Autoimmune haemolytic anaemia (AIHA) is a collective term for several disorders characterized by autoantibody-mediated destruction of erythrocytes. AIHA are classified into warm-antibody and cold-antibody types, depending on the optimal temperature of action of the autoantibody. Primary chronic cold agglutinin disease (CAD) has been considered more difficult to treat than warm-antibody AIHA. This is because of the lack of efficacy of therapy with corticosteroids or other non-specific immunosuppressive agents.

Unlike patients with warm AIHA, who often have general immune system dysregulation, patients with CAD probably have competent regulation of the immune system, which explains the lack of association between CAD and other autoimmune disorders. An increasing bulk of data has shown that primary CAD is a clonal, lymphoproliferative bone marrow disorder, which is most often non-progressive and clinically non-malignant. It is not surprising, therefore, that non-specific immunosuppression or mild cytotoxic therapy usually fails to induce remission, while more specific and potent therapy directed at the pathogenic B-cell clone is more likely to succeed.

In this issue of Blood Transfusion, Gueli and colleagues describe a complete remission of more than 3 years' duration following treatment with rituximab and bendamustine in a heavily pre-treated patient with CAD not responding to previous chemotherapies. The combination was well tolerated. If representative, this first published case observation may provide a clue to new treatment options in this challenging disease.

**Primary or secondary: disease or syndrome?**

The patient described by Gueli et al. had a cold agglutinin-mediated haemolytic anaemia associated with a B-cell lymphoproliferative bone marrow disorder which was difficult to classify according to the WHO lymphoma classification. In a population-based study of 86 patients with CAD, a clonal bone marrow lymphoproliferation, frequently described as lymphoplasmacytic lymphoma, marginal zone lymphoma or unclassified clonal B-cell proliferation, was demonstrated by bone marrow biopsy in 75% of the patients and by flow cytometry in 90%. Undoubtedly, these patients represent the same majority that has traditionally been classified as having primary CAD. The patient described by Gueli's group did, therefore, have typical primary CAD.

Electrophoresis of the patient's serum showed no monoclonal protein, which is the case in less than 10% of patients with primary CAD. This is probably a matter of sensitivity of the electrophoresis. In the remaining majority, a monoclonal immunoglobulin (Ig) can be found by serum electrophoresis and/or immunofixation provided the blood specimen is kept at 37-38 °C from the time of being collected to removal of serum from the clot. The monoclonal Ig is usually an IgMk, while IgG, IgA or λ phenotype is found in a few per cent of patients. Cold agglutinins with anti-I specificity are typically present at high titres in the serum of untreated patients, and the direct antiglobulin test (DAT) is invariably strongly positive for complement protein C3d.

The terms CAD and cold agglutinin syndrome (CAS) have been used in the literature in a rather confusing manner. The well-defined clinico-pathological entity exemplified by Gueli et al. and comprehensively described by others should be called a disease, not syndrome. CAS should be used as a collective term for the far more uncommon, true secondary cases with much more diverse aetiology and pathogenesis.

**Therapeutic options and perspectives**

Not all patients with CAD require drug therapy. For those with mild disease, with very slight haemolytic anaemia and no or negligible cold-induced circulatory symptoms, the non-pharmacological management described in detail elsewhere should still be appropriate. A population-based study showed, however, that in most patients CAD is not an "indolent" disease in terms of major clinical symptoms and quality of life. The patient described in the case report in this issue of the journal suffered from severe anaemia, which is the case in one-third of patients with CAD when defined as haemoglobin <8.0 g/dL. About 90% of the patients have cold-induced ischaemic symptoms, varying from mild to disabling; and complement-induced exacerbation during febrile diseases has been observed in two-thirds. Active therapy should, therefore, probably be considered indicated more often than traditionally recommended in the literature. The results of such therapy have improved dramatically during the last decade.
Typically, given the persisting but undeserved popularity of corticosteroids in the treatment of this specific type of AIHA, the patient described by Gueli’s group had received steroid therapy without any improvement before being referred to their department\(^4\). Corticosteroids result in some degree of partial remission in less than 15% of patients with CAD; and the few patients who do respond, usually require unacceptably high doses in order to maintain the response\(^5\). Corticosteroids should not, therefore, be used to treat CAD\(^6,7\).

Rituximab monotherapy has been shown to induce partial remissions in about 50% of patients\(^8,9\). Those who experience relapse after having been previously treated with rituximab may respond to a second or even a third series of monotherapy with monoclonal antibody and the treatment is well tolerated. Despite a somewhat disappointing median response duration of about 1 year, single agent therapy with this rituximab should still be considered first-line treatment in some patients.

Combination therapy with fludarabine and rituximab is very efficient, resulting in remissions in approximately 75% of the patients, complete responses in 20%, and a median response duration of more than 66 months\(^10\). However, because of the toxicity profile, this treatment is not suitable for all patients with CAD requiring therapy\(^11\). Short-term toxicity including grade 3-4 neutropenia in approximately 40% of patients should lead to caution in the very old and comorbid patients; and the possible long-term leukemogenic potential may be a concern in the occasional young patients\(^12-18\). Nevertheless, the fludarabine and rituximab combination remains a well-documented and often successful choice in reasonably fit, elderly individuals as well as those patients in whom rituximab monotherapy has failed to induce remission.

It is to be hoped that future therapies directed at the pathogenic B-cell clone might be as efficient as the rituximab-fludarabine regimen but less toxic. Such new drug combinations would allow more CAD patients to achieve long-lasting improvement, possibly increasing the frequency of complete remissions and providing opportunities for those in whom treatment with rituximab-fludarabine fails. Although the possibility of successfully combining rituximab and bendamustine in CAD is far from being documented by this single case report, the observation by Gueli and colleagues\(^6\) is promising and should prompt systematic studies. Patients with CAD requiring therapy should be included in prospective trials whenever available.

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References


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