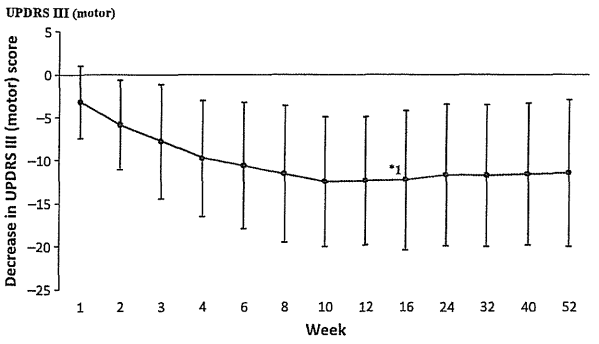
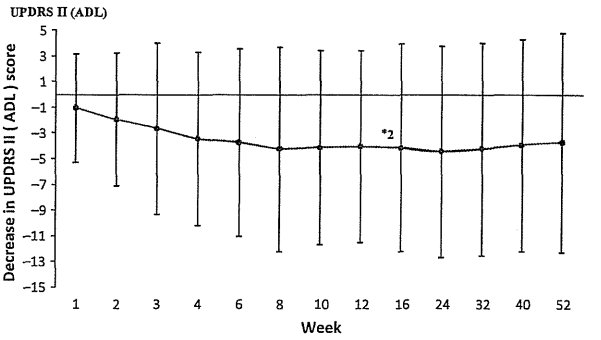


*1: Efficacy analysis (LOCF) at the final endpoint up to week 16 demonstrated a mean (SD) change from baseline in the Japanese UPDRS III (motor) score of −11·3 (8·21).



*2: Efficacy analysis (LOCF) at the final endpoint up to week 16 demonstrated a mean (SD) change from baseline in the Japanese UPDRS II (ADL) scores of −3·9 (3·22).

Fig. 4. The ordinate represents decrease in the Japanese UPDRS III (motor) and UPDRS II (ADL) score and the abscissa weeks. The mean value and standard deviation (SD) of each visit are shown.

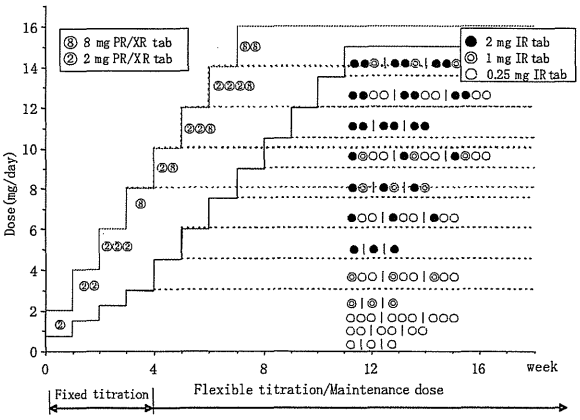


Fig. 5. Dosage comparison between PR/XR tablets and IR tablets.

known that increased daily dose frequency is generally associated with decreased compliance.[16] It has been reported that drugs are not properly used in 20% of patients with PD because of compliance issues[17] and that there is a high frequency of errors in terms of timing or dosage.[18] The IR tablet formulation requires 11 dose changes to reach the maximum dose of 15 mg/day whereas the PR/XR tablet formulation requires seven dose changes to reach the maximum dose of 16 mg/day (Fig. 5). In addition, the PR/XR tablet formation is associated with lower inter-individual variability in the plasma ropinirole concentration than the IR tablet formulation in non-Japanese subjects. In this study, the plasma C_{max} and AUC_{0-24} of ropinirole, SK&F104557 and SK&F89124 were not affected by intake of food after administration of PR/XR tablets. Food also did not affect the production of metabolites SK&F104557 or SK&F89124. Compared with a previous study of Japanese patients with PD treated with IR tablets (0·75–15 mg/day) thrice daily[19] and a non-Japanese clinical study involving patients with PD treated with PR/XR tablets,[20] the safety profile of PR/XR tablets was similar in this study with no new safety signal identified.

What is new and Conclusion: This study shows that compared with the IR tablets, the PR/XR tablets can be administered to Japanese patients with PD at a reduced daily dose frequency and adjusted to the maintenance dose with fewer dose changes. The PR/XR product also produces a smaller diurnal variation in the plasma ropinirole concentration.

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Brief communication

Analysis of *C9orf72* repeat expansion in 563 Japanese patients with amyotrophic lateral sclerosis

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Abstract

Recently, a hexanucleotide repeat expansion in *C9orf72* was identified as the most common cause of both sporadic and familial amyotrophic lateral sclerosis (ALS) and frontotemporal dementia in Western populations. We analyzed 563 Japanese patients with ALS (552 sporadic and 11 familial) using fluorescent fragment-length analysis of *C9orf72* and repeat-primed polymerase chain reaction analysis. Haplotype analysis was performed for 42 single nucleotide polymorphisms in patients with *C9orf72* repeat expansion. *C9orf72* repeat expansion was found in 2 patients with sporadic ALS (2/552 = 0.4%) and no patients with familial ALS (0/11 = 0%). In the probands' families, 1 primary progressive aphasia patient and 1 asymptomatic 76-year-old individual exhibited *C9orf72* repeat expansion. All of the patients with the *C9orf72* repeat expansion carried the 20-single nucleotide polymorphism consensus risk haplotype. The frequency of the *C9orf72* repeat expansion among Japanese patients is much lower than in Western populations. The existence of a 76-year-old asymptomatic carrier supported the notion of incomplete penetrance. The *C9orf72* mutation should be analyzed in sporadic ALS patients after determining their family histories not only of frontotemporal dementia but also of primary progressive aphasia.

Keywords: Amyotrophic lateral sclerosis; *C9orf72*; Incomplete penetrance; Sporadic; Aphasia; Frontotemporal dementia

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder that primarily affects motor neurons in the spinal cord, brain stem, and cerebral cortex, typically leading to death within a few years. Five to ten percent of ALS cases are familial, and the remaining cases are believed to be sporadic (Valdmanis et al., 2009). A number of genes causing ALS with a dominant mode of inheritance have

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been discovered, such as *SOD1*, *TARDBP*, *FUS*, *VAPB*, *ANG*, *VCP*, *OPTN* (Ticozzi et al., 2011), and *UBQLN2* (Deng et al., 2011). Moreover, there is increasing clinical and pathological evidence for the hypothesis that ALS and frontotemporal dementia (FTD) constitute an overlapping continuum of diseases (Lomen-Hoerth et al., 2002; Neumann et al., 2006). Recently, the expansion of a noncoding GGGGCC hexanucleotide repeat in the *C9orf72* gene has been reported to be a major cause of both ALS and FTD (DeJesus-Hernandez et al., 2011; Gijselinck et al., 2012; Renton et al., 2011) and the most common genetic abnormality in familial and sporadic forms of both ALS and FTD, particularly in Western populations (Chiò et al., 2012; DeJesus-Hernandez et al., 2011; Gijselinck et al., 2012; Renton et al., 2011; Sabatelli et al., 2012; Stewart et al., 2012). In the present study, we describe the incidence and demographic and clinical features associated with the *C9orf72* mutation in a large cohort of Japanese ALS patients. We also perform haplotype analysis to investigate whether Japanese patients have the same risk haplotype as European patients (Gijselinck et al., 2012; Laaksovirta et al., 2010; Mok et al., 2012).

2. Methods

2.1. Subjects

We obtained a total of 760 DNA samples from the Japanese Consortium for Amyotrophic Lateral Sclerosis Research (JaCALS; Appendix A). A total of 563 (11 familial and 552 sporadic) patients were diagnosed with ALS according to the El Escorial revised criteria (Brooks et al., 2000) and classified as bulbar-onset, spinal-onset, FTD-ALS, or other (see Supplementary Table 1 for details). We had determined the family histories of ALS but not FTD or primary progressive aphasia (PPA) in all of the patients when they were enrolled as patients with sporadic ALS (SALS). We recruited 197 control subjects, none of whom had a medical or family history of neurodegenerative disorders. The mean age at onset of the patients with ALS was 60.4 ± 11.7 years (range 20–86), and the mean age at sampling of the controls was 60.6 ± 10.3 years (range 26–83). All of the subjects were unrelated Japanese individuals. Written informed consent was obtained from all of the subjects. The ethical committees at the participating institutions approved this study.

2.2. Fluorescent fragment-length analysis of C9orf72 and repeat-primed PCR analysis

The normal repeat number of the GGGGCC hexanucleotide was determined in all of the patients and control subjects using genotyping primers, as previously described (DeJesus-Hernandez et al., 2011). To provide a qualitative assessment of the presence of *C9orf72* repeat expansions, we performed repeat-primed polymerase chain reaction (PCR), as previously described (DeJesus-Hernandez et al., 2011).

2.3. Haplotype analysis

We genotyped 42 single nucleotide polymorphisms (SNPs) across 232 kilobase of Chromosome 9p21, which were first described as the founder haplotype in the Finnish ALS population (Laaksovirta et al., 2010), using primers (Supplementary Table 2) to determine whether our Japanese patients carried the haplotype associated with a risk of ALS. These 42 SNPs included the 20-SNP consensus risk allele that had recently been detected in genome-wide association studies in several populations (Mok et al., 2012). We also performed haplotype analysis with 4 microsatellites (D9S1121, D9S169, D9S270, and D9S104) flanking the *C9orf72* GGGGCC repeat, as previously described (Gijselinck et al., 2012) (Fig. 1).

