Merry Christmas for Patients with Hemophilia B
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Hemophilia B (also known as Christmas disease) is due to deficiency of coagulation factor IX (FIX). In this issue of the Journal, Nathwani et al. report the first unequivocal evidence of successful gene therapy for hemophilia B — a major advance in this field.1 This success for hemophilia may translate into gene therapy for other blood protein deficiencies.

Hemophilia is due to deficiency in a coagulation factor and results in a bleeding disorder that often involves joints and muscles. The most common types are hemophilia A and B, which are due to deficiencies of factor VIII and FIX, respectively, and show X-linked inheritance. The first written account of hemophilia was in the 2nd century in the Babylonian Talmud, when Rabbi Judah decreed, “If she circumcised her first child and he died, and a second one also died, she must not circumcise her third child.”2

The first reported case of hemophilia due to FIX deficiency was in 1952 and was called “Christmas disease” after the patient, a 10-year-old boy named Stephen Christmas.3 Queen Victoria of the United Kingdom (1819–1901) was the most famous carrier of the hemophilia B gene. Although the protein and the gene were not known during her lifetime or the lifetimes of her affected male progeny (members of the royal families of the United Kingdom, Spain, Germany, and Russia), recent analysis of polymerase-chain-reaction assays of bones exhumed from the graves of Czar Nicholas II and his family showed that the FIX gene was mutated in his son Alexei Romanov, who had hemophilia.4 At least nine sons, grandsons, or great-grandsons of Queen Victoria were affected with hemophilia B, and the average age at death was 24 years.

FIX concentrates were first used in the late 1960s to treat patients with hemophilia B, and their routine use for bleeding episodes increased the median lifespan to 63 years.5 Although enthusiasm for protein therapy was temporarily dampened by the HIV epidemic in the early 1980s, improved methods for producing FIX have increased its safety. Recently, implementation of prophylactic rather than on-demand treatment has reduced the risk of crippling joint disease.6

With the success of protein therapy, why would gene therapy be needed? In the United States and other developed countries, annual costs for a single adult patient of clotting factors for hemophilia are approximately $150,000 for on-demand therapy and $300,000 for prophylaxis,6 which could incur a lifetime cost of over $20 million. In developing countries, prophylactic and frequent on-demand therapy is not affordable, and patients still have chronic joint disease and die young.7

Nathwani et al. report the truly remarkable finding that a single intravenous injection of an adenovirus-associated virus (AAV) vector that expresses FIX can successfully treat patients with hemophilia B for more than a year.1 AAV is a small (4.8 kb), nonpathogenic, single-stranded DNA virus from the parvovirus family. The vector was generated by replacing the coding sequence for the cap and rep genes of the virus with a liver-specific promoter and the FIX coding sequence. The vector was packaged in cells that express cap and rep from a different piece of DNA that does not enter viral particles, thus generating a replication-incompetent vector that cannot propagate after gene transfer. Preclinical studies had shown that AAV vectors could be expressed from liver in large animals for at least...
10 years. In this study, patients were treated with an AAV vector that used the capsid protein from serotype 8 (AAV8). Two patients received $2 \times 10^{11}$ viral particles per kilogram of body weight and achieved about 1% of normal FIX activity, two patients received a threefold higher dose and achieved about 2.5% of normal activity, and two patients received a 10-fold higher dose and achieved about 7% of normal activity. Expression has been seen for over 6 months in all patients, and prophylactic use of factor concentrate has either been eliminated or reduced. Since the vector is estimated to cost $30,000 per patient, dramatic cost savings have already been achieved.

Should the practicing hematologist rush to order this gene therapy vector if it is approved by the Food and Drug Administration? The answer is probably yes, but the risks of this procedure are not yet totally clear. In one patient in this AAV8 trial, alanine aminotransferase levels were found to be about five times the upper limit of normal at 2 months after gene therapy, and there was in vitro evidence of cytotoxic T lymphocytes (CTLs) that reacted with epitopes of the AAV8 capsid protein. Prednisolone therapy resulted in normalization of the liver enzyme level within a month, and FIX expression at 6 months was 3% of normal, which was 30% of the peak FIX activity seen shortly after gene therapy. A somewhat similar result was seen in a previous trial of hemophilia B gene therapy with an AAV2 vector, in which an increase in liver enzyme levels was associated with the generation of CTLs specific for the AAV2 capsid protein. However, this patient completely lost FIX expression, leading the investigators to conclude that the CTL response destroyed all transduced liver cells. The finding that the CTL response eliminated transduced cells and gene expression in the AAV2 but not in the AAV8 trial may be related to the glucocorticoid therapy used in the latter study. Alternatively, the more rapid uncoating of AAV8 than of AAV2 capsid proteins from viral particles may allow the AAV8 capsid proteins to be degraded by most transduced cells before the immune system can find and destroy them. These results raise the concern that patients with a more recent immunologic memory of the AAV8 capsid may develop a fulminant hepatitis.

In sum, this gene therapy trial with an AAV8 vector for hemophilia B is truly a landmark study, since it is the first to achieve long-term expression of a blood protein at therapeutically relevant levels. If further studies determine that this approach is safe, it may replace the cumbersome and expensive protein therapy currently used for patients with hemophilia B. This technology may soon translate into applications for other disorders, such as lysosomal storage diseases, alpha-1-antitrypsin deficiency, and hyperlipidemias.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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