

# Acute haemolysis secondary to low dose of intravenous immunoglobulins

ROZITA M, MOHAMAD FADLI AR, RIZNA AC

Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre (UKMMC),  
Jalan Yaacob Latif, 56000 Cheras, Kuala Lumpur, Malaysia

## ABSTRACT

Intravenous immunoglobulin is beneficial in treating lupus nephritis at various stages of treatment. It is generally well tolerated with mild and transient side effects. We report a case of a young man with recalcitrant lupus nephritis who was treated with three courses of intravenous immunoglobulin of 100 grams, 60 grams and 15 grams respectively within 5 months. During the last course, he developed acute haemolysis on day 3 of treatment; haemoglobin dropped by 3 grams, elevated lactate dehydrogenase, reticulocytosis and haemoglobinuria. Full blood picture revealed typical haemolysis findings. Immediate improvement was observed after stopping the immunoglobulin and with transfusion of 2 pints of packed cell.

**Keywords:** systemic lupus erythematosus, lupus nephritis, immune thrombocytopenic purpura, immunoglobulin

## INTRODUCTION

Intravenous immunoglobulin (IVIG) is a valuable fractionated blood product that contains > 90% of IgG and 10% of Ig M and IgA. It is widely used in various spectrums of autoimmune diseases including systemic lupus erythematosus (SLE) with or without renal involvement.<sup>1</sup> In Lupus Nephritis (LN), IVIG has been demonstrated to be beneficial at various stages of treatment.<sup>1</sup> At present there is no consensus on the IVIG dosing intervals and treatment duration. The most commonly used is 400mg/kg/day in 4-5 divided doses (high dose). Even though there are centres reported beneficial effects with a low dose regimen (85mg/kg/day in 4-5 divided doses), it was commonly associated with poor re-

sponse on thrombocytopenia, alopecia, vasculitic and proteinuria.<sup>2</sup> Generally, IVIG is well tolerated with mild and transient side effects. However, severe anaphylactic reactions, acute renal kidney injury, thromboembolic events, aseptic meningitis, neutropenia, pseudo-hyponatremia and autoimmune haemolytic anaemia (AIHA) have been reported in rare cases.<sup>3</sup> Significant haemolysis is reported to be between 1.6 to 6.7 % although the true incidence may be higher due to unreported cases of low degree haemolysis.<sup>4</sup> Most of the reported haemolysis was observed with high dose of IVIG. Here we report a case of acute haemolysis in a young man with refractory LN who received a total of 15 grams of IVIG (~0.2gram/kg).

**Correspondence:** Dr Rozita Mohd  
Department of Medicine, PPUKM, Jalan Yaacob  
Latiff, Cheras, 56000 Kuala Lumpur, Malaysia.  
Contact no: +60122022794, Fax no :  
+6091456934, Email : rozi8286@gmail.com

## CASE HISTORY

A 33-year-old man was diagnosed with SLE in 1998 with cerebral lupus and musculoskeletal

involvement. He was treated with high dose steroids, hydroxychloroquine and maintained with low dose steroid thereafter. He developed LN a year later requiring higher steroid dose and cyclophosphamide therapy followed by maintenance with cyclosporine A, azathioprine and low dose prednisolone. He achieved full remission with normal renal function and complete resolution of proteinuria.

Subsequently he developed multiple relapses of LN with/without autoimmune haemolytic anaemia in March 2004, May 2007, February 2009 and October 2011. During his last relapsed in 2011, intravenous cyclophosphamide was recommenced however it was prematurely terminated due to the development of left leg *Pseudomonas spp* cellulitis. Despite completed 6 week course of anti-pseudomonal antibiotic, he was readmitted in Jan 2012 with progressive severe nephrotic state with anasarca with autoimmune haemolytic anaemia precipitated by candidaemia. He also developed hospital acquired pneumonia and new areas of cellulitis due to *staphylococcus aureus* septicaemia and needed prolonged course of antibiotic and antifungal. He was covered with steroid of 1mg/ kg with IVIG 20grams/ day for 5 days. In March 2012, he developed sudden cortical blindness due to retinal vasculitis and developed recurrent seizure due to cerebral lupus. He was pulsed with low doses of IV methylprednisolone for 3 days, IVIG 20 grams daily for 3 days and commenced on IV rituximab 500 mg weekly for 6 doses. His vision improved and his renal function remained stable with creatinine of 200 umol/L despite persistent heavy proteinuria.

