TCH346 as a neuroprotective drug in Parkinson's disease: a double-blind, randomised, controlled trial

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Summary

Background **There is an important unmet medical need in Parkinson's disease for a neuroprotective treatment that slows or stops disease progression. TCH346 is a potent anti-apoptotic drug that protects against loss of dopaminergic neurons in laboratory models. Our aim was to assess TCH346 as a neuroprotective drug in patients with Parkinson's disease.**

Methods **Patients presenting at 45 international movement disorder clinics with early untreated Parkinson's disease were assessed as part of this parallel-group, double-blind, randomised controlled trial. 301 eligible patients were randomly assigned 12–18 months' treatment with TCH346 at a daily dose of 0·5 mg (n=78), 2·5 mg (n=79), or 10 mg (n=73), or placebo (n=71), followed by a 4 week washout period. The primary outcome measure was time to development of a disability requiring dopaminergic treatment. Secondary outcome measures were the annual rate of change in the unified Parkinson's disease rating scale (UPDRS) and the PDQ-39, a measure of quality of life. Analyses were by intention-to-treat. This study is pending registration with ClinicalTrials.gov.**

Findings **255 patients completed the study. TCH346 did not differ from placebo for any of the study outcomes. Treatment was needed in 26 (34%) patients in the TCH346 0·5 mg group, 30 (38%) in the TCH346 2·5 mg group, 24 (33%) in the TCH346 10 mg group, and 23 (32%) in the placebo group. There were no significant differences between groups. There were no differences between groups in the annual change in the UPDRS or PDQ-39 either. Few patients withdrew because of adverse events and none was judged to be related to the study intervention.**

Interpretation **TCH346 did not show evidence of a neuroprotective effect. The discrepancy between the preclinical promise of TCH346 and the clinical outcome could have arisen because of the use of laboratory models that do not accurately reflect the pathogenesis of Parkinson's disease, the doses of study drug used, insensitive clinical endpoints, and the patient population selected for study.**

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Introduction

Parkinson's disease is a progressive, age-related, neurodegenerative disorder that is prevalent worldwide and affects around 1 000 000 people in each of North America and Europe. Clinically, the disease is characterised by bradykinesia (slowness), rigidity (stiffness), tremor, and gait dysfunction with postural instability.[1] The pathological hallmark of Parkinson's disease is degeneration of dopamine neurons in the substantia nigra pars compacta with a consequent loss of striatal dopamine.[2] Current treatment is based on a dopamine replacement strategy that primarily uses dopamine agonists or levodopa.[3,4] Typically, patients with Parkinson's disease gain a large benefit from this approach, especially in the early stages of the disease; however, long-term treatment can be complicated by motor fluctuations and dyskinesias.[1,4] Furthermore, disease progression is associated with the emergence of features that are not adequately controlled by levodopa (eg, gait dysfunction, freezing, postural instability, autonomic dysfunction, sleep disturbances, mood disorders, psychosis, and dementia)[1,4] and that are probably associated with degeneration of non-dopaminergic extra-nigral neurons.[5] These characteristics can represent a major source of disability for patients and might even necessitate nursing-home placement. Surgery can effectively control motor complications in some patients, but does not improve features that are not controlled by levodopa.[6] Thus, despite the best available anti-parkinsonian treatments, Parkinson's disease can be associated with intolerable disability. The development of a neuroprotective treatment that slows or stops disease progression and avoids the development of disability is a critical priority in the management of this disease. Up to now, no treatment has been established to modify the progressive course of Parkinson's disease or to prevent neurodegeneration.

Several drugs (eg, selegiline, dopamine agonists, and ubidecarenone) have been tested as putative neuroprotective agents in Parkinson's disease by use of clinical or imaging biomarkers to assess disease progression.[7–10] Although some studies have shown positive results, they have been confounded by symptomatic or pharmacological effects that have prevented a definite determination of whether the study intervention had a disease modifying or neuroprotective effect.[11,12] A promising drug for study as a putative neuroprotective agent in Parkinson's disease is TCH346 (N-methyl-N-propargyl-10-aminomethyl-dibenzo[b,f]-oxepin, also referred to as CGP3466). This novel drug incorporates a propargyl ring within its molecular

