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**Case report 2**

# Successful treatment of refractory autoimmune haemolytic anaemia with a proteosome inhibitor: First reported case from Sri Lanka

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**Key words:** autoimmune haemolytic anemia, proteasome inhibitor

## Abstract

Autoimmune haemolytic anaemia (AIHA) is a haematological disorder with an incidence of 1-3 per 100,000 individuals/ year[1]. Around 40%-50% of AIHA cases are idiopathic[2]. We present a case of AIHA in a young boy who was refractory to multiple treatment lines, but eventually achieved complete remission after treatment with the proteasome inhibitor, bortezomib. The patient was refractory to multiple lines of treatment including prednisolone, intravenous immunoglobulin (IVIg), methylprednisolone, rituximab, cyclophosphamide and mycophenolate mofetil. He eventually had a beneficial response to a proteasome inhibitor-based combination with bortezomib plus mycophenolate mofetil. The treatment of refractory AIHA can be challenging. Patients with AIHA refractory to primary or secondary treatments must resort to receiving novel therapeutic modalities including combinations targeting plasma cell, T and B-cell proliferation.

## Introduction

Autoimmune haemolytic anaemia (AIHA) is a haematological disorder with an incidence of 1-3 cases per 100,000 individuals annually[1]. Its pathophysiology involves IgG, IgM, or both types of antibodies targeting antigens on red blood cells (RBCs), leading to premature destruction of erythrocytes through the reticuloendothelial or complement systems in the liver and spleen. Around 40%-50% of AIHA cases are idiopathic, primarily caused by immune system activation, deficiency, or dysregulation. The remaining cases are linked to conditions such as other autoimmune or lymphoproliferative diseases, immunodeficiencies, infections, pregnancy, solid tumors, allogenic stem cell transplants, and drug reactions[2]. Severe AIHA is defined when the unsupported haemoglobin (Hb) level falls below 80 g/L and transfusions are required at intervals of 7 days or less[3]. The mortality rate of primary AIHA is approximately 20% over a follow-up period exceeding four years, with infection, myocardial infarction, pulmonary embolism, and multiorgan failure accounting for the major causes of death[4]. The primary management strategy involves immune suppression with agents such as steroids, intravenous immunoglobulin (IVIg), rituximab, azathioprine, mycophenolate mofetil, cyclosporine, cyclophosphamide and splenectomy in resistant cases.

We present a case of AIHA in a young boy who was refractory to multiple treatment lines but eventually achieved complete remission after treatment with a proteasome inhibitor, bortezomib. This is the first reported case of successful use of bortezomib for AIHA in Sri Lanka.

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## Case report

A 19-year-old boy presented with severe anaemia (Hb 45 g/dL) and related symptoms. His past medical history and family history were unremarkable. On examination, he was pale and icteric had no lymphadenopathy or hepatomegaly, but showed mild splenomegaly (13 cm). His blood smear indicated features suggestive of immune haemolysis, megaloblastic anaemia and a thalassaemia trait. Haemolytic markers showed a reticulocyte count of 0.2% and indirect bilirubin of 9.1 µmol/ L. The direct antiglobulin test (DAT) was strongly positive (4+) with IgG 2+ and C3d 2+ specificity. A CT scan of his neck, chest, abdomen, and pelvis showed no signs of lymphoma or solid organ malignancies. Virology screen was negative including parvovirus serology. ANA was also negative.

His follow-up blood smears became leucoerythroblastic with evidence of dysplasia, prompting a bone marrow biopsy. The bone marrow revealed erythroid hyperplasia with dyserythropiesis, but no features of a haematological or non haematological malignancy. Due to reticulocytopenia and dysplasia, erythropoietin therapy was started. Initially, he was treated with intravenous (IV) methylprednisolone (1 mg/kg for 2 days) alongside B12 and folic acid supplements, but there was no response. He was then given intravenous immunoglobulin (IVIg) 1g/kg for 2 days, which raised his Hb to 80 g/L and was discharged on oral steroids. His Hb remained stable for 1-2 months, but returned with severe anaemia (Hb 31 g/L).

During this second presentation, his Hb stayed below 50 g/L despite repeated transfusions and he remained reticulocytopenic with a reticulocyte count between 0.05-0.3%. He showed mild indirect hyperbilirubinemia with normal LDH level and DAT remained positive for IgG and C3d. An ultrasound of the abdomen revealed moderate splenomegaly (16.6 cm). He was again treated with IVIg and methylprednisolone, while erythropoietin therapy was continued, but he did not respond and developed a type II myocardial infarction when his Hb dropped to 20 g/L.

