Tolcapone addition improves Parkinson's disease associated nonmotor symptoms

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Abstract

Background: Addition of catechol-O-methyltransferase inhibitors to a conventional levodopa/dopadecarboxylase inhibitor regimen improves motor symptoms in patients with Parkinson's disease. Optimizing dopamine substitution is also beneficial for nonmotor features.

Objectives: To investigate the efficacy of supplemental tolcapone intake on nonmotor symptoms.

Design/methods: A total of 125 levodopa-treated patients additionally took tolcapone in this observational trial. Initially and following 4 weeks of tolcapone intake, the neurologist scored with Unified Parkinson's Disease Rating Scale parts I, II, IV, the nonmotor symptoms scale for Parkinson's disease and recorded the off time. The patients rated themselves with the EuroQuol, its visual analogue scale and the nonmotor screening questionnaire. Caregivers reported the daily duration of care giving.

Results: All scores improved except for Unified Parkinson's Disease Rating Scale part IV and domains 4, 5 and 8 of the nonmotor symptoms scale for Parkinson's disease.

Conclusion: This trial demonstrates that tolcapone addition may improve nonmotor features.

Keywords: nonmotor symptoms, Parkinson's disease, tolcapone

Introduction

Parkinson's disease (PD) is a progressive, disabling neurodegenerative disorder with onset of motor and nonmotor features [Barone *et al.* 2009]. Motor and nonmotor symptoms considerably limit quality of life. Treatment of nonmotor symptoms nowadays has gained increasing importance in addition to an optimum motor behavior in PD [Chaudhuri *et al.* 2007]. Best possible dopamine substitution and thus therapy of motor behavior is an essential prerequisite for alleviation of nonmotor symptoms in patients with PD [Barone *et al.* 2009]. Out of the array of dopaminergic neurotransmission modulating or substituting compounds, levodopa (L-dopa) is the most efficacious and best tolerated compound for the control of motor symptoms in patients with PD. Peripheral L-dopa metabolism of L-dopa/dopadecarboxylase inhibitor (DDI) formulations predominantly employs the pathway via the enzyme catechol-O-methyltransferase (COMT). Blocking of COMT activity with entacapone or tolcapone further reduces peripheral L-dopa degradation,

as it prolongs the plasma half life of L-dopa and elevates the delivery of L-dopa to the brain [Marsala *et al.* 2012]. Entacapone only acts in the periphery, whereas tolcapone also enters the blood–brain barrier and therefore may act centrally [Ceravolo *et al.* 2002; Russ *et al.* 1999]. Thus tolcapone may also slow the degradation of other catecholamines [Marsala *et al.* 2012; Truong, 2009]. Neurotransmission of these biogenic monoamines is also altered in patients with PD and may contribute to the onset of nonmotor symptoms, that is, depression [Barone *et al.* 2009]. Accordingly, prior pilot trial outcomes demonstrated beneficial effects of tolcapone on depression [Fava *et al.* 1999; Moreau *et al.* 1994]. But small clinical studies also described an improved cognition and cortical information processing following tolcapone application in patients and healthy volunteers. Dopamine increase via central COMT inhibition relative selectively improves prefrontal physiologic efficiency and thus cognitive behavior, in particularly apathy and motivation [Apud *et al.* 2007; Gasparini *et al.* 1997;

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Kayser *et al.* 2012; Roussos *et al.* 2009]. Thus central COMT inhibition is more regionally restricted in contrast to the effects of biogenic aminergic stimulants, such as amphetamine, which enhance transmission of dopamine, norepinephrine and 5-hydroxytryptophan in widespread regions of the brain. Therefore these psychostimulants possess a high potential for abuse and tolerance in contrast to tolcapone [Apud *et al.* 2007]. All these considerations warrant confirmation by an observational pilot trial on the therapeutic efficacy of tolcapone on nonmotor symptoms beside its well known beneficial effect on motor behavior in patients with PD [Marsala *et al.* 2012]. Particularly, non-motor features cause caregiver burden and patient distress. Therefore a trial on the efficacy of tolcapone, evaluated by the treating neurologist, the patients themselves and their caregivers with corresponding suitable rating scales makes sense [Müller and Woitalla, 2010]. Such an approach was not performed in a clinical study which tested the efficacy of a COMT inhibitor [Marsala *et al.* 2012]. The objective of this pilot trial was to investigate the impact of supplemental tolcapone intake on onset and severity of nonmotor symptoms in patients with PD treated with L-dopa/DDI in an exploratory, prospective open-label fashion.

