Effects on Spasticity and Neuropathic Pain of an Oral Formulation of Δ9-Tetrahydrocannabinol in Patients With Progressive Multiple Sclerosis

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ABSTRACT

Purpose: The aim of the present study was to evaluate the efficacy of an oral formulation of Δ9-tetrahydrocannabinol (ECP002A) in patients with progressive multiple sclerosis (MS).

Methods: This accelerated proof-of-concept study consisted of 2 phases: a crossover challenge (dose-finding) phase and a 4-week, parallel, randomized, placebo-controlled treatment phase. Twenty-four patients with progressive MS and moderate spasticity were enrolled. During the treatment phase, biomarkers for efficacy and secondary pharmacodynamic effects were measured at baseline and after 2 and 4 weeks of treatment. Serum samples were collected to determine pharmacokinetic properties and perform population modeling. Safety and tolerability profiles were assessed based on adverse events and safety measurements.

Findings: Pain was significantly reduced when measured directly after administration of ECP002A in the clinic but not when measured in a daily diary. A similar pattern was observed in subjective muscle spasticity. Other clinical outcomes were not significantly different between active treatment and placebo. Cognitive testing indicated that there was no decline in cognition after 2 or 4 weeks of treatment attributable to ECP002A compared with placebo.ImplicationsThis study specifically underlines the added value of thorough investigation of pharmacokinetic and pharmacodynamic associations in the target population. Despite the complex interplay of psychoactive effects and analgesia, the current oral formulation of Δ9-tetrahydrocannabinol may play a role in the treatment of spasticity and pain associated with MS because it was well tolerated and had a stable pharmacokinetic profile. (*Clin Ther*. 2017;▮:▮▮▮–▮▮▮)

Key words: cannabinoid, multiple sclerosis, pain, spasticity, Δ9-tetrahydrocannabinol.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory disease of the nervous system characterized by highly variable clinical aspects and an unpredictable course.[1] Of the many symptoms encountered in MS, muscle spasticity and spasms occur in up to 75% of patients.[2] These symptoms often lead to considerable distress from reduced mobility and interference with activities of daily living. Other disabling features include sensory symptoms (eg, pain), present in up to 86% of the patients.[3] Spasticity refers to feelings of stiffness and a wide range of involuntary muscle spasms (sustained muscle contractions or sudden movements). Spasticity may be as mild as the feeling of tightness of muscles or may be so severe as to produce painful, uncontrollable spasms of extremities. Spasticity may also produce feelings of pain or tightness in and around joints and can cause lower back pain. Although spasticity can occur in any limb, it is much more common in the legs.

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The endogenous cannabinoid system appears to be tonically active in the control of spasticity,[4,5] and cannabinoids have been proposed in MS because of their ability to reduce the subjective feeling of spasticity.[6] Cannabinoids modulate motor cortical excitability probably through the presynaptic cannabinoid receptor CB1 that controls the release of neurotransmitters from axonal terminals.[7,8] Δ9-Tetrahydrocannabinol (Δ9-THC) is one of the cannabinoids in the *Cannabis sativa* plant and a direct partial agonist of the cannabinoid receptor CB1.

Several studies have examined the effect of (synthetic forms of) Δ9-THC in the treatment of multiple sclerosis. No significant effects of doses between 10 and 25 mg (total daily dose, twice-daily dosing) of oral Δ9-THC were observed on spasticity as measured on the Ashworth scale in a large population. However, a small but clinically relevant benefit of treatment with cannabis extract or Δ9-THC capsules of dosages up to 25 mg/d was found in secondary outcome measures of perception of spasticity and mobility.[9] Several other studies have also found an effect of Δ9-THC on subjective measures of spasticity[10,11] and pain in patients with MS[9,12] at different dosing regimens. Another study comparing the effects of an oral formulation of Δ9-THC to a cannabis plant extract and to placebo did not reveal efficacy in the treatment of spasticity of either product.[13]

Oral bioavailability of Δ9-THC is variable because of significant first-pass effect, and the current formulation of Δ9-THC, ECP002A,* was found in a Phase I study to have superior pharmacokinetic (PK) properties to previous formulations, leading to more stable Δ9-THC plasma levels without high peaks and thus expected early onset of treatment effects.[14] It has a tablet formulation of pure Δ9-THC that was produced using an emulsifying drug delivery technology (Alitra [Echo Pharmaceuticals B.V., Weesp, the Netherlands]). This technology was designed to improve the uptake of poorly soluble lipophilic compounds, using less surfactant (<10% w/w). The present study was designed to investigate the PK properties, tolerability, and effects on spasticity and pain of this formulation in a cohort of 24 patients with primary and secondary progressive MS, using a crossover challenge (dose-finding) phase and a 28-day parallel treatment period.

*Trademark: Namisol® (Echo Pharmaceuticals, Weesp, the Netherlands).

METHODS

This study was designed as a hybrid between a typical multiple-dose study to investigate PK, pharmacodynamic (PD), and safety profiles and a first-in-patient study to establish proof of concept and hence considered to be an accelerated proof-of-concept study that consisted of 2 phases. The challenge phase was designed as a randomized, double-blind, placebo-controlled, 2-way crossover design to determine the optimal effective dose of ECP002A to treat spasticity of each individual and limit the risk of adverse events, using PK/PD modeling. Each of the 2 visits in the challenge phase consisted of up-titration of 3 consecutive drug administrations with a 100-minute interval in ascending order. If well tolerated, the 3 dose levels were predetermined to be 3, 5, and 8 mg, leading to a total daily dose of 16 mg, which was based on the PK and PD findings in the previous study.[14] Between the administrations of Δ9-THC or placebo, different measurements for safety profile, tolerability, and biomarkers were performed. Between the 2 visits was a washout period of 7 to 14 days.

The 4-week treatment phase was performed in a randomized, double-blind, placebo-controlled parallel fashion to determine the safety profile, tolerability, and efficacy of ECP002A in patients with MS with spasticity and pain. On the basis of the findings of the challenge phase, patients start with a predetermined daily dose divided over 3 intakes. After 2 weeks of treatment, the dose for each patient was evaluated and increased when considered appropriate. The study was approved by the Medical Ethics Committee of the VU University Medical Center (Amsterdam, the Netherlands).

The study was conducted according to the Dutch Act on Medical Research Involving Human Subjects and in compliance with Good Clinical Practice and the Declaration of Helsinki. The study is registered in the European Union Clinical Trials Register under protocol number 2010-022033-28 and in the Dutch clinical trial registry (www.toetsingonline.nl) under dossier number NL34443.029.10. The study was performed by the Centre for Human Drug Research (Leiden, the Netherlands) and VU University Medical Center (Amsterdam, the Netherlands) and was funded by Echo Pharmaceuticals.

Twenty-four patients 18 years or older with a diagnosis of progressive (primary or secondary) MS according to the revised McDonald criteria[15] who had