The Effect of Prior Exposure to Dopamine Agonists (DA) on Response to Treatment With Gabapentin Enacarbil in Adult Patients With Moderate-to-Severe Primary Restless Legs Syndrome: Pooled Analyses From 3 Randomized Trials

P5.289

William G. Ondo,[1] Neal Hermanowicz,[2] Diego García Borreguero,[3] Mark Jaros,[4] Richard Kim,[5] Gwendoline Shang[5]

[1]The University of Texas Medical School at Houston, Houston, TX; [2]University of California Irvine Movement Disorders Program, Irvine, CA; [3]Sleep Research Institute, Madrid, Spain; [4]Summit Analytical, LLC, Denver, CO; [5]XenoPort, Inc., Santa Clara, CA

Introduction

- Restless legs syndrome (RLS) (also known as Willis-Ekbom disease) is a common sensorimotor disease resulting in an urge to move the legs that worsens in the evening and at rest, and is transiently improved with activity.[1]
- Over the past 10 years, dopamine agonists (DA) – 3 of which are FDA-approved for the treatment of RLS – have been the mostly widely used medications for RLS.
- Though initially effective, DA benefit lessens over time, both through acclimation and more commonly through augmentation, which is a worsening of RLS symptoms during treatment leading to an overall increase in RLS severity with an earlier onset compared with the time before treatment initiation.[2]
- Gabapentin enacarbil (GEn) is a non-dopaminergic drug in the alpha-2-delta ligand class that is an actively transported prodrug of gabapentin. It has been approved by the United States FDA at a dose of 600 mg once daily for the treatment of moderate-to-severe primary RLS in adults.[3]
- In 3 randomized, double-blind, placebo-controlled studies in adult patients with moderate-to-severe primary RLS (XP052/XP053/XP081), GEn significantly improved RLS symptoms compared with placebo with regard to the mean change from baseline in IRLS total score and the proportion of responders on the investigator-rated Clinical Global Impression–Improvement (CGI-I) scale at week 12. In all 3 studies the most commonly reported adverse events (AEs) were somnolence and dizziness.[4–6]
- When physicians contemplate starting treatment with an agent with a different mechanism of action than a DA, it is of clinical significance whether prior treatment with a DA would have an effect on the efficacy of the new agent.

Objective

- To investigate the effect of prior DA exposure on response to GEn treatment in adult patients with moderate-to-severe primary RLS, pooled data from the XP052, XP053, and XP081 studies were analyzed, comparing outcomes for patients with and without prior DA exposure.

Methods

Study design

- The study designs of the three 12-week, randomized, double-blind, placebo-controlled trials XP052, XP053, and XP081 have previously been published.[4–6]
  - In XP052, GEn 1200 mg once daily was compared with placebo
  - In XP053, GEn 1200 mg and 600 mg once daily were compared with placebo
  - In XP081, the pharmacokinetics, efficacy and safety of GEn 600 mg, 1200 mg, 1800 mg, 2400 mg, and placebo were examined
- In all 3 studies, patients had a diagnosis of RLS using the IRLS Study Group criteria,[1] RLS symptoms ≥15 days during the month prior to screening (or, if on treatment, similar symptom frequency before treatment initiation), documented RLS symptoms for ≥4 of the 7 consecutive evenings/days during the baseline period, IRLS total score ≥15, and had discontinued DA or other RLS treatment ≥2 weeks prior to baseline, if previously taken. Patients with a history of RLS augmentation or end-of-dose rebound (worsening of symptoms as the drug is wearing off) with previous DA treatment were excluded.

