Short communication

A randomized trial of relamorelin for constipation in Parkinson's disease (MOVE-PD): Trial results and lessons learned

The Parkinson Study Group1, Ronald F. Pfeiffer, M.D.

Department of Neurology, Oregon Health & Sciences University, 3181 SW Sam Jackson Park Road, Portland, OR 97239-3098, United States

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Abstract

Background: Bowel dysfunction, including both slow transit constipation and defecatory dysfunction, is a frequent and often troubling nonmotor manifestation of Parkinson’s disease (PD). A variety of agents are employed for the treatment of constipation in PD, but dissatisfaction with available treatment approaches is common. Relamorelin is a synthetic ghrelin agonist that has demonstrated prokinetic properties within the gastrointestinal tract.

Methods: We carried out a multi-center, randomized, double-blind, placebo-controlled study of relamorelin in patients with PD experiencing chronic, inadequately controlled constipation.

Results: Only 18 of an intended 56 subjects completed the trial, in part because of the unexpected occurrence of multiple partially complete bowel movements in constipated PD patients, which made many subjects ineligible for participation.

Conclusions: Although recruitment goals were not met, which precluded demonstration of any potential beneficial effect of relamorelin, unique and important insights with regard to the nature of constipation in PD were recognized, which hopefully will lead to more effective clinical trials in the future. It is clear that what PD patients understand as constipation may be more complex than previously realized and does not appear to be characterized by decreased stool frequency alone.

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1. Introduction

Bowel dysfunction is a well-known nonmotor feature of Parkinson's disease (PD) and involves two distinct components: decreased bowel movement frequency secondary to slowed colonic transit (slow transit constipation) and difficulty with the act of defecation due to pelvic floor and anal sphincter dysfunction (dyssynergic defecation). Constipation can become evident up to 20 years before the development of the more traditional motor features of PD. Bowel dysfunction often is mentioned by individuals with PD as one of their most troubling symptoms. Although a wide variety of treatments are utilized in the management of constipation, very few have been specifically studied for their efficacy in the setting of PD [1–3].

Ghrelin, a 28 amino residue peptide, is the natural ligand for ghrelin or growth hormone secretagogue 1a (GHS-1a) receptors, which are present throughout the gastrointestinal (GI) tract [4]. Ghrelin has prokinetic properties within the GI tract, but its short half-life and plasma instability hinder clinical utility. The pharmacodynamic limitations of ghrelin have led to the investigation of synthetic ghrelin agonists as prokinetic agents. Relamorelin (RM-131) is a synthetic pentapeptide ghrelin receptor agonist that is more potent, more stable and has a longer half-life than ghrelin itself [5]. Relamorelin accelerates gastric emptying in diabetic gastroparesis [6], stimulates the frequency of distal antral motility contractions in healthy volunteers [7], stimulates propagated colonic contractions [8], accelerates colon transit and increases the number of spontaneous bowel movements in women with chronic constipation [9]. The therapeutic benefits of ghrelin or ghrelin analogs have not been evaluated in constipation related to neurodegenerative diseases like PD.

We carried out a Phase 2 multicenter, randomized, double-blind, placebo-controlled, parallel group study (MOVE-PD) to investigate the pharmacodynamics, efficacy and safety of relamorelin in the treatment of constipation in individuals with PD who had experienced unsatisfactory control of chronic constipation with currently available therapy.

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2. Materials and methods

2.1. Study design

MOVE-PD was conducted by 15 sites in the Parkinson Study Group. The study was approved by the Institutional Review Board at the University of Rochester and at each participating institution, and by the Western Institutional Review Board (WIRB). All participants provided written informed consent prior to participation.

The study was originally designed to include 56 subjects. Following completion of a screening evaluation and determination of eligibility (see Supplementary Table 1 for criteria), all study subjects were entered into the initial phase of the study (Period 1), which was a 14-day, single-blind, baseline period in which all participants received placebo. During this time, information on bowel habits, abdominal symptoms, and global measures was collected (see Supplementary Table 2 for specific details). Subjects who continued to meet all entry criteria during their participation in Period 1, including having 3 or fewer bowel movements per week, were then randomized to receive either relamorelin 100 mcg subcutaneous injection daily or placebo for the second 14-day segment of the trial (Period 2). Treatment was then discontinued and participation concluded with a 7-day post-treatment follow-up visit.

Efficacy was assessed using a stool diary and patient-reported outcome instruments that assessed stool frequency, consistency, strain, and completeness of evacuation (see Supplementary Table 2 for specific details). Safety and tolerability were evaluated by assessment of adverse events, clinical laboratory evaluations (see Supplementary Table 3 for specific tests), electrocardiograms, physical examinations, vital signs, and concomitant medication review. Motor PD function was assessed using the Unified Parkinson’s Disease Rating Scale [10].

