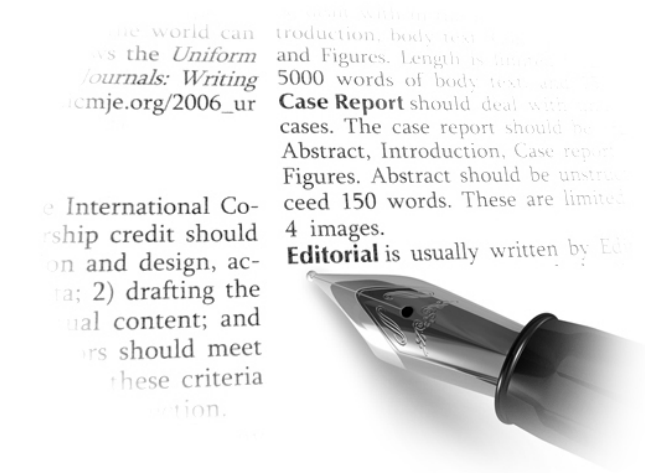

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Editorial

Attempts to treat patients with hemophilia, the "royal disease"

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"Our poor family seems persecuted by this awful disease, the worst I know." Queen Victoria (1819–1901) of the United Kingdom of Great Britain and Ireland wrote in her diary. She is well known as the most famous carrier of hemophilia, the "royal disease", and had passed on the disease to several royal families in Europe through her daughters.

Since first described in a hemophilia patient by Lawrence and Johnson in 1941 [1], inhibitor development has been the most serious complication of hemophilia A treatment. Inhibitor development occurs in up to 36% of patients with severe hemophilia A [2, 3]. The inhibitor is an alloantibody against factor VIII (FVIII), which if developed during hemophilia treatment, impairs FVIII activity and thus neutralizes the effect of the "factor replacement" therapy, leading to increased complications and therapeutic cost [4]. Some genetic and environmental risk factors for inhibitor development are well known; however, it is still unclear why some, but not other patients, develop inhibitors. The inhibitors in hemophiliacs may be temporary or can be eradicated with immune tolerance induction (ITI) therapy. The recent study (International Immune Tolerance Study) of 115 "good-risk" subjects with severe hemophilia A and high-titer inhibitors showed that there was no difference between the low-dose (50 IU/kg 3 times/week) and high-dose (200 IU/kg/day) regimens in achieving tolerance, with the former taking longer [5]. These data might be important for nations with limited resources. Although the eradication of inhibitors and recommencement of FVIII replacement therapy is a long-term goal in treating inhibitor patients, ITI therapy has limited indications and a success rate of 63–80% [6].

Patients with high-titer inhibitors and intractable bleeding episodes should be given recombinant activated factor VII (r-FVIIa) or activated prothrombin complex concentrate (aPCC), called the hemostatic bypassing agent (to circumvent FVIII in the coagulation pathway), as the first choice therapy. The FEIBA NovoSeven Comparative (FENOC) Study evaluated the hemostatic efficacy of both products on 96 joint bleeds of 48 inhibitor patients and showed nearly equivalent efficacy, with both agents being effective and safe, although a substantial number of patients reported different efficacies for both agents [7]. Nevertheless, 10–20% of bleeding events in hemophiliacs with high-titer inhibitors cannot be controlled by either r-FVIIa or aPCC alone and thus may need sequential combined bypassing therapy (SCBT).

The rationale for the use of a combination of r-FVIIa and aPCC is based on data from experiments using a rabbit stasis model, where an early thrombotic effect was shown, indicating the synergistic effect of both agents on thrombus formation during stasis [8]. Clinically, SCBT is predicated upon the fact that neither bypassing agent controls bleeding completely and the response of each individual patient to either agent differs [9]. These aspects were also observed in the FENOC study [7], where up to 43.8% of subjects considered one product more effective than the other.

A recent study employing a comprehensive literature search revealed that a significant number of patients treated with SCBT experienced complications such as thrombosis:

5 of 9 patients with acquired hemophilia and 5 of 40 with congenital hemophilia, among which 4 cases were fatal [8]. Moreover, no randomized controlled study has been carried out to investigate SCBT. Hence, the sequential use of both bypassing agents should have strict indications as mentioned earlier and should be accompanied by a thorough follow up to assess for thrombosis, including disseminated intravascular coagulation.

In the current issue of **Blood Research**, Han and Park report their retrospective experience with the use of SCBT to treat 5 bleeds in 4 hemophilia A patients with high-titer inhibitors and refractoriness to both bypassing agents used individually [10]. The bleeds were associated with various clinical conditions: peripherally inserted central catheter (PICC) insertion, small bowel surgery, hemothorax, and 2 total knee replacements. Patients were treated by infusing aPCC every 8 or 12 hours with administration of 1 or 2 doses of r-FVIIa between the doses of aPCC (50–100 IU/kg aPCC and 90 μg/kg r-FVIIa). The dosage and intervals were similar to those used in previous studies [7]. Twelve- to 24-hour bleeding episodes were controlled satisfactorily with no thrombotic events associated with SCBT. Because there is a paucity of data on the treatment of high-titer inhibitor patients, this report contributes valuable information for the management of bleeding episodes in such patients in Korea. It is hoped that a prospective, randomized, and controlled study of SCBT will be carried out in Korea in the near future to overcome the limits of this retrospective study.

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