Role of photopheresis in the treatment of refractory cellular rejection in kidney transplantation☆

Papel de la fotoaféresis en el tratamiento del rechazo celular agudo refractario en trasplante renal

To the Editor,

Extracorporeal photopheresis is an immunomodulatory technique based on the apoptotic effects of 8-methoxypsoralen (8-MOP) and ultraviolet A (UVA) light on leukocytes. It is widely used in T-cell-mediated diseases such as cutaneous T-cell lymphoma, graft vs host disease, rheumatoid arthritis, and systemic lupus erythematosus.[1] Its use as prophylaxis for acute rejection (AR) in lung and heart transplants seems promising. However, there are few published articles on its use in the treatment of acute cellular rejection refractory to conventional treatment in renal transplant patients.

We present the case of a 56-year-old man, who received a cadaveric donor renal transplant in May 2013. Induction immunosuppression was with basiliximab, tacrolimus, mycophenolate mofetil, and steroids. Renal function was immediate and maintained until 16 days post-transplant, when it deteriorated. Percutaneous renal biopsy was performed, demonstrating Banff type Ib acute cellular rejection. Anti-HLA, anti-MICA, and antiendothelial antibodies were negative. The patient received salvage therapy with methylprednisolone (3×500 mg) and thymoglobulin (1.25 mg/kg; total cumulative dose, 410 mg) without improvement. Seventeen days later a second renal biopsy was performed, reported as Banff type IIa acute cellular rejection, with mild intimal arteritis. Given the clinical course and refractoriness to treatment, with serum creatinine (SCr) of 2.97 mg/dL, photopheresis was prescribed (14 sessions, once per week, with Therakos® UVAR XTS® System) along with nonspecific human gammaglobulin (200 mg/kg; total dose, 80 g). Following this, a progressive improvement was seen in renal function, with SCr of 2.3 mg/dL on discharge. Renal function remained stable for 9 months, then deteriorated slightly, with a SCr of 2.62 mg/dL, so it was decided to start a new course of photopheresis (6 sessions, once weekly). There was a good response to treatment (7 months later, the current SCr of 1.9 mg/dL) and no treatment-related infectious complications were noted.

Prophylactic treatment with photopheresis in renal transplant patients in addition to standard immunosuppression has shown improvement in renal function at 6 months and an increase in regulatory T-cells (Tregs).[2] Regarding its use in refractory AR, data from the literature are scarce, and, at times, contradictory. Horina et al. describe 3 patients treated with monthly photopheresis, who had no improvement in renal function, re-starting dialysis after a few months.[3] However, in other publications, more frequent schedules have been associated with improvement of renal function.[4] Dall'Amico et al. describe 4 patients with different types of cellular rejection, who had previously received OKT3, with improvement in renal function after the first cycle of photopheresis treatment. Renal function remained stable one year later, allowing a reduction in immunosuppressive therapy.[5] Weekly, fortnightly, and monthly schedules were used, up to a total of 19 sessions.

The different mechanisms by which photopheresis exerts its beneficial effects are not completely understood. It seems to be related to triggering an immunomodulatory response of alloreactive T cells exposed to 8-MOP and to UVA light. It is likely that important roles are played by the synthesis of interleukins (especially TNF, IL-10, and IL-6) and the increase in regulatory T-cells (CD4+, CD25+ and FoxP3+), which increase progressively in number after each session. These mechanisms could explain why the benefits in cutaneous T-cell lymphoma are seen from the second or third month, while in AR they can be seen after a few days.

Currently, photopheresis could be useful as salvage therapy in cases of acute cellular rejection refractory to conventional treatment in renal transplants. More extensive investigation is needed to test its efficacy and safety.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Adamski J, Kinard T, Ipe T, Cooling L. Extracorporeal photopheresis for the treatment of autoinmune diseases. Transfus Apher Sci. 2015;52:171–82.
2. Kusztal M, Koscielska-Kasprzak K, Gdowska W, Zabinska M, Myszka M, Klak R, et al. Extracorporeal photopheresis as an antirejection prophylaxis in kidney transplant recipients: preliminary results. Transplant Proc. 2011;43:2938–40.
3. Horina JH, Mullegger RR, Horn S, Holzer H, Halwachs G, Kerl H, et al. Photopheresis for renal allograft rejection. Lancet. 1995;346:61.