Rescue medication (polyethylene glycol 3350) was permitted during Period 1 and Period 2 for individuals who went four days or longer without a bowel movement. On the fifth day, subjects could receive an enema (sodium phosphate, monobasic/sodium phosphate, dibasic) for their constipation. If there was no response to the enema by 24 h, a second enema could be given.

3. Study medication

Relamorelin and matching placebo were supplied by Rhythm Pharmaceuticals (Boston, MA). Relamorelin was formulated for injection as an isotonic solution in 5% mannitol. Each syringe contained either 100 mcg of relamorelin in 5% mannitol or 5% mannitol (as placebo) for injection. The fill volume of each syringe was 300 mcL. Doses were administered by subcutaneous injection into the abdomen once daily before breakfast. The dose level of relamorelin for this study was chosen based on prior Phase I studies in normal volunteers and by review of blinded safety data from ongoing Phase II studies in individuals with chronic idiopathic constipation [source: Rhythm Pharmaceuticals].

4. Statistical analysis

The rates of bowel movements, spontaneous bowel movements, complete bowel movements, complete spontaneous bowel movements, and days without bowel movements were compared between the treatment groups using a negative binomial regression model that included treatment group as the factor of interest and the rate observed during Period 1 as a covariate, with an offset of the natural logarithm of the number of diary days in Period 2. The results from questionnaires were compared between the treatment groups using exact Wilcoxon rank sum tests. All statistical tests were performed using a 5% significance level (two-tailed).

5. Results

Recruitment goals were not met. Only 37 of the intended subjects were enrolled into Period 1 and of those, only 18 of the intended 56 subjects were eligible to continue into Period 2, the active treatment phase. Ten of these 18 subjects were assigned to relamorelin, 8 to placebo, and all completed full participation in the trial (Fig. 1). Baseline characteristics were generally comparable between the relamorelin and placebo groups, particularly with respect to the rates of bowel movements (Table 1). Although complete bowel movements were slightly more frequent in relamorelin-treated subjects, there were no significant differences between the relamorelin and placebo groups with respect to bowel movement outcomes (Table 2). During Period 2, four subjects used rescue treatment, two in the relamorelin group and two in the placebo group. Analysis of a number of other questionnaire items also demonstrated no significant differences between the two groups (Supplementary Table 4).

Vital signs, laboratory results, and electrocardiogram results were similar in placebo- and relamorelin-treated subjects. Adverse events were infrequently reported during Period 2, with no event other than headache (2 subjects in each group) reported by more than one subject. No serious adverse events were reported.

Compliance was excellent in both groups, with the mean (standard deviation) of the percentage of expected doses taken being 99.3 (1.5) in the relamorelin group and 88.5 (24.7) in the placebo group.

6. Discussion

Given the recruitment shortfall and the high rate of failure to proceed from Period 1 to Period 2 of the protocol, it is not surprising that significant clinical benefits could not be detected for relamorelin. The fact that only 18 individuals, instead of the originally intended 56, were randomized and completed the study, resulted in limited power and inconclusive findings concerning the potential benefit of relamorelin. To the extent that it could be assessed in this small group of patients, relamorelin was well tolerated, without serious adverse effects at the dosage studied.

Despite failing to reach its recruitment targets, the MOVE-PD study yielded some unique and important insights regarding the nature of constipation and how it should be assessed in individuals with PD. These insights can inform the design of future clinical trials of agents for this indication. We encountered challenges in identifying subjects who met the entry criteria and, even more importantly, who continued to meet these criteria moving into the randomized treatment period.

The Rome III criteria were utilized to define constipation (Supplementary Table 5), but all subjects, per protocol, had to meet the criterion of a history of an average of 3 or fewer defecations per week. Thirty-seven individuals met the initial eligibility criteria and were entered into Period 1; however, only 18 were randomized into Period 2, the double-blind, active treatment phase of the trial. The primary reason for failure to randomize was the unexpected recording of greater than 3 bowel movements per week during Period 1.

Several potential explanations for this phenomenon merit consideration. One possibility is that bowel movement frequency is subject to a placebo effect, as has been the case for other PD symptoms. This has not been observed in previous relamorelin studies involving subjects with chronic idiopathic constipation [9]. Another possibility is that patients underestimated their bowel movement frequency prior to enrollment. A tendency to overestimate the severity of constipation (or underreport the frequency of defecation) was noted previously in a study of...
idiopathic chronic constipation in which only 49% of all subjects who thought they passed 3 or fewer stools per week were confirmed to do so when they completed stool diaries prospectively [11].