Subjects and methods

Subjects

A total of 125 patients with PD were included in this study [78 men, 47 women; age: 70 ± 7.8 years (mean $\pm$ standard deviation, SD); duration of PD: 9.7 ± 5.9 years; Hoehn and Yahr stage: 2.7 ± 0.9 ; Unified Parkinson's Disease Rating Scale (UPDRS): 62.6 ± 23.5 , daily L-dopa/DDI dosage: 531.9 ± 268.4 mg]. They were recruited in 47 study centers. The allowed upper limit for recruitment of study participants was 12 in each centre. Inclusion criteria were diagnosis of idiopathic PD according to the UK Brain Bank criteria [Hughes *et al.* 1992], Hoehn and Yahr stage between II and IV, minimum age 18 years, prior L-dopa/DDI therapy and previous treatment with entacapone [duration of entacapone application: 2.2 ± 2.1 years (mean $\pm$ SD); dosage: 750 ± 376.9 mg, n (number of treated patients with PD): 92] with insufficient response or missing tolerability directly before study participation or in the drug history of the patient. The concomitant drug regimen (pramipexole: $n = 43$; amantadine: $n = 27$, ropinirole: $n = 19$; rasagiline: $n = 16$; rotigotine: $n = 10$; piribedil: $n = 9$; cabergoline: $n = 6$; selegiline: $n = 5$; trihexyphenidil,

biperiden, budipine, bromocriptine, pergolide: $n = 1$ each) had to be stable for at least 4 weeks before inclusion in the trial. Occurrence of wearing off or unpredictable off phenomena ($n = 98$) was not mandatory, the existence of an insufficient motor situation ($n = 27$) also fulfilled the criterion for study participation. Exclusion criteria were administration of tolcapone in the last 4 weeks before study entry, current treatment with nonselective monoamine oxidase inhibitors, known hypersensitivity to tolcapone or its metabolites, abnormal liver function or liver disease, hyperthermia, neuroleptic malignant syndrome, rhabdomyolysis or pheochromocytoma in the patient history.

Design

Tolcapone 100 mg (three times a day) was added to a conventional L-dopa/DDI regimen in this observational open trial. Prior treatment with entacapone was stopped. The additional concomitant PD therapy should remain stable, but changes were allowed and were noticed. Antiparkinsonian drug modifications were performed by the treating neurologist during the whole course of the trial at all three visits. Initially and after 4 weeks of adjunctive tolcapone intake, patients were scored with parts I, II, IV of the UPDRS, the nonmotor symptom assessment scale for PD (NMSS) by their neurologist [Chaudhuri *et al.* 2007; Fahn *et al.* 1987]. He also recorded the daily off time within a diary supported interview. The patients ($n = 68$) rated themselves with the EuroQuol (EQ-5D), the EQ-5D visual analogue scale (VAS) and the nonmotor screening questionnaire (NMSQuest) [Chaudhuri *et al.* 2006; Siderowf and Werner, 2001]. Caregivers ($n = 68$) reported the daily duration of care giving (DDCG) in domains, like food and drug intake, clothing, transport, use of rest rooms, personal hygiene, housework, prevention of dangerous incidents and so on [Müller and Woitalla, 2010]. The self rating of the patients and the evaluation of caregiver burden were not mandatory. Monitoring of liver enzymes was performed at visits I, 14 days later (intermediate) and at visit II (4 weeks later).