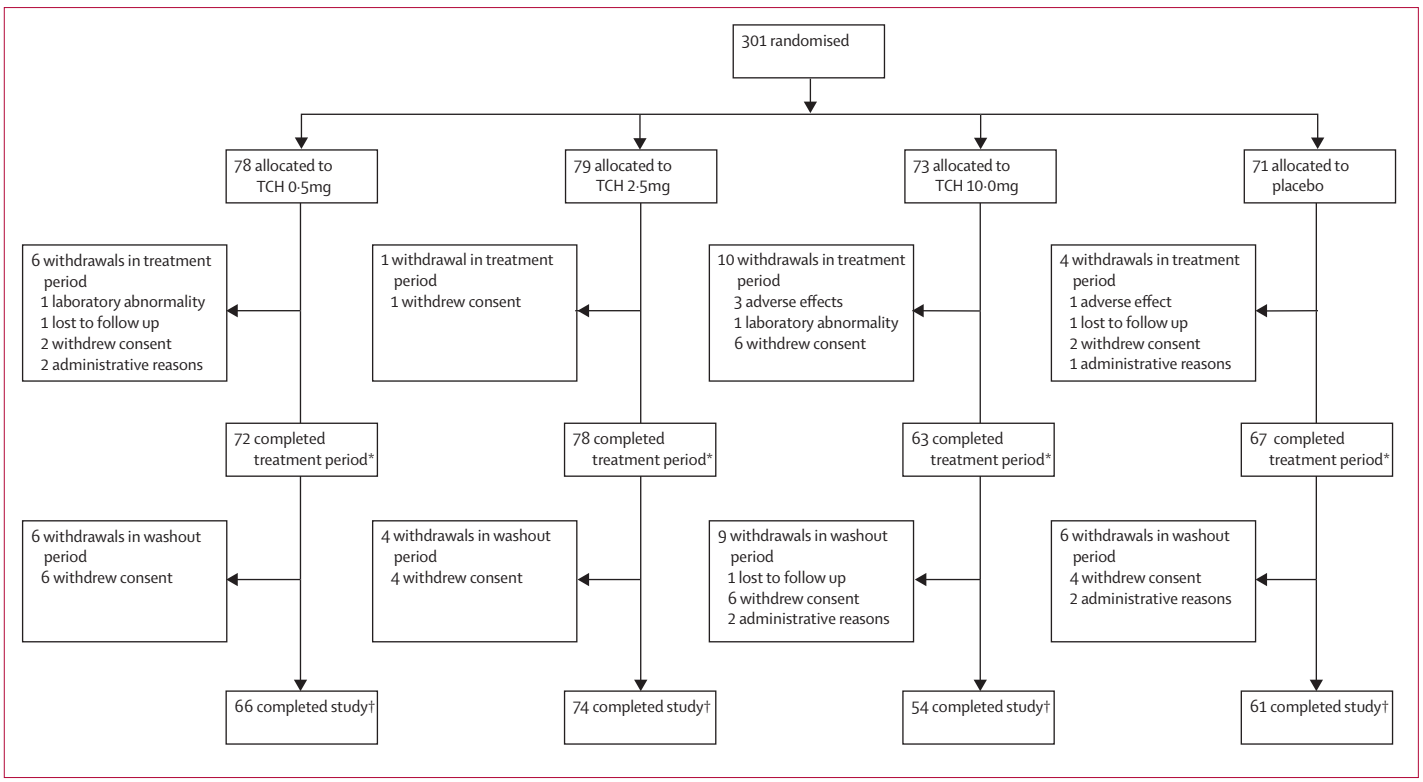

Figure 1: **Trial profile**

*Treatment period completed when need for symptomatic treatment was identified during the double-blind period or when study intervention was continued until end of the double-blind treatment period as planned in the protocol. †Patients completed both the double-blind treatment period and the withdrawl period.

structure and resembles the antiparkinson drug selegiline, but does not inhibit monoamine oxidase B and therefore was not anticipated to have confounding symptomatic effects in clinical trials. Like other propargylamines,[13] TCH346 has been shown to prevent degeneration of dopamine neurons in various in-vitro models of programmed cell death[14–19] and to protect against behavioural abnormalities and neurodegeneration in animal models of Parkinson's disease.[20,21] In these studies, TCH346 provided neuroprotective effects at picomolar concentrations. The drug is thought to exert its protective effects by interacting with the glycolytic enzyme GAPDH,[16] which has been implicated in the initiation of apoptosis.[22] Propargylamines such as TCH346 are now known to provide neuroprotection by preventing the stress-induced translocation of GAPDH from the cytoplasm to the nucleus where it blocks the transcriptional upregulation of protective molecules such as BCL-2 and superoxide dismutase.[14,15] In preclinical safety studies and in phase I trials in healthy volunteers and patients with Parkinson's disease, TCH346 was well tolerated and free of clinically significant adverse effects or laboratory abnormalities (unpublished). Here, we describe the results of the first double-blind, placebo-controlled trial examining TCH346 as a possible neuroprotective drug in Parkinson's disease.

Methods

Patients

Patients were enrolled between January, 2002, and November, 2003, at 45 international sites. Eligible individuals were men or women older than 30 years who had a diagnosis of idiopathic Parkinson's disease based on having at least two of three cardinal features (bradykinesia, rigidity, resting tremor). Participants could not have received previous antiparkinson medication (with the exception of a short challenge with levodopa or a dopamine agonist to confirm the diagnosis) and could not be more than stage 2 on the Hoehn and Yahr scale, which classifies the disease into clinical stages ranging from mild (stage 1) to bed-bound (stage 5).[23] Exclusion criteria comprised atypical parkinsonian features, serious concurrent illness, substantial laboratory abnormality according to the judgment of the investigator, known hypersensitivity to selegiline or tricyclic antidepressants, treatment with a dopamine receptor blocking drug within 30 days before randomisation, history of alcohol or drug abuse within the previous year, or treatment with another experimental drug within 30 days before randomisation. Women of childbearing potential had to have a negative pregnancy test immediately before study entry and were required to practice mechanical means of contraception throughout the study.