RESEARCH LETTER

blood advances

TO THE EDITOR:

Sustained hematologic remission after discontinuation of sutimlimab treatment in patients with cold agglutinin disease

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Cold agglutinin disease (CAD) is a rare form of autoimmune hemolytic anemia (AIHA) that leads to fatigue, a risk of thromboembolic events, and agglutination-mediated acrocyanosis.[1-3] Binding of cold agglutinins to their antigen on red blood cells causes agglutination, fixes complement C1, and initiates the classical complement pathway.[4] This leads to coating of the red blood cells with C3b and eventual extravascular hemolysis in the liver.[5] Upstream inhibition of the classical complement pathway is a novel treatment in CAD. The monoclonal antibody sutimlimab binds to C1s, prevents downstream opsonization of red blood cells, and thereby effectively stops hemolysis, reduces fatigue, and increases hemoglobin levels.[6-9]

In vitro, C1s inhibition with sutimlimab significantly inhibited complement-mediated activation and proliferation of primary human B cells.[10] Treatment with sutimlimab may therefore alter the pathogenic humoral immune response in patients with CAD. As of now, there is no clinical data available to support that concept in patients. We report post-trial observations of 3 patients with CAD after the end of the long-term treatment with sutimlimab.

This observational study (post-trial observations) was conducted between February 2021 and March 2022. Previously, 3 patients with CAD who responded to treatment with sutimlimab were transitioned from a named patient program (NPP)[7] to an open-label extension of the original phase 1b study.[6] Weight-adapted, fixed-dose 1-hour infusions of 5.5, 6.5, or 7.5 g of sutimlimab were given every other week for ~3 years.[6] After the study termination, follow-up visits with increasing intervals were performed after discontinuation of sutimlimab. This was done because we expected immediate relapse of hemolysis[2,6,7] as soon as sutimlimab concentrations would drop below threshold concentrations of ~20μg/mL.[11] We repeatedly observed and were able to predict such recurrences of hemolysis, when we empirically performed dose findings in these patients.[7] Patient follow up was performed for 12 months after sutimlimab discontinuation and included measurements of hemoglobin, bilirubin, lactate dehydrogenase (LDH), and C4. Sustained hematologic remission was defined as near on-treatment hemoglobin levels without overt signs of hemolysis. Hematologic relapse (recurrence of hemolysis) was defined as a fall of hemoglobin accompanied by a reciprocal rise of bilirubin. The study received approval from the Ethics Committee of the Medical University of Vienna EK 1849/2014 EudraCT 2014-003881-26 and was conducted according to the Declaration of Helsinki.

All included patients with CAD were female and aged between 72 and 78 years at the start of the study. (Table 1). Durations of prior, consecutive treatment with sutimlimab in the extension trial ranged from 34 to 39 months.[12] At the start of the study, patient 1 and 2 tested negative for Immunoglobulin M (IgM) and IgG in the direct antiglobulin test (DAT) with a cold agglutinin titer of 256. Patient 3 tested positive for IgM autoantibodies (and intermittently IgG autoantibodies, suggestive of mixed AIHA) with a cold agglutinin titer >1024 (Table 2).

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Data are available on request from the corresponding author, Bernd Jilma (bernd.jilma@meduniwien.ac.at).

The full-text version of this article contains a data supplement.

Table 1. Baseline characteristics and previous treatments received for cold agglutinin disease

Patient	Additional hematologic condition	Age at sutimlimab discontinuation	Sex	Thromboembolic events	Disease duration [y]	Previous treatment for CAD
1	CAD after LPL	75	F	Venous thrombosis	9	Steroids, rituximab/bendamustine
2	n/a	78	F	Pulmonary embolism	6	Steroids, IV immunoglobulins, rituximab
3	mixed AIHA (*MYD88-*)	81	F	n/a	15	Steroids, rituximab, IV immunoglobulins

N/a, not applicable/available.

Sutimlimab halted hemolysis and increased hemoglobin to normal/near normal levels in patients 1 and 2. Residual hemolysis was observed in patient 3 and coincided with an attenuated treatment response.[12] Patient 3 continued testing positive for IgM autoantibodies in DAT (Coombs test), whereas the other 2 patients did not.

Hematologic remission persisted in patients 1 and 2 for up to 12 months after the discontinuation of sutimlimab (Figure 1). Patients 1 and 2 remained symptom-free (including acrocyanosis) and consistently showed stable hemoglobin levels without signs of overt hemolysis as measured by bilirubin, C4, haptoglobin, or lactate dehydrogenase levels (supplemental Figure 1). During follow-up visits, patients 1 and 2 repeatedly tested negative for IgM or IgG autoantibodies in DAT, whereas patient 3 showed a positive DAT for IgM (and intermittently IgG) autoantibodies.

Patient 1 repeatedly showed normal hemoglobin and bilirubin levels throughout the observation period. Although LDH and C4 levels remained stable, haptoglobin levels showed a steady downward trend, potentially indicative of compensated hemolysis.

