effective and well-tolerated first-line treatment of adult LCH, except in patients with lung involvement and impaired lung function, because of IP-LCH or systemic disease with pulmonary involvement.[7] Moreover, it is also not clearly established whether IP-LCH may spread to other organs. Plasmatic and urinary cell-free DNA for KRAS^{G12D} defect research should therefore help answer this question.[3] Adding atorvastatin to smoking cessation or to other therapeutic approaches in IP-LCH, or even in systemic disease, could be a promising and harmless first-line treatment option.

Kamata et al hypothesized that atorvastatin acts in *KRAS* mutation-related IP-LCH via the suppression of mevalonate pathway upstream of isoprenoid lipids' production. These lipids are required for RAS prenylation and function. Because KRAS function is involved in inflammasome and NF-kB production of the proinflammatory interleukin-1b, atorvastatin could also act in IP-LCH by inhibiting this cytokine, which is pathogenic in ECD and possibly LCH.[8-10]

Even though the authors' work is exciting, there are 2 concerns: mouse models are not always comparable to humans and hope raised by the use of 3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitors in the treatment of the inflammatory component of mevalonate kinase deficiency have been rather disappointing so far. However, considering the widespread use and the relative safety of these drugs in clinical practice, their assessment in IP-LCH should be undertaken rapidly.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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Comment on Berentsen et al, page 537

Hot therapy for cold agglutinin disease

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In this issue of *Blood*, Berentsen et al report remarkably high response rates, long-term efficacy, and acceptable toxicity of rituximab with bendamustine in patients with primary cold agglutinin disease (CAD) evaluated in a prospective trial of the Nordic Group.[1]

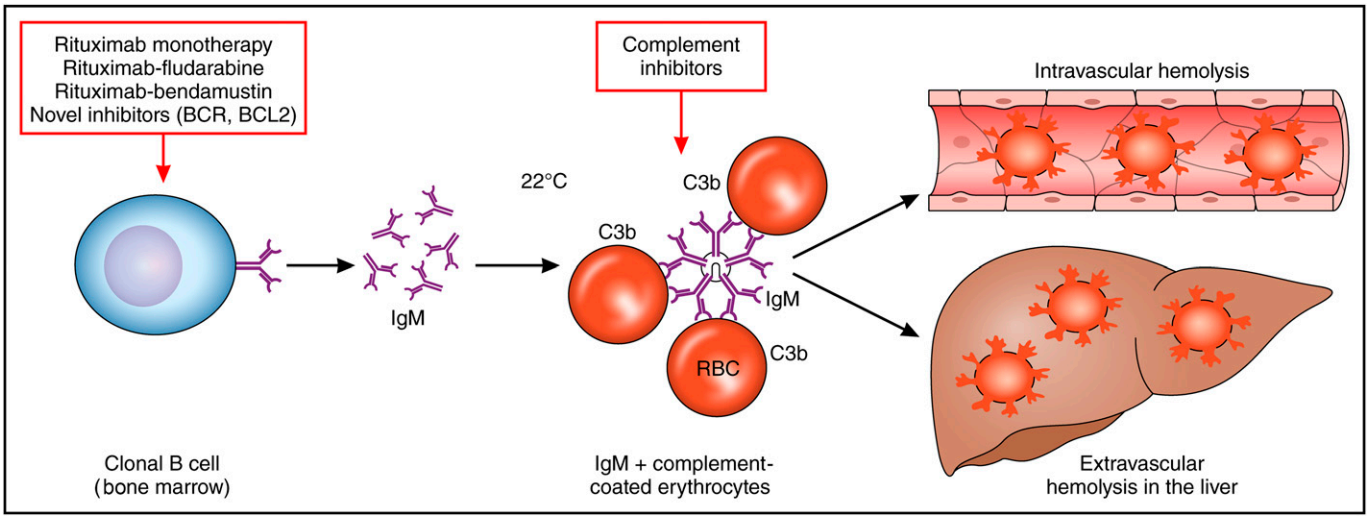
Primary CAD is a lymphoproliferative B-cell disorder resulting in autoimmune hemolytic anemia after exposure to low temperatures (see figure).[2] The antibodies produced are usually immunoglobulin Mκ (IgMκ) and directed against the I carbohydrate antigen on erythrocytes. Even in the absence of histological signs of lymphoproliferation, a clonal B-cell receptor rearrangement provides proof of its clonal origin in almost all patients. Further evidence of the clonality of this disease is the preferential use of certain B-cell receptors (IGHV4-34) and the detection of B-cell–specific mutations.[3,4] Binding of the IgM antibodies results in coating of erythrocytes with complement C3b and subsequent destruction by predominantly extravascular hemolysis.

