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Review

Clinical tests of neurotrophic factors for human neurodegenerative diseases, part 1: Where have we been and what have we learned?

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ABSTRACT

Over the past 25 years, about 3 dozen clinical reports have been published regarding the safety and possible efficacy of neurotrophic factors in patients with various neurodegenerative diseases. This effort involved a half dozen different neurotrophic factors, using at least 5 different general delivery approaches for ALS (amyolateral sclerosis), peripheral neuropathies, PD (Parkinson's disease) and AD (Alzheimer's disease). While none of these efforts have yet produced efficacy data sufficiently robust or reliable to establish neurotrophic factors as treatments for any human disease, the obstacles encountered and novel information reported, when viewed collectively, provide important insight to help future efforts. Three consistent themes emerge from these publications: (1) unexpected and undesirable side effects, at times serious, have plagued many efforts to deliver neurotrophic factors to humans; (2) the magnitude and consistency of clinical benefit has been disappointing; (3) by far that most consistently proposed reason for the side effects and poor efficacy has been inadequate dosing and delivery.

This paper reviews and attempts to synthesize the available data derived from clinical tests of neurotrophic factors for neurodegenerative diseases. The obstacles encountered, the solutions attempted, and the lessons learned are discussed. The vast majority of solutions have involved changes in dosing paradigms and dose levels, which has primarily led to improved safety outcomes. However, lack of adequate efficacy remains a significant issue. While current efforts continue to focus exclusively on still-further changes in dosing parameters, a review of available data argues that it may now be the time to ask whether other, non-dose-related variables should be given more serious consideration as being responsible for the great divide that exists between the robust effects seen in animal models and the relatively weak effects seen in human neurodegenerative patients. Foremost among these appears to be the severe degeneration seen in the majority of patients enrolled in past and current trials testing neurotrophic factors in humans. A companion paper (Bartus and Johnson, 2016), reviews the contemporary data and concludes that compelling empirical evidence already exists for enrolling earlier-stage subjects as likely essential to achieving more robust and reliable benefit.

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1. Introduction: clinical efforts to capture the 'promise of neurotrophic factors'

It is well-established that endogenous neurotrophic factor proteins, long-ago shown to play essential roles in neuronal differentiation, survival, and connectivity during development, are also able to restore morphology and function of degenerating neurons in adulthood, when applied exogenously. Over the past several decades, a rich research history has accumulated regarding the therapeutic promise of neurotrophic factors, rendering any repetition of their potential here superfluous. What may be less familiar to current investigators is the 25-year history involving clinical testing of the safety and efficacy of neurotrophic factors for human diseases. This effort includes approximately 3 dozen different clinical reports of 6 different neurotrophic factors delivered by several alternative routes and methods to subjects diagnosed with ALS, peripheral neuropathies, Alzheimer's and Parkinson's disease. Some studies tested hundreds of subjects while others were seminal case reports. Though none produced data sufficiently compelling to establish any neurotrophic factor as a treatment for any human disease, there is no doubt that much has been learned in the course of conducting these human studies. The question is, to what extent this accumulated insight might be used to improve the probability of future success in the clinic.

This review will explore some of the major reasons why the long-term effort to translate the therapeutic potential of neurotrophic factors to the human clinic has proven to be so difficult. Because no study or approach has yet produced data sufficient for FDA or EMA approval, this review will focus less on the strength of the efficacy data generated and more on some of the general obstacles encountered or issues identified throughout the conduct of these studies. Though most contemporary efforts attempting to translate neurotrophic factors to the clinic have now migrated toward a CNS-anatomic-targeting approach, the vast majority of early efforts used systemic injections, producing whole-body exposure of the neurotrophic factor. Despite this difference, these early studies encountered obstacles and issues similar to many seen today and therefore remain relevant to advancing contemporary and future efforts.

2. The early efforts: systemic delivery

While the very first clinical report testing a neurotrophic factor as a possible treatment for neurodegenerative disease described the effects of NGF (nerve growth factor) infused into the basal ganglion of a Parkinson's disease patient (Olson et al., 1991), that single-subject case report was very much an 'outlier' and way ahead of its time. That is, beginning in the early 1990s and continuing through the early part of the next decade, the greatest clinical activity with neurotrophic factors employed subcutaneous (sc) injections to produce systemic exposure of the protein. Between 1993 and 2001, a dozen clinical reports were published describing the results of systemic exposure of recombinant human CNTF, IGF-1, NGF or BDNF to patients with either ALS or peripheral neuropathies (Table 1).

2.1. Efforts to treat ALS

Among the earliest efforts to test the value of neurotrophic factors in ALS was a series of trials administering subcutaneous (sc) injections of recombinant human CNTF (rhCNTF or ciliary neurotrophic factor), culminating in several reports published in the early to mid-1990s (Brooks et al., 1993; ALS CNTF Treatment Study, ACTS Phase I-II Study Group, 1995; ALS CNTF Treatment Study Group, 1996). Two notable reports, published within a year of each other described randomized, multi-dose, double-blind, controlled trials involving hundreds of patients each (Miller et al., 1996; ALS CNTF Treatment Study Group, 1996). Both reported serious, dose-limiting side effects, particularly involving weight loss and anorexia, with no clear evidence of benefit. As discussed in the next section, the problems of dose-related side effects and inability to achieve reliable efficacy with the sc delivery approach eventually prompted other investigators to address those issues with changes in the dosing paradigm to intrathecal delivery.

A similar sc administration approach was adopted by other investigators in the mid-to-late 1990s for rhBDNF (recombinant human brain-derived neurotrophic factor) in ALS (BDNF Study Group, 1995; BDNF Study Group, Phase III, 1999). Though dose-limiting side effects were not seen in either of the two studies, efficacy was also not achieved. The authors repeated what would become a recurring

Table 1
Publications reporting novel findings following systemic administration of neurotrophic factors to humans.

Neurotrophic factor	Disease/disorder	Delivery method	Route	First author	Year published
rhCNTF	ALS	Protein injection	Subcutaneous	Brooks	1993
rhCNTF	ALS	Protein injection	Subcutaneous	ALS CNTF Study Grp	1995
rhBDNF	ALS	Protein injection	Subcutaneous	BDNF study group	1995
rhCNTF	ALS	Protein injection	Subcutaneous	ALS CNTF Study Grp	1996
rhCNTF	ALS	Protein injection	Subcutaneous	Miller	1996
rhIGF-1	ALS	Protein injection	Subcutaneous	Lai	1997
rhNGF	Healthy volunteers	Protein injection	Intradermal	Dyck	1997
rhNGF	Diabetic neuropathy	Protein injection	Subcutaneous	Apfel	1998
rhIGF-1	ALS	Protein injection	Subcutaneous	Borasio	1998
rhBDNF	ALS	Protein injection	Subcutaneous	BDNF Study Group	1999
rh-NGF	HIV-assoc. neuropathy	Protein injection	Subcutaneous	McArthur	2000
rhNGF	Diabetic neuropathy	Protein injection	Subcutaneous	Apfel	2000
rh-NGF	HIV-assoc. neuropathy	Protein injection	Subcutaneous	Schifitto	2001
rhIGF-1	ALS	Protein injection	Subcutaneous	Sorenson	2008