Neuroprotection in Parkinson's Disease: Myth or Reality?

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Parkinson's disease (PD) is a chronic, progressive, neurodegenerative disorder with no cure. Therapies that delay or halt disease progression are urgently needed, but finding such therapies has been difficult. In this article, we review historical and recent clinical trial work in the field of neuroprotection. Several issues have arisen during the search for disease-modifying therapies, including challenges in selecting appropriate therapeutic targets, assessing potential therapies, and selecting the proper patient population to study. Advances in the understanding of PD pathogenesis are presented as they relate to selecting potential therapeutic targets, and issues with preclinical testing are described. We review recent innovations in clinical trial design, including futility studies and delayed-start designs that promise to make clinical testing more efficient. It is hoped that ongoing work in this field will lead to treatments that delay the progression of PD.

Introduction

Parkinson's disease (PD) is a chronic, progressive, neurodegenerative disorder with the cardinal symptoms of tremor, rigidity, and bradykinesia. The search for neuroprotective therapies has spanned 20 years and enrolled over 5000 patients to date [1]. Unfortunately, we are still without a definitive neuroprotective therapy in PD, a problem PD shares with other neurodegenerative disorders. There may be several reasons for this. First, we may not have chosen the right interventions to study. This task is challenging, and rational target selection requires knowledge of disease pathogenesis and animal models that successfully predict outcomes in humans. These are two issues that require further study in PD. Second, the effects we are trying to detect are modest and therefore difficult to distinguish from random variation. This requires large sample sizes to guard against rejecting a potentially effective therapy. In this sense we may simply have not enrolled a sufficient number of individuals in clinical trials to date.

Two other potential problems are outcome selection and clinical trial design. Historically, PD trials have used measurement of motor symptoms as a primary outcome. However, several factors may affect motor symptoms at any given time, and separating a neuroprotective benefit from a symptomatic improvement is difficult. Given the likely effect size of a single therapy, practical and important issues of sample size, power, study length, and study cost can hamper effective execution of a rigorous, fully powered trial. Innovations in clinical trial design may be necessary to detect modest long-term effects that are nonetheless clinically meaningful.

The final problem is that perhaps "neuroprotection" is the wrong word. Neuroprotection has been defined in several different ways, but generally it is considered a therapy that slows, prevents, or reverses neuronal loss or dysfunction, leading to improved patient function. Inherent in this definition is the assumption that we can effectively measure "neuronal loss or dysfunction" in humans. Unfortunately, we cannot yet do this; no outcome has been conclusively linked to neuroprotection. Without an accepted measure for neuroprotection, it will continue to be difficult to determine if treatments have this effect.

Choosing Therapeutic Targets: A Selective Review of PD Pathogenesis

Stress hurts: mitochondria, the oxidative stress response, and cell death

Mitochondria and oxidative stress have long been implicated in the pathogenesis of PD, based initially on pathologic data from postmortem PD brains and toxin-induced animal models of PD [2]. Further research identified decreased mitochondrial complex I and II/III activity in the platelets of early untreated PD patients, suggesting that the changes were not due simply to end-stage disease processes or drug therapy [3]. Abnormal mitochondrial complex I activity and other oxidative stress mechanisms promote α-synuclein aggregation [4], providing a connection between two pathogenic mechanisms

in PD. Advances in PD genetic research have provided additional evidence supporting the role of mitochondrial dysfunction and oxidative stress in PD pathogenesis. Mutations in the *DJ-1* gene are associated with early-onset PD [5]. Although the function of its protein product is unknown, it has been implicated in the oxidative stress response, in D2 dopamine receptor signaling, and as a cellular chaperone [6••]. PINK1 (PTEN-induced kinase 1) a mitochondrial-associated kinase whose frequency in PD ranges from 1% to 8% [6••]. The protein products from *PINK1* and a third gene, *Omi/HTRA2*, may share a common pathway by regulating the mitochondrial response to oxidative stress and apoptosis [7]. These findings have triggered extensive interest in compounds that support mitochondria or mitigate the oxidative stress response. Several such compounds were identified in a systematic assessment of potential neuroprotective agents in PD [8], and two compounds, creatine [9•] and coenzyme Q10 [10], are entering large-scale efficacy trials.

