Monoclonal antibody effective in treating life-threatening renal disease

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(Medical Xpress)—Two clinical studies have shown that the monoclonal antibody eculizumab is effective in treating patients with atypical hemolytic uremic syndrome (aHUS), a life-threatening, chronic, and progressive inflammatory disease.

The results are published this week in the *New England Journal of Medicine*.

One of the four sites for the clinical trial in the United States was at Emory University School of Medicine and Children's Healthcare of Atlanta, and was led by principal investigator Larry Greenbaum, MD, PhD, Marcus Professor of Pediatrics at Emory and chief of nephrology at Children's. The trial was conducted in the Pediatric Research Center affiliated with the Atlanta Clinical and Translational Science Institute (ACTSI), part of the CTSA network sponsored by the National Institutes of Health.

aHUS leads to thrombotic microangiopathy (TMA), which causes blood clots in capillaries and small blood vessels. Patients with aHUS have a lifelong risk of systemic complications of TMA, including damage to multiple organ systems.

Although aHUS was previously managed with plasma exchange or infusion (PE/PI), the underlying problems persist, and end-stage renal disease or death occurs in approximately 33 to 40 percent of patients during the first clinical episode. Within a year, up to 65 percent of

patients managed with PE/PI have permanent kidney damage, progress to end-stage renal disease, or die. In aHUS patients who have kidney transplants, 60 to 90 percent lose the transplants within a year.

Eculizumab binds to the human C5 complement protein and blocks production of pro-inflammatory proteins. It was previously approved for the treatment of the blood disorder paroxysmal nocturnal hemoglobinuria (PNH), and the results of these trials led to FDA approval of eculizumab for the treatment of aHUS.

The two Phase 2 studies enrolled a total of 37 patients who were not responding to PE/PI or who had no platelet count decrease >25 percent for 8 weeks during PE/PI. Participants in each study were treated for 26 weeks and longer-term extensions. Effectiveness was measured by an increase in platelet counts and TMA event-free status (no platelet decrease >25 percent, PE/PI, or new dialysis). Secondary measures were renal outcomes, health-related quality of life, and safety.

The studies found that eculizumab significantly reduced complement-mediated TMA, as indicated by normalization of hematologic measures and reduction in interventions for TMA. In the first trial, the platelet count significantly increased from baseline. In the second, 80 percent of the patients had TMA event–free status.

Eculizumab also resulted in significant improvement in all secondary measurements. In one of the studies, four out of five patients receiving dialysis were able to discontinue dialysis following initiation of eculizumab. Earlier intervention was associated with significantly greater improvement in kidney function. No cumulative toxicity or serious infection-related adverse events were found.

"This study showed that eculizumab is effective in treating patients with this chronic, life-threatening disease, and we were pleased to be one of

the participating sites," says Greenbaum. "This drug is a true therapeutic breakthrough for these patients."

Provided by Emory University