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2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

# Sutimlimab vs B-Cell–Targeted Therapy in Cold Agglutinin Disease: Which Is the Optimal Approach?

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Bruno Fattizzo (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Italy) Yoshitaka Miyakawa (Saitama Medical University, Japan) Catherine Broome (Division of Hematology, MedStar Georgetown University Hospital, United States)

**Abstract:**
Cold agglutinin disease (CAD) is a rare autoimmune hemolytic anemia caused by monoclonal IgM autoantibodies that bind to red blood cells and trigger hemolysis through activation of the classical complement pathway. Cold agglutinins are produced by a clonal population of lymphocytes recognized by the WHO as a low grade lymphoproliferative disorder. Traditional therapy relied on B-cell–targeted immunosuppression with rituximab which mainly yielded partial responses in about half of the patients. The combination of rituximab with fludarabine or bendamustine significantly increased and prolonged response rates, though with a substantial infectious risk. Sutimlimab, the first C1s complement inhibitor, has shown efficacy in rapidly and sustainably increasing hemoglobin levels, reducing hemolysis, and significantly improving quality of life. However, the drug does not act on the B-cell clone and does not decrease the cold agglutinins. Therefore, several unmet needs remain, including identifying patients who can discontinue sutimlimab while maintaining remission, developing combination strategies effective against cold-induced symptoms, and improving infection prevention and control of hemolytic flares. This perspective article briefly recapitulates the pathophysiology of CAD, outlines the evolution of its treatment landscape, and focuses on the role of sutimlimab—its clinical positioning, therapeutic benefits, and management considerations—offering insights into optimizing care for patients with this challenging condition.

**Conflict of interest:** COI declared - see note

**COI notes:** BF was involved as SI in the clinical trial CARDINAL and CADENZA. He received consultancy and speaker's bureau from Alexion, Janssen, Sanofi, Sobi, Roche, Novartis and Recordati; received research funding from Agios and Zenas Biopharma. YM was involved as PI in the clinical trial CARDINAL and received research grants from Argenx, Kissei, Chugai, Novartis, Sanofi, Takeda, and UCB, consulting fees from Argenx, Zenyaku Kogyo, Kyowa Kirin, Novartis, lecture fees from Kissei, Sanofi, Takeda, and participate in advisory board by Argenx, Sanofi, Takeda, Novartis and UCB. CMB was involved as PI in the clinical trial CARDINAL and CADENZA, has received research support from Alexion, Argenx, Electra, Novartis, and Sanofi; honoraria from Alexion, Argenx, and Sanofi; and advisory board fees from Argenx, Novartis, and Sanofi.

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Bruno Fattizzo[1,2], Yoshitaka Miyakawa[3], Catherine Broome[4]

1. Dipartimento di Oncologia ed Emato-Oncologia, Università degli Studi di Milano
2. Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy
3. Department of Hematology, Saitama Medical University, Saitama, Japan
4. Division of hematology/Oncology, MedStar Georgetown University Washington DC, USA

**Corresponding author**: Bruno Fattizzo, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, via Francesco Sforza 35, 20122, Milan, Italy; bruno.fattizzo@unimi.it; +390255033256

**Running head**: Modern treatment of cold agglutinin disease

**Keywords**: autoimmune hemolytic anemia; cold agglutinin disease; rituximab; sutimlimab; bendamustine; flludarabine.

**Summary**

Cold agglutinin disease (CAD) is a rare autoimmune hemolytic anemia caused by monoclonal IgM autoantibodies that bind to red blood cells and trigger hemolysis through activation of the classical complement pathway. Cold agglutinins are produced by a clonal population of lymphocytes recognized by the WHO as a low-grade lymphoproliferative disorder. Traditional therapy relied on B-cell–targeted immunosuppression with rituximab which mainly yielded partial responses in about half of the patients. The combination of rituximab with fludarabine or bendamustine significantly increased and prolonged response rates, though with a substantial infectious risk. Sutimlimab, the first C1s complement inhibitor, has shown efficacy in rapidly and sustainably increasing hemoglobin levels, reducing hemolysis, and significantly improving quality of life. However, the drug does not act on the B-cell clone and does not decrease the cold agglutinins. Therefore, several unmet needs remain, including identifying patients who can discontinue sutimlimab while maintaining remission, developing combination strategies effective against cold-induced symptoms, and improving infection prevention and control of hemolytic flares. This perspective article briefly recapitulates the pathophysiology of CAD, outlines the evolution of its treatment landscape, and focuses on the role of sutimlimab—its clinical positioning, therapeutic benefits, and management considerations—offering insights into optimizing care for patients with this challenging condition.

## 1. Introduction

Cold Agglutinin Disease (CAD) is a rare form of autoimmune hemolytic anemia (AIHA), characterized by the presence of IgM autoantibodies (cold agglutinins, CAs) reacting with red blood cells (RBCs) at temperatures below the body temperature of 37°C. CAs are generally monoclonal, produced by a monoclonal CD20+ B-cell lymphoid infiltrate in the bone marrow. Once bound to the I antigen on the surface of red blood cells the CA-antigen complex triggers the activation of the classical complement pathway via C1s, leading to the fixation of complement C3b on the RBC resulting in extravascular hemolysis primarily in the liver, where C3 receptors are present on the macrophages (Kupffer cells) [1,2]. In situations where complement amplifying conditions are present (infections, trauma, surgery, etc.) terminal complement cascade activation may occur leading to intravascular hemolysis in addition to the baseline extravascular hemolysis [1,2]. Clinical features of CAD include anemia of various degrees of severity, asthenia, exertional dyspnea, dark urine, and rarely biliary lithiasis. Notably, CAs also cause agglutination of red blood cells leading to cold-induced peripheral symptoms like acrocyanosis, sometimes confused with “Raynaud phenomenon”, mottling of the face and décolleté, observed in approximately one-third of patients, and, rarely, acral necrosis. Agglutination of the RBCs is independent of complement activation [3].

