Small Intestinal Bacterial Overgrowth in Parkinson's Disease: Tribulations of a trial

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Small Intestinal Bacterial Overgrowth (SIBO) is characterized by increased bacterial density in the small intestine caused by proximal migration of colonic bacteria [1]. It has been associated with worse motor function [2,3], longer off time [4], and more episodes of delayed-on and no-on in Parkinson's disease (PD) patients [4]. The eradication of SIBO with rifaximin, a non-absorbable antibiotic [5], improved motor fluctuations in PD patients in a small (n=14), unblinded, non-randomized trial [4].

We aimed to evaluate the efficacy and safety of rifaximin for OFF time reduction in SIBO-positive PD patients with at least 4 hours/day of OFF time in a pilot, single-center, double-blind, placebo-controlled, randomized clinical trial (NCT 02470780). PD patients must have had SIBO positivity, diagnosed with a combination of lactulose breath test (LBT) and glucose breath test (GBT) as described elsewhere [1,3,4]. Patients needed to be on stable antiparkinsonian therapy for at least 30 days before recruitment and anticipated to last until completion of the study. Exclusion criteria were (1) signs of cognitive impairment (according to Montreal Cognitive Assessment (MoCA) <24); (2) comorbid non-PD-associated gastrointestinal (e.g., achlorhydria) or systemic disease that may alter the administration of breath tests or study drug; (3) known allergy to rifaximin; (4) pregnancy or breastfeeding; (5) use of proton pump inhibitors, immunosuppressive drugs, medications that modify GI motility (such as prokinetics, laxatives, anticholinergics, and tricyclic antidepressants), antibiotics or any other drugs that affect the intestinal flora 30 days prior to enrollment. Subjects were randomized into a 3-month double-blind phase of rifaximin (550 mg) or matching placebo tablets three times per day for 7 days, followed by an unblinded, 3-month open-label phase for the placebo-receiving subjects. Subjects were instructed to maintain a stable medication list and diet for the 3-month double-blind phase. Daily diaries total OFF time, Patient Global Impression of Change (PGI-C) and adverse events (AE) were measured

at 1, 3, 4 and 6 months. The same breath test machine, equipment, and source of study supplies were used for all subjects and visits. This study was conducted in accordance with good clinical practice and the Declaration of Helsinki. The study protocol was approved by the institutional ethics committee (UC IRB #2015-2175) and written informed consent was obtained from all participants.

We expected to enroll 24 participants between August 2015 and May 2017. However, only 6 out of 20 screened patients met SIBO-positivity. Two were subsequently excluded (one spontaneously converted to SIBO-negative; one opted to modify antiparkinsonian treatment). The four enrolled subjects (2 men) had a mean age of 66.2±7.4 years, Hoehn & Yahr score of 2.2±0.5, and total levodopa equivalent daily dose of 1,427±1,157 mg. Two of the 4 recruited patients had less OFF time at baseline than the 4-hour cut-off during screening (2.8 and 0 hours), likely representing diary-entry error by these subjects, rather than natural fluctuation toward improvement.

Subjects treated with rifaximin maintained their SIBO-positive status at month 1 (subject A, positive; subject B, borderline positive), while subjects in the placebo group changed their SIBO status at month 1 (subject C, negative; subject D, borderline positive) and at month 4 (subject C, positive; subject D, negative) (Figure). Total OFF time decreased irrespective of treatment allocation at month 1. PGI-C worsened in rifaximin-treated subjects at month 1, and improved in the placebo-treated subjects. Subjects did not receive additional medications or dietary modifications within the 3-month double-blind phase. Subject A reported intake of a proton pump inhibitor at the 3-month visit (after SIBO status determination). No drug-related AE were observed.

The results of this 2-year effort are considered inconclusive. In addition to the difficulties associated with the study protocol (relatively high OFF time cut-off, time-demanding screening visits, strict dietary preparations, hardware difficulties with GBT and LBT machine), the spontaneous changes in SIBO status suggested that further trial continuation, even beyond the original timeframe, would have been futile. Even the basic recording of OFF and ON time was misunderstood by two patients despite training sessions, which reflected cognitive limitations of the home diary. The SIBO-positive status after rifaximin treatment could be explained by treatment failure, but this would represent a three-fold increase from previous descriptions (75% vs. 22.2% [4]), despite using a higher rifaximin dose. We have no explanation as to why patients treated with placebo converted to SIBO-negative. Semi-quantitative interpretation of the GBT and LBT results may have also resulted in classification changes not due to the intervention. Altogether, these “tribulations of a trial” should be taken into consideration for any future evaluations of SIBO treatment strategies in PD.