A careful review of data from participants in the MOVE-PD study revealed another aspect of the inclusion criteria that may have impacted successful completion of the study. Upon reviewing the reports of participants who were withdrawn from the study during Period 1 because of an overabundance of bowel movements, it became apparent that for some individuals, the problem was not that they were having bowel movements on too many days, but that they were having multiple small bowel movements during the course of one day, often accompanied by a sense of incomplete evacuation. It was as if they were completing their bowel movement in “installments,” sometimes recording several small bowel movements within an hour, rather than evacuating the entire contents in one single effort. Whether this is a phenomenon peculiar to PD is unknown. When this phenomenon was recognized by the Steering Committee, an attempt was made to compensate for this by redefining the primary outcome variable in the study from the frequency of “spontaneous bowel movement” to the frequency of “complete spontaneous bowel movement” and by reverting to the original Rome III criteria in which the criterion of fewer than 3 bowel movements per week was by itself not

Table 1
Baseline characteristics of trial participants.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relamorelin (n = 10)</th>
<th>Placebo (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62.9 (6.2)</td>
<td>65.5 (11.4)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>50.0%</td>
<td>62.5%</td>
</tr>
<tr>
<td>UPDRS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental</td>
<td>2.7 (1.9)</td>
<td>0.9 (1.0)</td>
</tr>
<tr>
<td>ADL</td>
<td>8.4 (4.9)</td>
<td>7.3 (3.0)</td>
</tr>
<tr>
<td>Motor</td>
<td>17.9 (10.3)</td>
<td>21.5 (10.2)</td>
</tr>
<tr>
<td>Total</td>
<td>29.0 (13.7)</td>
<td>29.6 (11.4)</td>
</tr>
<tr>
<td>On/off fluctuations (%)</td>
<td>90%</td>
<td>50%</td>
</tr>
<tr>
<td>Bowel movement rate</td>
<td>4.1 (1.1)</td>
<td>4.0 (2.1)</td>
</tr>
<tr>
<td>Spontaneous bowel movement rate</td>
<td>4.1 (1.1)</td>
<td>3.8 (2.3)</td>
</tr>
<tr>
<td>Complete bowel movement rate</td>
<td>1.3 (1.1)</td>
<td>1.6 (1.0)</td>
</tr>
<tr>
<td>Complete spontaneous bowel movement</td>
<td>1.3 (1.1)</td>
<td>1.6 (1.0)</td>
</tr>
<tr>
<td>Days with no bowel movements</td>
<td>2.9 (1.1)</td>
<td>3.0 (2.1)</td>
</tr>
<tr>
<td>Average consistency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel movements</td>
<td>2.7 (1.2)</td>
<td>3.1 (1.6)</td>
</tr>
<tr>
<td>Spontaneous bowel movements</td>
<td>2.7 (1.2)</td>
<td>2.6 (1.2)</td>
</tr>
<tr>
<td>Average ease of passage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel movements</td>
<td>3.2 (0.5)</td>
<td>3.4 (0.8)</td>
</tr>
<tr>
<td>Spontaneous bowel movements</td>
<td>3.2 (0.5)</td>
<td>3.6 (0.6)</td>
</tr>
</tbody>
</table>

Values are mean (standard deviation) unless otherwise indicated.

UPDRS = Unified Parkinson’s Disease Rating Scale; ADL = Activities of daily living.

* Rates are expressed as the number per week (7 days).

A careful review of data from participants in the MOVE-PD study revealed another aspect of the inclusion criteria that may have impacted successful completion of the study. Upon reviewing the reports of participants who were withdrawn from the study during Period 1 because of an overabundance of bowel movements, it became apparent that for some individuals, the problem was not that they were having bowel movements on too many days, but that they were having multiple small bowel movements during the course of one day, often accompanied by a sense of incomplete evacuation. It was as if they were completing their bowel movement in “installments”, sometimes recording several small bowel movements within an hour, rather than evacuating the entire contents in one single effort. Whether this is a phenomenon peculiar to PD is unknown. When this phenomenon was recognized by the Steering Committee, an attempt was made to compensate for this by redefining the primary outcome variable in the study from the frequency of “spontaneous bowel movement” to the frequency of “complete spontaneous bowel movement” and by reverting to the original Rome III criteria in which the criterion of fewer than 3 bowel movements per week was by itself not
mandatory as long as 2 or more of the 6 criteria for constipation were satisfied. However, this modification was made too late to prevent premature closure of the study.