The key diagnostic test in CAD is the direct antiglobulin test (DAT) otherwise known as the direct Coombs test), which is negative or weakly positive for IgG and strongly positive for the complement fraction C3d. Subsequently, the titer of the CA should be determined on warm serum. A diagnosis of CAD is generally considered when the CA titer >1:64, although lower titers may be observed following immunosuppression or in cases of high autoantibody avidity. Once the diagnosis is confirmed, additional evaluation should include, serum protein electrophoresis, serologies for hepatotropic and herpes viruses, HIV, and QuantiFERON-TB Glod plus testing, as well as bone marrow assessment and contrast-enhanced CT scan. This evaluation is critical to distinguish CAD from cold agglutinin “syndrome” (CAS), where CAs are detected in patients with established lymphoproliferative neoplasms or acute infections (e.g., Mycoplasma pneumonia or EBV), but also to detect conditions that may require active prophylaxis during immunosuppressive therapy (e.g., HBV or Tubercolosis) [1-3].

In addition to hemolysis and circulatory symptoms CAD may be complicated by thromboses (15-20%) and infections (20-30%). The former maybe more commonly seen in association with overt intravascular hemolysis with the release of RBC microparticles and nitric oxide depletion but can occur at any time even in patients with mild compensated hemolysis. Primary VTE prophylaxis with low molecular weight heparin has been proposed for patients with LDH > 1.5 × ULN and associated risk factors (immobilization, infections, obesity, cardiovascular risk factors, etc.) [4,5]. Infections in CAD patients are often associated with immunosuppressive therapies, although the underlying lymphoproliferative disease and advanced age of CAD patients also represent risk cofactors. An awareness that Infections can also trigger complement activation, thereby exacerbating hemolysis as observed during the COVID-19 pandemic is essential for management of CAD patients [6].

Traditionally, the treatment of CAD has focused on immunosuppressive therapies such as rituximab with or without chemotherapy in an attempt to target the B lymphocyte clone responsible for the production of the autoantibodies. This strategy is characterized by a definite duration of treatment (i.e. one to a few months) with the possibility of obtaining long-term responses off-therapy and is potentially active on both hemolysis and CA induced circulatory symptoms. The efficacy of this approach is limited to a proportion of patients and the long-term immunosuppression with the relative increase in infection risks have prompted the development of targeted therapies. In this context, sutimlimab, a humanized monoclonal antibody that acts as a selective inhibitor of the complement protein C1s, represents a novel therapeutic frontier for patients with CAD. In this review, we will discuss the pros and cons of B-cell targeting agents and of

sutimlimab, as well as the remaining unmet clinical needs for CAD patients in an effort to define optimal treatment scenarios in this rare AIHA.

## 2. B-cell targeting agents

Indication for treatment in CAD is generally considered to be symptomatic hemolytic anemia or circulatory symptoms. This occurs in approximately 75% of patients [7], while the remainder are managed with monitoring, protection from cold and temperature fluctuations, and supplementation with folic acid and any other deficient nutrients. Corticosteroids may sometimes be active in CAD only when administered at very high doses and therefore can only be used during the initial weeks while diagnostic workup is being completed and should not be used to manage CAD long term. Notably, splenectomy is contraindicated in CAD since most of the hemolytic process occurs extravascularly in the liver. Finally, in patients with inadequate reticulocytosis (i.e. bone marrow responsiveness index <121) stimulation with recombinant erythropoietin is effective and reduces transfusion need [8,9].

### *Rituximab in Monotherapy and combinations*

Rituximab (intravenous, 375 mg/sm/week for 4 weeks), an anti-CD20 monoclonal antibody, has been widely used off label in the treatment of CAD. It targets CD20-positive B lymphocytes, endeavoring to reduce the production of pathogenic CAs (Figure 1). Observational studies have reported overall response rates (ORR) ranging from 45% to 54%, with a median time to response of 4-6 weeks and median duration of response of approximately 12 months. Complete responses are rare, and relapses are frequent, indicating partial efficacy of monotherapy [7,10].

The combination of rituximab with fludarabine, a purine analogue, has demonstrated improved efficacy, achieving an ORR of 76% with 21% of complete responses with median time to response of 4 months and a median duration of response of approximately 66 months. This regimen has been associated with significant hematologic toxicity, including grade 3–4 neutropenia in over 40% of patients and severe infections in nearly 60% [11]. Therefore, its use requires careful evaluation of the risk-benefit ratio, especially in elderly or immuno-compromised patients.

An alternative therapeutic option is the combination of rituximab with bendamustine, an alkylating agent with immunosuppressive activity, median time to response 1.5 to 2 months and an ORR of 71%, with a complete response rate of 40%. The safety profile appears more favorable when compared to the fludarabine regimen, with severe neutropenia occurring in 33% of patients and a relatively low incidence of severe infections (11%) [12].

Overall, these immunosuppressive regimens are of fixed-duration, with the potential to address both hemolysis and cold-induced circulatory symptoms. Given the relatively favorable risk/benefit ratio, rituximab monotherapy is generally considered the standard frontline immunosuppressive therapy choice for CAD. Rituximab-bendamustine is the second line choice or perhaps first line choice in younger patients with CAD without comorbidities. Due to its toxicity profile, rituximab-fludarabine is generally discouraged except in the young fit patient.

### *Novel B-cell targeting agents: Bruton's tyrosine kinase (BTK), phosphoinositide 3-kinase (PI3K), and B-cell activating factor (BAFF) Inhibitor, anti-plasma cell agents*

BTK inhibitors, such as ibrutinib, and PI3K inhibitors, used in lymphoproliferative disorders, are emerging as potential therapeutic options due to their role in inhibiting B-cell receptor signaling. Although clinical data specific to CAD remain limited, preliminary results suggest potential benefits in cases refractory to conventional treatments. In particular, oral Ibrutinib a BTK inhibitor at 420 mg daily demonstrated efficacy

in 13 out of 15 patients with CAD/CAS in a retrospective analysis , with a median hemoglobin increase of 5.6 g/dL from baseline, transfusion independence, and improvement of peripheral symptoms in 9 out of 9 patients, with complete resolution in 6 [13] the caveat in this report is that all patients had an underlying lymphoproliferative disorder such as CLL or Waldenström. A clinical trial with Zanubrutinib, another BTK inhibitor, is currently enrolling [NCT06067048]. Parsaclisib a PI3K inhibitor administered orally at a dose of 1–2.5 mg daily in a phase II study has demonstrated a response rate of approximately 40% in patients with CAD [14]. Finally, a phase 1 study is ongoing investigating povetacicept, a (BAFF) inhibitor, administered subcutaneously once every 4 weeks for 6 doses in patients with CAD, warm antibody autoimmune hemolytic anemia, and immune thrombocytopenia (ITP) [NCT05757570].