Pooled analysis

- Patient-level data were pooled for patients receiving GEn (600 mg or 1200 mg) or placebo once daily from the XP052, XP053, and XP081 trials.
- The safety population comprised all patients who had received at least one dose (or any portion of a dose) of study medication. Efficacy analyses were performed on the modified intent-to-treat population (MITT; all patients in the safety population who had a baseline and ≥1 post-baseline IRLS assessment) using last observation carried forward (LOCF).
- The efficacy outcomes were mean change from baseline to week 12 in IRLS total score and the proportion of responders (rated "much" or "very much" improved) on the investigator-rated Clinical Global Impression Improvement (CGI-I) scale at week 12.
  - Results were compared within each treatment group for DA-naïve and DA-exposed patients.
- For the change from baseline IRLS total scores, the effects of prior DA exposure were analyzed using a mixed-effect model for repeated measures (MMRM) with an unstructured covariance matrix, including fixed effects for treatment, visit, treatment-by-visit interaction, baseline DA history (yes/no), DA history-by-treatment interaction, DA history-by-visit interaction, and DA history-by-treatment-by-visit interaction.
- For the percentage of CGI-I responders, the effect of prior DA exposure was analyzed using a logistic regression model with the following factors: treatment, DA history (yes/no), and DA history-by-treatment interaction.
- Safety and tolerability, including evaluations of all AEs, were analyzed according to multiple clinical and laboratory assessments.

Results

- Demographic and baseline characteristics are shown in Table 1.
  - In this pooled analysis, 19.7% (132/671) of patients had been previously exposed to DAs. Within this group, ropinirole was the most frequently reported prior DA across the 3 treatment arms.
  - In general, a greater proportion of DA-exposed patients had severe RLS at baseline compared with DA-naïve patients (IRLS total score ≥24; 59.8% vs 42.7%).
  - Of the DA-naïve patients, 82.0% (159/194) in the placebo group, 84.7% (111/131) in the GEn 600 mg group, and 86.0% (184/214) in the GEn 1200 mg group completed their respective study.
  - Of the DA-exposed patients, 82.0% (41/50) in the placebo group, 90.0% (27/30) in the GEn 600 mg group, and 86.5% (45/52) in the GEn 1200 mg group completed their respective study.

Table 1. Baseline characteristics of DA-naïve and DA-exposed patients (MITT population)

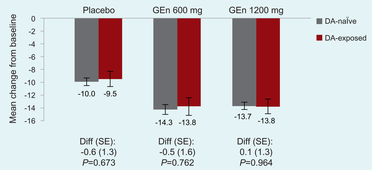
Characteristic	DA-naïve (n=539)			DA-exposed (n=132)		
	Placebo (n=194)	GEn 600 mg (n=131)	GEn 1200 mg (n=214)	Placebo (n=50)	GEn 600 mg (n=30)	GEn 1200 mg (n=52)
Age at screening, mean years (SD)	49 (12.8)	47 (12.9)	50 (12.0)	50 (10.3)	52 (11.3)	54 (14.4)
Sex, n (%)						
Female	122 (62.9)	75 (57.3)	122 (57.0)	29 (58.0)	21 (70.0)	31 (59.6)
Male	72 (37.1)	56 (42.8)	92 (43.0)	21 (42.0)	9 (30.0)	21 (40.4)
Race, n (%)						
White/Caucasian	186 (95.9)	123 (93.9)	206 (96.3)	48 (96.0)	29 (96.7)	50 (96.2)
Mean IRLS total score, n (%)						
<24 at baseline	116 (59.8)	67 (51.2)	126 (58.9)	18 (36.0)	14 (46.7)	21 (40.4)
≥24 at baseline	78 (40.2)	64 (48.9)	88 (41.1)	32 (64.0)	16 (53.3)	31 (59.6)
Duration of RLS symptoms, years Mean (SD)	13 (12.3)	13 (12.8)	14 (13.3)	17 (15.1)	18 (12.1)	16 (16.8)
Prior RLS treatment, n (%)						
Yes[a]	39 (20.3)	20 (15.5)	31 (14.6)	50 (100.0)	30 (100)	52 (100.0)
Prior dopamine agonist treatment, n (%)						
Ropinirole	n/a	n/a	n/a	39 (78.0)	26 (86.7)	38 (73.0)
Pramipexole	n/a	n/a	n/a	9 (18.0)	5 (16.7)	10 (19.2)
Levodopa-carbidopa	n/a	n/a	n/a	7 (14.0)	2 (6.7)	4 (7.7)
Rotigotine	n/a	n/a	n/a	2 (4.0)	2 (6.7)	2 (3.8)
Pergolide mesilate	n/a	n/a	n/a	1 (2.0)	0 (0.0)	0 (0.0)
Levodopa	n/a	n/a	n/a	0 (0.0)	0 (0.0)	1 (1.9)

