

## **Kidney Transplant Immunosuppression: Is the Verdict In?**

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In the December 20, 2007 issue of the *New England Journal of Medicine*, Ekberg and colleagues report results from the Efficacy Limiting Toxicity Elimination (ELiTE)-Symphony study, an 83 center, 15 nation trial, comparing conventional doses of cyclosporin A in combination with corticosteroids and mycophenolate mofetil, but without the use of an anti-lymphocyte antibody during the induction phase, to three regimens employing the anti-interleukin 2 receptor monoclonal antibody, dacluzimab, mycophenolate mofetil, and corticosteroids in combination with lower than ordinary target levels of one of cyclosporine, tacrolimus or sirolimus for the prophylaxis of acute cellular rejection in recipients of kidney transplants. Creatinine clearance as calculated from the Cockcroft-Gault formula and allograft survival were highest, and the frequency of biopsy proven acute cellular rejection, lowest in the tacrolimus cohort. Serious adverse events were most common among recipients randomized to the sirolimus arm, but new onset post-transplant diabetes mellitus and diarrhea were most likely to occur in those patients treated with tacrolimus. Several other investigators have noted early allograft survival benefit for recipients treated with tacrolimus in combination with mycophenolate and corticosteroids when compared to those receiving cyclosporine-based regimens.<sup>2</sup> However, longer term studies have not uniformly confirmed this apparent advantage for tacrolimus-anchored immunosuppression. Concerns regarding generalization specific to this current investigation by Ekberg et al include the case mix of the study cohort, drug exposure, pharmacodynamic and pharmacokinetic interactions,

and study time frame. The primary outcome of the Ekberg et al study was glomerular filtration rate at one year. As short-term patient and allograft survival has improved, longer survival has become more important, the same rationales that drove the design of the Elite-Symphony study, aiming to minimize toxicity while ensuring good survival outcomes, are equally applicable to much longer periods of consideration. It is estimated that 43.3% of all kidney transplant recipients (41.1% of 148,933 deceased donor kidney transplants and 59.1% of 40,071 living donor transplants) would be alive at 15 years.<sup>9</sup> Many post-transplant concerns, particularly the toxicity of immunosuppressive agents, are much more likely to be evident during long-term follow-up, and the health and quality of life tradeoffs between a measurable, but small, average improvement in creatinine clearance needs to be compared to the medical and psychological consequences of increased rates of diabetes or chronic diarrhea that might be experienced, even if by a minority of recipients. Data endorsing the short-term efficacy of combination immunotherapy with tacrolimus, mycophenolate and corticosteroids is compelling and reproducible. The Ekberg et al study, employing relatively low initial tacrolimus trough level targets, and more conventional mid-range dosing strategies does not address the question of whether limiting initial tacrolimus dosing will conserve the efficacy of immunosuppressive regimens and reduce the toxicity of tacrolimus-based regimens over time. Whether this approach would improve long-term kidney function of renal allografts, and overall health and quality of life of kidney transplant recipients remains unanswered.