LETTER TO THE EDITORS

Nocardiosis in graft recipients of kidneys from extended-criteria donors following switch to belatacept complicated by acute rejection

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Dear Editors,

Belatacept has increasingly been used as a replacement for calcineurin inhibitors (CNI) in kidney transplant recipients (KTRs) with poor graft function in the early post-transplant period, allowing to improve kidney function in these most often elderly patients, transplanted from extended-criteria donors [1,2]. When there is still limited insight into the safety of such approach, we report three cases of nocardiosis occurring in this setting. As illustrated in Table 1, all patients were older than 70 years, one was diabetic, and the two others developed post-transplant diabetes. Conversion to belatacept occurred between 95 and and 202-day post-transplantation. Following an initial improvement, they presented with acute kidney injury warranted an allograft biopsy (time from belatacept conversion ranging from 80 to 120 days) revealing T-cell-mediated rejection. While rejection's treatment was efficient and belatacept pursued, *Nocardia* infection occurred 45–80 days after. All patients had respiratory symptoms associated with fever. Morphological assessment showed nodular lesions (Fig. S1) without extra-pulmonary dissemination, and *nocardia nova* was identified in all cases. Table 1 reports empirical and definitive antibiotic treatment and modification in immunosuppressant. While two out of three patients were cured, the third patient relapsed shortly after stopping treatment with cerebral dissemination leading to stop all immunosuppressive therapy and restarted antibiotics for 12 months.

To the best of our knowledge, this is the first report of nocardiosis in patients receiving belatacept. Incidence of nocardiosis in KTRs is between 0.04% and 1.2% with death rate around 15% [3,4]. As in our patients, lung involvement (typically nodular) is predominant, but a potential dissemination, especially cerebral, must be systematically sought.

In our elderly and diabetic KTRs, who received, due to rejection, high-dose steroids (and even in one case anti-thymocyte globulin), nocardiosis was presumably promoted by the global immunosuppressive burden, highlighted by occurrence of other opportunistic infections and by severe lymphopenia, rather than by co-stimulation blockade by belatacept per se.

In BENEFIT and BENEFIT-EXT, except for higher rates of EBV-PTLD in seronegative EBV patients, the risk of serious infection was no different from that associated with the control arm ciclosporin [5,6] and was roughly similar in conversion studies [7]. However, in a recent cohort that specifically investigated opportunistic infection in KTRs switched to belatacept, a high incidence was found, especially in patient resembling our own: switched early (before 6 months) and with poor eGFR at conversion (<25 ml/min/1.73 m^2) [7]. Rejection after the switch was not considered, probably due to the weak incidence. In line with this, our observation supports that KTRs early switched to belatacept with poor renal function are susceptible to opportunistic infection, even if there are necessarily CNI-free.

With regard more specifically to nocardiosis, this latter point is of particular interest. Nocardiosis risk factors in solid organ transplant recipients have been well investigated in two case–control studies [3,4]. While our patients were presenting with some of them (steroid prescription often in a context of rejection, age, diabetes, lymphopenia), the only one well-established after accounting for confounding factors was tacrolimus exposure, raising the question whether this association was due to a specific

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Table 1. Characteristics of three kidney transplant recipients with pulmonary nocardiosis following belatacept conversion complicated by cellular rejection

	1	2	3
Sex	M	M	F
Age D/R (years)	73/65	72/79	83/85
Anti-HLA immunization	Neg	Neg	Pos
Reason for transplant	Diabetic nephropathy	Hypertensive nephropathy	Hypertensive nephropathy
Diabetes	Yes	NODAT	NODAT
Status CMV (D/R)	Pos/Pos	Neg/Neg	Neg/Neg
Preconversion SCr (mg/dl) eGFR (ml/min/1.73 m^2)	Dialysed	5.2/11.9	2.8/17
Time to belatacept conversion (days)	88	118	202
Preconversion IS	Tacrolimus MPA 360 mg ×2/day	Tacrolimus MPA 360 mg ×2/day	Tacrolimus Prednisone 5 mg
Nadir postconversion SCr (mg/dl) eGFR (ml/min/1.73 m^2)	3.9/16.2	4.4/14.3	2.5/19.5
Postconversion IS	Bela MPA 360 mg ×2/day	Bela MPA 360 mg ×2/day	Bela Prednisone 5 mg
Rejection event			
Time from belatacept conversion (days)	80	120	102
Grade	TCMR 1a	TCMR III	TCMR Ib
Treatment	Iv steroids	Iv steroids + rATG (5d)	Iv steroids
Postrejection maintenance IS	Bela MPA 360 mg ×2/day Prednisone 10 mg	Bela MPA 720 ×2 Prednisone 10 mg	Bela MPA 180 ×2/day Prednisone 20 mg
Nadir postrejection SCr (mg/dl)/eGFR (ml/min/1.73 m^2)	3.2/20.7	3.5/18.6	2.2/22.5
Nocardia infection			
Time from rejection (days)	80	60	45
Clinical involvement	Pulmonary	Pulmonary	Pulmonary
Radiological findings	• Pulmonary consolidations • Centrilobular nodules • Pleural effusion	• Pulmonary nodules and infiltrate with ground-glass opacities and interlobular septal thickening • Nodule cavitation • Pleural effusion	• Mass surrounded by ground-glass opacities and interlobular septal thickening • Nodule cavitation nodule
Lymphocyte count cell/mm^3	51	9	36
Neutrophils count cell/mm^3	3120	2670	8700
Type of positive sample	Bronchial aspirate, BAL	Sputum	Bronchial aspirate, BAL
Causative agent	Nocardia nova	Nocardia nova	Nocardia nova
Coexisting infection	CMV in preceding month	Herpetic stomatitis in preceding month Pulmonary Mucormycosis	Oropharyngeal candidiasis
Treatment			
Empirical therapy	Meropenem + clindamycine	Linezolide + ceftriaxone	Linezolide + ceftriaxone

