One-Year Open-Label Study of Entacapone in Patients with Advanced Parkinson Disease

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Background and Purpose: A carboxy-O-methyl transferase inhibitor entacapone has been introduced as an adjuvant drug for Parkinson disease (PD) patients. Although clinical trials reported beneficial role of entacapone, a long-term trial over 3 years failed to show significant effect. The goals of this study were to evaluate the clinical benefit and the efficacy of entacapone in an open clinical practice.

Methods: After the completion of a double-blind placebo-controlled entacapone study, 149 patients from 4 centers were included. Antiparkinsonian medications were optimized by the judgment of the neurologists in charge. The clinical global impression (CGI) scale was obtained at 6 months and 1 year after the initiation of entacapone treatment.

Results: Of the 149 patients, 117 patients chose to try entacapone in an open-label fashion. Sixty-nine (59%) patients completed the 1-year trial. Twenty-nine patients discontinued entacpaone before 6 months, and 19 between 6 months and 1 year during trial. Twelve patients out of 48 patients discontinued entacapone because of its poor efficacy. The CGI scale was 3.9 (±1.5) at the beginning of the trial, 4.3 (±1.1) at 6 month, and 3.8 (±1.3) at 1 year, respectively. The CGI scale of those who discontinued between 6 month and 1 year was 3.4 (±1.7), which was worse, but insignificantly, than that of the continuer.

Discussion: The dropout at 1 year of our study was very high at 41%. Even though entacapone is indicated for advanced PD patients with motor fluctuation, the fluctuators commonly have dyskinesia and mental symptoms, which can become more troublesome with entacapone. In the patients with advanced PD, the clinical efficacy and side effects should be carefully considered in a long-term use of entacapone.

J Clin Neurol 3(2):82-85, 2007

Key Words : Parkinson disease, Entacapone, Long-term efficacy

INTRODUCTION

A carboxy-O-methyl transferase inhibitor (COMT inhibitor) entacapone (COMTAN®) was introduced as an adjuvant drug for the patients with Parkinson disease (PD). It has been known to delay metabolism of levodopa without affecting the peak plasma concentration or time to reach the peak concentration, which prolongs the duration of action of exogenous levodopa and its bioavailability. However, the extent of clinical benefit of entacapone needs further clarification.

Several clinical trials over 1 or 6 months duration reported increased “on” time, which was considered

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useful in case of wearing-off in advanced PD.[1-3] On the contrary, Unified Parkinson disease Rating Scale (UPDRS) scores were not improved in a 3-year trial of entacapone.[4] Moreover, Fenelon et al's 3-month study failed to show significant change in 'on' time and 'off' time.[5] Their argument for the effectiveness of entacapone was based on the improvement of UPDRS part IV item 39 and investigator's global assessment of change.

In Korea, our group conducted a multicenter randomized double-blind placebo-controlled entacapone study in PD patients with motor fluctuation.[6] The study demonstrated that 1) entacapone is a safe and well-tolerated drug, 2) although the duration of 'on' and 'off' time were not significantly changed, entacapone showed an overall significant beneficial effect in the PD patients with wearing-off phenomenon.

After the completion of the study, patients were given the choice of prescribing entacapone free of charge. The goals of this open-label study were to evaluate 1) the clinical benefit of entacapone under the usual circumstances of outpatient clinic without the restriction of a clinical trial, and 2) the efficacy of entacapone in a more prolonged period than typical 3 months clinical study duration. We report our experience of entacapone in an open-label trial over 1 year, which showed the limited role of entacapone as an adjuvant therapy in the patients with advanced PD.

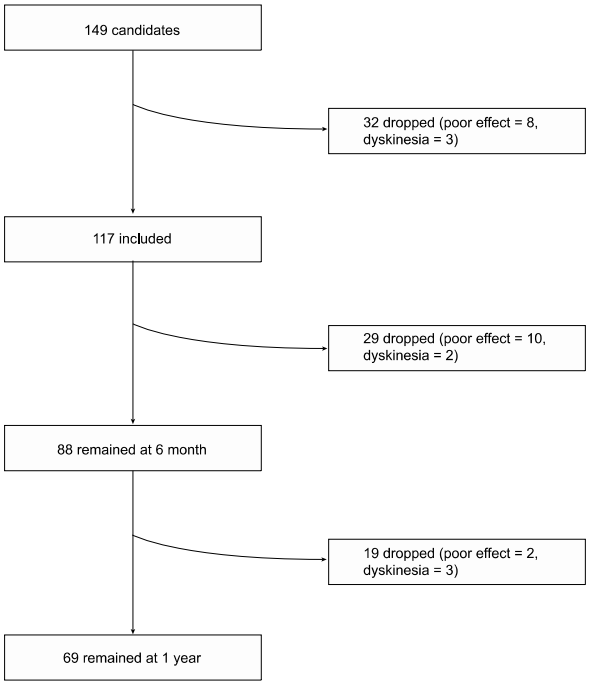

Figure 1. Flow diagram shows the number of patients remained at 6 months and 1 year of the trial. Other reasons for discontinuation of entacapone are described in the text.

