CASE STUDY 1

Inhibitor Patient Requiring High Dose Therapy with rVIIa as well as Sequential Therapy with FEIBA

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A 30-year-old man from Mexico presented with hematuria. He was wheelchair-bound due to hemiparesis resulting from a traumatic spinal cord bleed at age 3. He had developed a right calf pseudotumor involving the fibular head. He had been treated with cryoprecipitate and red cell transfusions in Mexico until roughly 2003, when factor concentrates became available. He emigrated to the USA in 2006 and presented to the HTC for comprehensive care. He was known to have an FVIII inhibitor which was said to be low titer and low responding. He clinically responded to FVIII infusions.

His initial evaluation at our HTC revealed a Bethesda titer of 5 BU as well as infection with HIV and hepatitis B. He had frequent urinary tract infections due to a neurogenic bladder, requiring intermittent straight catheterization.

The patient underwent a right leg amputation below the knee for control of his expanding pseudotumor with hemostasis provided by FVIII given by continuous infusion. FVIII levels were maintained at 100% for 1 week, then b.i.d. bolus dosing was maintained for a further week. The Bethesda titer rose and peaked at 28 BU. Hemostasis was then maintained using rVIIa.

At the time of this episode, the patient had been dosing with rVIIa, 90–100 mcg/kg every 2 h × 3 doses daily without improvement in hematuria and mild right flank pain. His hemoglobin had fallen from his baseline of 9.5 to 6.6 g/dL. A CT scan of the abdomen and pelvis showed a right ureteral filling defect without other masses or hydronephrosis.

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High doses of rVIIa up to 270 mcg/kg every 2–3 h failed to lead to hemostasis, and he eventually required sequential therapy with APCCs for cessation of hematuria.

Two months later, he was re-admitted due to bilateral deltoid hematomas from immunizations administered in another clinic. He could no longer push himself in his wheelchair, and rVIIa was providing unreliable hemostasis at home. He began ITI with monoclonal FVIII at 100 units/kg b.i.d. He subsequently had no further bleeding episodes, and his Bethesda titer reached 0 within 4 months.

Q1	What are the rationale and the data supporting the use of rVIIa at doses higher than 90–120 mcg/kg?

We presume that the rate of thrombin generation is critical for the formation of a stable fibrin clot. However, the exact relationship between the bolus dose of rVIIa administered and the patient's level of thrombin generation has yet to be defined. Substantial inter-individual variation in thrombin generation has been shown following rVIIa treatment: doses of 90–120 mcg/kg may, in some individuals, be sufficient to produce enough thrombin, whereas other patients may require higher, recurrent dosing.

Dr. Salaj and colleagues (2009) analyzed the bleeding patterns of Czech adult hemophilia patients with high responding inhibitors obtained by the HemoRec registry. In this retrospective analysis, patients who were treated after 2 h of bleeding onset experienced fewer rebleeding episodes when high-dose rVIIa was used (15.8% and 0%; <120 mcg/kg and >250 mcg/kg, respectively). Initial high-dose rVIIa was also associated with a decline in total rVIIa consumption.

A number of case series have also investigated the use of high-dose rVIIa in the treatment of bleeding episodes in inhibitor patients. For example, Kenet and colleagues (2003) assessed the efficacy and safety of a rVIIa "megadose" (300 mcg/kg bolus) as treatment for bleeds in three young inhibitor patients. Of 114 bleeds, 95 responded to a single dose. Pain relief was faster and therapy duration significantly shorter than with continuous infusion (CI) regimens or standard boluses (90 mcg/kg every 3 h). Rebleeding occurred in 9.6% of cases, and 19 of 114 episodes required a second bolus injection. They concluded that treatment of bleeds with a rVIIa megadose in young inhibitor patients is effective and well tolerated.

In summary, some patients clinically fail to respond to standard dose rVIIa. In these patients, it may be reasonable to carefully titrate the dose of rVIIa upward until a clinical response is achieved.

Q2	What are the rationale and the data supporting the use of sequential bypassing agent therapy?

Approximately 10–20% of bleeding episodes cannot be controlled with a single bypassing agent. There have been case reports as well as case series describing the use of rVIIa, followed by an APCC. In these cases, the addition of FXa is felt to contribute to the thrombin generation achieved by rVIIa alone. This has been shown by in vitro experiments on thrombin generation in a cell-based model of hemostasis. This should be considered a salvage maneuver, because of the increased risk of thrombosis. Indeed, elevated D-dimer levels have been seen in some patients treated with this protocol. Drs. Ingerslev and Sørensen (2011) reviewed 17 reports detailing the parallel use of bypassing agents in the same bleeding episode in 49 patients. Five of nine patients with hemophilia developed thrombotic events. Five of 40 patients with congenital hemophilia with inhibitors also had thromboembolic events. Four cases were fatal. If this regimen is used, careful monitoring for thrombotic events is critical.

Q3	When should ITI be considered in an adult inhibitor patient?

In general, immune tolerance therapy (ITI) is most successful when undertaken in patients whose inhibitors have been present for a shorter period of time. Some adult patients have had their inhibitors since childhood, however, without being offered ITI. If these patients experience significant numbers of severe bleeding episodes and have morbidity associated with them, then it is reasonable to consider undertaking ITI. The patient should have no contraindications, such as an inability to adhere to a stringent medical regimen, chronic dental or dermal infections which are likely to lead to CVAD infections, or lack of insurance coverage.

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