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**Anti–IL-2 Receptor Antibodies versus Anti-Thymocyte Globulin for Induction Therapy in Kidney Transplantation**

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The latest annual report from the Scientific Registry of Transplant Recipients showed that in 2006 21% of kidney recipients in the United States received no induction therapy at the time of transplantation, whereas 42% received anti-thymocyte globulin (ATG) and 29% received anti–IL-2 receptor antibodies. A number of different induction agents deplete T lymphocytes, including monoclonal OKT3 and polyclonal ATG, ATGAM, and ALG. Of these four, ATG (Thymoglobulin), made from rabbits immunized with thymocytes, has been used more frequently every year since its introduction in 1998, whereas use of the others has been negligible in the last 5 yr. MAbs to the IL-2 receptor (IL-2R Abs) block T cell activation and proliferation. The two Food and Drug Administration–approved IL-2R Abs, daclizumab (Zenapax) and basiliximab (Simulect), have similar efficacy and adverse effects, but basiliximab is administered as two doses within 4 d of transplantation, whereas daclizumab is administered as five infusions over 8 wk. This difference in convenience of administration likely explains the more frequent use of basiliximab. The IL-2R Abs were introduced in 1997, and their use increased until approximately 2001 but has declined somewhat since then with the rising popularity of ATG.

Interestingly, no randomized, controlled trials of ATG versus placebo have been performed. In contrast, IL-2R Abs have been the subject of numerous placebo-controlled, randomized trials, which showed a reduction in rejection rates by 28 to 42% compared with placebo. Before the trial of Noel et al. in this issue of JASN, at least four randomized, controlled trials compared ATG with IL-2R Abs. Three of these used triple immunosuppression with cyclosporine, mycophenolate mofetil, and steroids and were limited to patients with low immunologic risk. In all three trials, 1-yr rejection, graft survival, and patient survival were the same in the ATG and basiliximab groups. These trials also reported either trends or statistically significantly higher rates of cytomegalovirus infection with ATG compared with IL-2R Abs. A fourth trial, by Brennan et al., compared ATG with basiliximab in the context of cyclosporine-based triple immunosuppression but in high-risk recipients. This trial did not show any difference between ATG and basiliximab in the primary end point, a composite including rejection, delayed graft function, graft loss, and death; however, patients receiving ATG had a lower acute rejection rate (15.6 versus 25.5%; \(P = 0.02\)).

Like the study by Brennan et al., the study by Noel et al. is a better-designed, randomized, controlled trial limited to high-risk recipients. It also compares ATG with IL-2R Ab on a background of triple immunosuppression. The study by Noel et al. was performed in France and Belgium and enrolled <3% of patients with diabetes and >40% with glomerulonephritis. The study by Brennan et al. did not specify causes of renal failure, but the patients were predominantly from centers in the United States, where the proportion of patients with diabetes is likely to be higher and glomerulonephritis lower. The patients in the study by Noel et al. study were also more likely to be repeat transplants (70 versus 10% in the study by Brennan et al.) and had higher panel-reactive antibodies (peak 72 versus 14% in the study by Brennan et al.). The study by Noel et al. also targeted slightly higher ATG dosages (8.75 versus 7.5 mg/kg), used the IL-2R Ab daclizumab rather than basiliximab,
and used tacrolimus rather than cyclosporine. The main finding, however, is strikingly similar, with ATG having a lower 1-yr rejection rate of 15.0% versus 27.2% (P = 0.016), with no differences in graft or patient survival between the two groups. Thus, this study confirms the results of Brennan et al. and extends them to a different patient population and to different IL-R Abs and calcineurin inhibitors. In particular, the improved rejection rates with ATG apply to regimens based on tacrolimus, which is now much more commonly used than cyclosporine. The greater potency of ATG compared with IL-2R Abs in preventing acute rejection is therefore unequivocal. As with several previous trials, Noel et al. found a trend toward more cytomegalovirus infections with ATG than with IL-2R Ab (18.6% versus 10.5%; P = 0.093).

In interpreting trials in kidney transplantation, it is important to remember that the ultimate goals are to maximize graft and patient survival, and acute rejection is a surrogate end point. Rejection is often associated with worse graft survival, so using this surrogate end point is a practical solution to the difficulties in performing trials of sufficient size and duration to show differences in graft and patient survival; however, many have noted that improvements in rejection rates during consecutive historical eras have not been matched by improvements in graft survival. In addition, studies that have compared ATG with IL-2R Abs did not show that lower rejection rates translate into better graft survival. For example, Brennan and Schnitzler used an elegant technique to extend the follow-up of patients in his study by matching them with their United Network for Organ Sharing–reported data 5 yr after transplantation. In these high-risk patients, rejection rates were still significantly lower with ATG than basiliximab, but graft and patient survival were no different. In low-risk patients, Kyllo nen et al. found similar rejection rates between ATG and IL-2R Ab, but graft survival after 5 yr with basiliximab (96.6%) was statistically higher than with no induction (84.2%), a difference that did not reach statistical significance with ATG (90.6%). Finally, a United Network for Organ Sharing database analysis found that after adjustment for demographic and immunologic risk factors, treatment with ATG versus IL-2R Ab is associated with lower rejection rates but similar graft survival.

The trial by Noel et al. confirms that ATG is a more potent immunosuppressive agent than IL-2R Abs and that high-risk kidney transplant patients should receive ATG; however, this trial should not be interpreted as sounding a death knell for using IL-2R Abs. Compared with IL-2R Abs, more potent immunosuppression with ATG does not seem to improve graft survival and is likely to have more infectious complications. IL-2R Abs reduce rejection rates and improve graft survival compared with no induction and have an unusually benign adverse effect profile; therefore, in choosing immunosuppression protocols, it seems reasonable to use ATG in high-risk patients and IL-2R Abs in low-risk patients. Until further studies are performed, exactly where to draw the line between these two populations remains in the realm of clinical judgment.

**DISCLOSURES**

None.

**REFERENCES**


