

The 'Minnesota' bone-marrow transplantation clinical trial in people with RDEB: the early results

The long-awaited early results of the first clinical trial of bone-marrow transplant in children with recessive dystrophic epidermolysis bullosa (RDEB), carried out at the University of Minnesota in the USA, have now been published in the scientific press (Ref. 1). The results for the first seven children treated are reported in this paper. Nevertheless, it is still very early days following the transplantation treatment, and the full results with the long-term outcomes for these pioneering patients and their families may take a long time, possibly years, to become clear. Perhaps the message is 'Proceed, but with extreme caution'. As the researchers who undertook this trial say: "Despite the potential benefits of marrow transplantation, it is a high-risk therapeutic approach that could shorten the expected survival of patients with recessive dystrophic epidermolysis bullosa, particularly those with less severe clinical manifestations."

In this early-stage clinical study, seven children between the ages of 15 months and 14 years have been treated to date. One child died before receiving the transplantation, probably as a result of the essential pre-transplantation medical treatment, and another child died some six months after receiving the transplantation, because of transplant rejection and infection.

In the six patients who received transplants, all showed some improvement in wound healing and reduced blister formation, at least for a period of time after transplantation. This trial shows that, while bone-marrow transplant is a severe medical procedure, not to be undertaken without serious consideration of the possible consequences, it can, in principle, provide some apparent benefits to some patients with severe RDEB. However, a great deal of further work is needed to refine the procedure, and to study what the long-term effects – both benefits and unwanted side-effects – are for the people treated to date.

The only care available to people with RDEB at present is palliative care of individual wounds, and treating the pain, limitations and complications that arise from chronic wounds and cumulative scarring and damage to the skin and internal body linings (mucosa). Most other treatments at clinical stages of development (fibroblast therapy, grafting gene therapy, protein therapy) at present also only aim to treat local areas of skin that can be accessed by grafting or injection. However, there are other types of therapy, mainly stem-cell based, in early development which aim to provide whole-body treatment. Bone-marrow transplant is a type of stem cell therapy.

Box 1: How does bone-marrow transplantation work?

The aim of bone marrow transplant, a type of stem cell therapy, is a systemic (i.e. whole-body treatment) correction of the underlying genetic EB fault. Bone marrow is a source of 'stem cells', which are cells that have the ability to reproduce themselves indefinitely, and become many types of body-tissue cells, including skin cells. Thus, in treated RDEB patients, the donor bone marrow from people without EB should have the ability to provide a new, inexhaustible supply of stem cells which can, through the blood circulation, go to the skin and become healthy new skin stem cells. Umbilical cord blood is another source of similar stem cells, and some patients in the trial received both bone-marrow and cord-blood from healthy donors. The clinical trial follows earlier preclinical research in mice with EB which showed that bone-marrow transplants could correct the gene defect in skin and result in improved skin strength and wound healing.

So what were the actual results, and what do they mean?

- ***Increased collagen VII, but no normal anchoring fibrils:***

Although five of the six patients treated showed increases in the amount of collagen VII in the correct location in the skin – between the outer epidermis and lower dermis layers – this collagen was not arranged in the normal structures called ‘anchoring fibrils’ that hold the two layers of skin together in non-EB skin. An increase in wispy, thin, filaments was observed in some patients, and these may be responsible for improved skin strength. Whether or not the increased collagen is produced all, in part, or not at all from the donor cells is not clear – it may be that at least some of the new collagen is extra faulty collagen produced from the patient’s own cells, stimulated by the transplant procedure.

- ***Bone-marrow donor cells do go to the skin:***

Five of the six patients who received transplants had substantial levels of donor cells present in the skin, showing that the donor cells survived, migrated from the blood system to the skin and settled down there. The level of donor cells varied from patient to patient, and from one area of the body to another, but was on average around one-fifth of cells found in the skin. What is not yet known is how long the donor cells will persist in the skin, what type of cell they become, and whether they will remain at levels sufficient to have beneficial effects.

- ***The treated patients did not react badly to the new collagen:***

Although a couple of the patients had very little or no detectable collagen VII before transplantation, none of the six patients transplanted developed any antibodies to the newly formed collagen, showing that their bodies did not react against the collagen. Although one patient died following treatment as a result in part of rejection of the transplant, this was not a reaction to the new collagen – his donor was not a perfect tissue match and this may well be the reason. These results are promising, though it is not yet clear whether the treatment would be suitable for those people with RDEB who are known for certain to produce absolutely no collagen VII.

