

Highlights in Nonmalignant Hematology From the 2019 American Society of Hematology Meeting

December 7-10, 2019, Orlando, Florida

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Complement Inhibition Shows Promise in Autoimmune Hematologic Disorders

Two recent studies support the use of sutimlimab, an investigational inhibitor of the classical pathway of complement, in patients with cold agglutinin disease (CAD) or chronic immune thrombocytopenic purpura (ITP).

In the first study, a phase 3, open-label, single-arm, multicenter study called Cardinal (A Study to Assess the Efficacy and Safety of BIVV009 in Participants With Primary Cold Agglutinin Disease Who Have a Recent History of Blood Transfusion), Dr Alexander Röth and colleagues enrolled 24 adults with a confirmed diagnosis of CAD and a recent history of transfusion. Eligibility criteria included a baseline hemoglobin level of 10 g/dL or lower, a total bilirubin level above normal, and 1 or more blood transfusions in the prior 6 months. Patients received intravenous sutimlimab on days 0 and 7, followed by biweekly infusions.

The mean age of the patients was 71.3 years, and 62.5% were female. The mean baseline hemoglobin level was 8.6 g/dL (range, 4.9-11.1 g/dL). The median number of transfusions in the 6 months before enrollment was 2, and 62.5% of the patients had failed to respond to prior therapies.

The hemoglobin levels increased rapidly after the first infusion of sutimlimab, with a mean increase of 1.2 g/dL at the end of week 1 and of 2.3 g/dL at the end of week 3. The estimated mean hemoglobin level rose by 2.6 g/dL during assessment (an average of weeks 23, 25, and 26), and 13 of 24 patients (54.2%) had a response to treatment, defined as an increase in the hemoglobin level of at least 2 g/dL or a hemoglobin level of at least 12 g/dL.

The mean total bilirubin level, a marker of hemolysis, dropped markedly within hours of infusion and normalized by week 3. Patient quality of life as measured on the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) scale showed significant improvement, increasing from a mean of 32 points to a mean of 43 points out of 52.

Although 22 of the 24 patients experienced 1 or more treatment-emergent adverse events (AEs), no serious

treatment-emergent AEs were related to sutimlimab.

In the second study, by Dr Catherine Broome and colleagues, 7 adults with chronic, severe ITP and an inadequate response to 2 or more prior therapies were enrolled in an open-label, phase 1 trial of sutimlimab. Participants, who were not allowed to be on any other treatment for ITP, received sutimlimab on days 0 and 7, then biweekly for up to 21 weeks (part A). This was followed by a scheduled washout to evaluate relapse and response to re-treatment in a re-treatment/continuation arm (part B) that lasted for an additional year. The mean age of the patients was 44.9 years, and 85.7% were female.

Just 24 hours after the first dose of sutimlimab, the mean platelet count increased from $27.9 \times 10^9/L$ to $81.3 \times 10^9/L$. By day 7, the mean platelet count was $206.3 \times 10^9/L$. The mean platelet count remained higher than $50 \times 10^9/L$ throughout part A. By day 14, 57% of patients had responded to treatment, defined as a platelet count higher than $50 \times 10^9/L$.

Four patients completed a washout period at the end of part A and were re-treated in part B. Sutimlimab washout resulted in a recurrence of thrombocytopenia in all of these patients, but re-treatment was effective at increasing the platelet count from an average of $16.0 \times 10^9/L$ to higher than $100 \times 10^9/L$.

Regarding safety, 6 patients experienced a total of 30 treatment-emergent AEs, but no patients discontinued part A owing to an AE. Two patients experienced a total of 3 serious treatment-emergent AEs, of which 1 (migraine) was considered possibly to have been related to sutimlimab.

Broome CM, Roeth A, Kuter DJ, et al. Inhibition of the classical pathway of complement with sutimlimab in chronic immune thrombocytopenic purpura patients without adequate response to two or more prior therapies [ASH abstract 898]. *Blood*. 2019;134(2)(suppl).

Röth A, Barcellini W, D'Sa S, et al. Inhibition of complement C1s with sutimlimab in patient with cold agglutinin disease (CAD): results from the phase 3 Cardinal study [ASH abstract LBA-2]. *Blood*. 2019;134(2)(suppl).

Commentary: Sutimlimab is a first-in-class humanized monoclonal anti-C1s antibody that is a selective inhibitor of C1s, preventing the formation of the C1 complex and therefore inhibiting classical pathway activation.

The first study, by Röth and colleagues, was a pivotal trial of sutimlimab in CAD, a rare autoimmune hemolytic disease in which symptoms are triggered by classical complement pathway activation. In this study, the patients who received sutimlimab had markedly improved hemoglobin levels, required fewer blood transfusions, and felt significantly less fatigued. These results support the potential use of this novel complement-targeted therapy for CAD.

