ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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A Preventive Approach to the Management of Severe Hemophilia A

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H&O How is severe hemophilia A currently managed?

LV The management of severe hemophilia A involves a multidisciplinary approach with a team that includes hematologists, nurses, physical therapists, social workers, nutritionists, and psychologists. The role of the orthopedic surgeon has diminished, primarily because of the more widespread use of preventive treatment in the form of prophylaxis. Since 1965, cryoprecipitate has been available to treat bleeding. With improvements in the purification of proteins, therapy advanced through plasma-derived products and is now based on recombinant products. With safer and purer high-quality products, prophylaxis is clearly the standard of care at this point. The incidence of joint disease has been diminished.

H&O What improvements are needed in the management of hemophilia A?

LV The current factor products are infused intravenously. Venous access can be difficult, especially in young children. Adults can also have problems with venous access, either because of scarred veins or joint disability that precludes their physical ability to receive infused factor concentrate. The other main problem with the current intravenous factor product is the half-life; these drugs must be infused frequently, usually 2–3 times per week, in order to provide near-complete protection. Most efforts in drug development are focused on extending the half-life, both for factor VIII and factor IX. The goal is to develop an oral drug or an intravenous drug that could be administered once a week or, optimally, every other week. A third issue involves the extremely high cost of these products, which limits availability for certain groups of patients in the United States and, worldwide, precludes treatment for probably 90% of hemophilia patients, who live in developing and underdeveloped countries.

H&O Could you please discuss your recent study comparing prophylaxis regimens in hemophilia A?

LV This international, multicenter study involved patients with severe hemophilia A. All patients were treated first with an on-demand regimen for 6 months. Afterward, they were randomized to receive prophylaxis with factor VIII in 1 of 2 regimens. The first was the standard regimen that is used internationally: factor VIII at a dose between 20–40 IU/kg administered every 48 hours, usually every other day. The second regimen was an experimental arm consisting of a pharmacokinetically tailored dose that was patient-specific to provide protection on a 3-day dosing schedule. Patients in this arm first underwent a pharmacokinetic analysis, which assessed their recovery of the factor and the half-life. Based on this analysis, a calculation was performed in order to determine the optimal dose that would maintain a factor VIII level exceeding 1%

at 72 hours, the time at which the next dose would be scheduled. That dose was then administered every third day over the course of 1 year.

The results were remarkable. Both prophylaxis regimens reduced the annual bleeding rate—the number of bleeding episodes per year—from approximately 44 episodes during the on-demand period to 1 or fewer episodes in either of the prophylaxis periods.

H&O What are some areas of future research in this field?

LV The key issue will be to determine the impact of these types of dosing regimens on joint outcomes, an area not specifically assessed in this study. Although data were collected regarding soft-tissue bleeding and joint bleeding, there was no formal assessment of the joint outcomes. In future studies, we would hope to determine whether these pharmacokinetically-driven regimens can avoid the development of joint disease in patients who present without it, and, in other words, maintain the stability of joints and prevent further deterioration in joint function in patients with existing disease.

Suggested Readings

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