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The Successful use of Eculizumab to Switch off Haemolysis in Aggressive warm IgM Autoimmune Haemolytic Anaemia: Case Report and Literature Review

M Garg[1], S Agarwal[2] and M Altohami[1]
1 University Hospitals of Leicester NHS trust, Dept. Of Haematology.
2 Nottingham University Hospitals NHS trust, Dept. Of Radiology.

NHS University Hospitals of Leicester NHS Trust
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INTRODUCTION

Eculizumab is a recombinant humanized monoclonal antibody that targets complement factor 5 and prevents assembly of the membrane attack complex on membranes of target cells following initiation of complement cascade via classical or other pathways. In the UK, it is licensed for treatment of haemolysis in Paroxysmal Nocturnal Hemoglobinuria (PNH) and atypical Haemolytic Uremic Syndrome (aHUS). The role of Eculizumab in other Haemolytic conditions is not well defined. Here, we describe a case of aggressive warm IgM Haemolytic anaemia which failed to respond to standard therapeutic interventions but has responded to Eculizumab therapy with complete sustained remission, and present a literature review.

AIM

- Our patient had life-threatening haemolysis. Eculizumab use led to a dramatic response with immediate cessation of transfusion requirements.
- This is to our knowledge the first report of Eculizumab use for primary IgM warm AIHA.
- Most interest in the use of Eculizumab in immune haemolytic anaemia relates to cold agglutinins disease, where the pathogenetic role of complements is well known. Anti-complement therapy are not currently investigated in wAIHA.

Eculizumab

- Eculizumab is a recombinant humanized monoclonal antibody that targets complement factor 5 and prevents assembly of the membrane attack complex on membranes of target cells following initiation of complement cascade via classical or other pathways.
- We undertook extensive literature review that identified the off-label use of Eculizumab in 12 cases of immune haemolysis (5 CAD, 2 PCH, 1 ABO incompatible blood transfusion, 3 wAIHA, and 1 mixed AIHA) in addition to 2 patients with PNH who also had AIHA.
- Our case, to our knowledge, is the first report of Eculizumab use in primary IgM wAIHA.

Clinical Findings in IgM wAIHA

- Warm IgM AIHA is very rare. The largest case series to date has included 49 patients collected over 25 years in a reference laboratory receiving samples from across the USA.
- It has been reported in all age groups from early childhood to late adulthood and in the elderly.
- Haemolysis is usually florid leading to rapid drop in Hb and physiologic decompensation.
- A case fatality rate of 22% has been reported.
- Patients commonly acquire neurological deficits and systemic inflammatory response likely due to the uncontrolled complement activation, +/- physical properties of the warm reactive IgM.

Serological Characteristics of Warm IgM AIHA

Diagnosing IgM wAIHA is difficult and requires specialised testing.
In the largest serologic study in IgM to date, the following serologic findings were reported:

- Agglutination persisted in well-washed RBCs after centrifugation in 38/49.
- The agglutinins react optimally at 30 to 37, and the titre at 4 c is usually < 64.
- Using tube DAT method, 23/49 samples were positive for complements only, 3/49 were positive for IgM only and 9/49 were positive for IgM with C3, IgG or IgA.
- 18/24 samples were positive for IgM using FITC anti-IgM flow cytometry.

CASE REPORT

A 58 years old man presented to our hospital's emergency department with a 2 weeks' history of fever, shortness of breath, jaundice, headache, vomiting and very dark almost black colour urine. He started to feel unwell during a recent trip in Italy which he had linked to mosquito bites. He had an episode of generalized tonic seizure with eye rolling, stiffness, urination and loss of consciousness and came straight to hospital. Examination revealed pallor, icterus, and mild splenomegaly.
Initial testing showed Hb 63, WCC 16.3, Platelets 313, INR 1.2, APTT ratio 0.9, fibrinogen 3.7, creatinine 71, ALT 41, ALP 67, bilirubin 164, LDH 1607, B12 224, Folate > 20,Ferritin 1230, IgG 11.9, IgA 5.26, IgM 0.32 and plasma viscosity 1.51. Blood film examination showed spherocytes, irreversible agglutination, polychromasia and nucleated RBCs.
Monospecific DAT including IgG, IgM, IgA, C3d and C3c was done at our local laboratory and was negative. Repeat DAT testing at a reference transfusion laboratory showed 1+ IgM and negative IgG, IgA, C3c and C3d. A pan-reactive autoantibody was identified on Bio-Rad IAT and Bio-Rad enzyme IAT. Warm washed LISS tube IAT confirmed the absence of alloantibodies. BM biopsy revealed active trilineage haemopoiesis with megaloblastoid hyperplastic erythropoiesis and no evidence of lymphoproliferative disease.
Cultures were negative. Testing for HIV, HBV, HCV, Parvovirus B19, malaria, Treponemal antigen and fungal infections was negative. Serology for EBV and CMV was consistent with past exposure. ANA, ANCA and other autoantibodies, and cryoglobulin were negative.

