

myocardial infarction or coronary death, a 24% decrease in the need for coronary bypass surgery, and a 17% decrease in the rate of fatal or nonfatal stroke.<sup>2</sup> The recently reported results of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial of rosuvastatin (20 mg per day) show that even patients with moderate risk can benefit very substantially from statin treatment.<sup>3</sup> The study included only patients with initial LDL levels below 130 mg per deciliter (median, 108 mg per deciliter) and achieved on-treatment levels averaging 55 mg per deciliter. Statin treatment decreased all-cause mortality by 20%, the primary end point of combined cardiovascular events by 44%, myocardial infarction by 54%, and stroke by 48%. What do we have in our medical bag that can match that? Moreover, the statins are probably safer than aspirin, and they are cost effective.<sup>4</sup> Finally, there is good reason to believe that

even more striking results may be seen when we start treating hypercholesterolemia in patients at an earlier age.<sup>5</sup>

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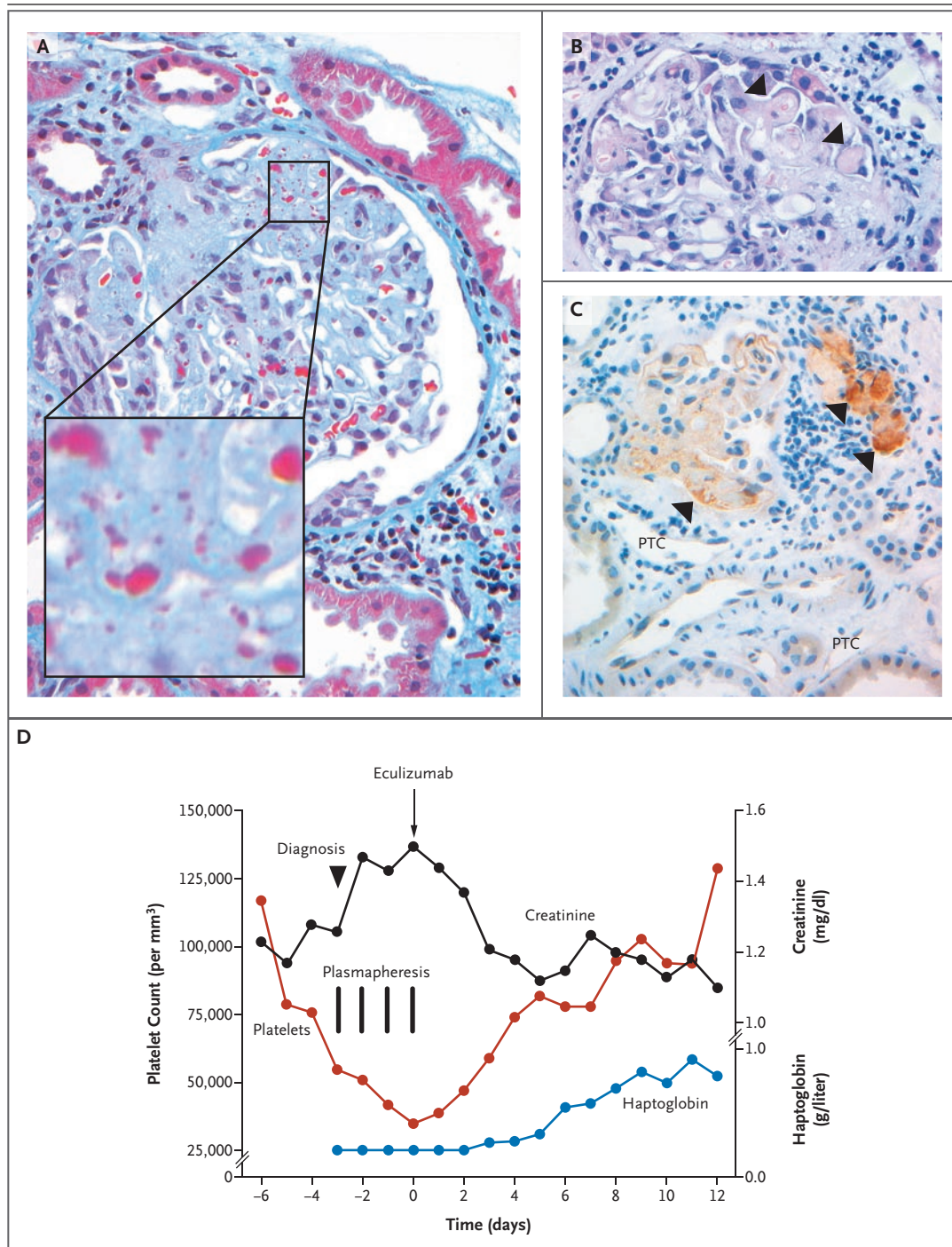
## Ecuzumab for Atypical Hemolytic–Uremic Syndrome

