Letter to the Editor

Response to "Innovation in Hemophilia Therapies—'And Miles to Go, before [We] Sleep'"

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We read with interest the correspondence by Farugia,[1] in response to several articles appearing in a recent issue of *Seminars of Thrombosis & Hemostasis*.[2–5] These comments provide us with an opportunity to offer additional considerations, related both to the correspondence[1] and also to our own manuscript published in that issue.[2]

Following the cloning of *F8* and *F9* genes more than 30 years ago, replacement therapy for persons with hemophilia (PWH) has witnessed an exciting era, owing to the development of recombinant products (from first-generation products to the last generation of products expressing extended half-life), which combined several technological solutions aimed to improve both hemostatic efficacy and safety.[6,7] In parallel, continuous improvements in terms of purity and viral inactivation of plasma-derived factor VIII (FVIII) and factor IX (FIX) products, along with recent results from the SIPPET study,[8] which documented their higher FVIII inhibitor safety profile over earlier recombinant products, have rendered the FVIII products of this newer class a very attractive therapeutic option for PWH. In this scenario, it is clear that the therapeutic armamentarium for hemophilia A and B is now well supplied, with more than 50 plasma-derived and recombinant products currently licensed worldwide,[9] and thus we believe that the greater availability of a large number of factor concentrates with different pharmacokinetic properties will provide an overall positive clinical outcome in an era of increasingly personalized therapy for PWH.

Another, but no less important, aspect is the increasing level of competition among different commercial products, which it is expected to have beneficial economic effects, as emphasized by Farugia.[1] Unfortunately, this is not always true and there are some countries (like Italy) where the price of available factor concentrates still remains too high. This phenomenon is difficult to reconcile, as many currently available recombinant products have been on the market for more than 25 years, so that their initial (expensive) development costs have been fully compensated during their many years of commercialization. Perhaps a national, rather than regional, centralization of the contracts for hemophilia therapy could have a positive effect in lowering the prices of these products.

Our last consideration is in regard to the newer therapies, still under investigation, but not based on deficient factor replacement, which have also been discussed by us in the highlighted issue of *Seminars in Thrombosis & Hemostasis*[2] as well as elsewhere.[9,10] The results of preclinical and early clinical studies clearly show that the therapeutic utilization of these innovative agents is not meant to replace current products for hemophilia therapy but to be complementary to them. We believe that the goal of these drugs is that of postponing the exposure to exogenous FVIII and FIX, thus minimizing or at least delaying the risk of developing inhibitors, which are currently the most serious complication of hemophilia therapy. Such a novel therapeutic strategy would have a beneficial effect not only on the quality of life of PWH but also on economic implications, considering the high costs related to the management of hemophilia patients with inhibitors.[11] Thus, when considering these innovative therapies, we must place in balance not only their likely higher costs but also those saved from the reduction of the incidence of treatment-related complications.

In conclusion, we want to highlight that thanks to so much progress made over the past 50 years, there is no doubt that among the most frequent monogenic inherited disorders (cystic fibrosis, thalassemia, muscular dystrophy), hemophilia currently enjoys the most efficacious and safe treatment.

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