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Horizon scanning technology prioritising summary

Recell® system for autologous cell harvesting and delivery

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**Australian
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Register
of New
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IMPACT SUMMARY

ReCell (Avita Medical, Cambridge, United Kingdom) is the first commercial keratinocyte cell spray system introduced into clinical practice. It is a novel autologous cell harvesting system for epidermal replacement in patients with skin defects and does not require the use of laboratory facilities for cell culturing.

BACKGROUND

The process of epidermal replacement is a key step towards healing of post-traumatic or iatrogenic scars as it restores keratinocytes, Langerhans cells and melanocytes that are commonly lost in severe injuries. At the time of writing, skin grafts (meshed and unmeshed) are the gold standard of treatment for burns and have been proven to be an effective and easy technique to perform. Previous studies have demonstrated that it is capable of achieving good aesthetic results and prevent contractures. However, one major disadvantage of grafts is the fact that for large burn areas the need for coverage (due to high infection risk) is counteracted by the difficulty of finding non-involved donor skin of sufficient size (Gravante et al 2007).

Since 1975, procedures to culture keratinocytes has been available (Rheinwald and Green 1975). As keratinocytes are rapidly dividing epidermal cells, large numbers can be grown in a relatively short time from a small biopsy sample. Cultured and non-cultured skin products are a growing group of materials in which techniques have been employed to expand available autograft, either by creating cultured keratinocyte sheets or suspensions, or enzymatically generating non-cultured epithelial cell suspensions (Eisenbud *et al.* 2004). Though the use of autologous cells is immunologically safe, there are issues with cost, short shelf-life, fragility and the need for custom preparation (Eisenbud *et al.* 2004). In addition, tissue engineers would require time to produce large amounts of keratinocytes, fibroblasts or both, therefore temporary skin coverage with cadaveric skin or dermal substitutes is necessary (Mis et al 2004, Callcut et al 2006).

Recently, trials have been conducted on the use of keratinocyte cell sprays in animals and *in vitro* trials as a potentially new method of for the delivery of epidermal cells for the treatment of acute burns, wounds and scars (Cervelli et al 2009). In 2005, the ReCell system was introduced into clinical practice. It is a single use, disposable device that allows for immediate processing (without need for laboratory services) of a small split-thickness biopsy including keratinocytes, melanocytes, Langerhans cells and fibroblasts. The biopsy is then digested and the cells are diluted in a lactate solution. The suspension is sprayed onto the target site with a ratio of 1 cm² of the biopsy sample to 80cm² of the damaged area (Gravante et al 2007). The ReCell system basically enables rapid delivery of keratinocytes without the need for cell culturing and acts as a stand-alone harvesting, processing and delivery unit.

CLINICAL NEED AND BURDEN OF DISEASE

In Australia, 50855 skin grafts (allograft, synthetic, split skin etc.) were performed in public hospitals from 2007 to 2008 (Australian Institute of Health and Welfare 2009). Currently, autograft is the best replacement for lost skin. However, in clinical practice

this is not always possible (if the area affected is large), as there may be insufficient amount of skin from donor sites for autografting. Allografts and xenografts can be used as temporary wound coverage but there are issues with graft rejection, availability, cultural and ethical implications and the possibility of disease transfer.

DIFFUSION

The ReCell system has been approved for use in 33 countries to date. In Australia, ReCell was approved by the Therapeutic Goods Administration in May 2006 and was listed in the Australian Register of Therapeutic Goods (Clinical Cell Culture 2006). It is intended for use in patients with injuries of up to 2% of the body surface or 320cm². However, the use of ReCell does not appear to be widespread within the Australian healthcare system and is primarily utilised in Western Australia (Royal Perth Hospital).

At the time of writing, ReCell is currently undergoing a randomised US clinical trial for FDA regulatory approval. Previously, a US trial was performed in 2006 but did not achieve adequate patient enrolment due to the use of strict selection criteria. This trial was suspended by Avita Medical in July 2008 as it failed to adequately address concerns raised by the FDA regarding study endpoints, patient follow-up and statistical analysis of collected data. The new trial is expected to address these concerns and is scheduled to be completed at the end of 2010 (Proactive Investors 2009).

COMPARATORS

The key comparators to the ReCell system are conventional skin grafts, biological skin replacements and bioengineered skin substitutes.

SAFETY AND EFFECTIVENESS ISSUES

Study description

Four clinical studies on ReCell were identified and retrieved for inclusion in this summary.