3. Results

3.1. Detection of C9orf72 repeat expansion

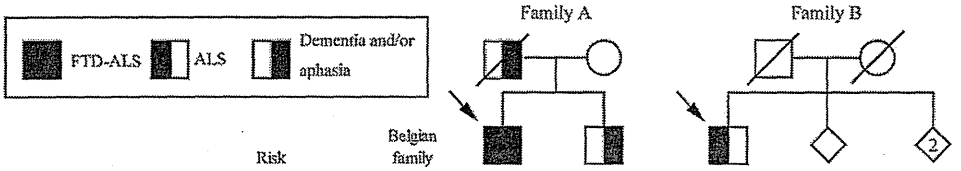
The *C9orf72* repeat expansion was found in 2 of 522 Japanese patients (2/552 = 0.4%) with SALS and none of the 11 patients (0/11 = 0%) with familial ALS (FALS) using repeat-primed PCR (Table 1). Patient A-I with a *C9orf72* mutation was classified as SALS in this study, but after detecting the mutation, we found that patient A-II (a brother of patient A-I) developed aphasia and dementia and had a *C9orf72* mutation (Fig. 1). The average repeat number based on fluorescent fragment-length analysis was 3.65 ± 2.43 (range 2–13 repeats) in 561 ALS patients without the *C9orf72* mutation. A subsequent analysis of 197 healthy controls did not detect any *C9orf72* mutation. The average repeat number was 3.69 ± 2.46 (range 2–14 repeats) in the 197 controls. The mean age at disease onset in patients with *C9orf72* mutation, including patient A-II, was 64.7 ± 6.1 years (range 57–72). The genotypes of all individuals with the *C9orf72* mutation were detected for the 20 SNPs spanning a 140-kilobase segment concordant with the recently identified risk haplotype on chromosome 9p (Mok et al., 2012) and 24 or 25 consecutive SNPs in the 42-SNP Finish risk haplotype (Laaksovirta et al., 2010) (Fig. 1, Supplementary Table 3).

3.2. Clinical presentations of individuals with C9orf72 mutation

3.2.1. Patient A-I (family A)

Patient A-I was a 65-year-old man who reported weakness in the left leg. The weakness progressed, and he developed fasciculation. At age 66, a neurological examination revealed dementia. His Mini Mental State Examination score was 23/30, and his Frontal Assessment Battery score was 13/18. He also exhibited dysarthria and weakness, atrophy, and fasciculation in the tongue and all 4 modalities. His tendon reflexes were diminished, and the plantar re-

A)



B)

Marker	Position	Risk allele	Freq JPT	Belgian family DR14	Patient A-I	Patient A-II	Patient B-I	Subject B-II
rs725804	27458939	A	A=0.081		C/C	C/C	C/C	C/C
rs10511816	27468461	T	T=0.105		T/G	T/G	G/G	G/G
rs1444533	27477874	A	A=0.553		A/A	A/A	A/G	A/G
rs1822723*	27478052	C	C=0.669		C/C	C/C	C/C	C/C
rs4879515*	27482235	T	T=0.645		T/T	T/T	T/T	T/T
rs895023	27483959	T	T=1.000		T/T	T/T	T/T	T/T
rs868856*	27489251	T	T=0.247		T/T	T/T	T/T	T/T
rs7046653*	27490967	A	A=0.250		A/A	A/A	A/A	A/A
rs2440622	27495418	A	A=0.988		A/A	A/A	A/A	A/A
rs1977661 *	27502986	C	C=0.651		C/C	C/C	C/C	C/C
rs903603*	27529316	C	C=0.341		C/C	C/C	C/T	C/T
rs10812610*	27533984	C	A=0.680		C/C	C/C	C/A	C/A
rs2814707*	27536397	A	A=0.058		A/A	A/A	A/G	A/G
rs3849942*	27543281	A	A=0.076		A/A	A/A	A/G	A/G
C9orf72	27546544..27573842			mutation	**mutation**	**mutation**	**mutation**	**mutation**
rs12349820	27553876	T	T=0.890		T/T	T/T	T/T	T/T
rs10122902*	27556780	G	G=0.738		G/G	G/G	G/G	G/G
rs10757665*	27557919	T	T=0.890		T/T	T/T	T/T	T/T
rs1565948*	27559733	G	G=0.600		G/G	G/G	G/G	G/G
rs774359*	27561049	C	C=0.070		C/C	C/C	C/T	C/T
rs2282241*	27572255	G	G=0.326		G/G	G/G	G/T	G/T
rs1948522*	27575785	C	C=0.837		C/C	C/C	C/C	C/C
rs1982915*	27579560	G	G=0.238		G/G	G/G	G/A	G/A
rs2453556*	27586162	G	G=0.448		G/G	G/G	G/A	G/A
rs702231*	27588731	A	A=0.634		A/A	A/A	A/A	A/A
rs696826*	27589657	G	G=0.983		G/G	G/G	G/G	G/G
rs2477518*	27599746	T	T=0.820		T/T	T/T	T/T	T/T
D9S270	28404862 .. 28404948			327	327/325	327/325	323/323	323/323
D9S104	28771379 .. 28771576			168	158/158	158/158	158/171	158/171

Fig. 1. (A) The pedigrees of the 2 families with *C9orf72* repeat expansion. To maintain confidentiality, several unaffected individuals who died early in families A and B are not shown. Probands are indicated by arrows. (B) The genotyping data of the single nucleotide polymorphisms (SNPs) and microsatellites. Twenty SNPs, which comprised a recently identified consensus risk haplotype (Mok et al., 2012), are shown with an asterisk. See Supplementary Table 3 for details of the analyses of 42 SNPs (Laaksovirta et al., 2010) and microsatellites (Gijselinck et al., 2012). Alleles possibly shared between our subjects and patients in Western populations are shown in bold. The genotypes of all 4 subjects with respect to the 20 SNPs were found to be concordant with the risk haplotype (Mok et al., 2012). All of the positions of SNPs and microsatellites were from NC_000009.11. Abbreviations: ALS, amyotrophic lateral sclerosis; Freq JPT, Frequency in Japanese in Tokyo from International HapMap project (International HapMap Consortium, 2003); FTD, frontotemporal dementia.

sponse was extensor on the left. He had neither dysphagia nor dyspnea. No sensory abnormalities were noted. Extensive screening for causes of motor neuropathy was negative. The diagnosis was clinically probable ALS-laboratory supported (Brooks et al., 2000) and FTD-ALS.

3.2.2. *Patient A-II (family A)*

This patient was a 57-year-old man who presented with difficulty speaking. He was believed to have suffered from a mental disease after being imprisoned because of his involvement in a fatal car accident. At age 64, he was severely dysfluent and could barely speak. Logoclonia was particularly prominent. However, he did not exhibit any violent behavior or other behavioral abnormalities. He also did not display any clinical features of motor neuron disease. Brain magnetic resonance imaging revealed severe frontotemporal lobar atrophy. PPA was considered the most likely diagnosis.

3.2.3. *Patient B-I (family B)*

Patient B-I was a 72-year-old man who presented with gait disturbance and weakness in the proximal lower extremity muscle. His family history was negative for motor neuron disease and dementia (Fig. 1). The muscle weakness and atrophy progressed and spread to the other parts of his body despite treatment with intravenous gamma globulin. At age 74, he could not roll over while sleeping. A neurological examination showed marked muscle atrophy in his arms and shoulders and prominent fasciculation in his legs. The deep tendon reflexes were decreased in his limbs, and he had no pathological reflexes. Sensations in all 4 modalities were intact. At age 75, he developed dyspnea and dysphagia and started noninvasive positive pressure ventilation and intravenous hyperalimentation. He died of respiratory insufficiency at age 76. An autopsy was not performed. The diagnosis was clinically suspected ALS (Brooks et al., 2000).

Table 1
Frequencies of ALS patients with *C9orf72* and *SOD1* mutations in different countries

Study	Population	*C9orf72*			*SOD1*	
		Familial ALS	Sporadic ALS	Mean AAO (range), years	Familial ALS	Sporadic ALS
This study, 2012	Japanese (JaCALS)	0% (0/11)	0.4% (2/552)	64.7 (57–72)	NA	NA
Akimoto et al. (2011)	Japanese (JaCALS)	NA	NA	NA	NA	1.6% (4/255)
DeJesus-Hernandez et al. (2011)	Mixed[a]	23.5% (8/34)	4.1% (8/195)***	54.5 (41–72)	11.8% (4/34)	0% (0/195)
Renton et al. (2011)	Finish	46.4% (52/112)**	21.0% (61/290)***	53 (30–71)	NA	NA
Gijselinck et al. (2012)	Flanders-Belgian	46.7% (7/15)*	4.9% (6/122)***	54.5 (38–64)	0% (0/16)	0% (0/125)
Stewart et al. (2012)	Unknown[b]	27.4% (17/62)	3.6% (6/169)**	58.2 (39–82)	Total 8.2% (19/231)	
Byrne et al. (2012)	Ireland	40.8% (20/49)*	4.9% (19/386)***	56.3 (NA)	Total 0% (0/191)	
Cooper-Knock et al. (2012)	Northern England	42.9% (27/63)*	7.0% (35/500)***	57.3 (27–74)	Total 2.5% (14/563)	
Chiò et al. (2012)	Italian	37.5% (45/120)*	NA	59.0 (NA-80)	0% (0/141)	NA
	Sardinian	57.1% (12/21)**	NA	60.4 (NA)	NA	NA
	German	22.0% (9/41)	NA	56.4 (NA)	NA	NA
Majounie et al. (2012)	England	45.9% (45/98)**	6.8% (62/916)***	NA	NA	NA
	German	21.7% (15/69)	5.2% (22/421)***	NA	NA	NA
	Italian	37.8% (34/90)*	4.1% (19/465)***	NA	NA	NA
	Sardinian	57.9% (11/19)**	7.8% (10/129)***	NA	NA	NA
	USA White	US total 36.2% (59/163)*	5.4% (48/890)***	NA	NA	NA
	USA Hispanic		8.3% (6/72)***	NA	NA	NA
	USA Black		4.1% (2/49)	NA	NA	NA
	Australian	NA	5.3% (14/263)***	NA	NA	NA
	Israeli	21.4% (3/14)	NA	NA	NA	NA
	Indian	NA	0% (0/31)	NA	NA	NA
	Asian	5.0% (1/20)	0% (0/238)	NA	NA	NA
	Pacific islander/Guam	NA	0% (0/90)	NA	NA	NA
Sabatelli et al. (2012)	Italian	NA	3.7% (60/1624)***	58.6 (49–65)	NA	NA
	Sardinian	NA	6.8% (9/133)***	62.9 (58–63)	NA	NA

