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EDITORIAL

Hemophilia treatments and the paradox of choice

In 2002, when an Irish patient was asked about what choice he had for his hemophilia treatment in the 1980s, he jokingly said, left arm or right arm for the infusion. At the time, the number of available products was very limited, and the medical profession was paternalistic, making most of the decisions on patient treatment. This contrasts with the number of available treatments today [1] and the use of shared decision-making in assisting treatment choice [2].

Very few, if any, inherited diseases have seen the number of available treatments increase as much as hemophilia. Until 10 years ago, the treatments were the result of the evolution of purer recombinant products until they contained no human or animal proteins and through modifications extending their half-life, so less frequent administration was required. The extension of half-life for factor (F)IX products was much more impressive from the start, resulting in them being used for prophylaxis once a week or less frequently. Until recently, the extension of FVIII half-life using pegylation or by linking it to the Fc fragment of immunoglobulin was much more modest, resulting in the ability to use them for prophylaxis twice a week [1]. The recent introduction of Altuviiio (Altuvoct in Europe) (Sanofi-SOBI) has meant that there is now a FVIII concentrate with a truly extended half-life, allowing for prophylaxis once per week linked to greater protection [3].

The last 5 years have seen a revolution in the treatment of persons with hemophilia with the introduction of 3 classes of alternative non-FVIII/IX replacement products: the bispecific antibody mimetic, rebalancing agents, and gene therapy treatments. The introduction of the bispecific antibody, emicizumab, has been dramatic, with a major impact in severe hemophilia A, especially in those with antibodies to FVIII (inhibitors), where the annual bleed rate with this subcutaneous therapy is now around 1 bleed per year [4]. Emicizumab has also had a major impact on the treatment of hemophilia A without inhibitors, where in many countries it is now the treatment of choice. It has also freed newly diagnosed children and their parents from the burden of regular intravenous infusions and prevented the requirement for central venous access devices. The rebalancing agents that can be used for prophylaxis are about to enter the market for prophylaxis for all persons with hemophilia, but the real unmet need is hemophilia B with inhibitors for whom there are currently no other good treatments. Their impact on hemophilia A without inhibitors, hemophilia A with inhibitors (where emicizumab is an established therapy), and hemophilia B without inhibitors is more difficult to predict. Gene therapy has been considered a major breakthrough, but the high cost, variability in response, and durability issues in the case of hemophilia A have limited its impact so far [1].

The result of the evolution and revolution of effective and safe hemophilia treatments has been a dramatic improvement in both life expectancy and quality of life of affected individuals. One hundred years ago in Sweden, the mean life expectancy of persons with severe hemophilia was 12 years of age, while in 2023, in the United Kingdom, this increased to 78 years, just short of the United Kingdom's mean life expectancy of the male population at 82 years [5,6]. We have now seen persons with severe hemophilia climb Everest, compete professionally in the Tour de France, compete in triathlon events, and even live to almost 100 years of age; one of our persons with severe hemophilia A in Sheffield died during the COVID-19 pandemic, 3 months before his 100th birthday.

There is a common misconception that the increase in number of available products makes the choice of what to choose easier, but this is not the case. In his classic book, The Paradox of Choice, Barry Schwartz shows how the dramatic explosion of choice in everyday life has paradoxically become a problem rather than a solution [7]. Individuals feel happier when they are given a simple choice, but when the number of choices increases, the degree of happiness diminishes. With the added complexity of choice, clinicians and hemophilia patient organizations must take a more nuanced approach to education, taking time to explain options to patients, providing educational materials that are comprehensible, and employing a medium that patients will use (Table). The World Federation of Hemophilia shared decision-making tool [1] is an example of a useful tool that can be used to help prepare patients for therapy decisions. We are slowly moving away from the situation where the patient is informed what his treatment will be, followed by a discussion on how this fits with their life and planned activities. We are moving toward an initial discussion on the patient's life goals and planned activities and then examining the treatment options that will best facilitate these. This is a paradigm shift in thinking.

The choice of hemophilia treatments is unfortunately only a distant dream for most of the world's hemophilia population living in resource-poor countries and where having any treatment is a luxury [1]. The World Federation of Hemophilia Humanitarian Aid program saves and transforms lives, but it is not a long-term solution, although it can be a step toward sustainable care in countries [8]. The increasing range and complexity of therapies available can be an advantage to

TABLE Factors contributing to the choice of product.

Route of administration: subcutaneous vs intravenous
Plasma-derived vs recombinant
Standard vs extended half-life
Prophylaxis alone or for both prophylaxis and treatment
Risk of inhibitor development
Clotting factor concentrate vs nonfactor therapy
Repeated dosing vs one-off gene therapy
Long-term safety established vs uncertain
Product approval and marketing in the country of residence
Cost
Reimbursement and insurance system in a country

countries in seeking more cost-effective options and, therefore, more availability as competition increases, if countries have an effective procurement system. Some of the highly effective new treatments are relatively easy to manufacture, and when the patents run out, it may be possible to manufacture them generically and make them available to those countries that can pay very little for hemophilia treatments. If it is possible to provide regular medications against HIV in resource-poor countries, it should be possible to also provide hemophilia treatments for the same populations.

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The authors contributed equally to the writing of the manuscript.

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