Transplant drug preserves kidneys, avoids toxicity

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The experimental drug belatacept can prevent graft rejection in kidney transplant recipients while better preserving kidney function when compared with standard immunosuppressive drugs, data from two international phase III clinical trials show.

The results are published in the March issue of the *American Journal of Transplantation*.

The senior author of the paper describing BENEFIT (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial) is Christian P. Larsen, MD, DPhil, director of the Emory Transplant Center and chair of the department of surgery at Emory University School of Medicine. The lead author is Flavio Vincenti, MD, professor of medicine (nephrology) at University of California, San Francisco.

Thomas C. Pearson, MD, DPhil, professor of surgery at Emory and co-director of the kidney/pancreas transplant program at Emory Transplant Center, is a co-author on a companion paper describing belatacept's performance on "extended criteria" kidney transplants (Kidneys from donors that are older or have other factors associated with shorter graft survival).

The drugs most transplant patients now rely on to inhibit their immune systems and prevent graft rejection have serious side effects. The class of drugs known as calcineurin inhibitors (cyclosporine and tacrolimus,

for example) can damage the kidneys and lead to high blood pressure and diabetes.

The data from the BENEFIT trial, which tracked 666 kidney transplants at 100 sites around the world, shows that patients taking belatacept had similar graft survival rates to those taking cyclosporine, while maintaining higher kidney function and lower blood pressure and cholesterol. In addition, instead of requiring patients to take pills twice every day, in the case of calcineurin inhibitors, belatacept can be given every few weeks.

Trial data and side effects:

The BENEFIT trial, which was sponsored by Bristol Myers Squibb, compared three regimens: a more intensive and a less intensive course of belatacept treatment and a standard cyclosporine course.

All patients received a temporary course of an anti-T cell antibody called basiliximab and the standard transplant drugs mycophenolate mofetil and corticosteroids.

After one year, the proportion of patients with impaired kidney function (defined through glomerular filtration rate) was 55 percent for more intensive and 54 percent for less intensive, compared to 78 percent for cyclosporine. Patients' blood pressure, cholesterol and blood sugar profiles were also more favorable with belatacept.

More patients experienced acute rejection -- a temporary flare-up of the immune system against the donated kidney -- under belatacept (22 percent for more intensive, 17 percent for less) compared to 7 percent with cyclosporine. However, in most cases the acute rejection was successfully treated with drugs and did not lead to graft failure.

With belatacept, there was a higher incidence of a serious complication called post-transplant lymphoproliferative disorder (PTLD) - five patients total in the BENEFIT trial, compared to one with cyclosporine. PTLD is associated with infection with the Epstein-Barr virus, which many humans have as a low-level chronic infection. The authors say PTLD might be reduced by avoiding use of belatacept in Epstein-Barr-nad′ve patients.

Belatacept, whose development was significantly contributed to by Larsen and Pearson in collaboration with other investigators at Emory University and researchers at Bristol Myers Squibb, is a "costimulation blocker," which inhibits one of two signals T cells require to trigger an immune response.

Belatacept 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/Orencia) is FDA approved to treat rheumatoid arthritis.

In the 1990s, Larsen and Pearson found that CLTA4-Ig could control graft rejection in mice, but it didn't work as well in non-human primates. Researchers at Bristol Myers Squibb sifted through mutations to find two that made CTLA4-Ig bind tighter to its target. Larsen and Pearson then showed that the modified protein could be effective in a non-human primate model for kidney transplant at Emory's Yerkes National Primate Research Center.

More information:

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