Bortezomib, a proteasome inhibitor that's mechanism of action includes suppression of protein synthesis in B lymphocytes and plasma cells, thereby reducing the production of pathogenic IgM has also been evaluated in patients with rituximab-refractory CAD. In a clinical study involving 19 patients, monotherapy with a single cycle of bortezomib at 1.3 mg/m² administered twice weekly for a total of 4 doses induced a response in approximately 32% of cases, with some durable responses observed. [15]. Several case reports and case series have been published on the use of the anti-CD38 monoclonal antibody daratumumab, administered intravenously at a dose of 16 mg/kg weekly followed by a spaced maintenance regimen, in patients with various forms of autoimmune hemolytic anemia, including CAD, with benefit observed in approximately half of treated patients. In particular, among 7 CAD patients from a retrospective series, overall Hb response was 57%, and 4 out of 6 patients with acrocyanosis had improved symptoms [16].

Novel B-cell targeting therapies, and anti-plasma-cell agents may have a role in CAD patients who cannot tolerate other therapy or who have relapsed after other therapy. The efficacy of these therapies in reducing the CA and therefore treating peripheral cold-induced circulatory symptoms may indicate use in patient whose main symptoms are IgM mediated.

## 3. Therapy with Complement inhibitors: Efficacy, Quality of Life, and Adverse Effects

### *Complement inhibitors other than sutimlimab*

Using the knowledge gained from the treatment of paroxysmal nocturnal hemoglobinuria (PNH), another complement mediated hemolytic anemia, complement inhibitors developed for PNH were investigated in CAD. The anti-C5 inhibitor eculizumab, targeting the terminal complement cascade, was evaluated in a small open-label phase 2 trial involving 12 CAD and 1 CAS patients. Results demonstrated decreased LDH and transfusion requirements though only a modest increase in Hb. Safety profile was favorable, although cold-induced circulatory symptoms were not improved. The lack of efficacy on Hb was generally explained by the absence of an effect on the proximal portion of the classical complement pathway and continued generation of C3b with ongoing extravascular hemolysis [17]. Pegcetacoplan, a proximal C3 inhibitor, has been evaluated in an open-label phase 2 study enrolling 13 CAD patients (plus 11 wAIHA patients); median hemoglobin increased by ~2.4 g/dL, hemolysis markers were decreased, and improved fatigue scores over up to 48 weeks were noted, with most patients experiencing treatment-emergent adverse events (e.g., injection site reactions, infections) but no serious adverse events attributed to the drug, suggesting a favorable safety/tolerability profile [18]. More recently, in a multicenter phase 2 basket study of the oral factor B inhibitor iptacopan, 10 CAD patients received treatment and 50 % met the primary hemoglobin response criterion (≥1.5 g/dL increase) at 12 weeks, with improvements in hemolytic markers and predominantly mild adverse events reported [19]. Neither of these complement inhibitors have been further developed into a phase 3 trial in CAD.

### *Sutimlimab*

Sutimlimab (formerly known as BIVV009 or TNT009) is a humanized IgG4 monoclonal antibody that selectively inhibits the C1s subunit of the complement C1 complex. This prevents activation of the classical complement pathway, drastically reducing C3 activation and subsequent C3b deposition on the erythrocyte surface, thereby preventing complement mediated extravascular hemolysis. It is important to note that the mechanism of action of sutimlimab does not interfere with activation of the alternative or lectin pathways of complement, thus partially preserving innate immune function.

**a. Clinical efficacy**

The first-in-human phase 1b study evaluated 10 CAD participants with a median disease duration of 5 years (range 1–20 years). Notably, 6 of these participants had a diagnosis of lymphoplasmacytic lymphoma with MYD88 mutation or indolent lymphoma (i.e. CAS). Seven out of ten patients responded and became transfusion independent, with median hemoglobin increase of 1.6 g/dL in one week and of 3.9 g/dL within six weeks, along with normalization of bilirubin levels within 24 hours in most patients. Hemolysis recurred 3–4 weeks after the last dose of sutimlimab, coinciding with declining drug plasma levels. Re-exposure to sutimlimab under a compassionate use program restored hemolysis control. One patient with 60% MYD88+ lymphoid infiltration had an optimal response. All infusions were well tolerated without the need for premedication. No serious drug-related adverse events were observed [20]. In the compassionate use program, co-administration of erythropoietin, rituximab, or ibrutinib in individual patients was safe, with no adverse interactions [21]. In the 3-year follow-up, sutimlimab's continued efficacy was confirmed in 4 patients, with a single episode of breakthrough hemolysis occurring in a patient with recurrent urinary tract infections, and no thrombotic events reported [22].

In the phase 3 CARDINAL trial, patients with CAD who had required transfusions within the prior 6 months received intravenous sutimlimab (6.5 or 7.5 g based on body weight) on days 1 and 7, then every 14 days. Vaccination against Neisseria meningitidis (ACYW135, B), Streptococcus pneumoniae, and Haemophilus influenzae B was required. Among 24 treated patients, 54% achieved the composite primary endpoint (hemoglobin >12 g/dL, ≥2 g/dL increase from baseline, and transfusion independence weeks 5–26). Mean Hb increased by 2.6 g/dL by week 26, and bilirubin normalized by week 3. Time to response is rapid with Hb increase notes as soon as week 3 and improvement in hemolysis markers noted by week 1. Seventeen patients (71%) remained transfusion-independent, and rapid inhibition of classical complement pathway activity was observed by dedicated assays. Adverse events occurred in 92%, with 29% serious but none treatment-related; no meningococcal infections were reported [23]. One- and two-year follow-up confirmed sustained efficacy and safety [24,25].

In the phase 3 randomized, placebo-controlled CADENZA trial, sutimlimab significantly increased Hb, with a mean rise of 2.66 (standard error 0.3) g/dL at 26 weeks, achieving ≥11 g/dL in 73.7% of patients, with normal bilirubin and near-complete complement inhibition [26]. Benefit was observed within the first week and replicated after crossover in the placebo-arm. Notably, sutimlimab did not demonstrate a significant improvement in cold induced symptoms such as acrocyanosis. Some patients in the trial did report a worsening of cold induced circulatory symptoms in spite of Hb and QoL improvements. Following 9-week washout, complement inhibition reversed with recurrence of anemia. Treatment-emergent adverse events were common but mostly mild; no systemic lupus or meningococcal infections occurred [27].

