RESEARCH ARTICLE

Once-Weekly Subcutaneous Delivery of Polymer-Linked Rotigotine (SER-214) Provides Continuous Plasma Levels in Parkinson's Disease Patients

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ABSTRACT: Background: Extensive scientific and clinical evidence indicates that continuous delivery of a dopaminergic agent is associated with significant reduction in motor complications compared with intermittent oral dosing with the same agent. There has been an intensive effort to develop a method of providing continuous plasma levels of a dopaminergic agent that avoids the need for surgical therapy or an infusion system. Studies in MPTP-treated monkeys demonstrate that once-weekly injections of polymer-linked rotigotine provide continuous plasma levels and antiparkinsonian benefits.

Methods: We performed a multicenter open-label, multiple-ascending-dose-ranging cohort study to evaluate the safety, tolerability, and pharmacokinetics of polymer-linked rotigotine in PD patients.

Results: A total of 19 patients were evaluated in 4 cohorts in doses of 20 50, 100, and 200 mg of polymer-linked rotigotine, administered subcutaneously once weekly. The study demonstrated remarkably stable dose-related plasma levels of total and free rotigotine with no accumulation or dumping. Treatment was generally safe and well tolerated. One subject in the 50-mg group discontinued because of hives, which cleared rapidly with antihistamine treatment.

Conclusions: This study demonstrates that once-a-week subcutaneous administration of polymer-linked rotigotine provides relatively constant plasma levels of rotigotine and is safe and well tolerated. These findings suggest that this convenient method of delivery of rotigotine has the potential to treat or prevent motor complications in PD patients without the need for a surgical procedure or an infusion system. This approach may also prove applicable to other agents such as apomorphine that can be linked to this polymer © 2020 International Parkinson and Movement Disorder Society

Key Words: continuous delivery; Parkinson's disease; polymer-rotigotine

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Levodopa remains the most effective medical therapy for Parkinson's disease (PD). However, chronic treatment is associated with the development of motor complications (motor fluctuations and dyskinesias) that can be a source of considerable disability for many patients. Laboratory and clinical evidence suggests that motor complications are related to the nonphysiologic restoration of brain dopamine with intermittent oral doses of standard formulations of levodopa.[1] As dopamine levels in the brain are normally maintained at a relatively constant level,[2,3] it has been hypothesized that more continuous delivery of a short-acting dopaminergic agent such as levodopa would be more physiologic and associated with a reduced frequency of motor complications. Indeed,

studies in both MPTP-treated monkeys and PD patients demonstrate that continuous delivery of levodopa or a short-acting dopamine agonist is associated with reduced frequency of both motor fluctuations and dyskinesias compared with intermittent doses of the same agent.[4-6] This concept has now been confirmed in prospective double-blind studies showing that continuous intraintestinal infusion of levodopa or continuous subcutaneous infusion of apomorphine significantly reduces off time without increasing dyskinesia compared with optimized doses of standard oral levodopa.[7,8] However, the duodopa procedure is associated with surgical morbidity that can be serious (eg, pancreatitis, peritonitis), complications related to the jejunal tube (eg, displacement, obstruction), and the complications and inconvenience of wearing an infusion system. Similarly, there are side effects associated with continuous subcutaneous infusion of apomorphine primarily related to potentially troublesome skin lesions and also the need for an infusion system. Accordingly, there has been an intensive search for alternative and more convenient methods of providing continuous delivery of a dopaminergic agent as treatment for motor complications in PD patients that avoids the need for both a surgical therapy and an infusion system with the attendant complications and inconvenience.[9] This goal, however, has proven difficult to achieve; numerous attempts to develop a therapy that avoids the need for surgery or an infusion system have failed,[10-12] and no such therapy is currently available.