Two months later he presented with recurrent pseudomonas septicaemia with septicemic shock. His serum creatinine doubled, became oliguric and eventually requiring haemodialysis support. Clinically he remained in a severe nephrotic state with anasarca. He was started with intravenous immunoglobulin

on 11/5/2012 (5g twice/day) and 24 hours after receiving a total IVIG dose of 15grams, he was noted to have dark coloured urine and his haemoglobin level dropped from 10.4 g/dL to 7.6g/dL. His serum LDH was 2416 IU/L, Direct Coomb's Test was positive, peripheral blood smear showed reticulocytosis with spherocytes (Fig 1) and urine for haemoglobin tested positive (Fig 2). IVIG was discontinued and 5 days later his urine became clear and haemoglobin stabilised at 10-11 g/dL after transfusion of 2 pints of packed red cell.

## DISCUSSION

There are numerous literatures reporting the beneficial effects of IVIG in the treatment of LN<sup>1</sup>. However to date, it is mainly anecdotal. No solid recommendation available on the use of IVIG in LN treatment. The existing data demonstrated varied practices with the use of IVIG as part of induction protocol, whilst the others demonstrated its efficacy for maintenance or as a salvage regimen.<sup>1</sup> In our practice as described in this case, IVIG is being used primarily as a second line therapy in LN patients who failed the standard regimen with high dose corticosteroid and cyclophosphamide therapy or may be considered as a first line in conjunction with high dose corticosteroid in patients with concomitant autoimmune haemolytic anaemia due to active SLE.

Acute haemolysis has been increasingly recognized complication of IVIG. Recipients who are at high risk includes highly sensitized HLA patients or patients with underlying inflammatory state, non-O blood group especially blood group A, and higher titres of anti A/B in IVIG content.<sup>5</sup> There is no gender preponderance but one case series describes female predominance.<sup>6</sup>

IVIG related haemolysis is defined when haemolysis occurs within 10 days of IVIG exposure together with a positive direct antiglobulin test (DAT) and presence of at least two of other biochemical tests including

reticulocytosis, significant spherocytosis, elevated LDH, haemoglobinaemia, haemoglobinuria, unconjugated hyperbilirubinaemia and low haptoglobin levels. Most of the mentioned features were present in our patient except for a DAT which we didn't perform as the haemolysis evidence was classical. Based on the severity of grading, our patient would fall into the grade 2 category with a reduction of 3 grams in haemoglobin with the baseline of > 10g/dL.

A double hit mechanism has been proposed as a cause of haemolysis. Haemagglutination of red blood cells in the recipient following a passive transfer of anti A and anti B from IVIG were constituted the first hit whereas in the second hit it was believed due to accelerated removal of the sensitized red cells in patients with underlying inflammatory state.<sup>6</sup> Haemolysis was postulated will only be clinically significant when there is sufficient amount of anti A and anti B to activate complement with a sufficiently over-activated reticuloendothelial system.<sup>5</sup> Thus, it explains why acute haemolysis was normally seen with high dose of IVIG. In our case, we believe apart from the second hit phenomenon, the amount of anti A and anti B from 3 different courses of IVIG could have been accumulated and be sufficient enough to cause haemagglutinin during the third course of therapy despite lower doses compared to the reported literature. Furthermore he is blood group A positive which put him in the high risk category.

Once the haemolysis is recognized, the principle of management is by immediately stopping IVIG therapy. Replacement of blood group O transfusion has been recommended to prevent further antigen- antibody reaction in patients who had a positive DAT. In preventing haemolysis, there are strict recommendations on the preparation of IVIG which include the selection of donors, ratio of types of plasma, removal of haemagglutinins,

production of blood group specific products, rejection of batches with high agglutinins titres and cross matching with the recipient.<sup>5</sup> For patients with morbid obesity, a policy of ceiling dose of IVIG is advisable.

## **CONCLUSION**

With widely use of IVIG regardless of the disease indication, the clinician should aware of acute haemolysis even at low doses as it is potentially life threatening and patient receiving IVIG should be monitored for any reaction during the treatment.

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