- ***What are the risks of the procedure itself?***

Bone-marrow transplantation is by its very nature a severe procedure, because the patient’s own bone marrow must be destroyed using chemotherapy before the donor bone marrow can be given. The chemicals used to do this are highly toxic to the body, posing risks of organ failure and death: one patient in this trial is considered to have died from damage to the heart as a result of the chemotherapy, and most patients had problems from which they gradually recovered. RDEB patients often have medical problems in addition to skin wounds and these can be exacerbated by chemotherapy: two patients who already had kidneys that did not work well had to have dialysis while they recovered, and all patients had significant inflammation of the mucosa. Furthermore, the patient’s own immune system is wiped out along with their bone marrow, laying them open to all sorts of infections, until the donor bone marrow establishes itself, restoring a new immune system. Several of the patients acquired infections, or had worsening of problems associated with infected wounds, or activation of dormant viral infections.

There are also, as yet unknown, possible side effects. As the researchers acknowledge, it is not known whether the risk of squamous-cell carcinoma, already significant in RDEB patients, may be affected, either because of the procedure itself, or as a result of incomplete correction of the underlying EB fault.

- ***Will the improved skin condition last?***

This is unknown at present, and many questions remain. Not only does the long-term fate of the donor cells need to be followed, but to what extent the effect of increased collagen is owing to these cells, and whether it will continue, and have benefits for the skin, is unknown. In several of the treated patients, the levels of both collagen and donor cells increased with time – this might be expected if the donor cells gradually increase proportionally, and/ or continue to have an effect in increasing collagen. However, in another patient, the level of both collagen and donor cells present in the skin decreased with time. One patient showed a clinical improvement despite no apparent increase in collagen VII – is there some other mechanism at work that increases skin strength?

What next?

In an independent commentary, published alongside the research paper on the trial, Professor Leena Bruckner-Tuderman, Deputy Chair of DEBRA's Medical and Scientific Advisory Panel, points out that future trials must establish benefits by consistent objective analysis of wound improvement, as it is hard to distinguish the possible benefits of improved routine medical care during the trial. In addition, future work must focus on the long-term benefits and side-effects of transplantation, as the effects of bone-marrow transplant treatment of another collagen-defect condition, called osteogenesis imperfecta, tail off after a couple of years. She also indicates that it is important to address the issue of the need to treat children as young as possible to avoid accumulation of the largely irreversible damage that occurs in RDEB, countered by the difficult decision to treat children, who are still reasonably well, with such a high-risk procedure. Nevertheless, as she notes: "the study by Wagner and colleagues gives cautious hope that effective therapy of recessive dystrophic epidermolysis bullosa and other genetic skin diseases may one day be available."

In addition to following the clinical outcomes of the patients treated to date, a great deal of further research to understand what is going on in the body of people with RDEB treated by bone-marrow transplantation is necessary, so that the procedure can be refined to make it safer and more effective long-term.

Such questions include:

- Which are the important stem cells in bone marrow?
- Where do donor cells go in the body, and what type of cells do they become?
- Are the donor cells responsible for the clinical benefits seen?
- Will the donor cells survive long-term and continue to produce a beneficial effect?
- Is the new collagen produced from the donor cells only, from the patient's own cells, or a mixture?
- Are there other effects beyond increased collagen production that are responsible for the clinical benefit?
- Can bone-marrow transplantation be made safer for EB patients?
- Might bone marrow transplantation increase the cancer risk?

A further clinical trial, at the University of Columbia in New York, is already underway, in which the chemotherapy protocol is of reduced severity, in the hope that the side-effects will be less severe: at present it is not known whether this will have the desired effects or not.

Research projects, funded by DEBRA, are already underway to unravel the underlying reasons for the apparent clinical response after bone marrow transplantation, and to identify what cells or other factors in bone marrow are responsible for any benefits and the mechanism by which they act. Gaining this improved understanding through fundamental research will point the way to designing and refining therapies that are as safe and effective as possible for EB patients.

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Bone Marrow Transplantation for Recessive Dystrophic Epidermolysis Bullosa

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