Rotigotine is a potent dopamine agonist that provides antiparkinsonian effects in MPTP monkeys.[13] Transdermal (patch) delivery of rotigotine has been shown to provide antiparkinsonian benefits in PD patients,[14-18] but is associated with a high incidence of local skin reactions and itchiness[19] and has not been shown to be able to provide constant plasma levels. SER-214 is a poly(2-ethyl-2-oxazoline), POZ, polymer conjugate of the dopamine agonist rotigotine (Fig. 1). Studies in rodents and MPTP monkeys have demonstrated that once-a-week injections of SER-214 provide relatively continuous dose-related plasma levels of rotigotine with antiparkinsonian benefits and no clinically significant cutaneous adverse events.[20,21] In the present report, we describe the results of a multicohort study testing the safety, tolerability, and PK profile of increasing doses of SER-214 in patients with Parkinson's disease.

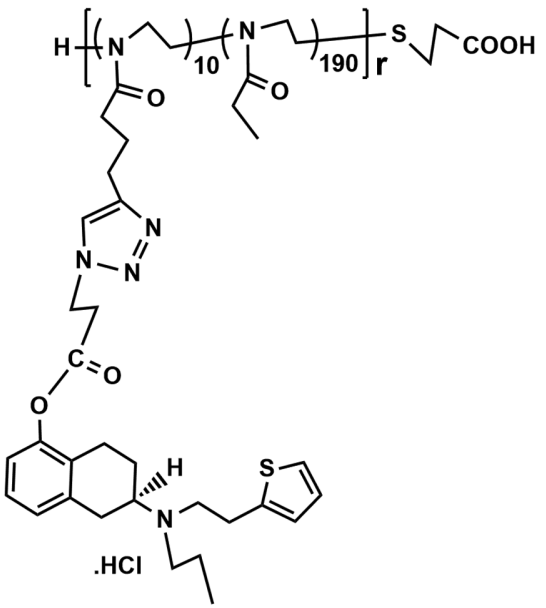

FIG. 1. Chemical structure of POZ-rotigotine (SER-214). The *S*-isomer of rotigotine is attached to a propyl linker (indicated in blue) at the single phenolic hydroxyl and then stably attached to the pendent groups of the POZ polymer. When hydrolyzed by an esterase in the blood, rotigotine is released in its active form.

Methods

Subjects

Subjects identified for the study provided institutional review board–approved written informed consent and completed screening procedures within 28 days prior to the baseline visit. Entry criteria included PD consistent with UK Brain Bank criteria, treatment with stable doses of levodopa without motor complications or with motor complications that were not clinically significant, and ability to return for all visits. Stable doses of catechol-O-methyl transferase and monoamine oxidase-B (MAO-B) inhibitors were permitted. Exclusion criteria included the use of another dopamine agonist and clinically significant medical, surgical, psychiatric, or laboratory abnormalities in the judgment of the investigator.

Design

The study was designed as a multicenter open-label, multiple-ascending-dose-ranging cohort study in which initial doses were gradually increased to determine maximal tolerated dose, and doses to be tested in subsequent clinical trials. Four cohorts were dosed as described in Table 1, and a safety visit was performed 2 weeks after the final dose. Subjects received SER-214 via a subcutaneous injection once a week in a standard 1-mL tuberculin syringe; injection sites were not repeated. Prior to each dosing, patients came to the clinic in the practically defined off state (having withheld antiparkinsonian medications for approximately 12 hours). Patients had 5–11 visits depending on their cohort (see Table 1) to permit titration to the desired study dose, which was then maintained for 2 weeks. Interval telephone calls were performed to assess for adverse events. In each cohort, a 1-week washout period followed the last injection. A dosing committee evaluated safety and PK data following completion of each cohort and decided if it was safe to continue and if there was a need for modification in the desired dose regimen for the next cohort. There were 4 subjects in cohort 0 and 5 subjects in each of the subsequent cohorts. Unified

