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INVITED COMMENTARY

Weight-based dosing of alemtuzumab: an ounce of prevention?

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Alemtuzumab is a lymphocyte-depleting humanized monoclonal antibody that targets CD52 and binds to T and B lymphocytes, macrophages, monocytes and natural killer cells [1]. It was approved decades ago for the treatment of B-cell chronic lymphocytic leukemia (CLL), and the use of alemtuzumab in kidney transplantation was first described in the late 1990s as a drug that could promote tolerance and allow for maintenance drug minimization [2]. Although there has been variability in dosing in renal transplantation [3–5], alemtuzumab is typically administered at a dosage of 30 mg intravenously once or twice in the perioperative transplant period, which is a fraction the cumulative dosage used for CLL. Its usage in kidney transplantation remains off label.

Alemtuzumab produces significant and at times profound leucopenia by promoting complement-dependent lysis of lymphocytes in circulation and opsonization in lymphatic tissue. It has therefore been used to facilitate minimization of maintenance immunosuppressive therapy with strategies including the use of calcineurin inhibitor (CNI) monotherapy and CNI-sparing therapy [3,6–8]. The efficacy of induction therapy with alemtuzumab in prevention of early rejection has been well described. In a large multicenter randomized trial of 852 kidney recipients in the United Kingdom, patients received alemtuzumab 30 mg IV × 2 doses (or 1 dose if age ≥60) vs. the CD25 antibody basiliximab. Alemtuzumab patients had a significant reduction in CNI therapy and a much higher rate of early corticosteroid withdrawal compared to basiliximab patients. Despite this relative minimization of maintenance therapy in the alemtuzumab cohort, rejection rates at 6 months post-transplantation were significantly lower at 7% compared to 16% in the basiliximab group ($P < 0.001$) [9].

Given such potency, the risk of infection related to leucopenia remains a concern with the use of alemtuzumab. In the multicenter trial described above, leucopenia occurred in 36% in the alemtuzumab cohort compared to 10% of those who received basiliximab ($P < 0.001$). BK virus infections were also more common in alemtuzumab recipients (although other opportunistic infections occurred at a similar rate). Other studies have noted a greater risk of serious and opportunistic infections in alemtuzumab patients. In one trial of early corticosteroid withdrawal, 474 patients were divided based on predefined high- and low-risk status. High-risk patients were then randomized to a single 30 mg dose of alemtuzumab vs. 6 mg/kg of

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anti-thymocyte globulin (ATG). Low-risk patients were randomized to alemtuzumab vs. basiliximab [10]. In the high-risk cohort, rates of serious infections were similar between induction groups, while in the low-risk group, serious infections were more common after alemtuzumab compared to basiliximab (35% vs. 22%, $P = 0.02$). A single center experience from Wisconsin also noted an overall increase in the rate of opportunistic infections and a higher rate of cytomegalovirus (CMV) in 632 patients who received alemtuzumab compared to a cohort that received other induction therapy (85% basiliximab) over a 5-year period [11]. Additional case reports have described the occurrence of aggressive fungal and mycobacterial infections after alemtuzumab induction therapy [12–14].

In this edition of Transplant International, Willicombe and colleagues compared outcomes of patients who received standardized versus weight-based dosing of alemtuzumab [15]. They retrospectively analyzed data on 888 recipients of alemtuzumab from their single center from 2005 to 2015. All patients had at least 1 year of follow-up, and patients with ABO mismatching, positive crossmatch, or baseline donor specific antibodies (DSA) were excluded from analysis. From 2005 to 2011, patients received a standard 30 mg IV single dose of alemtuzumab for induction therapy ($n = 544$). After 2011, patients received a weight-based dosage of 0.4 mg/kg up to a maximum of 50 mg ($n = 344$). All patients were targeted to receive CNI monotherapy with tacrolimus after initial induction therapy and 1 week of corticosteroids.

Patients who received the adjusted dosage of alemtuzumab (AD) were slightly older and had higher rates of sensitization at baseline compared to the standard dosage (SD) group. The mean weight for both groups was approximately 75 kg, indicating that a substantial subset of the AD group received a dosage under 30 mg. There were no differences seen between groups in terms of rejection, antibody-mediated rejection, development of DSA, or patient and graft survival. Alternatively, differences in lymphocyte and monocyte subsets became evident at 1 month post-transplantation, and lymphocyte subsets were persistently higher at all time points in the AD group. The investigators found that by multivariable modeling, AD patients had a reduced risk of wound infections, urinary tract infections, and fungal infections. No differences were seen with viral infections, including CMV and BK. The overall findings were supported by a subanalysis of patients separated by weight <75 kg vs. >75 kg. Infectious risk was reduced only in the lower-weight AD cohort for whom a dose reduction of alemtuzumab would have applied.

Limitations of this analysis include the historical comparison between groups along with its retrospective design. In addition, findings may not be generalizable to patients on more aggressive maintenance immunosuppressive therapy with agents such as mycophenolate mofetil and corticosteroids. However, with waning enthusiasm for minimization of maintenance therapy in the current age [16], there is an even greater need for caution with the use of depleting induction therapy. One strength of this analysis was the preferential benefit of AD in lower-weight patients, supporting the use of weight-based dosing to improve upon safety. Importantly as well, there was no increased risk of rejection or graft loss in the weight-based cohort. The analysis was large and well-powered owing to the authors' years of experience with alemtuzumab therapy, and they should be commended on this novel report, which demonstrates that an ounce (or a few milligrams) of prevention may indeed be worth a pound (or kilogram) of cure.

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