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4. Wolfe JT, Tomaszewski JE, Grossman RA, Gottlieb SL, Naji A, Brayman KL, et al. Reversal of acute renal allograft rejection by extracorporeal photopheresis: a case presentation and review of the literature. J Clin Apher. 1996;11:36–41.
5. Dall'Amico R, Murer L, Montini G, Andreetta B, Franco-Zanon G, Zacchello G, et al. Succesful treatment of recurrent rejection in renal transplant patients with photopheresis. J Am Soc Nephrol. 1998;9:121–7.

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Late onset of de novo atypical hemolytic–uremic syndrome presented on a simultaneous pancreas and kidney transplant recipient successfully treated with eculizumab

Presentacion tardía de síndrome hemolítico–urémico atípico de novo en receptor de trasplante reno-pancreático resuelto con eculizumab

Dear Editor,

Atypical hemolytic–uremic syndrome (aHUS) is an extremely rare, genetic, chronic, and progressive inflammatory disease[1] caused by defects in complement system. These defects result in systemic thrombotic microangiopathy involving damage to multiple organ systems including renal dysfunction.[1–7] Genetic mutations have been detected in around 50% of the reported cases. Regarding renal transplant patients, expanded criteria donors, infection by cytomegalovirus or BK, use of CNI or m-TOR inhibitors and antibody-mediated rejection (AMR) have been related to de novo post-transplant aHUS.[8] Graft failure is reported in 60–90% of patients within 1 year.[10] Eculizumab is a monoclonal antibody that binds to C5 complement protein avoiding the formation of the cell membrane attack complex.[6,7] We report herein a case of late onset of de novo post-transplant aHUS on a simultaneous pancreas and kidney recipient with severe systemic manifestations, without presenting acute graft rejection, successfully treated with limited doses of eculizumab remaining stable after one year of follow-up.

A 46-year-old woman with end stage renal disease secondary to type 1 Diabetes Mellitus underwent simultaneous pancreas and kidney transplant on October 2012 from deceased donor. Received induction with Basiliximab and maintenance treatment with mycophenolate mofetil, tacrolimus, and prednisone. Pancreatic and renal function were stable, creatinine (SCr) of 110 μmol/L. Tacrolimus through levels remained between 6 and 8 ng/ml. Seven months after transplant presented fever, abdominal pain, diarrhea and vomiting, acute graft dysfunction (SCr 438 μmol/L) and thrombocytopenia ($53 \times 10 \times 9$/L). She developed progressive anemia and thrombocytopenia and worsening of renal function requiring dialysis. Pancreas graft function remained preserved. Thrombotyc microangiopathy (TMA)was detected with lactate dehydrogenase (LDH) up to 1500 UI/L, undetectable haptoglobin and schistocytes. C3 was low, ADAMTS 13 of 79% and Shigella toxin was negative. Urinary tract infection by extended-spectrum beta-lactamase (ESBL)-klebsiella was present. Initial biopsy confirmed findings of TMA with severe tubulo-interstitial involvement and some focal glomerular involvement, without features of acute rejection. Discontinuation of tacrolimus, antibiotic treatment with meropenem and daily plasma exchange (PE) for 10 days were performed. The patient did not respond to therapy. Second renal biopsy showed persistent signs of TMA, worsening involvement of glomeruli with mesangiolysis without rejection (Fig. 1). Treatment with Eculizumab was started with 4 doses of 900 mg Eculizumab iv on a weekly basis, showing improvement of renal function, cessation of hemodialysis and hemolysis. Genetic screening did not detect mutations on factor I, factor H or factor MCP genes. Risk haplotype in heterozygosis for factor H and MCP genes were observed. Study of the complement alternate pathway showed low factor C3, factor H, normal expression of MCP (membrane cofactor protein) and negative anti-factor H antibodies. A third biopsy was performed showing predominance of chronic lessions of TMA and mild signs of acute TMA with interstitial fibrosis of 5–10% and some microhemorrhages, with ATN (Fig. 2). New course of 3 daily PE and final dose of 1200 mg of Eculizumab iv were prescribed.