In 2022, the Austrian group reported 2 of 3 CAD patients from the named patient program who maintained sustained responses after 3 years of sutimlimab, following discontinuation. One patient preserved normal Hb and bilirubin for 12 months, with stable LDH and C4 but decreasing haptoglobin suggesting mild compensated hemolysis. The second showed slight bilirubin and LDH increases 6 months post-discontinuation, while Hb remained normal. These findings provide the first clinical evidence of sustained hematologic remission after prolonged anti-C1s therapy [28]. The postulated underlying immunomodulatory mechanism is sutimlimab-mediated inhibition of complement-dependent B cell

activation and proliferation [29]. It has been demonstrated that the classical complement pathway mediates C3 opsonization of antigens responsible for the co-stimulation and activation of specific B lymphocytes. This process represents a “bridge” between innate and adaptive immunity. In an in vitro assay it has been shown that sutimlimab can inhibit this process.

**b. Quality of Life**

In both phase 3 studies, CARDINAL and CADENZA, a clinically and statistically significant improvement in quality of life (QoL) parameters was observed, particularly the reduction of fatigue as measured by the FACIT-Fatigue score, and improvements in SF-12 scores assessing physical and mental health. These benefits were reported by patients as early as the first week of therapy and were sustained for up to 2 years in the long term follow up evaluations confirming the added benefit of sutimlimab to patients not only at the laboratory level but also in terms of functional outcomes [30-33].

**c. Safety**

One of the most notable aspects of sutimlimab is its favorable tolerability profile. The adverse events reported were mostly mild to moderate in severity, and no cases of serious infections or thromboembolic events were observed during treatment. In the CADENZA trial, 21 patients (96%) in the sutimlimab arm experienced a total of 146, and 20 patients (100%) in the placebo arm experienced a total of 90 adverse events. Headache (22.7% vs 10.0%), hypertension (22.7% vs 0%), rhinitis (18.2% vs 0%), Raynaud phenomenon (18.2% vs 0%), and acrocyanosis (13.6% vs 0%) were reported more frequently in sutimlimab-treated patients compared with placebo. No patients developed clinical or laboratory evidence of systemic lupus erythematosus or meningococcal infections [27]. This characteristic differentiates sutimlimab from immunosuppressive therapy and supports its use in a frequently elderly and fragile patient population often affected by comorbidities.

The CARDINAL and CADENZA trials were conducted during the COVID-19 pandemic, as such investigators were advised to vaccinate enrolled patients against COVID-19 without interrupting treatment. Of the 61 patients who completed the studies, 47 received at least one dose of a COVID-19 vaccine. In the immunogenicity analysis (n = 27), all patients developed an immune response post-vaccination, with detectable anti-spike IgG antibodies. Analysis of six patients who received booster doses showed an increase in immune response from pre- to post-booster. COVID-19 vaccines were well tolerated in CAD patients treated with sutimlimab, and no signs of hemolytic exacerbation were observed following vaccination. [34]. This well compares with data on B-cell targeting agents that showed to impair immune response to COVID-19 vaccines in several reports.

**d. Real-world experiences**

In Japan, sutimlimab was approved in 2022, with safety and efficacy data from 7 patients previously treated in CARDINAL/CADENZA who entered the Japanese open-label extension (OLE); 71.4% were female, median age 70 years (range 46–83). Median OLE treatment duration was 47.1 weeks (range 15.1–49.1). All showed improvement in hemolytic parameters; one patient (14.3%) had a treatment-related urinary tract infection, and one died from renal failure unrelated to sutimlimab [35]. Finally, a recent real-world study confirmed safety and efficacy of sutimlimab in 54 patients treated through post-trial access or compassionate use programs in Austria, France, Germany, Italy, Japan, Spain, UK, and Australia. Sutimlimab was administered as monotherapy (n=42) or in combination with erythropoietin (8), corticosteroids (2), or both (2). Hb increased overtime: +2.0 g/dL at 2 weeks, +2.7 g/dL at 4 weeks, and +3 g/dL at 8 weeks, followed by sustained levels up to 24 months. All but 7 patients became transfusion independent. 13 patients had an infection (G3 in 7, 1 H. influenzae pneumonia), 1 thrombosis (DVT of basilic vein), and 8 hemolytic exacerbations. At the last follow up only one patient had died due to progressive WM with sepsis [36].

To summarize, sutimlimab provides a quick and effective control of complement induced hemolysis, though at the price of a long-term fortnightly intravenous infusion with a possible impact of patient's convenience and healthcare resource utilization. The drug seems suitable for acute CAD flares, whilst it does not work on peripheral symptoms.

**4. Discussion and perspectives**

CAD represents a complex clinical challenge, where the balance between therapeutic efficacy and safety is central to management and treatment must be individualized. Although traditional anti-B-cell agents have provided an effective treatment approach, the introduction of targeted therapies such as sutimlimab has the potential to revolutionize CAD management by offering a highly specific, effective, and well-tolerated option. Pros and cons of these approaches are summarized in Figure 2. Taking into account available evidence if B cell directed therapy is chosen based on patient symptoms, age, and comorbidities, frontline treatment with rituximab monotherapy or in association with bendamustine appears the most rational approach. The aims of this approach are reduction of the IgM autoantibody which has the potential to mitigate both IgM induced complement mediated hemolysis and agglutination mediated cold-induced circulatory symptoms. The finite period of treatment and the possibility of sustained remissions off therapy make this an attractive choice for some CAD patients. On the other hand, the risk of serious infections, the long time to response, the significant proportion of non-responding patients and of those who only achieve a partial response for less than 12 months advocate for the availability of more effective and potentially less toxic treatment. The selective inhibition of the classical complement pathway, combines a rapid clinical response and demonstrated improvement in quality of life, thus positioning sutimlimab as a milestone in modern CAD therapy. Available data from rigorous clinical trials suggest that sutimlimab may be the treatment of choice, particularly in cases where immunochemotherapy is either ineffective, not feasible, or where the main objective of therapy is to treat the complement mediated hemolytic anemia [37]. Future studies and real-world evidence will be essential to confirm and expand these findings, further defining optimal indications, treatment duration, and combination strategies. Among the open questions are the potential use of sutimlimab in patients with CAS, as observed in the phase 1b trial and Italian clinical experience, who may benefit from treatment when the underlying lymphoproliferative disease is controlled or inactive as well as the use of sutimlimab combined with or as a bridge to B cell directed therapy in patient who either need rapid control of hemolysis or in whom control of IgM is needed in addition to control of hemolysis It is important to note that sutimlimab does not eradicate the underlying B cell clone present in CAD, thus requiring long-term administration with a potential quality of life impact due to biweekly intravenous infusions. The safety profile of sutimlimab does however allow for home administration via home health care arrangements in some countries. Even if no data on sutimlimab in fulminant hemolytic crisis are available, the rapid, within 24 hours, onset of effect observed in the clinical trials in CAD is encouraging, and further investigation would be warranted in both CAD and CAS. While the clinical trials showed that treatment discontinuation led to recurrence of hemolysis in the majority of cases, early reports of sustained response after withdrawal do suggest a possible immunomodulatory role. New complement inhibitors with longer dosing intervals, such as riliprubart administered every 12 weeks in a phase 1 study, or more convenient oral agents like iptacopan evaluated in phase 2, may represent promising future therapeutic options for CAD patients. Combining sutimlimab with immunotherapy such as rituximab or inhibitors of BTK, PI3K, or plasma cells could potentially obviate the need for continuous therapy in the future (Figure 2). It should be noted that sutimlimab does not address acrocyanotic symptoms and is therefore not indicated for patients with severely disabling acrocyanosis. Finally, compared to other complement-mediated disorders such as paroxysmal nocturnal hemoglobinuria, the CAD population tends to be older, with an inherently compromised immune system, frequent hypogammaglobulinemia related to the underlying lymphoproliferative condition and prior therapies, potentially placing these patients at higher risk for serious infections. The long-term infectious risk remains to be clarified, emphasizing the importance of vaccination policies and patient education also including the possibility of intercurrent hemolytic events.

