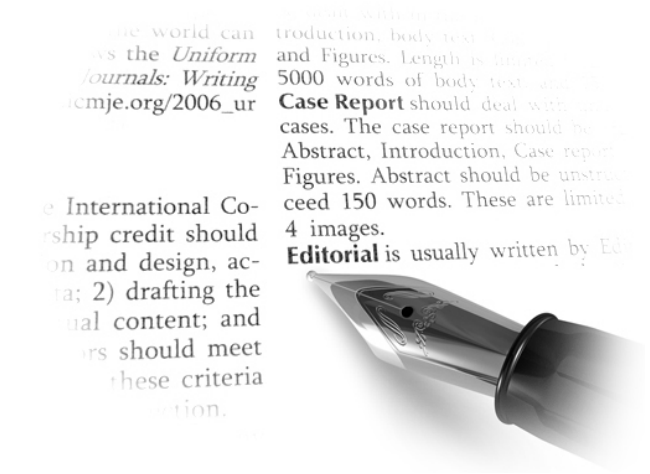

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Editorial

Diagnosis and treatment of autoimmune hemolytic anemia: classic approach and recent advances

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Autoimmune hemolytic anemia (AIHA) is an uncommon disorder characterized by hemolysis mediated by autoantibodies directed against self-red blood cells (RBC), with the incidence of 1–3 per 100,000/year and mortality rate of approximately 11% [1, 2]. AIHA is classified as warm AIHA (caused mainly by warm-reactive IgG-mediated extravascular hemolysis, comprising 75% of all AIHA cases), cold AIHA (usually due to complement-mediated intravascular hemolysis, comprising about 15%), and mixed type AIHA (less than 5%), based on the thermal range of autoantibodies involved in the pathogenesis [3].

The laboratory diagnosis of AIHA depends on the result of direct antiglobulin test (DAT) which shows positivity with anti-IgG (usually in warm AIHA) and/or anti-C3d (usually in cold AIHA) antisera, and also the presence of laboratory findings supporting hemolysis such as increase of serum lactate dehydrogenase (LDH), reticulocytosis and spherocytosis in peripheral blood smears. However, since DAT may produce false negative results (up to 10% of all AIHA cases) due to IgA autoantibodies, low affinity IgG or RBC-bound IgG below the detection threshold of the test, it is important to understand that not all AIHA cases show positive DAT results. For more sensitive diagnosis of AIHA, the uses of mono-specific anti-IgA antisera/low ionic strength solutions (LISS) and application of more sensitive techniques such as column agglutination test or flow cytometry can be considered [2, 4, 5].

The presentation of clinical symptoms is typically insidious over several months but some patients show acute severe symptoms. Presenting complaints of AIHA depends on the severity of anemia itself, ranging from asymptomatic compensated reticulocytosis with mild hyperbilirubinemia to acute fulminant hemolysis leading to jaundice, hematosplenomegaly, tachycardia and angina. Clinical features are determined by the presence of underlying diseases and degree of hemolysis, which depends on the autoantibody type. Patients with IgM warm-reactive AIHA are reported to have more severe hemolysis and higher death rates than those with other subtypes, and patients with cold AIHA tend to have more mild symptoms than those with warm AIHA [3]. The degree of anemia usually depends on the compensation represented by reticulocytosis and therefore, the patients with reticulocytopenia, which comprises 20% of adult and 39% of children patients with AIHA, would represent more severe clinical condition than those with reticulocytosis, and require strong RBC transfusion support [2, 6, 7].

The traditional treatment of warm AIHA was the use of corticosteroid as first-line therapy and conventional immunosuppressive drugs such as azathioprine and cyclophosphamide, or surgical splenectomy as second-line therapy in patients with insufficient response to corticosteroid. Recently, new therapeutic approaches such as the administration of rituximab (anti-CD20 monoclonal antibody),

