Transplant International

LETTER TO THE EDITOR

Successful treatment of acute kidney allograft rejection using extracorporeal photopheresis in the context of post-transplant lymphoproliferative diseases: three successive cases

Jean-François Augusto[1,2], Philippe Gatault[3], Johnny Sayegh[1], Anne-Sophie Garnier[1], Agnès Duveau[1], Elodie Merieau[3], Elodie Bailly[3], Jean-François Subra[1,2] & Matthias Büchler[3]

1 Service de Néphrologie-Dialyse-Transplantation, Université d'Angers, CHU Angers, Angers, France
2 CRCINA, INSERM, Université de Nantes, Université d'Angers, Angers, France
3 Service de Néphrologie et Immunologie Clinique, CHRU de Tours, Tours, France
E-mail: jfaugusto@chu-angers.fr

Dear Editors,

Kidney allograft loss occurs within 2 years in one third of patients with post-transplant lymphoproliferative disease (PTLD). Acute rejection (AR) risk is increased as a result of strong immunosuppression minimization following PTLD [1–3]. Here, we report extracorporeal photopheresis (ECP) use in three successive kidney transplant recipients for treatment of concomitant acute cellular and humoral rejection occurring after immunosuppression minimization following PTLD diagnosis. We used a standardized protocol associating ECP (CELLEX device; Therakos, Exton, PA, USA), methylprednisolone and intravenous immunoglobulin (IVIG, 2g/kg every 3 weeks) and prospectively assessed kidney function, donor-specific antibody (DSA) and graft histology (Table 1).

The first patient, a 17-year-old female, received induction with basiliximab and was maintained on tacrolimus (Tac), mycophenolic acid (MPA) and prednisone (Pred). At month 21, she developed PTLD unrelated to Epstein–Barr virus (EBV) with splenic and mesenteric lymph nodes. Tac was withdrawn, MPA decreased by 50% and Pred was maintained at 20 mg/day. At month 23, Scr rose to 150 µmol/l and graft biopsy showed cellular AR. Despite Tac reintroduction and five methylprednisolone pulses, AR was resistant and *de novo* anti-A1 and anti-A2 DSA developed leading to start IVIG. At month 24, Scr was 199 µmol/l and biopsy showed mixed rejection. As anti-thymocyte globulin use was not possible in the PTLD context, we maintained IVIG and started ECP. After three months (month 27) under ECP (16 sessions) and IVIG, Scr was 125µmol/l, DSA level decreased but biopsy showed persistent AR. ECP had to be stopped because of vascular access failure, and IVIG was continued for 6 more months. At month 33, biopsy exhibited complete AR regression, Scr was 86 µmol/L and IVIG was stopped. Long-term follow-up was favourable without PTLD recurrence and normal renal function (Figure S1).

The second patient, a 51-year-old female, was induced with basiliximab and maintained on Tac, MPA and Pred. Post-transplant Scr was 139 µmol/l, but she developed pre–renal acute kidney injury at month 2. At month 3, she developed EBV-induced PTLD with cervical and axillary lymph nodes. Tac was withdrawn, MPA decreased by 50% and Pred was maintained at 20 mg/day. At month 6, Scr increased to 169 µmol/l and *de novo* anti-DQ2 DSA was detected. Biopsy showed mixed AR, which was treated with Tac reintroduction, five methylprednisolone pulses, IVIG, six sessions of plasma exchange and one rituximab injection. At month 12, biopsy showed persistence of active lesions without chronic allograft glomerulopathy. Anti-DQ2 DSA level decreased, but a *de novo* anti-DP1 DSA was detected. We started ECP (25 sessions) and IVIG. At month 18, biopsy showed persistent AR with Scr at 139 µmol/l but DSA was no longer detectable. Then, we decided to stop IVIG and to maintain ECP (20 sessions). At month 24, biopsy showed improvement in AR lesions and we stopped ECP. Long-term follow-up was favourable with stable kidney function, undetectable DSA and no PTLD recurrence (Figure S2).

The third patient was a 9-year-old boy who received a graft from his mother. Post-transplant Scr was 78 µmol/l, and protocol biopsy at month 3 was normal.

doi:10.1111/tri.14006

Table 1. Patients 1, 2, 3: Scr levels and transplant histology according to Banf classification.

	Months (M) from transplantation	Serum creatinine (µmol/l)	Banff										
			g	i	t	v	ah	cpt	cg	ci	ct	cv	C4d
Patient 1	M23	150	0	3	3	0	0	3	0	0–1	0–1	0	0
	M23 + 2 weeks	199	1	2–3	2–3	0	0	2–3	0	1	1	1	0
	M27	126	1	1	0	0	0	2	0	2	2	0–1	0
	M33	86	0	0	0	0	0	0	0	2	2	0	0
Patient 2	M2	278	0	0-1	0	0	3	0–1	0	2	2	2	0
	M6	169	2	2	3	0	1	2	0	1	1	0	2
	M12	134	3	2	2	0	2	3	0	3	3	1	0
	M18	139	3	1	1	0	2	3	0	3	3	0	0
	M24	159	1	1	1–2	0	2	1	0	2	2	2	0
Patient 3	M12	162	1	x	2	0	1	0	0	3	3	0	0
	M27	105	0	0	1	0	0	0	0	1	1	0	0

At month 7, he developed multivisceral EBV-associated PTLD with graft localization leading to Tac and MPA withdrawal. He was maintained with 10 mg/day Pred. PTLD was treated with 6 rituximab injections resulting in complete regression of EBV replication and disappearance of hypermetabolisms on PET Scan. At month 12, Scr rose to 162 µmol/l, *de novo* anti-DQ7 DSA was detected and graft biopsy showed AR. Treatment consisted of 3 methylprednisolone pulses, ECP and MPA reintroduction. MPA was replaced by azathioprine for leukopenia. At month 20, Scr was 97 µmol/l and anti-DQ7 DSA level decreased, leading us to stop ECP. At month 27, *de novo* anti-B27 DSA was detected and anti-DQ7 DSA increased; however, a novel biopsy showed regression of AR lesions without chronic rejection features. Following this, we decided to reintroduce Tac. Long-term follow-up was good with stable kidney function, undetectable DSA and no PTLD recurrence (Figure S3).