Statistics

As some of the employed scales have no metric properties, only nonparametric tests were used. Comparisons were performed with the Wilcoxon signed rank test. The total number of comparisons was eight. Subscores of a rating scale were not considered for the correction. In Table 1 the significance of p values was set as follows:

Table 1. Comparison between moments I and II.

	Scale	I	II	<i>p</i>
Physician	UPDRS I	3.7 ± 2.64	2.74 ± 2.45	***
	UPDRS II	17.04 ± 8.38	13.48 ± 8.09	***
	UPDRS IV	6.94 ± 4.64	6.43 ± 4.50	ns
	OFF-Time	186.4 ± 146	88.91 ± 73.04	***
	NMSS	55.77 ± 36.81	40.05 ± 34.07	***
	NMSS domain 1	2.80 ± 3.15	2.1 ± 3.33	**
	NMSS domain 2	10.89 ± 7.92	7.15 ± 6.62	***
	NMSS domain 3	11.55 ± 12.65	8.36 ± 10.97	***
	NMSS domain 4	1.08 ± 2.76	0.77 ± 1.87	ns
	NMSS domain 5	6.78 ± 7.36	5.88 ± 6.97	ns
	NMSS domain 6	4.33 ± 4.7	3.38 ± 4.46	**
	NMSS domain 7	7.87 ± 8.26	6.49 ± 6.97	*
	NMSS domain 8	3.61 ± 6.04	3.32 ± 6.05	ns
	NMSS domain 9	6.78 ± 6.8	5.15 ± 5.35	***
Patient	NMSQuest	10.65 ± 5.4	8.16 ± 4.73	***
	EQ-5D	9.02 ± 1.79	8.06 ± 2.1	***
	VAS	46.65 ± 16.27	55.39 ± 17.6	***
Caregiver	DDCG	389.9 ± 404.9	308.3 ± 361.4	***

All data are given as mean ± standard deviation. I = first rating; II = second rating.
 * Wilcoxon $p < 0.00625$, ** $p < 0.00125$, *** $p < 0.000125$; ns, not significant.
 DDCG, daily duration of care giving; EQ-5D, EuroQuol; NMSQuest, nonmotor screening questionnaire; NMSS, nonmotor symptom assessment scale for PD; NMSS domain 1, cardiovascular including falls; NMSS domain 2, sleep/fatigue; NMSS domain 3, mood/cognition; NMSS domain 4, perceptual problems/hallucinations; NMSS domain 5, attention/memory; NMSS domain 6, gastrointestinal tract; NMSS domain 7, urinary; NMSS domain 8, sexual function; NMSS domain 9, miscellaneous; OFF, daily off time (min); PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; UPDRS I, UPDRS mental behavior; UPDRS II, UPDRS activities of daily living; UPDRS IV, UPDRS complications of therapy; VAS, EQ-5D visual analogue scale.

* $p < 0.00625$; ** $p < 0.00125$; *** $p < 0.000125$. Differences between evaluation at moments I and II were computed and used for the correlation analysis, which was done with Spearman rank correlations. The total number of correlations was 35, therefore in Table 2 the significance levels were adjusted (* $p < 0.0014$; ** $p < 0.00029$; *** $p < 0.000029$). The whole analysis was looked upon as exploratory in this pilot study.

Ethics

Legal issues and ethical conduct

This study was performed according to Section 67.6 of AMG (Arzneimittelgesetz, German Medicines Act). The observation plan and all other relevant documents were reviewed by an independent ethics committee (Sächsische Landesärztekammer, Ethikkommission, Dresden). All required information on the study was communicated to the BfArM (Federal Institute of Drugs and Medical Devices), the KBV (National

Association of Statutory Health Insurance Physicians) and the GKV (National Confederations of Statutory Health insurances funds). The investigation represented a noninterventional study, that is, the rules imposed for this observational plan did not interfere with the physician's common therapy. Patients' written informed consent regarding the forwarding and storing of medical data was obtained by the physicians. An assessment with UPDRS III (motor examination) was not allowed by the ethics committee.

