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Molecular Therapy

Cell Phones and Landlines: The Impact of Gene Therapy on the Cost and Availability of Treatment for Hemophilia

Hemophilia treatment evolved rapidly in the latter half of the twentieth century, a period during which the disease went from one that was nearly always fatal in childhood or adolescence for those severely affected to one that is now, although still a chronic condition requiring lifelong medical management, characterized by a nearly normal life span and quality of life for those who have access to optimal treatment.[1]

Advances in blood fractionation brought on by World War II led to the realization that hemophilia could be ameliorated by transfusion of plasma, which contained the clotting factors that were missing in these patients. The development of cryoprecipitate by Judith Graham Pool in 1964 concentrated factor VIII by a factor of 10 over the concentration in plasma, making normal hemostasis a possibility for people with severe hemophilia A.[2] Further purification efforts resulted in purified lyophilized plasma proteins that could be stored at home and mixed and self-infused on demand upon the first signs of a bleed. Thus, hemophilia became one of the first diseases to be treated with enzyme replacement therapy, which led to marked improvement in both the length and quality of life.

That the plasma concentrates put patients at risk for viral hepatitis[3] seemed a modest price to pay for these advances. However, the arrival of HIV in the blood supply in the early 1980s resulted in the infection of most patients with severe hemophilia in the Western world.[4] As controversies raged over how to ensure the safety of plasma-derived concentrates, biotechnology companies developed and licensed recombinant clotting factor concentrates in the late 1980s, providing a safe alternative that was free from the risks of viral bloodborne diseases. More recently, advances in donor screening and testing, along with enhanced viral reduction and elimination processes, have eliminated the risk of HIV and hepatitis C virus transmission in the current generation of plasma-derived products.

Today, the management of severe hemophilia in the Western world is based largely on studies pioneered by Inge-Marie Nilsson and her colleagues at the Swedish hemophilia centers,[5] which established that prophylactic infusions of clotting factor concentrates two or three times a week, with a goal of maintaining factor levels in the blood at >1% of normal at all times, could prevent most of the serious and life-threatening bleeds in hemophilia.[6] However, the need for frequent and lifelong intravenous infusions, coupled with the high costs that prevent access to treatment for most of the developing world's hemophilia population, has continued to motivate the search for better treatments and, ultimately, for a cure.

The cost of the current optimal treatment regimen for an adult male patient with severe disease in the United States has been estimated to be $300,000/year.[7] The obvious corollary of this is that countries with lower gross national product levels cannot afford optimal medical management for their citizens with severe hemophilia. For those in less prosperous countries, life expectancy and quality of life are lower, and for those in the poorest nations, with limited access both to factor concentrates and to medical expertise, the disease is still fatal in childhood and adolescence.[1]

It is against this backdrop that the current developments in hemophilia gene therapy must be considered. Nathwani and colleagues, in a trial jointly sponsored by St Jude Children's Research Hospital and University College London, recently reported that intravenous infusion of an adeno-associated viral–8 (AAV-8) vector expressing a self-complementary, codon-optimized human *F9* gene has given rise to long-term (observation still ongoing) expression of clotting factor after a single injection.[8–10] There have been no serious adverse events, although the asymptomatic transaminase elevation previously reported following administration of an AAV2 vector in two subjects with severe hemophilia B now appears in a new light,[9–12] suggesting that the

role of capsid-directed immune responses merits further study. Subjects in the current trial, however, have experienced conversion of their hemophilia from severe to moderate or mild.[10] An important next goal will be to replicate these results and to elucidate the role of capsid-directed immune responses on the safety and efficacy of the approach.

The results in this trial have critical implications for hemophilia treatment worldwide, although the implications may vary from one area to another given that management differs so widely based on resources and access to sophisticated medical services. For people in resource-poor countries, where access to factor is limited and transportation to a medical center can be a formidable challenge, the ability to undergo a single high-tech intervention that renders patients much less likely to experience life-threatening bleeding events can spell the difference between life and death.

For someone who already has access to optimal medical management, the availability of a single treatment would also be a boon, dramatically easing the burdens—and potentially the cost—of a lifelong prophylactic regimen. It also seems clear that treatment may eventually comprise a combination of gene therapy supplemented by protein infusion when higher levels of factor are needed, e.g., for surgical procedures. The choice of therapy will ultimately be influenced by what a patient feels most comfortable with, and by the costs of treatment to both the patient and the health-care system. However, without any question, hemophilia gene therapy will have a profound effect on treatment availability in areas that have traditionally lacked access to optimal treatment regimens.

In this sense, one can draw an analogy between hemophilia gene therapy and telephone technology. For businesswomen and soccer dads in the Western world, cell phones are a convenience that allows faster and easier communication. By contrast, for those living in areas without landlines, cell phones constitute the difference between availability of telecommunication and its complete absence. Similarly, it is not unreasonable to foresee that developing countries could skip steps in development—e.g., from limited or no specialized hemophilia treatment to a situation in which, following a single high-tech intervention, people with hemophilia could experience a reasonable quality of life without the need for access to frequent and sophisticated medical interventions. There will probably be no single pathway to achieving access, but gene therapy is increasingly likely to be an important part of achieving the long-term goal of treatment for all.

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