



53rd Annual Meeting & Exposition of the American Society of Hematology

San Diego, California / December 10-13, 2011

Targeted Therapy for Complement Inhibition: Preventing Life-threatening Thrombosis

San Diego - Paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) are 2 diseases driven by the complement system that respond to a monoclonal antibody (MAb) that binds to the human C5 complement protein and inhibits activation of the terminal complement. The efficacy of targeted therapy validates the biochemistry of the underlying pathology and provides insight about how complement contributes to pathologic processes when regulation or defenses are abnormal. In patients with PNH or aHUS, preventing complement expression curbs symptoms and complications, including life-threatening thrombosis. The MAb eculizumab inhibits activation of the terminal complement and has been shown to normalize mortality rate in patients with PNH to an extent comparable to matched controls. In data presented at ASH, the MAb appears to offer the same relative advantage in aHUS by providing continuous control of symptoms and preventing progressive organ damage.

Chief Medical Editor: Dr. Léna Coïc, Montréal, Quebec

Paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) are rare but potentially fatal diseases. It has been estimated that 35% of PNH patients die within 5 years of diagnosis. For aHUS, >50% of patients have died, are on dialysis or have permanent renal damage within 1 year of diagnosis even if treated with plasma exchange.

Blocking Complement Activation

The development of a monoclonal antibody (MAb) directed at a step in the complement pathway has led to a substantial improvement in prognosis. By blocking a key protein in the cascade of complement activation, eculizumab can provide continuous protection. "Some of the patients in our series have been on therapy for >2 years with no evidence of a diminished effect. This is very reassuring because these patients do not have a good prognosis otherwise," reported Dr. Ulrike M. Reiss, St. Jude Children's Research Hospital, Memphis, Tennessee.

Presenting data from a multicentre collaboration on PNH in children and adolescents, Dr. Reiss indicated that eculizumab, first approved for the treatment of PNH in 2007, has prevented the most serious associated complications of the disease, i.e. thrombosis, pulmonary arterial hypertension, chronic kidney disease and death.

Like many cells produced in the bone marrow, red blood cells (RBCs) are protected from complement, the enzymatic response which lyses foreign bodies, by the regulatory proteins anchored to their cell membranes with glycosylphosphatidylinositol (GPI). In PNH, which can occur alone or in the setting of another bone marrow defect, impaired GPI production and loss of surface proteins leaves

RBCs vulnerable to complement, leading to anemia and, through a related defect in platelets, thrombosis. In aHUS, which can be acquired or familial, the underlying mechanism is uncontrolled activation of the complement system, with similar consequences to PNH and includes anemia, major thrombosis formation and thrombotic microangiopathy that damage the kidney, liver and other major organs.

In the series of activation and enzymatic steps that produce the lytic effects of complement, eculizumab, a recombinant humanized IgG antibody, specifically binds to the complement protein C5, preventing it from the cleavage required to form a membrane attack complex. In preventing the attack complex, the consequences of RBC vulnerability leading to hemolysis in PNH and the uncontrolled complement activation in aHUS are avoided.

Maintaining Protective Effect

These mechanisms are important for understanding the benefit of eculizumab and why the protective effect is likely to endure as long as patients remain on therapy. The recent data demonstrating efficacy and safety in children is valuable because about two-thirds of aHUS develop in childhood. PNH also occurs in both children and adults. However, both diseases can be difficult to diagnose at any age because of non-specific signs and symptoms, such as anemia and fatigue. Thus, evidence of hemolysis, such as elevated lactate dehydrogenase (LDH) levels, should trigger suspicion of PNH or aHUS.

The study of eculizumab in children with PNH was initiated in 2009 as a 12-week, open-label efficacy and safety analysis, but the follow-up continues because of the need for chronic treatment. In this study of 7 patients

between the ages of 11 and 17, the MAb was administered in a weight-based dosing with a range of 300 to 900 mg administered intravenously q7 to 14 days.

Given the high mortality rate in PNH, evidence of normalized survival relative to age-matched controls in adults supports treatment. Dr. Reiss reported that no systemic evaluation had been done in children. However, the trial results demonstrate that pediatric PNH patients receiving treatment have reduced intravascular hemolysis and treatment was well tolerated in the short term. "Consistent with results in adults, eculizumab infusions controlled intravascular hemolysis in pediatric patients as shown by rapid and sustained terminal complement inhibition as well as by a reduction in LDH," she told delegates. Also, a close inverse correlation was observed between serum eculizumab concentration levels and hemolysis. While hemolysis was in excess of 90% in all patients prior to therapy, it was fully inhibited when therapeutic concentrations were reached. Moreover, on consistent therapy, no breakthrough hemolysis was observed.

As with efficacy, the MAb's safety was found similar in children as in adults. Over the course of the study, 2 episodes of headache and 1 case of pyrexia were thought possibly related to treatment and 1 case of upper abdominal pain was considered probably related to eculizumab, but all were of mild severity. Serious adverse events—e.g. acute sinusitis, anemia, thrombocytopenia, acute otitis media and menorrhagia—were reported in 2 patients, but there was no consistent pattern. Dr. Reiss noted that during the formal study and during follow-up, the agent has been well tolerated.

"Based on the potential for life-threatening complications, this therapy has been helpful for allowing these children to lead relatively normal lives," stated Dr. Reiss, who noted that there has been little change in the status of children maintained on therapy over time. The effective dose identified during the formal study period has been maintained with no apparent loss of efficacy and no new tolerability issues.

The same type of positive results were generated in a series of 20 mostly adult patients treated for aHUS. While patients as young as 12 were eligible for this study, the median age was 28 years. All were being managed with chronic plasma exchange or

infusion (PE/PI) at the time of enrolment. After an observation period, patients were started on eculizumab 800 mg/week. The dose was raised to 1200 mg at week 5 but was subsequently administered q2 weeks. The primary end point was event-free status defined as at least 12 weeks of stable platelet count, no PE/PI and no new dialysis. Renal function and safety were among secondary end points.

Of the 20 patients, 16 had achieved event-free status by week 26. Of those followed out to 60 weeks, 17 had reached this status, according to Dr. Christoph Licht, Hospital for Sick Children, Toronto, Ontario. No patient in the initial 26-week data analysis or at the end of 60 weeks required an intervention for thrombotic microangiopathy. Moreover, there was steady improvement in renal function over the course of treatment, which again was seen after 26 weeks and after 60 weeks. Seven patients had adverse events that were possibly or probably related to eculizumab, but the therapy was found to have acceptable tolerability and safety in follow-up so far.

"Switching to chronic eculizumab therapy significantly changed the course of the disease in severe and prolonged renal insufficiency patients, resulting in sustained suppression of thrombotic microangiopathy," reported Dr. Licht, who characterized eculizumab as "the new standard of care for aHUS." While eculizumab is well tolerated for long-term treatment, Dr. Licht did caution that suppression of complement can increase the risk for some infections and patients should receive the meningococcal vaccine prior to initiating therapy. Further work is anticipated with this agent for other complement-related disorders.

Summary

The MAb eculizumab has altered the prognosis of patients with the complement-mediated diseases PNH and aHUS. While it does not cure the underlying pathology of these diseases, it can control symptoms indefinitely and appears to prevent the progressive damage that has associated these diseases with a poor long-term prognosis. The availability of an effective therapy for these diseases, previously managed with supportive care, increases the advantages for early diagnosis because of the opportunity to prevent end organ damage and death mediated by thrombotic microangiopathy. □

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PP12-042E DL