Our experience in MOVE-PD suggests that constipation in PD is characterized by a reduced number of complete, satisfactory bowel movements per week, but also may be accompanied by a compensatory increased frequency of small, partial, incomplete bowel movements (bowel movement by installment) that results in an increased amount of time spent in the bathroom struggling to accomplish satisfactory elimination. The MOVE-PD study suggests that eligibility criteria and endpoints useful for studying chronic idiopathic constipation are not suitable for PD-related constipation. It may be that a better way to measure bowel function in PD is to focus more on whether the bowel movement is complete and satisfactory, as opposed to simply counting the total number of bowel movements. Awareness of this phenomenon in PD and a resultant shift of focus from bowel movement frequency to completeness of, or satisfaction with, bowel action in future studies of constipation in PD might provide a more accurate picture of what constipation means to the PD patient and also may improve subject recruitment in studies. Although no significant treatment effects were identified in MOVE-PD, it may be noted that the outcomes that appeared to most favor relamorelin were those that enumerated complete bowel movements (Table 2).

Another barrier to recruitment in the MOVE-PD trial was an apparent reluctance of patients with PD to participate in a study that required daily subcutaneous injections. This also was evident in an earlier failed clinical trial of another injectable compound, neurotrophin-3 (NT3), for treating constipation in PD [12]. The striking under-utilization of subcutaneous apomorphine injections as “rescue” medication in the management of unexpected "off" periods in PD is, perhaps, another example of this reluctance. In contrast, this has not been a significant barrier in clinical trials involving individuals with chronic idiopathic constipation [9]. Why individuals with PD should be more cautious and reluctant to utilize subcutaneous injection therapy than individuals with chronic idiopathic constipation is unclear, but perhaps relates to concerns about physical difficulty administering the injections due to disease-related impairment of dexterity, personality characteristics of PD patients, or concerns about discomfort from the injections in the setting of reduced body and muscle mass. In any case, the development of ghrelin agonists that can be administered orally or topically could circumvent this issue and possibly ease acceptance of the agent in question.

Bowel dysfunction remains a significant feature of PD for which currently available treatment modalities are not always effective. Hopefully, lessons learned in MOVE-PD will lead to more effective future trial development and a therapeutic intervention that may provide disease-specific efficacy.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2017.02.003.

Appendix

Full list of all authors

Steering Committee: Ronald F. Pfeiffer MD (PI), Oregon Health & Science University; Eamonn MM Quigley MD (Co-PI), Houston Methodist Hospital; Stewart Factor DO, Emory University; Hubert Fernandez MD, Cleveland Clinic; Michael P. McDermott PhD, University of Rochester; Kathleen Shannon MD, University of Wisconsin.

Key Coordination Center Personnel: Cindy Casaceli MBA, Elisabeth A. de Blieck MPA, CCRC, Saloni Sharma MD, University of Rochester.

Key Sponsors: Keith Gottesdiener MD, Michelle L. Hylan, Rhythm Pharmaceuticals, Inc.

Coordination Center Project Lead: Elisabeth A. de Blieck, MPA, CCRC.

Key Statistics Assistance: Michael P. McDermott PhD, University of Rochester; Donald Hebert PhD, University of Rochester.

Investigators: Edward Drasby MD, Port City Neurology, Inc.; Alan Freeman MD, Emory University; John Goudreau DO PhD, Michigan State University; Andres Deik MD, University of Pennsylvania; Mark Lew MD, University of Southern California; Michelle Burack MD, University of Rochester; Ergun Uc MD, University of Iowa; Roger Kurlan MD, Atlantic Neuroscience Institute; John Morgan MD PhD, Augusta University; Irene Malaty MD, Aparna Wagle Shukla, MD, University of Florida; Matthew Brodsky MD,

Table 2

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted rates</th>
<th>Adjusted rate ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel movement</td>
<td>4.3 (1.5)</td>
<td>4.0 (2.1)</td>
<td>1.12</td>
<td>(0.81, 1.54)</td>
</tr>
<tr>
<td>Spontaneous bowel movement</td>
<td>4.3 (1.5)</td>
<td>3.9 (2.1)</td>
<td>1.11</td>
<td>(0.81, 1.53)</td>
</tr>
<tr>
<td>Complete bowel movement</td>
<td>2.1 (1.7)</td>
<td>1.3 (1.2)</td>
<td>1.40</td>
<td>(0.65, 3.01)</td>
</tr>
<tr>
<td>Complete spontaneous bowel movement</td>
<td>2.1 (1.7)</td>
<td>1.3 (1.2)</td>
<td>1.40</td>
<td>(0.65, 3.01)</td>
</tr>
<tr>
<td>Days with no bowel movement</td>
<td>2.7 (1.5)</td>
<td>3.0 (2.1)</td>
<td>1.06</td>
<td>(0.71, 1.58)</td>
</tr>
</tbody>
</table>

Values for unadjusted rates are mean (standard deviation). Rates are expressed as the number per week (7 days). Adjusted rate ratios and associated confidence intervals and p-values are based on negative binomial regression models that adjust for the outcome rate during the placebo run-in period (Period 1).
References