CT scan of the chest, abdomen and pelvis showed splenomegaly of 16.3 cm but no evidence of lymphadenopathy or other malignancy. CT scan of the brain did not reveal any cause for the convulsions.
Patient was started on antibiotics, Rituximab as 375 mg/m2 weekly IV infusions, IVIG and MMF. As haemolysis continued to worsen and transfusion requirement was very high 20u/4d (total of 28u/8d), a decision was made to use Eculizumab in an attempt to control haemolysis. Blood product requirement and haemolysis markers immediately dropped following a single dose (figure 1). The patient is still in complete remission 24 months after his initial presentation.
During the inpatient stay, the patient went on to develop progressive hearing loss. Brain MRI with contrast showed bilateral labyrinthine haemorrhage and multiple cortico-medullary thrombotic microhaemorrhages.

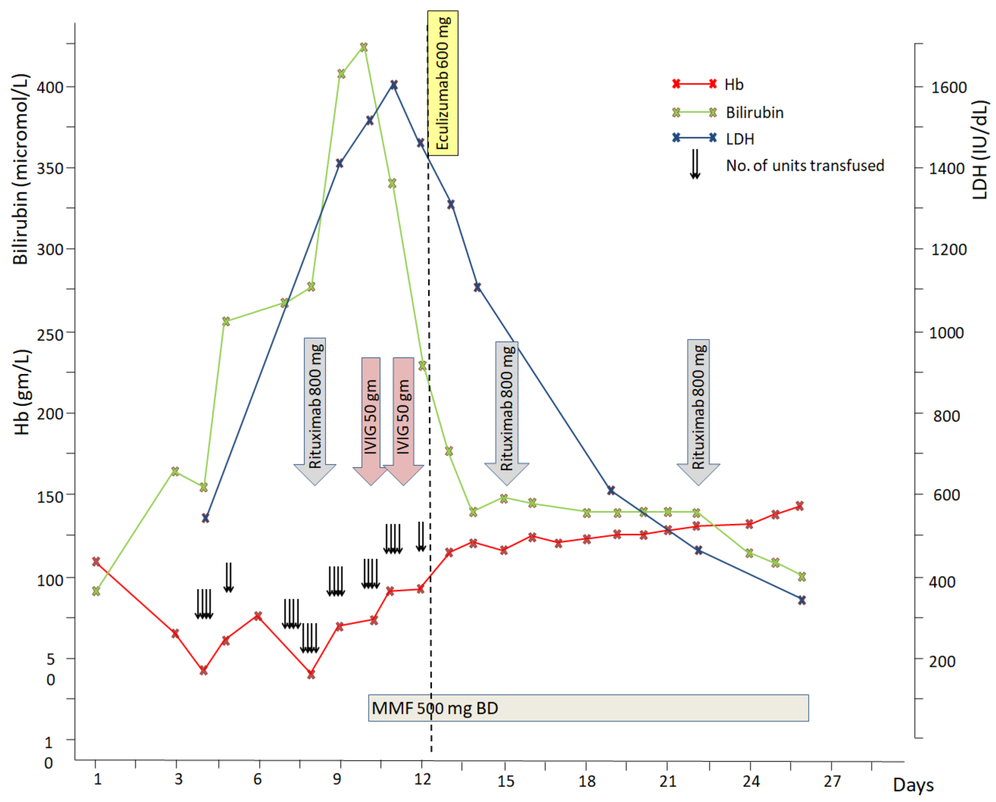

Figure 1: changes in Hb level, haemolysis markers and transfusion requirements in relation to therapeutic decisions.

CONCLUSIONS

IgM wAIHA manifests aggressive haemolysis and systemic inflammatory features, and is fatal in a large proportion of patients.

Our patient had life-threatening haemolysis. The administration of Eculizumab has resulted in immediate cessation of transfusion needs and reduction in haemolysis markers.

This, to our knowledge, is the first report of the use of Eculizumab in primary IgM wAIHA.

Immunosuppressive therapy for AIHA require time to work which ranges from days to weeks for steroids, several weeks for Rituximab and couple of months for immunosuppressive cytotoxic agents. Such a long wait is not possible for some cases with wAIHA that need an immediate control of haemolysis.

Complement inhibitors might have a role to play as a bridging therapy while other therapeutic modalities take full effect.

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CONTACT INFORMATION

drmohdomer@yahoo.com, OR: m.altohami@nhs.net .

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