The randomised, placebo-controlled trial by Back et al (2009) evaluated whether after ablation of leukodermic epidermis, the application of co-suspensions of non-cultured skin cells are capable of decreasing the time to re-epithelialisation and re-establishing pigmentation in vitiligo leukoderma. Thirteen patients (9 male, 4 female; mean age 51.2 years, range 18-77 years) with generalised, non-segmental vitiligo were included. At the treatment area, two 1cm² sites (labelled 'A' and 'B') were marked within the leukodermic patch (at least 2cm apart), and another two sites of the same size were marked 'C' and 'D'. Site C overlaid the border between the leukodermic and normo-pigmented skin and site D occurred in an adjacent area of normally pigmented skin (from which the donor biopsy was to be taken). The site at which each patient would receive the cell suspension was randomised using opaque, sequentially numbered, sealed envelopes prepared before commencement of the study. These envelopes were opened on the day of surgery by the skin engineering laboratory scientist preparing the cell suspensions. Both surgeon and

patient were blinded to treatment allocation. Either melanocyte/keratinocyte co-suspension in Dulbecco's Modified Eagle's Medium (DMEM) -2% autologous serum (treatment) or DMEM-2% autologous serum alone (placebo) were administered to the treatment sites. All patients were followed up for 12 months.

The randomised clinical trial by Gravante et al (2007) compared ReCell with conventional skin grafts for the treatment of deep partial thickness burns (ReCell: 42 patients; skin graft: 40 patients). Both patient groups were comparable for age, gender, type of burns and total burn surface area (TBSA). Only adult patients with involved areas of less than 320 cm² were recruited. Primary endpoints were the time for complete epithelialisation (both treated and biopsy site) and the aesthetic/functional quality of the epithelialisation. Aesthetic appearance of the epithelialisation was evaluated (Vancouver scar scale) with the assistance of one plastic surgeon that was unaware of the procedure (Gravante et al 2007). The duration of follow-up was not stated.

Cervelli et al (2009) performed a prospective case series study to determine the effectiveness of ReCell in 30 consecutive patients (10 men, mean age: 39 years) with post-traumatic and iatrogenic scars that did not improve with treatment (e.g. peeling, laser, microdermabrasion and dermabrasion). Postoperative follow-up consisted of 4 visits at weekly intervals up to 1 month, followed by visits at 3, 6, 12 and 24 months. Photographs of the treatment site were obtained and assessment of epidermal coverage and wound area were made 5 days postsurgery and at each visit. Primary outcomes were time for complete epithelialisation (treated and biopsy site) and the aesthetic/functional quality of the epithelialisation (colour, joint contractures). Pigmentation was assessed with the Vancouver scar scale (Cervelli et al 2009).

Mulekar et al (2007) performed a comparative case report study between ReCell and melanocyte-keratinocyte transplantation (MKT) for the treatment of vitiligo lesions in five patients (3 males). All patients had a minimum of two lesions at the same anatomical localisation. One lesion was treated with conventional melanocyte-keratinocyte transplantation (with Dulbecco's modified Eagle's medium [DMEM]) while the other was treated with ReCell (with sodium lactate as delivery medium). All patients were assessed by two physicians using photographs taken before treatment and 4 months after transplantation. Nonpigmented areas were measured at 4 months to determine percentage of repigmentation (Mulekar et al 2007).

Safety and Effectiveness

In the study by Back et al (2009) median time to re-epithelialisation was the same in the treated and untreated areas (7 days). The statistical model (Cox proportional hazards model) found no evidence for a difference in the time to re-epithelialisation between the treatment sites (P=0.76). The same was found of the overlapping of a study area onto normo-pigmented skin compared with treated (P=0.37) and untreated (P=0.64) areas. Minor infections at site C, which responded to conservative treatment, may have been responsible for slighted increased time to re-epithelialisation in this area. Time to re-

epithelialisation in the treated area was not affected by the number of cells applied in any of the patients (P=0.51).

Visual Pigmentation Scoring Scale¹ (VPSS) found normal pigmentation was achieved in 38% (5/13) of patients in at least one time point in the site receiving the cells. Two of these patients also achieved the same degree of pigmentation in the areas receiving the placebo in at least one time point. Another patient displayed two small spots of normal re-pigmentation at the site receiving the placebo. At 12 months follow-up, 84% of patients had no pigmentation in the treated area and 100% of patients had no pigmentation in the untreated area.

The leukodermic half of area C developed definite pigment in 3 patients. In one case the area had been mildly infected postoperatively and the pigmentation was apparent at the end of follow-up, but had faded to VPSS 3. In the second case pigmentation faded by 9 months follow-up, and in the third case pigmentation faded between 3 and 6 months with no margin definition seen by 12 months follow-up. Also by the end of follow-up, 92% of patients' leukodermic area had returned to pre-treatment status (no pigmentation in the vitiligo area). In areas A and B there was no evidence of new leukoderma or disease progression. In the normo-pigmented half of site C, four patients experienced hyperpigmentation and nine patients suffered from new leukoderma and lost all pigmentation in that half, persisting until the end of follow-up. As mentioned previously, minor infection of site C was apparent in three patients at day 7. These infections responded to simple, topical treatment. Site A and B were not affected by infection in any of the patient population.

At donor site D, only 15% (2/13) of patients returned to normo-pigmentation postoperatively. One patient healed with severe hyperpigmentation (present at 12 months follow-up), and the remaining patients suffered new leukoderma (complete loss of pigmentation) at this site. The occurrence of new leukoderma at sites with previously normal pigmentation is a result of the Koebner phenomenon.