[a]Includes patients whose treatment terminated prior to the month before the start of study drug, and those who received treatment within the month of the start of study drug or within the previous month.
DA: dopamine agonist; GEn: gabapentin enacarbil; MITT: modified intent-to-treat; RLS: restless legs syndrome; SD: standard deviation

Efficacy

- At week 12, there was no effect of prior DA exposure on the change in IRLS total score from baseline for the placebo, GEn 600 mg, or GEn 1200 mg groups (Figure 1).

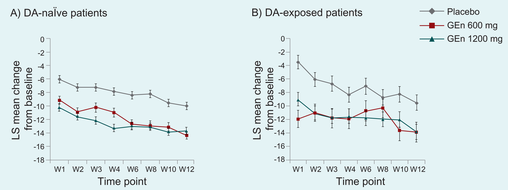
Figure 1. Mean change from baseline in IRLS total score in DA-naïve vs DA-exposed patients at week 12



DA: dopamine agonist; Diff: mean treatment difference; GEn: gabapentin enacarbil; IRLS: International Restless Legs Scale; LS: least squares; SE: standard error

- With the exception of week 1 in the placebo group, there were no statistically significant differences in change from IRLS total score from baseline between the DA-naïve vs DA-exposed patients in any treatment arm at any of the visits (Figure 2).

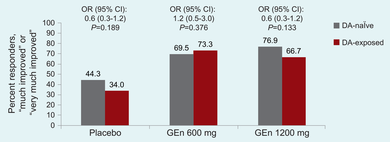
Figure 2. LS mean changes from baseline in IRLS total score by visit



DA: dopamine agonist; IRLS: International Restless Legs Scale; LS: least squares; GEn: gabapentin enacarbil; W: week

- There were no significant differences in the odds of being a CGI-I responder between the DA-naïve vs DA-exposed patients in any of the treatment groups (Figure 3).

Figure 3. Percentage of responders ("much" or "very much" improved) on the investigator-rated CGI-I in DA-naïve vs DA-exposed patients



CGI-I: Clinical Global Impression-Improvement; CI: confidence interval; DA: dopamine agonist; GEn: gabapentin enacarbil; OR: odds ratio

Tolerability

- The adverse event profile was similar between DA-exposed and DA-naïve patients (Table 2).
- The most commonly reported treatment-emergent AEs were dizziness and somnolence (Table 2).

Table 2. Most frequent treatment-emergent adverse events by treatment and prior DA history (naïve vs non-naïve) reported in ≥5% of the safety population[a]