The patients' perspective becomes crucial in choosing therapy for CAD. Some patients might put higher value in the potential for a durable response off therapy with a fixed duration therapy, though at the price of a more immunosuppressive regimen, whilst others might prefer to spare toxicity in spite of a longer-term treatment with iv sutimlimab every 2 weeks. Finally, the cost of complement inhibitors compared to traditional B-cell targeting agents might impact on a broader availability of such effective and safe treatment.

**References**


1. Berentsen S, Barcellini W. Autoimmune Hemolytic Anemias. N Engl J Med. 2021 Oct 7;385(15):1407-1419. doi: 10.1056/NEJMra2033982.
2. Berentsen S. How I treat cold agglutinin disease. Blood. 2021 Mar 11;137(10):1295-1303. doi: 10.1182/blood.2019003809.
3. Barcellini W, Fattizzo B. The evolving management algorithm for the patient with newly diagnosed cold agglutinin disease. Expert Rev Hematol. 2024 Jul;17(7):287-294. doi: 10.1080/17474086.2024.2366540.
4. Broome CM, Cunningham JM, Mullins M, Jiang X, Bylsma LC, Fryzek JP, Rosenthal A. Increased risk of thrombotic events in cold agglutinin disease: A 10-year retrospective analysis. Res Pract Thromb Haemost. 2020 Apr 9;4(4):628-635. doi: 10.1002/rth2.12333.
5. Fattizzo B, Bortolotti M, Giannotta JA, Zaninoni A, Consonni D, Barcellini W. Intravascular hemolysis and multitreatment predict thrombosis in patients with autoimmune hemolytic anemia. J Thromb Haemost. 2022 Aug;20(8):1852-1858. doi: 10.1111/jth.15757.
6. Fattizzo B, Pasquale R, Bellani V, Barcellini W, Kulasekararaj AG. Complement Mediated Hemolytic Anemias in the COVID-19 Era: Case Series and Review of the Literature. Front Immunol. 2021 Nov 25;12:791429. doi: 10.3389/fimmu.2021.791429.
7. Berentsen S, Barcellini W, D'Sa S, Randen U, Tvedt THA, Fattizzo B, et al. Cold agglutinin disease revisited: a multinational, observational study of 232 patients. Blood. 2020 Jul 23;136(4):480-488. doi: 10.1182/blood.2020005674.
8. Fattizzo B, Michel M, Zaninoni A, Giannotta J, Guillet S, Frederiksen H, et al. Efficacy of recombinant erythropoietin in autoimmune hemolytic anemia: a multicenter international study. Haematologica. 2021 Feb 1;106(2):622-625. doi: 10.3324/haematol.2020.250522.
9. Fattizzo B, Pedone GL, Brambilla C, Pettine L, Zaninoni A, Passamonti F, Barcellini W. Recombinant erythropoietin in autoimmune hemolytic anemia with inadequate bone marrow response: a prospective analysis. Blood Adv. 2024 Mar 12;8(5):1322-1327. doi: 10.1182/bloodadvances.2023011798.
10. Berentsen S, Ulvestad E, Gjertsen BT, Hjorth-Hansen H, Langholm R, Knutsen H, et al. Rituximab for primary chronic cold agglutinin disease: a prospective study of 37 courses of therapy in 27 patients. Blood. 2004 Apr 15;103(8):2925-8. doi: 10.1182/blood-2003-10-3597.
11. Berentsen S, Randen U, Vågan AM, Hjorth-Hansen H, Vik A, Dalgaard J, et al. High response rate and durable remissions following fludarabine and rituximab combination therapy for chronic cold agglutinin disease. Blood. 2010 Oct 28;116(17):3180-4. doi: 10.1182/blood-2010-06-288647.
12. Berentsen S, Randen U, Oksman M, Birgens H, Tvedt THA, Dalgaard J, et al. Bendamustine plus rituximab for chronic cold agglutinin disease: results of a Nordic prospective multicenter trial. Blood. 2017 Jul 27;130(4):537-541. doi: 10.1182/blood-2017-04-778175.
13. Jalink M, Berentsen S, Castillo JJ, Treon SP, Cruijsen M, Fattizzo B, et al. Effect of ibrutinib treatment on hemolytic anemia and acrocyanosis in cold agglutinin disease/cold agglutinin syndrome. Blood. 2021 Nov 18;138(20):2002-2005. doi: 10.1182/blood.2021012039.
14. Barcellini W, Pane F, Patriarca A, Murakhovskaya I, Terriou L, DeSancho MT, et al. Parsaclisib for the treatment of primary autoimmune hemolytic anemia: Results from a phase 2, open-label study. Am J Hematol. 2024 Dec;99(12):2313-2320. doi: 10.1002/ajh.27493.
15. Rossi G, Gramegna D, Paoloni F, Fattizzo B, Binda F, D'Adda M, et al. Short course of bortezomib in anemic patients with relapsed cold agglutinin disease: a phase 2 prospective GIMEMA study. Blood. 2018 Aug 2;132(5):547-550. doi: 10.1182/blood-2018-03-835413.
16. Jalink M, Jacobs CF, Khwaja J, Evers D, Bruggeman C, Fattizzo B, et al. Daratumumab monotherapy in refractory warm autoimmune hemolytic anemia and cold agglutinin disease. Blood Adv. 2024 Jun 11;8(11):2622-2634. doi: 10.1182/bloodadvances.2024012585.

