Bone-marrow transplant therapy for RDEB

The early results of the first-ever clinical trial of bone-marrow transplantation (BMT) to treat RDEB have recently been published in the scientific press.

The trial of BMT in children with recessive dystrophic epidermolysis bullosa (RDEB) is being carried out at the University of Minnesota in the USA. BMT is a severe medical procedure, not to be undertaken without serious consideration of the possible consequences. However, this trial appears to indicate that bone-marrow transplant – or, in future, related therapies – may, in principle, provide benefits to some patients with severe RDEB.

Nevertheless, it is still very early days following transplantation, and the full results with the long-term outcomes for these patients and their families may take a long time, possibly years, to become clear.

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.

**Why bone-marrow?**

Bone marrow is, in every person, the source of new cells of many types of body tissue, and this is why bone-marrow transplants from healthy donors have been used for many years to treat a variety of life-threatening conditions.

Bone marrow is a source of ‘stem cells’, which are cells with two important properties: the ability to reproduce themselves indefinitely (‘self-renewal’), and to become many other types of body-tissue cells (‘pluripotent’), including skin cells.

---

**‘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.’**

JE Wagner et al., (Researchers and clinicians at University of Minnesota undertaking the BMT clinical trial)

‘Bone Marrow Transplantation for Recessive Dystrophic Epidermolysis Bullosa’

*New England Journal of Medicine* August 12, 2010; 363; 7 pp 629 - 639

---

![Stem cells from bone-marrow diagram](chart)
**How can bone-marrow transplants help repair skin?**

Whether or not someone has EB, a person’s bone marrow is the ultimate renewable source of skin ‘stem cells’, a type of cell found in skin which can reproduce itself indefinitely to produce more skin cells.

If skin is injured, by a cut or a blister, the wound sends out chemical messages into the bloodstream to say “help needed!” – these messages recruit cells from the bone marrow that are circulating in the bloodstream to the wound site.

The cells settle down in the skin and mature into skin stem cells, thereby helping to repair the skin.

Bone-marrow transplant therapy is therefore a type of ‘stem-cell’ therapy, in that it provides the treated patient with a new supply of genetically correct stem cells from the bone marrow of a healthy donor. The faulty cells in the bone marrow of the patient must first be destroyed by chemotherapy: cells from the donated bone marrow then replace the faulty cells in the bone marrow of the patient and eventually are able to produce healthy new cells of various body tissues.

**How might bone-marrow transplantation cure RDEB?**

The aim of bone marrow transplant is a systemic (i.e. whole-body treatment) correction of the underlying genetic EB fault, by providing a new supply of bone-marrow from a donor who does not have EB.

In RDEB, the Collagen 7 gene is faulty, with various mutations resulting in faulty or absent Collagen VII protein. This in turn results in the loss of the collagen anchoring fibrils which hold the epidermis and dermis layers of the skin together.

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, able to produce the collagen. Umbilical-cord blood is another source of similar stem cells, and some patients in the trial have 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.

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

In this ongoing early-stage clinical study, 12 children and young adults with RDEB have been treated so far, but the publication reports only on the first seven children between the ages of 15 months and 14 years treated to date.

Two of the seven children treated died: one before receiving the transplantation, probably as a result of the essential pre-transplantation medical treatment, the other
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.

**What are the results so far, 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 in the skin, it was not arranged in the normal structures called ‘anchoring fibrils’ that hold the two layers of skin together in non-EB skin. ‘Wispy’ fibrils were seen, but it’s not known what they are, and whether they strengthen the skin.

- **Bone-marrow donor cells do go to the skin:**
  Most 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. What is not yet known is how long the donor cells will persist in the skin and at levels sufficient to benefit skin strength.

- **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. 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.

- **Will the improved skin condition last?**
  This is unknown at present, and many questions remain. Whether the donor cells last, and to what extent the increased collagen and benefits to the skin is owing to these cells, is unknown. One patient showed a clinical improvement despite no apparent increase in collagen VII – is there some other mechanism at work that increases skin strength?

---

**Why is bone-marrow transplant risky?**

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.

RDEB patients often have medical problems in addition to skin wounds and these can be exacerbated by chemotherapy.

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.
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.

**What next?**

Further research on BMT therapy will establish the long-term benefits and side-effects of transplantation. A better understanding will also point the way to designing and refining therapies that are as safe and effective as possible for EB patients.

Key research 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?*

Research projects, several funded by DEBRA, are already underway to investigate some of these important questions.

**What alternatives to BMT therapy are being developed?**

Different therapies will be suitable for different patients, and balance individual patient needs and wishes as well as safety and efficacy. BMT will not be appropriate for all types of EB, or even all patients with RDEB. For this reason, research also continues on gene therapy, protein therapy and other cell therapies.

Some therapies target local healing (grafting with genetically corrected skin, or injections into the skin of collagen protein, or cells such as the fibroblast-cell therapy); others target systemic, whole-body, healing (injections into the bloodstream of bone-marrow transplants, or other stem cells). Some aim for temporary improvement (fibroblast or protein therapy), whereas others aim for permanent cure (bone-marrow transplant, or grafting with genetically corrected skin).

DEBRA funds basic research into the mechanisms of EB (which creates new ideas for better treatments), and preclinical testing of possible treatments which are in quite advanced stages development. As with any technology, basic questions related to likely safety and efficacy must be answered before testing a treatment on any patient. Even when a particular treatment is proved to work in principle, continued research will lead to refinements in safety, efficacy, ease of treatment and cost.

For all types of EB, DEBRA prioritises research into:

- *Genetics and Biology of EB*
- *Cancer*
  - *Diagnostics*
  - *Therapies*
  - *Prevention*
- *EB Therapy Development*
  - *Gene therapy*
  - *Cell therapy*
  - *Protein therapy*
  - *Molecular regulation of gene expression*
- *Clinical care*