TABLE 1. Cohort dosing

SER-214 dosing table		Week 1 (day 1)	Week 2 (day 8)	Week 3 (day 15)	Week 4 (day 22)
Cohort 0	Dose:	20 mg SER-214			
	Volume:	0.1 mL			
	Rotigotine equivalent:	~2.4 mg			
Cohort 1	Dose:	50 mg SER-214	50 mg SER-214		
	Volume:	0.25 mL	0.25 mL		
	Rotigotine equivalent:	~6.0 mg	~6.0 mg		
Cohort 2	Dose:	50 mg SER-214	100 mg SER-214	100 mg SER-214	
	Volume:	0.25 mL	0.50 mL	0.50 mL	
	Rotigotine equivalent:	~6.0 mg	~12.0 mg	~12.0 mg	
Cohort 3	Dose:	50 mg SER-214	100 mg SER-214	200 mg SER-214	200 mg SER-214
	Volume:	0.25 mL	0.50 mL	1.0 mL	1.0 mL
	Rotigotine equivalent:	~6.0 mg	~12.0 mg	~24.0 mg	~24.0 mg

Parkinson's Disease Rating Scale (UPDRS) part III was performed 6 hours after dosing at each visit by investigators certified in performing this assessment. Other evaluations performed at each visit included UPDRS parts I and II, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP), Epworth Sleep Scale (ESS), and Columbia Suicide Severity Rating Scale (C-SSRS). Pharmacokinetic studies were performed 0 1, 2, 4, and 8 hours after each injection at the designated study dose for each cohort, and once a day following titration injections and at a midpoint between each injection (3–4 days). In addition, adverse events, blood chemistry, and EKGs were collected at each visit.

Determination of Plasma Levels

Blood samples for pharmacokinetic (PK) analysis of released (free) rotigotine and total releasable (total) rotigotine were taken by venipuncture in a forearm vein. The blood was processed with ethylenediaminetetraacetic acid/sodium fluoride as the anticoagulant, and 500 μL of plasma was aliquoted into cryogenic tubes containing 40 μL of 3N HCl acid as a stabilizer and stored at < -20°C prior to analysis. The concentration of total and free rotigotine was determined using high-performance liquid chromatography and mass spectrometry as we have previously described.[21] The concentration of rotigotine in each plasma sample was compared with a standard control and was calculated using regression analysis.[22]

Statistics

The primary goal of the study was to assess safety, tolerability, and pharmacokinetics of once-weekly administered SER-214. Safety and tolerability were assessed on all randomized patients who received a dose of study drug (the intention-to-treat [ITT} population). The primary safety end point was adverse events, which

TABLE 2. Demographics

CohortSafety data set (n = 19)	Cohort 0 20 mg (n = 4)	Cohort 1 50 + 50 mg (n = 5)	Cohort 2 50 + 100 + 100 mg (n = 5)	Cohort 3 50 + 100 + 200 + 200 mg (N = 5)
Characteristic	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	61.0 (8.7)	67.0 (7.3)	67.6 (7.4)	63.2 (11.0)
Height (cm)	179.5 (10.2)	170.2 (13.5)	167.6 (7.1)	172.6 (8.5)
Weight (kg)	103.5 (19.5)	83.2 (28.6)	72.7 (6.9)	77.0 (8.6)
BMI (kg/m^2)	31.8 (2.9)	28.2 (7.2)	25.9 (1.9)	25.8 (1.6)
Characteristic	Count (%)	Count (%)	Count (%)	Count (%)
Sex — female— male	1 (25.0%) 3 (75.0%)	3 (60.0%) 2 (40.0%)	2 (40.0%) 3 (60.0%)	1 (20.0%) 4 (80.0%)
Race — white	4 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)
MMSE — 29— 30	2 (50.0%) 2 (50.0%)	0 (0.0%) 5 (100.0%)	1 (20.0%) 4 (80.0%)	0 (0.0%) 5 (100.0%)

