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Acquired Hemophilia A after Stem Cell Transplant for Sickle Cell Disease: Treatment with Recombinant Porcine Factor VIII (OBI-1) and Tolerance Induction with Rituximab/Prednisone

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Hematopoietic stem cell transplantation (HSCT) has been employed to treat sickle cell disease in select patients with appropriate donors. In light of the morbidity of myeloablative conditioning regimens used for treatment of malignant hematologic diseases, transplant strategies with minimal conditioning and closely matched (typically sibling) donors have been developed. The goal is to minimize transplant morbidity/mortality and graft-versus-host disease (GVHD), as well as to decrease the amount of immunosuppression required to prevent graft rejection. Currently, in sickle cell anemia patients at NIH who have undergone non-myeloablative conditioning (300 cGy + alemtuzumab) and sibling donor (8/8 match) HSCT maintained with sirolimus, 87% (27/31) have been converted from sickle cell anemia phenotype to normal without graft-versus-host disease or major complications from the transplant [1, and unpublished data]. Treatment of a FVIII inhibitor in a HSCT recipient presents additional challenges, since maintenance of the graft that restores normal hematopoiesis is critical. We describe management of a case of acquired hemophilia A in a sickle cell anemia patient following HSCT.

Case Report

A 44 year old African-American asplenic male with sickle cell disease (HbSS) underwent allogeneic HSCT in September 2009 at the National Institutes of Health (NIH). Upon engraftment, the patient had 97% donor myeloid and 30% donor lymphoid chimerism, and was free of his sickle cell disease with a HbA of 97%. Post-transplant he was maintained on sirolimus for GVHD prevention, Bactrim for PCP prophylaxis, and PCN-VK as pneumococcal prophylaxis due to absence of his spleen. Twenty-eight months later, he experienced onset of minor soft tissue hemorrhage associated with a long aPTT and low

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Martin Lee was a consultant to Inspiration Biopharmaceuticals, Inc., the holder of the OBI-1 IND before Baxter Healthcare.

FVIII activity (14% of normal). Other pertinent coagulation studies were normal (not shown).

FVIII levels ranged from 10–14% for two months, but he then had acute onset of pain, swelling and decreased grip strength in the right hand, consistent with a compartment syndrome. He was treated initially at a community hospital with Humate-P® at a dose of 3000 U every 12 hours, which normalized the aPTT and corrected the FVIII to 121% permitting emergency fasciotomies of the palmar and volar surfaces of the forearm. Both fasciotomy wound sites were covered by split thickness skin grafts harvested from the anterior right thigh; hemostasis at all sites was satisfactory, and blood loss was minimal. He was then transferred to a tertiary care center for ongoing treatment. After 4 days' treatment on the same 3000 U Q 12 hour dose of Humate-P®, peak FVIII levels declined to only 18%.

He was transferred to NIH and was empirically switched to Kogenate® due to in vitro mixing studies suggesting less FVIII inhibition of this product (data not shown). There was no improvement after Kogenate® (Figure 1) and he was then treated with NovoSeven® at doses of 90 µg/kg Q 4 hours, starting eleven days after surgery. Despite inhibitor bypassing therapy, the patient had recurrence of forearm pain, swelling, decreased grip strength, decreased range of motion, and numbness in the right hand, consistent with renewed bleeding. His human FVIII inhibitor titer was 12 BIAU, but < 1 BIAU for porcine FVIII. Recombinant porcine FVIII (OBI-1) was obtained under IND 10695 (Baxter Healthcare Corporation, Westlake Village, CA) and a first dose of 200 units/kg was given 16 days after his fasciotomies. A FVIII level of 540 U/dL was obtained 20 minutes after the first treatment, and the volume of distribution was 2652 mL and the half-life was 16.3 hrs. The patient's upper extremity was elevated with a custom sling and within 8 hours the pain was diminished (4/10 vs. 7/10), and grip strength measured by dynamometer went from 8 lbs. to 55 lbs. compared to unaffected left hand grip strength of 110 lbs.

A second OBI-1 dose of 100 units/kg was given three days later (19 days after surgery). A FVIII level of 621 U/dL was obtained 20 minutes later and the volume of distribution was 2287 ml with a half-life of 14.7 hrs. Within two weeks the patient had improved range of motion, pain-free status, and right hand grip strength of 82 lbs. The patient's grip strength was restored to 101 lbs with a physiatry and occupational therapy hand program.

Rituximab and high dose corticosteroids were started concomitant with porcine FVIII treatment. After 375 mg/m² rituximab weekly times two, and a third dose of 100 mg/m² times one, the inhibitor titer to human FVIII declined from 12 BIAU to less than 0.5 BIAU within three weeks (Figure 2), and there was no loss of donor erythropoiesis (HbA remained >96%). Concomitantly, the patient's endogenous FVIII rose to >100% of normal by day 22, and remained normal after completion of three doses of rituximab and a complete taper of prednisone over the next two months.