Compared to conventional skin grafts for burns, the time required for the ReCell procedure was significantly longer (59 ± 4 vs. 20 ± 6 minutes, $p < 0.001$). As expected, area harvested was larger for conventional skin grafting (2.2 ± 1 vs. 110 ± 50 minutes, $p < 0.001$). Gravante et al (2007) noted that complete healing was achieved within 13 days by ReCell and 12 days for conventional grafting, which was comparable for both patient groups. Both groups were similar with regards to aesthetic quality, pigmentation and vascularity. The authors noted that 33% of patients (27/82) developed at least one contracture at hospital discharge after 1 month post-surgery. Of these, 12 were ReCell

¹ Visual Pigmentation Scoring Scale:

NL (new leukoderma) = no pigmentation (previously pigmented area)

0 = no pigmentation (vitiligo area)

1 = minimal pigmentation

2 = slight pigmentation

3 = normal pigmentation

4 = slight hyperpigmentation

5 = marked hyperpigmentation

patients (12/42, 29%) and 15 were skin graft patients (15/40, 38%). No intraoperative or postoperative adverse effects were reported throughout this study.

Cervelli et al (2009) stated that all 30 patients completed the 1 year follow-up and 15 completed the full 2 year follow up. Plastic surgeon assessments for aesthetic and functional outcomes were excellent in 60% (18/30), good in 20% (6/30), fair in 10% (3/30) and poor in 10% (3/30). Pigmentation, according to the Vancouver scar scale, was normal in 60% (18/30), slight in 30% (9/30) and moderate in 10% (3/30). The authors noted that texture, consistency, extensibility and pliability were of good quality while pain was minimal and did not hinder daily activities. At 4 weeks, repigmentation was achieved in 60% of patients (18/30) and in another 10 patients in 7 weeks. Repigmentation did not occur in 6.7% of patients (2/30). No complications were observed throughout this study (Cervelli et al 2009).

In patients treated for vitiligo, Mulekar et al (2007) noted that 60% (3/5) of patients had clinical stability at 1, 3 and 5 years, respectively. At 4 months, patients 1 and 5 achieved complete repigmentation at both ReCell and conventional MKT sites. Meanwhile, patient 4 achieved 65% repigmentation at the ReCell site and complete repigmentation at the MKT site. Patients 2 and 3 had doubtful clinical stability at the time of cell transplantation, patient 2 achieved <50% repigmentation with ReCell/MKT while patient 3 did not achieve any repigmentation (Mulekar et al 2007). Overall, repigmentation was comparable for both techniques.

COST IMPACT

There are no cost-effectiveness studies on ReCell to date. Evidence from the only randomised trial to date indicated that the use of ReCell for burns significantly prolongs the procedure compared to conventional skin grafts, which may increase overall costs. However, this should be considered in view of the fact that ReCell may decrease laboratory processing time in patients with large affected areas.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified from the retrieved material.

OTHER ISSUES

Clinical Cell Culture Ltd. Donated 5 ReCell kits for the study on vitiligo patients conducted by Mulekar et al (2007).

Harvesting of donor skin for processing into cellular suspension is not without risk. In patients with vitiligo the Koebner phenomenon on such 'biopsy' sites is common (75%) and poor scarring at such sites is possible (as it is with any split skin graft donor site) (Personal communication 2010). Failure to adequately check the setting on a dermatome, especially when harvesting skin from hidden sites such as the axilla, can result in deep

trauma to vascular and neurological structures, and poor/delayed healing can occur (Personal communication 2010).

SUMMARY OF FINDINGS

Early peer-reviewed evidence of ReCell indicates that the procedure is feasible, safe and well tolerated by patients. The preparation of the cell suspension is relatively easy and does not require laboratory services. However, there are no clear advantages relative to current treatments for burns, scar reconstruction and vitiligo in terms of patient outcomes. At the time of writing, ReCell does not substitute (at least in the immediate future) traditional skin grafting for burns treatment. Nevertheless, as ReCell only requires the harvesting of small biopsy samples and substantially reduces laboratory processing time, there is potential for its application in the management of patients with large skin defects or in emergency situations.

HEALTHPACT ACTION

The evidence suggests that ReCell is capable of achieving similar outcomes to conventional treatment for burns, scar reconstruction and vitiligo. However, additional comparative studies with larger patient groups are necessary to determine the effectiveness of ReCell and to determine where it fits in current clinical treatment pathways. There is some agreement in the literature that ReCell is probably best utilised in cases with large affected areas where conventional grafting is difficult or requires cell culturing to cover the site, however no studies have been conducted to assess this. Additional data from the ongoing FDA trial would be useful. HealthPACT will note the development of this technology but further assessment by HealthPACT is not necessary at this time.

NUMBER OF STUDIES INCLUDED

Total number of studies	4
Level II intervention evidence	2
Level IV intervention evidence	2

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SEARCH CRITERIA TO BE USED

ReCell OR autologous cell suspension, Keratinocytes/transplantation*, Skin transplantation/methods*.