17. Röth A, Bommer M, Hüttmann A, Herich-Terhürne D, Kuklik N, Rekowski J, Lenz V, Schrezenmeier H, Dührsen U. Eculizumab in cold agglutinin disease (DECADE): an open-label, prospective, bicentric, nonrandomized phase 2 trial. Blood Adv. 2018 Oct 9;2(19):2543-2549. doi: 10.1182/bloodadvances.2018024190. PMID: 30291112; PMCID: PMC6177646.
18. Roman E, Fattizzo B, Shum M, Hanna W, Lentz SR, Araujo SSS, Al-Adhami M, Grossi FV, Gertz MA. Safety and efficacy of pegcetacoplan treatment for cold agglutinin disease and warm antibody autoimmune hemolytic anemia. Blood. 2025 Jan 23;145(4):397-408. doi: 10.1182/blood.2023022549. PMID: 39486046.
19. Röth A, Barcellini W, Ademokun C, Jang J, Lozano ML, Ferreiras DV, Pascual-Izquierdo C, Chitnis S, Matviykiv S, Vitaliti A, Chen C, Katsanou V, Chawla R, Al-Samkari H. Iptacopan for Immune Thrombocytopenia and Cold Agglutinin Disease: A Global Phase 2 Basket Clinical Trial. Am J Hematol. 2025 Dec 9. doi: 10.1002/ajh.70147. Epub ahead of print. PMID: 41366634.
20. Jäger U, D'Sa S, Schörgenhofer C, Bartko J, Derhaschnig U, Sillaber C, et al. Inhibition of complement C1s improves severe hemolytic anemia in cold agglutinin disease: a first-in-human trial. Blood. 2019 Feb 28;133(9):893-901. doi: 10.1182/blood-2018-06-856930.
21. Gelbenegger G, Schoergenhofer C, Derhaschnig U, Buchtele N, Sillaber C, Fillitz M, et al. Inhibition of complement C1s in patients with cold agglutinin disease: lessons learned from a named patient program. Blood Adv. 2020 Mar 24;4(6):997-1005. doi: 10.1182/bloodadvances.2019001321.
22. Gelbenegger G, Jaeger U, Fillitz M, D'Sa S, Cartwright R, Shafer F, et al. Sustained sutimlimab response for 3 years in patients with cold agglutinin disease: A phase I, open-label, extension trial. Br J Haematol. 2022 Aug;198(4):e59-e62. doi: 10.1111/bjh.18289.
23. Röth A, Barcellini W, D'Sa S, Miyakawa Y, Broome CM, Michel M, et al. Sutimlimab in Cold Agglutinin Disease. N Engl J Med. 2021 Apr 8;384(14):1323-1334. doi: 10.1056/NEJMoa2027760.
24. Roth A, Barcellini W, D'Sa S, Miyakawa Y, Broome CM, Michel M, et al. Complement C1s inhibition with sutimlimab results in durable response in cold agglutinin disease: CARDINAL study 1-year interim follow-up results. Haematologica. 2022 Jul 1;107(7):1698-1702. doi: 10.3324/haematol.2021.279812.
25. Röth A, Barcellini W, D'Sa S, Miyakawa Y, Broome CM, Michel M, et al. Sustained inhibition of complement C1s with sutimlimab over 2 years in patients with cold agglutinin disease. Am J Hematol. 2023 Aug;98(8):1246-1253. doi: 10.1002/ajh.26965.
26. Röth A, Berentsen S, Barcellini W, D'Sa S, Jilma B, Michel M, et al. Sutimlimab in patients with cold agglutinin disease: results of the randomized placebo-controlled phase 3 CADENZA trial. Blood. 2022 Sep 1;140(9):980-991. doi: 10.1182/blood.2021014955.
27. Röth A, Berentsen S, Barcellini W, D'Sa S, Jilma B, Michel M, et al. Long-term efficacy and safety of continued complement C1s inhibition with sutimlimab in cold agglutinin disease: CADENZA study Part B. EClinicalMedicine. 2024 Jul 18;74:102733. doi: 10.1016/j.eclinm.2024.102733.
28. Gelbenegger G, Jäger U, Fillitz M, Schörgenhofer C, Sillaber C, Jilma B. Sustained hematologic remission after discontinuation of sutimlimab treatment in patients with cold agglutinin disease. Blood Adv. 2023 May 23;7(10):1987-1990. doi: 10.1182/bloodadvances.2022008574.
29. Nikitin PA, Rose EL, Byun TS, Parry GC, Panicker S. C1s Inhibition by BIVV009 (Sutimlimab) Prevents Complement-Enhanced Activation of Autoimmune Human B Cells In Vitro. J Immunol. 2019 Feb 15;202(4):1200-1209. doi: 10.4049/jimmunol.1800998.
30. Röth A, Broome CM, Barcellini W, Tvedt THA, Miyakawa Y, D'Sa S, et al. Long-term sutimlimab improves quality of life for patients with cold agglutinin disease: CARDINAL 2-year follow-up. Blood Adv. 2023 Oct 10;7(19):5890-5897. doi: 10.1182/bloodadvances.2022009318. Erratum in: Blood Adv. 2024 Jun 11;8(11):2650. doi: 10.1182/bloodadvances.2024013366.
31. Röth A, Barcellini W, Tvedt THA, Miyakawa Y, Kuter DJ, Su J, et al. Sutimlimab improves quality of life in patients with cold agglutinin disease: results of patient-reported outcomes from the CARDINAL study. Ann Hematol. 2022 Oct;101(10):2169-2177. doi: 10.1007/s00277-022-04948-y.