In the second study, researchers looked at the use of sutimlimab in patients with refractory ITP. Despite the recent additions of the oral thrombopoietin receptor agonist avatrombopag (Doptolet, Dova) and the oral SYK inhibitor fostamatinib (Tavalisse, Rigel) into the therapeutic armamentarium for the treatment of chronic ITP, successful and sustained resolution remains elusive for more than 20% of patients. This trial provides the first clinical evidence that the classical complement pathway plays a critical role in the pathophysiology of chronic ITP and may be yet another promising target for its treatment, confirming the heterogeneity of this disease. In the future, individualized therapy for ITP, based on the mechanism of autoimmune platelet destruction, may become routine.

Crizanlizumab Safe for Use in Sickle Cell Disease

Crizanlizumab (Adakveo, Novartis) is well tolerated and has a favorable safety profile in patients with sickle cell disease (SCD) who have a history of vaso-occlusive crises (VOCs), according to a pooled analysis.

For this study, Dr Julie Kanter and colleagues pooled data from two phase 2 studies of crizanlizumab in SCD: SUSTAIN (Study to Assess Safety and Impact of SelG1 With or Without Hydroxyurea Therapy in Sickle Cell Disease Patients With Pain Crises), which served as the basis for the approval of crizanlizumab, and SOLACE-Adults (Pharmacokinetics and Pharmacodynamics Study of SEG101 in Sickle Cell Disease Patients With Vaso-Occlusive Crisis), which is ongoing. All patients received 2 doses of crizanlizumab at 5 mg/kg two weeks apart, followed by the recommended dose of 5.0 mg/kg monthly.

Of the 111 patients included in the analysis, 94 experienced at least 1 AE (although only 36 were considered treatment-related), with the most common being headache (19.8%), nausea (16.2%) and back pain (15.3%). Most AEs were mild or moderate and resolved spontaneously, although 26 patients (23.4%) had a grade 3 or higher AE and 1 patient (0.9%) had a grade 4 AE (a neoplasm). Only 6 patients (5.4%) experienced a serious AE with a suspected relationship to crizanlizumab (5.4%), of which only 3 were grade 3 or higher. Twenty-eight patients (25.2%) discontinued treatment prematurely

(the majority, 23 patients, as part of the SUSTAIN trial). Two on-treatment deaths occurred in SUSTAIN, but neither was considered related to crizanlizumab.

Infections developed in 51 patients (45.9%), the most common being upper respiratory tract infection and urinary tract infection; the data suggested no increased risk for or severity of infection with crizanlizumab. Although 2 patients (1.8%) experienced infusion-related reactions, the events were not serious and did not lead to discontinuation. Bleeding events were rare and nonserious.

Kanter J, Liles DK, Smith-Whitley K, et al. Crizanlizumab 5.0 mg/kg exhibits a favorable safety profile in patients with sickle cell disease: pooled data from two phase II studies [ASH abstract 991]. *Blood*. 2019;134(2)(suppl).

Commentary: Crizanlizumab received US Food and Drug Administration (FDA) approval in November 2019 to reduce the frequency of VOCs in patients 16 years of age or older with SCD (all genotypes). The drug is a monoclonal antibody that targets P-selectin glycoprotein, which is expressed on activated endothelial cells and platelets. Binding P-selectin blocks interactions among endothelial cells, platelets, red blood cells, and leukocytes and thus mitigates vascular obstruction and vascular ischemia.

The FDA approval was based on results from the randomized SUSTAIN trial, which was published by Ataga and colleagues (*N Engl J Med*. 2017;376[5]:429-439). In this trial, 198 patients with SCD and a history of VOCs were randomly assigned to receive either placebo or crizanlizumab at a dose of 2.5 or 5.0 mg/kg. The higher dose was associated with a mean of 1.63 crises per year, whereas the placebo group had a mean of 2.98 crises per year (45.3% reduction; $P=.01$). Crizanlizumab also delayed the time to first VOC after the start of treatment from 1.4 months to 4.1 months. These benefits were even greater in a post hoc analysis of per-protocol vs intention-to-treat populations and were achieved with minimal toxicity.

The study of Kanter and colleagues extends the experience with crizanlizumab to include 111 patients receiving the medication for a mean of 46 weeks. The focus of these authors was on safety, and their analysis indicated that the risk for infections, bleeding events, or AEs was not increased with crizanlizumab exposure. Interestingly, an anti-drug antibody developed in only 1 subject and was transient. Thus, long-term crizanlizumab appears to be safe and well tolerated. Data are not yet available to determine whether the long-term use of crizanlizumab can preserve end-organ function, whether higher doses of crizanlizumab would improve clinical results, whether concurrent hydroxyurea therapy would be synergistic, or whether adherence would become a problem with the prolonged crizanlizumab regimen. We also lack significant real-world experience with crizanlizumab.

