Evaluate Vantage

November 17, 2010

AHA 2010 – Little hope for gene therapy in ischaemic limbs

Amy Brown

If there was any lingering hope that Vical's gene therapy might show efficacy in regrowing leg arteries, it has been completely dashed. In trial results that were declared definitive by the lead investigator, Temusi showed itself to be no better than placebo for averting leg amputations and death in patients with critical limb ischaemia (CLI), another blow for a gene therapy space hoping for a big success (*AHA Preview – Novel therapies creating excitement at heart conference, November 10, 2010*).

There was little expectation that the full Tamaris phase III trial data would be more positive than the topline results announced in September (*Gene therapy suffers another blow as Temusi crashes out, September 23, 2010*). However, in detailing the data at the American Heart Association meeting, lead investigator Dr William Hiatt suggested that gene therapy is unlikely to bear fruit in the angiogenic approach to treating the debilitation condition.

"This is a definitively negative trial," said Dr Hiatt, a professor of cardiovascular research at the University of Colorado. He added: "The concept of angiogenesis is still alive. Cell-based therapy is really the next thing."

Dire diagnosis

CLI is an extremely disabling condition, resulting in 100,000 amputations each year, and a critical unmet need as 20% of CLI patients die and 35% have undergone an amputation in the first year after diagnosis,

Amputation rates in the US have not declined in the last 30 years, said Dr Doug Losordo, director of the Feinberg Cardiovascular Research Center at Northwestern University, "signalling the need to develop novel strategies for these patients."

Commenting on the trial results, Dr Losordo pointed to possible flaws in the trial design, including expansion into Eastern European and South American sites where the population might have a genetic resistance to the therapy, as well as an unexpectedly low amputation rate in the placebo arm that made statistical significance more difficult to achieve.

But Dr Hiatt's description of the trial as definitive suggests little interest in exploring subgroups that may benefit from the therapy, and trial sponsor Sanofi-Aventis is widely expected to cancel the programme.

Growing well

Also known as NV1FGF, Temusi is a DNA vaccine encoding fibroblast growth factor-1 (FGF-1), a protein thought to stimulate the growth of blood vessels. Vical's technology constructs plasmids containing the DNA used in the therapy – in the case of Temusi, FGF-1.

Temusi came through with positive phase II data and was thought to be one of the more promising candidates in the gene therapy space (*Therapeutic focus - Will hopes evaporate as gene therapy pipeline flows?, August 25, 2010*). Certainly, Vical's dominating presence in gene therapy made the Temusi setback a bit easier to withstand, although in its wake the company sold $32m in new shares.

That the lead investigator is leaning toward a cell-based therapeutic approach is telling about gene therapy's promise in CLI, although a leading researcher in cardiac cell regeneration cautions against the idea of separating the two as genes can change cell behaviour.

"They are going to be combined," said Dr Piero Anversa director of the Center for Regenerative Medicine at Brigham and Women's Hospital in Boston. "I don't think that cell therapy should be seen as so different or distinct from gene therapy. I think that's a mistake."

For Vical, that is little consolation, however, as it appears its candidate may be laid to rest.

Trial ID	NCT00566657 (Tamaris)