Zonisamide improves wearing off in Parkinson’s disease without exacerbating dyskinesia: Post hoc analysis of phase 2 and phase 3 clinical trials

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ABSTRACT

Introduction: Although phase 2 and 3 clinical trials in Japan showed that zonisamide improved wearing off in patients with Parkinson’s disease (PD), no studies to date have evaluated whether zonisamide improves wearing off in patients with PD without exacerbating dyskinesia. Therefore, we examined this hypothesis in a post hoc analysis of pooled data from the previous phase 2 and 3 trials.

Methods: Both trials evaluated zonisamide 25 mg and 50 mg versus placebo during a 12-week treatment period. In our analysis, primary efficacy variables were adjusted mean change in wearing off (evaluated as change in “off” time) and dyskinesia from baseline to 12 weeks. Dyskinesia was evaluated using Unified Parkinson’s Disease Rating Scale (UPDRS) part 4 items 32 (4-32; duration of dyskinesia) and 33 (4-33; disability of dyskinesia) score. Criteria outcomes included rates of patients meeting specific criteria based on off time plus UPDRS part 4-32 or 4-33.

Results: A total of 212 patients were included in this analysis. Zonisamide 50 mg significantly reduced off time and UPDRS part 4-33 score at week 12 versus placebo without increasing UPDRS part 4-32 score. The proportion of patients receiving zonisamide 50 mg who met the criterion “Off time decreased and UPDRS part 4-33 score did not increase” was significantly higher than that of patients receiving placebo.

Conclusion: Zonisamide improves wearing off without exacerbating dyskinesia in Japanese patients with PD. Moreover, zonisamide 50 mg may improve dyskinesia. Further studies are needed to prospectively determine the benefits and clinical relevance of zonisamide on dyskinesia.

1. Introduction

Parkinson’s disease (PD) is a progressive, neurodegenerative disorder that increases in prevalence with advancing age and is characterized by clinical manifestations that include resting tremor, rigidity, bradykinesia, and postural instability [1,2]. Levodopa is the standard treatment to improve parkinsonism among patients with PD; however, levodopa treatment for prolonged periods can induce motor complications, including wearing off and dyskinesia [1,2], which is a common and disabling complication of disease progression that can have a severe effect on activities of daily living [3,4] and quality of life [5]. The improvement of wearing off without exacerbating dyskinesia is therefore a therapeutic goal in patients who experience wearing off [6]. To this end, the most frequently attempted therapeutic approach is optimization of the levodopa regimen and/or adjustment of adjunctive drugs; however, this strategy is often unsuccessful and underlines a major unmet therapeutic need for patients with PD [7,8].

Zonisamide, originally approved for the treatment of epilepsy, was previously shown in phase 2 and 3 clinical trials [9–11] to be safe and effective, with a clear benefit on wearing off and motor function compared with placebo in patients with PD. Based on these outcomes, zonisamide was approved in Japan for the treatment of patients with PD [12]. Although the precise mechanism of action of zonisamide as an anti-parkinsonism drug remains unclear, a number of pharmacological mechanisms have been proposed, including dopaminergic [13,14], non-dopaminergic [15,16], and neuroprotective effects [17–19].

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In a previous phase 3 trial of zonisamide, an improvement in wearing off was observed in patients with PD (assessed by changes in “off” time) without any worsening of dyskinesia [9]. Furthermore, a previous meta-analysis showed that there was no significant difference in the incidence of dyskinesia between groups of patients receiving zonisamide and those receiving placebo [20]. Preclinical studies in models of levodopa-induced dyskinesia have produced conflicting data, with zonisamide shown to either improve [21] or have no effect on [22,23] levodopa-induced dyskinesia.

To date, no studies have prospectively evaluated the effect of zonisamide on dyskinesia for PD patients with dyskinesia or the effect of zonisamide on dyskinesia as the primary endpoint. The precise clinical effect of zonisamide on dyskinesia thus remains unclear. Based on the available evidence, zonisamide may improve wearing off in patients with PD without exacerbating dyskinesia. We therefore performed a post hoc analysis of pooled data from the phase 2 and 3 clinical trials [9,10] to evaluate this hypothesis.

2. Methods

2.1. Trial design and treatment

The phase 2b/3 and phase 3 trials were 12-week, double-blind, placebo-controlled, parallel-treatment, randomized, multicenter trials in Japan, and were designed to evaluate the efficacy and safety of zonisamide as adjunctive treatment compared with placebo in patients with PD who showed insufficient response to levodopa. The detailed trial design and primary results of these clinical trials have been published previously [9,10].