Patient 2 showed a slight increase in bilirubin, accompanied by a mildly elevated LDH level, at around 6 months after sutimlimab discontinuation, but hemoglobin remained stable within the normal range. Over time, LDH levels reached a plateau slightly above the normal range and haptoglobin fell eventually below the limit of quantification at 12 months. Despite subtle signs of hemolysis, normal hemoglobin levels persisted, bilirubin levels remained stable just above the normal range, and the patient did not complain about any CAD-related symptoms.

In contrast, patient 3 suffered from the expected relapse 7 weeks after discontinuation of sutimlimab and developed severe transfusion-dependent hemolysis.

This is the first clinical evidence of sustained hematologic remission in some patients with CAD following discontinuation of anti-C1s treatment. The underlying immunomodulatory mechanism may be explained by sutimlimab-induced inhibition of complement-mediated activation and proliferation of B cells.[10]

Considering the discrepancy between previous relapses during short washout periods and now sustained response, several aspects may contribute to sustained hematologic response following discontinuation of sutimlimab treatment. Identifying factors that may be able to predict immunomodulation and long-term response following sutimlimab discontinuation will help to guide future treatment. The following factors may contribute to it: (i) sustained hematologic remission occurred only in patients testing negative for IgM and IgG autoantibodies in the DAT. In these patients, autoantibody titers did not exceed 256; this was in contrast to the higher cold agglutinin titers in the relapsing patient as well as her IgM+ DAT. Thus, autoantibody status and titer might be predictive factors of response to treatment with sutimlimab and its ability to influence pathologic B-cell activation. In addition to autoantibody status and titer, both (ii) treatment duration and (iii) dose of sutimlimab may present crucial factors to induce a sustained hematologic response after sutimlimab discontinuation. In contrast to the previously performed NPP, patients received sutimlimab treatment continuously for an extended period of time in the open-label extension trial (patient 1: 38 months, previously 22 months; patient 2: 34 months, previously 6 months; patient 3: 39 months, previously 22 months).[12] The cumulative total exposure to sutimlimab was ~4 years for each patient.[7,12] In the extension trial higher doses (6.5-7.5 g) were used than in the NPP (final dose of 5.5 g).

For the relapsing patient 3, another factor might have contributed: she had mixed-type AIHA (occasionally IgG + DAT), which might

Table 2. Treatment details and follow-up data of included patients

Patient	Cumulative dose of sutimlimab in the extension trial [g]	Duration of participation in the extension trial [mo]	Cumulative exposure to sutimlimab (NPP + extension trial) [mo]	Monospecific Coombs test (DAT) at sutimlimab discontinuation	Cold agglutinin titer at sutimlimab discontinuation	Monospecific Coombs test (DAT) at 12 mo	Sustained hematologic remission
1	519.5	38	58	Anti-IgG – Anti-IgM – Anti-C3d –	256	Anti-IgG - Anti-IgM - Anti-C3d +++	yes
2	475.0	34	39.5	Anti-IgG – Anti-IgM – Anti-C3d +	256	Anti-IgG - Anti-IgM - Anti-C3d ++	yes
3	503.5	39	59	Anti-IgG –* Anti-IgM ++ Anti-C3d ++	>1024	Anti-IgG + Anti-IgM +++ Anti-C3d ++	no

Results of the monospecific Coombs test before treatment have been reported previously.[12]
Cumulative doses of sutimlimab in the NPP are shown in the appendix.
*Patient 3 intermittently tested positive for IgG autoantibodies, compatible with mixed AIHA.

