Belatacept as maintenance therapy in kidney transplant recipients with ANCA-associated vasculitis

Sirs,

Kidney transplantation (KT) is considered the best kidney replacement therapy (KRT) modality in eligible patients with end-stage kidney disease (ESKD), including antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) induced ESKD. Anti-rejection therapy usually consists in a combination of calcineurin inhibitor (CNI) and mycophenolate mofetil (MMF). For a decade, a novel immunomodulatory agent targeting T-cell co-stimulation, belatacept, has been increasingly used (1). Herein, we report a series of 6 KT recipients with AAV who received belatacept.

Patient 1. A 24-year-old woman with anti-myeloperoxidase (anti-MPO) positive microscopic polyangiitis (MPA) received a first kidney transplant. Six months post-KT, CNI was converted to belatacept because of CNI-induced vascular lesions. Four years after the conversion, the immunosuppressive regimen was changed to a CNI-azathioprine combination in the hope of a pregnancy.

Patient 2. A 33-year-old woman with anti-MPO positive MPA, received a first kidney transplant. Belatacept was part of her initial anti-rejection regimen. At last follow-up, 3 years post-KT, she had experienced neither graft rejection nor AAV relapse.

Patient 3. A 44-year-old man with anti-MPO-positive MPA received a first kidney transplant. ANCA were still positive at this time. Three years post-KT, he was converted to belatacept because of biopsy-proven CNI-induced vascular lesions. Seven months later, he was diagnosed with an AAV renal relapse, treated with rituximab for induction and converted back to a CNI-MMF combination. Six months later, the ANCA title decreased but SCr and proteinuria remained elevated. However, indication for graft biopsy to assess AAV residual renal activity was considered futile. Indeed, it was decided that immunosuppression would not be intensified because of recent neoplastic complications.

Patient 4. A 63-year-old man with anti-proteinase 3 (anti-PR3) positive granulomatosis with polyangiitis (GPA) received a first kidney transplant. Belatacept was part of his initial anti-rejection regimen. He experienced neither graft rejection nor AAV relapse during the follow-up but ocular toxoplasmosis 10 years post-transplantation leading to the withdrawal of belatacept which could not prevent a fatal outcome.

Patient 5. A 66-year-old man with anti-MPO-positive MPA received a first kidney transplant. His initial anti-rejection maintenance therapy consisted in steroids, CNI and mechanistic target of rapamycin inhibitor (mTORi). He was converted to a belatacept-MMF combination within a month post-KT. One year after belatacept initiation, the patient had experienced neither graft rejection, nor AAV relapse.

Patient 6. A 39-year-old man with anti-MPO positive MPA received a first kidney transplant. ANCA were positive at the time of KT. Eleven months post-transplantation, CNI was converted to belatacept because of CNI-induced thrombotic microangiopathy. At last follow-up, 10 months after conversion to belatacept, he had experienced neither graft rejection nor AAV relapse.

In the present series (Table I), one patient out of 6 (17%) presented an AAV relapse while under belatacept roughly corresponding to a relapse rate of 0.05 per patient year. Usually, the AAV relapse rate in KTRs is estimated to be below 0.03 per patient-year (2-6), although guidelines do not consider CNI or MMF as first-line maintenance therapies in AAV (7-9). On the other hand, co-stimulation blockade has been tested in non-severe relapsing granulomatosis with polyangiitis (Wegener's) without raising any efficacy or safety concern (10) and MMF may be used in patients with contraindication to azathioprine, rituximab or methotrexate (7). Therefore, one may hypothesise that a belatacept-MMF combination may fare well regarding the risk of relapse of AAV in KTRs although, the small number of patients in the present series precludes any conclusion. However, it most importantly draws the attention on the lack of data regarding the risk of relapse after KT with belatacept and could conversely renew the interest of co-stimulation blockade in AAV.

M. Martins[1], *MD*
A. Morel[2], *MD*
C. Laurent[3], *MD*
N. Kamar[4], *MD, PhD*
D. Anglicheau[5], *MD, PhD*
M. Matignon[2], *MD, PhD*
C. Vigneau[1], *MD, PhD*
D. Guerrot[3], *MD, PhD*
N. Chavarot[5], *MD*
J.M. Chemouny[1], *MD, PhD*

[1]University of Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de Recherche en Santé, Environnement et Travail) - UMR_S 1085, Rennes; [2]APHP (Assistance Publique-Hôpitaux de Paris), Hôpital H. Mondor-A. Chenevier, Service de Néphrologie et Transplantation, Créteil; [3]Service de Néphrologie, CHU Rouen, INSERM - U1096, Rouen;

Table I. Demographics and characteristics of the patients converted to belatacept.