Patients in both clinical trials were randomized to receive zonisamide 25 or 50 mg/day or placebo, as add-on to levodopa. Although a zonisamide 100 mg/day arm was also included in the phase 2b/3 trial, this arm was excluded from the present analysis because the approved dosages of zonisamide for PD in Japan are 25 mg and 50 mg. The primary endpoint in the phase 2b/3 trial was change from baseline in the total score of Unified Parkinson’s Disease Rating Scale (UPDRS) part 3 at week 12. The primary endpoint in the phase 3 trial was change from baseline in the daily “off” time at week 12.

The trials were registered in JAPIC Clinical Trials Information (registration numbers: JapicCTI-050099 [phase 2b/3] and JapicCTI-101198 [phase 3]). Both protocols were approved by the institutional review board at each participating site. All patients provided written informed consent prior to participation, and the trials were conducted according to the principles of the Declaration of Helsinki.

2.2. Patients

The phase 2b/3 trial included 347 patients at 58 centers and the phase 3 trial included 422 patients at 65 centers. Clinical assessment included the UPDRS conducted in the “on” state every 2 weeks. Patient diaries were used to record the daily “on” and “off” state.

In both trials, eligible patients were adults aged 20–80 years (74 years in the phase 3 trial) who had initially responded to levodopa therapy but subsequently showed an insufficient response. Key differences in the inclusion criteria between the trials were that the phase 2b/3 trial included patients who exhibited an insufficient response to levodopa therapy while the phase 3 trial included patients whose mean daily “off” time was ≥ 2 h for the final 7 days of the run-in period. The full details of the inclusion and exclusion criteria have been published previously [9,10]. For the present analysis, patients with dyskinesia and an “off” time ≥ 2 h at baseline were included. The patient disposition for the two clinical trials in the pooled analysis is shown in Fig. 1.

2.3. Outcome measures

This was a post hoc analysis of the pooled data from the phase 2b/3 and phase 3 trials to evaluate the effects of zonisamide 25 mg and 50 mg versus placebo on wearing off and dyskinesia. The primary efficacy variables were adjusted mean change in wearing off and dyskinesia from baseline to 12 weeks. Wearing off was evaluated as the change in “off”
time and dyskinesia was the score of UPDRS part 4 items 32 (part 4-32; duration of dyskinesia) and 33 (part 4-33; disability of dyskinesia).

The criteria outcomes were the rates of patients who met one of two criteria. Criterion 1 was (1) Off time decreased and (2) UPDRS part 4-32 score not increased, comprising C1-2: (1) Off time decreased and (2) UPDRS part 4-33 score decreased. Criterion 2 was (1) Off time decreased and (2) UPDRS part 4-32 score unchanged plus C1-2: (1) Off time decreased and (2) UPDRS part 4-33 score decreased.

The time course of change from baseline in off time, UPDRS part 4-32 and part 4-33 scores were also evaluated at weeks 4, 8, and 12.

2.4. Statistical methods

For patient demographics and clinical characteristics at baseline, the statistical value or number (%) was analyzed for each item. Differences in patient demographics and clinical characteristics at baseline were evaluated using the Cochran-Mantel-Haenszel test stratified by trial for categorical variables and analysis of variance with trial as the fixed effect for continuous variables. A mixed-effect model for repeated measures was used to evaluate change from baseline, with treatment group, visit, trial, and treatment-by-visit interaction as fixed effects, and baseline value as a covariate. Differences in the frequency of patients who met the post hoc analysis criteria were evaluated using the chi-squared test. Two-sided p values < 0.05 were considered statistically significant in between-group comparisons versus placebo. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patients

The pooled dataset included 212 patients randomized across the two clinical trials who met the inclusion criteria for the post hoc analysis (dyskinesia and an “off” time ≥ 2 h at baseline). Of these, 66 patients received 25 mg zonisamide, 72 received 50 mg zonisamide, and 74 received placebo (Table 1). The mean patient age was 63.7 years, 69 (32.5%) patients were male, and the mean duration of PD was 11.1 years. The mean levodopa dose was 436 mg/day. Regarding other concomitant medications, the mean dose of levodopa-equivalent doses was 581 mg/day; other medications are listed in Table 1, along with the UPDRS part 3 and 4 data. The mean UPDRS part 4 score was 6.1 and the mean off time was 6.6 h for the total patient population. The detailed patient characteristics for the pooled dataset are presented in Table 1.