Results

Comparisons

Table 1 reports the improvement of the nonmotor symptoms, the reduction of the caregiver burden, and the better quality of life scores following the additional tolcapone intake. The NMSS subscores of the domains perceptual problems/hallucinations, attention/memory and sexual function were not better at moment II. Only the UPDRS IV did

Table 2. Correlation analysis between computed differences of rating outcomes of moments I and II.

Variable 1	Variable 2	<i>R</i>	<i>p</i>
NMSQuest (I–II)	NMSS (I–II)	0.38	**
NMSQuest (I–II)	DDCG (I–II)	0.41	**
NMSQuest (I–II)	EQ-5D (I–II)	0.54	***
NMSQuest (I–II)	VAS (I–II)	–0.48	***
NMSS (I–II)	UPDRS II (I–II)	0.41	**
NMSS (I–II)	UPDRS IV (I–II)	0.38	**
NMSS (I–II)	EQ-5D (I–II)	0.39	**
UPDRS II (I–II)	UPDRS I (I–II)	0.47	***
UPDRS II (I–II)	UPDRS IV (I–II)	0.32	*
UPDRS II (I–II)	DDCG (I–II)	0.39	**
UPDRS II (I–II)	EQ-5D (I–II)	0.34	*
UPDRS I (I–II)	UPDRS IV (I–II)	0.34	*
UPDRS IV (I–II)	NMSS (I–II)	0.38	**
UPDRS IV (I–II)	DDCG (I–II)	0.40	*
DDCG (I–II)	NMSS (I–II)	0.41	*
DDCG (I–II)	EQ-5D (I–II)	0.53	***
DDCG (I–II)	VAS (I–II)	–0.52	***

Spearman *R* = correlation coefficient. (I–II) = difference between moment I and II. Only significant outcomes are shown and only the NMSS total score was included in the analysis.
 * $p < 0.0014$, ** $p < 0.00029$, *** $p < 0.000029$; ns, not significant.
 DDCG, daily duration of care giving; EQ-5D, EuroQuol; NMSQuest, nonmotor screening questionnaire; NMSS, nonmotor symptom assessment scale for PD; UPDRS, Unified Parkinson's Disease Rating Scale; UPDRS I, UPDRS mental behavior; UPDRS II, UPDRS activities of daily living; UPDRS IV, UPDRS complications of therapy; VAS, EQ-5D visual analogue scale.

not decrease, whereas UPDRS I and UPDRS II scores were lower at the second assessment.

Correlations

Table 2 shows the significant correlations of the computed differences between the various rating scale outcomes at moments I and II. It is noticeable that evaluations of nonmotor symptoms by the patients and physicians were related to each other. There were also relationships between change of time for care giving, variation of nonmotor symptom expression and shift of quality of life scores. This is an observational trial which reports on the efficacy of a PD drug from the three perspectives: the treating physician, the patient and the patient's caregivers. The significant associations found also reflect the value of the three-dimensional evaluation of a drug effect by caregivers, patients and physicians.

Changes of concomitant Parkinson's disease drug therapy

Additional tolcapone intake was followed by 55 alterations of L-dopa/DDI dosage [performed

at visit I: n (total number of changes) = 29; performed at intermediate visit: n = 20; performed at visit II: n = 6] and 26 changes in other concomitantly applied PD drugs (performed at visit I: n = 8; performed at intermediate visit: n = 12; performed at visit II: n = 6).

Safety and dropouts

There were no clinically relevant liver enzyme elevations of alanine aminotransferase [intermediate moment: n (number of observations) = 2 (2 respectively 6 U/L (units/liter)); III: none] or aspartate aminotransferase (intermediate moment: none; moment III: 2 with 8 U/L). Twenty unwanted side effects were recorded in 13 patients; one adverse event, onset of constipation unrelated to study medication, was classified as severe. Onset of common dopaminergic side effects [n (number of observations) = 4] and diarrhea (n = 3) were reasons for study discontinuation. A further five patients prematurely dropped out of the study. Reasons for discontinuation were withdrawal of the patient's consent (n = 4) and unknown reason (n = 1).

