2012 and December 2013, there were 12 early losses of kidney allografts. Continued immunosuppressive therapy was proposed for all patients but one. This latter patient had a full HLA match with his donor. Hence, the 11 remaining patients were given immunosuppressive therapy for 3 months after having given their written informed consent. Before transplantation, all patients had received mycophenolate mofetil (1 g) and a steroid pulse (10 mg/kg). Ten of the 11 patients also received an induction therapy of polyclonal antibodies ($n = 2$) or anti-CD25 monoclonal antibodies ($n = 8$). After transplantation, all patients were given calcineurin inhibitors, mycophenolic acid, and steroids. After the kidney allograft nephrectomy, all patients were given tacrolimus (target trough level of 4–6 ng/ml), mycophenolate mofetil (500 mg b.i.d.), and low-dose steroids (5 mg/day) for 3 months.

Anti-HLA antibodies were assessed for class I HLAs in A/B and class II in DR/DQ IgG before and after transplantation, using Labscreen single Ag HLA detection tests (One Lambda, Canoga Park, CA, USA). After allograft nephrectomy, anti-HLA antibodies were tested on day 15 and at months 1, 3, 6, 9, and 12 postnephrectomy. A baseline mean fluorescence intensity value of >500 was considered positive.

Before transplantation, complement-dependent cytotoxicity cross-matches were negative for all patients. The median time between transplantation and allograft nephrectomy was 1 day (range: 0–2) in the group that continued immunosuppressive therapy and 1 day (range: 0–5) in the group that promptly stopped immunosuppressive therapy after allograft nephrectomy, termed the controls (P = ns). None of the graft losses were related to an acute rejection episode. One patient from the immunosuppression group had psychiatric complications at 1 week after the allograft nephrectomy and stopped all immunosuppressive drugs. Another patient from the same group presented

