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CONTROL OF BLEEDING ASSOCIATED WITH HEMOPHAGOCYTIC SYNDROME IN CHILDREN: An Audit of the Clinical use of Recombinant Activated Factor VII

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□ *This paper presents 2 cases of hemophagocytic lymphohistiocytosis (HLH) in whom recombinant factor VIIa (rFVIIa) was used for the management of hemorrhage. Both patients were diagnosed as HLH and were bleeding from the gut, which could not be controlled. Patients received rFVIIa at total doses of between 90 and 180 μg/kg body weight. Hemostatic affect was achieved in both of the patients but lasted only a short time. The response was achieved after 1 h of administration of rFVIIa, lasting for 24 h. The use of rFVIIa was well tolerated. These 2 patients suggest that rFVIIa is a beneficial agent in the management of hemorrhage in patients with HLH, although for a permanent homeostasis the control of primary disease is essential.*

Keywords hemophagocytic syndrome, hemorrhage, hemostasis, recombinant factor VIIa

Hemophagocytic Lymphohistiocytosis (HLH) is a disease of hyper-inflammation with particularly inadequate immune response [1]. It is a life-threatening disorder resulting in infiltration of different organs, especially liver, spleen, bone marrow, and central nervous system, with lymphocytes and macrophages with extensive hemophagocytosis [1, 2]. Being classified as primary and secondary, there is no clear-cut distinction between the two categories for clinical symptoms, documented infection and initial course of disease.

Primary HLH is an autosomal recessive disease that is due to mutations in the perforin, UNC13D, and syntaxin 11 genes [3]. Mutations in one of the three genes can be found in 80% of the Turkish patients [4]. Consanguineous marriages are very common, even reaching to 25% in some regions of Turkey, which causes the incidence of this autosomal recessive disease to be higher than in other countries.

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The diagnosis of HLH is often difficult and, in the past, it frequently could not be established before the patient's death [5, 6]. The main problem has been the lack of a specific marker for the disease, in which the clinical picture is nonspecific and mostly suggestive of disseminated infection or hematological malignancy. Mortality is high if the disease is not treated adequately. Besides hypofibrinogenemia and thrombocytopenia, a more profound and sometimes life-threatening coagulopathy may be the clinical presentation.

In this paper, we present 2 cases, one case of familial HLH, and a patient with Henoch-Schönlein-associated secondary HLH, whose diseases were uncontrolled and, furthermore, the clinical pictures were severe hemorrhage. We decided to administer recombinant factor VIIa (rFVIIa) to obtain sufficient hemostasis, when multiple surgical reexplorations and numerous transfusions of blood products (FFP, platelets, red blood cell concentrates) were no longer options. Recombinant factor VIIa was developed for the treatment of patients with hemophilia and inhibitors [7]. Recently, its use has been reported as a general hemostatic agent for coagulopathy or thrombocytopathy [8, 9].

The patients' parents were provided with information regarding the risks and benefits of using rFVIIa and written consent was obtained for each case.

CASE 1

A 1.5-year-old girl of consanguineous parents was admitted with abdominal distension. She was noted to have a submandibular lympadenomegaly sized 6 × 5 cm and hepatosplenomegaly. Hemophagocytosis was seen on bone marrow aspirate and a diagnosis of HLH was made. She was also evaluated for HLH gene mutations in Karolinska University but no known mutations were detected. Laboratory analyses revealed bicytopenia with white blood cell count (WBC), 8800/mm^3; hemoglobin (Hb), 6.5 g/dL; platelets, 23,000/mm^3; peripheral smear, 10% neutrophil; total cholesterol, 383 mg/dL; triglyceride, 891 mg/dL; ferritin, 1500 ng/mL (24–336); prothrombin time (PT), 15 s (10.8–13.9); activated partial thromboplastin time (aPTT), 43.2 s (26.6–40.3); and fibrinogen, 77.5 mg/dL (150–350). She received intravenous immunoglobulin (0.5 g/kg), steroid (10 mg/m^2), etoposide (150 mg/m^2), and cyclosporine (6 mg/kg) for treatment of HLH. After 1.5 months of treatment, a severe fresh rectal bleeding started and 4 bags of fresh frozen plasma, 2 bags of platelet from apheresis, and 3 bags of red blood cell units were transfused. The bleeding continued, which required transfusions at increasing frequency. Tranexamic acid (25 mg/kg) was administrated but no response was seen. As she continued to bleed and became hypotensive, inotropic support was given. Later, recombinant factor VIIa with a dose of 90 μg/kg (total: 4 mg) was given. The same dose