Cellular indigestion: PD as a proteasomal disorder

Pathologically, PD is defined by loss of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies, which are cytoplasmic neuronal inclusions that contain several cellular proteins, including α-synuclein. Most mutations resulting in familial PD phenotypes are associated with the presence of Lewy bodies at autopsy, including mutations in α-synuclein itself. Recently, Braak et al. [11••] have outlined an ascending pathologic staging of PD based on the systematic spread of Lewy body inclusions throughout the brain. α-Synuclein likely plays an important role in PD pathogenesis, although mutations do not cause the majority of sporadic PD, and researchers are actively seeking to understand more about its function, processing, and accumulation.

In addition to the formation of Lewy bodies, additional evidence suggests the proteasomal system may be impaired in PD. Proteasomes are responsible for protein degradation and digest short peptides, oxidized proteins, and proteins labeled with ubiquitin [12•]. In this way, they remove damaged or abnormal proteins that would otherwise interfere with normal cell function. Inhibition of the proteasomal system, whether by toxins, oxidation, protein aggregation, or energy failure, leads to continued protein aggregation with inclusion formation. This ultimately activates apoptotic programs leading to cell death [13]. Pathologic data show that proteasomal function is impaired in PD [14], although whether this impairment occurs early or late in the disease is unclear. The link between the proteasomal system and PD is strengthened by genetic data identifying mutations in *PARK2* (an E3 ubiquitin ligase) and *UCHL-1* (ubiquitin carboxyl-terminal hydrolase) in PD kindreds. The search for agents supporting proteasomal function or inhibiting protein aggregation may result in new treatments for PD and other neurodegenerative diseases.

Preclinical Testing: Lost in Translation

The MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and 6-OHDA (6-hydroxydopamine) models induce selective dopamine cell loss and have been very successful at identifying symptomatic (dopaminergic) therapies. However, their track record at selecting effective neuroprotective therapies is poor. TCH346, an antiapoptotic drug with structural similarities to selegiline, showed great promise in both in vitro and animal models, including a rat 6-OHDA model and a primate MPTP model [15]. In a large, randomized trial of 301 patients, however, TCH346 showed no evidence of a neuroprotective effect. CEP-1347, another antiapoptotic agent, also showed excellent preclinical promise but did not demonstrate a clinical effect [16•]. These results suggest that these models may successfully predict neuronal protection in animals, but they do not predict a slowing of disease progression in humans.

There are several explanations for this. First, both MPTP and 6-OHDA are toxins that selectively damage the dopaminergic system. They therefore will not necessarily address other neurotransmitter systems disabled in PD. This fact is reflected clinically in the abundance of treatments for motor symptoms compared with the near-total lack of interventions for nonmotor symptoms, such as postural instability and cognitive impairment. Second, both toxins are given acutely or subacutely, and the resultant damage may better approximate a single toxic hit rather than progressive neurodegeneration. Third, neuroprotective therapies are frequently given to animals before the toxins are given. This entirely contradicts the human experience, in which the initial pathogenic event is presumed to occur several years before PD is diagnosed and individuals become available for neuroprotective therapy. Finally, neither MPTP nor 6-OHDA models result in the formation of Lewy bodies, whereas Lewy bodies are nearly universally present in brains of humans with PD.

These concerns suggest that other preclinical models are urgently needed if we are to properly select neuroprotective therapies. The great strides made in PD genetics make several unique models possible, and these models may better represent the progressive nature of PD. Another option is a proteasomal inhibition model. McNaught et al. [17] used proteasomal inhibitors to induce an apomorphine-responsive progressive parkinsonism in adult rats. This model was associated with Lewy body–like inclusion bodies and cell death in the substantia nigra as well as in the locus ceruleus and dorsal motor nucleus of the vagus. However, several other groups have been unable to replicate these promising findings and the model remains controversial [18••].

Clinical Trials: Issues with Measuring Neuroprotection

Which patient population should be enrolled in clinical trials?

Although at first patient selection would seem a simple matter, the issue is actually quite complicated. Intuitively, patients who are identified as early in the disease course as possible would be expected to benefit most from neuroprotective agents. However, no tests are available to identify premanifest PD. Additionally, it may be difficult to conclusively distinguish early PD from other neurodegenerative parkinsonisms (multisystem atrophy, progressive supranuclear palsy), vascular parkinsonism, or drug-induced parkinsonism. Clinical diagnostic accuracy estimates vary, but reach 90% at best [19]. Little information is available about the extent of damage already present at the time symptoms begin, whether this damage is permanent or reversible, and the type and extent of compensatory mechanisms in play as the disease progresses. Finally, the clinical presentation of PD is variable, and whether this phenotypic variation represents individual susceptibilities or separate pathogenic mechanisms is unknown.