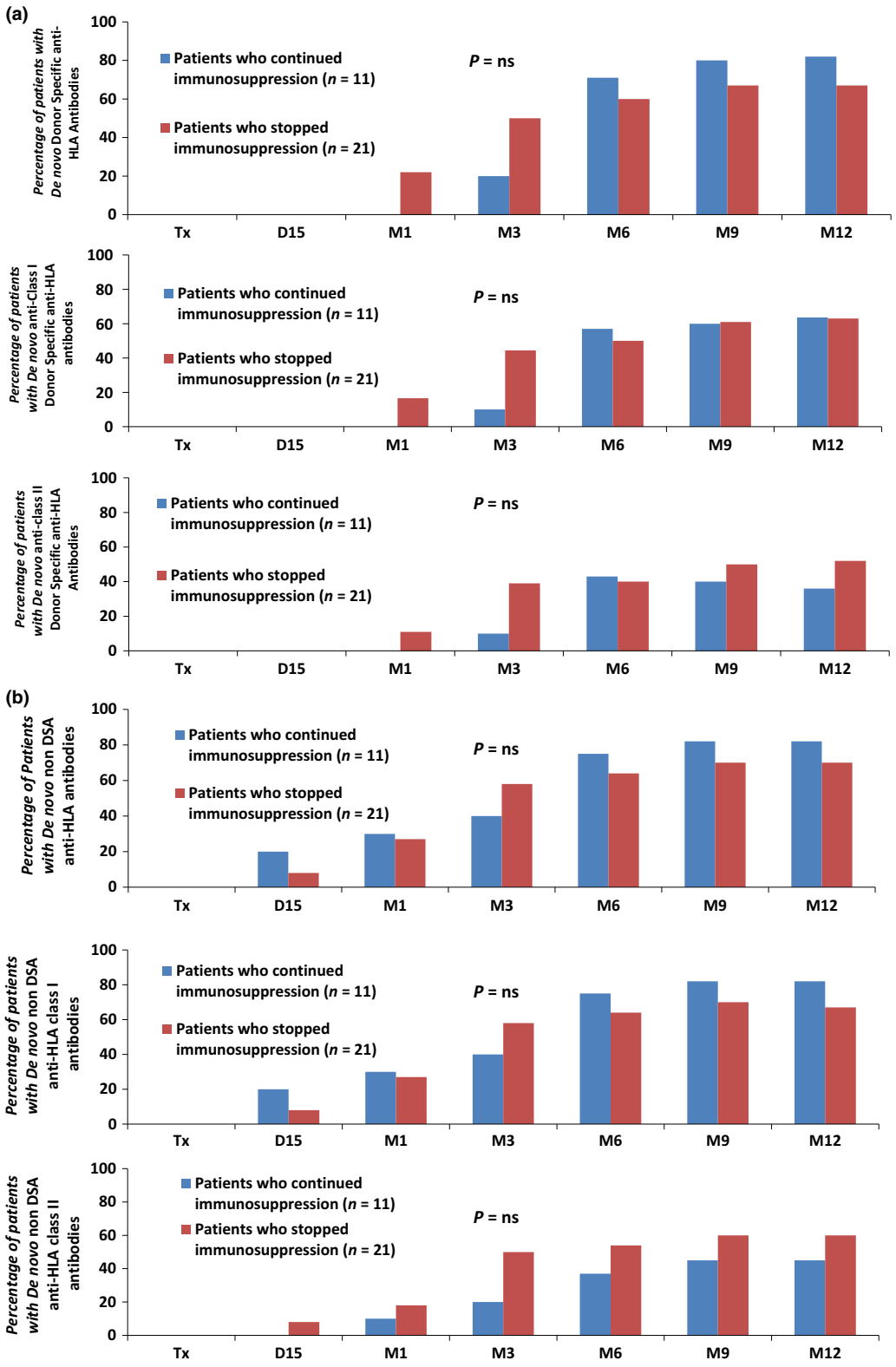

Figure 1 (a) Development of *de novo* anti-HLA DSAs after an allograft nephrectomy in patients who continued or did not continue immunosuppression treatment. (b) Development of *de novo* non-DSA anti-HLA antibodies after an allograft nephrectomy in patients who continued or did not continue immunosuppression treatment.

with infectious aortitis at 3 weeks postallograft nephrectomy: Immunosuppressive therapy was then stopped. The other nine patients received immunosuppressive drugs for the scheduled 3-month period.

Before transplantation, no patient had detectable anti-HLA class I/ II DSAs (Fig. 1). At 1 year postallograft nephrectomy, anti-class I, II, and I+II DSAs were present, respectively, in 5 (45%), 2 (18%), and 2 (18%) patients who had continued immunosuppressive treatment and in 4 (19%), 2 (9%), and 8 (38%) of the controls (P = ns).

Before transplantation, 73% and 86% of patients had no anti-HLA antibodies in the immunosuppressive group and the control group, respectively (P = ns). We did not observe any difference concerning the occurrence of anti-HLAs other than DSAs during the follow-up (Fig. 1b).

Three of the 11 (27%) patients who continued immunosuppressive therapy presented with serious infectious complications during treatment: herpes encephalitis at 80 days postallograft nephrectomy, infectious aortitis that required immediate surgery on day 21 postallograft nephrectomy, and an infection at the surgical site (day 10). In the control group, two of the 21 (9.5%) patients presented with a serious infectious complication, that is, bacteremia on day 10 and severe acute respiratory syndrome on day 5 postallograft nephrectomy (P = ns). The outcomes were good for all five patients. Complications at the surgical site occurred more frequently in patients who continued immunosuppressive therapy, that is, 4 of the 11 patients (including one hematoma, one lymphocele, one surgical-site infection, and one eventration), compared with only one of the 21 patients that required a surgical-site revision in the control group (P = 0.04).

Previous reports have shown that even early allograft failure, when it has required an allograft nephrectomy within the first hours or days after transplantation, is associated with a significant risk of sensitization [3,5]. To the best of our knowledge, no study has previously assessed the effect of continuing immunosuppressant treatment after early graft nephrectomy on the occurrence of anti-HLA antibodies. In this study, in patients who continued immunosuppressive therapy, we did not observed a reduction of allosensitization. In addition, the incidence of surgical complications was significantly greater in those who continued immunosuppressant treatments; more infectious complications were also observed in this group, although this was not statistically significant. Several published studies show that continuing immunosuppressive therapy after allograft failure is associated with increased comorbidities and infectious-disease complications [6,7].

Despite the small number of patients, our preliminary results suggest that maintaining immunosuppressive treatment after early allograft nephrectomy could not prevent allosensitization. Future larger prospective studies are required.

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