erythropoiesis-stimulating agents, other immunosuppressive agents such as cyclosporine A (CsA), mycophenolate mofetil (MMF), danazol (synthetic anabolic steroid) have become available and there has been increasing evidence of success. These therapies can be applied in patients who show unsuccessful response to corticosteroid/splenectomy or relapse after splenectomy [2]. There is general consensus that corticosteroid is the first-line treatment for patients with warm AIHA, providing a response rate of 70–85%. However, approximately 20–30% of patients still need second-line therapy and corticosteroid is relatively contraindicated in patients with diabetes, uncontrolled hypertension, obesity, osteoporosis, peptic ulcer or children [2, 8]. Splenectomy is thought to be the most effective conventional second-line therapy, providing high initial response rates up to 82% in patients with warm AIHA. However, its superior efficacy over other second-line treatment options has not been confirmed, and both the lack of reliable predictors for outcomes and many surgical complications including the risk of overwhelming sepsis hinder wide application of splenectomy [2]. Rituximab (so called "medical splenectomy") is another effective second-line therapy, providing high initial response rates up to 87% and prolonged disease free survivals of 56% up to 2 years with reduced adverse reactions. However, the significant higher benefit of rituximab monotherapy beyond other treatment options has not been confirmed, and both unpredictable effect of treatment and low long-term (5 years) remission rates of 20% can be another obstacle in the wide application of rituximab monotherapy [2, 8]. Other therapeutic options such as danazol, CsA, MMF and erythropoiesis-stimulating agents have been reported to possess additional benefit in patients with warm AIHA, but their clinical benefits should be further validated in the future clinical trials. In patients with refractory warm AIHA, administration of high dose cyclophosphamide, alemtuzumab (anti-CD52 monoclonal antibody), or ofatumumab (anti-CD20 monoclonal antibody that targets different epitope compared to rituximab) can be considered as the "last option" treatments, although the toxicity of alemtuzumab hinder the wide application of this drug [2, 8].

RBC transfusions in patients with warm AIHA can theoretically have increasing risk of additional hemolysis. However, based on the belief that increased oxygen-carrying capacity provided by the transfused RBCs may be enough to satisfy patient's oxygen need until other treatment options become effective, RBC transfusion still has its clinical benefit as a supportive treatment option especially in patients with symptomatic cardiovascular diseases in which sufficient oxygen supply is important. A recent study demonstrated that regardless of autoantibody type, DAT specificity, DAT strength and corticosteroid therapy status, the transfusion of "the least incompatible" RBC to patients with autoantibodies yielded similar hemoglobin levels without increases of hemolysis risk compared with those with alloantibodies only and those with no antibodies who were transfused compatible RBC [9]. These findings support the benefit of RBC transfusion in patients with AIHA.

The treatment of cold AIHA should be confined to patients with symptomatic anemia and/or the presence of RBC transfusion dependences. RBC transfusion can be performed relatively safe compared to warm AIHA. The efficacy of corticosteroid treatment has not been confirmed, being effective in reduced fraction of patients up to 35%, and splenectomy is usually not effective since RBC destruction by C3b-mediated opsonization primarily occurs in liver, not in spleen. However, rituximab has been recommended as the first-line treatment in patients with cold AIHA, providing response rates of 60% and duration of median 1 year [2, 8].

In this issue of **Blood Research**, Prabhu *et al.* [10] reported single center data regarding the clinical characteristics and treatment outcomes in primary AIHA. This study showed similar patient distributions between warm AIHA (48% of total cases) and cold AIHA (46% of total cases), which is different from previous researches [1-3]. In addition, this study identified the trend of reticulocytopenia in patients with severe anemia, which is consistent with previous reports [2, 6, 7], but good response rates to corticosteroid in patients with cold AIHA as well as warm AIHA (92% and 87%, respectively), which is different results from previous reports [2, 8]. This study reflects the heterogeneity in the disease characteristics of AIHA, which requires further validation in terms of clinical characteristics and treatment outcome to various drugs used in patients with AIHA.

In conclusion, the improvement of drugs enabled more stratified approach for patients with first-line corticosteroid-refractory AIHA. It is current concept that the second-line therapy would be splenectomy and rituximab, and thereafter any of immunosuppressive drugs. RBC transfusion would be an effective supporting treatment option as a bridge therapy. Novel drugs can be considered as the final option in AIHA patients who are refractory to all other drugs. However, the choice of second or further-line therapies would depend on the clinician's personal experiences and opinions.

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