MICA Antibodies Linked to Kidney Transplant Failure

September 26, 2007 | Vaccines [1]

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Kidney recipients with antibodies to major-histocompatibility-complex class I-related chain A (MICA) antigens found in endothelial cells were 63% more likely to experience transplant rejection than those without MICA sensitization (P=0.028), according to the results of a large retrospective study reported in the Sept. 27 issue of the New England Journal of Medicine.

The antibodies were significantly associated with rejection only among patients receiving their first transplant, those with good human leukocyte antigen (HLA) matching, and those with no HLA antibody reactivity, said Peter Stastny, M.D., of the University of Texas Southwestern Medical Center here, and colleagues.

Although MICA may provide new tools against transplant rejection, "HLA remains the cornerstone of transplantation immunology," commented Willy Albert Flegel, M.D., of the Institute for Clinical Transfusion Medicine and Immunogenetics in Ulm, Germany, in an accompanying editorial.

Prospective clinical studies are needed to determine whether MICA-matching donors and recipients or efforts to prevent MICA sensitization could reduce transplant failure, Dr. Flegel added.

The researchers analyzed stored pretransplant serum samples from 1,910 patients in 13 countries who received a kidney from a deceased donor between 1990 and 2004.

Each serum sample was tested for immunoglobulin G (IgG) anti-HLA class I and II reactivity, HLA antibodies, and IgG antibodies against MICA antigens.

Overall, the 11.4% of patients with anti-MICA antibodies before transplantation were more likely to have kidney-allograft rejection.

The one-year graft-survival rate was 88.3% among patients with anti-MICA antibodies compared with 93.0% among patients without MICA antibodies (P=0.01). At five years, the graft-survival rate remained better in the group without MICA antibodies.

The difference was greatest in patient subgroups considered at lowest risk for graft rejection.

The odds for transplant rejection were higher for MICA sensitization in first transplant patients than among patients receiving a second or subsequent transplant (hazard ratio 1.86, P=0.009, versus 0.77, P=0.68). For patients receiving their first transplant, graft survival was 87.8% with MICA antibodies compared with 93.5% among those without the antibodies (P=0.005).

Among patients who received well-matched kidneys (no more than one HLA-A, HLA-B, or HLA-DR mismatch), sensitization against MICA reduced allograft survival (83.2% versus 95.1%, HR 4.97, P=0.002).

But, the effect of MICA antibodies on allograft loss was not significant for less well-matched kidneys with two to four HLA mismatches (HR 1.29, P=0.36) or those with five or six HLA mismatches (HR 1.63, P=0.50).
Likewise, MICA sensitivity was a significant factor in transplant rejection only in patients without panel-reactive HLA antigens (HR 1.85, P=0.003) and not those with HLA antibodies (HR 0.88, P=0.84). Simultaneous presence of both HLA and MICA antibodies was rare, though (less than 4% of patients).

These findings "may hint that anti-MICA antibodies have an influence independent of HLA," Dr. Flegel said.

Furthermore, "HLA and clinical conditions other than immunization against MICA are more important than the presence of these antibodies," he added, "because no possible MICA effect was apparent in patients with HLA mismatches, retransplantation, or both."

The cause of MICA sensitization did not appear to be blood transfusion, Dr. Stastny and colleagues said. The frequency of transfusions was statistically similar between kidney transplant patients with and without anti-MICA antibodies (P=0.15).

"These findings are in sharp contrast to the known effect of transfusions in the production of antibodies against class I and class II HLA antigens," the researchers said.

They speculated that "cross-reactivity with substances from the environment may play a role in priming the immune system" against MICA antigen. However, the mechanism by which anti-MICA antibodies develop before transplantation remains unknown, they said.

The study was also limited by lack of kidney donor DNA, which did not allow "formal proof of donor specificity," the investigators said.

If studies can prove this association, "it will be important to develop strategies to reduce or eliminate the effect of MICA antibodies on kidney-graft outcome," they concluded.

The study was supported by the University of Texas Southwestern Medical Center and the University of Heidelberg. Dr. Stastny reported serving as an invited speaker at histocompatibility workshops sponsored by One Lambda. Other members of the research group reported conflicts of interest for Roche, Bristol-Myers Squibb, Biotest and Genzyme. Dr. Flegel reported no conflicts of interest.

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