HIGH-DOSE INTRAVENOUS IMMUNOGLOBULIN IN THE MANAGEMENT OF IMMUNE HEMOLYSIS IN PATIENTS WITH THALASSEMIC DISEASE : FACTORS WHICH DETERMINE REFRACTORINESS

Wanchai Wanachiwanawin[1], Pensri Pootrakul[2], Suthat Fucharoen[2] and Anong Piankijagum[1]

[1]Division of Hematology, Department of Medicine, Faculty of Medicine, Siriraj Hospital;
[2]Thalassemia center, Faculty of Graduate Studies, Mahidol University, Bangkok 10700, Thailand.

Abstract. We report our experience with high dose intravenous immunoglobulin (IVIg) in 3 thalassemic patients who had evidence of possible immune hemolysis. In 2 patients who had serious sepsis, their responses to IVIg were only partial and transient. The other patient who had marked splenomegaly had no evidence of response to IVIg. Both serious infections and large spleen may hamper the effect of IVIg and should be considered before IVIg is to be used in thalassemia.

INTRODUCTION

Thalassemia, both α- and β-, as well as hemoglobin (Hb) E are very prevalent in South-East Asia (Fucharoen and Winichagoon, 1987). β-Thalassemia/Hb E disease is one of the common forms of thalassemic disease found in Thailand (Wasi *et al,* 1969). Complex thalassemic syndromes such as Hb AE Bart's disease (α-thalassemia 1/ -thalassemia 2/Hb E) are also described (Wasi, 1981). In adults, patients with β-thalassemia-Hb E disease usually have more clinical problems than do the other forms. Varying degrees of severity in β-thalassemia/Hb E disease have been reported (Wasi *et al,* 1985). It may be affected by a number of factors including hypersplenism, infections, association with α-thalassemia, malnutrition, etc. A previous study revealed the high occurrence of a positive direct antiglobulin test in thalassemic patients (Krautrachue *et al,* 1980). This finding suggests that autoimmune hemolysis is another possible factor contributing to anemia in some cases of thalassemic diseases. Patients with severe forms of thalassemic diseases require frequent blood transfusions and alloantibodies against red blood cell antigens may develop (Sirchia *et al,* 1985). Alloimmune hemolysis may lead to refractoriness to subsequent blood transfusions.

Immune hemolysis in thalassemia, either auto- or alloantibody induced, presents a problem in clinical management. Susceptibility to infections during prolonged corticosteroid administration may increase morbidity and mortality in thalassemic patients (Aswapokee *et al,* 1988). Recently high-dose intravenous immunoglobulin (IVIg) has been used successfully for the management of chronic idiopathic thrombocytopenic purpura (ITP) (Fehr *et al,* 1982; Salama *et al,* 1983), and is possibly effective in autoimmune hemolytic anemia (MacIntyre *et al,* 1985). High-dose IVIg, therefore, should be a potential agent for therapy of immune hemolysis in thalassemia (Argiolu *et al,* 1990). We describe here an attempt to use a high-dose IVIg in 3 patients with thalassemic diseases who had episodes of immune hemolysis.

REPORT OF CASES

IVIg was administered in 3 patients with thalassemic diseases, two with β-thalassemia/Hb E disease and one with Hb AE Bart's disease, who had evidence of immune hemolysis. The clinical data are summarized in Table 1 and the description of the clinical course of each individual is presented as follows :

Table 1

Clinical features of 3 thalassemic patients receiving IVIg.

Patient/age/sex	Underlying disease	Spleen status	Nature of the immune hemolysis	Hb/Hct before IVIg	Dose of IVIg	Response to IVIg	Comment
1/33/M	β-thal/Hb E	splenectomy 23 yrs before	auto- and allo-antibodies	4 g%/13%	400 mg/kg/day × 3 days	partial and transient	died from uncontrolled infection
2/29/F	AE Bart's disease	10 cm below costal margin	autoantibodies	-/17%	400 mg/kg/day × 3 days	partial and transient	died from sepsis
3/40/M	β-thal/Hb E	12-15 cm below costal margin	alloantibodies	3 g%/-	400 mg/kg/day × 4 days	none	huge spleen

Patient 1 (PS: β-thalassemia/Hb E 57/1990)

A 33 year-old male with the diagnosis of β-thalassemia/Hb E disease was admitted in August 1990 because of paraparesis and severe anemia. Splenectomy was performed when he was 10 years old and his hemoglobin level was maintained at 6-8 g/dl without packed red cell (PRC) transfusion except during the episodes of infections and spinal cord compression from extramedullary hematopoiesis in 1985 and 1986. During the last 2 years, his hemoglobin level went down to 4-5 g/dl when he required frequent blood transfusions, 2 units monthly. Progressive paraparesis and incontinence of urination developed two weeks prior to the admission.