Cohortʟ-dopa (+DDC)	Cohort 0 20 mg n = 3/4	Cohort 1 50 + 50 mg n = 1/5	Cohort 2 50 + 100 + 100 mg n = 4/5	Cohort 3 50 + 100 + 200 + 200 mg n = 4/5	Total n = 12/19
Mean ± SD (mg)	366.7 ± 57.7	300.0 ± NA	587.5 ± 232.3	475 0 ± 359.5	470.8 ± 247.2
Min–Max (mg)	300.0 – 400.0	300.0 – 300.0	300.0 – 800.0	200.0 – 1000.0	200.0 – 1000.0
ʟ-dopa (+DDC) only	n = 1/4	n = 0/5	n = 2/5	n = 1/5	n = 4/19
MAO-B only	n = 0/4	n = 2/5	n = 0/5	n = 0/5	n = 2/19
≥2 Therapies	n = 2/4	n = 1/5	n = 2/5	n = 4/5	n = 9/19

TABLE 3. Summary of PK parameters for plasma-released rotigotine in the weeks with a full PK assessment

CohortPK data set (n = 18)	Cohort 0 20 mg (n = 4)	Cohort 1 50 + 50 mg (n = 5)	Cohort 2 50 + 100 + 100 mg (n = 4)	Cohort 3 50 + 100 + 200 + 200 mg (n = 5)
Injection[a]	First[a] injection (20 mg)	First injection (50 mg)	Second injection (100 mg)	Third injection (200 mg)
PK parameter	Mean (range)	Mean (range)	Mean (range)	Mean (range)
AUC_{0-last} (ng·h/mL)	14.7 (2.5–71.8)	19.4 (7.6–55.2)	31.7 (2.9–287.9)	59.7 (39.7–126.7)
C_{max} (ng/mL)	0.119 (0.01–0.77)	0.205 (0.06–0.67)	0.360 (0.07–3.32)	0.491 (0.29–1.14)
t_{max} (h)	80.9 (8–146)	76.6 (71–95)	78.6 (0-167)	79.1 (4–168)
Injection[a]	NA	Second injection (50 mg)	Third injection (100 mg)	Fourth injection (200 mg)
PK parameter (steady state)	NA	Mean (range)	Mean (range)	Mean (range)
$AUC_{0-\tau}$ (ng·h/mL)	NA	12.4 (5.9–19.7)	25.6 (17.1–58.9)	58.3 (39.3–132.1)
$C_{SS,av}$ (ng/mL)[b]	NA	0.074 (0.035–0.117)	0.152 (0.102–0.351)	0.347 (0.234–0.786)
Fluctuation (%)[c]	NA	87.6 (50–156)	94.6 (38–163)	64.6 (24–145)

[a]First injection on day 1, second injection on day 8, third injection on day 15, fourth injection on day 22.
[b]$C_{SS,av} = AUC_{0-\tau}/\tau$ (the average steady state concentration).
[c]$(C_{SS,max} - C_{SS,min})/C_{SS,av}$.

