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Research Article

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Participating centers and investigators are listed in the Appendix.

KEYWORDS

Parkinson's disease • tolcapone • entacapone • COMT inhibition • motor fluctuations

ABSTRACT

This double-blind study examined the efficacy and safety of replacing entacapone with tolcapone in fluctuating Parkinson’s disease (PD) patients. Patients receiving entacapone for ≥15 days were randomly assigned to continue entacapone (n = 75) or switch to tolcapone (n = 75) and were followed up for 3 weeks. Efficacy measures included changes in on time (without disabling dyskinesia) and an investigator’s global assessment (IGA). The on time increased by ≥1 hour/day (primary efficacy measure) in 43% of entacapone-treated patients and 53% of tolcapone-treated patients, and by ≥3 hours/day in 13% and 25%, respectively. The IGA indicated moderate/marked improvements in 25% of entacapone patients and 39% receiving tolcapone. Response rates (the proportion of patients with ≥1 hour/day increase in on time and improvements on IGA) were 17% with entacapone and 32% with tolcapone. Dyskinesia was the most common adverse event affecting 29% of entacapone and 31% of tolcapone recipients. One patient in each group had elevated liver enzymes, resulting in treatment withdrawal (levels returned to normal thereafter in both cases). In conclusion, within the limits of the protocol, there was a tendency for tolcapone to offer enhanced efficacy in patients with fluctuating PD, despite optimized entacapone therapy. Tolcapone can be considered, therefore, for patients whose motor fluctuations are inadequately controlled by their existing regimen. © 2006 Movement Disorder Society

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ARTICLE TEXT

The management of advanced Parkinson's disease (PD) requires complex treatment regimens containing several pharmacological agents. The cornerstone of therapy is levodopa (combined with benserazide or carbidopa).[1][2] However, long-term use of levodopa is complicated by motor fluctuations, including end-of-dose “wearing-off,” which are related in part to variations in the plasma concentration of levodopa. These complications may be reduced by peripheral inhibition of the enzyme catechol-O-methyltransferase (COMT).[3][4] Two COMT inhibitors, tolcapone and entacapone, have been introduced in the past years, and both agents have demonstrated benefits in reducing wearing-off fluctuations.[5-14] Two open-label reports comparing tolcapone and entacapone have suggested that tolcapone is the more effective agent.[15][16] and this difference in response would be predicted by the pharmacological differences between the agents.[17] However, in 1998, three fatal cases of acute hepatitis were reported in patients receiving tolcapone without liver monitoring.[18] This finding led to the drug's suspension in
Europe and its use in the United States as a last resort and only in combination with stringent liver function monitoring. To compare the benefits of tolcapone and entacapone, we conducted the present study, in which patients with treatment-resistant fluctuating PD were randomly assigned to continue treatment with entacapone or to switch to tolcapone.

PATIENTS AND METHODS
This randomized, double-blind, active-controlled study was conducted at 32 centers in Finland, France, Germany, Spain, Sweden, Switzerland, and the United States. The trial protocol was to provide information about the relative efficacy of tolcapone in comparison with entacapone in support of the European Medicines Agency's (EMEA's) decision to lift the suspension of tolcapone. The study was conducted in accordance with the Declaration of Helsinki as amended in October 2000, or with the laws and regulations of the relevant country, whichever afforded greater protection to the participant. All patients gave written informed consent to participate.

Patients were included in the study if they had PD diagnosed ≥5 years previously, with significant fluctuations (≥3 hours/day off time, according to daily diaries) despite best medical therapy, including up to 12 daily doses of levodopa (maximum total dose 3,000 mg/day), and entacapone 200 mg with each dose of levodopa (maximum 10 doses/day). Patients were excluded if they had current or previous liver disease.

Eligible patients entered an open optimization phase of ≥10 days, in which they received their existing PD treatment regimen, including entacapone 200 mg with each dose of levodopa. During this phase, the levodopa dosage was adjusted until the optimal balance between efficacy (i.e., reduced off time and time with disabling dyskinesia) and tolerability (e.g., nausea, sedation) was achieved. If no change in symptom control was observed despite two increases in levodopa totaling at least the average dose (total daily dose divided by number of daily intakes), no further dosage adjustments were made; these patients were still considered to have had their treatment optimized. Once the optimal balance between efficacy and tolerability was achieved or no further change was observed, the regimen was maintained for ≥5 days before the patient could progress into the double-blind phase of the trial. Patients were randomly assigned into the double-blind phase if their existing regimen had been stable for ≥5 days, their diaries on the final 3 days before randomization showed ≥3 hours/day of off time despite treatment optimization, with no more than two 30-minute periods of invalid information on the diaries, and their Unified Parkinson's Disease Rating Scale Activities of Daily Living (UPDRS ADL) score was ≥12 when they were in the off state.

