Bone-marrow transplants for RDEB and JEB Update 2013

The first trial of bone-marrow transplantation (BMT) in children with recessive dystrophic EB (RDEB) led to an improvement in skin condition in some individuals (see 2010 DEBRA handout).

To make further improvements in the effectiveness of BMT, the challenge has been to identify which cells in the bone-marrow have the beneficial effects, and to get a better understanding of how they work in the skin to strengthen it and reduce blistering. In addition, a major clinical challenge is to make the BMT procedure safer and less physically traumatic for the patients who undergo it: BMT is, by its nature, a very severe procedure which has a significant risk of mortality from a variety of complications, and frequently has a long and difficult recovery period that can last many months.

Two further BMT clinical trials – modifications to the clinical-trial protocol
There have since been two further follow-up BMT clinical trials in which various modifications to the treatment were made in the hope of making it both safer and more effective. The full results of these trials are expected to be published later in 2013 after full analysis of the results, but some preliminary findings and recommendations for future trials can be considered now.

Bone marrow used in transplants contains a mixture of different types of stem cells and people who have had transplants have cells in their skin that are derived from this mixture. Following BMT, cells known as HSC (haematopoietic stem cells) are the source of new keratinocytes in the epidermis, and also some other fibroblast-like cells in the dermis. But, cells derived from another type of stem cell, MSC (mesenchymal stem cells), are also found in the skin of people who have had bone-marrow transplants. This is important because MSC are known from other studies to reduce inflammation and otherwise modify the immune response, as well as helping in tissue repair. It might therefore be expected that including MSC in a bone-marrow trial could have major benefits: it might help to reduce the damage from the chemotherapy ‘conditioning’ (i.e. chemotherapy needed to ‘knock-out’ the patient’s own bone marrow so that the donor bone marrow is accepted by the body) used before the trial, as well as reduce any immune response to the donor bone marrow.

The 2nd clinical trial
In the second trial, MSC from healthy donors without EB were administered along with BMT. In addition, the treatment was extended to include patients with JEB. JEB is very different from RDEB in several ways. JEB is genetically very diverse, with mutations in six genes known. In addition, all the proteins involved in JEB are made by the keratinocyte cells of the epidermis, rather than the fibroblasts of the deeper dermis skin layer. Earlier studies with an animal model of JEB had shown that MSC could increase the level of such proteins, and thus provided support for using BMT with JEB patients. The use of BMT with MSC showed that JEB patients could, in principle, benefit from bone-marrow transplant, in that the protein laminin 332 was increased, and assembled correctly in the skin, resulting in stronger skin and less blistering. However, as with RDEB patients, the chemotherapy ‘conditioning’ which is used to knock out the patient’s own bone-marrow so that the body can receive the donor bone marrow, proved too much for one of the two Herlitz JEB patients treated.
The 3rd clinical trial
In a third trial, it was decided to try to reduce the intensity of the chemotherapy ‘conditioning’ treatment. While this might mean that not all the patient’s own bone-marrow will be knocked out, and thus patients treated will have a mixture of their own, and the donor’s, bone marrow, this should reduce the treatment complications and mortality. BMT with added MSC was used again used to treat children with RDEB or JEB.

The most important outcome of the third trial was that none of the RDEB patients treated died. Furthermore, their recovery was much quicker, and they were able to go home, rather than spending lengthy periods hospitalized as a result of complications, as had been the case previously.

What has been learned….what are the next steps?
The next step is to consider carefully what has been learned from these trials before planning the next trials. Of the 18 patients with RDEB who have undergone the BMT procedure, 12 are alive and have incorporated the donor’s bone marrow (i.e. the graft has taken). Of the 6 Herlitz-JEB patients treated to date, 3 have survived, and one shows increased laminin. However, although stronger, the skin of this patient is very inflamed, and does not look normal, and the next step is to further research to try to understand why this is so.

One conclusion is that the treatment protocol needs to be adapted to suit the type of EB a patient has, and perhaps even the type of mutation: not all EB patients will be eligible for exactly the same type of treatment. Furthermore, there will be a need to study carefully what happens to the clinical condition of the patients treated to date, as well as what happens to the cells in their skin over time. It has been seen that, for some RDEB patients at least, the numbers of donor-derived cells increase with time, and the amount and quality of collagen in their skin continues to improve.

It seems to be the case that reduced ‘conditioning’ greatly improves not only the survivability of the procedure, but also how well the patient is after the procedure: patients were all able to be discharged from hospital without the complications and lengthy hospital stays – sometimes lasting many months – of patients who has received the full chemotherapy treatment.

These three trials are just the first step, and both further research, and careful review of the clinical trials to date will help develop safer and more effective treatments for people with EB.