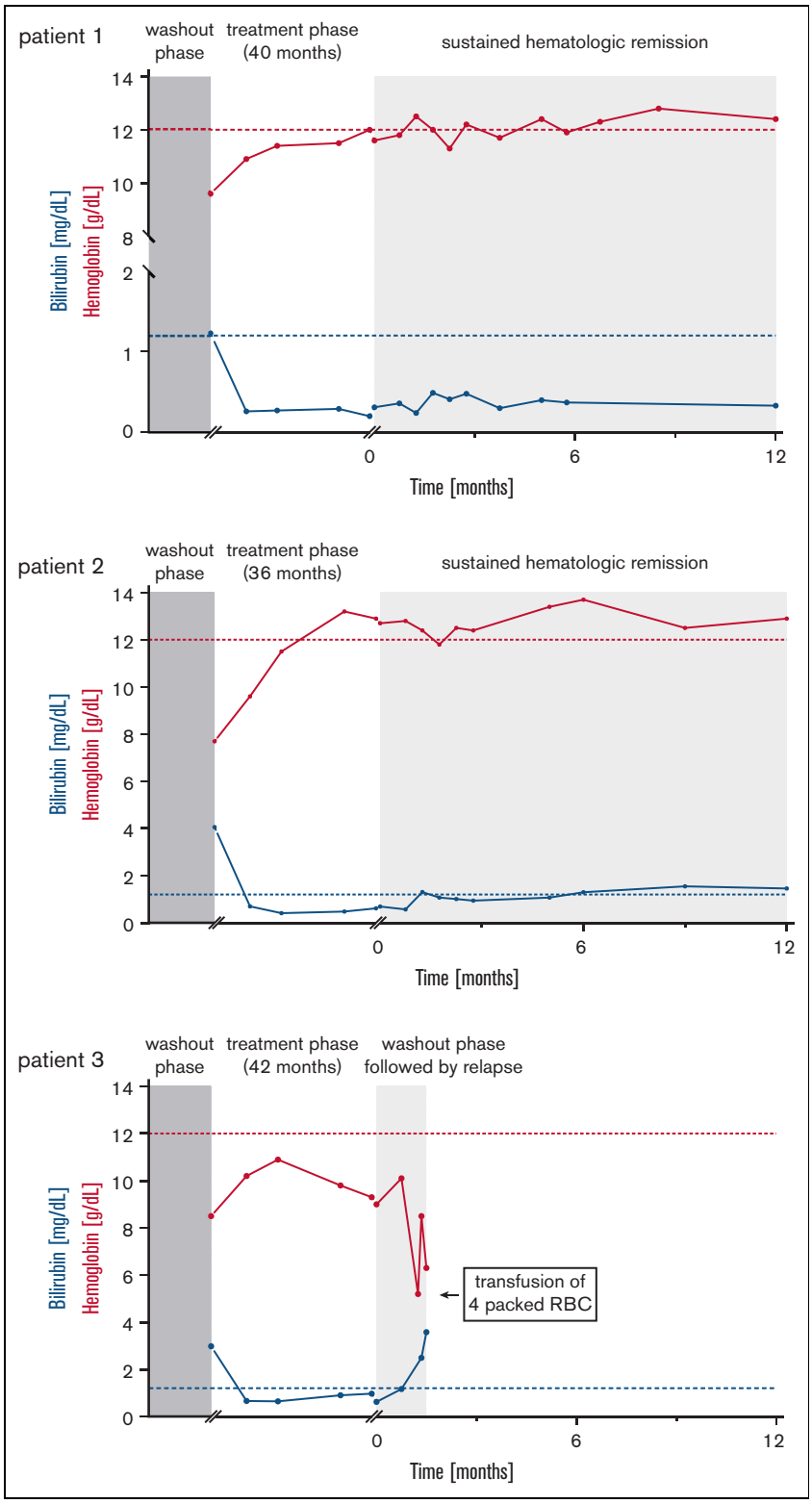

Figure 1. Sustained hematologic remission after discontinuation of long-term treatment with sutimlimab. Time course of hemoglobin and bilirubin levels of the 3 included patients is shown for 3 phases: (i) washout from the NPP, (ii) long-term treatment with sutimlimab in the extension trial (abridged), and (iii) follow up after discontinuation of sutimlimab treatment. (i) The planned drug washout after end of the NPP induced the expected hemolysis in all 3 patients. (ii) Initiation of sutimlimab rapidly abrogated hemolysis and increased hemoglobin levels in all patients. (iii) In patients 1 and 2, steady near normal hemoglobin levels were observed for up to 12 months following discontinuation of sutimlimab. Bilirubin levels remained within the normal range in patient 1 and showed a small increase just above the normal range in patient 2. Patient 3 relapsed and developed transfusion-dependent anemia around 7 to 8 weeks after the last dose of sutimlimab. RBC, red blood cells.

have influenced the therapeutic effect of sutimlimab because patient 3 did not show the same magnitude of overall treatment response as compared with the other 2 patients. Consequently, the attenuated treatment effect may preclude additional effects on B cells. Although further studies with larger sample sizes are needed to confirm our results, these interesting findings may potentially have implications for the extended use of complement inhibitors even in other diseases. In a follow-up study from the cardinal trial, 22 patients were transitioned into an open-label extension trial and received sutimlimab for up to 3 years.[13] After sutimlimab

discontinuation, only 1 patient did not show a return of hemolysis but was re-treated soon thereafter as part of yet another extension program.

Considering the about 50% response rate of rituximab therapy (with very few complete responses),[14] its limited median response duration of less than 1 year[15,16] and accompanying toxicity when combined with cytotoxic agents (eg, bendamustine),[17] the prospect of well-tolerated complement inhibition with sutimlimab and subsequent sustained hematologic response may make it a viable alternative for the long-term therapy of CAD.

In conclusion, we observed hematologic remission in 2 of 3 patients with CAD following discontinuation of long-term treatment with 6.5 to 7.5 g sutimlimab every other week. Lack of IgM autoantibodies in the DAT might be predictive of sustained hematologic response after the treatment discontinuation of sutimlimab.

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