**TO THE EDITOR:** Atypical hemolytic–uremic syndrome is a disease of uncontrolled complement activation associated with a high mortality rate, and most cases progress to end-stage renal disease.<sup>1</sup> About 50% of patients with this syndrome carry mutations in genes encoding complement proteins.<sup>2</sup> Complement inhibition has been suggested for the treatment of atypical hemolytic–uremic syndrome,<sup>3</sup> but currently no data on this treatment option are available. We report on a case of atypical hemolytic–uremic syndrome that was successfully treated with ecuzumab, a humanized monoclonal antibody that blocks complement activity by cleavage of the complement protein C5, thereby preventing the generation of the inflammatory peptide C5a and the cytotoxic membrane-attack complex, C5b-9. Ecuzumab has been approved for the treatment of paroxysmal nocturnal hemoglobinuria.<sup>4</sup>

End-stage renal disease due to atypical hemolytic–uremic syndrome developed in a woman at 25 years of age. At 30 years of age, after 5 years of undergoing dialysis, she received a cadaveric renal transplant. Five weeks after transplantation, atypical hemolytic–uremic syndrome recurred and led to the loss of transplant function despite 18 plasma exchanges. The patient underwent dialysis for another 7 years until she received a second

### Figure 1 (facing page). Pathological Findings and Laboratory Values.

In Panel A, elastic Masson's trichrome stain shows thrombotic microangiopathy with numerous intracapillary erythrocytes. The inset shows magnification of the area with red-cell fragments. In Panel B, hematoxylin and eosin stain shows hyaline microthrombi that occlude glomerular capillaries (arrowheads). In Panel C, immunostaining for complement protein C4d was positive in glomerular capillaries and preglomerular arterioles (arrowheads), indicating an activation of the complement system. C4d staining of peritubular capillaries (PTC), an indicator of humoral rejection, was negative. Panel D shows the time course of the platelet count and laboratory values used to determine the occurrence of hemolysis in the patient who underwent renal transplantation (ecuzumab was administered at 0 days). When atypical hemolytic–uremic syndrome was diagnosed (arrowhead), tacrolimus was discontinued and plasma exchange was performed four times (vertical black bars indicate treatments). Despite this treatment, atypical hemolytic–uremic syndrome was aggravated, as indicated by the progressive decrease in platelets to 35,000 per cubic millimeter and the deterioration of transplant function indicated by an increase in the creatinine level to 1.5 mg per deciliter. A single dose of 600 mg of ecuzumab was administered (arrow), and measurements of total complement activity (data not shown) showed that ecuzumab completely blocked the complement system. After treatment with ecuzumab, haptoglobin levels normalized after 8 days, the platelet count increased, and the creatinine level decreased, indicating recovery of transplant function.



cadaveric transplant at 37 years of age. Six weeks after the second transplantation, atypical hemolytic-uremic syndrome again recurred. The onset of atypical hemolytic-uremic syndrome may have been associated with the additional use of tacrolimus, which the patient received after three episodes of cellular rejection developed.

Genetic analysis revealed a novel heterozygous missense mutation in exon 10, codon 475 (Y475S), of the gene encoding complement factor H. This missense mutation leads to a substitution of a serine by a tyrosine that belongs to the highly conserved residues of the factor H protein sequence; this sequence may be responsible for the

observed reduction in the plasma level of factor H to 180  $\mu\text{g}$  per milliliter (normal range, 284 to 528). Furthermore, we detected a homozygous deletion comprising at least exon 2 within the *CFHR1* gene.<sup>5</sup> No mutation was found in the *MCP* or *CFI* genes. Transplant biopsy specimens showed thrombotic microangiopathy (Fig. 1A through 1C).

Since recurrent atypical hemolytic–uremic syndrome leads to graft loss in more than 90% of patients, we decided to administer a single dose of 600 mg of eculizumab after renal function worsened in this patient despite four plasma exchanges. After the administration of eculizumab, the total complement activity was completely blocked, the hemolysis resolved, and the transplant function recovered (Fig. 1D). The patient's renal graft function has been stable for 8 months.

These findings show the positive effect of complement inhibition on the course of atypical hemolytic–uremic syndrome in our patient and, in our view, the use of eculizumab in atypical hemolytic–uremic syndrome warrants further investigation.

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## Eculizumab for Congenital Atypical Hemolytic–Uremic Syndrome

**TO THE EDITOR:** Atypical hemolytic–uremic syndrome of infancy is a rare disorder that is associated with thrombotic microangiopathy and acute renal failure. It often involves complement dysregulation.<sup>1,2</sup> Plasma infusions have variable efficacy, and end-stage renal disease often develops in children who are unresponsive to plasma therapy.<sup>1,2</sup> We report on a patient with congenital relapsing atypical hemolytic–uremic syndrome who was unresponsive to plasma therapy but had a response to eculizumab, a humanized monoclonal antibody against terminal complement protein C5.<sup>3</sup>

An 18-month-old boy was admitted with a fourth relapse of congenital atypical hemolytic–uremic syndrome. He was born at 34 weeks' gestation, and thrombotic microangiopathy developed within the first 8 days after birth. The hemoglobin was 8.5 g per deciliter, the platelet count  $18 \times 10^3$  per microliter, and the blood urea nitrogen 34 mg per deciliter. The creatinine level was 1.0 mg per deciliter, and the lactate dehydrogenase (LDH) level was 6077 U per liter (normal value, <920 U per liter). A blood smear showed schistocytes. These findings were consistent with congenital atypical hemolytic–uremic syndrome.