AIDS

Alemtuzumab Induction Therapy in HIV Positive Renal Transplant Recipients

--Manuscript Draft--

Manuscript Number:	
Full Title:	Alemtuzumab Induction Therapy in HIV Positive Renal Transplant Recipients
Article Type:	Correspondence
Section/Category:	
Keywords:	HIV; renal transplant; kidney transplant, Alemtuzumab
Corresponding Author:	Florence E McLean, BM BCh St George's Hospital London, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	St George's Hospital
Corresponding Author's Secondary Institution:	
First Author:	Florence McLean
First Author Secondary Information:	
Order of Authors:	Florence McLean
	Esther Gathogo
	Dawn Goodall
	Sabine Kinloch
	Rachel Jones
	Frank A Post
Order of Authors Secondary Information:	

Alemtuzumab Induction Therapy in HIV Positive Renal Transplant Recipients

Mclean FE,[1] Gathogo E,[2] Goodall D,[3] Jones R,[4] Kinlcoh S,[5] Post FA,[6]

1. Department of Renal Medicine, St George's Hospital, London, UK
2. Department of Renal Sciences, King's College London, London, UK
3. Imperial College Kidney and Transplant Centre, Hammersmith Hospital, London, UK
4. Department of HIV Medicine, Chelsea and Westminster Hospital, London, United Kingdom
5. Division of Infection and Immunity, University College London, London, United Kingdom
6. Department of HIV Research, King's College Hospital NHS Foundation Trust, London, United Kingdom.

Correspondence to Dr Florence McLean, Renal Offices, St George's University Hospitals NHS Foundation Trust, London, SW17 0RE. Email: florence.mclean@doctors.org.uk

Renal transplantation has been associated with excellent patient and graft survival outcomes in HIV positive patients [1-3]. However, the incidence of acute allograft rejection (AR) remains high [4], with 31-48% of patients experiencing an episode of AR in the first year [1, 5]. The use of tacrolimus, a more potent calcineurin inhibitor than ciclosporin, has been associated with a reduced risk of AR [1, 6]. It is possible that more potent induction therapy may further reduce the risk of early AR. Alemtuzumab is a humanized monoclonal antibody targeted at CD52, a cell surface antigen present on both B and T lymphocytes, which has a profound lymphocyte depleting effect. While Alemtuzumab, which is not currently licensed for transplantation in the UK, has been associated with lower rates of AR in HIV negative renal transplant recipients [7], experience in HIV positive renal transplant recipients is limited.

Case 1

A 57 year old Black Caribbean man underwent deceased-donor renal transplantation in 2013 for end-stage diabetic nephropathy (HLA mismatch: 3). At the time of transplantation, his antiretroviral therapy consisted of abacavir, lamivudine and raltegravir; he was cytomegalovirus (CMV) IgG positive, his CD4 T-cell count was 394 cells/mm^3, HIV RNA undetectable, and he had no history of opportunistic infections or malignancy. He received preconditioning therapy with alemtuzumab (35mg) followed by tacrolimus (titrated up to and maintained around 16 mg/day in the first year, aiming for trough concentrations of 5-8 ng/ml), with glucocorticoid cover for one week, valganciclovir prophylaxis for three months, co-trimoxazole prophylaxis for six months, and isoniazid.

Case 2

A 47 year old Black African man also underwent deceased donor renal transplantation in 2013 for end-stage kidney disease secondary to HIV-associated nephropathy (HLA mismatch: 3). At the time of transplantation, his antiretroviral therapy also consisted of abacavir, lamivudine and raltegravir; he was CMV IgG positive, his CD4 T-cell count was 328 cells/mm^3, HIV RNA undetectable, and he had no history of opportunistic infections or malignancy. He received alemtuzumab (30mg) followed by tacrolimus (titrated up to 16 mg/day in the first two months), with glucocorticoids for one week and the same prophylactic regimen as Case 1.

