

TO THE EDITOR:

Effect of ibrutinib treatment on hemolytic anemia and acrocyanosis in cold agglutinin disease/cold agglutinin syndrome

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In cold-antibody mediated autoimmune hemolytic anemia (cAIHA), red blood cell (RBC) autoantibodies lead to complement-mediated hemolysis with or without symptoms of acrocyanosis after exposure to low temperatures. cAIHA is a rare disease with an incidence of 0.5 to 1.9 cases/million per year, depending on the climate.^{1,2} cAIHA can be divided into cold agglutinin disease (primary CAD) and cold agglutinin syndrome (CAS). In primary CAD, >90% of patients have a low level of immunoglobulin M (IgM) paraproteinemia, accompanied by a low-proliferating clonal B-cell lymphoproliferative disorder with specific pathologic and genetic features, typically limited to the bone marrow.^{1,3-5} MYD88^{L265P} somatic mutations are mostly absent.⁵ CAS, on the other hand, is secondary to other conditions including B-cell malignancies.

The RBC autoantibody in CAD/CAS is typically IgMκ directed against the I antigen and may lead to peripheral RBC agglutination and acrocyanosis, as well as activation of the classical complement cascade, resulting in hemolysis.⁶ For patients with significant hemolytic anemia or acrocyanosis despite conservative measures such as thermal protection, there is no curative treatment. Treatment recommendations are based on small studies and expert opinion. Rituximab is the most accepted first-line treatment, with an overall response rate of 50% and median duration of response of less than 1 year.⁵ Cytotoxic combinations such as rituximab-bendamustine or rituximab-fludarabine produce more sustained remissions; however, time to response can take months.^{7,8}

Clinical trials with novel complement inhibitors are ongoing and show promising results on the hemolytic anemia, whereas acrocyanosis is not expected to improve because this is mediated by the IgM autoantibody itself and not related to complement activation.⁹⁻¹¹ Therefore, a noncytotoxic treatment that could lead to rapid and long-lasting resolution of hemolysis and acrocyanosis is currently lacking.

Bruton tyrosine kinase (BTK) inhibitors are highly effective in Waldenström macroglobulinemia (WM) and chronic lymphocytic

leukemia (CLL). WM is localized in the bone marrow and accompanied by an IgM paraproteinemia, similar to CAD.¹² In WM, BTK inhibition leads to rapid suppression of IgM levels, with deepest and quickest responses seen in patients with somatic MYD88^{L265P} compared with MYD88 wild type.¹³⁻¹⁵ CLL is accompanied by AIHA in 5% to 10% of cases,¹⁶⁻¹⁸ and retrospective studies show ibrutinib efficacy in this setting.^{16,19,20} However, more than 90% of AIHA in CLL is because of warm IgG autoantibodies, and CAS secondary to CLL is quite rare.^{17,21,22} Data on the effect of BTK inhibition in primary CAD or CAS secondary to CLL or WM are lacking.

We hypothesized that BTK inhibition could be an effective treatment of CAD/CAS-related AIHA and acrocyanosis. Indeed, a recent international consensus article and expert opinions on cAIHA suggest treatment with the BTK inhibitor ibrutinib in refractory patients.^{4,5,23} However, there are no published data on this approach. Furthermore, ibrutinib is less effective in MYD88 wild-type WM, raising the question of whether ibrutinib would indeed be effective in primary CAD, which is mostly MYD88 wild type.^{3,5} Here, we aimed to evaluate the efficacy of ibrutinib on anemia, hemolysis, and acrocyanosis in patients with primary CAD and CAS.

We therefore undertook a multinational retrospective study of patients with cAIHA treated with a BTK inhibitor. Inclusion criteria were cAIHA, diagnosed as a combination of anemia, hemolysis (defined by increased reticulocytes, lactate dehydrogenase [LDH], and bilirubin with a decreased haptoglobin), and/or severe acrocyanosis, in combination with a positive direct anti-globulin test for complement deposition according to current practice.^{4,5} Each investigator was asked to report all consecutive patients with cAIHA that were started on any type of BTK inhibitor. Laboratory and clinical data were collected via a preformed questionnaire regarding underlying disease, bone marrow pathology, hemolytic parameters, and patient-reported acrocyanosis (scored as stable, better, or resolved) at diagnosis, 1, 3, 6, and 12 months, and last date of follow-up. Patients were followed from April 2014 until February 2021 at 10 centers

