

Therapeutic focus - Beyond the bandage for venous ulcers



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The disappointing data from Smith & Nephew's venous leg ulcer project HP802-247 might have knocked a promising cell therapy from the pipeline, but wound management specialists have a number of candidates lined up that could change the standard of care from bandaging and compression to a more active biological intervention (see table).

Wound management therapies have moved beyond topical corticosteroids like Elocon to dressings and gels that provide a tissue scaffold that can speed the body's own healing process. The next wave includes some more cell therapy approaches and projects that aim to modulate intercellular communication to assist in the rebuilding of skin layers.

Compression and bandages

These skin ulcers are a consequence of sustained venous hypertension. They occur typically in the leg because of poorly functioning venous valves or failure of the calf muscle to assist in pushing blood back toward the heart, causing reflux; if the veins are not strong, ulceration can occur. Once a wound is established, pain, infection and septicaemia can be complications.

The UK's Nice estimates a prevalence of 1-3 per 1,000 people, and 20 per 1,000 in people over 80. Risk factors include age, obesity, immobility, and a history of varicose veins or deep vein thrombosis. They share some common characteristics with diabetic foot ulcers and pressure sores, making therapies that address them attractive commercial projects thanks to their wide potential use.

Venous ulcers are typically treated with cleaning, debridement, dressings and compression bandages to aid blood flow. In the case of persistent sores surgeons may intervene and repair veins to prevent reflux of blood; this treatment course might not improve healing rates but can prevent recurrence when combined with compression therapy.

Many of the projects in development are part device and part biological therapy, such as dressings that deliver cells that provide a framework to rebuild tissue over the wound (see table). This analysis focuses on such projects and omits treatments like active wound dressings and anti-infectives.

Selected novel agents in the venous leg ulcer space

Phase	Project	Company	Pharmacology class
Marketed	DermaPure	Tissue Regenix Group	Wound healing agent
Approved	Excellagen	Taxus Cardium	Collagen type I
Phase III	HP802-247	Smith & Nephew	Wound healing agent
	CureXcell	MacroCure	Wound healing agent
Phase II	Nexagon	CoDa Therapeutics	Connexin43 (Cx43) inhibitor
	LL-37	Pergamum	AMP mimetic
	Granexin	FirstString Research	Connexin43 (Cx43) mimetic

Small private companies are the order of the day, making this space look more like medtech than biotech.

An exception to this rule was Smith & Nephew, which spent \$782m to acquire Healthpoint Biotherapeutics, a woundcare subsidiary of Texas-based DFB Pharmaceuticals, for access to a line of established products, along

with the phase III HP802-247 ([Healthpoint buy to double Smith & Nephew's US wound operations](#), November 28, 2012). But the rule may well re-establish itself following the failure of a recent trial of the product.

The 12-week, 440-patient study assessed HP802-247, a spray-on suspension of allogeneic keratinocytes and fibroblasts, in combination with standard compression therapy. The product was not shown to close venous leg ulcers more quickly than compression therapy alone. A second trial in Europe with a similar design is expected to read out in 2016.

This is reminiscent of Shire's failure with Dermagraft, a cell therapy that had once been in the hands of Smith & Nephew and acquired by Shire in its \$750m takeout of Advanced BioHealing. Failure in pivotal venous leg ulcer research led to a dwindling of its commercial market, and Shire earlier this year sold the Dermagraft assets to Organogenesis.

Thus the companies in this space probably need phase III validation before big pharma groups will sign on.

Tissue scaffolds

So far, a more successful approach has come from a couple of small companies – California's Taxus Cardium Pharmaceuticals Group and the UK's Tissue Regenix. Both have recently received Q codes in the US for their Excellagen and DermaPure products, allowing for billing of federal health programmes.

The former is purified bovine collagen gel applied to a wound with a syringe and covered with a dressing, intended to assist in the rebuilding of skin tissue. The latter is an allogenic graft made from human donor skin from which DNA and cells have been removed.

Tissue Regenix launched DermaPure in the US in June. Struggling Taxus Cardium, on the other hand, has decided against launching and is looking to partner Excellagen.

Cell therapy and gap junctions

The cell-therapy approach is not dead in phase III. MacroCure, a Nasdaq-traded company based in Israel, is trialling a suspension of donor-derived white blood cells called CureXcell that is applied to the wound in the belief that growth factors, cytokine secretions and other regulatory mechanisms are in balance through the healing process. Two phase III trials are under way, one in venous leg ulcers and one in lower extremity ulcers in patients with diabetes; the former is scheduled to read out in 2016, the latter in 2015.

Phase II is seeing some protein-based therapies emerge. FirstString Research and CoDa Therapeutics are taking the novel approach of modulating intercellular communications channels through the gap junction protein connexin43. This protein is involved in inflammatory response and scarring, and by downregulating it the two companies hope to encourage skin regeneration.

A private South Carolina-based group, FirstString, last year reported positive wound closure data from Granexin Gel in venous leg ulcers and diabetic foot ulcers, and has indicated that it will begin pivotal trials in 2014. Nexagon, from private California-based CoDa, completed phase II early last year, but little news has emerged since these positive data were released.

The Swedish group Pergamum, funded by Karolinska Development, last month reported peer-reviewed publication of positive data from its phase II trial of LL-37. This is a peptide believed to have antimicrobial and tissue-building properties that is not present in chronic wounds.

Pergamum's topical formulation showed a significant improvement in healing rate when compared to placebo in two of three doses.

Treatment for these painful and persistent sores remains rather basic when compared with medical advances in other conditions. The aging of the populations of Western countries, not to mention the rise in such conditions as cardiovascular disease and diabetes that have been identified as risk factors, means the number of people needing treatment for this condition will increase in the coming years. Drug and device companies are certain to continue trying to come up with novel therapies.

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