On admission he was moderately anemic with a hematocrit of 22%. Paraparesis with muscle power grade 1-2 were noted. He had fever and infiltration of the right lower lung was evident on the chest x-ray examination. To improve the symptoms of spinal cord compression, packed red cell (PRC) transfusion and administration of deep x-ray therapy to the spinal cord at lower thoracic level were planned. Unfortunately, a positive direct Coombs' test was recorded and alloantibodies to Jk^b and N blood group antigens were detected. Ten mg dexamethasone were then administered intravenously every six hours and one unit of the most compatible PRC was transfused. His hematocrit level gradually dropped from 22 to 19% and 14% during 4 days post PRC transfusion (Fig 1). He became deeply jaundiced and passed dark urine. Another unit of PRC was given without any improvement. Although the pyrexia disappeared, drowsiness was observed. Gram negative bacilli were recovered from hemoculture and a third course of cephalosporin was prescribed. Due to the evidences of uncontrolled infection and progressive severity of anemia, 400 mg/kg/day IVIg was infused intravenously daily for three consecutive days. Although his hematocrit value was stable at 14% after IVIg therapy for 7 days, he expired a week later (third week of hospitalization) due to complicated diabetes mellitus and progression of the pneumonia.

Patient 2 (KK : AE Bart's disease 15/1989)

A 29-year-old woman with AE Bart's diseases (α-thal 1/α-thal 2/Hb E) was admitted to Siriraj Hospital because of fever for 4 days. She had been asymptomatic until three years previously when she had exercise intolerance and progressive dyspnea. At first seen she was found to be moderately anemic and mildly icteric. She had a typical thalassemic appearance with prominent hepatosplenomegaly. Hematologic examination revealed hemoglobin 5.3 g/dl, hematocrit 22.5%, white blood cell count 4800/mm^3, neutrophils 56%, lymphocytes 43%, basophil 1%, platelet count 587,000 per cumm. The red cells were hypochromic, microcytic, with prominent anisopoikilocytosis and polychromasia. Hemoglobin electrophoresis showed hemoglobins A, E and Bart's (12% E, 7.3% Bart's). The patient required occasional PRC transfusion until 4 months before admission the requirement increased up to 2-3 units each month.

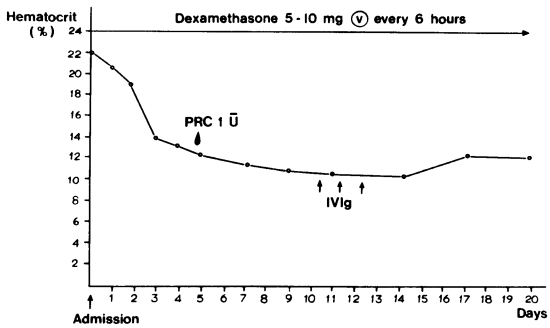

Fig 1—Time course of hematocrit levels in patient 1

Four days before admission she had high fever and watery diarrhea, followed by oliguria and increasing dyspnea. The physical examination revealed a pale, orthopneic patient. Three hours after admission she had hypotension. Dopamine was then administered to keep the systolic blood pressure at 100-110 mmHg. Two hours later she developed cardiac arrest. Cardiopulmonary resuscitation restored her vital signs and she was transferred to the intensive care unit. Ceftriaxone was administered to combat gram negative bacilli which were recovered from hemoculture and identified as *Escherichia coli* and *Klebsiella pneumoniae*. After 24 hours of admission her hematocrit level dropped from 18% to 7% without evidence of bleeding. The direct Coombs' test was strongly positive. Ten mg of Dexamethasone were then administered intravenously every six hours. Three consecutive units of PRC transfusion gave inappropriate and only transient rise of hematocrit value. High dose IVIg (400 mg/kg/day) was administered for three days with a transient improvement of anemia occurred, represented by an increase of the hematocrit from 17% to 20%. However, the hematocrit decreased to 15% 1-2 days after the last dose of IVIg. The clinical course was later stormy and she succumbed to uncontrolled infection after 26 days of admission.

Patient 3 (PSi: β-thalassemia/Hb E 43/1967)

A 40-year-old man with β-thalassemia/hemoglobin E disease was admitted for splenectomy. He had been found to have splenomegaly since childhood. Six years previously he had occasional episodes of low grade fever, exercise intolerance and anemia requiring 1-2 units of PRC each year. When he was first seen at Siriraj Hospital, he was found to be markedly anemic and have huge splenomegaly. Hematologic examination revealed hemoglobin 3.1 g/dl, hematocrit 9.3%, MCV 66 fl, MCH 22 pg, MCHC 33 g/dl, white cell count 7700/mm^3, neutrophils 56%, lymphocytes 44%. The platelet count was normal.