Table 1. Baseline characteristics

Case	Sex	Age, y	Bone marrow histology	MYD88 L265p mutation	Total IgM, g/L	Previous treatment	Hb, g/dL, at start of ibrutinib	Duration of ibrutinib treatment at time of data collection (mo)
1	M	73	CLL	ND	7	Steroids, IVIG†	7.5*	17
2	M	66	CLL	ND	0.9	Steroids, rituximab, fludarabine	11.2	12
3	M	58	CLL	ND	0.3	None	8.8*	24
4‡	M	66	CLL	ND	0.4	Steroids, rituximab†§	6.0*	2
5¶	M	85	CLL	ND	ND	Steroids, rituximab, chlorambucil-obinutuzumab, MMF	9.0*	15
6	M	81	SLL	ND	1.5	rituximab, bendamustine, bortezomib†	6.9*	29
7	F	67	CAD	Negative	4.4	Rituximab, bendamustine, fludarabine	8.2	10
8	M	71	CAD	Negative	26	Steroids, DRC, rituximab	11.9	10
9	F	81	CAD	ND	1.0	Steroids, rituximab, chlorambucil	9.0*	3
10	F	72	CAD	ND	2.1	Rituximab (3 cycles),† DRC, darbeopetin†	5.0*	6
11	M	67	LPL/WM	Negative	25	Rituximab, DRC, rituximab-maintenance	9.2*	82
12	F	66	LPL/WM	Negative	12	Rituximab	7.2*	60
13	F	71	LPL/WM	Positive	27	Plasmapheresis†	8.2*	39
14	F	55	LPL/WM	Positive	66.2	Steroids	5.9*	12
15	F	68	LPL/WM	Positive	32.7	Steroids, rituximab (2 cycles), bortezomib-DRC, ixazomib	10.6	6
Median (range)		68(55-85)			5.7(0.3-66.2)	3(0-5)	8.2(5.0-11.9)	12(3-82)

CAD, primary cold agglutinin disease; CLL, chronic lymphatic leukemia; DRC, dexamethasone, rituximab, cyclophosphamide; F, female; IVIG, intravenous immunoglobulin; LPL, lymphoplasmacytic lymphoma; M, male; MMF, mycophenolate mofetil; ND, not determined; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

*Transfusion dependent at start ibrutinib therapy.

†Therapy received within 3 months before start ibrutinib therapy.

‡After 2.5 months of ibrutinib therapy, patient switched to intensive chemotherapy because of the diagnosis of a Richter's transformation.

§Patient was treated with C1 inhibitor (Cinryze), a one-time gift of vincristine, and plasmapheresis within 2 weeks after the start of ibrutinib.

¶Patient started on ibrutinib therapy because of disabling acrocyanosis in the absence of hemolytic anemia.

||Patient died of melanoma (diagnosed prior to initiation of ibrutinib).

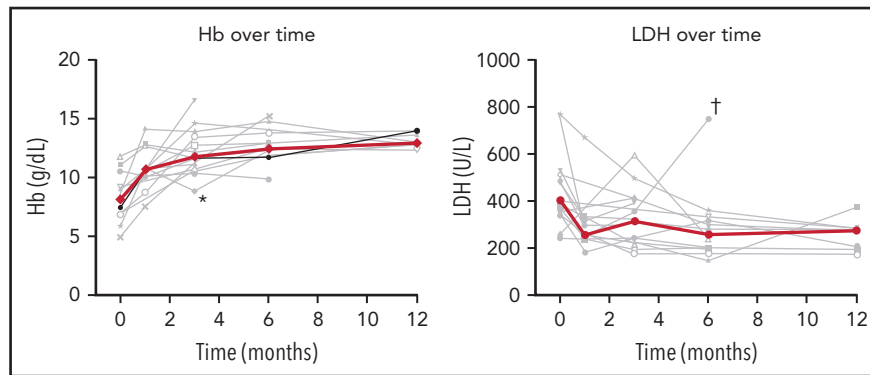


Figure 1. Hb and LDH response after the initiation of ibrutinib therapy. Gray lines represent individual data of Hb and LDH; bold line represents median Hb and LDH over time. *Hb decrease at 3 months was considered related to hospital admission for a hip fracture and surgery. †Increased LDH was considered related to the initiation of G-CSF for neutropenia, because other hemolytic parameters were not increased.

