LETTER TO THE EDITOR  Clinical

Walk a mile in the moccasins of people with haemophilia

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The ethics of haemophilia gene therapy research

This issue of Haemophilia contains an article entitled ‘Staunch Protections: The Ethics of Haemophilia Gene Transfer Research’ by Jonathan Kimmelman. In this paper, Dr Jonathan Kimmelman, PhD, raises some appropriate ethical issues such as the need to demonstrate clearly and publish a beneficial effect in animal models prior to performing clinical trials, and the importance of obtaining consent that is truly informed. However, we disagree with his belief that it is ethically inappropriate to include people from economically disadvantaged countries in clinical trials, and believe that patients from throughout the world should have access to clinical trials.

Current therapy of severe haemophilia involves intensive factor replacement therapy for preventing bleeding-related damage to joints and other organs. While this is very effective, there are several difficulties with such an approach, such as venous access in small children, inhibitor formation, cost, the impact on the quality of life and the overall psychological burden of living with an incurable disease. Gene therapy refers to a treatment in which a gene that encodes a therapeutic protein is transferred into the cells of a patient. This results in the continuous production of the protein, and could translate into a permanent cure for people with haemophilia. Indeed, gene therapy has had a substantial therapeutic effect in dogs with haemophilia that has been maintained for almost 10 years without adverse effects. This is a truly remarkable achievement, and if translated into clinical practice, could dramatically improve the lives of people with haemophilia throughout the world.

A major tenet of the article by Dr Kimmelman is that it is ethically wrong to include subjects from economically disadvantaged countries in clinical trials. He states that ‘hemophilia gene transfer trials present a particular ethical challenge because they involve subjects whose medical condition is stabilized by standard therapies’. This statement ignores the fact that treatment for approximately 75% of the people with haemophilia in the world who live in economically disadvantaged countries is inadequate. In addition, many people with haemophilia in developed countries are not able to get optimal treatment for various reasons [1].

Here, we present data on the survival and morbidity of the people with haemophilia in India as an example for how existing treatments do not stabilize the condition of patients in economically developing countries. India has a factor VIII usage rate of 0.01 international units (IU) per capita, while the USA has a factor VIII usage of 3.4 IU per capita [2]. Thus, the USA uses 340-fold as much factor VIII per person as does in India. A critical question is whether or not this reduced factor usage results in increased mortality and morbidity in the people with haemophilia in India. Among the 6980 persons with haemophilia who were in the national registry in India in 2004, 44% were under 15 years of age, 35% were between 15 and 30 years, 16% were between 30 and 50 years and only 5% were above 50 years of age. In contrast, counties with a gross national product that is greater than $10 000 such as the USA have 370% as many people with haemophilia who are older than 19 years as people who are younger than 13 years [3]. Thus, on the basis of these data, the USA has many more older people than younger people with haemophilia than are found in India, which strongly suggests that people with haemophilia have a reduced survival in India. Although it is possible that this discrepancy might reflect an overall difference in longevity, the average lifespan for males of 66 years in India is
only modestly lower than that of 75 years in the USA [4]. Another way to assess survival indirectly is to consider the frequency of haemophilia in different countries, as the incidence of haemophilia is similar in different populations [5]. According to the World Federation of Hemophilia global Survey in 2005, there are only 1.1 persons with haemophilia per 100 000 in the population in India, which is only 21% of the value of 5.1 persons with haemophilia per 100 000 found in the USA [6]. This further suggests that people with haemophilia have a reduced lifespan in India, although it remains possible that this difference could reflect reduced diagnosis or population differences.

Another factor to consider is the morbidity of haemophilia in different countries. A report on musculoskeletal function in people with haemophilia in India with a mean age of 14 years and a range from 7 to 40 years demonstrated that although most people could perform activities of daily life such as eating and dressing, many required assistance, and 29% were unable to run [7]. In contrast, a recent study performed in the USA demonstrated that 93% of boys with haemophilia A who received prophylaxis with factor VIII had normal joints by radiographic analyses at 6 years of age [8], and it is likely that such a dramatic improvement in joint disease will be maintained with continued prophylaxis. However, this was at a cost of $300 000 per year [8], and only 17% of patients in the USA received primary prophylaxis prior to 2006 [1], which was in part because of health insurance issues. A different study found that 79% of people with haemophilia in India who were older than 25 years were severely disabled, and 51% of people who were older than 18 did not work [9]. Thus, although frequent administration of high doses of factor VIII can reduce joint disease, most people in economically disadvantaged countries and a few people in developed countries do not have access to this very expensive treatment, and suffer substantial morbidity.

Dr Kimmelman states that it is unethical to recruit subjects from economically disadvantaged countries into clinical trials for haemophilia primarily because they may not have access to gene therapy in the future. However, if patients from developing countries participate in these trials and a successful therapy does develop, it may be reasonable to expect the sponsors or manufacturers of these products to make them available in countries with emerging economies at an affordable cost. In addition, as the science of gene therapy develops, it is possible that scientists and biotechnology companies in these countries may themselves manufacture products for gene therapy. It is certain that no potentially curative treatment will be available if these trials do not progress.

There is an old Native American saying that you cannot know a man until you walk a mile in his moccasins. Anyone involved in ethical decisions regarding gene therapy for haemophilia should at least watch people with haemophilia walk a mile (or in some cases attempt to walk, but fail because of joint disease) to have an inkling of the benefit that would derive from a simple, long-lasting and effective therapy. Nevertheless, none of us without haemophilia can truly understand the daily physical and psychological challenges that face someone with a deficiency of a coagulation factor, and the decision to participate in a clinical trial should be left to each individual after the regulatory agencies are satisfied that there is a reasonable assurance of safety, and after providing the person with haemophilia with appropriate information on the potential risks and benefits. Many clinical trials are open to eligible individuals worldwide. With access to information as it is today, is it fair to deny access to a person with haemophilia who wants to participate in such a trial if he understands its limitation? To imply that including patients who have treatment responsive disease (‘stable subjects’ referred to in this paper) but who still volunteer to participate in phase I trials is ‘trading’ on their hopes for a cure is perhaps an insult to both the philanthropic patients and the physicians, and indeed the entire medical team involved in obtaining consent from the subject and conducting the trial. One has to accept that there are individuals who most willingly participate in clinical trials understanding fully well that they may not benefit from it.

In summary, we believe that people with haemophilia in both developing and developed countries have something to gain either for the individual or for the group by participating in gene therapy trials. Dr Kimmelman underestimates the burden of haemophilia as it is currently managed and thus the potential benefits from gene therapy, particularly in developing countries, although there are certainly some risks involved. We do, however, strongly concur with the need to proceed as carefully as possible, and to provide patients with as much information as is available including the magnitude and duration of the benefit of gene therapy in animal models, the frequency of observed adverse effects and potential long-term effects that have not yet been observed in animal models.
Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

References

6 http://www.wfh.org/2/7/7_0_Link7_GlobalSurvey2005.htm