In the randomized, double-blind phase, patients either continued to take entacapone or switched to tolcapone 100 mg three times daily (t.i.d.), while maintaining their other antiparkinsonian treatments. The first daily dose of tolcapone was taken in the morning with the first dose of levodopa, and the second and third doses of tolcapone were taken 6 and 12 hours later. Patients receiving entacapone were given placebo tablets t.i.d. to mimic tolcapone tablets, and patients receiving tolcapone were given placebo capsules with each dose of levodopa to mimic entacapone capsules. Patients remained on this treatment for 3 weeks, during which time the levodopa dosage could again be adjusted up or down as required to achieve optimal benefit (starting 1-3 days after randomization). The number of levodopa intakes could not be changed during double-blind treatment. Therefore, if the patient needed to have their total daily levodopa dosage adjusted, this was achieved by changing the amount of levodopa taken at each intake. The levodopa dosage had to be stable for the last 5 days of the double-blind phase. All other antiparkinsonian medication was maintained at the same dose throughout the study; any treatments for other disorders could be changed if it was considered to be necessary to treat new or worsened symptoms. The duration of 3 weeks was chosen because, given the speed of onset of effect of both COMT inhibitors, this time frame was deemed sufficient to identify a difference in effect.

There were five scheduled visits for efficacy and safety assessments: at screening; randomization (≥15 days after screening); and weeks 1, 2, and 3 after randomization. On the 3 days before each visit, patients completed diaries to record their PD status (in 30-minute blocks) as one of five categories: asleep, on, on with disabling dyskinesia, off, or missing. An investigator's global assessment (IGA) was conducted at the final visit and was based on interviews with the patients and all recorded information.
Adverse events were recorded throughout the double-blind phase of the study. Their relationship to the trial medication was rated by the investigator as probably, possibly, remotely, or not related. The investigator also classified the events as mild, moderate, or severe. Laboratory measures were recorded at each visit. The reference ranges for normal values were 0 to 25 U/L for aspartate aminotransferase (AST) and 0 to 30 U/L for alanine aminotransferase (ALT). Values that were above 50 U/L or that increased by ≥50% were considered to be marked laboratory abnormalities. Treatment was withdrawn if a patient had values above the normal limit on 2 consecutive days or a marked value on one occasion.

A sample size of 160 patients was planned, to provide 92% power to detect a 20% difference in the proportion of patients responding to treatment at the 5% two-sided significance level. This strategy was assuming a 5% response rate in the entacapone-treated group and a 25% response rate in the tolcapone-treated group. Ten patients were not enrolled, as they did not meet the inclusion criteria or refused to participate. The primary endpoint was the proportion of patients with a mean increase in on-time (without disabling dyskinesia) of ≥1 hour/day from the end of the open optimization phase to the end of the double-blind phase (3 weeks later), according to patient diaries. The secondary endpoint was the proportion of patients showing moderate or marked overall improvement in the IGA at the end of the double-blind phase. Tertiary endpoints were the changes in daily levodopa dose and UPDRS scores from randomization to the end of the double-blind phase. In addition, we evaluated the following: mean change in on time, with any patients with missing diary data considered to have no change; the proportion of patients in each group with an increase in on time (without disabling dyskinesia) of ≥3 hours/day; and the proportion of patients having an increase in on time of ≥1 hour and a moderate or marked improvement according to the IGA.

All patients who were randomized and received at least one dose of the study medication were included in the “all patients treated” (APT) population, with the last observation carried forward if data from later visits were missing. The per-protocol (PP) population included all patients who were randomized and completed the study according to the protocol. For the safety analysis, all patients who were randomized, received at least one dose of the study drug and had at least one further assessment were included.

The null hypothesis was that there would be no difference in responder rates between the two treatment groups. The $\chi^2$ test was used to analyze the equality of responder rates and to compare the proportion of patients with moderate or marked IGA scores at the 0.05 level in the APT population. The tertiary endpoints are reported using descriptive statistics, with no statistical probability testing.

Randomization numbers were computer generated by F. Hoffmann-La Roche, Basel, Switzerland (Roche), and were allocated sequentially at each center in the order in which patients were enrolled. The randomization list was not available at study centers and was concealed from all those involved in the conduct of the study.