3.2. Off time

Zonisamide 50 mg significantly reduced the mean daily off time at week 12 by 0.98 h (p < 0.01) compared with placebo. There was no significant difference in the change in off time from baseline at week 12 between zonisamide 25 mg and placebo (Fig. 2A). In the time course analysis, the off time in the zonisamide 50 mg group was significantly decreased in week 4 compared with placebo (p < 0.01) and this decreased level was maintained until week 12. In the 25 mg group, the off time was marginally decreased at week 4 and thereafter remained virtually unchanged until week 12. Off time in the placebo group was essentially unchanged over the 12-week trial period.

3.3. Dyskinesia

There was no significant difference in the change in the UPDRS part 4-32 score on duration of dyskinesia from baseline at week 12 between zonisamide and placebo (Fig. 2B). Zonisamide 50 mg significantly decreased the UPDRS part 4-33 score on disability of dyskinesia from baseline at week 12 by 0.20 (p < 0.01) compared with placebo (Fig. 2C). There was no significant difference in the change of the UPDRS part 4-33 score from baseline at week 12 between zonisamide 25 mg and placebo.

In the time course analysis, UPDRS part 4-32 scores were essentially unchanged at week 12 in all groups. For UPDRS part 4-33, the score decreased continuously in the zonisamide 50 mg group until week 12, and the score change from baseline at week 12 was significantly greater than that with placebo (p < 0.01). In the zonisamide 25 mg group and placebo group, the UPDRS part 4-33 score was essentially unchanged until week 12.
3.4. Criteria outcomes

The proportion of patients who met Criterion 1 (off time decreased and UPDRS part 4-32 score not increased) in the zonisamide 50 mg group was 56.9% (41/72), which was higher than that of placebo (47.9% [35/73]), although the difference was not significant (Fig. 3A). For zonisamide 25 mg, the proportion of patients who met Criterion 1 was 48.5% (32/66) and no difference from placebo was observed. For Criterion 2 (off time decreased and UPDRS part 4-33 score not increased), the proportion of patients who met the definition in the zonisamide 50 mg group was 66.7% (48/72), which was significantly higher ($p < 0.05$) than that in the placebo group (46.6% [34/73]) (Fig. 3B). The proportion of patients who met Criterion 2 in the zonisamide 25 mg group was 54.5% (36/66), which was higher than that for placebo, although the difference was not significant. The proportion of patients who met sub-criterion 2-2 (Off time decreased and UPDRS part 4-33 score not increased) in the zonisamide 50 mg group was 58.3% (43/72), which was higher than that in the placebo group (46.6% [34/73]) ($p < 0.05$).
4. Discussion

In the present analysis, zonisamide 50 mg reduced off time and dyskinesia disability (UPDRS part 4-32 score) without increasing dyskinesia duration (UPDRS part 4-33 score). The proportion of patients in the zonisamide 50 mg group who met Criterion 2: “Off time decreased and UPDRS part 4-33 score decreased” was significantly higher than that in the placebo group. Taken together, these results suggest that zonisamide 50 mg improves wearing off without exacerbating dyskinesia in PD patients. The findings of the present analysis align with those observed in the phase 3 trial, in which a deterioration in UPDRS part 4-33 score was not observed in the zonisamide group [9].

The proposed pharmacologic mechanisms responsible for the anti-parkinsonian activity of zonisamide include both dopaminergic (activation of dopamine synthesis and release and inhibition of monoamine oxidase-B) and non-dopaminergic (blockade of sodium channels and T-type calcium channels) functions [12]. Given that dyskinesia has been reported to be associated with non-physiological dopaminergic stimulation [24], the results of the present analysis may be explained by the non-dopaminergic mechanism of action of zonisamide [25–27]. In this context, zonisamide was shown to ameliorate levodopa-induced dyskinesia and inhibit up-regulation of adenosine A2A and endocannabinoid CB1 receptors in a rat model of PD [28]. Furthermore, genetic silencing of the T-type calcium channel has previously been demonstrated to have a preventative and ameliorating effect on dyskinesia in PD [29], further suggesting that the non-dopaminergic mechanism of zonisamide may contribute to its inhibition and improvement of dyskinesia in PD.