Key: AAO, age at onset; ALS, amyotrophic lateral sclerosis; JaCALS, Japanese Consortium of Amyotrophic Lateral Sclerosis Research; NA, not available.
[a] Mixed included 229 ALS patients from Mayo Clinic, Florida: White (212), Asian (1), Pacific Islander (1), and Black or African American (15).
[b] Unknown included 231 ALS patients from the ALS Clinic of Vancouver Coastal Health and the University of British Columbia (Vancouver General Hospital and GF Strong Rehabilitation Centre sites).
* $p < 0.05$, compared with our results (2-tailed, Yates's χ^2 test).
** $p < 0.01$, compared with our results (2-tailed, Yates's χ^2 test).
***$p < 0.001$ compared with our results (2-tailed, Yates's χ^2 test).

3.2.4. Subject B-II (family B)

Subject B-II, a sibling of Patient B-I, had a *C9orf72* mutation but did not have symptoms of dementia or motor neuron disease until age 76 (Fig. 1).

4. Discussion

We began this study considering patients without family histories of ALS to be SALS because our cohort included only family histories of ALS but not FTD or PPA. Although it may be difficult to describe the real frequency in SALS because 1 of the SALS patients had a family member who developed PPA, the frequencies of the *C9orf72* mutation in Japanese patients were 0.4% (2/552) in SALS and 0% (0/11) in FALS according to this classification. In contrast, the frequencies of the *C9orf72* mutation fall within the ranges of 21%–57% in FALS and 3%–21% in SALS in Western populations (Table 1), and the *C9orf72* mutation has been reported as the most common genetic cause of FALS and SALS in Western populations (Byrne et al., 2012; Chiò et al., 2012; Cooper-Knock et al., 2012; DeJesus-Hernandez et al., 2011; Gijselinck et al., 2012; Majounie et al., 2012; Renton et al., 2011; Sabatelli et al., 2012; Stewart et al., 2012). However, the *C9orf72* mutation in this study was not more frequent than the *SOD1* mutation in Japanese SALS patients (0.4% and 1.6%, Table 1) (Akimoto et al., 2011). Considering these data, the *C9orf72* mutation is more common than the *SOD1* mutation in Western populations but not in Japan, suggesting different genetic backgrounds. Our results may explain the association study of rs2814707 on 9p21.2, which was reported to be the most significantly associated SNP with SALS in Caucasian but not in Japanese and Chinese populations (Iida et al., 2011). A recent report revealed that the rate of expansion in Asian FALS and SALS was 5% (1/20) and 0% (0/238), respectively (Majounie et al., 2012). An analysis of the SNPs on chromosome 9p revealed that all 4 subjects with the *C9orf72* mutation and another Japanese subject from the previously mentioned report (Majounie et al., 2012) share a shorter region of the risk haplotype

than Western populations. Thus, the haplotype bearing the *C9orf72* mutation was only shared in a narrow region between Western and Asian populations, suggesting that the *C9orf72* mutation may be an old mutation in human migration history from Western to East Asia. This mutation was estimated to be approximately 1500 years old (Majounie et al., 2012).

Bulbar onset and cognitive impairment have been reported to be more common in ALS patients with the *C9orf72* repeat expansion (Chiò et al., 2012; Cooper-Knock et al., 2012; DeJesus-Hernandez et al., 2011; Sabatelli et al., 2012; Stewart et al., 2012). We did not find any patients with bulbar onset, but we identified 2 patients with dementia. Although the age at onset has been known to be lower in SALS patients with the *C9orf72* mutation than in those without this mutation (Sabatelli et al., 2012), our patients exhibited a relatively older age at onset (Table 1).

Although apparently sporadic patients with *C9orf72* mutation have been detected worldwide (Byrne et al., 2012; Cooper-Knock et al., 2012; Sabatelli et al., 2012), it was not known whether this phenomenon was due to incomplete penetrance or to spontaneous expansion of the GGGGCC hexanucleotide repeat from a nonpathogenic parental form (ie, a de novo expansion). In this study, we found a 76-year-old healthy individual with a *C9orf72* mutation (Subject B-II), as described in previous studies (Majounie et al., 2012; Renton et al., 2011). This discovery suggests not de novo expansion but incomplete penetrance, which explains the existence of apparently sporadic patients with the *C9orf72* mutation. Although it has been reported that the penetrance of the *C9orf72* mutation is almost full by 80 years by Kaplan–Meier analysis of 603 mutant gene carriers and 5 neurologically healthy individuals, further studies of family members of patients with the *C9orf72* mutation will be required to calculate the true penetrance and to improve genetic counseling.

Finally, we found a PPA patient with the *C9orf72* mutation after detecting the mutation in a SALS patient, suggesting the importance of collecting information regarding whether SALS patients have a family history of dementia or aphasia. Therefore, the possibility of *C9orf72* mutation should be investigated when clinicians meet with SALS patients after determining their family histories of FTD or PPA. Furthermore, our data supported Byrne and colleagues' suggestion that a family history of FTD should also be included in the revised definition of FALS (Byrne et al., 2012).

Disclosure statement

All of the authors disclose no conflicts of interest. The study was approved by the ethical committees of the participating centers. All participants gave written informed consent.

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Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2012.05.011.

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Long-term efficacy and safety of gabapentin enacarbil in Japanese restless legs syndrome patients

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ABSTRACT

Several short- and long-term studies conducted in Europe/North America have demonstrated good efficacy and tolerability of 600–1800 mg gabapentin enacarbil (GEn). However, no studies have evaluated the efficacy of long-term treatment with GEn in Asian patients. Therefore, the objective of this study was to evaluate the efficacy and safety of long-term treatment with GEn in Japanese patients with restless legs syndrome (RLS) in a multicenter open-label study.

RLS patients aged 20–80 years were allocated to receive oral GEn 1200 mg/day for a treatment period of 52 weeks. International Restless Legs Syndrome Scale (IRLS) score, investigator- and patient-rated Clinical Global Impression (CGI) scores, Pittsburgh Sleep Quality Index (PSQI) total scores and subscores, and short form (SF)-36 subscores were assessed, and adverse events (AEs) were monitored. In 181 patients (mean age, 54.9 ± 12.2 years; BMI, 23.0 ± 2.6 kg/m^2) IRLS score decreased from 24.4 ± 0.4 at baseline to 6.3 ± 0.6 at week 52, with a reduction of −18.0 ± 0.6. The IRLS responder rate was 80.3% at week 52. ICGI and PCGI responder rates were 87.1% and 87.1%, respectively. PSQI and SF-36 also showed significant improvements. AEs were reported in 96.2% of patients but remained mild-to-moderate in nearly all the cases. Serious AEs occurred in 1.6%. Dizziness and somnolence were noted in 46.2% and 41.2% of patients, respectively, and mostly occurred during the first 4 weeks. No episodes of augmentation were reported.

In conclusion, long-term treatment with GEn improved RLS symptoms as well as investigator- and patient-reported outcomes in Japanese patients with moderate-to-severe RLS, with an acceptable safety profile. Randomized, double-blind, placebo/active-controlled trials are desirable to confirm these preliminary results.

1. Introduction

Restless legs syndrome (RLS) is a neurological disorder characterized by a variety of unpleasant sensations, most commonly in the legs, which provoke an irresistible urge to move the affected areas. The prevalence of RLS is 5–10% in white populations (Ohayon and Roth, 2002; Winkelman et al., 2006a) and 2–4% in Japanese populations (Nomura et al., 2008a,b). The irritable sensations in RLS are most commonly experienced while the affected individual is at rest, especially during the evening or at nighttime. Consequently, RLS is associated with insomnia, depression and deterioration of quality of life (QoL) (Allen et al., 2005; Kushida et al., 2007; Rothdach et al., 2000).

In terms of its pathophysiology and treatment, RLS is accepted as a disorder of the central nervous system (Trenkwalder and Paulus, 2010). Although its etiology is not fully understood, dopaminergic dysfunction, genetic background, and abnormal brain iron metabolism seem to be critical factors for the development of RLS (Trenkwalder and Paulus, 2010). Dopaminergic agonists (DAs) are the most commonly used treatments against RLS. However, these drugs are associated with a high risk of adverse events (AEs) including compulsive behaviors, nausea, dizziness, and somnolence, which affect considerable numbers of patients, leading to discontinuation of therapy in many cases (Earley and Silber, 2010). Furthermore, treatment with DAs might cause augmentation–expansion of the affected body areas and earlier onset and paradoxical worsening of RLS symptoms despite increasing the dose-limiting long-term maintenance therapy (Högl et al., 2010; Winkelman and Johnston, 2004).