RESULTS
Of the 150 patients who were randomized into the study (n = 75 in each treatment group), all 150 were included in the APT and safety analyses, whereas 122 patients were included in the PP analysis (entacapone, n = 60; tolcapone, n = 62). The reasons for exclusion from the PP analysis were protocol violations (entacapone, n = 12; tolcapone, n = 12), adverse event (entacapone, n = 1), refusal of treatment (entacapone, n = 1), or other reasons (entacapone, n = 1; tolcapone, n = 1). The baseline characteristics of the 2 groups were not substantially different (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Baseline patient and disease characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
</tr>
<tr>
<td>Entacapone</td>
</tr>
</tbody>
</table>

### Table 2. Efficacy results

<table>
<thead>
<tr>
<th>Efficacy variable</th>
<th>PP population</th>
<th>APT population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Entacapone (n = 60)</td>
<td>Tolcapone (n = 62)</td>
</tr>
<tr>
<td>Patients with increased on time of ≥1 hour/day, n (%)</td>
<td>28 (47%)</td>
<td>36 (58%)</td>
</tr>
<tr>
<td>Patients with moderate/marked improvement on IGA, n (%)</td>
<td>16 (27%)</td>
<td>25 (40%)</td>
</tr>
<tr>
<td>Mean change in total levodopa</td>
<td>-0.20</td>
<td>-3.01</td>
</tr>
</tbody>
</table>

In the APT analysis, 4 patients in each group did not complete 3 weeks of treatment. The reasons were safety issues discussed in detail below (entacapone, n = 2; tolcapone, n = 1), protocol violations (entacapone, n = 1; tolcapone, n = 3), and refusal of treatment (entacapone, n = 1). The shortest duration of treatment was 7 days in the entacapone group and 4 days in the tolcapone group. Both the mean and the median duration of treatment was 21 days in each group. All patients in the tolcapone group received tolcapone 100 mg t.i.d., giving a total daily dose of 300 mg. In the entacapone group, the mean total daily dose was approximately 1,200 mg.

The efficacy results are summarized in Table 2. In the APT population, numerically more patients on tolcapone than on entacapone had ≥1 hour/day increase in on time after 3 weeks of treatment (the primary endpoint), with 32 patients on entacapone (43%) and 40 patients on tolcapone (53%) achieving this outcome, but this result was not statistically significant (*P* = 0.19).
Of the entacapone-treated patients who were rated as improved on the IGA, 7 (9%) showed a marked improvement, and 12 (16%) showed a moderate improvement. In the tolcapone group, 12 patients (16%) showed a marked improvement, and 17 (23%) showed a moderate improvement according to the IGA. Thus, overall there was a tendency toward more improvement in patients on tolcapone than on entacapone (entacapone, n = 19; tolcapone, n = 29; P = 0.08).

The total levodopa dosage increased slightly during the optimization phase before randomization (3.2% increase in dose in patients who went on to be randomly assigned to the entacapone group; 3.6% increase in those who went on to tolcapone) and decreased slightly during the double-blind phase (entacapone, -0.4%; tolcapone, -2.3%; Table 2). For UPDRS assessments (Table 2), the greatest difference between the 2 groups was in Subscale III (Motor function), with mean changes of -1.3 with entacapone and -3.0 with tolcapone.

The results of the exploratory analyses, using more stringent definitions of response, are shown in Table 2. Mean daily on time increased by twice as much in the tolcapone group as in the entacapone group during the double-blind phase (entacapone 0.65 hours/day increase, tolcapone 1.34 hours/day increase). Similarly, the proportion of patients with an increase in on time of ≥3 hours/day in the tolcapone group was nearly double that in the entacapone group (13% and 25%, respectively). In the PP population, the difference between groups reached statistical significance. The on time increased by a mean of 0.77 and 1.63 hours/day in the entacapone and tolcapone groups, respectively, and 12% and 29% of patients, respectively, had increases in on time of ≥3 hours/day. According to the composite endpoint of response
(defined as ≥1 hour/day improvement in on time and moderate or marked improvement on IGA), significantly more tolcapone-treated patients than entacapone-treated patients responded (17% on entacapone; 32% on tolcapone; \( P = 0.04; \) APT population).

During double-blind treatment, 40 patients (53%) in the entacapone group and 43 patients (57%) in the tolcapone group reported at least one adverse event. One patient receiving entacapone withdrew from the study because of a fall, but this event was considered to be unrelated to the study medication. The most frequent adverse event was dyskinesia (Table 3). All other adverse events were experienced by fewer than 5% of patients. There were no marked differences between the treatment groups in the number of patients reporting an event or in the type of events reported. Of the other adverse events that affected ≥3% of patients, two cases of hallucination in the entacapone group, and one case each of dizziness, dystonia, and nausea in the tolcapone group were considered to be probably related to study medication. Few adverse events were rated as severe: one report of dyskinesia in an entacapone-treated patient, and two reports of dyskinesia and one each of anxiety, constipation, nausea, and abdominal pain in tolcapone-treated patients.