Discussion

There was an improvement in nonmotor symptoms in patients with PD following the introduction of tolcapone with concomitant adjustment of the antiparkinsonian drug regimen in this trial. The NMSS decrease in domain 3 and to a lesser extent in domain 2 could hypothetically reflect a certain dopamine substituting effect of tolcapone in the mesolimbic system and affiliated dopamine-sensitive frontal brain structures, but this theory should be confirmed with an entacapone and placebo-controlled, double-blind three-arm trial. However, there are findings from experimental human studies that report an improvement in apathy and related features similar to functional MRI findings obtained from healthy volunteers [Apud *et al.* 2007; Fava *et al.* 1999]. As the central mode of action of tolcapone does not impact cholinergic neurotransmission, no beneficial effect was observed in the NMSS domain attention/memory. Questions concerning attention and memory refer more to cognitive dysfunction and particularly reflect short-term memory. This brain task is related to a predominant cholinergic deficit and is less dopamine sensitive [Apud *et al.* 2007]. An increased dopamine substitution via central COMT inhibition may support onset of hallucinations and perceptual problems in PD. Accordingly, no deterioration in domain 4 was found. However, it is known from previous clinical trials with tolcapone that this compound alleviates UPDRS I and II scores and further symptoms related to enhanced dopaminergic neurotransmission, such as gastrointestinal and urinary function. In this respect, the reduction of the patient-generated NMSQuest score supports the NMSS results. Generally we assume that lowered expression of nonmotor symptoms in our cohort results from diminished off phenomena, which are closely associated with the onset of certain nonmotor symptoms [Witjas *et al.* 2002]. But we also included patients with PD who were not receiving optimized drug titration without wearing off phenomena. This may be one reason why we found no effect regarding UPDRS IV. A further cause may be that UPDRS IV assesses off symptoms and also dyskinesia. This kind of motor complication may be aggravated by tolcapone application according to older trial results [Marsala *et al.* 2012; Sethi *et al.* 2010]. Thus the present investigation confirms these older study outcomes and again demonstrates that tolcapone is safe in clinical practice as no clinically relevant liver enzyme

elevations appeared during the monitoring interval [Marsala *et al.* 2012; Sethi *et al.* 2010]. The study design did not allow evaluation of nonmotor features in relation to motor complications since we evaluated patients only once with predominant historical information due to the scales used. This study focused more on the potential effect of tolcapone, in contrast to another recently published trial on the association between motor and nonmotor symptoms in patients with fluctuating PD [Storch *et al.* 2013].

However, it is new that the patients themselves and their caregivers demonstrated the beneficial effects of adjunctive treatment with a COMT inhibitor in association with the concomitant adaptive titration of dopamine-substituting compounds. Thus, the observed significant correlations between the computed differences of the various applied scales support the value of this study. There were significant associations within the various assessments. It is noteworthy that relationships also appeared between the computed outcomes of the patients and the differences in scores, which resulted from the physicians and the caregivers. Thus, the results of the correlation analysis particularly underline the validity of this three-dimensional evaluation of a drug effect. In this respect, the present trial also supports the expressiveness of self-completed questionnaires for patients and caregivers [Chaudhuri *et al.* 2006; Müller and Woitalla, 2010].

This study also has some limitations. First, it was open. Second, there was no placebo control. Third, it allowed a further titration of necessary, additional dopamine-substituting drugs. Therefore one may assume that the observed positive effects cannot be attributed to tolcapone application alone but to an optimization of dopamine-substituting drugs in general. Fourth, a large number of study sites recruited the study population in this trial, which was funded by a pharmaceutical company.

In conclusion, this observational pilot study describes a beneficial effect on nonmotor symptoms, quality of life and caregiver burden following the additional introduction of tolcapone in at least L-dopa/DDI treated patients with PD with a need for optimized drug titration. This is shown by scoring outcomes performed by physicians, patients themselves and their caregivers with the corresponding suitable rating scales.

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Conflict of interest statement

The author received honoraria for talks and consulting from MEDA Pharmaceuticals.

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