To date, no trial has presented a direct comparison between zonisamide and other anti-parkinsonian drugs on the effect on dyskinesia. However, a previous meta-analysis comparing the efficacy and safety of zonisamide and other anti-parkinsonian drugs on the effect on dyskinesia and inhibit up-regulation of adenosine A2A and endocannabinoid CB1 receptors in a rat model of PD [28]. Furthermore, genetic silencing of the T-type calcium channel has previously been demonstrated to have a preventative and ameliorating effect on dyskinesia in PD [29], further suggesting that the non-dopaminergic mechanism of zonisamide may contribute to its inhibition and improvement of dyskinesia in PD.

To date, no trial has presented a direct comparison between zonisamide and other anti-parkinsonian drugs on the effect on dyskinesia. However, a previous meta-analysis comparing the efficacy and safety of zonisamide and other anti-parkinsonian drugs on the effect on dyskinesia [30], highlighting the current inadequacy in treatment options for this patient population. Zonisamide, therefore, represents a potential strategy to address this inadequacy as no significant difference in the incidence of dyskinesia between zonisamide and placebo was observed previously [20], and the potential to improve dyskinesia has been shown in the current analysis. In Japan, zonisamide is indicated for progressive PD with wearing off under the category of other adjunctive treatments in the 2018 clinical practice guideline for PD [31]. Data from the present trial suggest that zonisamide may be appropriate for the treatment of wearing off in PD, regardless of whether dyskinesia is present.

4.1. Limitations

The present analysis has some limitations, including the post hoc trial design, the inclusion of Japanese patients only, the small number of participants, and the short trial durations. In addition, the LEDD in the present study was slightly lower than those in other reports [32–34], and this may have contributed to a lower risk of dyskinesia in this study. Further research is therefore needed to confirm the generalizability of these results. Furthermore, the original trials were not specifically designed to investigate dyskinesia as a primary endpoint. A dyskinesia rating scale such as the Unified Dyskinesia Rating Scale [35] might have allowed a more precise and clinically relevant change in dyskinesia to have been detected in the trial populations. Finally, the baseline UPDRS part 4-32 and 33 scores were low, limiting the possibility to estimate the effect on a high degree of dyskinesia and troublesome dyskinesia in the present analysis.

4.2. Conclusions

The results of this post hoc analysis indicate that zonisamide 50 mg improves wearing off without exacerbating dyskinesia in patients with PD. Moreover, zonisamide 50 mg may potentially improve dyskinesia. Further prospective studies are warranted to investigate the potential benefits and clinical relevance of zonisamide on dyskinesia in this patient population.

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Data sharing statement

Data sharing policy of Sumitomo Dainippon Pharma Co., Ltd. is available at https://www.ds-pharma.com/rd/clinical/clinical_study_data.html. In response to requests from researchers, Sumitomo Dainippon Pharma Co., Ltd. may allow access to clinical study data provided that such requests have been reviewed and approved by an independent review panel of experts.

Contributor statements

Y.T., H.M., and Y.M. provided substantial contributions to the trial conception and design and wrote the manuscript. M. N. was involved in the design of the trial and data analysis. All authors were involved in data interpretation. All authors discussed and agreed on the content of the manuscript prior to submission for publication.

Some results of this trial were previously presented as a poster presentation at the 62nd Annual Meeting of the Japanese Society of Neurology that took place on May 19–22, 2021.

Declaration of interest

Y.T. has received honoraria from Sumitomo Dainippon Pharma Co., Ltd., Eisai Co., Ltd., Takeda Pharmaceutical Co., Ltd., Novartis Pharma K.K., AbbVie GK, Otsuka Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., Sunwells Co., Ltd., and Nipro Co., Ltd. M. N., H.M., and Y.M. are employees of Sumitomo Dainippon Pharma Co., Ltd.

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References

[1] T.N. Tran, T.N.N. Vo, K. Frei, D.D. Truong, Levodopa-induced dyskinesia: clinical features, incidence, and risk factors, J. Neural Transm. (Vienna) 125 (2018) 1109–1117.
[2] S. Ouma, J. Fukae, S. Fujioka, S. Yamamoto, T. Hatano, A. Yoritaka, Y. Okuma, K. I. Kashibara, N. Hattori, Y. Tsuboi, The risk factors for the wearing-off phenomenon in Parkinson’s disease in Japan: a cross-sectional, multicenter study, Intern. Med. 56 (2017) 1961–1966.
[3] R. Palhwa, S. Isaacson, J. Jimenez-Shahed, I.A. Malatty, A. Deik, R. Johnson, R. Patni, Impact of dyskinesia on activities of daily living in Parkinson’s disease: results from pooled phase 3 ADS-5102 clinical trials, Parkinsonism Relat. Disord. 60 (2019) 118–125.
[4] M. Coelho, D. Abreu, L. Correia-Guedes, P.P. Lobo, M. Fabbri, C. Godinho, J. Domingos, L. Albuquerque, V. Freitas, J.M. Pereira, B. Cattoni, H. Carvalho, S. Reimao, M.M. Rosa, A.G. Ferreira, J.I. Ferreira, Disability in activities of daily living and severity of dyskinesias determine the handicap of Parkinson’s disease patients in advanced stage selected to DBS, J. Parkinsons Dis. 7 (2017) 255–261.
[5] M. Pechevs, C.E. Clarke, P. Vieregge, B. Khoshnood, C. Deschaseaux-Vonet, G. Berdeaux, M. Ziegler, G. Trial Study, Effects of dyskinesias in Parkinson’s
disease on quality of life and health-related costs: a prospective European study, Eur. J. Neurol. 12 (2005) 956–965.

