SIGNIFICANCE STATEMENT

The use of mammalian target of rapamycin inhibitors has been recognized as a potential immunosuppressive strategy to reduce exposure to calcineurin inhibitors (CNI), but there has been no consensus on the optimum protocol for safety and efficacy. This large international trial of >2000 *de novo* transplant patients used a novel binary end point that assessed both immunosuppressive efficacy and graft function. The study found that at 1 year, an everolimus-based regimen with reduced CNI exposure was noninferior to the current standard of mycophenolic acid with standard CNI exposure. Cytomegalovirus and BK virus infections were significantly reduced under everolimus. These results provide evidence that a *de novo* regimen of everolimus with low-exposure tacrolimus maintains immunosuppression and preserves graft function, while reducing viral infections, offering an alternative to conventional CNI-mycophenolate protocols.