Table 1. Continued.

	1	2	3
Definitive therapy	Clindamycine + doxycycline	Cotrimoxazole	Doxycycline
Duration	4 months	4 months	6 months
Post-Nocardiosis IS	Bela Prednisone 5 mg	Bela Prednisone 10 mg	Bela Prednisone 5 mg MPA 180 mg ×2
Outcome			
Nocardiosis	Cured	Cured	Failure, relapse with cerebral localization stop IS and rechallenge antibiotic for 12 months
FU post-Nocardia diagnosis (months)	16	6	11
SCr (mg/dl)/eGFR (ml/min/1.73 m^2)	3.8/16.7	Dialysis	2.9/16.4

All patients received a 250 mg bolus of methylprednisolone combined with rabbit anti-thymocyte globulin (rATG) administrated at 1.5 mg/kg/day for two days as induction therapy. Maintenance immunosuppressive therapy consisted of tacrolimus (target trough level 6–8 ng/ml for 3 months, then 6 mg/kg) combined with acid mycophenolic [(MPA) 720 mg twice daily for 3 months, then 360 mg twice daily]. At the time of the switch, belatacept was administered at 5 mg/kg on days 1, 15, 30 and then monthly, tacrolimus weaning protocol was as follow: 100% on day 1, 50% on day 15 and 0% on day 30. Following rejection treatment consisted of five bolus iv steroids of decreasing dose (5 mg/kg day 1, 4 mg/kg day 2, 3 mg/kg day 3, 2 mg/kg day 4, and 1 mg/kg day 5) followed by 1 mg/kg po with a progressive decrease over 3 months, the patient with arteritis (TCMR grade III) additionally received rATG at 1.5 mg/kg/day for 5 days.

BAL, broncho-alveolar lavage; Bela, belatacept; D/R, donor/recipient; eGFR, glomerular filtration rate estimated using the MDRD formula; F, female; FU, follow-up; IS, immunosuppression; M, male; MPA, mycophenolate acid; NODAT, new onset diabetes after transplant; SCr, serum creatinine; TCMR, T-cell-mediated rejection.

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effect of tacrolimus, or whether it reflects the level of immunosuppression. Our observation supports that latter assumption and must warn clinicians that in such tacrolimus-free patients receiving belatacept and otherwise severely immunocompromised, nocardiosis should be considered in front of a febrile respiratory condition.

SUPPORTING INFORMATION

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

Figure S1. Chest CT scan of pulmonary nocardiosis.

REFERENCES

1. Le Meur Y, Aulagnon F, Bertrand D, *et al*. Effect of an early switch to belatacept among calcineurin inhibitor-intolerant graft recipients of kidneys from extended-criteria donors. *Am J Transplant* 2016; **16**: 2181.
2. Brakemeier S, Kannenkeril D, Dürr M, *et al*. Experience with belatacept rescue therapy in kidney transplant recipients. *Transpl Int* 2016; **29**: 1184.
3. Peleg AY, Husain S, Qureshi ZA, *et al*. Risk factors, clinical characteristics, and outcome of Nocardia infection in organ transplant recipients: a matched case-control study. *Clin Infect Dis* 2007; **44**: 1307.
4. Coussement J, Lebeaux D, van Delden C, *et al*. Nocardia infection in solid organ transplant recipients: A multicenter European case-control study. *Clin Infect Dis* 2016; **63**: 338.
5. Vincenti F, Charpentier B, Vanrenterghem Y, *et al*. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). *Am J Transplant* 2010; **10**: 535.
6. Durrbach A, Pestana JM, Pearson T, *et al*. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). *Am J Transplant* 2010; **10**: 547.
7. Bertrand D, Chavarot N, Gatault P, *et al*. Opportunistic infections after conversion to belatacept in kidney transplantation. *Nephrol Dial Transplant* 2020; **35**: 336.