Asymptomatic Proximal Deep Vein Thrombosis Predicts Mortality

The mortality rate of acutely ill patients is significantly higher if ultrasound reveals the presence of asymptomatic proximal deep vein thrombosis (ASxDVT), according to a new analysis.

For the analysis, Dr Gary Raskob and colleagues analyzed data from 7036 patients in the MAGELLAN study (Venous Thromboembolic Event Prophylaxis in Medically Ill Patients), a randomized clinical trial that evaluated rivaroxaban (Xarelto, Janssen) vs enoxaparin for the prevention of venous thromboembolism (VTE) in acutely ill medical patients. Routine compression ultrasonography was performed at day 10 and at day 35.

After 90 days, an analysis revealed that patients with ASxDVT and those with symptomatic VTE (SxVTE) were significantly more likely to die of any cause than were those without VTE (all-cause mortality rates of 11.4% and 29.2% vs 4.8%, respectively).

Raskob GE, Spyropoulos AC, Cohen AT, et al. Increased risk of death in acutely ill medical patients with asymptomatic proximal deep vein thrombosis or symptomatic venous thromboembolism: insights from the Magellan study [ASH abstract 163]. *Blood*. 2019;134(2)(suppl).

Commentary: In the past, the detection of ASxDVT by duplex Doppler ultrasound has been used as an efficacy endpoint in thromboprophylaxis studies. The PREVENT study (Prevention of Recurrent Venous Thromboembolism), published by Vaitkus and colleagues in *Thrombosis and Haemostasis* in 2005, analyzed 90-day mortality rates in 1738 acutely medically ill patients who were randomly assigned to dalteparin (Fragmin, Pfizer) vs placebo for thromboprophylaxis for 30 days and subsequently underwent compression ultrasound of the proximal and distal leg veins after 21 days. The researchers found that the mortality rate was significantly higher in the patients with ASxDVT than in those with no DVT (13.75% vs 1.92%).

The results from Raskob and colleagues underscore the importance of implementing VTE prophylaxis in acutely medically ill patients. The results also validate the use of ASxDVT as an endpoint in thromboprophylaxis clinical trials.

Apixaban Benefits Patients With Cancer and VTE

Apixaban (Eliquis, Bristol-Myers Squibb) reduces major bleeding, other clinically relevant bleeding, and recurrent VTE compared with low-molecular-weight heparin (LMWH) in patients with cancer who have experienced VTE, according to a new study. Apixaban also reduces the risk for recurrent VTE compared with warfarin in these patients.

For the study, Dr Alexander Cohen and colleagues examined data from 4 US commercial insurance claims databases. They identified more than 14,000 patients with VTE and active cancer who began taking apixaban (n=3393), LMWH (n=6108), or warfarin (n=4585) within 30 days after the first VTE event.

After follow-up lasting up to 6 months, the researchers concluded that patients with VTE and active cancer who initiated apixaban had a significantly lower risk for major bleeding, other clinically relevant bleeding, and recurrent VTE compared with those taking LMWH; they also had a lower risk for recurrent VTE compared with those taking warfarin.

Cohen AT, Keshishian A, Lee T, et al. Safety and effectiveness of apixaban, LMWH, and warfarin among venous thromboembolism patients with active cancer: a retrospective analysis using four US claims databases [ASH abstract 326]. *Blood*. 2019;134(2)(suppl).

Commentary: Recent sets of clinical guidelines from professional societies and consensus groups have continued to recommend the use of LMWH in lieu of warfarin or direct oral anticoagulants (DOACs) to prevent recurrent VTE in patients with cancer. These strategies have been based on a limited number of robust, well-conducted, prospective randomized clinical trials, which have had restrictive eligibility requirements for participation and consequently may have introduced selection bias. Many trials are in progress; however, the well-designed Hokusai VTE Cancer Trial (*N Engl J Med*. 2018;378[7]:615-624) revealed fewer VTE recurrences with edoxaban (Savaysa, Daiichi Sankyo) vs LMWH (hazard ratio, 0.71) but an increase in bleeding complications (hazard ratio, 1.77). A similar trend was noted in the SELECT-D trial with rivaroxaban (*J Clin Oncol*. 2018;36[2]:2017-2023). In addition, the smaller ADAM-VTE study with apixaban, which was presented by Dr Robert McBane at the 2018 ASH annual meeting (abstract 421), revealed equivalent efficacy and bleeding risk compared with LMWH.

Cohen and colleagues provide real-world experience with apixaban vs LMWH or warfarin for secondary thromboprophylaxis in patients with active cancer who are at high or very high VTE risk. Because physician choice determined the treatment modality, some degree of selection bias was likely. In any case, their findings should provide physicians with perspective and confidence that DOACs can be used safely and effectively in patients with active cancer while we await the conclusions from large, ongoing randomized controlled trials.

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