Sutimlimab Therapy in Cold Agglutinin Disease

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Introduction

Cold agglutinin disease (CAD) is a form autoimmune hemolytic anemia caused by a proliferation of low grade clonal B-cells that produce monoclonal IgM cold agglutinins. IgM binds erythrocyte surface antigens at low temperatures, leading to activation of the classical complement pathway. This results in C3 deposition on erythrocytes and subsequent extravascular hemolysis. Multiple therapies are available for CAD, including complement targeted and B-cell directed therapy. Sutimlimab, a monoclonal antibody directed against complement protein C1s, selectively inhibits classical pathway activation and represents a potential approach to disrupt the mechanism of hemolysis in CAD.

Case

A 53-year-old woman with a two-year history of CAD managed without transfusions developed severe fatigue, dark urine, and myalgias while traveling abroad. While returning to the United States, she experienced a syncopal episode boarding the final flight of her trip and was transported to the emergency department. Laboratory evaluation revealed a hemoglobin level of 3.3 g/dL, and ECG demonstrated ST segment depression in the lateral precordial leads. She was emergently transfused with five units of packed red blood cells, resulting in resolution of the ST segment changes, and was discharged after her hemoglobin level remained stable.

Following this episode, she began treatment with four-week cycles of rituximab. After two treatment cycles, she remained intermittently transfusion dependent. Treatment was transitioned to sutimlimab following lack of improvement with rituximab and was administered every two weeks. Four weeks after starting sutimlimab, her hemoglobin increased to 14.2 g/dL. Eight months later, her hemoglobin remained within the normal range on sutimlimab infusions administered every four weeks.

Discussion

Sutimlimab selectively inhibits C1 complement proteins, preventing initiation of the classical complement pathway when IgM binds to surface antigens of erythrocytes. By interrupting complement activation at its initial step, sutimlimab targets the primary mechanism of hemolysis in CAD and provides an alternative to therapies directed at interfering with monoclonal antibody production by B-cells. The quick and sustained improvement in hemoglobin observed in this case is consistent with clinical trial data demonstrating that classical complement inhibition can effectively prevent hemolysis and restore hemoglobin levels. This case provides an excellent example of the central role of complement mediated hemolysis in CAD and demonstrates the clinical efficacy of targeted complement inhibition with sutimlimab.