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AUTHORS' ROLES

J. A. Vizcarra: conception and organization of research project; design, execution and review of statistical analysis; writing of the first draft of manuscript.

H. Wilson-Perez: organization and execution of research project; review and critique of statistical analysis; review and critique of manuscript.

A. Fasano: review and critique of manuscript for important intellectual content.

A. J. Espay: guarantor; conception, organization and execution of research project; design, review and critique of statistical analysis; review and critique of manuscript.

All the co-authors listed above gave their final approval of this manuscript version and agreed to conditions noted on the Journal Publishing Agreement.

INFORMATION ON AUTHOR ACCESS TO DATA

Drs. Espay, Wilson-Perez, and Vizcarra had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

FINANCIAL DISCLOSURES

Dr. Vizcarra none.

Dr. Wilson-Perez none.

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Figure: Small intestinal bacterial overgrowth status, OFF time and Patient Global Impression of Change

Letters A, B, C, and D represent each an individual patient. SIBO, Small intestinal bacterial overgrowth; PGI-C, Patient global impression of change; N/A, non-applicable.

Figure(s)

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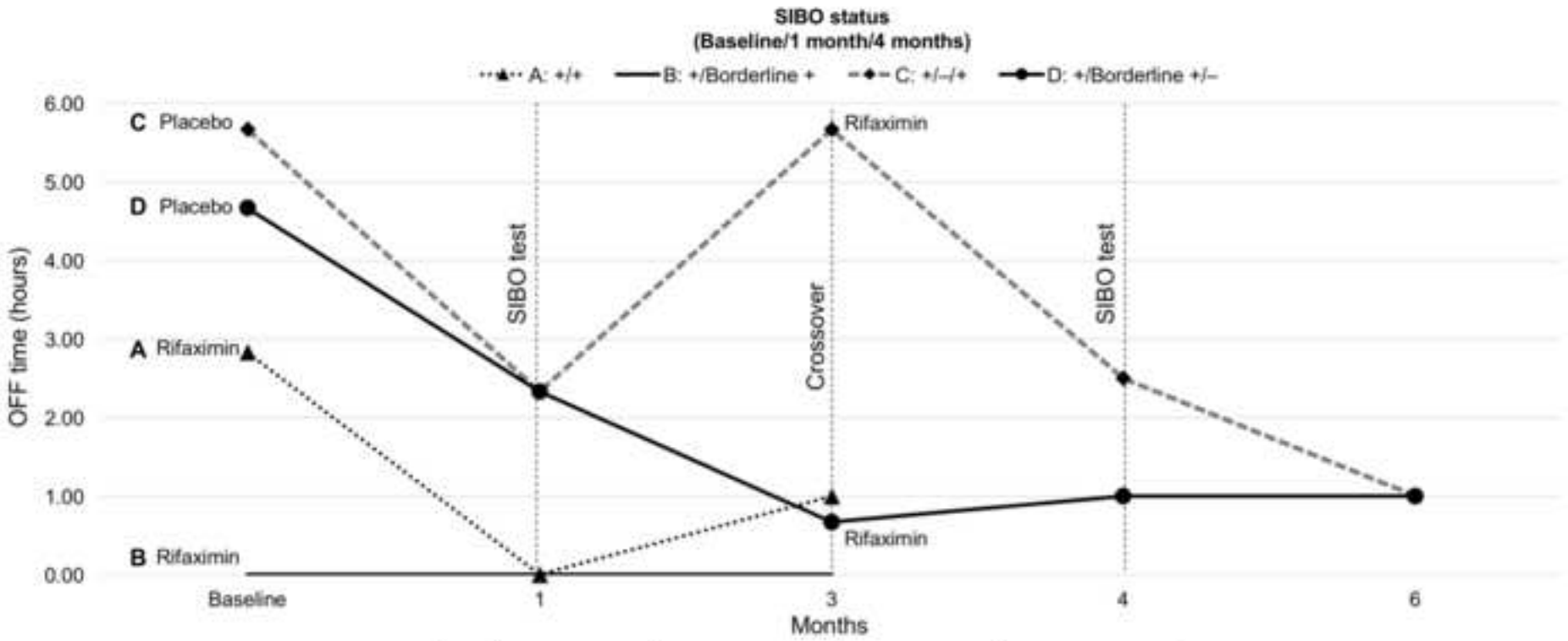

PGI-C:

	Month 1	Month 3	Month 4	Month 6
A	Minimally worse	Minimally worse	N/A	N/A
B	Minimally worse	Very much worse	N/A	N/A
C	Minimally improved	Minimally worse	Much improved	Minimally improved
D	Minimally improved	Minimally improved	Minimally improved	Much improved