of rFVIIa was repeated 2 times at 2-h intervals. Bleeding ceased for 24 h, but restarted after this period. To control the bleeding 5 bags of red blood cell units and 4 bags of fresh frozen plasma was given. rFVIIa infusion was repeated with the same dose. After homeostasis was achieved, a laparotomy was performed to find the bleeding point. During laparotomy diffuse microvascular hemorrhage was detected, which filled the small bowel and colon with blood. Although a resection of 12 cm of ileum was performed, bleeding area could not be found and the patient continued to bleed. Small bowel histology showed evidence of a hemophagocytic lymphohistiocytic infiltration in mucosa, submucosa, and the muscle layer. Despite the surgery and intensive supportive care, the patient died of multiorgan failure shortly afterward.

CASE 2

A previously healthy 4-year-old boy presented with edema of his entire body. Physical examination revealed pretibial edema and palpable purpura. Laboratory analyses revealed WBC, 21,400/mm^3; Hb, 9.6 g/dL; platelet, 244,000/mm^3; PT, 11.7 s; aPTT, 28.4 s; D-dimer, 978 μ/L (50–285); total protein, 4.5 g/dL; albumin, 2.2 g/dL; +3 proteinuria, +2 hematuria in the urine, which suggested a diagnosis of Henoch-Schönlein purpura (HSP) nephritis. During follow-up his urine output decreased and he was started on hemodialysis. Hemoglobin had fallen to 6.5 g/dL, but no hemolysis was seen in peripheral smear and direct Coombs was negative, which were investigated to rule out the diagnosis of hemolytic uremic syndrome. After bicytopenia (Hb, 5.6 g/dL; platelet, 54000/mm^3), ferritin (1328 ng/mL), and triglyceride (401 mg/dL) were detected, the diagnosis of HLH secondary to HSP was considered. Massive oral and rectal bleeding began and in spite of 8 bags of red blood units, 4 bags of platelets from apheresis, and tranexamic acid treatment, he continued to pass melena stool despite a normal coagulation profile. A dose of 90 μg/kg (total: 3 mg) rFVIIa was infused. There was a 2-h interval between the 2 doses, and thereafter bleeding ceased for 2 h. Because of the cost of rFVIIa and because the bleeding-arrested time interval was short, no additional dose was given to the patient and bleeding restarted immediately after 2 h. Soon after, the patient died despite intensive blood component transfusions. An extensive surface area of ulcerated bowel mucosa due to vasculitis was detected in laparoscopic biopsied material, just before his death.

DISCUSSION

HLH is characterized by hypercytokinemia. This condition leads to disseminated intravascular coagulation and thrombocytopenia [1]. The

continuous effect of hypercytokinemia and infections activates platelets and the clotting system, resulting in consumption of clotting factors and a decrease in platelet count [1, 2]. It may be associated with serious hemorrhagic diathesis. Treatment is supportive, including replacement with red blood cells and platelet suspension. We used rFVIIa as an alternative treatment in these cases and hemostatic effect was achieved in both of the patients, but was short-lived. As a result of hemorrhagic diathesis, an excessive use of platelets and fresh-frozen plasmas are needed. In our cases, bleeding could not be controlled despite massive substitution of blood, fresh-frozen plasmas, thrombocytes, and other hemostatic drugs.

rFVIIa was originally designed to treat life-threatening bleeding in patients with hemophilia A or B with inhibitors. Now it is being used successfully in patients with severe hemorrhage for varying reasons [8–10]. In HLH the experience with rFVIIa is very limited. There is one case report where excessive bleeding that occurred due to HLH was successfully stopped with rFVIIa [11].

