Phase II clinical trial of fibroblast therapy for RDEB completed

We're able to report here on the results of a recently completed project to develop and test fibroblast cell therapy for people with RDEB. The clinical trial was part of a DEBRA UK-funded project ‘Fibroblast cell therapy for epidermolysis bullosa – a phase II clinical trial and associated research’, led by Professor John McGrath.

Why fibroblast cell therapy?

The recently completed Phase II clinical trial of fibroblast cell therapy for RDEB builds on a great deal of laboratory research, and the previous 'pilot' trial.

The benefits and safety of fibroblast injections had been seen in many studies of RDEB mice.

The next step was a 'pilot' trial of 13 patients with RDEB, which showed that injections into the skin, of fibroblasts from unrelated donors, are apparently safe, and have the potential to improve skin strength and reduce blistering.

It was also discovered that injecting the same fibroblasts into the edges of chronic wounds in people with RDEB can stimulate wound healing, lessen the need for dressings and improve quality of life. But those reports were anecdotal and therefore a phase II clinical trial of allogeneic fibroblast therapy in RDEB represented the next landmark in therapy development.

The Phase II clinical trial

After extensive screening to find people with RDEB most likely to benefit, and for whom the treatment would be safe, 11 people with RDEB were recruited to the Phase II clinical trial. The clinical trial took place within the Clinical Research Facilities and Biomedical Research Centre based at King’s College London and The Guy’s and St Thomas’ NHS Foundation Trust, which is also home to the UK’s National Epidermolysis Bullosa clinical and diagnostic services.

Each person received a single series of intradermal injections of allogeneic fibroblasts or placebo (inactive solution) into the skin. Over a period of time following the injections, wound healing, pain, quality of life aspects, and safety, were assessed in detail through blood tests and clinical monitoring. Analysing the large amount of patient data from clinical trial, however, needs to be very thorough to be certain of the results, and this was completed in May 2013.

The Phase II trial showed:

- that injecting fibroblasts is safe and that in some people these cells can speed up wound healing compared to the control solution.
- that the most of the wound healing benefits from the fibroblasts came during the first 28 days after a single injection.
- the study also taught us that some bigger wounds are likely to require repeated injections of fibroblasts if improvement is to be maintained.
- In addition, many people find the current injection procedures painful. Further work is planned to address issues concerning the best dosing schedules, and the best means of cell delivery in future studies.

However, the trial was unable to achieve statistical significance (important as absolute proof to the regulatory authorities that something does, or doesn’t, work) because there were not quite enough patients enrolled in the trial.
How does fibroblast therapy work?

The second part of the DEBRA-funded project aimed to expand our knowledge of how fibroblasts have their beneficial effects.

In treated RDEB patients, it was not known whether the benefits derive from the fresh C7 being produced by the injected fibroblasts, an increase of the patient’s own faulty C7, or whether the injection and subsequent mild inflammation somehow passes signals and stimulates the body to respond in other ways to strengthen the skin (a paracrine effect) by production of C7 in both fibroblasts and keratinocytes. One idea developed by the research group is that the injected fibroblasts may act through a complex signalling process inside the skin involving proteins called growth factors, such as one known as heparin-binding epidermal growth factor-like growth factor (HB-EGF).

This study confirmed previous findings that HB-EGF can increase C7 in both keratinocytes and fibroblasts. However, from knowledge of the way in which HB-EGF works, there are concerns that using HB-EGF clinically might increase the risk of skin cancer, a risk already higher in people with RDEB.

The study therefore investigated another growth factor, EGF, and showed that can also increase C7 production in both keratinocytes and fibroblasts. EGF works in a different way from HB-EGF and is therefore expected to have a lower risk of causing skin cancers; it may therefore be studied further as a possible treatment for RDEB to promote wound healing.

A protein found in blood, known as high mobility group box-1 (HMGB-1) was also studied as levels of this protein correlate with clinical severity in RDEB – the more severe the RDEB, the higher the level. HMGB-1 causes cells called mesenchymal stem cells (MSC) to move from within bone marrow into the bloodstream. When MSC reach the skin via the bloodstream, they can settle down and develop into skin stem cells, and thereby contribute to wound healing. HMGB-1 is released into the bloodstream from keratinocytes in blisters, and therefore acts as way for wounds to ‘call’ for MSC to repair damaged skin.

