Evaluate Vantage

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Therapeutic Focus - Diabetic foot ulcer market in need of healing

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Diabetic foot ulcers might not immediately spring to mind when contemplating major unmet medical needs, but in terms of lack of effective treatment options and huge costs to healthcare systems, the condition ranks pretty high. A debilitating and dangerous disorder which affects an estimated 45 million patients worldwide, current treatment practice will at best heal the ulcers of just half of all sufferers.

Yet the pipeline of new candidates is particularly thin and big pharma companies are conspicuous by their absence. Huge development challenges, caused by a poor understanding of these complex ulcers, a lack of decent simulation models and trial recruitment issues, are blamed for the lack of breakthroughs. “Over the last 40-50 years many things have been tried and many things have failed. Treatment hasn’t really moved along much,” says Didier Cowling, co-founder and chief executive of Kuros Biosurgery, one of the few companies left in the space which recently completed enrolment in a phase IIb study of its candidate, KUR-211.

Big but complex

There are approximately 285 million diabetics worldwide, with one in three Americans projected to develop the disease in their lifetime. Roughly 15% of diabetics develop an ulcer at some point and of these sufferers 15% will require amputation of toes, a foot or leg. Six million patients worldwide could therefore suffer amputation of some sort due to an ulcers.

Diabetic foot ulcers are caused by a combination of a loss of sensitivity, especially in the lower extremities, and vascular damage. Patients often do not sense damage to the skin, resulting in a small injury that develops into an ulcer. Due to impaired wound healing capabilities and an increased risk for infection, diabetic foot ulcers often only heal very slowly or not at all, leading to major complications.

“These are diseases with complex etiology”, says Mr Cowling. “These wounds are all very different in their pathology and repair process; even the same ulcer will heal in different ways in different places.”

Development pitfalls

The lack of decent understanding of diabetic foot ulcers is compounded by two main challenges facing the development of new treatment options.

The first is that pre-clinical models are poorly predictive of eventual human success in the clinic, a feature which is particularly unique to chronic wounds. “You cannot simulate this in a test tube. It’s a whole body problem and very difficult to simulate as you can’t aim for a particular target,” says Mr Cowling. “You have to go into human studies mainly on a theory or hypothesis, so many people don’t do it because it is too risky and expensive.”

And once a product does make it into the clinic, the second major challenge appears to be recruitment into trials.

“One of the issues is slow recruitment, as you can only go for patients that aren’t at risk of losing their limbs,” says Paul Kemp, who has been involved in the development of two ulcer treatments, Apligraf and Cyzact.

Organogenesis, where Mr Kemp was vice president of research, launched the cell-based product Apligraf in 1997. Mr Kemp then founded UK biotech Intercytex; Cyzact failed in a phase III trial in 2009 for venous leg ulcers and has since been abandoned.

He believes there is a desire to only enrol patients with full feeling in their limbs. “Any numbness means it is difficult to register any side effects because the patient doesn’t feel any pain and also the patient is at greater risk of losing their limb in the first place. This puts you into a small subset, so recruitment is slow which increases the cost of the trial.”

Taking new candidates into large pivotal trials is therefore particularly problematic if the patient pool is

restricted, which perhaps explains why just one candidate is currently undergoing a phase III trial (see pipeline table below).

Lots of tactics, poor success

Protocols to treat diabetic foot ulcers are not particularly standardised, mainly due to a lack of well controlled studies for the various devices, gels and dressings which are mostly used after the ulcers are 'debrided' – cut right back, often surgically but also through the use of chemicals, enzymes and even maggots, removing the chronically diseased tissue to try and get fresh tissue and blood into the ulcer.

Various dressing types can then be applied, most of which create a moist wound-healing environment, often in conjunction with antibiotics to fight off the high risk of infection.

In terms of more active therapeutic agents, the likes of Dermagraft or Regranex may also be applied to the ulcer, particularly if the ulcer is extensive and fails to respond to other treatments. Apligraf, more of a skingraft type product, can also be applied.

Marketed Therapeutic Agents for Diabetic Foot Ulcers			
Product	**Pharmacological Class**	**Company**	**Originator**
Dermagraft	Fibroblast derived dermal substitute	Shire	Advanced Tissue Sciences
Apligraf	Tissue-engineered skin	Organogenesis	Organogenesis
Regranex (becaplermin)	Platelet-derived growth factor (PDGF)	Systagenix Wound Management/Johnson & Johnson	ZymoGenetics
Easyef (nepidermin)	Epidermal growth factor	Daewoong Pharmaceutical	Daewoong Pharmaceutical
Citoprot-P	Epidermal growth factor	Bioven	Centre for Genetic Engineering and Biotechnology
Regen-D 150	Epidermal growth factor	Bharat Biotech	Bharat Biotech

Another approach which Mr Cowling says is gaining some significant traction is the use of a vacuum device, also referred to as negative pressure wound therapy. The vacuum draws out excess fluid from the wound and helps to increase blood flow to the area around the ulcer.

Overall treatment of diabetic foot ulcers is therefore an intensive daily wound management issue, an overall burden which Shire estimates to cost $3bn in the US alone. And according to Mr Cowling "only 35 to 50% of patients will see their ulcers heal".

Thin pipeline

As for the products currently in clinical trials, the table below lists the agents that have some active therapeutic activity; it excludes antibiotics and products which just try to stimulate a wound healing environment.

