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Long-term Use of Eculizumab in Kidney Transplant Recipients

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Eculizumab is a first-in-class monoclonal anti-C5 antibody that binds specifically to the complement protein C5, and is effective in treating atypical hemolytic uremic syndrome (aHUS).[1] Patients with end-stage renal disease due to aHUS may require dialysis or a kidney transplant, and have an increased risk of aHUS recurrence after transplantation. In addition, *de novo* HUS can occur in 3% to 14% of transplant recipients. Increased risk of recurrence was found in 20% of patients carrying a mutation in the gene encoding for Membrane Cofactor Protein, in 22% for patients with anti-Complement Factor H (CFH) antibodies present, and in as many as 88% of those with mutations in CFH and in Complement Factor I.[2] Zuber *et al.*[3] proposed to stratify renal transplantation candidates into risk levels of recurrence: high-risk patients include those who have already experienced recurrence in a previous graft and who had mutations in CFH; patients at moderate risk of recurrence include those with anti-CFH antibodies, mutations in Complement Factor I, mutations of unknown functional significance, or no mutations identified; and patients at low risk of recurrence are those who have isolated mutations in Membrane Cofactor Protein and/or those with anti-CFH antibodies cleared from circulation.

Emerging evidence supports the efficacy of eculizumab in preventing aHUS recurrence in the kidney grafts of transplant recipients. Prophylactic therapy with eculizumab should be started in patients with moderate to high risk, whereas patients with low risk should only be monitored. Preemptive treatment should continue after transplantation according to the standard schedule; however, the duration of treatment has yet to be determined.[4]

Shiga Toxin *Escherichia coli* (STEC)-HUS is a secondary form of aHUS due to Shiga-like toxin-producing *E. coli* or Shigella infection. Most cases of STEC-HUS have a favorable outcome, although 5% to 25% of patients progress to end-stage renal disease and undergo kidney transplantation. The disease recurs in fewer than 1% of cases, thus prophylactic treatment with eculizumab before transplantation is not recommended. However, rare reports of posttransplant recurrences have been reported.[2] We describe a patient affected by STEC-HUS with slow progression to end-stage renal disease, and complement dysregulation due to anti-CFH antibodies. She was considered to be at high risk of aHUS before transplantation, and was treated with eculizumab. After 36 months, she continues to receive treatment because anti-CFH antibodies are still present despite immunosuppressive therapy.[5] This case indicates that screening of HUS-associated genes should be performed in patients on dialysis following severe episodes of STEC-HUS, as there may be undiagnosed cases of aHUS in patients with STEC infection and a genetic background of impaired complement regulation.[6]

The article, "Eculizumab use for kidney transplantation in patients with a diagnosis of atypical hemolytic uremic syndrome," presents the outcomes of long-term treatment with eculizumab in kidney transplant recipients previously affected by HUS.[7] In this observational study, Siedlecki *et al.*[7] followed 87 patients who were diagnosed with aHUS and received eculizumab before and during their most recent transplant. In addition, 101 patients initiated eculizumab post-transplantation. This second group was subdivided into patients diagnosed with aHUS either before or after their most recent transplant. All of the patients in the treatment arm took eculizumab for 1 year after transplantation. The authors compared the outcomes of all subjects treated with eculizumab with those of patients not treated with eculizumab. Within 6 months of transplantation, graft function was significantly better in patients who

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took eculizumab before and during their most recent transplant compared with patients who took eculizumab posttransplantation.[7] The findings suggest that starting eculizumab therapy early improves outcomes and lowers the risk of aHUS recurrence. The authors found that earlier aHUS diagnosis and treatment improved posttransplant outcomes as well.[7]

In conclusion, studies document the efficacy of eculizumab in the prevention and treatment of aHUS in both patients with native and transplanted kidneys. Further, knowledge of a complement mutation can be used to predict the risk of recurrence of aHUS and help to identify which patients should start prophylactic therapy. However, several questions remain unanswered regarding safety, dosing, and duration of treatment. In fact, anti-C5 therapy can be associated with its own risks.[8] Limited data regarding duration suggest treatment with eculizumab for a range of 1 to 2 years after transplantation. Le Quintrec *et al.*[4] demonstrated that the rate of recurrence decreased 2 years after transplantation, whereas authors of a recent international consensus report on pediatric aHUS considered treatment withdrawal after the first year of transplantation. They recommend more studies on the risk of aHUS in native kidneys to determine the risk of early relapse in patients with high-risk mutations. Therefore, controlled randomized trials are needed to reduce the risks of eculizumab treatment while maximizing its benefits.

DISCLOSURE

All the authors declared no competing interests.

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