Sex	Age at KT (years)	ANCA type	AAV phenotype	Time from last AAV relapse to KT	Treatment of last pre-KT AAV relapse (Induction/Maintenance)	ANCA at KT	Initial anti-rejection therapy (Induction/Maintenance)	Time from KT to belatacept initiation	Time from belatacept intiation to AAV relapse	Duration of belatacept exposure
F	24	MPO	MPA	77	Steroids-RTX/MMF	negative	Basiliximab/Steroids-CNI-MMF	5	-	48
F	33	MPO	MPA	34	Steroids-RTX/RTX	negative	Thymoglobulin/Steroids-Belatacept-MMF	0	-	43
M	47	MPO	MPA	31	Steroids-PE-oral CYC/MMF	positive	Basiliximab/Steroids-CNI-MMF	37	7	6
M	63	PR3	GPA	60	Steroids-IV CYC/ND	negative	Basiliximab/Steroids-Belatacept-MMF	0	-	123
M	66	MPO	MPA	35	Steroids-RTX/RTX	negative	Basiliximab/Steroids-MMF-mTOR inhibitor	0,5	-	23
M	39	MPO	MPA	10	Steroid-IV CYC/AZA converted to RTX	positive	Basiliximab/Steroids-CNI-MMF	11	-	9

AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; AZA: aziathropine; CNI: calcineurin inhibitors; CYC: cyclophosphamide; GPA: granulomatosis with polyangiitis; KT: kidney transplantation; MMF: mycophenolate mofetil; MPA: microscopic polyangiitis; MPO: anti-myeloperoxidase; mTOR: mechanistic target of rapamycin; PE: plasma exchange; PR3: anti-proteinase 3; RTX: rituximab; ND: no data. Time in months.

[4]*Service de Néphrologie et de Transplantation d'Organes, CHU Toulouse;*
[5]*Service de Néphrologie et Transplantation Adulte, Hôpital Necker-Enfants Malades, Université de Paris, Assistance Publique-Hôpitaux de Paris, France.*

Please address correspondence to:
Jonathan Chemouny,
Service de Néphrologie,
CHU de Rennes, Hôpital Pontchaillou,
2 rue Henri Le Guilloux,
35033 Rennes, France.
E-mail: jonathan.chemouny@chu-rennes.fr

Competing interests:
D. Anglicheau reports personal fees for consultancies with Bristol Myers Squibb. The other co-authors have declared no competing interests.

References

1. BERTRAND D, CHEDDANI L, ETIENNE I *et al*.: Belatacept rescue therapy in kidney transplant recipients with vascular lesions: a case control study. *Am J Transplant* 2017; 17: 2937-44.
2. GERA M, GRIFFIN M-D, SPECKS U *et al*.: Recurrence of ANCA-associated vasculitis following renal transplantation in the modern era of immunosupression. *Kidney Int* 2007; 71: 1296-301.
3. PARK ES, AHN SS, JUNG SM, SONG JJ: Renal outcome of kidney-transplantation in Korean recipients with ANCA-associated vasculitis. *Clin Exp Rheumatol* 2018; 36 (Suppl. 111): S115-20.
4. GÖÇEROĞLU A, RAHMATTULLA C, BERDEN AE *et al*.: The Dutch Transplantation in Vasculitis (DUTRAVAS) Study: outcome of renal transplantation in antineutrophil cytoplasmic antibody-associated glomerulonephritis. *Transplantation* 2016; 100: 916-24.
5. MARCO H, MIRAPEIX E, ARCOS E *et al*.: Long-term outcome of antineutrophil cytoplasmic antibody-associated small vessel vasculitis after renal transplantation. *Clin Transplant* 2013; 27: 338-47.
6. GEETHA D, EIRIN A, TRUE K *et al*.: Renal transplantation in antineutrophil cytoplasmic antibody-associated vasculitis: a multicenter experience. *Transplantation* 2011; 91: 1370-5.
7. YATES M, WATTS RA, BAJEMA IM *et al*.: EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis* 2016; 75: 1583-94.
8. FELICETTI M, GASPAROTTO M, FRIGO AC *et al*.: Renal involvement at baseline can predict major renal relapse in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. *Clin Exp Rheumatol* 2020; 38 (Suppl. 124): S201-6.
9. FELICETTI M, TREPPO E, POSARELLI C *et al*.: One year in review 2020: vasculitis. *Clin Exp Rheumatol* 2020; 38 (Suppl. 124): S3-14.
10. LANGFORD CA, MONACH PA, SPECKS U *et al*.: An open-label trial of abatacept (CTLA4-IG) in non-severe relapsing granulomatosis with polyangiitis (Wegener's). *Ann Rheum Dis* 2014; 73: 1376-9.