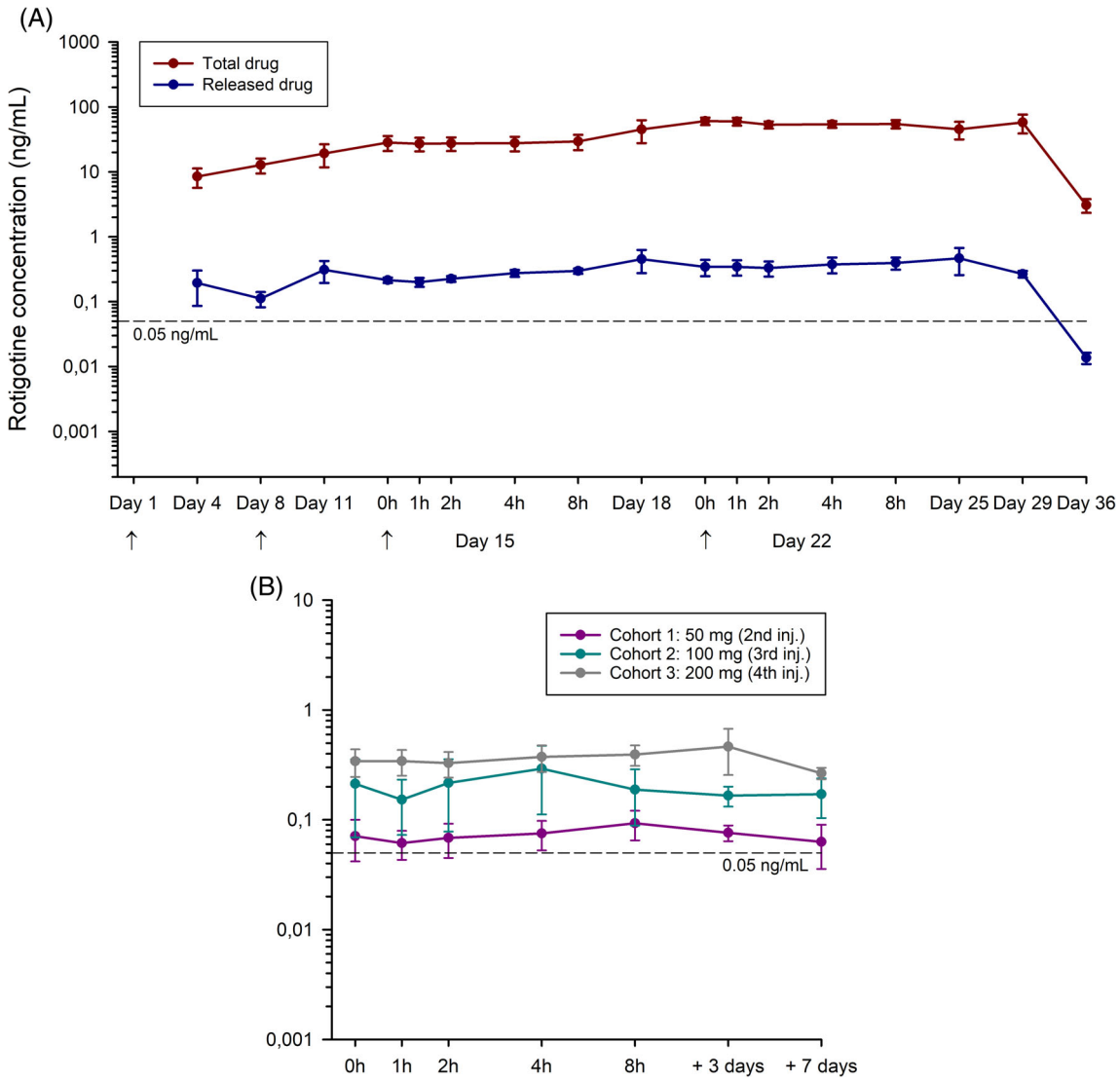

FIG. 2. (A) Mean ± SE total and released (free) plasma rotigotine concentrations for patients in cohort 3 demonstrating the remarkable stability of plasma levels after once-weekly injections of 50 mg on day 1, 100 mg on day 8, and 200 mg on days 15 and 22. Note specifically the lack of variability with the tight SEs and the lack of evidence of drug dumping or accumulation. Note also that both polymer conjugate and released drug clear promptly within 1 week of the final dose. (B) Mean ± SE plasma levels of released (free) rotigotine during the final week of treatment following a single injection of the desired dosage. Note that plasma concentrations of rotigotine are dose-related and the stability of plasma levels with each dose during the final week of treatment. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4. UPDRS part III scores

Cohort	Cohort 1 (n = 5)	Cohort 2 (n = 4)	Cohort 3 (n = 5)
	Second injection (50 mg)	Second injection (100 mg)	Second injection (200 mg)
UPDRS part III baseline (mean)	23.4	23.8	21.6
UPDRS part III mean change from baseline[a]	−0.2 (1.5)	−3.8 (3.6)	−5.8 (6.8)

[a]Change in UPDRS III score between baseline and visit of second injection measured 6 hours after the time of the injection.