PCR amplification of donor and recipient DNA showed that the patient had an H2 FVIII haplotype sequence and the female donor was heterozygous for the FVIII H1 and H2 haplotypes. Mixing studies suggested less activity against Kogenate® (an H1 haplotype) than other FVIII products. Assay of stored samples (Figure 2) showed that before the

compartment syndrome the inhibitor titer (4.2 BIAU) against a recombinant H2 haplotype FVIII (Recombinate®) was higher than that (1.9 BIAU) against a recombinant FVIII with H1 haplotype (Kogenate®). However, by the time of his compartment syndrome his inhibitor reacted equally to all forms of FVIII. No inhibition of OBI-1 porcine FVIII was seen prior to treatment, or in the 90 day period after treatment (Figure 2).

IgG anti-FVIII antibodies were detected in archived samples from the time of transplantation, two years before the compartment syndrome. These persisted well after the FVIII level was normal and the inhibitor was absent (Figure 3a). IgG₄ subclass antibodies to FVIII (Figure 3b) showed anti-FVIII IgG₄ antibodies only at the time of the acquired hemophilia (from January 2012 to March 2012). After March 2012, when IgG antibodies to FVIII were still detectable, IgG₄ antibodies were absent. IgG₄ antibodies were more reactive against Recombinate® (H2 haplotype) than Kogenate® (H1 haplotype) or Xyntha® (indeterminate haplotype) in January 2012 (onset of bleeding) and were first detectable to Recombinate® in September 2011, when IgG₄ antibodies to Kogenate® or Xyntha® were not detectable (Figure 3b). At the peak of the bleeding, IgG and IgG₄ antibody titers to FVIII were equal for all FVIII variants tested.

We restored normal hemostasis in our patient with OBI-1 (recombinant porcine FVIII), thereby averting permanent damage to his right arm from a compartment syndrome. This gratifying result was due to the lack of reactivity of the patient's inhibitor with OBI-1; further, he did not make antibodies against porcine FVIII following treatment. This is similar to the experience in acquired hemophilia with Hyate C®, a plasma-derived porcine FVIII product no longer available [2, 3].

We also eliminated the inhibitor with rituximab and prednisone while preserving his normal hematopoiesis. Due to the 10–14% residual FVIII activity and lack of serious bleeding we were initially reluctant to undertake an immunosuppression regimen that might endanger his transplant. When forced to act by the compartment syndrome, we used rituximab and prednisone rather than cyclophosphamide, hoping not to harm normal donor erythropoiesis.

That FVIII-binding IgG antibodies were present two years before the onset of acquired hemophilia is consistent with the finding that 3% to 19% of normal people have FVIII binding antibodies [4–6]. However, only IgG₄ anti-FVIII antibodies are specifically associated with acquired hemophilia and inhibitors in patients with hemophilia A. The IgG₄ subclass antibodies were likely the causative agents of bleeding in our patient, since they were detectable only at the time of bleeding episodes. Early in the course of his acquired hemophilia the titers of IgG₄ FVIII binding antibodies were higher against Recombinate® (an H2 haplotype FVIII) than Kogenate® (an H1 haplotype FVIII). In contrast, IgG antibodies titers were actually higher against Kogenate® than Recombinate®.

Tiede *et al* demonstrated that exposure to exogenous FVIII through transfusion (or pregnancy) may contribute to inhibitor risk [7]. Viel *et al* [8] showed that African-Americans with congenital hemophilia A have a higher risk for inhibitor development and FVIII inhibitors are more likely to have uncommon FVIII haplotypes not seen in Caucasians. Our patient was hemizygous for FVIII haplotype H2 and his donor was heterozygous for H1 and

H2. We speculate that “mismatch” of factor VIII haplotypes between donor and recipient might have contributed to inhibitor development, but we cannot prove this in a chimeric immune system that was in part from a donor heterozygous for factor VIII H1 and H2 haplotypes.

Regardless of the mechanism by which the inhibitor arose in our patient, this case serves as a useful example of successful management of bleeding with OBI-1 and subsequent elimination of the inhibitor without disrupting his stem cell transplant.

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Figure 1.

Factor VIII levels during NIH admission for continued treatment of compartment syndrome of the right forearm. Human factor VIII (Humate-P® and Kogenate®) were administered with no increment in factor VIII level, followed by multiple doses of recombinant human factor VIIa, then two doses of OBI-1 (recombinant porcine factor VIII) at 200 U/kg and 100 U/kg.

Figure 2.

Factor VIII inhibitor titers prior to treatment with OBI-1, and subsequent inhibitor eradication with rituximab/prednisone. Factor VIII inhibitor titers to human and porcine factor VIII (a), and inhibitor titers to defined factor VIII haplotype plasma (b). Bethesda inhibitor assays done with Nijmegen modifications. In panel (a) R indicates rituximab 375 mg/m² (long arrow) or 100 mg/m² (short arrow).

Figure 3. Factor VIII-binding antibodies with specificity to various recombinant forms of factor VIII, measured by sandwich ELISA: (a) IgG isotype antibodies; (b) IgG₄ subclass antibodies.