INVITED COMMENTARY

PLX-PAD Treatment of Critical Limb Ischaemia: A Clinically Effective Cell Therapy at Long Last?

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Despite the plethora of techniques for open and endovascular treatment of critical limb ischaemia (CLI), significant numbers of patients require amputation within months of presentation, signalling the need for better treatments. Delivery of cells capable of stimulating new blood vessel growth heralded a novel, advanced therapy that promised to achieve limb salvage in patients that had exhausted all other options. This was more than two decades ago. To date, however, the impressive results reported in animal studies have not been reproduced in clinical trials. Previous studies have been criticised for recruiting end stage limbs with no hope of salvage, failing to include adequate controls, delivering low cell numbers in a single injection and poor follow up. In this issue of EJVES, Norgren et al.[1] present the PLX-PAD Cell Treatment of Critical Limb Ischaemia (PACE) study, which aims to assess the clinical efficacy of a novel cell therapy product in a clinical trial designed to address the shortcomings of previous similar efforts.[2]

Patients with CLI recruited into PACE, across 50 European and American sites, will be randomised to receive either Pluristem's PLX-PAD (a population of placenta derived mesenchymal like stromal cells) or a placebo control cell carrier solution. PLX-PAD is an allogeneic proprietary product, shown to promote angiogenesis via the production of pro-angiogenic factors that stimulate endothelial cell proliferation. It can be produced and stored readily prior to administration, reducing the burden of bone marrow harvesting procedures on patients. The allogeneic nature of the product circumvents the functional impairment in autologous cells observed in some studies.[3] Patients will receive a total of 300 million PLX-PAD cells in 30 separate injections along the length of the affected leg. The procedure will be carried out twice with eight weeks between treatments. Follow up will be for at least one year, with amputation free survival as the primary endpoint. Secondary endpoints include ulcer healing, quality of life scores, transcutaneous oxygen, and ankle or toe brachial pressure index changes.

PACE promises to improve on previous studies that have used single injections of illdefined, mixed cell populations that lack potency, but there remain some contentious issues. Exclusion of Rutherford 6 CLI patients and those with any tissue loss above the ankle may significantly limit recruitment, a problem that prematurely has curtailed a number of similar trials to date. Inclusion of patients as early as two weeks after an endovascular limb intervention may confound results as the restoration of flow and perfusion may not yet have reached steady state. In this scenario, any delayed benefits from the initial revascularisation procedure may be erroneously attributed to the cells delivered. While PLX-PAD improves perfusion in the ischaemic mouse hindlimb via angiogenesis (i.e. capillary sprouting), it remains to be seen whether these cells are also able to induce arteriogenesis that is more likely to produce a stable and functional collateral network that can sustain improvements in limb perfusion in men. Adopting a quantifiable measure of limb perfusion, such as serial scanning using BOLD CMR,[4] would have informed objectively changes in perfusion after treatment but no doubt this would have increased the complexity and cost associated with delivering the study.

Overall, PACE is a well designed trial and clearly not just a clone of previous endeavours. It is a significant step towards developing clinically useful cell therapies for CLI and its outcome will be eagerly awaited.

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