Defining outcome measures

Several outcome measures have been used in clinical neuroprotective trials (eg, Unified Parkinson's Disease Rating Scale [UPDRS] and time to levodopa therapy), but these measures evaluate changes in symptoms and provide no direct evidence for modifying the underlying disease process. Given the complex and probably multiple pathogenesis of neurodegeneration, the most likely effect of a single therapy is a modest but meaningful slowing of progression. It is difficult to definitively separate a short-term symptomatic effect from a neuroprotective benefit based on clinical rating scales that emphasize motor symptoms. Additionally, the slow progression of symptoms, particularly in patients receiving dopaminergic therapy, means studies usually must run at least 12 months to document measurable change [9•,20]. Therefore, outcomes that measure nonmotor aspects of PD may be useful in measuring disease-modifying effects. Cognitive symptoms, for example, are relatively unresponsive to current symptomatic therapies in early PD and continue to progress over time despite optimal medical management of motor symptoms. Consequently, outcomes from rating scales, such as the Montreal Cognitive Assessment (MoCA) [21], in nondemented populations may provide evidence of a disease-modifying effect that can be separated from any effect on motor symptoms.

To improve outcome measurement using currently available scales, some researchers are using a global statistical test. This analysis technique combines information from multiple correlated outcomes into a single measure of treatment effectiveness [22]. If all of the outcomes of interest respond to treatment effects in the same direction, the power of this test is increased above more traditional approaches. If the outcomes respond differently to treatment, the power to detect a significant difference is reduced. This kind of analysis may be useful for diseases such as PD, where outcome measurement is complex and several outcomes may be needed to fully capture the range of PD symptoms. Conversely, therapies that affect only a single aspect of PD would be expected to perform less well with this kind of end point.

Because of the complexities surrounding clinical outcome measurement, the research community is actively searching for a useful biomarker to measure disease progression. α-Synuclein is an appealing candidate because it is a major component of Lewy bodies and because mutations in α-synuclein result in familial forms of PD [23,24]. α-Synuclein has been measured in plasma [25] and cerebrospinal fluid [26], and α-synuclein levels have been used to distinguish individuals with PD from unaffected controls. Other potential biomarkers include smell testing [27] and alterations in gene expression as measured by genome-wide expression scans [28], which seek to identify individuals with early PD and distinguish them from other forms of parkinsonism.

Several studies have examined radiotracer neuroimaging biomarkers for PD progression. The Parkinson Study Group enrolled 361 individuals in a randomized, blinded, placebo-controlled trial that sought to identify if levodopa hastened the progression of PD [29]. During the trial, 142 patients were enrolled in a substudy evaluating single-photon emission computed tomography (SPECT) imaging (using ^{123}I-β-CIT) to evaluate the effect of levodopa on striatal dopamine transporter density. Clinically, the patients on the highest dose of levodopa responded best at 42 weeks, an effect that persisted despite a 2-week washout period. Conversely, the SPECT data showed that the levodopa groups had a significantly greater decline in dopamine-transporter density, suggesting a potentially toxic effect of levodopa. This disconnect between clinical response and imaging outcome was also noted in two separate trials of dopamine agonists versus levodopa as treatments for PD. The first study (Comparison of the Agonist Pramipexole versus Levodopa on Motor Complications of Parkinson's Disease [CALM-PD]) compared pramipexole versus levodopa as initial therapy for PD [30]. In this study, which also used β-CIT, 301 patients were randomized to receive either levodopa or pramipexole, and a subset of 82 patients underwent imaging. At 46 months, patients taking levodopa had better UPDRS scores and less freezing, although they had more dyskinesias. In contrast, the substudy imaging data again showed more decline in the levodopa group [31]. The second study (Remacemide as an Adjunct to Levodopa [REAL-PET]) [32] enrolled 186 patients in a trial comparing ropinirole with levodopa, using a reduction in putaminal ^{18}F-dopa intake as the primary outcome variable [32]. After 2 years of follow-up, the researchers

reported the levodopa group had better symptomatic control over PD as measured by "on" UPDRS scores, despite imaging showing an increase of one third in relative rate of decline compared with the agonist arm.