Abbreviations: AE, adverse event; DA, dopaminergic agonist; GEn, gabapentin enacarbil; ICGI, Investigator-rated Clinical Global Impression; IRLS, International Restless Legs Syndrome Scale; PCGI, Patient-rated Clinical Global Impression; PSQI, Pittsburgh Sleep Quality Index; QoL, quality of life; RLS, restless legs syndrome; SF, short-form.

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To avoid these limitations of dopaminergic treatment, other anti-RLS therapies have been considered, including opioids and anticonvulsants.

Because of its anticonvulsant and antineuralgic properties, the GABA derivative drug gabapentin is regarded as an important candidate drug for the treatment of RLS. Indeed, gabapentin was recommended in the treatment algorithms for RLS developed by the Restless Legs Syndrome Foundation (Silber et al., 2004) and the Movement Disorder Society (Trenkwalder et al., 2008b). Several randomized double-blind and open-label studies have demonstrated that gabapentin improves the symptoms of RLS (Garcia-Borreguero et al., 2002; Happe et al., 2003; Micozkadioglu et al., 2004; Thorp et al., 2001). However, the intestinal absorption of orally administered gabapentin shows marked interpatient variability rendering unpredictable treatment responses. Therefore, to improve plasma exposure, the gabapentin prodrug gabapentin enacarbil (GEn) was developed (Cundy et al., 2008). GEn is absorbed via high-capacity nutrient transporters throughout the gastrointestinal tract and is rapidly converted to gabapentin, providing dose-proportional exposure (Cundy et al., 2004).

Several short-term randomized controlled trials have been conducted to determine the clinical efficacy of GEn in RLS (Merlino et al., 2009). These studies demonstrated greater efficacy of GEn versus placebo in terms of improvements in RLS symptoms and measures of sleep quality over 2 weeks in moderate-to-severe patients (Kushida et al., 2009; Walters et al., 2009). In a longer-term study with a 24-week, single-blind phase followed by a 12-week, randomized, double-blind, placebo-controlled phase, GEn (1200 mg/day) maintained improvements of RLS symptoms for up to 9 months (Bogan et al., 2010). Similarly, Ellenbogen et al. (2011) reported that 600–1800 mg doses of GEn were generally safe and well tolerated in a 52-week open-label extension following a 12-week randomized double-blind placebo-controlled phase. However, no studies have evaluated the efficacy of long-term treatment with GEn in Asian patients.

Therefore, the primary objective of this study was to evaluate the efficacy and safety of long-term (≥1-year) treatment with GEn in Japanese patients with RLS. The second aim was to evaluate the effects of GEn on QoL and subjective sleep disturbances of the patients. In addition, we tried to identify the factor(s) associated with the improvements in RLS symptoms following GEn treatment.

2. Methods

2.1. Study design

This was a multicenter, open-label study to evaluate the efficacy and safety of GEn (GEn is licensed from XenoPort, Inc.) for long-term treatment of RLS. The study was approved by institutional review boards/independent ethics committees at each participating institution, and the protocol conformed to the Declaration of Helsinki. All patients provided written informed consent prior to enrollment. This study was registered with Astellas Pharma protocol no. 8825-CL-0005.

2.2. Patients

Male and female outpatients aged 20–80 years who had been diagnosed with RLS according to the diagnostic criteria established by the International RLS Study Group (Allen et al., 2003; American Academy of Sleep Medicine, 2005), including International Restless Legs Syndrome Scale (IRLS) score ≥15, presence of RLS symptoms on ≥15 days per month and ≥4 days per week preceding inclusion in this study, were enrolled. The target number of subjects was 120, based on the Long-Term Treatment Guideline of the Pharmaceutical Affairs Bureau, Ministry of Health, Labour and Welfare, Japan, which states that a minimum of 100 patients should be treated for 52 weeks for appropriate safety evaluation, with no upper limit. Patients using DAs or gabapentin within 1 week before or any anti-RLS treatment within 2 weeks before the start of the pretreatment observation period were excluded, as were those with an estimated creatinine clearance <60 mL/min determined using the Cockcroft–Gault formula. Pregnant or lactating women and individuals with serum ferritin <20 ng/mL were also excluded from the trial. Moreover, although neurophysiological tests (e.g. nerve conduction studies) were not performed, individuals with movement disorders and/or abnormal neurological findings were excluded.

2.3. Treatment

After completing the 1-week pretreatment observation period, GEn was administered orally once daily after the evening meal at an initial dose of 600 mg/day for 3 days and then uptitrated to 1200 mg/day for a total treatment period of 52 weeks. At week 12, the dose could be increased to 1500 mg/day in patients with an inadequate clinical response to 1200 mg/day or decreased to 900 mg/day for patients showing poor tolerance to GEn. After the 52-week treatment period, patients were administered GEn 600 mg/day for 7 days (dose-tapering period), which was followed by a 1-week treatment-free follow-up period to monitor withdrawal symptoms.

2.4. Safety and efficacy endpoints

Efficacy was assessed by determining the IRLS score at weeks 0, 1, 2 and 4, and every 4 weeks thereafter through to week 52, as well as during the 1-week follow-up period. Patients who achieved an IRLS total score ≤10 were defined as "IRLS responders", and the IRLS responder rate was determined. We also assessed improvements in Investigator-rated and Patient-rated Clinical Global Impression (ICGI and PCGI), Pittsburgh Sleep Quality Index (PSQI) total score and subscores, and short-form (SF)-36 subscores. Patients whose improvements based on ICGI and PCGI were rated as "much improved" or "very much improved" were defined as ICGI/PCGI responders, and the responder rates were determined.

Safety assessments were performed throughout the treatment period and included AEs, changes in vital signs, laboratory tests, and ECG. Assessments of AEs and vital signs were made in weeks, 0, 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 53 and 54 as well as at discontinuation. Laboratory tests were performed at weeks 0, 2, 4, 8, 12, 20, 28, 36, 44 and 52 as well as at discontinuation. ECG was performed during the pre-treatment observation period and at weeks 12, 28 and 52 as well as at discontinuation. Dizziness and somnolence were defined as specific AEs and subjected to further analysis.

2.5. Statistical analysis

The full analysis set (FAS) comprised patients who received investigational product and were assessed for at least one efficacy evaluation variable. The safety analysis set (SAS) consisted of patients who received at least one dose of investigational product.

Summary statistics were calculated for the change in IRLS score, PSQI and SF-36 at each time-point versus baseline with paired *t*-tests. The change in IRLS score was assessed by multiple regression analysis using baseline IRLS total score, sex, age, BMI and duration of RLS morbidity as covariates. Logistic regression analysis on the factors associated with IRLS responder was also performed using baseline IRLS total score, sex, age, and BMI as independent variables.

AEs and adverse drug reactions were evaluated, and the rates of the events were calculated. Summary statistics were calculated for clinical laboratory values, 12-lead ECG findings, blood pressure and pulse rate, while frequencies were calculated for discrete data.

All statistical analyses were performed using PC-SAS software system version 8.2 (SAS Institute, Cary, NC).

3. Results

3.1. Patient disposition

Of 266 patients who provided consent to participate in this study, 182 were eligible for inclusion and enrolled (Fig. 1). All patients who entered the study received the investigational product. Of these, 49 discontinued treatment mainly due to AEs ($n=24$) and withdrawal of consent ($n=16$). A total of 133 patients completed the 52-week treatment period. Nearly all patients who completed the treatment period and approximately one-third of those who withdrew during the treatment period entered the dose-tapering and follow-up periods. One patient violated the study protocol; the remaining, 181 patients were included in the FAS.

3.2. Patient characteristics

The baseline characteristics of the patients in the FAS ($n=181$) are shown in Table 1. The mean (±SD) age was 54.9±12.2 years, body weight was 60.2±9.4 kg, and body mass index was 23.0±2.6 kg/m^2. The mean duration of RLS was 10.6±11.0 years, and 18 patients (9.9%) had a family history of RLS.

3.3. Treatment duration and dose changes

The mean duration of treatment with GEn was 283 days, and the overall compliance rate was 91.4%. Of 182 patients treated with GEn, the daily dose was increased to 1500 mg in four individuals because of insufficient efficacy. None of these patients withdrew from the study after the dose increase. The dose of GEn was reduced to 900 mg in 18 patients because of AEs (Table 1). These patients, except for one who discontinued the treatment due to withdrawal of consent, completed the trial period.

Table 1
Baseline characteristics of the patients (FAS, $n=181$).

Parameter	
Sex M/F, n (%)	88 (48.6)/93 (51.4)
Age, mean (range), years	54.9±12.2 (21–76)
BMI, mean (range), kg/m^2	23.0±2.6 (18.5–29.6)
Duration of RLS morbidity, years	10.6±11.0
IRLS total score	24.4±5.1
Final daily dosage prior to tapering, n (%)	
600 mg[a]	8 (4.4)
900 mg	18 (9.9)
1200 mg	151 (83.4)
1500 mg	4 (2.2)

Values are expressed as mean±SD. FAS: full analysis set.
[a] Patients who discontinued treatment during the first 3 days, before uptitration to 1200 mg/day.