MATERIALS AND METHODS

The multicenter double-blind placebo-controlled entacapone study included 197 parkinsonian patients from 5 centers.[6] Inclusion criteria were 1) PD meeting the diagnostic criteria of UK PD Brain Bank, 2) age between 30-80 years old, 3) Hoehn and Yahr stage (HY stage) at 'on' time between 2 and 4, 4) 'off' duration longer than 2 hours per day. The study was approved by Institutional Review Boards.

After completion of the 8 weeks study, patients were given the choice of prescribing entacapone free of charge. Of the five centers that participated in the mother study, 4 centers joined in this study. Entacapone was adjusted according to the individual needs from 100 mg to 200 mg per dosing. Antiparkinsonian medications were optimized by the judgment of the neurologists in charge. Data on age, sex, duration of disease and levodopa treatment, and HY stage were collected. The clinical global impression (CGI) scale (1-7: No change=4, much worsened=1, much improved=7) was obtained by the investigators at base line, 6 month and 1 year after treatment.[7] Side effect profiles and reasons for drug discontinuation were followed up over 1 year.

RESULTS

The joining 4 centers had 149 participants who completed the preceding double-blind study. Of the 149 patients, 117 patients (male=48, female=69) chose to try entacapone in an open-label fashion (Fig. 1). Mean age (±SD) of the patients was 57.5 (±9.5) years. Mean duration of disease and levodopa treatment was 7.9 (±3.8) and 5.6 (±3.0) years respectively. HY stage at 'on' time was 2.3 (±0.5). Sixty-nine (59.0%) patients remained on entacapone therapy till the end of 1-year trial (Fig. 1).

Dropout rate was similar in each center. Twenty-nine (24.8%) patients discontinued entacpaone before 6 months, and 19 (16.2%) between 6 months and 1 year during trial. Twelve patients (25%) out of 48 patients discontinued entacapone because they felt entacapone was not effective. Other reasons for discontinuation of entacapone were aggravated dykinesia (5) and psychiatric symptoms (10), gastrointestinal side effects (5), other medical problems (3), yellow urine (2), peripheral edema (1), knee pain (1), and death (1). Eight patients were lost during follow-up. The exact reasons were unknown in 5 patients.

The CGI scale was 3.9 (±1.5) at the beginning of this open-label trial, 4.3 (±1.1) at 6 month and became worse 3.8 (±1.3), respectively (p=0.004). The CGI scale of those who discontinued between 6 month and 1 year after entacapone treatment was 3.4 (±1.7), which was worse, but insignificantly, than that of the continuer (p=0.07).

There were no significant differences in age, disease duration, and levodopa treatment duration between the patients who completed 1-year trial and those who discontinued. HY stage at the beginning time of trial was more advanced in those who discontinued than those who completed an open trial (2.4 versus 2.2; p=0.019).

DISCUSSION

It may be assumed that patients who entered into this open-label study were getting benefit from entacapone and that patients who did not were not getting benefit or had side effects from entacapone. However, the dropout rate is very high up to 41% at 1 year of our study. The reasons for discontinuations were no clinical benefit in 25%, side effects in 48%, and unknown in 17%. As entacapone was given free of charge in our study, financial problem was not the reason for discontinuation. This very high discontinuation rate is similar to that of Larsen et al's 3-year open labeled study which reported discontinuation of entacapone in up to 40.9% of the patients enrolled.[4] We also found the holistic negative opinion on the effectiveness of entacapone (worsened CGI scale at 1 year), even in those who continued the medication. Although various factors such as the change in the other antiparkinsonian medication and progression of PD could be assumed as the reason why CGI became worse even in the continuer, they could not be answered in this study. Another possibility is that entacapone could not meet the high expectation of these advanced PD patients with multiple problems.

The weak point of this study may be that we did not evaluate the objective parameters such as duration of "on" and "off" time and changes of levodopa dose. However, although patients may be more critical or more demanding of drug efficacy than the investigators are, we believe subjective satisfaction on the part of patients is an important measure of drug efficacy in antiparkinsonian medications.

Even though entacapone is primarily indicated for advanced PD patients with motor fluctuation, fluctuators commonly have dyskinesia and mental symptoms, which can be more troublesome with entacapone. It may be partly supported by the data that disease severity by HY stage at the beginning of entacapone trial was more advanced in those who discontinued (2.2 versus 2.4; p=0.019).

It should be further evaluated whether the efficacy and side effects of entacapone could meet the needs of the patients with more advanced PD in long-term use. Rather, as the daily levodopa dose reduction was commonly reported in the previous long-term entacapone studies without significant change in UPDRS, entacapone may be more helpful in early stages of PD with emerging motor complication, in which 'wearing off' without significant dyskinesia is a predominant feature and levodopa dose is still small.[2,4]

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