The pipeline is dominated by products containing a growth factor, a validated approach given the approval and reasonably widespread use of Regranex. However, Mr Kemp prefers the cell-based approach and is sceptical about the benefits of using specific growth factors. "The issue is getting the right amount of growth factor in the right place at the right time. A single growth factor is no magic bullet. The idea of using cells that are normally presented in the dermis to repair the wound has a more interesting future."

Kuros' KUR-211 contains a modified variant of platelet-derived growth factor (PDGF); Mr Cowling naturally sees potential in a more effective single growth factor. The Kuros agent incorporates PDGF into a fibrin sealant, applied to the wound as a foam, designed to sustain delivery of PDGF to the site to hopefully improve the frequency and speed of healing.

Recruitment of 211 patients into the phase IIb trial was completed earlier this month and results should be available in the first half of 2012. Baxter has been involved in the development of KUR-211 since 2005, but both companies will look for a third partner to take the product into phase III trials, assuming the phase IIb data is positive.

Pipeline Therapeutic Agents for Diabetic Foot Ulcers			
Status	**Product**	**Pharmacological Class**	**Company**
Phase III	HO/03/03	Protein kinase C (PKC) modulator	HealOr
Phase II	KUR-211	Platelet-derived growth factor (PDGF)	Kuros Biosurgery/Baxter International
	DSC127	Angiotensin (1-7)	Derma Sciences
	BBR-012 (isoniazid)	Wound healing agent	Bridge BioResearch
	BioChaperone PDGF-BB Program	Platelet-derived growth factor (PDGF)	Adocia
	BM-MNC	Stem cell therapy	Shenzhen Beike Biotechnology
	Chrysalin (rusalatide)/TP508	Thrombin mimic	Capstone Therapeutics
	Excellarate	Platelet-derived growth factor (PDGF) gene therapy	Cardium Therapeutics
	EPO	Erythropoietin	The Cytonet Group
	CVBT-141B	Fibroblast growth factor (FGF)	CardioVascular BioTherapeutics

Other products trying to improve the effectiveness of single growth factors include Adocia's BioChaperone PDGF-BB Program and CVBT-141B from CardioVascular BioTherapeutics.

Adocia is developing a liquid spray formulation of PDGF-BB, the active agent in Regranex, using its BioChaperone technology, which it believes can reduce the dose of growth factor required by a third and therefore cost much less than Regranex. A phase IIa study is ongoing in India using Regranex as an active comparator and results should be released by the end of the year.

CVBT-141B contains fibroblast growth factor-1 as its active ingredient, the company has completed phase II studies and is currently seeking fast track status from the FDA. Encouraging phase IIb data showed 100% closure of diabetic wounds within five months of treatment with FGF-1, whereas one-third of placebo-treated wounds remained open. Additionally, 57% of FGF-1 treated patients had complete wound closure after eight weeks, while none achieved this in the placebo group.

Alternatives

The most advanced pipeline candidate is HealOr's HO/03/03, currently undergoing a phase II/III trial in the US and India, adopting a slightly more novel approach as a Protein kinase C (PKC) modulator. By modulating PKC activation and PKC inhibition the product stimulates several biochemical pathways simultaneously, reducing inflammation and promoting the growth of fibroblasts and other skin cells.

The 146-patient trial should complete by the end of the year and the primary efficacy endpoint is the level of complete wound closure after 14 weeks.

Another more novel product currently attracting keen interest is Derma Sciences' angiotensin analogue, DSC127. Encouraging phase II results in May helped the company raise $29m through a private placement the following month. That money will be used to start a phase III trial in the first half of 2012, although Derma is also considering partnering options. PII data showed complete wound healing in 73% of patients receiving DSC127 after 24 weeks, compared to 46% with placebo.

Regaining interest

The list of companies developing new candidates to treat diabetic foot ulcers as the prevalance of the disease soars highlights the extent to which industry has turned its back on this sector.

As with many therapeutic areas struggling to attract big pharma interest and funding in general, the chequered developmental history has played a big part, such that the mention of 'wound healing' can be a big

turnoff.

“Big pharma guys shy away from wound healing,” says Mr Kemp. “Yes it’s a big market but it is full of lots of little players. There is nothing dramatically new in terms of science and it is seen as a graveyard for a lot of products and companies. So it is not an attractive sector to be in.”

Yet Shire recently paid $750m for Advanced BioHealing, essentially to purchase Dermagraft, a regenerative bio-engineered skin substitute along similar lines as Apligraf and one of the leading products on the US market. Mr Kemp believes Advanced BioHealing were particularly astute in positioning themselves more in the diabetes space than as a wound healing company.

The recent failure of Dermagraft in a pivotal trial to treat venous leg ulcers (*Shire loses with Dermagraft and wins with Firazyr, August 25, 2011*), has increased the pressure on Shire to meet their bullish predictions for the size of the diabetic foot ulcer market and the product's potential. Analysts have pencilled in sales this year of $186m to rise to $344m by 2016 in this setting, valuing the product at around $725m, according to *EvaluatePharma’s NPV Analyzer*.

Shire’s move on Advanced BioHealing has certainly helped to raise the profile of this medical need and shown that a big company is willing to take a punt on the market. But it will likely take some impressive late stage clinical data before big pharma’s interest is piqued and research dollars start to swell the research pipeline.