In the short term, blood tests for HMGB-1 may be a useful new way to measure disease severity either routinely, or as an important test for RDEB individuals participating in clinical trials of therapies. Further work is being done to validate HMGB-1 as a clinically useful measure (a ‘biomarker’), and is also being assessed in individuals with RDEB who are participating in the EBSTEM clinical trial of injected intravenous MSC.

So is fibroblast therapy now available to those who want it?

The answer to that is both ‘yes’ and ‘no’. The Phase II trial needed to enrol 25 patients to be sure that the results would be statistically meaningful, but it was only possible to enrol 11 patients. It had been hoped that, with a strong positive result from this trial, the regulatory authorities (the MHRA in the UK) would only require a further small trial to confirm the results, but now, a further big trial is needed.

However, until such time as that is possible, Intercytex, the company which has worked closely with Professor John McGrath’s group throughout the clinical trials, and which provides the fibroblasts for the therapy, is able to supply clinics via a “specials” license. This means that legally the treatment is available now to any patient who wants it but it has to be requested by clinicians – the company cannot market or promote it.

During this ‘specials’ phase the company is happy to provide the therapy at cost. So far, full reimbursement is already provided by the NHS (via National Commissioning) for the first three patient treatments on a named-patient basis. These patients have requested additional treatments.

What is a ‘specials’ license?

Intercytex Ltd has obtained a ‘Specials’ licence from the UK Medicines Healthcare Products Regulatory Agency (MHRA). This enables the company to manufacture and release the fibroblasts as an unlicensed ‘advanced therapy medicinal product’ (ATMP) intended for specific patients if the “relevant medicinal product which is supplied to fill a “special need” and in response to a bona fide unsolicited order, formulated in accordance with the specification of a doctor, dentist or supplementary prescriber and for use by his individual patients on his direct responsibility. This license followed a rigorous inspection and audit of Intercytex’s operation and its GMP (good manufacturing practice) facilities carried out by the MHRA inspectors and is in addition to Intercytex’s IMP (Investigational Medicinal Products) license which permits the manufacture and release of ATMPs for use in clinical trials.
Working in partnership with industry

The clinical trial has been a collaboration with the small biopharma company Intercytex, which has worked closely with Professor McGrath’s group, not only on this Phase II trial, but on the preceding pilot-phase clinical trial.

The company Intercytex was not only the sponsor for the recent phase II clinical trial, but has provided the fibroblasts for injection in both trials. Intercytex has also provided the expertise and considerable time in discussions with the regulatory authorities, and providing the extensive documentation required to get permission to go ahead with the clinical trials. Furthermore, Intercytex plans to continue working with Professor McGrath’s group to develop ways to deliver the fibroblasts to the skin effectively and with minimum inconvenience to the person treated.

Next steps...

While ways of funding further trials, and ongoing provision of the therapy, are being investigated, further research is going on to determine how best to provide the therapy. The clinical trial pointed to several aspects important for further development of the therapy.

The clinical trial showed that the treatment was most beneficial in the first 28 days following injection, suggesting that the effects of repeat-treatments should be investigated before the next clinical study.

Intradermal injection was uncomfortable or painful for some patients, and the company is working to develop less uncomfortable injection systems: it has a UK government grant to develop a less painful injector system, and is working with Manchester University to examine micro-needle delivery systems.

Funding through a further UK government initiative is allowing investigation of ways of extending the ‘shelf-life’ of the fibroblasts, important in turning the treatment into a more useable and affordable product. At present, a limiting feature of providing a living-cell therapy is the relatively short shelf life of the products.

Into the future...

Fibroblast therapy appears to offer at least some people with RDEB a treatment that brings improved skin healing and reduced blistering, with relatively few side-effects. Although not a cure, it appears relatively safe. As Professor John McGrath says “The fibroblast trial has taught us that these cells can improve wound healing in RDEB, although some people found the injections a bit painful. We know we need to come up with a better device to deliver the fibroblasts into the skin without causing pain and are working on this. Injecting fibroblasts into skin appears to be helpful in healing small stubborn wounds in some people with RDEB and so there is clinical value in pursuing this form of treatment.”

The clinical trial of fibroblast therapy, and associated research into the mechanisms underpinning the beneficial effects seen, provide valuable information and point the way towards developing not only improved fibroblast therapy but other types of cell therapy for EB too.

Dr C Robinson, DEBRA International Research Manager  December 2013