[6] V. Vijayaratnam, T. Foltynie, Therapeutic strategies to treat or prevent off episodes in adults with Parkinson’s disease, Drugs 80 (2020) 775–796.

[7] E. Schaeffer, A. Piloto, D. Berg, Pharmacological strategies for the management of levodopa-induced dyskinesia in patients with Parkinson’s disease, CNS Drugs 28 (2014) 1155–1184.

[8] T. Müller, D. Woitalla, H. Russ, K. Hock, D. Haeger, Prevalence and treatment strategies of dyskinesia in patients with Parkinson’s disease, J. Neural Transm. 114 (2007) 1023–1026.

[9] M. Murata, K. Hasegawa, I. Kanazawa, Y. Fukushima, K. Kochi, R. Shimazu, Japan Zonisamide on PD Study Group, Zonisamide improves wearing-off in Parkinson’s disease: a randomized, double-blind study, Mov. Disord. 30 (2015) 1343–1350.

[10] M. Murata, K. Hasegawa, I. Kanazawa, Japan Zonisamide on PD Study Group, Zonisamide improves motor function in Parkinson disease: a randomized, double-blind study, Neurology 68 (2007) 45–50.

[11] M. Murata, R. Hanajima, H. Maruyama, O. Konishi, Y. Ugawa, Zonisamide for treating Parkinson’s disease, in: P. Riederer, G. Lux, R. Muñoz, W. Le, T. Nagatsu (Eds.), NeuroPsychopharmacotherapy, Springer International Publishing, Cham, 2020, pp. 1–9.

[12] M. Okada, S. Kaneko, T. Hirano, K. Mizuno, T. Kondo, Z.P.S. Group, T. Kimura, K. Yoshida, T. Abe, Randomized placebo-controlled trial of zonisamide in patients with Parkinson’s disease, Neurrol. Clin. Neurosci. 4 (2016) 10–15.

[13] R. Hanajima, H. Maruyama, O. Konishi, Y. Ugawa, Zonisamide for treating Parkinson’s disease, in: P. Riederer, G. Lux, R. Muñoz, W. Le, T. Nagatsu (Eds.), NeuroPsychopharmacotherapy, Springer International Publishing, Cham, 2020, pp. 1–9.

[14] M.T. Uemura, T. Asano, R. Hikawa, H. Yamakado, R. Takahashi, Zonisamide inhibits monoamine oxidase and enhances motor performance and social activity, Neurosci. Res. 124 (2017) 25–32.

[15] M. Murata, Novel therapeutic effects of the anti-convulsant, zonisamide, on Parkinson’s disease, Curr. Pharm. Des. 10 (2004) 687–693.

[16] H. Miwa, J. Koh, Y. Kajimoto, T. Kondo, Effects of T-type calcium channel blockers on a parkinsonian tremor model in rats, Pharmacol. Biochem. Behav. 97 (2011) 656–659.

[17] K. Ikeda, M. Yanagihashi, K. Miura, Y. Ishikawa, T. Hirayama, T. Takazawa, H. Miwa, J. Koh, Y. Kajimoto, T. Kondo, Effects of zonisamide on dopaminergic system, Epilepsy Res. 22 (1995) 193–205.

[18] M.T. Uemura, T. Asano, R. Hikawa, H. Yamakado, R. Takahashi, Zonisamide inhibits monoamine oxidase and enhances motor performance and social activity, Neurosci. Res. 124 (2017) 25–32.

[19] S. Yamamura, K. Ohoyama, H. Nagase, M. Okada, Zonisamide enhances delta receptor-associated neurotransmitter release in striato-pallidal pathway, Neuropharmacology 57 (2009) 1229–1239.

