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INVITED COMMENTARY

Alemtuzumab: right drug, right dose?*

Richard Haynes[1] and Peter Friend[2]

1 Specialist Registrar, Oxford Kidney Unit, Churchill Hospital, Oxford, UK
2 Professor of Transplantation, Nuffield Department of Surgery, University of Oxford, Oxford, UK

Correspondence
Peter Friend MD, FRCS, Oxford Transplant Centre, Churchill Hospital, Oxford, OX3 7LJ, United Kingdom. Tel: +44 1865 221297; fax: +44 1865 765063; e-mail: Peter.friend@nds.ox.ac.uk

Conflict of Interest
PF is chief investigator and RH clinical coordinator of the Campath, Calcineurin inhibitor and Chronic allograft nephropathy (3C) study.

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Induction therapy is routinely used in most kidney transplants to reduce the risk of rejection during the early postoperative period of highest immunological risk. In Europe, nonlymphocyte depleting therapy with anti-CD25 monoclonal antibodies is used most frequently, whereas in the United States, depleting therapy with antithymocyte globulin is used more frequently. There are theoretical benefits of lymphocyte depletion for induction: First, ischaemia reperfusion injury is a potent stimulus to antigen presentation and immune activation. If critical coordinators of the immune response (T lymphocytes) are absent at the time of surgery, the immediate immunological effects of ischaemia reperfusion may be reduced. Second, the absence of T lymphocytes enables lower levels of maintenance immunosuppression, limiting the adverse effects of these drugs (particularly nephrotoxicity). Third, there is some evidence that when the immune system reconstitutes after depletion, it does so in a fashion more tolerant of the transplant. However, lymphocyte depleting therapy is an imprecise science. We know little about the optimum degree and duration of lymphocyte depletion, nor do we have reliable surrogate markers for the degree to which the alloimmune response has been suppressed; indeed, it is very likely that the response is heterogeneous.

Alemtuzumab (Campath) was first used for induction treatment in 1998 by Calne *et al.* [1]. Until recently, published data on Campath were based on uncontrolled observational series or single-centre studies. However, larger randomized controlled studies are now beginning to clarify some of the uncertainties around alemtuzumab. The multicentre study by Margreiter *et al.* [2] was one such study and suggested that alemtuzumab roughly halves the risk of acute rejection (10 vs. 19 events: hazard ratio 0.46; 95% confidence interval 0.22–1.00). Although the control group did not receive any induction therapy, this result has since been confirmed both in a meta-analysis and in a larger prospective randomized trial comparing alemtuzumab with basiliximab [3,4].

Despite these randomized trial data, there is persisting uncertainty around the use of alemtuzumab. The published trials have not tested whether using alemtuzumab to spare calcineurin inhibitors (by minimization or complete withdrawal) improves long-term outcome. Furthermore, studies published to date are too small to detect moderate-sized

hazards which are plausible, given the potency of alemtuzumab. The larger INTAC study did suggest an excess of serious infection with alemtuzumab (57 vs. 38 events, $P = 0.02$) [4]. However, even this study is possibly too small and follow-up too short to detect rarer but more serious hazards, such as malignancy and auto-immunity. There is a need therefore both for larger trials (such as the United Kingdom's current 3C Study) and for collaborative individual patient data meta-analysis of the totality of the data [5].

In this issue of *Transplant International*, Boesmueller *et al.* [6] address another uncertainty about the use of alemtuzumab – that of optimal dose. Current practice varies between centres; the original description by Calne *et al.* used two 20 mg doses and this was the pattern followed by Margreiter *et al.* [1,2]. Other centres use one or two 30 mg doses, including the INTAC study which tested a single 30 mg dose [4]. A trial of alemtuzumab monotherapy (in which all patients required treatment for rejection) used relatively large doses (60–80 mg) to deplete both the circulation and lymphoid tissues of lymphocytes [7].

The simple advantage of a 30-mg dose is that alemtuzumab comes in 30 mg vials, and hence, there is no wastage. Alemtuzumab is considerably less expensive than anti-CD25 antibodies and using a single 30 mg vial increases this cost-saving. To address the question of dose in the context of the previously published trial [2], Boesmueller *et al.* [6] further recruited 66 patients and treated them with a single 30 mg dose of alemtuzumab instead of two doses of 20 mg, otherwise following the published protocol. The results in this group of patients were broadly similar to those observed in the previous (2 dose) alemtuzumab arm of the trial. As the authors point out, this was not a randomized study and it is susceptible to the biases of previous observational cohorts that have used historical controls, which hinder their ability to detect true treatment effects [8]. The authors have presented their data transparently and not attempted to adjust for differences in baseline characteristics, but the small size of the study also limits the reliability of any conclusions that can be drawn.

Cost-savings apart, is the dose of alemtuzumab crucial? In the UK, a 30-mg vial of alemtuzumab costs about €300 which is about 1% of the total €25 000 first year cost of transplantation. The doses that are used in solid organ transplantation are small compared with those used in other fields. Alemtuzumab is used by neurologists to treat multiple sclerosis in doses up to 264 mg (over 2 years) [9]. The current licensed indication for alemtuzumab is in the treatment of chronic lymphocytic leukaemia where doses of 90 mg per week are used for up to 12 weeks (total dose over 1 gram). The difference between 30, 40 and 60 mg total dose used in renal transplantation should be viewed in this context.

A reduction in rejection rate has been the primary outcome in this and other studies. However, rejection rate is a surrogate outcome parameter and not, of itself, relevant unless predictive of graft survival. There remain two more fundamental questions over the use of alemtuzumab in renal transplantation: first, whether it enables patients to be managed safely in the long-term with lower levels of maintenance drugs and that this leads to improved renal function, less chronic allograft nephropathy and concomitantly improved long-term graft survival; second, whether it is as safe as conventional therapy in terms of opportunistic infections and malignancy.

Larger trials of alemtuzumab are required to define its role in kidney transplantation and to establish whether its theoretical benefits translate into these real benefits. Further detailed work is needed on the dynamics of lymphocyte depletion and repopulation, individual patient monitoring and methods to engender a tolerogenic state. Until such studies are done, the dose of alemtuzumab is likely to remain arbitrary.

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