### Table 3. Prevalence of adverse events occurring in ≥3% of patients in either group

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Entacapone: n = 75</th>
<th>Tolcapone: n = 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyskinesia</td>
<td>22 (29%)</td>
<td>23 (31%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Hallucination</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Fall</td>
<td>3 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (1%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Dystonia</td>
<td>0</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (3%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Liver enzymes &gt; ULN</td>
<td>2 (3%)</td>
<td>7 (9%)</td>
</tr>
</tbody>
</table>

ULN, upper limits of normal.

Nine patients had liver enzyme levels that were above the upper limit of normal (reference range: AST, 0-25 U/L; ALT, 0-30 U/L) on at least one occasion during double-blind treatment (entacapone, n = 2; tolcapone, n = 7). There were 7 patients who continued on treatment, and the liver enzyme levels returned to normal, whereas 2 patients stopped treatment. In the entacapone group, a 47-year-old woman had AST levels of 31 U/L at day 15 and 29 U/L at day 16; treatment was stopped, therefore, and the levels returned to normal 7 days after withdrawal of entacapone. In the tolcapone group, a 51-year-old man with a history of alcoholism had AST levels of 55 U/L at day 13 and 28 U/L at day 14; tolcapone was withdrawn, and the patient’s liver enzymes returned to normal.

**DISCUSSION**

Although there were no statistically significant differences between the 2 groups of patients in the primary and secondary endpoints (patients with an increase in on time of at least 1 hour/day and patients rated as improving on the investigator’s global assessment), there was a numerical advantage for tolcapone for all
outcomes. Improvements in the exploratory outcomes, using more stringent definitions of response, were in favor of tolcapone in the APT and PP populations (overall increase in on time, patients with an increase in on time of ≥3 hours/day, composite of patients with an increase in on time of ≥1 hour/day, and an improved IGA rating).

The lack of statistical significance in the primary and secondary endpoints was due, at least in part, to the unexpectedly high improvements in both groups. The study was powered on the assumption that there would be a 5% increase in the proportion of patients with ≥1 hour on time/day in the entacapone group and a 25% increase in the tolcapone group. In fact, the improvements were 43% and 53%, respectively. The trial was designed with an open optimization phase to ensure that patients were receiving the maximal benefit from levodopa plus entacapone (in terms of best balance between efficacy and tolerability) before randomization into the double-blind phase. It is possible that the regimen had not been fully optimized at the start of the double-blind phase. It may be that the duration of the optimization phase (≥10 days) or of the stabilization phase (≥5 days) was actually not sufficient to ensure an optimal levodopa regimen. Alternatively, the continued improvement in the entacapone group might simply be a placebo effect, but confirmation of this effect would require a longer study period.

The double-blind phase of the trial lasted only 3 weeks, because clinical experience with COMT inhibitors indicates that the majority of patients respond rapidly. The few patients who have not shown a response within 3 weeks are unlikely to respond at all, and licensing regulations in the United States and Europe mandate that tolcapone be withdrawn if no response is seen by then.

In the present study, the safety profiles of tolcapone and entacapone were similar. The most common adverse event was dyskinesia, which occurred at a similar frequency in the 2 groups. Diarrhea and other nondopaminergic adverse events were infrequent, but this finding is likely due to the short duration of the present trial, because diarrhea usually occurs between weeks 6 and 12 of treatment. All 9 cases of elevated liver transaminase activity, except 1 case with a history of alcoholism, were within one or two times the upper limit of normal; in all cases, liver enzyme concentrations returned to normal with no clinical impact. Within the limits of the protocol imposed by the EMEA and the finding of significant treatment differences in the exploratory analyses only, we conclude that there were no serious side effects with either treatment and that there was a tendency toward increased efficacy of tolcapone over entacapone.

Acknowledgements
The trial was designed in accordance with the European Medicines Agency (EMEA) requirements and was sponsored by F. Hoffmann-La Roche, Basel, Switzerland. Ernest Dorflinger, MD, was the Clinical Science Leader for the study, and Cornelia Irl, PhD, was the project statistician.

APPENDIX
The following centers and lead investigators were involved in this trial: Finland: Hyvinkää Hospital (Esko Kinnunen); University Hospital, Oulu (Vilho Myllylä). France: Hôpital de la Salpêtrière, Paris (Yves Agid); CHU Nantes (Philippe Damier); Hôpital Saint-Antoine, Paris (Marie Vidalilhet); CHU Gabriel Montpied, Clermont-Ferrand (Franck Durif); CHU Grenoble (Pierre Pollak); Centre Regional de Geriatrie, Canetepie (Isabelle Rivier); CHU Rennes (Marc Verin); Hôpital Leopold Bellan, Paris (Marc Ziegler); Hôpital du Pays d'Aix, Aix en Provence (Francois Viallet). Germany: Stadtkrankenhaus, Hanau (Horst Baas); Waldklinik Bernburg (Irene Gemende); Arzthehaus an der Marienkirche, Neubrandenburg (Joachim Glass); University
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