Packed red cell transfusions were ineffective. The hemoglobin concentration was only 5 g/dl after transfusion and it returned to the base-line level of 3 g/dl within one week. Although the direct Coombs' test was negative, he was found to have multiple alloantibodies, anti-Le^a, anti-Le^b, anti-E, C and S. Because of poor response to blood transfusion, hypersplenism was diagnosed and splenectomy was planned. Since the patient was severely anemic, attempts to raise the hemoglobin before splenectomy were made. Prednisolone 60 mg/day was ineffective, therefore 400 mg/kg/day of IVIg was administered for four days. There was no significant change of the hemoglobin concentration and splenectomy was done after the hemoglobin was raised to 5 g/dl by blood transfusion. After splenectomy the hemoglobin level was raised above 5 g/dl without blood transfusion.

Summary of the clinical data (Table 1)

Of 3 reported cases, two were β-thalassemia/hemoglobin E disease, one AE Bart's disease (α-thal 1/α-thal 2/Hb E). One β-thalassemia/hemoglobin E patient had been splenectomized since childhood; the other had marked splenomegaly (below the umbilicus). Immune hemolysis resulted from autoantibody or alloantibodies in patients 2 and 3 respectively. In patient 1 there was evidence of both auto- and alloantibodies. IVIg was used in a standard high dose of 400 mg/kg/day for 3-4 days. Two patients died subsequently from uncontrolled sepsis.

DISCUSSION

Association between thalassemia and autoimmune hemolytic anemia (AIHA) is well documented (Krautrachue *et al,* 1980). The autoantibodies could be either IgG, IgM or IgA and reacted to red cells at 37°C better than any other temperature. The pathogenesis of autoimmune hemolysis in thalassemia is unknown. Polyclonal activation is possible in thalassemic patients as demonstrated by increased levels of serum immunoglobulins in some patients (Wasi *et al,* 1971). Abnormal red cells in thalassemia may result in altered epitopes on the membrane antigens recognized by natural autoantibodies as occurs in senescent red cells or red cells in particular hemoglobinopathies (Lutz *et al,* 1988). There has been preliminary evidence of increased binding of immunoglobulins (Igs) and/or complement (C) on red cells and erythroblasts even from thalassemic patients without clinical AIHA (Malasit *et al,* submitted; Wiener *et al,* submitted). It is not known how much contribution is made by immune hemolysis to anemia in these patients.

Thalassemic patients who have severe anemia require frequent blood transfusions. These patients may develop alloantibodies against red cell antigens (Spanos *et al,* 1990). The occurrence of such alloantibodies may lead to immune hemolysis and subsequent unresponsiveness to blood transfusions. Auto- and alloantibodies may occur in the same thalassemic patient as was observed here in the patient 1.

Management of immune hemolysis in thalassemia can be difficult and complicated by the fact that thalassemic patients are susceptible to infections (Aswapokee *et al,* 1988). Infection itself may aggravate immune hemolysis and its occurrence may also make corticosteroids non-ideal agents for the treatment of immune hemolysis in thalassemic patients. Recently high dose IVIg has been proven to be useful in the management of ITP (Newland, 1986). The results of high dose IVIg in the management of autoimmune hemolytic anemia are conflicting (MacIntyre *et al,* 1985; Wendell *et al,* 1987). However there has been a report of successful management of autoimmune hemolytic anemia complicating thalassemia major (Argiolu *et al,* 1990).

The 3 reported thalassemic patients exhibited recently developed severe anemia, two with evidence of autoantibodies either alone or with alloantibodies, one with alloantibodies. In patients 1 and 2, infections played a major role in aggravating hemolysis while in patient 3 marked splenomegaly might have been responsible for severe anemia. High dose intravenous immunoglobulin (IVIg) was used in these patients after failure of corticosteroid administration. Serious infections in patients 1, 2 made the long term use of high dose corticosteroids impractical. We therefore tried high dose IVIg in these patients. Although IVIg may exert nonspecific, global immune suppression (Newland, 1988), its benefits are well known in patients with immunodeficiency who have serious bacterial infections. During the period of decreasing hematocrit IVIg gave partial and transient improvement of the anemia in both patient 1 (Fig 1) and patient 2. In patient 2, the initial improvement was no longer maintained after the second dose of IVIg. Both patients succumbed to uncontrolled infections shortly after IVIg was tried. The very transient response in our patients 1 and 2 suggests that initial reticuloendothelial Fc receptor blockade was overcome by overwhelming reticuloendothelial stimulation from uncontrolled sepsis.

IVIg had no effect on the hemoglobin concentration in patient 3. Unresponsiveness of the treatment suggests that hypersplenism rather than immune hemolysis may have played a role in precipitating the anemia in this patient. On the other hand, it may indicate that it is not possible to block a large pool of Fc receptors in a huge spleen.

From our experience with high dose IVIg in 3 thalassemic patients, we may conclude that although IVIg is potentially useful in management of immune hemolysis, its efficacy is limited by a number of factors such as ongoing systemic infections and large reticuloendothelial mass. Since IVIg is expensive, these factors should be considered in order to make its use cost effective.

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