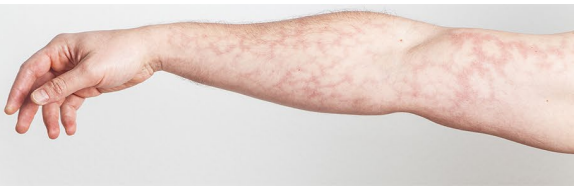
PROMOTING RECOGNITION, DIAGNOSIS AND TREATMENT OF COLD AGGLUTININ DISEASE



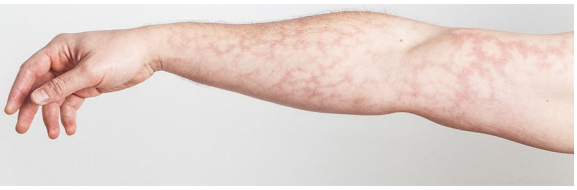
CLINICAL INSIGHTS

Patients with the rare hematologic disorder, cold agglutinin disease (CAD), can present acutely in the emergency department or with more chronic symptoms to primary care physicians or other specialists who are challenged to recognize the presentation of this condition.

Until the approval of sutimlimab-jome in February 2022, there were no approved treatments available; many times, patients were are not offered any therapeutic intervention until their anemia became quite severe. Sutimlimab-jome is indicated to decrease the need for red blood cell transfusion due to hemolysis in adults with CAD.

Because of the high mortality rate among those suffering from CAD, it is important to be aware of the diagnostic criteria, as well as the current and novel treatment options with the goal of increasing hemoglobin levels, avoiding the need for transfusions, and improving circulatory symptoms.

- Multiple studies have shown that patients with CAD have an increased risk of developing both venous and arterial thromboembolic events—62% higher than a matched cohort,[1]as well as resulting in reduced quality of life based on the need for transfusions, doctors' visits, fatigue, shortness of breath, and modifying daily activities. In addition, further studies have shown patients who are diagnosed with CAD vs a non-CAD matched population, have a higher mortality rate.[2,3]
- We know infections can increase complement activity in patients with CAD. These patients need to be on early and adequate antibiotic therapy. Viral infections need to be taken seriously because they can trigger hemolytic crises.
- It is critical to recognize signs and symptoms and accurately diagnose patients with CAD so appropriate management may be offered. Diagnostic markers for CAD include reduced hemoglobin levels, an increased reticulocyte count, an elevated lactate dehydrogenase, an elevated bilirubin, and a reduced haptoglobin.
- The diagnostic criteria in CAD include chronic hemolysis, a polyspecific direct antiglobulin test (DAT) positive, a monospecific DAT, which is positive for C3, and a cold agglutinin titer greater than or equal to 64. A bone marrow evaluation is also advised to look for a monoclonal population of lymphocytes.
- Treatment goals include improving anemia and increasing hemoglobin levels.
- Transfusions should be avoided for a variety of reasons, including iron overload and potential alloimmunization.
- It is important to improve circulatory symptoms that can be caused by cold temperatures. Therapeutic management in autoimmune hemolytic anemias relates specifically to antibody type. Treatment needs to be appropriate for IgM-mediated autoimmune hemolytic anemia.
- First-line treatment strategies include the use of rituximab monotherapy in patients who have multiple comorbidities or who are particularly frail. The response rate is only about 50%, with almost exclusively partial responses, and the median duration of response is only about 12 months.[4,5]
- Second-line therapies include combined rituximab with bendamustine for relatively fit patients who can withstand the potential side effects of neutropenia.[6]
- Combination therapies did increase the response rate over monotherapy, although more than 25% of patients are still not responding, and some patients continue to hemolyze.
- Other second-line treatment strategies include fludarabine and rituximab, again for fit patients. Response rate was about 76%, and there were some sustained remissions, but with adverse events, including



prolonged cytopenias.[5,7] Common and more serious adverse events in the combination therapeutic interventions, include neutropenia.

- Sutimlimab-jome is a C1s inhibitor, and the focus of two phase 3 trials. The **CARDINAL** trial was an open-label, single-group trial in patients with CAD and a recent history of transfusion (within 6 months of enrollment), while the **CADENZA** trial was a randomized, placebo-controlled trial in patients with CAD but without a recent transfusion.[8,9] Results of the CARDINAL trial showed that sutimlimab-jome halted hemolysis, increased hemoglobin, decreased the need for a transfusion, reduced bilirubin, and reduced fatigue.[8] Results of the CADENZA trial showed that sutimlimab-jome significantly increased hemoglobin, reduced bilirubin, and reduced fatigue.[9] Adverse events judged to be related to sutimlimab-jome were generally mild to moderate.
- Steroids should not be used to treatment patients with CAD, as they are ineffective in CAD.
- The **CADENCE registry** is a global registry to provide perspective and longitudinal data on patients with CAD. The registry will help with the understanding of demographics, clinical presentation and characteristics, comorbidities and disease burdens, patterns, and use of CAD treatments, long-term clinical outcomes, health-related quality of life, and different geographic locations. The registry is available at https://coldagglutininnews.com/2021/01/07/cadence-registry.

It is important to order all the necessary diagnostic tests to assess whether anemia is related to hemolysis. The recent approval of sutimlimab-jome ushers in a new era in the treatment of patients with CAD and should address key unmet needs with other therapies. Other medications are in clinical development.