Both patients experienced profound CD4 and CD8 T-cell depletion (<10 and <20 cells/mm^3) in the first 3 months post-transplantation with subsequent recovery. In both cases, HIV and CMV viral loads remained undetectable throughout, and no AR, opportunistic infection or malignancy occurred. Case 1 had prolonged, low level EBV viraemia (21,000 copies/mL) without evidence of post-transplant lymphoproliferative disease, and case 2 experienced a gradual decline in estimated glomerular filtration rate (eGFR, from 53 to 32 ml/min/1.73m^3) at 2 months; a renal biopsy revealed acute tubular necrosis. Calcineurin inhibitor toxicity was suspected and graft function improved when the dose of tacrolimus was reduced to 8-10mg/day. Both patients had well-functioning grafts at their most recent visit (eGFR 75 and 50 ml/min/1.73m^3).

Here we report two cases of renal transplantation in HIV positive patients on an integrase inhibitor containing antiretroviral regimen who received induction therapy with alemtuzumab. Our experience concurs with that of Tan et al. who treated three HIV-positive recipients of live-donor renal allografts with alemtuzumab (30mg, plus short term glucocorticoids) and tacrolimus maintenance immunosuppression, reporting no acute rejection, opportunistic infections or malignancy during median follow up of 39 months [8]. A further 29 HIV positive patients received a renal transplant with alemtuzumab induction therapy up to 2011 in the United States although complications such as opportunistic infections and malignancy were was not reported [4]. Our data suggest that the clinical utility of alemtuzumab in HIV positive kidney transplant recipients warrants further investigation, especially in those at high immunological risk of AR or when glucocorticoid-sparing, low-intensity calcineurin inhibitor exposure is desirable. Such studies, however, should evaluate the long term safety of severe T cell depletion in this population.

References

1. Stock PG, Barin B, Murphy B, Hanto D, Diego JM, Light J*, et al.* **Outcomes of Kidney Transplantation in HIV-Infected Recipients.** *N Engl J Med* 2010,**363**:2004-2014.
2. Gathogo EN, Hamzah L, Hilton R, Marshall N, Ashley C, Harber M*, et al.* **Kidney transplantation in HIV-positive adults: the UK experience.** *Int J STD AIDS* 2014,**25**:57-66.
3. Roland ME, Barin B, Huprikar S, Murphy B, Hanto DW, Blumberg E*, et al.* **Survival in HIV-positive transplant recipients compared with transplant candidates and with HIV-negative controls.** *AIDS* 2016,**30**:435-444.
4. Locke JE, James NT, Mannon RB, Mehta SG, Pappas PG, Baddley JW*, et al.* **Immunosuppression regimen and the risk of acute rejection in HIV-infected kidney transplant recipients.** *Transplantation* 2014,**97**:446-450.
5. Gathogo E, Jose S, Jones R, Levy JB, Mackie NE, Booth J*, et al.* **End-Stage Kidney Disease and Kidney Transplantation in HIV-Positive Patients: An Observational Cohort Study.** *J Acquir Immune Defic Syndr* 2014,**67**:177-180.
6. Gathogo E, Harber M, Bhagani S, Levy J, Jones R, Hilton R*, et al.* **Impact of Tacrolimus Compared With Cyclosporin on the Incidence of Acute Allograft Rejection in Human Immunodeficiency Virus-Positive Kidney Transplant Recipients.** *Transplantation* 2016,**100**:871-878.
7. Hanaway MJ, Woodle ES, Mulgaonkar S, Peddi VR, Kaufman DB, First MR*, et al.* **Alemtuzumab induction in renal transplantation.** *N Engl J Med* 2011,**364**:1909-1919.
8. Tan HP, Kaczorowski DJ, Basu A, Khan A, McCauley J, Marcos A*, et al.* **Living-related donor renal transplantation in HIV+ recipients using alemtuzumab preconditioning and steroid-free tacrolimus monotherapy: a single center preliminary experience.** *Transplantation* 2004,**78**:1683-1688.