3.4. Efficacy

The mean (±SE) baseline IRLS score was 24.4±0.4 and decreased to 14.5±0.6 after 1 week of treatment, representing a statistically significant change from baseline of −9.9±0.6 ($p<0.001$). As shown in Fig. 2, the IRLS score continued to decrease throughout the treatment period, and the decrease remained statistically significant through to week 52. The IRLS score at week 52 was 6.3±0.6, representing a change from baseline of −18.0±0.6. The IRLS responder rate was 80.3% at week 52, while the ICGI and PCGI responder rates were 87.1% and 87.1%, respectively. The time-course of changes in IRLS, ICGI and PCGI responder rates is depicted in Fig. 3.

The scores for PSQI and SF-36 at week 52 were significantly improved in comparison with the baseline values (all domains, $p<0.001$ except for Use of Sleep Medicine (C6) of PSQI, $p=0.041$,

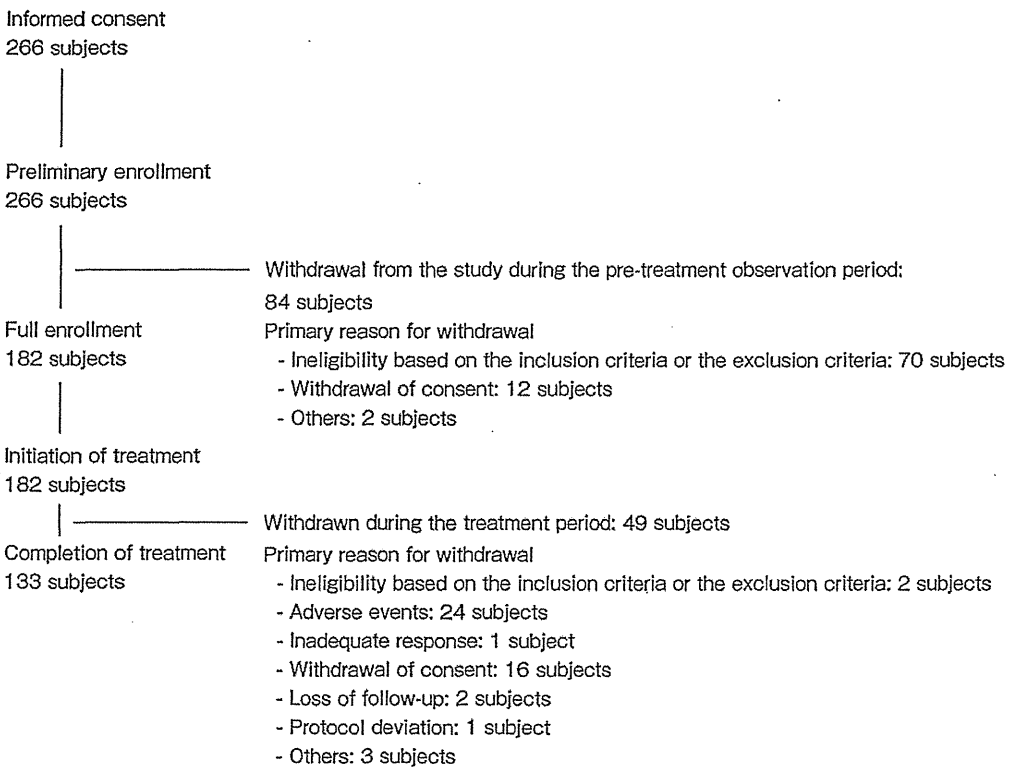

Fig. 1. Patient disposition.

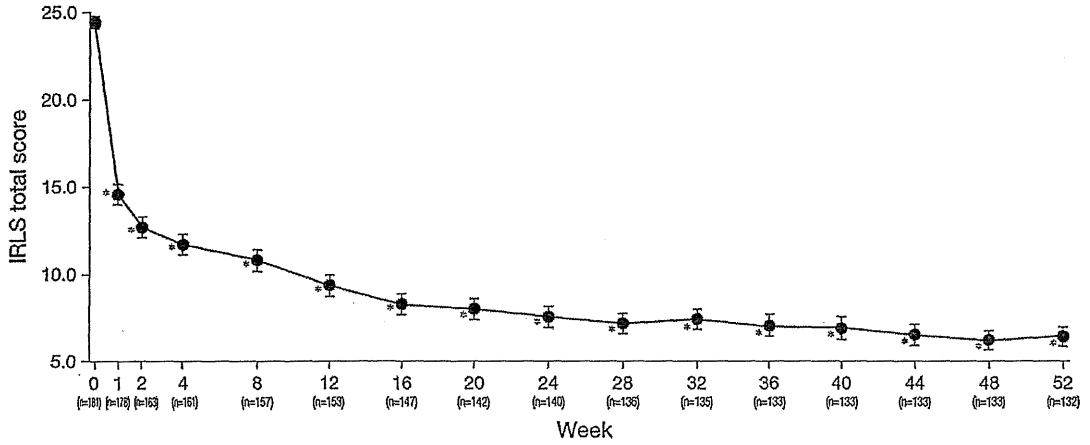

Fig. 2. Change in IRLS total score over 52 weeks of treatment with GEn (FAS). Values are expressed as mean ± SE. *$p<0.001$ vs week 0 (paired t-test).

and Physical Functioning of SF-36, $p=0.003$, Table 2). At the completion of treatment, the change in the total PSQI score from baseline was −2.9 ± 3.41. Changes in subscores were as follows: −0.6 ± 0.85 for Sleep Quality (C1), −0.6 ± 1.06 for Sleep Latency (C2), −0.5 ± 0.84 for Sleep Duration (C3), −0.5 ± 0.98 for Habitual Sleep Efficacy (C4), −0.2 ± 0.56 for Sleep Disturbance (C5), −0.1 ± 0.43 for Use of Sleep Medicine (C6), and −0.4 ± 0.97 for Daytime Dysfunction (C7). Score changes in each SF-36 subscale at the completion of treatment from baseline were 2.00 ± 11.793 for Physical Functioning, 1.64 ± 26.794 for Role Physical, 8.01 ± 24.662 for Bodily Pain, 4.69 ± 15.264 for General Health, 5.46 ± 20.994 for Vitality, 3.36 ± 25.292 for Social Functioning, 1.00 ± 23.421 for Role Emotional, and 3.17 ± 19.764 for Mental Health.

3.5. Multiple regression analysis and logistic model analysis

Multiple regression analysis revealed that a high baseline IRLS total score and male sex were significantly associated with the reduction in IRLS score (baseline IRLS total score: $\beta=-0.59$, $p<0.001$; male sex: $\beta=-4.23$, $p=0.001$). Meanwhile, logistic regression analysis showed that low baseline IRLS total score and male sex were significantly associated with higher responder rates to treatment with GEn (baseline IRLS total score: OR = 0.928, 95% CI = 0.868–0.992, $p=0.0275$; male sex: OR = 0.417, 95% CI = 0.204–0.853, $p=0.0166$). On the other hand, age and BMI were not associated with the reduction in IRLS score or the IRLS responder rate.

3.6. Safety

AEs and treatment-related AEs were reported in 96.2% and 90.7% of patients, respectively. Serious AEs occurred in 3 of 182 patients (1.6%), including one death due to lymphoma that was considered possibly related to treatment with GEn on the basis of a temporal relationship. AEs arising in ≥5% of patients are summarized according to their frequency and severity in Table 3. The most common AEs included dizziness ($n=84$; 46.2%), somnolence ($n=75$; 41.2%), and nasopharyngitis ($n=55$; 30.2%). Moderate AEs reported in at least two patients included dizziness in 18 patients, somnolence in 17 patients, nausea in four patients, blood creatine phosphokinase increased in three patients, and headache in three patients.

AEs led to discontinuation in 24 patients (13.2% of total subjects). All of these AEs were mild or moderate in severity and most commonly included dizziness ($n=8$; 4.4%), nausea ($n=5$; 2.7%), followed by vertigo, headache and somnolence ($n=3$; 1.6% each). AEs led to a reduction of GEn dose in 18 patients (9.9%).

Laboratory values and vital signs after the start of treatment were comparable with those before stating GEn. During treatment, one patient experienced two episodes of QT prolongation that were not

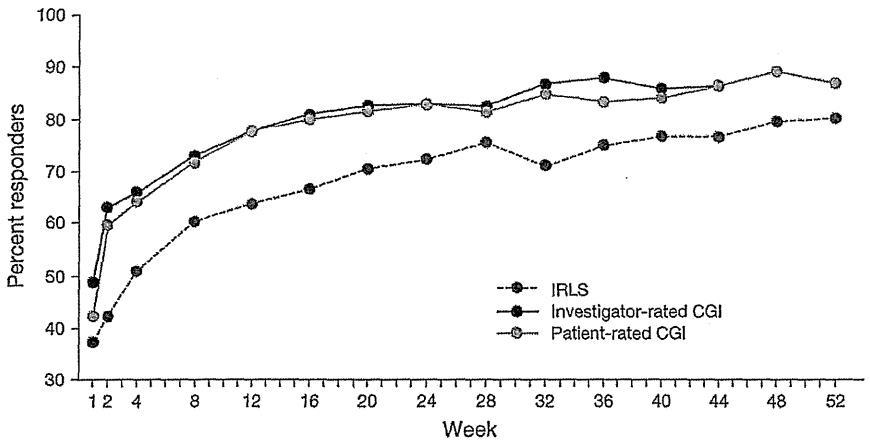

Fig. 3. Time-course of responder rates for IRLS (IRLS total score ≤10), ICGI and PCGI ("much improved" or "very much improved").

Table 2
Comparisons of PSQI and SF-36 scores between baseline and week 52 of the treatment period.

