重篤な下肢虚血に関するトライアルで遺伝子治療は不成功に終わった（Abstract＃21790）

TAMARIS：実験的遺伝子治療は末梢血管疾患患者の下肢切断または死亡を防止しなかった

TAMARIS: Experimental gene therapy did not prevent amputation or death in patients with peripheral vascular disease

遺伝子治療は重篤な末梢血管疾患(PAD)により足潰瘍を来した患者の下肢切断または死亡を防止しなかったとのレイトブレイキング臨床試験の結果が2010年AHA学会で発表された。過去のphase 2トライアルの勇気づけられる結果に反して、NV1FGF遺伝子治療の重篤下肢虚血における下肢切断回避率に関するトライアル（NV1FGF Gene Therapy Trial on Amputation-Free Survival in Critical Limb Ischemia）−phase 3無作為化二重盲検プラセボコントロールトライアルにおいて、NV1FGFとして知られる細胞増殖因子による実験的遺伝子治療を受けた患者はプラセボを投与された患者と比較して結果が良好ではなかった。この12ヵ月間のスタディにおいて、研究者らは重症PAD患者259人（男性70%、平均年齢70歳）をプラセボ治療群に無作為に割り付け、一方266人の患者は遺伝子治療細胞増殖因子を投与された。プラセボを投与された患者のうちトライアル中に下肢切断に至ったのは21%であったのに対し、遺伝子治療を施行された患者におけるその割合は26%であった。プラセボ群の15%が死亡し、一方遺伝子治療群では 18%が死亡した。これらの結果に有意差はなかった。

Full Text

Gene therapy did not prevent amputations or death among patients with severe peripheral vascular disease and resulting foot ulcers, according to a late-breaking clinical trial presented at the American Heart Association's Scientific Sessions 2010.

Despite encouraging data from the Phase 2 trial, patients treated with the experimental gene therapy growth factor known as NV1FGF did not fare better than those given placebo among participants in the NV1FGF Gene Therapy Trial on Amputation-Free Survival in Critical Limb Ischemia - Phase 3 Randomized Double-Blind Placebo-Controlled Trial (TAMARIS).

Scientists designed NV1FGF to stimulate new blood vessel growth to increase blood flow to save the legs and prolong the lives of patients with peripheral artery disease (PAD).

"Overall, it's a very disappointing result," said William R. Hiatt, M.D., a co-author of the study. "Patients with peripheral artery disease are very sick and at high risk of limb loss and death. We desperately need new medical advances to treat this population."

The trial's patients, who suffered from critical limb ischemia, had exhausted available options and were highly likely to have a leg amputated or die from their disease. Because of the severe lack of blood flow in their legs, many patients had severe leg and foot pain and painful foot ulcers.

Researchers conducted the study after an earlier, smaller study showed "quite positive" results for ulcer healing. "It's troublesome after having a quite remarkable Phase 2 trial," said Hiatt, professor of medicine and cardiology at the University of Colorado School of Medicine and president of CPC Clinical Research, a non-profit cardiovascular and clinical trials research organization affiliated with the University of Colorado in Aurora, Colo.

"There was a lot of promise for gene therapy to treat coronary and peripheral artery disease over the last decade," he said. "We hope that the next phase of stem cell based therapy will have better results."

In the 12-month study, researchers randomly assigned 259 patients to receive an inactive placebo treatment, while 266 patients received the gene therapy growth factor. The patients, who came from 30 countries, were at high risk of losing a leg because of severe PAD. The patients had foot ulcers as well as low blood pressure in the ankle or foot and were not good candidates for surgical revascularization, a procedure to restore blood flow.

More than half the patients had diabetes - far higher than the rate of diabetes in the general population, which is about 10 percent. "Diabetes predisposes you to ulcers, so this is not unexpected," Hiatt said.

The patients and their doctors didn't know if the eight injections they received contained placebo or NV1FGF, which is still an experimental therapy in the United States. They received injections in leg muscles on days one, 15, 29 and 43 of the study.

Of patients on placebo, 21 percent suffered a major amputation during the trial, compared to 26 percent of those on the gene therapy regimen. Fifteen percent of the placebo group died, compared to 18 percent of the gene therapy group. These results were not significantly different.

Seventy percent of the participants were men, the average age was 70. Sixty-one percent had a history of smoking and 54 percent had a history of coronary artery disease.

In future studies, researchers should focus on stem cell-based therapy and stem cell lines that promote angiogenesis, growth of new blood vessels, Hiatt said. "That's the next step in my mind. Angiogenesis remains a viable treatment option to study."

Co-authors are Eric Van Belle, M.D., Ph.D.; Sigrid Nikol, M.D., Ph.D.; Lars Norgren, M.D., Ph.D.; Iris Baumgartner, M.D., Ph.D.; Vickie Driver, M.D., Ph.D. and Jill Belch, M.D. Professor Belch was the chair of the steering committee and will be the primary author on the study results. Author disclosures are on the abstract.

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