Although the exact mechanism of rFVIIa is not clear, it seems to initiate thrombin formation in interaction with tissue factor, and higher doses activate factor X binding to activated platelets, leading to thrombin formation. Both tissue factor-dependent and -independent enhancement of thrombin generation has been suggested to play a role. Thrombin has many functions, including activation of platelets through their thrombin receptor, the cleavage of fibrinogen to produce fibrin, and the subsequent stabilization of clot by the actions of activated factor XIII [8].

Therefore, rFVIIa seems to be effective in generating thrombin formation where this is needed, also in patients with a deficiency of clotting factors and thrombocytopenia and thrombocytopathy [8]. This may explain the successful outcome in our cases.

The most important side effect of rFVIIa is the potential to induce thrombotic events. When administered at pharmacological doses, rFVIIa circulates at a concentration 1000 times greater than normal. It would be expected that a systemic hypercoagulable state would be precipitated [8, 12]. There were no thrombotic events in our patients. The administration of rFVIIa achieved a hemostatic affect but lasted for a short time. The first patient was not transfused for 24 h. She needed additional treatment of rFVIIa to achieve hemostasis for surgery. At the second patient, hemostasis lasted a shorter time. We believe that rFVIIa can be useful for diseases in which supportive treatment is not sufficient to control the bleeding. We thought that rFVIIa would be more effective if we were able to use it at the beginning of bleeding. At the terminal period, the effect of this product would not be permanent, which is important for cost-effectivity.

Because of its high cost and the lack of controlled studies, the use of rFVIIa is limited to special clinical situations. Nevertheless, its application should be considered when conventional options are exhausted and it

seems to be indicated by the prognosis of the patient. In our patient rFVIIa was not able to act as a lifesaving agent, as patients were not in remission from their disease, although it was able to control excessive intractable bleeding for a while.

REFERENCES

[1] Henter JI. Hemophagocytic lymphohistiocytosis (HLH). *Hematol/Oncol Clin North Am.* 1998;12:417–433.
[2] Janka GE, Schneider EM. Modern management of children with hemophagocytic lymphohistiocytosis. *Br J Hematol.* 2004;124:4–14.
[3] Zur StadtU, Schmidt S, Kasper B, et al. Linkage of familial hemophagocytic lymphohistiocytosis (FHL) type-4 to chromosome 6q24 and identification of mutations in syntaxin. *Hum Mol Genet.* 2005;14:827–834.
[4] Janka GE. Hemophagocytic lymphohistiocytosis. *Hematology.* 2005;10:104–107.
[5] Palazzi DL, McClain KL, Kaplan SL. Hemophagocytic syndromes in children: an important diagnostic consideration in fever of unknown origin. *Clin Infect Dis.* 2003;36:306–312.
[6] Kakkar N, Vasishta RK, Banerjee AK, Marwaha RK, Thapa BR. Familial hemophagocytic lymphohistiocytosis: an autopsy study. *Pediatr Pathol Mol Med.* 2003;22:229–242.
[7] Scharrer I. Recombinant factor VIIa for patients with inhibitors to factor VIII or IX or factor VII deficiency. *Hemophilia.* 1999;5:253–259.
[8] Aitken M. Recombinant factor VIIa. *Emerg Med Australas.* 2004;16:446–455.
[9] Mittal S, Watson HG. A critical appraisal of the use of recombinant factor VIIa in acquried bleeding conditions. *Br J Hematol.* 2006;133:355–363.
[10] Laffan M, O'Connell N, Perry D, Hodgson A. Analysis and results of the recombinant factor VIIa extended-use registry. *Blood Coagul Fibrinolysis.* 2003;14(Suppl 1):S35–S38.
[11] Miller CG, Stringer MD, Sugarman I, Richards M. The use of recombinant factor VIIa for bleeding in paediatric practice. *Hemophilia.* 2005;11:171–174.
[12] Roberts HR, Monroe DM, Hoffman M. Safety profile of recombinant factor VIIa. *Semin Hematol.* 2004;41:101–108.