Epub 2022 Aug 23. Erratum in: Ann Hematol. 2024 May;103(5):1803. doi: 10.1007/s00277-024-05709-9.
32. Röth A, Broome CM, Barcellini W, Jilma B, Hill QA, Cella D, et al. Sutimlimab provides clinically meaningful improvements in patient-reported outcomes in patients with cold agglutinin disease: Results from the randomised, placebo-controlled, Phase 3 CADENZA study. Eur J Haematol. 2023 Mar;110(3):280-288. doi: 10.1111/ejh.13903.
33. Röth A, Broome CM, Barcellini W, Jilma B, Hill QA, Cella D, et al. Sustained improvements in patient-reported outcomes after long-term sutimlimab in patients with cold agglutinin disease: results from the CADENZA study open-label extension. EClinicalMedicine. 2024 Jul 18;74:102732. doi: 10.1016/j.eclinm.2024.102732.
34. Fattizzo B, Röth A, Broome CM, Khan U, Wardęcki M, Cordoba M, Barcellini W. COVID-19 vaccine safety and immunogenicity in patients with cold agglutinin disease receiving concomitant sutimlimab. Am J Hematol. 2024 Apr;99(4):789-791. doi: 10.1002/ajh.27234.
35. Miyakawa Y, Sato E, Ogawa Y, Nishimura JI, Nishimi M, Kawaguchi O, et al. Long-term safety profile of sutimlimab in adult Japanese patients with cold agglutinin disease. Int J Hematol. 2024 Dec;120(6):656-664. doi: 10.1007/s12185-024-03842-9.
36. Fattizzo B, Sambruna E, Miyakawa Y, Michel M, Visco C, Fillitz M, et al. Real world use of sutimlimab in patients with cold agglutinin disease: An international study. Blood 2025; 146 (Supplement 1): 1100. doi: https://doi.org/10.1182/blood-2025-1100
37. Jäger U, Barcellini W, Broome CM, Gertz MA, Hill A, Hill QA, Jilma B, Kuter DJ, Michel M, Montillo M, Röth A, Zeerleder SS, Berentsen S. Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting. Blood Rev. 2020 May;41:100648. doi: 10.1016/j.blre.2019.100648. Epub 2019 Dec 5. PMID: 31839434.

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**Figure legends**

**Figure 1. Physiopathology and targeted therapies for cold agglutinin disease.**

**Figure 2. Pros and cons of B-cell targeting agents versus sutimlimab in the management of cold agglutinin disease.**

**Table 1. Clinical trials evaluating B-cell directed therapies and complement inhibitors for cold agglutinin disease.** Notably different response criteria were used in each trial.

| Drug(s) studied | Study design | Patients/ courses of therapy, n | OR,% | CR,% | Hb increase, g/dL | Median response duration, months | Toxicity | Publication | Pros | Cons |
|---|---|---|---|---|---|---|---|---|---|---|
| Rituximab | Prospective, nonrandomized | 27/37 | 54 | 4 | 4.0 | 11 (observed) | Low | Blood. 2004;103 (8):2925-2928 . | Low toxicity | long time to response<br>short response duration<br>Decreased response to vaccines |
| Rituximab | Prospective, nonrandomized | 20/20 | 45 | 5 | 3.1 | 6.5 (observed) | Low | Leuk Lymphoma. 2006;47(2):253260 | | |
| Bendamustine + Rituximab | Prospective, nonrandomized | 45/45 | 71 | 40 | 4.0 | >32 (observed) | Relatively low, manageable | Blood. 2017;130 (4):537-541. | Higher percentage of complete responses<br>Long response duration in responders | Time to response<br>33% of patients with grade 3-4 neutropenia |
| Bendamustine + Rituximab | Follow-up, part of larger study | 45/45 | 78 | 53 | Not reevaluated | >88 (estimated) | Long-term: low | Blood. 2020;136(4):480-488 | | |
| Fludarabine + Rituximab | Prospective, nonrandomized | 29/29 | 76 | 21 | 3.1 | >66 (estimated) | Significant | Blood. 2010;116 (17):3180-3184 | Higher percentage of complete responses<br>Long response duration in responders | Time to response median 4 months<br>41% had Grade 3-4 hematologic toxicity |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Bortezomib, Dexamethasone, Rituximab | Prospective, nonrandomized | 23 | 96% | 83% | NA | NA | low | J Clin Oncol 27, 3830-3835, 2009 | Responses observed even in patients refractory to rituximab | May cause peripheral neuropathy, helps zoster, reversible neuropathy |
| Bortezomib | Prospective,<br>non randomized | 19/1 | 31.6 | 15.8 | 2.7 | 16 | low | *Blood (2018) 132 (5): 547–550.* | *Low toxicity* | *Low response rate, small study* |
| Sutimlimab | Prospective,<br>non randomized | 24/q 2 weeks | 54 | NA | 2.6 | NA | low | N Engl J Med 2021;384:1323-1334 | Rapid response<br>High response rate, Fatigue improves | Need for ongoing therapy<br>Does not address acrocyanotic symptoms<br>Need vaccination |
| Sutimlimab | Randomized placebo controlled | 42/q 2 weeks | 72.7 | NA | 2.7 | NA | low | Blood 2022 Sep 1;140(9):980-991 | Rapid response<br>High response rate, Fatigue improves versus placebo | Need for ongoing therapy<br>Does not address acrocyanotic symptoms<br>Need vaccination |
| Eculizumab | Prospective, nonrandomized | 13/q 2 weeks | NA | NA | 0.8 | NA | low | Blood Adv. 2018 Oct 9;2 (19):2543-2549 | Rapid response on LDH and decrease of transfusions. | Little improvement in Hb. No effect on peripheral symptoms. |
| Pegcetacoplan | Prospective, nonrandomized | 10/ daily | NA | NA | 2.4 | 48 weeks | low | Blood. 2025 Jan 23;145(4):397-408. | High Hb improvement and hemolytic markers amelioration. | Possible meningococcal, pneumococcal, hemohilus infection. |
| Iptacopan | Prospective, nonrandomized | 10/daily | 50 | NA | 1.8 | NA | low | Blood 144, 2457-2458, 2024 abstract | Low toxicity, short time to response, oral capsule | Possible meningococcal, pneumococcal, hemohilus infection. |

