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Vascular Endothelial Growth Factor Gene Transfer for Diabetic Polyneuropathy

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Diabetic neuropathy is the most common neuropathy in the industrialized world. The cause of the disorder is poorly understood, which complicates development of effective therapies.¹ Optimum glycemic control decreases the risk for development of peripheral neuropathy,^{2,3} but there are not yet any therapies that effectively reverse impaired nerve function. Current pharmacological approaches, therefore, focus primarily on reduction of painful symptoms. In this issue of *Annals*, Ropper and colleagues⁴ report the results of a phase 2 randomized trial of intramuscular gene transfer using plasmid vascular endothelial growth factor (VEGF) to treat diabetic neuropathy. VEGF is a proangiogenic growth factor, and the hypothesis underlying Ropper and colleagues'⁴ approach is that microvascular ischemia is an important cause of diabetic polyneuropathy.^{5,6} In this trial, either VEGF-expressing plasmid or placebo was injected into multiple sites in one leg, and the contralateral leg was used to adjust for changes occurring independent of the therapeutic intervention. The primary end point was improvement in the adjusted sensorimotor symptom score and the trial successfully met this test of efficacy. Although there was an increased incidence of serious adverse events associated with the treatment, the increase did not achieve statistical significance.

These results are interesting and potentially important for several reasons in addition to the obvious potential impact on the immense problem of diabetic neuropathy. First, therapeutic trials of growth factors for diseases of the nervous system have conspicuously failed in the past, and validation of the results of this trial would provide renewed support for the concept of growth factor therapies for neural disorders. Second, the method of delivery of the therapeutic protein, gene transfer using injection of a plasmid, would also represent an advance for treatment of the nervous system. However, the authors themselves are appropriately cautious about their results and comment in their abstract that the findings are not conclusive. They also clearly outline some of the weaknesses of the trial including its small sample size, the use of two different isoforms and dose escalation of VEGF, and the use of a nonstandard scale for grading diabetic neuropathy. In addition, the largest improvements in symptoms in this study were found in the untreated legs of placebo-treated patients. As a result, the adjustment of scores for the treated leg relative to the untreated leg both increased the estimated treatment effect and reduced its standard error, resulting in a statistically significant treatment effect. As the authors note, this tempers any conclusions, and a larger study is necessary to validate the results.

Interest in the use of neurotrophic factors as therapies for neurological diseases derives both from their capacity to promote neuronal survival and regeneration, and from evidence that impaired neurotrophic support contributes to the pathophysiology of many disorders including diabetic neuropathy.^{7–14} Clinical trials of injection of recombinant human nerve growth factor (rhNGF) in diabetic neuropathy were initially positive in phase 2 trials but

failed in a larger phase 3 trial.^{15,16} Reasons for this failure may have included “a robust placebo effect, inadequate dosage, different study populations, and changes in the formulation of rhNGF.”¹⁷ Ropper and colleagues⁴ comment that the same issues apply to the VEGF study described in this issue of *Annals*. Clinical trials of brain-derived neurotrophic factor in diabetic neuropathy also failed.¹⁸ Of particular relevance is the recently reported lack of efficacy in phase 2 trials in diabetic neuropathy of SB-509, an injectable formulation of a transcription factor designed to upregulate the expression of the gene encoding VEGF-A.

The rationale for use of proangiogenic factors such as VEGF in diabetic neuropathy is based on the hypothesis that diabetic neuropathy results from microvascular damage and from shunting of blood through epineurial vessels.^{19–21} In diabetic rats, several proangiogenic factors including VEGF, insulin-like growth factor-1, and basic fibroblast growth factor have protected against the development of neuropathy. However, each of these growth factors including VEGF^{22–24} acts on multiple cell types and exerts trophic effects in addition to the proangiogenic ones. It is noteworthy that in one study in diabetic mice, the protective effects of VEGF gene therapy against sensory nerve dysfunction occurred independent of angiogenesis.²⁵ It is thus quite possible that the putative efficacy of VEGF in diabetic neuropathy is related to provision of trophic support rather than effects on the vasa nervorum.

Growth factors such as VEGF are proteins and, in general, cannot be administered orally. Alternate methods of delivery include injection of recombinant protein, administration of small molecule analogues, or administration of molecules that increase expression of endogenous growth factor. Gene therapy provides another approach, and there are a number of potential ways of delivering DNA to express the factor of interest including viral vectors or injections of either plasmids or liposomes containing DNA. Ropper and colleagues⁴ study injected plasmids into multiple sites in one leg. The authors comment that it is unlikely that this approach generates circulating levels of VEGF sufficient to treat the neuropathy.²⁶ This approach thus has the advantage of limiting potential systemic effects of the growth factor. However, it also suggests that treatment of patients with neuropathy would require injection into all affected limbs.

Although the findings in this study are promising, and there are substantial supportive preclinical data for the efficacy of VEGF in diabetic neuropathy, it should be noted that most secondary measures in this trial did not show any benefit. Unfortunately, the history of clinical trials in diabetic neuropathy is littered with initially promising therapies that ultimately failed in larger clinical trials. Notably, the authors were both candid and cautious about making firm conclusions about the efficacy or safety of the treatment, and indicate that a larger trial will be necessary. We will all await that trial with great interest.

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