	Baseline ($n=181$)	Week 52 ($n=132$)	p value[a]		Baseline ($n=181$)	Week 52 ($n=132$)	p value[a]
PSQI total score	8.5	4.9	$p<0.001$	SF-36			
Sleep Quality (C1)	1.8	1.0	$p<0.001$	Physical Functioning	89.36	93.22	$p=0.003$
Sleep Latency (C2)	1.8	1.0	$p<0.001$	Role Physical	86.15	93.61	$p<0.001$
Sleep Duration (C3)	1.8	1.3	$p<0.001$	Bodily Pain	71.99	83.73	$p<0.001$
Habitual Sleep Efficacy (C4)	0.8	0.2	$p<0.001$	General Health	60.33	67.29	$p<0.001$
Sleep Disturbance (C5)	1.0	0.7	$p<0.001$	Vitality	56.84	66.43	$p<0.001$
Use of Sleep Medicine (C6)	0.1	0.0	$p=0.041$	Social Functioning	84.32	92.61	$p<0.001$
Daytime Dysfunction (C7)	1.1	0.6	$p<0.001$	Role Emotional	85.50	92.05	$p<0.001$
				Mental Health	69.12	75.95	$p<0.001$

Values are means.
[a] Paired t-test (two sided, $\alpha=0.05$).

considered clinically significant but were reported as AEs possibly related to the investigational product. Both events were mild and resolved during the study.

No specific AEs suggestive of withdrawal symptoms were reported during the dose-tapering or follow-up period. No incidence of investigator-reported augmentation was noted.

3.7. Dizziness and somnolence

Since dizziness and somnolence were the most common AEs, we analyzed the incidence and the prevalence of these AEs in each 4-week period of the study. In most patients, dizziness and somnolence occurred early during the treatment period, usually within 4 weeks after starting treatment (Fig. 4). The incidence of these specific AEs gradually declined as the study progressed. The rates of new-onset dizziness and somnolence were 42.3% and 37.4%, respectively, in the first 4 weeks of treatment. After week 4, the rates of new onset dizziness and somnolence were 0.0–2.4% and 0.0–1.4%, respectively. The prevalence of these events gradually decreased over time (dizziness: 42.3% (0–4 weeks) to 9.2% (week 52); somnolence: 37.4% (0–4 weeks) to 13.7% (week 52)).

4. Discussion

In this study conducted in Japanese patients, treatment with GEn for 52 weeks elicited marked improvements of RLS symptoms as well as both patient- and investigator-rated assessments of the disease. These findings extend those reported in previous studies of GEn, which revealed significant improvements of RLS symptoms that were observable as early as 1–2 weeks after starting treatment (Kushida et al., 2009; Walters et al., 2009). Notably, the magnitude of improvements of symptoms observed in our study is broadly comparable with that seen in long-term studies of DAs such as pramipexole (Inoue et al., 2010; Montplaisir et al., 2006a; Partinen et al., 2008), rotigotine (Oertel et al., 2008; Trenkwalder et al., 2008a) and ropinirole (Garcia-Borreguero et al., 2007; Montplaisir et al., 2006b). Furthermore, our study was the first to show that GEn improved other outcome measures, including aspects of QoL and subjective sleep disturbance. These findings are consistent with the results of previous studies evaluating the use of DAs or short-term GEn for the treatment RLS (Giorgi et al., 2006; Kushida et al., 2009; Winkelman et al., 2006b).

Table 3
Adverse events (AEs) occurring in ≥5% of patients according to frequency and severity (SAS, $n=182$).

Preferred term	n (%)	Severity, n (%)	
		Mild	Moderate
Dizziness	84 (46.2)	66 (36.3)	18 (9.9)
Somnolence	75 (41.2)	58 (31.9)	17 (9.3)
Nasopharyngitis	55 (30.2)	55 (30.2)	–
Blood CPK increased	29 (15.9)	26 (14.3)	3 (1.6)
Blood uric acid increased	18 (9.9)	18 (9.9)	–
Constipation	15 (8.2)	15 (8.2)	–
Feeling abnormal	14 (7.7)	13 (7.1)	1 (0.5)
Back pain	13 (7.1)	12 (6.6)	1 (0.5)
Eosinophil count increased	12 (6.6)	11 (6.0)	1 (0.5)
Glucose urine present	12 (6.6)	12 (6.6)	–
Abdominal discomfort	10 (5.5)	10 (5.5)	–
ALT increased	10 (5.5)	10 (5.5)	–

ALT: alanine aminotransferase, CPK: creatine phosphokinase, SAS: safety analysis set.

We conducted exploratory analyses to identify factors that might influence the magnitude of change of IRLS score from baseline to week 52 and the IRLS responder rate. Multiple regression analysis revealed that the change in IRLS total score was significantly greater in patients with high baseline scores than in patients with low baseline scores. On the other hand, logistic regression analysis showed that patients with low baseline scores were significantly associated with being IRLS responders following GEn treatment. The discrepancy between these results suggests the difficulty in identifying the treatment response of GEn from the severity of the disorder before starting the treatment. Our exploratory analyses also detected significant differences between the sexes, with a greater reduction of IRLS score and a higher IRLS responder rate in men than in women. The underlying reason for this finding is unclear; possibly it is an artifact of the fairly small sample size. Further research with a larger sample of patients may shed more light on the possibility of a differential response to GEn between the sexes.

In this study, the most frequently observed AEs were, as expected from previous studies of GEn in RLS (Bogan et al., 2010; Kushida et al., 2009), nervous system-related disorders such as dizziness and somnolence, infections such as nasopharyngitis, and gastrointestinal disorders such as abdominal discomfort and constipation. Although somnolence and dizziness occurred in almost half of our patients and dizziness, at a rate of 4.4%, was the most frequently noted AE leading to discontinuation, the majority of AEs were mild to moderate in intensity and resolved during the study. On the other hand, the relatively high incidence rate of AEs observed during this study (>90%) and the higher rates of dizziness and somnolence arising in Japanese patients compared with those in patient populations in Western countries (Bogan et al., 2010) should be considered, and caution exercised when prescribing GEn, particularly during the early period of treatment.

Interestingly, in the present study, the prevalence of dizziness and somnolence gradually decreased over time, indicating that these symptoms were transient and resolved spontaneously. Most cases were mild and symptoms led to a dose reduction in only 18 patients, most of whom were able to continue treatment after reducing the dose. These findings suggest good tolerability of GEn for long-term treatment of RLS. Furthermore, unlike in previous studies of dopaminergic agents, no episodes of augmentation were reported during long-term treatment with GEn in the present study.

This study has some limitations that should be considered. Most importantly, this study was an observational study and not a randomized, controlled trial. The protocol followed an open-label design and

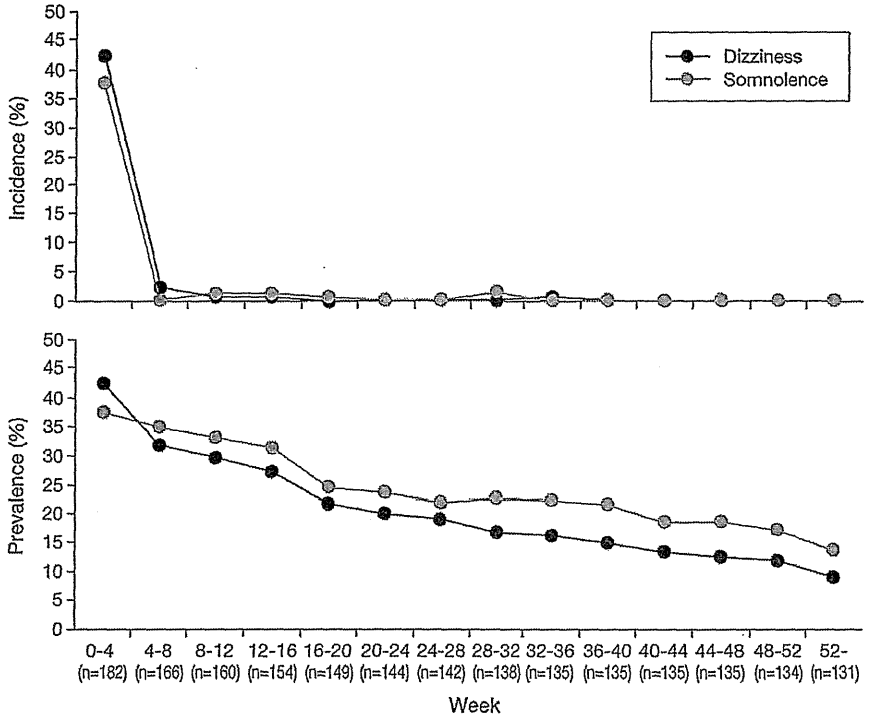

Fig. 4. Incidence (new onset) and prevalence (all cases) of dizziness and somnolence.

there was no control group. Thus, it was not possible to determine whether the improvements in RLS symptoms observed in this study were solely due to the prescribed treatment, or to what extent there was a placebo effect—as is normally the rule rather than the exception in studies using IRLS score as efficacy endpoint (Fulda and Wetter, 2008). Nevertheless, the marked reduction in IRLS score, clear improvement of measures of sleep disturbance and QOL, and the high IRLS responder rate demonstrate the clinical usefulness of GEn in Japanese patients with RLS. Randomized, double-blind, placebo/active-controlled trials are desirable to confirm these preliminary results.

5. Conclusion

In conclusion, this study revealed that long-term treatment with GEn improved RLS symptoms as well as investigator- and patient-reported outcomes in Japanese patients with moderate-to-severe RLS, along with an acceptable safety profile. Therefore, GEn seems to be a useful new addition to the treatment armamentarium against RLS.