Figure 1

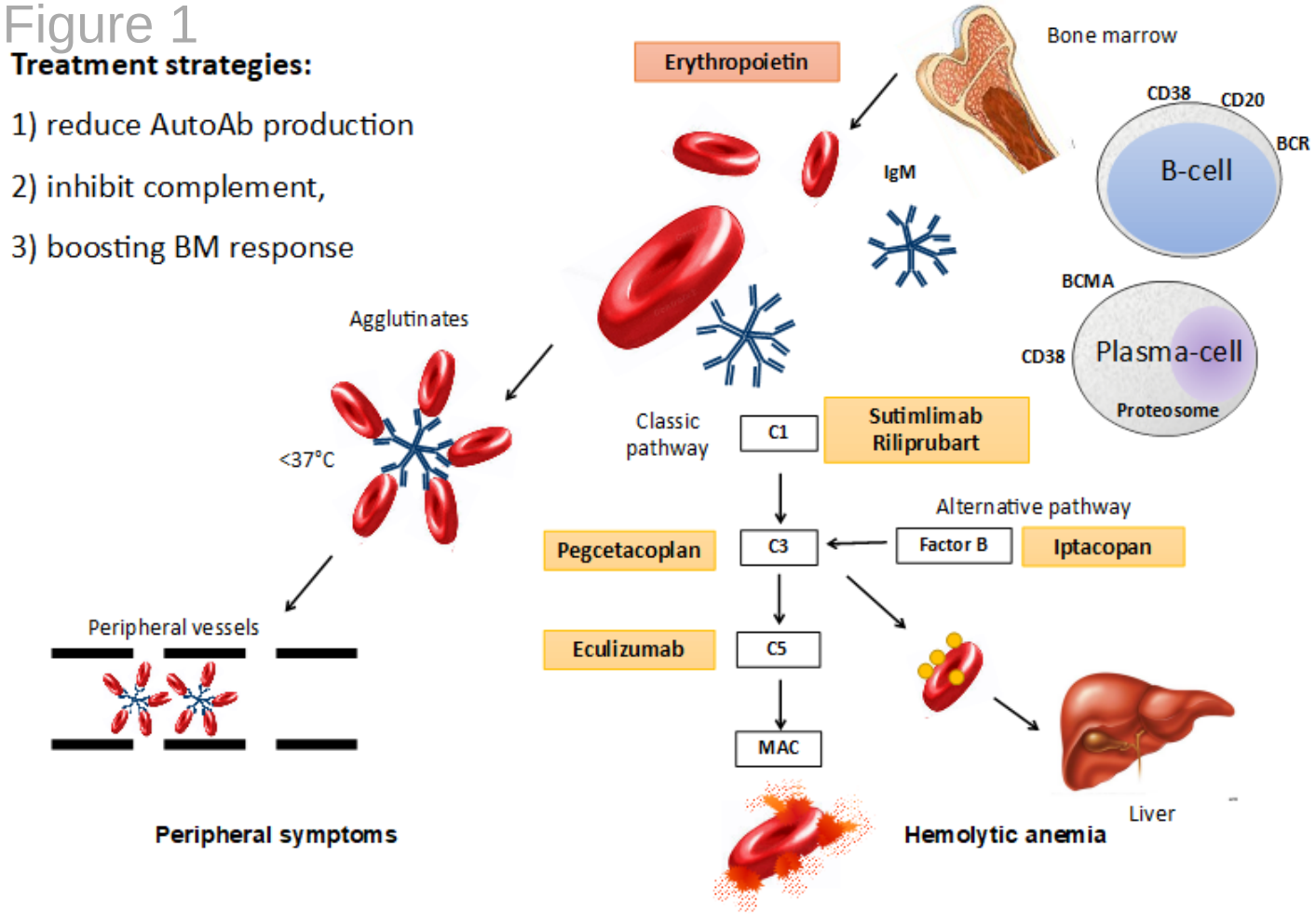


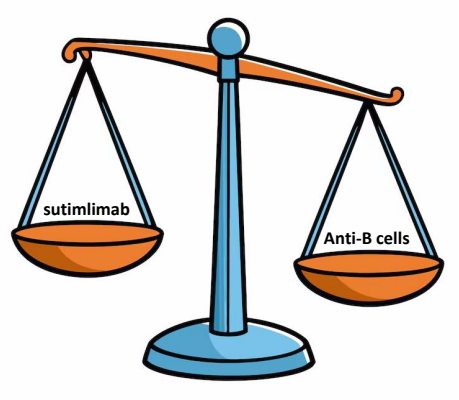
Figure 2

Figure 2

**B-cell targeting therapies**

**Pros**
- Definite treatment duration
- About 50-60% responses, mainly partial
- Possibility of responses off-treatment
- Effective on cold-induce circulatory symptoms

**Cons**
- Responses are mainly partial
- Longer time to response of 1-4 months
- Prolonged hypogammaglobulinemia and infections are a feared adverse event




**Indications**
- C3d mediated hemolytic anemia
- Moderate to severe cold induced peripheral symptoms
- Frontline therapy of symptomatic CAD

**Combined treatment with rituximab and sutimlimab**

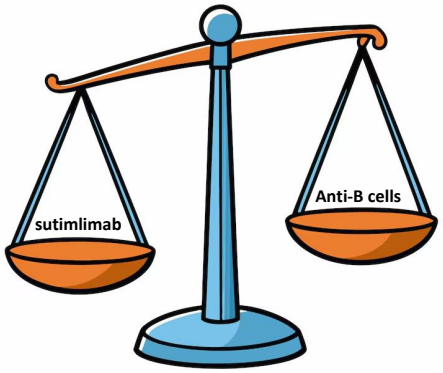
**Potentials:**
- Quick control of hemolysis
- Higher rates of complete responses
- Effect also on cold induced circulatory symptoms
- potential of persistent response off therapy after sutimlimab discontinuation
- Reduced frequency of relapses and need of immunosuppression
- Reduced rate of infections and thrombosis

**Patient's preference and costs are crucial**

**Sutimlimab**

**Pros**
- Quick responses in about 2 weeks
- About 70% responses and transfusion independence
- Improved patient reported outcomes
- Limited toxicities

**Cons**
- Ineffective on cold induced peripheral symptoms
- Long-term treatment to avoid relapse (IV every 14 days)
- Risk of encapsulated infections and breakthrough hemolysis
- Need of patient education
- High costs of long-term therapy




**Indications**
- C3d mediated hemolytic anemia
- Mild to moderate cold induced peripheral symptoms
- Failure of rituximab monotherapy