were summarized descriptively by cohort (and visit/time). The primary end point for tolerability was the percent completers. Pharmacokinetic and efficacy assessments were performed in patients who were randomized, received study drug, and had a postrandomization PK/efficacy evaluation (the mITT population). The key pharmacokinetic parameters were calculated using noncompartmental analysis for extravascular delivery, and for each subject in each cohort. Phoenix WinNonlin version 6.4 (Certara USA, Princeton, NJ) was used to determine C_{ss}, C_{max}, t_{max}, $t_{1/2}$, $AUC_{0-\tau}$, and AUC_{0-last}. Change from baseline in UPDRS Part III score was the end point for efficacy and was analyzed by cohort using a mixed model for repeated measures with baseline/predose score as a covariate.

Results

Nineteen early, untreated, or stably treated PD subjects were enrolled in the study at 4 study sites (University of Alabama, MD Clinical Florida, Duke University, Medical College of Georgia); all but 1 patient completed their assigned treatment regimen. Baseline demographics are provided in Table 2. Four subjects were enrolled in cohort 0 and received a single dose of 20 mg. Five subjects were enrolled in each of the other 3 cohorts and were treated with 2 weekly doses of 50-, 100-, or 200-mg subcutaneous injections of SER-214 after 0–2 weeks of dose titration, as shown in Table 1. The study cohorts were somewhat heterogeneous with respect to baseline PD characteristics. Three subjects (75%) were levodopa users in cohort 0, 1 (20.0%) in cohort 1, and 4 (80.0%) in cohorts 2 and 3. Motor fluctuations were experienced by 2 subjects (50.0%) in cohort 0, none in cohort 1, 3 (60.0%) in cohort 2, and 1 (20.0%) in cohort 3. The mean predose UPDRS III (motor) scores at screening were 35.8 points in cohort 0, 23.4 points in cohort 1, 23.8 points in cohort 2, and 21.6 points in cohort 3.

The total maximum exposure to SER-214 was 20 mg (~2.4 mg rotigotine equivalents) over 1 week for subjects in cohort 0, 100 mg (~12 mg rotigotine equivalents) over 2 weeks for subjects in cohort 1, 250 mg (~30 mg rotigotine equivalents over 3 weeks) for subjects in cohort 2, and 550 mg (~66 mg rotigotine equivalents over 4 weeks) for subjects in cohort 3.

The PK profiles of released plasma rotigotine (PR) are provided in Table 3. There was a slow rise in the levels of plasma rotigotine, with an apparent C_{max} on days 3–4.

TABLE 5. Summary of SER-214 TEAEs by preferred term, cohort, and dose

CohortSafety data set (n = 9)	Cohort 0 20 mg (n = 4) f n %	Cohort 1 50 + 50 mg (n = 5) f n %	Cohort 2 50 + 100 + 100 mg (n = 5) f n %	Cohort 3 50 + 100 + 200 + 200 mg (n = 5) f n %	Total (n = 19) f n %
Treatment-emergent adverse event (TEAE)	2 2 50.0	5 2 40.0	6 4 80.0	4 2 40.0	17 10 52.6
Headache	0	2 1 20.0	2[a] 2 40.0	0	4 3 15.8
Nausea	1 1 25.0	0	0	1 1 20.0	2 2 10.5
Chest discomfort	0	2 1 20.0	0	0	2 1 5.3
Back pain	0	0	1[a] 1 20.0	0	1 1 5.3
Bradycardia	0	0	0	1 1 20.0	1 1 5.3
Diarrhea	0	0	1 1 20.0	0	1 1 5.3
Hypotension	0	0	0	1 1 20.0	1 1 5.3
Injection-site bruising	1 1 25.0	0	0	0	1 1 5.3
Irritability	0	1 1 20.0	0	0	1 1 5.3
Somnolence	0	0	1 1 20.0	0	1 1 5.3
Syncope	0	0	0	1 1 20.0	1 1 5.3
Urticaria	0	0	1 1 20.0	0	1 1 5.3

F, frequency of event; n, number of patients experiencing event.