Despite ongoing transfusions, his Hb remained critically low. He received IV rituximab (375 mg/m$^2$ weekly for 4 weeks) without success. Third line immunosuppressants were tried including cyclophosphamide, mycophenolate mofetil (MMF) and azathioprine with minimal effect. He underwent three cycles of therapeutic plasma exchange also with no significant response. Finally, he was treated with subcutaneous bortezomib (1.3 mg/m$^2$ on days 1, 4, 8, and 11 of a 21-day cycle for 6 cycles). He began to show improvement during the first cycle with his Hb rising to 70 g/L. Even before completing six cycles, he achieved complete remission (CR) with Hb of 12.1g/dl. Currently he remains in CR.

## Discussion

Managing and predicting the outcome of refractory AIHA remains a challenge. This complexity arises from the disease's intricate pathophysiology, patient variability and lack of large-scale clinical trials and standardized treatment protocols. The first line treatment for AIHA typically involves corticosteroids, which are effective in about two-thirds of patients[5]. However, the remaining one-third require additional therapies such as rituximab, splenectomy, azathioprine, cyclophosphamide and cyclosporine. Rituximab is the preferred second line treatment due to its higher effectiveness and tolerability[5].

Patients with AIHA often face infectious complications due to the immunosuppressive nature of their treatment, and those who undergo splenectomy are at higher risk for severe infections[6]. Additionally, venous thromboembolic events occur frequently in AIHA patients, with 15%-33% of adults with warm AIHA experiencing such events[7].

Most AIHA cases present with reticulocytosis, reflecting increased red blood cell production. However, in some cases, compensatory reticulocytosis may be insufficient or absent due to factors like marrow infiltration, vitamin deficiencies, infections (e.g., parvovirus B19) or autoimmune reactions against erythroid precursor cells[9]. In addition, reticulocytopenia can be observed in a minority of patients despite having evidence of erythroid hyperplasia in the bone marrow[10]. Reticulocytopenia in AIHA is rare and

indicates severe disease with a poor prognosis[8]. Reticulocytopenic AIHA is a medical emergency due to the high transfusion need, poor outcome and high mortality. There is evidence for the use of erythropoietin in such instances[11].

Reticulocytopenia in our patient also brought the suspicion of hyperhaemolysis syndrome, which is a rare complication of AIHA. However, his Hb didn't improve neither to transfusion free intervals nor to IVIg infusions.

Our patient was refractory to all standard lines of treatment during the first relapse, but obtained a complete response following bortezomib therapy. There are many case reports in literature where bortezomib (a 26S proteasome inhibitor) has been used as a successful therapy for immune haemolytic anaemia. Bortezomib inhibits the ubiquitin-proteasome pathway which then brings about apoptosis through an augmented unfolded protein response in antibody-producing cells[12]. Additionally, it has widespread immune system effects by downregulating NF-kB's inflammatory signaling, impairing antigenic presentation and depleting autoreactive T cells, B cells and plasma cells, thereby reducing antibody and autoantibody responses. Since AIHA is an autoantibody mediated process, agents suppressing B-cell and plasma cell autoimmunity have been proven effective in its therapy. In one case report, the authors successfully used bortezomib to treat a patient with pure red cell aplasia secondary to ABO-mismatched stem cell transplantation and used the same experience in a patient with cold agglutinin disease secondary to IgM κ monoclonal gammopathy. These findings support the use of bortezomib for treatment of AIHA by targeting plasma cells responsible for producing pathogenic autoantibodies[13].

Daratumumab is an IgG kappa anti-CD38 monoclonal antibody approved for treatment of plasma cell neoplasms. In another case report, a patient with AIHA following an allogeneic haematopoietic stem cell transplantation was successfully treated with daratumumab leading to improvement of haemolysis[14]. The role of complement is increasingly recognized in the etiopathogenesis of haemolytic anemias. Thus, the terminal complement inhibitor eculizumab is emerging as a novel treatment strategy for AIHA. In one trial, inhibition of terminal complement activation by eculizumab led to a significant reduction in haemolysis, decreasing anaemia, fatigue, and the need for blood transfusions[15]. Despite multiple treatment options many patients with AIHA remain refractory to treatment. Ongoing studies are exploring novel therapies targeting plasma cells, B-cell lineage and other pathways. For instance, there are ongoing clinical trials evaluating daratumumab, BTK inhibitors and other agents in adults with AIHA to advance current treatment. Future novel combination therapies hold promise. Further research and clinical trials are needed to achieve progress in therapy for patients with refractory AIHA. In the absence of high-quality evidence-based trials, case reports such as this provide important information on the management of severe refractory AIHA.

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