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VASCULAR DISEASE

GENE THERAPY FOR CLI DISAPPOINTS

The results of the phase III clinical trial TAMARIS show that gene therapy targeted to increase expression of fibroblast growth factor 1 (also called heparin-binding growth factor 1, and encoded by the *FGF1* gene) does not reduce major amputation or death in patients with critical limb ischemia (CLI). "The results were a big disappointment [because] ... the phase I and II studies looked very promising," says Jill Belch, one of the trial investigators.

Professor Belch has investigated peripheral vascular disease for most of her life, and was "struck by the huge mortality and cardiovascular morbidity experienced by these patients ... and the poor quality of life for them both before and after amputation."

Fibroblast growth factor 1 modulates endothelial-cell function and promotes angiogenesis. In the trial, 525 patients with CLI unsuitable for revascularization were randomly allocated to receive either the human *FGF1* gene or a matched placebo. Eight intramuscular injections were given to the ischemic leg once every fortnight for 4 weeks, and the patients were followed-up for 1 year. The incidence of the primary end point of major amputation or death was not different in the active group compared with the control group (36% versus 33%, hazard ratio 1.11, 95% CI 0.83–1.49, $P=0.48$).

Although these data do not support the use of single-gene therapies in the treatment of CLI, the contrasting findings from earlier trials "give very strong support to the need for large phase III studies, despite the cost and potential delay in getting effective treatments to the patients," observes Professor Belch. The TAMARIS researchers will now consider gene therapies that target multiple sites in the angiogenesis pathway for treating CLI.

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Original article Belch J. *et al*. Effect of fibroblast growth factor NV1FGF on amputation and death: a randomised placebo-controlled trial of gene therapy in critical limb ischaemia. *Lancet* **377**, 1929–1937 (2011)