Clinical Management of Cold Agglutinin Disease: Current Approaches and Novel Therapeutic Options
Instructions

This information is provided as an educational resource for healthcare providers. It is not intended to be a substitute for review of the underlying reference materials and scientific literature. Healthcare providers should make all treatment decisions based on their medical judgement and the clinical profile of the individual patient. The following document cannot be copied, modified, used or distributed without the express written consent of Bioverativ.
Cold Agglutinin Disease Is Classified as Primary or Secondary

- **Primary chronic cold agglutinin disease**
  - Arises spontaneously
  - Clonal B-cell disorder
  - There are currently no approved therapies specifically for those with cold agglutinin disease

- **Secondary cold agglutinin syndrome**
  - Associated with malignancy or acute infection
  - Less common than primary cold agglutinin disease
  - Treatment of the underlying disorder may be required

Primary Cold Agglutinin Disease Is a Serious Chronic Illness Associated With Significant Disease Burden

- Symptoms include anemia, fatigue, weakness, weight loss, dyspnea, hemoglobinuria, acrocyanosis, and Raynaud’s phenomenon, which significantly impacts quality of life\(^1\)

- Disease burden is high and includes risks associated with chronic transfusions (eg, iron overload) and thromboembolic events secondary to hemolysis\(^2\)–\(^5\)

Despite Multiple Lines of Therapies, Unmet Needs Still Exist in Addressing All Aspects of Cold Agglutinin Disease

- **86%** of patients had ≥2 lines of therapy
- **72%** of patients had at least 1 severe anemia event within first year of follow-up
- **7** severe anemia events per patient year
- **65%** of patients had at least 1 transfusion
- Mean of **11** transfusions per patient year
- Mean of **3.5** therapies per patient
- **67%** of patients had a severe anemia event within 6 months of their initial therapy

Although Patients Receive Treatment, Anemia Is Persistent

The Pathogenesis of Primary Cold Agglutinin Disease Has Therapeutic Implications

- Cold agglutinins are autoantibodies that bind RBCs at cold temperatures\(^1\)
- The antibody–antigen complex at the surface of RBCs activates the classical complement pathway, leading to hemolysis (extravascular hemolysis being the primary driver)\(^1\)
- Patients present with anemia and fatigue, among other serious symptoms\(^2\)

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**BCL2**, B-cell lymphoma 2; **BCR**, B-cell receptor; **C**, complement; **IgM**, immunoglobulin M; **RBC**, red blood cell.

Considerations for Treatment of Primary Cold Agglutinin Disease

- No consensus on treatment algorithm

- Therapy is often directed at the degree of anemia\(^1,2\)

- Other areas of unmet need that may require treatment considerations:
  - Hemolysis
  - Chronic fatigue
  - Thromboembolism risk

- Some patients have acute presentation and require rapid treatment
  - Unmet need for effective treatment with fast onset of action

Nonpharmacologic Measures of Treatment Have Limitations

- Avoiding the cold is only a temporary measure, with no trials establishing efficacy\(^1,2\)
- RBC transfusions treat anemia,\(^1\) but are associated with complications such as hemochromatosis and poor quality of life
  - Between 40% and 100% of patients require transfusion\(^3\)
- Plasmapheresis may be used in acute hemolytic crises but provides only temporary remission\(^2,3\)

Current Pharmacologic Approaches: Corticosteroids and Rituximab

- **Corticosteroids**
  - Suppresses the aberrant expression of antibodies (eg, IgM)\(^1\)
  - Mostly ineffective, with response rates as low as 14%\(^2\)
  - Need for high doses prohibits use over the long term and is no longer recommended\(^1,3\)

- **Rituximab**
  - Targets CD20-positive B cells
  - May be used as monotherapy or in combination with other therapies, such as fludarabine or bendamustine\(^4–6\)

IgM, immunoglobulin M.

Anti-CD20 Therapy in Patients With Cold Agglutinin Disease

- Complete response ranges from 3% to 40% with rituximab monotherapy or combination, and duration of treatment effect may be limited
- Response rates can increase in those who receive combination therapy; however, there is an associated increase in the rate of adverse events, including severe neutropenia and secondary infections
- Deaths have been reported in combination trials

### Additional Pharmacologic Therapies in Cold Agglutinin Disease

<table>
<thead>
<tr>
<th>Class</th>
<th>Findings</th>
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<tbody>
<tr>
<td><strong>Immunosuppressants</strong></td>
<td></td>
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<tr>
<td>Chlorambucil</td>
<td>Some improvement in hemoglobin and normalizing of serum IgM; considered to impart little benefit(^1,2)</td>
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<tr>
<td>Cyclophosphamide</td>
<td>Little benefit(^1)</td>
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<tr>
<td>Cladribine</td>
<td>Little to no benefit; only up to 13% of patients respond to cladribine(^1,3,4)</td>
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<tr>
<td><strong>Immunotherapy</strong></td>
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<tr>
<td>Intravenous Immunoglobulins</td>
<td>Limited efficacy in AIHA; no established benefit in cold agglutinin disease(^5)</td>
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<td><strong>Tyrosine Kinase inhibitor</strong></td>
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<tr>
<td>Ibrutinib</td>
<td>Efficacy in B-cell malignancies, including Waldenström macroglobulinemia(^6)</td>
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| Bortezomib          | • Case reports suggested improvement in hemoglobin levels, markers of hemolysis, and results in independence from transfusion\cite{1-3}  
  • Phase 2 study showed a 31.6% overall response rate in patients with refractory cold agglutinin disease (N = 21)\cite{4} |
| **Biologic**        |                                                                                                                                                                                                 |
| Eculizumab          | • Case reports suggested eculizumab can reduce hemolysis, reverse transfusion dependence, and improve fatigue/quality of life\cite{5-7}  
  • Phase 2 study showed improvement in hemolysis and transfusion requirement but no significant increase in Hemoglobin (median increase 0.9 g/dL)\cite{8} |

Stanford Longitudinal Study (n=29): Key Findings

- **72%** of patients had at least one severe anemia event within first year of follow-up
  - 7 severe anemia events per patient year

- **65%** of patients had at least one transfusion
  - Mean of **11** transfusions per patient year

- Mean of **3.5** therapies per patient
  - **67%** of patients had a severe anemia event within 6 months of their initial therapy

- **17%** of patients had a thrombotic event

- **93%** of patients used outpatient healthcare services within first year of disease onset
  - Median of **26** outpatient visits per patient
Stanford Study Cohort: Example Patient Journeys

Patient 54, A 48-month CAD Journey

- IVIG
- Prednisone
- Cyclophosphamide

Patient 111, A 19-Month CAD Journey

- Dexamethasone
- Rituximab
- Mycophenolate mofetil
- Cyclosporine