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Role of the funding source

Astellas Pharma Inc. was involved in the study design and data collection but not in the writing of the report or in the decision to submit the paper for publication.

Authors' contributions

All authors contributed to study conception/design and writing of the report. YI performed data analysis and interpreted the results. All authors read and approved the final manuscript.

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Patient Related Outcome Measures

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ORIGINAL RESEARCH

Patient perspectives on Parkinson's disease therapy in Japan and the United States: results of two patient surveys

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Background: Despite evidence suggesting that patient attitudes towards therapy may influence treatment outcomes, the impact of these factors on treatment for Parkinson's disease is poorly understood. These two surveys, based in Japan and the US, investigated the attitudes of patients towards antiparkinsonian medications, the complications of these therapies, and how these differ across geographies.

Methods: The US PRELUDE survey collected data from May 13 to May 20, 2003, from 300 interviews with patients with Parkinson's disease from the National Parkinson Foundation. The Japanese survey was carried out from June to December 2008 in a stepwise manner using questionnaires (n = 3548) followed by interviews with those who had consented to participate in the questionnaire (n = 407). Both surveys assessed the attitudes of patients towards therapies for Parkinson's disease and associated complications.

Results: Dyskinesia was not a major challenge of therapy for Parkinson's disease, and wearing-off caused greater concern in the US, while hallucinations had a greater emphasis in Japan. Patients who had previously experienced dyskinesia were less concerned about this side effect than those who had not. Although pill burden was thought to be a concern in the US, Japanese patients did not indicate that pill burden would limit their drug intake. There were also discrepancies between the perspectives and concerns of patients and those of their treating physicians.

Conclusion: Recognizing patient perspectives regarding therapies for Parkinson's disease and associated complications, as well as certain cultural influences, is important in the management of parkinsonian symptoms. Acknowledging these concerns may improve the standard of care in patients with Parkinson's disease. In addition, improved patient education and effective patient–physician communication in both countries may improve compliance and treatment outcomes in patients with the disease.

Keywords: Parkinson's disease, patient concerns, dyskinesia, wearing-off, hallucinations

Introduction

It is generally accepted that patient health and therapeutic outcomes are influenced by beliefs about and attitudes toward medications, and expectations from therapy, as well as level of education and awareness about the disease and its management.[1,2] This is particularly true for long-term, chronic illnesses, whereby patients must make lifestyle adjustments to accommodate increasing disability.[2,3] Patient decisions to follow a recommended treatment are also likely to be influenced by beliefs about medications and understanding about a medical illness. For example, despite the prevalence of available therapies, there is a high rate of early treatment discontinuation in patients suffering from depression, owing to factors such as a perceived stigma of mental

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health problems, which consequently impacts therapeutic outcome.[4] Although it is evident that these factors play a role in treatment outcomes, the influence of patient perspectives towards therapy has not been well documented.

Patient attitudes regarding Parkinson's disease (PD) may influence the types and dosing frequencies of medications available for symptomatic treatment. PD is a progressive, chronic illness that impacts motor abilities and quality of life. The armamentarium for PD management includes many agents that are associated with a wide range of benefits and potential risks. For example, levodopa is associated with an increased risk of motor complications, including dyskinesia and motor fluctuation (wearing-off), while the side effects of dopamine agonists include hallucinations, somnolence, edema, and impulse control disorders.[5,6] Tailoring therapy according to individual unique symptoms is important to achieve successful treatment outcomes.[5] Patient perspectives on treatment strategies, and the differences in these factors across different geographies, are poorly defined. Understanding these differences may improve therapeutic outcomes.

To this end, two surveys were conducted, one in the US and another in Japan, to investigate the attitudes and concerns of patients regarding PD therapy. The results of these surveys suggest unmet needs regarding PD therapy, as well as discrepancies between patient and physician perspectives. They also identify cultural differences in patient attitudes.

Materials and methods

PRELUDE (PRoject to Examine Levodopa Utilization DEcisions) was a two-part survey carried out in the US, comprising patient and physician questionnaires.

Patient survey

Data were collected from May 13 to May 20, 2003, from 300 interviews of people with PD currently using levodopa-carbidopa therapy. The respondents were sampled from the National Parkinson Foundation list of 10,000 email newsletter recipients; invitations to participate in the survey were embedded in the National Parkinson Foundation email newsletter and sent each day until all 300 questionnaires were completed. Each respondent was assigned an individual identification number and password to ensure that patients only completed the survey once. For each participant, a US $15 honorarium for completing the study and a US $15 donation to the National Parkinson Foundation were given.

Physician survey

In this part of the survey, data were collected online between April 16 and 29, 2003, from 328 general neurologists, 74 movement disorder specialists, and 54 primary care physicians. To qualify, all physicians must have treated patients with PD (at least some with levodopa-carbidopa) and have been in practice for $\geq$2 years and $\leq$30 years.

Japanese survey

This survey focused on patient attitudes toward PD and its treatment, and was completed in Japan from June to December 2008 in a stepwise manner, initially with questionnaires, then interviews with those who had consented in the questionnaire to be interviewed.

Questionnaires were sent to approximately 7000 members of the Japan Parkinson Disease Association and about 1200 nonmembers. Data were collected from 4011 respondents between July and August 2008. A total of 387 participants who received deep brain stimulation were excluded, and 3548 evaluable respondents were assessed. A total of 2316 of these patients provided their consent to participate in interview-based research. Patients were extracted at random.

A total of 407 of the patients who responded to the questionnaire-based survey participated in the on-site, interview-based survey between August and December 2008. Thirty-six participants who received deep brain stimulation were excluded from the analysis relating to drug medication.

The presence of wearing-off or dyskinesia was determined in both parts of the survey. In the questionnaire-based survey, this was accomplished by enquiring about the efficacy of medication. During the interview part of the survey, patients were asked to record the severity of symptoms in relation to timing of each dose in a diary for one day prior to the interview. Symptom severity was based on patient self-perception and was measured using the Hoehn and Yahr scale by examining physicians.

Results

Patient characteristics

Patient characteristics for both the Japanese and US PRELUDE studies are summarized in Table 1. Patients with potential motor fluctuations and several years of treated PD were recruited in both surveys. In Japan, 95% of patients were receiving levodopa, mostly as therapy supplementary to dopamine agonists or monoamine oxidase B inhibitors. Between 70% and 80% of the US PRELUDE respondents were receiving levodopa therapy; around half of these

Table 1 Patient characteristics

Patient characteristics	Japanese study	US study
Mean age (years)	69	N/A
Duration of PD (years)	3–9 (majority)	7 (mean)
Patients receiving levodopa (%)	95	70–80
Patients receiving DAs (%)	85	57
Patients receiving MAO-B inhibitors (%)	42	N/A
Patients receiving COMT inhibitors, including entacapone (%)	25	29

Abbreviations: PD, Parkinson's disease; DA, dopamine agonists; MAO-B, monoamine oxidase B; N/A, not applicable; COMT, catechol-O-methyl transferase.

received dopamine agonist treatment before initiating levodopa-carbidopa therapy.

Attitude towards motor complications and other adverse effects

Wearing-off is a concern for PD patients

In the US PRELUDE study, more PD patients were concerned about wearing-off (55%) than about dyskinesia (23%, Figure 1). Although primary care physicians generally agreed with this concern (63%), specialists considered dyskinesia to be a greater concern (32% of neurologists and 50% of movement disorder specialists, compared with 7% of primary care physicians).

Balance between adverse effects and efficacy of medication

In Japan, more than half of patients experiencing fluctuations preferred to avoid the adverse effects of antiparkinsonian medication rather than obtain effective relief from bradykinesia (Figure 2). However, the number of patients preferring relief from bradykinesia gradually increased with escalating symptom severity during off periods. This preference for avoiding adverse effects was similar in patients with (47.6%) and without (47.9) wearing-off. When interviewed, Japanese patients who preferred to avoid adverse effects were more concerned about hallucinations (44.6% of unaided responses) than other adverse effects such as constipation (12.2%), drowsiness (9.5%), or nausea (6.8%). In fact, compared with hallucinations, dyskinesia was identified as an important adverse effect by fewer Japanese patients (Figure 3).

Balance between dyskinesia and efficacy of medication

In the overall population, Japanese patients experiencing on/off fluctuations preferred to avoid dyskinesia (about 45%) rather than achieve relief from bradykinesia (about 25%). Patients who had not yet experienced dyskinesia were more keen to avoid this complication (approximately 55%) rather than obtain relief from bradykinesia (approximately 45%), whereas patients who had already developed dyskinesia were less concerned about this adverse effect (approximately 40%). Reasons for this concern in patients who had not yet experienced dyskinesia included anticipation of the mental burden of this adverse effect from observing it in other patients. They were also concerned that dyskinesia might prevent them from carrying out normal daily activities, such as working, and were worried about others' reactions to these abnormal movements when in public. In contrast, patients with mild dyskinesia tended to prefer improved mobility versus avoiding dyskinesia (nearly 42% versus 32%). However, patients who had experienced severe dyskinesia indicated they would rather avoid this adverse effect (about 42%) than obtain relief from bradykinesia (around 37%).

