Study shows new approach to prevent antibody-mediated damage in kidney transplants

June 2 2009

Early results from a Mayo Clinic research study demonstrate the effectiveness of a new approach to blocking an important part of the immune system that causes severe damage to some kidney transplants. Historically, these patients have been very difficult to treat successfully because their immune systems are already primed with antibodies to destroy the donor organ. These findings were presented today at the American Transplant Congress.

Results show that the drug under study, called eculizumab, prevents antibody-mediated kidney transplant rejection by inhibiting the immune system's activation of one of the body's important defense mechanisms -- the complement system. Antibody-mediated rejection is a major barrier to transplant in patients with antibodies against their living donors sometimes called "positive crossmatch kidney transplants."

Though the results are preliminary and the study is ongoing, Mayo Clinic's lead author, Mark Stegall, M.D., said the data suggest that eculizumab therapy may be a turning point for this select group of high risk kidney transplantation patients. "This innovative approach has the potential to make this type of high risk transplant possible for more people while improving outcomes," he says

Positive crossmatch patients have antibodies in their blood against foreign "tissue types" that are present on donor kidneys. These tissue

types, termed Human Leukocyte Antigens (HLA), are the reason the transplant patient's body perceives the donated kidney as "non-self" tissue. These antibodies result from previous transplants, blood transfusions or pregnancies.

Increasingly recognized as a major problem, high levels of these antibodies delay transplantation, as evidenced by the approximately 7,000 people on the United Network for Organ Sharing (UNOS) kidney waiting list who are still looking for a match. Mayo Clinic has long been a leader in devising innovative approaches to help this challenging group of kidney patients, and these latest findings about eculizumab add to the expertise and options offered to patients.

This work suggests a novel way to block antibody-mediated tissue injury. The Mayo team showed that eculizumab blocks the part of the immune system known as the complement system, which initiates tissue destruction. In this study, 10 positive crossmatch kidney transplant patients were treated with eculizumab. None of the treated patients developed antibody-mediated rejection compared to historical controls in which 60 percent with similar levels of antibody would have developed antibody-mediated rejection.

"These results are great news because they mean that none of the treated patients developed the most serious complication that normally threatens the transplant. This represents a quantum leap in this area," explains Dr. Stegall.

High levels of antibodies were once considered an absolute contraindication to kidney transplantation; however, Mayo Clinic researchers and other groups have developed new protocols to successfully overcome antibody barriers -- mostly in the setting of living donation. Without such protocols, most of these patients would die without ever receiving a kidney transplant. Despite their general success,

these protocols, which have been in use for almost a decade, have been complicated by a high rate of antibody-mediated damage which can lead to early graft injury that shortens the lifespan of the transplant. Preventing antibody-mediated rejection has been difficult. This new therapy may be a first step toward improved outcomes in these high-risk recipients.

In addition to the 10-sample study in which tissue destruction was prevented in all patients, the Mayo team presented a related, more detailed analysis of the ability of eculizumab to prevent kidney damage at the microscopic level. This study involved 62 tissue biopsies from 50 kidney transplant patients. The biopsies were analyzed using the electron microscope for evidence of the mechanism and process of tissue destruction.

Results showed that when acute antibody-mediated rejection occurs, it involves changes observable by electron microscope in the endothelial cells lining the kidney blood vessels. These changes correspond with high levels of antibodies against the donor circulating in the patient's blood serum. And importantly, by blocking a specific part of the immune system with eculizumab, doctors prevented endothelial activation. These results suggest the endothelial lining may be a potential target for developing new drugs
to stop antibody-mediated tissue destruction so that more positive crossmatch patients can be successfully transplanted. More research is needed to confirm these findings.

Source: Mayo Clinic (news : web)

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