Because of the discordance between clinical outcome and imaging outcomes, neuroimaging's usefulness as a biomarker for underlying disease progression remains uncertain. Similar to clinical rating scales, imaging that concentrates on dopamine processing may only provide an assessment of a therapy's effect on the dopamine system, rather than measuring the underlying pathophysiology. In addition, measurements of dopamine processing will not identify important nondopaminergic factors in PD. Other tracers will likely be needed to better capture nondopaminergic and neurodegenerative processes in PD [33•].

Clinical trial design

In the absence of a biomarker capable of measuring neurodegeneration, researchers are exploring innovative clinical trial designs to detect disease-modifying effects. The delayed-start design has been proposed as a method to detect such effects in a therapy that also improves symptoms [34••]. In this design, patients are randomized to one of two treatment arms. In one arm, treatment begins immediately. In the other (delayed-start) arm, patients begin on placebo and are switched to active treatment after a delay, usually 6 to 12 months. If the therapy under investigation has only a symptomatic benefit, then the delayed group should catch up to the early-treatment group. However, if the therapy is modifying the underlying disease course, then the first arm should continue to perform better than the delayed-start arm regardless of initial symptomatic benefit. Using this design, a study of 404 patients randomized to rasagiline or placebo found that subjects taking rasagiline for the entire 12-month trial showed significantly less decline on the UPDRS than those who started rasagiline after a 6-month delay [35]. This promising result has prompted a larger 18-month study to attempt to confirm the initial findings [36].

The delayed-start design attempts to answer a concern raised in delayed-washout designs: what length of washout time is needed to fully eliminate the effect of an intervention? For some researchers, however, delayed-start design raises the question of a prolonged wash-in period, in which a therapy may have a prolonged and progressive symptomatic benefit due to effects on compensatory mechanisms, without truly having any effect on the underlying disease pathogenesis. Although this is a theoretical concern, a counterargument is that any therapy that affects compensatory mechanisms would modify the course of disease and therefore be useful, even though it is not purely neuroprotective [37]. A practical concern is the danger of differential dropout between the treatment and placebo arms during the initial delay phase, which endangers the benefits of randomization by making the treatment arms not equivalent [38•]. Concerns about a prolonged symptomatic effect require knowledge of the intervention's mechanism of action, whereas issues of differential dropout may be addressed by adjusting the method for data analysis [39].

The futility study design identifies ineffective therapies within a relatively short time frame while minimizing cost and the exposure of patients to nonbeneficial interventions [40••]. A futility trial is usually short (6–18 months) and may use a single active treatment arm compared with historical controls. These trials may be unblinded or may use a small placebo group to preserve blinding and check the accuracy of historical placebo effects. Futility designs are attractive for several reasons. First, using historical controls permits considerable reductions in sample size while preserving study power. Second, futility trials use one-sided statistical tests because they are only designed to prove a treatment is ineffective; they are not designed to detect efficacy. This increases power for any given sample size. Finally, futility trials can be completed within 1 to 2 years, which allows therapies that appear promising in a futility design to move forward relatively rapidly.

Futility studies do not test for efficacy and should not be compared with comparative efficacy trials (the traditional phase 3 trial). Futility studies are an early-stage screening design, and they are most useful when the hypothesized effect size is modest; large effect sizes can be tested in a definitive efficacy trial with only a small increase in sample size. For this design to be effective, the historical placebo rate must be constant and well defined. Changes in the placebo rate over time can increase the chances of committing either type I errors (ie, rejecting a potentially effective treatment) or type II errors (ie, proceeding with an ineffective treatment). Outcome measures that are vulnerable to changes in practice styles or ancillary care can therefore damage a futility study by increasing the potential for erroneous interpretation [41]. Recent studies have employed a futility design using a concurrent placebo group to avoid the potential problems with historical controls [42].

Conclusions

Neuroprotection, as defined in the introduction, is an exciting goal for both scientific and medical reasons. It is too restrictive, however, to exclusively focus on this goal and neglect other opportunities to impact patient health. Although we cannot measure neuroprotection as currently defined, researchers already have the tools required to measure a sustained clinical benefit in motor and nonmotor domains of PD, as well as a delay in accumulation of disability. Any therapy that modifies the course of disease would be useful to patients, whether it is truly "neuroprotective" or not. Perhaps it is time to discard the narrow definition of neuroprotection and broaden our focus to include any therapy that

demonstrates prolonged clinical benefit. In this way, we can best capitalize on the recent advances in PD pathogenesis, preclinical models, and clinical trial design to improve the health of individuals with PD.

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