The efficiency of ECP in kidney transplantation (KT) remains difficult to assess, given the heterogeneity of both patients' conditions and concomitant use of ECP with other immunosuppressants [4]. As a consequence, no guidelines are yet available for its use in KT [5]. Here, we used ECP for AR occurring in the specific setting of PTLD following KT. Treatment of PTLD requires a dramatic decrease in immunosuppressive treatment that is further associated with a high rate of AR [2,6]. In such situations, treatment of severe AR is often limited, depending on PTLD stage, but also on the delay between PTLD diagnosis and AR.

Our observations suggest a beneficial effect of ECP for controlling AR. After initiation of ECP, we observed a decrease in DSA MFI in patients 2 and 3, suggesting that ECP may control antibody-producing B cells. We also observed regression of acute glomerular lesions in all patients without the development of major chronic lesions related to antibody-mediated rejection. The immune mechanisms induced by ECP remain poorly understood. They are supposed to be related to the reinfusion of irradiated mononuclear cells [7, 8] that induce regulatory T cells and promote the production of regulatory cytokines. Whether ECP may also modulate other immune cells such as T follicular helper cells or natural killer cells would merit investigation given the critical role of these cell subsets in AR pathophysiology.

The optimal duration of ECP remains undetermined. We decided to stop treatment in patients 2 and 3 after achieving good biological, immunological and histological responses. As also found for GvHD patients, the response we observed in patient 1 may suggest that the first 2 or 3 months of therapy are very crucial.

We believe that ECP should be used at an early stage of AR and before the development of irreversible tissue injury. ECP appears to be safe, and our observations suggest that it may be an efficient therapeutic option for kidney allograft rejection following PTLD. Furthermore, these observations support the need for prospective trials for investigating whether ECP may have a place for prevention or treatment of AR in other conditions.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The patients gave their consent for the use of their medical data. No organs from executed prisoners were used in this study.

Transplant International 2021; 34: 2415–2417

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Case1: Clinical course, Scr, DSA level and treatment. Abbreviations: Tac, tacrolimus; MPA, mycophenolate acid; Pred, prednisone; MP, methylprednisolone pulses; ECP, extracorporeal photopheresis; IVIG, intravenous immunoglobulin; Scr, serum creatininemia; MFI, mean fluorescence intensity; PTLD, post-transplant lymphoproliferative disease.

Figure S2. Case 2: Clinical course, serum Scr, DSA level and treatment. Abbreviations: Tac, tacrolimus; MPA, mycophenolate acid; Pred, prednisone; MP, methylprednisolone pulses; PE, plasma exchange; ECP, extracorporeal photopheresis; IVIG, intravenous immunoglobulin; Scr, serum creatininemia; MFI, mean fluorescence intensity; RTX, Rituximab; PTLD, post-transplant lymphoproliferative disease.

Figure S3. Case 3: Clinical course, Scr, DSA level and treatment. Abbreviations: Tac, tacrolimus; MPA, mycophenolate acid; AZA azathioprine; Pred, prednisone; MP, methylprednisolone pulses; ECP, extracorporeal photopheresis; IVIG, intravenous immunoglobulin; Scr, serum creatininemia; MFI, mean fluorescence intensity; RTX, Rituximab; PTLD, post-transplant lymphoproliferative disease.

REFERENCES

1. Sprangers B, Riella LV, Dierickx D. Posttransplant lymphoproliferative disorder following kidney transplantation: a review. *Am J Kidney Dis* 2021; **78**: 272.
2. Caillard S, Porcher R, Provot F, *et al*. Post-transplantation lymphoproliferative disorder after kidney transplantation: report of a nationwide French registry and the development of a new prognostic score. *J Clin Oncol* 2013; **31**: 1302.
3. Caillard S, Lamy FX, Quelen C, *et al*. Epidemiology of posttransplant lymphoproliferative disorders in adult kidney and kidney pancreas recipients: report of the French registry and analysis of subgroups of lymphomas. *Am J Transplant* 2012; **12**: 682.
4. Ahrens N, Geissler EK, Witt V, *et al*. European reflections on new indications for extracorporeal photopheresis in solid organ transplantation. *Transplantation* 2018; **102**: 1279.
5. Knobler R, Arenberger P, Arun A, *et al*. European dermatology forum: Updated guidelines on the use of extracorporeal photopheresis 2020 - Part 2. *J Eur Acad Dermatol Venereol* 2021; **35**: 27.
6. Dierickx D, Habermann TM. Post-transplantation lymphoproliferative disorders in adults. *N Engl J Med* 2018; **378**: 549.
7. Hannani D. Extracorporeal photopheresis: tolerogenic or immunogenic cell death? Beyond current dogma. *Front Immunol* 2015; **6**: 349.
8. Pilon C, Stehlé T, Beldi-Ferchiou A, *et al*. Human apoptotic cells, generated by extracorporeal photopheresis. Modulate allogeneic immune response. *Front Immunol* 2019; **10**: 2908.