While the disease is sometimes perceived as benign, the majority of patients need blood transfusions, and up to 20% suffer from thrombotic events. Moreover, cold-induced circulatory symptoms and anemia have a negative impact on the quality of life of patients, particularly during the winter months.[5,6]

There is currently no approved treatment for CAD, and instead of international guidelines based on standardized clinical trials, we have to rely on expert opinions.[7]

The best available treatment option is the anti–CD20 antibody rituximab. This results in overall response rates of 50% to 60%, but with a time to response of several weeks and a median response duration of only 11 months.[8] Given these unsatisfactory results, it seems appropriate to evaluate combination treatments of rituximab with chemotherapy for CAD, since its etiology and survival times are similar to those of an indolent B-cell non-Hodgkin lymphoma (median overall survival ~10 years). Berentsen and colleagues have previously investigated rituximab and fludarabine.[9] Now, the Nordic Group reports on the combination of rituximab with bendamustine given for 4 cycles in 45 patients.[1] The overall response rate was 71%, with a remarkably high complete remission rate of 40% and a median duration of response of 32 months. In addition to the resolution of anemia, complete histologic regression of B cell infiltrates was observed in 53% of patients. The overall outcome compared favorably to both rituximab monotherapy and rituximab-fludarabine. Toxicity was higher than with single-agent rituximab, but the rates of neutropenia (33% grade 3/4) and infections (11%) were lower than with rituximab-fludarabine. The data from this prospective multicenter trial are extremely valuable; controlled trials in rare diseases are hard to conduct.

Therefore, rituximab-bendamustine should be regarded as the current best standard



Etiology and treatment of primary cold agglutinin disease. Clonal B cells in the bone marrow produce IgMκ antibodies against the I antigen, which bind to erythrocytes (RBC) at low temperatures. This results in coating of erythrocytes with complement C3b and subsequent destruction by intravascular, but predominantly extravascular, hemolysis in the liver. Treatment strategies include (1) direct targeting of the B-cell clone by rituximab or rituximab-containing immunochemotherapy and possibly B-cell receptor (BCR) or BCL2 inhibitors, or (2) interference with complement coating or erythrocyte destruction.

for primary CAD as first or subsequent treatment in patients able to tolerate immunochemotherapy in whom the treatment goal is maximal suppression of the causal B-cell clone. However, there are a few remaining issues: (1) efficacy and toxicity must be weighed against each other, taking into account the severity of the CAD and the patient's fitness; (2) nonchemotherapeutic options, such as the inhibitors ibrutinib, idelalisib, or venetoclax, should still be evaluated in clinical studies; (3) and the late onset of response with all rituximab-based therapies leaves room for rapidly acting treatments, such as complement inhibition.[10]

Until further studies addressing these issues are conducted, rituximab-bendamustine, as shown by the Nordic Group's prospective study, should be one of our first choices when treating CAD patients.

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● ● ● THROMBOSIS AND HEMOSTASIS

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Microbiome influences von Willebrand factor

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In this issue of *Blood*, Jäckel et al define an unexpected role for the microbiome in regulating murine plasma von Willebrand factor (VWF) levels. In particular, commensal gut microbiota are shown to regulate VWF synthesis in liver sinusoidal endothelial cells through a Toll-like receptor-2 (TLR2)–dependent pathway. Collectively, these novel findings provide important insights into the biological mechanisms through which commensal microbiota may modulate cardiovascular pathology.[1]

In the normal population, plasma VWF levels demonstrate significant interindividual variation. This variation in VWF levels has direct translational significance. Elevated levels of the VWF–factor VIII complex are associated with