Efficacy of gene therapy for SCID is being confirmed

In this issue of The Lancet, Bobby Gaspar and colleagues report successful immunological correction in four patients with the X-linked form of severe combined immunodeficiency (SCID-X1), a disease characterised by a block in the differentiation of T and natural-killer cells as a consequence of defective expression or function of γc-cytokine receptor-subunit, or both.1

Gaspar and colleagues’ report is welcome because they confirm data from a previous report that described a correction of immunodeficiency in nine of ten patients with SCID-X1.2,3 Meanwhile, Aiuti et al4 had previously reported the successful correction of the immunodeficiency caused by adenosine deaminase (ADA) deficiency in two (and now four) patients. Thus the four cases described in Gaspar and colleagues’ report from London bring to 18 (ie, 14 with SCID-X1 and four with ADA deficiency) the total number of SCID patients treated by an optimised ex vivo retroviral-mediated gene-transfer protocol into CD34+ haemopoietic precursor cells. Remarkably, 17 of these 18 patients had their immunodeficiencies corrected with clear and sustained clinical benefits. The data show that the results of this gene-therapy strategy are reproducible.

However, the therapy relies on the growth advantage provided to transduced lymphocyte precursors in the SCID environment. The kinetics of T-cell development and sustained benefit appear to be independent from the conventional variables that influence the outcome of allogeneic haemopoietic stem-cell transplantation, such as age, clinical status (especially pulmonary infection), and degree of HLA disparity between donor and recipient.5 In SCID-X1, a conditioning regimen is dispensable, which thus prevents the early lethal toxicity observed in many severely infected patients who receive haploidentical haemopoietic stem-cell transplants. The absence of graft versus host disease in this situation also contributes to a potentially more favourable outcome. Therefore, because haploidentical haemopoietic stem-cell transplantation carries a good prognosis (survival ≥95%)6 in SCID patients aged less than 3 months old, and accounting for the potential adverse effect of gene therapy (see below) in that age group, it is reasonable to restrict gene therapy to SCID patients older than 3 months of age. Despite the low number (14) of SCID-X1 patients treated so far, we can see a correlation between the number of transduced precursor CD34+ cells injected and the quality of immunodeficiency correction. For future applications of this gene-therapy strategy, a lower threshold of about 3 million CD34+ γc+ cells per kg of bodyweight can be defined.2,3 The London protocol is different from the Paris protocol4 because in Gaspar’s protocol there is no fetal calf serum in the culture medium and the gibbon-leukaemia-virus envelope is used. Both factors could have a role in the apparently higher transduced rate achieved in B and myeloid cells compared with that seen with the Paris protocol. A longer follow-up will tell whether the higher transduced rate is relevant for long-term persistence of effective immunity, as suggested by the transduction of immature progenitor cells.

Clonal T-cell lymphoproliferations occurred in two patients with SCID-X1 who were successfully treated in Paris by gene therapy.6 The lymphoproliferations have obviously raised concerns about the safety of this strategy. So far, none of the patients treated in London have developed any severe adverse effects, nor have any of the patients manifested biological evidence of lymphoproliferation. Although the data are still preliminary, they support an association between the risk of severe adverse events and the patient’s age (≥3 months) at the time of gene therapy.7 Age as a safety consideration, balanced with the efficiency of gene therapy, which looks more efficient than conventional haploidentical haemopoietic stem-cell transplantation, has led researchers to resume the French trial with a lower age restriction (ie, the patient needs to be older than 3 months). Trials in the UK and USA are ongoing. The age restriction does not eliminate the need to improve the safety of vectors designed for future trials. A specific concern is avoiding the enhancer activity of the retroviral vectors’ long-terminal repeat.8 Overall, the available reports of gene therapy’s efficacy in SCID-X1 and ADA deficiency2,4 should encourage researchers to extend the treatment to target other life-threatening immunodeficiencies and, possibly, other genetic diseases of the haemopoietic system. In extending gene therapy to treat other conditions, we must carefully monitor patients, not only to detect potential toxic effects, but also to guide the setup of safer and more efficient gene-transfer strategies.
Comment

Vaccination and child mortality

A report in 2000 from Guinea Bissau suggested a worrisome association between diphtheria, pertussis, and tetanus (DPT) vaccination and mortality.1 In this issue of The Lancet, Robert Breiman and colleagues respond to concerns about DPT with a highly detailed and reassuring study of vaccination and mortality in Bangladesh.

At an epidemiology conference in Helsinki in 1989, Peter Aaby and I spent a few days discussing a problem: vaccines are usually introduced into developing countries with no assessment of their potential effect on overall mortality.1 The key issue is that if trials of vaccines are to show a beneficial effect, or at least that they cause no harm, the trials need to be so large that they are difficult to fund. Another problem is that once a vaccine has been shown to reduce mortality, requires great care. To attempt such a separation, a very large and detailed dataset is necessary. In particular, the process requires an accurate record of a large number of deaths. For example, the WHO expert committee found that in the original Aaby study, a change in the vaccine status of just two of the people who died made the result non-significant. Confidence intervals do not reflect the fragility of the analysis. The WHO committee concluded that the only evidence for an association between DPT and increased mortality was from Guinea-Bissau; such evidence was found in no other countries. This finding could be because of a country-specific issue or a peculiarity of the data.

Although Breiman and colleagues’ study contradicts the Guinea Bissau findings on DPT, they do find a benefit from both measles vaccine and from Bacillus Calmette-Guerin vaccine in early life that goes beyond what one would

"Marina Cavazzana-Calvo, Alain Fischer
Département de Biothérapie (MC-C) and Unité d’Immunologie et Hématologie Pédiatrique (AF), Hôpital Necker-Enfants Malades, 75015 Paris, France (MC)
m.cavazzana@nck.ap-hop-paris.fr
We declare we have no conflict of interest.
7 Myers LA, Patel DD, Puck JM, Buckley RH. Haematopoietic stem cell transplantation for severe combined immunodeficiency in the neonatal period leads to superior thymic output and improved survival. Blood 2002; 99: 872–78.

For personal use. Only reproduce with permission from Elsevier Ltd