worldwide (Italy, Denmark, Greece, Norway, The Netherlands, United Kingdom, and the United States). Hemoglobin (Hb) response was considered none, partial (PR; Hb 10-12 g/dL or ≥ 2 -g/dL increase), or complete (CR, Hb > 12 g/dL). Adverse events were graded according to the Common Terminology Criteria, version 5.0 (2017) (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

Fifteen patients with cAIHA treated with ibrutinib were included, of whom 4 had primary CAD and 11 CAS (5 WM, 5 CLL, 1 small lymphocytic lymphoma [SLL]). The patient baseline characteristics and response to treatment are summarized in Table 1. MYD88 mutational status was available for 7 patients: MYD88^{L265P} was detected in 3 patients with WM, whereas 2 patients with WM and 2 patients with primary CAD were MYD88 wild type. The median number of prior therapies was 3 (0-5). At baseline, 11 of 15 patients were transfusion dependent, and 9 of 15 reported symptoms of acrocyanosis. In 2 patients, treatment indication was refractory acrocyanosis only, without significant hemolytic anemia. Ibrutinib monotherapy was initiated at 420 mg/day in all patients. In 1 patient, rescue therapy was continued within the first 2 weeks of ibrutinib treatment (Table 1). At the time of data collection, median duration of ibrutinib therapy was 12 months (range, 3-82 months), and 13 patients were still on ibrutinib. Two patients discontinued therapy: 1 died because of metastatic melanoma diagnosed before ibrutinib initiation, and 1 switched to treatment of Richter's transformation, which retrospectively was present before the start of ibrutinib. No patients were lost to follow-up.

After initiation of ibrutinib, all 13 patients with cAIHA at baseline showed an improvement in hemoglobin resulting in 12 CR and 1 PR. In 12 of 13 patients with cAIHA at baseline, markers of hemolysis improved after initiation of ibrutinib; 1 hemolysis response was not evaluable because of missing data (Figure 1). At 1 month, 10 of 13 patients reached at least a partial Hb response, and Hb CR was reached after a median of 3 months (range, 1-12 months). The median best individual Hb increase from baseline was 5.6 g/L (range, 2.5-10.3 g/L), and all 11 transfusion-dependent patients became transfusion independent; 9 converted within 30 days. For 2 of 11 patients, data were lacking at 30 days, but both were transfusion independent at 3 months.

All 9 patients with acrocyanosis reported clinical improvement, of whom 8 were within 30 days and 1 was after 3 months, and complete resolution was accomplished in 6 of 9 patients. There were 5 grade 1 adverse events in 4 patients (3 bruising, 1 diarrhea, and 1 rash), mostly well-known side effects of ibrutinib. One patient had a grade 3 neutropenia that resolved after granulocyte colony stimulating factor (G-CSF) administration.

In summary, our data indicate that BTK inhibition may be an effective approach in the treatment of patients with cAIHA (CAD/CAS), regardless of underlying pathology or MYD88 mutational status, with a rapid and notable improvement of both the hemolytic anemia and acrocyanosis. A BTK inhibitor could be particularly useful in patients with CAD/CAS in whom chemotherapy fails or is considered too toxic. In particular, BTK inhibitors might be preferred over the novel complement inhibitors in patients with prominent acrocyanosis, which is not considered complement mediated.^{5,10} Limitations of this study are inherent to its retrospective design and the low incidence of CAD/CAS, including the potential for selection bias, the small number of cases, and the lack of a control group. Also, we cannot exclude the contribution of comedication given around the initiation of ibrutinib in 4 patients. Therefore, the data should be interpreted in this context until confirmed in a further prospective investigation of BTK inhibition in cAIHA.

All patients gave appropriate written informed consent based on local legislation. As we were not able to obtain informed consent from 1 patient, the local legal department gave approval to use the clinical information of this patient.

Authorship

Contribution: All authors were involved in data collection and the development of the manuscript; M.J., J.M.I.V., S.B., H.F., and S.D. designed the study; M.J. and J.M.I.V. analyzed the data; and all authors critically reviewed the manuscript.

