The search for an effective treatment for critical limb ischemia continues

May 30 2011

Despite showing promising results in a recent phase 2 trial, administration of a novel gene therapy (NV1FGF) to enhance the growth of new blood vessels in people with critical limb ischaemia (whose legs are damaged when blocked arteries lead to a lack of blood flow), does not reduce amputation or death, according to the results of the phase 3 TAMARIS trial.

The findings, published Online First in *The* Lancet, highlight the challenges of finding an effective treatment for critical limb ischaemia, the most severe form of peripheral artery disease, which affects one in ten adults older than 50 years in high-income countries and results in more than 150 000 amputations in the USA every year.

Currently, treatment for critical limb ischaemia is limited to surgical bypass or revascularisation (the use of stents or balloons) to improve blood flow and prevent amputation. However, these procedures are costly and up to 50% of patients require subsequent surgery for wound complications, and 20% need an amputation within 3-5 years. Furthermore, many patients are unsuitable for such procedures. The lack of treatment options has led to extensive research into the development of therapeutic angiogenesis (using gene therapy to induce blood vessel growth) to reduce the need for amputations, although its long-term effects are not known.

In the phase 2 TALISMAN trial, non-viral DNA delivery of the gene for fibroblast growth factor type 1 (NV1FGF) was well tolerated and

showed a large reduction in amputations and a trend toward reduced death.

To provide further evidence, the phase 3 TAMARIS trial recruited 525 patients unsuitable for revascularisation from 171 hospitals across 30 countries and randomly assigned them to intramuscular injections of NV1FGF (259 patients) or placebo (266).
After 1 year, no difference in time to major amputation or death was recorded between the groups.

The authors say: "TAMARIS provided no evidence that NV1FGF is effective in reduction of amputation or death…Thus, this group of patients remains a major therapeutic challenge for the clinician."

They conclude: "[These results] portray the challenges faced by the development programmes of single genes, such as extrapolation from conclusive animal studies to define optimum dose, vector, route, and duration of administration, as well as whether the administration of any one gene could result in therapeutic angiogenesis leading to the prevention of limb amputations."

In a Comment, Gerry Fowkes and Jackie Price from the University of Edinburgh, Edinburgh, UK point out that trials of gene therapy in critical limb ischaemia are prone to difficulties: "Patients usually have widespread cardiovascular disease, and angiogenesis might be inhibited by risk factors, such as dyslipidaemia and diabetes (In TAMARIS, 60•4% of patients had hyperlipidaemia and 53•3% had diabetes, although no difference in effect was noted in those without diabetes). Cardiovascular drugs, such as statins (62•5% of patients in TAMARIS) and angiotensin-converting enzyme inhibitors (51•4%), might also have inhibited angiogenesis. Furthermore, many experiments suggest¬ing efficacy are in young healthy animals, whereas patients are elderly with extensive disease and in whom gene therapy might be ineffective."

More information: The study can be found: www.thelancet.com/journals/lan … (11)60394-2/abstract

Provided by Lancet