[20] R. Hanajima, H. Maruyama, O. Konishi, Y. Ugawa, Zonisamide for treating Parkinson’s disease, in: P. Riederer, G. Lux, R. Muñoz, W. Le, T. Nagatsu (Eds.), NeuroPsychopharmacotherapy, Springer International Publishing, Cham, 2020, pp. 1–9.

[21] M. Oki, S. Kaneko, S. Morise, N. Takeouchi, T. Hashizume, A. Tuge, M. Nakamura, R. Wate, H. Kunaka, Zonisamide ameliorates levodopa-induced dyskinesia and reduces expression of striatal genes in Parkinson model rats, Neurosci. Res. 122 (2017) 45–50.

[22] H. Sano, A. Nambo, The effects of zonisamide on L-DOPA-induced dyskinesia in Parkinson’s disease model mice, Neurochem. Int. 124 (2019) 171–180.

[23] H. Nishijima, Y. Miki, S. Ueno, M. Tomiyama, Zonisamide enhances motor effects of levodopa, not of apomorphine, in a rat model of Parkinson’s disease, Parkinsons Dis. 2018 (2018) 8620783.

[24] A.J. Espay, F. Morgante, A. Merola, A. Fasano, L. Marsili, S.H. Fox, E. Bizarre, B. Picconi, P. Calabresi, A.E. Lang, Levodopa-induced dyskinesia in Parkinson disease: current and evolving concepts, Ann. Neurol. 84 (2018) 797–811.

[25] C.L. Schaaf, Zonisamide enhances slow sodium inactivation in Myxocela, Brain Res. 413 (1987) 185–188.

[26] Y. Tsuboi et al., Journal of the Neurological Sciences 430 (2021) 120026

[27] Y.C. Yen, C.H. Tai, M.K. Pen, C.C. Kuo, The T-type calcium channel as a new therapeutic target for Parkinson’s disease, Pflugers Arch. 466 (2014) 747–755.

[28] M. Oki, S. Kaneko, S. Morise, N. Takeouchi, T. Hashizume, A. Tuge, M. Nakamura, R. Wate, H. Kunaka, Zonisamide ameliorates levodopa-induced dyskinesia and reduces expression of striatal genes in Parkinson model rats, Neurosci. Res. 122 (2017) 45–50.

[29] K. Steece-Collier, J.A. Stancati, N.J. Collier, I.M. Sandoval, C.E. Sortwell, T.J. Collier, F.P. Manfredson, Genetic silencing of striatal CaV1.3 prevents and ameliorates levodopa dyskinesia, Mov. Disord. 34 (2019) 697–707.

[30] R. Stowe, N. Ives, C.E. Clarke, K. Handley, A. Furmston, K. Deane, J.J. van Hilten, K. Wheatley, R. Gray, Meta-analysis of the comparative efficacy and safety of adjuvant treatment to levodopa in later Parkinson’s disease, Mov. Disord. 26 (2011) 597–598.

[31] Development Committee for Parkinson’s Disease Treatment Guideline, Parkinson’s Disease Treatment Guideline 2018 [in Japanese], Igaku-Shoin, Tokyo. Available from: http://www.neurology.jp/guidelinem/parkinson_2018.html, 2018.

[32] N. Hattori, Y. Tsuboi, A. Yamamoto, Y. Sasagawa, M. Nomoto, ME2125-3 Study Group, Efficacy and safety of safinamide as an add-on therapy to L-DOPA for patients with Parkinson’s disease: a randomized, double-blind, placebo-controlled, phase II/III study, Parkinsonism Relat. Disord. 75 (2020) 17–23.

[33] F. Stocchi, I. Vacca, P. Grassini, C. Tomino, G. Gaminini, M. Canali, V. D’Antoni, M. Voltterrani, M. Torti, Overnight switch from rasagiline to safinamide in Parkinson’s disease patients with motor fluctuations: a tolerability and safety study, Eur. J. Neurol. 28 (2021) 349–354.

[34] M. Takahashi, M. Fujita, N. Aini, M. Saki, A. Mori, Safety and effectiveness of istradefylline in patients with Parkinson’s disease: interim analysis of a post-marketing surveillance study in Japan, Expert. Opin. Pharmacother. 19 (2018) 1635–1642.

[35] C.G. Goetz, J.G. Nutt, G.T. Stebbins, The unified dyskinesia rating scale: presentation and clinimetric profile, Mov. Disord. 23 (2008) 2398–2403.