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Footnote

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REFERENCES

- Berentsen S, Barcellini W, D'Sa S, et al. Cold agglutinin disease revisited: a multinational, observational study of 232 patients. *Blood*. 2020;136(4):480-488.
- Hansen DL, Berentsen S, Fattizzo B, Hansen PL, Barcellini W, Frederiksen H. Seasonal variation in the incidence of cold agglutinin disease in Norway, Denmark, and Italy. *Am J Hematol*. 2021;96(7):E262-E265.
- Randen U, Trøen G, Tierens A, et al. Primary cold agglutinin-associated lymphoproliferative disease: a B-cell lymphoma of the bone marrow distinct from lymphoplasmacytic lymphoma. *Haematologica*. 2014;99(3):497-504.
- Jäger U, Barcellini W, Broome CM, et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting. *Blood Rev*. 2020;41:100648.
- Berentsen S. How I treat cold agglutinin disease. *Blood*. 2021;137(10):1295-1303.
- Berentsen S, Tjønnfjord GE. Diagnosis and treatment of cold agglutinin mediated autoimmune hemolytic anemia. *Blood Rev*. 2012;26(3):107-115.
- Berentsen S, Randen U, Oksman M, et al. Bendamustine plus rituximab for chronic cold agglutinin disease: results of a Nordic prospective multicenter trial. *Blood*. 2017;130(4):537-541.
- Berentsen S, Randen U, Vågan AM, et al. High response rate and durable remissions following fludarabine and rituximab combination therapy for chronic cold agglutinin disease. *Blood*. 2010;116(17):3180-3184.
- Jäger U, D'Sa S, Schörgenhofer C, et al. Inhibition of complement C1s improves severe hemolytic anemia in cold agglutinin disease: a first-in-human trial. *Blood*. 2019;133(9):893-901.
- Gelbenegger G, Schoergenhofer C, Derhaschnig U, et al. Inhibition of complement C1s in patients with cold agglutinin disease: lessons learned from a named patient program. *Blood Adv*. 2020;4(6):997-1005.
- Röth A, Barcellini W, D'Sa S, et al. Sutimlimab in cold agglutinin disease. *N Engl J Med*. 2021;384(14):1323-1334.
- Berentsen S. Cold agglutinin-mediated autoimmune hemolytic anemia in Waldenström's macroglobulinemia. *Clin Lymphoma Myeloma*. 2009;9(1):110-112.
- Castillo JJ, Advani RH, Branagan AR, et al. Consensus treatment recommendations from the tenth International Workshop for Waldenström Macroglobulinaemia. *Lancet Haematol*. 2020;7(11):e827-e837.
- Treon SP, Xu L, Hunter Z. MYD88 mutations and response to ibrutinib in Waldenström's macroglobulinemia. *N Engl J Med*. 2015;373(6):584-586.
- Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. *N Engl J Med*. 2015;372(15):1430-1440.
- Vitale C, Salvetti C, Griggio V, et al. Preexisting and treatment-emergent autoimmune cytopenias in patients with CLL treated with targeted drugs. *Blood*. 2021;137(25):3507-3517.
- Fattizzo B, Barcellini W. Autoimmune cytopenias in chronic lymphocytic leukemia: focus on molecular aspects. *Front Oncol*. 2020;9:1435.
- Molica S, Polliack A. Autoimmune hemolytic anemia (AIHA) associated with chronic lymphocytic leukemia in the current era of targeted therapy. *Leuk Res*. 2016;50:31-36.
- Hampel PJ, Larson MC, Kabat B, et al. Autoimmune cytopenias in patients with chronic lymphocytic leukaemia treated with ibrutinib in routine clinical practice at an academic medical centre. *Br J Haematol*. 2018;183(3):421-427.
- Rogers KA, Ruppert AS, Bingman A, et al. Incidence and description of autoimmune cytopenias during treatment with ibrutinib for chronic lymphocytic leukemia. *Leukemia*. 2016;30(2):346-350.
- Manda S, Dunbar N, Marx-Wood CR, Danilov AV. Ibrutinib is an effective treatment of autoimmune haemolytic anaemia in chronic lymphocytic leukaemia. *Br J Haematol*. 2015;170(5):734-736.
- Hodgson K, Ferrer G, Pereira A, Moreno C, Montserrat E. Autoimmune cytopenia in chronic lymphocytic leukaemia: diagnosis and treatment. *Br J Haematol*. 2011;154(1):14-22.
- Jaeger U. Hot therapy for cold agglutinin disease. *Blood*. 2017;130(4):392-393.

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