Patient attitudes towards medication

In the US, patients' main concerns about levodopa-carbidopa were wearing-off, long-term side effects of levodopa-carbidopa therapy, and disease progression (Table 2). Although generally

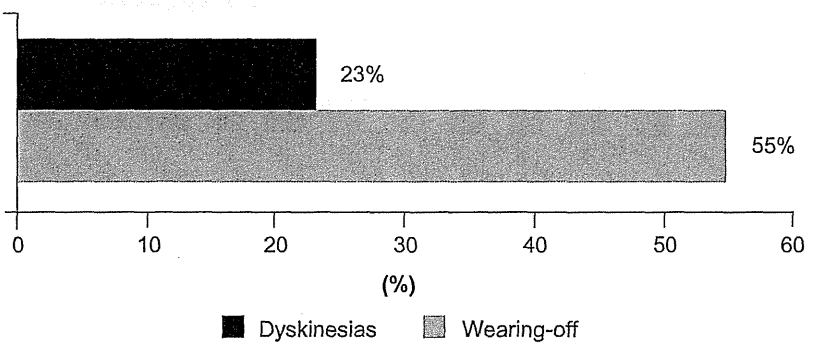

Figure 1 Percentage of patients in the US survey reporting dyskinesias or wearing-off as the greatest challenge of therapy.

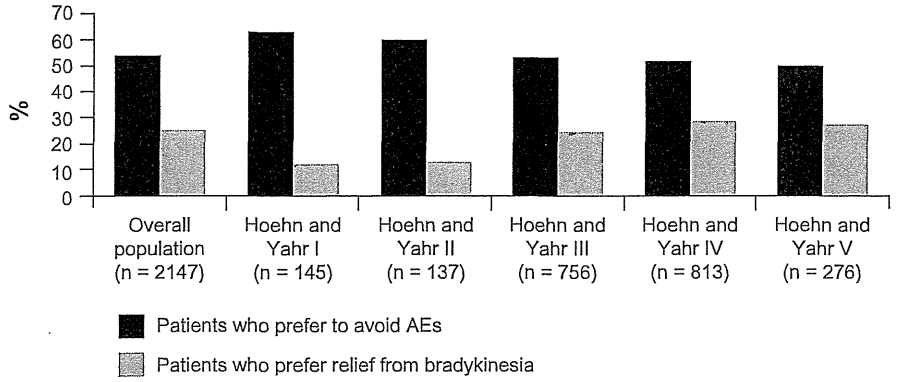

Figure 2 Percentage of patients in the Japanese survey who preferred to avoid adverse events compared with those who preferred relief from bradykinesia.
Note: Hoehn and Yahr[7] measurements were taken during off periods.
Abbreviation: AE, adverse effect.

satisfied with levodopa-carbidopa, 55% of US patients with PD were at least somewhat concerned about taking levodopa-carbidopa, mostly owing to information gathered from the Internet (69%) or from varied sources (58%). In addition, 26%–34% of patients indicated that their concern stemmed from information from physicians, support groups, or newsletters.

In Japan, the percentage of patients dissatisfied with current pharmacotherapy tended to increase with a longer duration of PD. In addition, patients who were not suffering from wearing-off were more satisfied with their current pharmacotherapy than those who were experiencing wearing-off symptoms (49% versus 36%, respectively).

Attitudes towards drug intake and dose increases

In the US, physicians felt strongly that patients would be more satisfied with reduced pill burden (96.3%). They also believed that drug dissatisfaction stemmed from inconsistencies in symptom control achieved with generic formulations of levodopa-carbidopa (62.6%).

When interviewed, Japanese patients generally preferred to obtain relief from bradykinesia (about 50%) rather than limit their medication intake (about 40%). This preference for symptomatic relief was similar in patients with or without wearing-off. The main reason for this preference was a desire to carry on with day-to-day activities, such as employment or housework. Patients who preferred to limit drug intake and dose were concerned about the adverse effects associated with increased pharmacotherapy (68.5%); concern about wearing-off accounted for 10.5% of unaided responses. Other reasons for preferring to limit dose intake included compliance (4.8%) and the apprehension that drugs may affect health (6.5%).

Interestingly, the levodopa-equivalent dose of antiparkinsonian medication did not differ between satisfied and dissatisfied patients in Japan. According to a survey of 121 Japan-based physicians at the 2008 Movement Disorders

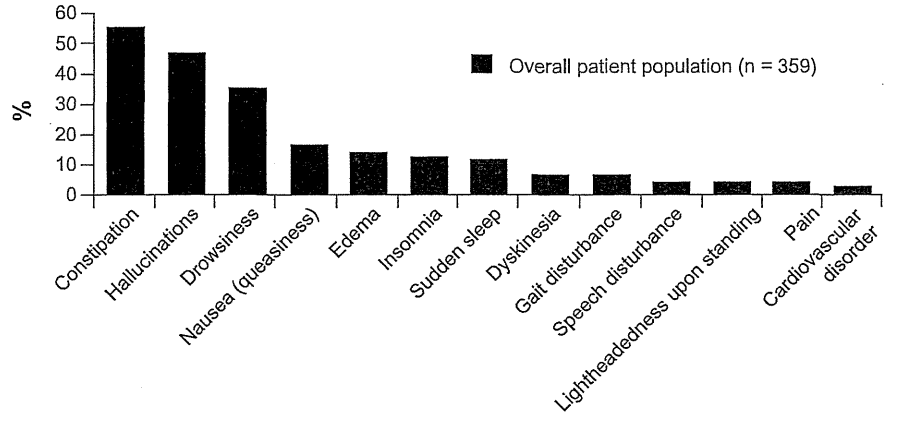

Figure 3 Adverse effects of antiparkinsonian medication that concerned patients in the Japanese survey.
Note: Patients who did not include a specific response were excluded from this analysis.

Table 2 Reasons patients in the US thought they were switched to levodopa-carbidopa, and why they were concerned about taking levodopa-carbidopa

Perceived reasons for being switched to LC[a]	**Patients (%)**[a]
My PD symptoms were getting progressively worse	55
My PD symptoms did not get worse, but I did not get good symptom control with previous treatments	16
I do not know/my doctor recommended it	15
I could not tolerate the side effects of previous treatments	10
Other reason	5
Concerns about taking LC	**Patients (%)**
Long-term side effects of LC, such as dyskinesias (uncontrolled movements, wiggles)	52
Benefits may begin to wear off sooner than desired	49
An indication that my PD might have advanced to a more severe stage	46
Immediate side effects of LC, such as nausea and vomiting	34
Fear that LC might make my PD worse	23
Being able to afford LC	21

Notes: [a]Respondents who were not initiated on levodopa (n = 110); patients who did not provide a specific response were excluded from this analysis.
Abbreviations: LC, levodopa-carbidopa; PD, Parkinson's disease.

Society of Japan conference held in Kyoto, the most commonly used daily dose of levodopa ranged from 300 mg to 400 mg.[8] For many Japanese providers, the highest daily dose of levodopa was 300 mg, even for patients with advanced PD. Consistent with this, about 17% of patients who were interviewed stated that they had been informed by their physician that their medication could no longer be increased, despite the suggestion of increasing motor disability.

Discussion

Despite being the most effective treatment for PD, the higher possibility of motor complications associated with levodopa may result in potential underdosing.[5] Although dyskinesias are often regarded as one of the most important complications of levodopa therapy,[9] this project suggests that dyskinesias were not a primary concern for patients surveyed in either the US or Japan. In the US, patients were more concerned about wearing-off, whereas other adverse effects, such as hallucinations, were of greater concern to Japanese patients. Interestingly, Japanese patients who had not yet experienced dyskinesia were more concerned about this adverse effect than those with a prior history of dyskinesia, possibly due to concern regarding the mental burden and hardship of the condition. Although primary care providers in the US recognized the importance of wearing-off, specialists considered dyskinesias to be of equal, if not greater, concern for patients. This suggests that patient concerns about dyskinesia may, in some cases, be overestimated by physicians, and may cause some hesitation when prescribing levodopa.

Patient perspectives on treatment options are, among other things, influenced by disease stage, symptom severity, and experience of adverse effects. Understanding patient attitudes towards PD therapies and the associated complications may help physicians devise individualized treatment strategies. There is currently a multitude of therapeutic options for patients with PD, and individual benefit varies significantly among patients. The benefit of efficient communication between the patient and the doctor in any culture cannot be overestimated, particularly when individualizing treatment. However, improved patient education and awareness is paramount for effective patient–physician communication. Patients need to understand the symptoms of PD, and be aware of the implications of certain therapies in order to be familiar with signs of disease progression or treatment complications.

The results of our US survey highlight a further discrepancy between physicians and patients as to reasons for initiation of levodopa-carbidopa therapy: while the majority of patients believed levodopa-carbidopa therapy was initiated because of progressive worsening of PD symptoms, 50% of family physicians and nearly a third of specialists initiated levodopa-carbidopa therapy at diagnosis. Furthermore, more than half of the US patients said they were at least somewhat concerned about taking levodopa-carbidopa, as a result of information obtained on the Internet or from physicians.

It is interesting to note that while US patients were most concerned about long-term side effects of their medication, such as dyskinesia and wearing-off, Japanese patients worried more about experiencing hallucinations. This is possibly due to the fact that the majority of Japanese patients in this study received dopamine agonist therapy. Hallucinations are more likely to occur with dopamine agonists than with levodopa,[6] and, in Japan, it is common clinical practice for patients with PD to be initiated on low-dose levodopa combined with dopamine agonists or amantadine. The higher use of dopamine agonists in Japan is also reflected in Japanese clinical trials compared with those conducted in the West.[10,11] Studies have reported a higher incidence of hallucinations in Japanese patients compared with Western patients, which is attributable to the higher doses of dopamine agonists used in the Japanese PD population.[12–14] Therefore, because hallucinations can impact on the quality of life of both patients and their caregivers,[15] it would seem pertinent for physicians in Japan to know how to avoid these adverse