At the 20-mg dose the levels of rotigotine were generally at the limit of detection, and no interpretation of actual levels could be determined for steady-state PK in this cohort. In the remaining cohorts, plasma levels were within the detectable and validated range. Plasma levels were dose related and highly stable with minimal fluctuation during the 2 weeks of constant dosing (Fig. 2a,b). The within-subject peak-trough fluctuations of total releasable rotigotine and PR were notably small. No distinct association was observed with sex or BMI. There was a decline in drug levels that fell below the limit of detection in the week following discontinuation of treatment. No evidence was found of burst release, drug dumping, or unexpected accumulation.

A dose-dependent trend for improvement in mean UPDRS scores was observed in cohorts 1–3 (change from baseline of −0.2 to 5.8; Table 4). These were not statistically significant, but the sample sizes were very small.

Adverse events are provided in Table 5. There were no deaths or serious AEs during the study. One subject in cohort 2 discontinued because of the development of generalized hives shortly after the 50-mg injection of SER-214. These rapidly cleared with administration of a single antihistamine dose and were not associated with any additional systemic complaints. All AEs were mild to moderate in intensity, and all recovered by the end of the study. There was no apparent dose relationship, and no patient experienced new onset or worsening of dyskinesia. There were no changes in parts I and II of the UPDRS, ESS, QUIP, and C-SSRS. There were no clinically significant laboratory or EKG abnormalities.

Discussion

This study demonstrates that a single injection of polymer-linked rotigotine (SER-214) provides continuous plasma levels of rotigotine that persist at a stable level for an entire week. The plasma levels of rotigotine following an injection of SER-214 are dose related and demonstrate minimal variability. Steady-state levels were achieved after approximately 3–4 days and remained highly constant, even following a second injection. The drug was gradually cleared over the course of 7 days when treatment was not continued. There was no evidence of burst release, drug dumping, or drug accumulation. Thus, there was no acute release of drug when it was first injected or accumulation of drug over time or after repeat injections. Titration to the designated dose was employed in order to minimize the risk of dopaminergic side effects such as nausea, vomiting, and orthostatic hypotension. One patient experienced hives and dropped out of the study, but this rapidly cleared with a single dose of an antihistamine. Other side effects were mild and transient. Otherwise polymer-linked subcutaneous injection of rotigotine was safe and well tolerated and not associated with any local skin reaction. Mean UPDRS part III scores were assessed 6 hours after each polymer-rotigotine injection on days when patients were seen in the practically defined off state and held off other antiparkinsonian medications until UPDRS evaluation was performed. Polymer-rotigotine provided a benefit in each cohort that was of progressively greater magnitude with higher doses. The number of subjects in this study is too small to permit meaningful statistical analyses, but the effect size (5.8 points) seen with the 200-mg injection was in the range of that seen with rotigotine and other dopamine agonists in clinical trials in early PD patients.

The present study demonstrates that weekly injections of SER-214 can provide continuous levels of a dopaminergic agent without the need for a surgical procedure or an infusion system. This suggests that delivery of a short-acting dopaminergic agent using this methodology may be able to provide improvement in both off time and dyskinesia compared with standard treatment with intermittent oral levodopa dosing and could be a valuable therapy for treating or preventing motor complications without the need for a surgical procedure or an infusion system. This methodology also offers the advantage and convenience of requiring only once a week therapy. Thus, these findings are of potentially great clinical importance. Importantly, this polymer-based strategy could also be used to provide continuous delivery of other potent dopaminergic agents such as apomorphine that can be linked to the polymer. Double-blind dose-ranging clinical trials testing safety and efficacy of SER-214 and other dopamninergic agents are planned. ■

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(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

C.W.O.: 2A, 3A
D.G.S.: 2A, 3B
K.K.: 2A, 3B
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