Adverse Event, n (%)	DA-naïve			DA-exposed		
	Placebo (n=195)	GEn 600 mg (n=133)	GEn 1200 mg (n=217)	Placebo (n=50)	GEn 600 mg (n=30)	GEn 1200 mg (n=52)
Any event	149 (76.4)	105 (78.9)	187 (86.2)	34 (68.0)	27 (90.0)	40 (76.9)
Somnolence	12 (6.2)	25 (18.8)	54 (24.9)	0 (0.0)	7 (23.3)	7 (13.5)
Dizziness	9 (4.6)	20 (15.0)	44 (20.3)	2 (4.0)	2 (6.7)	15 (28.8)
Headache	22 (11.3)	12 (9.0)	36 (16.6)	5 (10.0)	7 (23.3)	4 (7.7)
Nasopharyngitis	10 (5.1)	13 (9.8)	17 (7.8)	6 (12.0)	1 (3.3)	4 (7.7)
Nausea	8 (4.1)	5 (3.8)	15 (6.9)	4 (8.0)	4 (13.3)	4 (7.7)
Fatigue	10 (5.1)	5 (3.8)	15 (6.9)	1 (2.0)	3 (10.0)	3 (5.8)
Diarrhea	10 (5.1)	3 (2.3)	7 (3.2)	2 (4.0)	3 (10.0)	3 (5.8)
Upper respiratory tract infection	7 (3.6)	6 (4.5)	5 (2.3)	2 (4.0)	3 (10.0)	1 (1.9)
Dry mouth	4 (2.1)	4 (3.0)	11 (5.1)	1 (2.0)	1 (3.3)	1 (1.9)
Constipation	6 (3.1)	0 (0.0)	7 (3.2)	2 (4.0)	3 (10.0)	3 (5.8)
Insomnia	6 (3.1)	7 (5.3)	4 (1.8)	1 (2.0)	1 (3.3)	2 (3.8)
Irritability	3 (1.5)	2 (1.5)	8 (3.7)	0 (0.0)	4 (13.3)	3 (5.8)
Back pain	6 (3.1)	4 (3.0)	6 (2.8)	1 (2.0)	2 (6.7)	1 (1.9)
Sinusitis	5 (2.6)	2 (1.5)	6 (2.8)	1 (2.0)	3 (10.0)	1 (1.9)
Increased weight	3 (1.5)	2 (1.5)	7 (3.2)	2 (4.0)	2 (6.7)	2 (3.8)

[a]Additional AEs reported in ≥5% of the safety population (at an overall frequency lower than those shown in the table) were: flatulence, contusion, abnormal coordination, toothache, increased appetite, urinary tract infection, depression, viral gastroenteritis, neck pain.
DA: dopamine agonist; GEn: gabapentin enacarbil

Conclusions

- Overall, previous exposure to DAs, with at least a 2-week wash-out period, did not significantly alter the efficacy of GEn, the placebo response, or the AE profile in this pooled analysis of patients with moderate-to-severe RLS.
- The most frequent treatment-emergent AEs were somnolence and dizziness. The AEs reported in this analysis are consistent with the overall safety profile of GEn.[1]
- Limitations of this pooled analysis includes the lack of availability of data for the duration of time between DA use and study enrollment, reason for discontinuation of DA (eg., lack of initial efficacy, side effects, cost, augmentation, etc.), and DA dose.
- Despite these limitations, the question of whether previous exposure to a DA somehow affects the efficacy of an alternate agent after changing treatment remains an important clinical question; these data suggest that there is no apparent difference in efficacy with GEn whether a patient has or has not been previously exposed to a DA.
- Nevertheless, these data support the use of GEn in patients who were previously treated with DA after a ≥2-week washout period, as well as in those who are DA-naive.

References

1. Allen R, et al. *Sleep Med*. 2003;4:101–119.
2. Garcia-Borreguero D, et al. *Sleep Med*. 2007;8:520–530.
3. Horizant [Prescribing Information]. Santa Clara, CA: XenoPort, Inc; 2013.
4. Kushida C, et al. *Neurology*. 2009;72:439–446.
5. Lee D, et al. *J Clin Sleep Med*. 2011;282–292.
6. Lal R, et al. *Clin Neuropharmacol*. 2012;35:165–173.

Acknowledgments

These studies and this analysis were conducted by XenoPort, Inc., Santa Clara, CA. Financial support for medical writing was provided by XenoPort, Inc.

Disclosures

WO served as a speaker for UCB Pharma, Lundbeck, Merz, and TEVA and received grant support from US World Meds, UCB Pharma, and Ipsen. NH served as a consultant for Allergan, Amgen, GlaxoSmithKline, Lundbeck, Teva, UCB Pharma, and US Worldmeds, and received research support from Allergan, Biotie, Chelsea Therapeutics, Merck, Pfizer, and Teva. DGB served as a consultant for UCB, XenoPort Inc., Impax Pharmaceuticals, and Otsuka. MJ is a consultant to XenoPort, Inc. RK, and GS are employees of and own stock in XenoPort, Inc.

bit.ly/1jEZn9c