Transplant drug two-year study outcomes show superior kidney function

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Two-year results from phase III clinical trials show the experimental immunosuppressive drug belatacept can better preserve kidney function in kidney transplant recipients while preventing graft rejection when compared with the standard immunosuppressive drug cyclosporine.

The two-year results from the three-year BENEFIT (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial) and BENEFIT-EXT ("extended criteria") studies were presented Sunday at the American Transplant Congress in San Diego. A safety study that pooled long- term data also was presented.

In the BENEFIT trial, 666 patients were randomized to three groups and transplanted at 100 sites around the world, with 493 completing two years on treatment. In the BENEFIT-EXT study, 543 patients were randomized and transplanted, with 347 completing two years on treatment. The three treatment groups were less intensive (LI) and more intensive (MI) belatacept and a standard regimen of cyclosporine (CsA). All patients also received standard transplant regimens of the anti-T cell antibody basiliximab and drugs mycophenolate mofetil and corticosteroids.

Patient and graft survival after two years was similar among the belatacept and cyclosporine groups (94 percent MI; 95 percent LI; 91 percent CsA). The superior renal benefit of belatacept found after the first year of treatment was sustained in the second year, as measured by

glomerular filtration rate. The improvement in cardiovascular/metabolic risk profile with belatacept remained in year two, with an additional beneficial effect noted in LDL cholesterol. Eight additional patients experienced an episode of acute rejection in year two (four with belatacept, four with cyclosporine), but in most cases this was successfully treated with drugs and did not lead to graft failure.

The overall incidence rate of malignancies and serious infections remained comparable across the groups. Although in the second year there remained a higher incidence of post-transplant lymphoproliferative disorder (PTLD)-five belatacept patients vs. one cyclosporine patient-the overall safety profile remained similar across the groups. No additional benefits were seen in the MI vs. the LI belatacept group.

"Our goal in transplantation is to achieve a normal life span for our patients, and to have them survive dialysis-free with a functioning transplanted organ for that life span," says Christian P. Larsen, MD, DPhil, director of the Emory Transplant Center and chair of the Department of Surgery in Emory University School of Medicine.

"Today, the median survival of a transplant remains about 8-10 years, far short of what we'd like," Larsen adds. "While the calcineurin inhibitors, cyclosporine and tacrolimus, are potent immunosuppressant drugs, they are associated with multiple toxicities that limit transplant success. We have been working for years to develop new therapies that avoid the main complications and causes of death, including cardiovascular events, infections and malignancies. Our data with belatacept indicate it can better preserve kidney function while improving the risk for these complications."

Larsen, along with fellow Emory University transplant surgeon and researcher Thomas C. Pearson, MD, DPhil, Emory professor of surgery and co-director of the kidney/pancreas transplant program at the Emory

Transplant Center, made significant research contributions to the development of belatacept, in collaboration with other investigators at Emory, the Yerkes National Primate Research Center, and Bristol Myers Squibb.

A third study, which pooled safety data from phase II and phase III studies over 2.4 to 7 years, found that longer-term treatment with belatacept-based regimens was generally safe. The incidence of deaths and serious adverse events were lowest in the belatacept LI group. The overall incidence of malignancies remained low, but was slightly higher in the MI group. The incidence of herpes infections and tuberculosis (mostly in endemic areas) was low overall, but higher in the belatacept groups. Fifteen cases of PTLD occurred (13 with belatacept, 2 with cyclosporine), mainly in patients not previously exposed to Epstein-Barr virus, which many humans have as a low-level chronic infection. The researchers say PTLD might be reduced by avoiding use of belatacept in Epstein-Barr-nad′ve patients.

Belatacept is a "costimulation blocker" that inhibits one of two signals T cells require to trigger an immune response. It is a modified version of a fusion protein known as CTLA4-Ig, which mimics a regulatory molecule found on T cells and acts as a decoy. CTLA4-Ig (commercial name: abatecept/Orencis) is FDA approved to treat rheumatoid arthritis.

Provided by Emory University