CORRESPONDENCE

A Serious Adverse Event after Successful Gene Therapy for X-Linked Severe Combined Immunodeficiency

TO THE EDITOR: We recently reported (April 18 issue)[1] the sustained correction of X-linked severe combined immunodeficiency disease by ex vivo, retrovirally mediated transfer of the γc gene into CD34+ cells in four of five patients with the disease. These results have since been confirmed in four additional patients with typical X-linked severe combined immunodeficiency. Of the first four successfully treated patients, three continue to do well up to 3.6 years after gene therapy, whereas a serious adverse event occurred in the fourth patient. At a routine checkup 30 months after gene therapy, lymphocytosis consisting of a monoclonal population of Vγ9/Vδ1, γ/δ T cells of mature phenotype was detected. One proviral integration site was found, located on the short arm of chromosome 11 within the *LMO-2* locus, as determined with the use of linear-amplification mediated polymerase-chain-reaction analysis.[2] This proviral integration within the *LMO-2* locus was associated with aberrant expression of the LMO-2 transcript in the monoclonal T-cell population. Aberrant expression of *LMO-2* has been reported in acute lymphoblastic leukemia arising from T cells with α/β receptors, usually with the chromosomal translocation t(11;14).[3] Tests for replication-competent retrovirus were repeatedly negative in our patient's lymphocytes.

Between 30 and 34 months after gene therapy, the patient's lymphocyte count rose to 300,000 per cubic millimeter, and hepatosplenomegaly developed. Further investigations showed the presence of a t(6;13) translocation, which had not been detected 30 months after the therapy. Treatment with a chemotherapy regimen based on a high-risk protocol for acute lymphocytic leukemia (a protocol of the Dutch Childhood Leukemia Study Group) was initiated and has resulted, to date, in a dramatic reduction in the abnormal cells.

We interpret these findings as the consequence of the insertional mutagenesis event, a risk that is potentially associated with retrovirally mediated gene transfer and that has previously been considered to be very low in humans.[4] For this reason, a thorough reassessment of the potential risk of retrovirally mediated gene therapy is warranted. It is likely that additional factors may have contributed to the adverse event in our patient, including a varicella–zoster virus infection five months before clinically detectable lymphoproliferation, which may have stimulated immune reactivity of the γ/δ T-cell clone, or a selective growth advantage conferred by γc expression in the transduced cells. Genetic predisposing factors for childhood cancer are also possible, since medulloblastomas have developed in the proband's sister and a first-degree relative.

We have proposed to the French regulatory authorities a halt to our trial until further evaluation of the causes of this adverse event and a careful reassessment of the risks and benefits of continuing our study of gene therapy in patients with X-linked severe combined immunodeficiency can be completed. The latter will include a comparison with the outcome of the only available alternative therapy, haploidentical stem-cell transplantation.[5]

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Warfarin, Aspirin, or Both after Myocardial Infarction

TO THE EDITOR: Hurlen et al. (Sept. 26 issue)[1] showed that warfarin with or without aspirin, as compared with aspirin alone, was associated with a reduction in the risk of the composite end point of death, nonfatal myocardial infarction, or embolic stroke in patients with myocardial infarction but did not establish its clinical relevance. They did not assess the implications of the components of the end point for patients. As compared with aspirin alone, the absolute reduction in the rate of nonfatal myocardial infarction with warfarin alone was 0.6 percent per year and with warfarin plus aspirin was 1.1 percent. Patients are not likely to accept long-term warfarin therapy for such a modest reduction in a nondisabling, nonfatal condition. A similar reduction in the rate of events such as death or stroke is more likely to lead to acceptance of warfarin therapy. Hurlen et al., however, found no reduction in mortality and found a reduction in the rate of stroke of 0.3 percent per year with both warfarin and warfarin plus aspirin — too small to change clinical practice.

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1. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002;347:969-74.

TO THE EDITOR: Hurlen et al. found warfarin, alone or in combination with aspirin, to be superior to aspirin alone after acute myocardial infarction. Becker, in the accompanying editorial,[1] concluded on the basis of this and another study (the Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis 2 trial[2]) that anticoagulation therapy should be "strongly considered" after acute myocardial infarction.

We believe that the general applicability of the findings of these two trials is severely limited by the restricted use of coronary intervention. American College of Cardiology–American Heart Association guidelines[3] recommend coronary angiography for patients with acute myocardial infarction associated with ST-segment elevation who have spontaneous or provocable ischemia and for most patients with acute myocardial infarction not associated with ST-segment elevation, who clearly benefit from an early, aggressive approach. The value of warfarin has been demonstrated in patients who, for the most part, do not undergo early coronary intervention. Conceivably, anticoagulation may be beneficial in patients who leave the hospital with severe narrowing of the infarct-related artery, but it may not be as beneficial in patients who are discharged af-