

Safety and Efficacy of a Transdermal Rotigotine for the Treatment of Fatigue and Quality of Life in Patients with Parkinson's Disease

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Received 8 October 2015; accepted 10 November 2015; published 13 November 2015

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Abstract

Aim: To evaluate safety and efficacy of a transdermal rotigotine for the treatment of fatigue and quality of life (QOL) in patients with Parkinson's disease (PD). This was a multi-sites open-label study of 58 PD patients (male 26, female 32) who met a Japanese PD diagnosis criterion. They received a transdermal rotigotine 4.5 mg/day for 8 weeks. We added a rotigotine on the previous anti-Parkinson's drugs. Clinical signs were evaluated by Hoehn-Yahr (H-Y) stage, unified Parkinson's disease rating scale (UPDRS), fatigue severity scale (FSS), and Euro quality of life (QOL). The scores of UPDRS improved from 35.2 ± 8.0 (mean \pm SD) to 31.8 ± 8.3 ($P = 0.14$). There was no significant improvement or worsening of the H-Y stages. The scores of FSS improved from 57.3 ± 12.7 (mean \pm SD) to 50.1 ± 11.8 ($P = 0.061$). The scores of QOL improved from 38.1 ± 11.1 to 48.3 ± 10.0 ($P = 0.068$). Our data demonstrate that, in a small sample size, administration of a transdermal rotigotine was associated with few side effects and was modestly effective for the treatment of fatigue and QOL in patients with PD.

Keywords

Parkinson's Disease, Non-Motor Symptoms, Fatigue, Quality of Life, Transdermal Rotigotine

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1. Introduction

Patients with Parkinson disease (PD) primarily complain motor symptoms such as akinesia, muscle rigidity or involuntary movements [1]-[3]. However, they have been also affected by non-motor symptoms, autonomic dysfunction, fatigue, sleep disorders, depression, and so on [4]. Non-motor symptoms occur across all stages of PD. Clinicians point that they may have a more significant impact on patients' quality of life (QOL) than motor symptoms [5] [6]. Non-motor symptoms have been under-recognized, and their pathogeneses remain unclear. Dysfunction of dopaminergic and non-dopaminergic systems is considered to contribute to the development of non-motor symptoms in PD [7]. Advent of drug therapy for PD can fairly control motor symptoms, but effect of dopaminergic drugs for non-motor symptoms remains poorly understood.

A transdermal patch formulation of the non-ergolinic dopamine agonist rotigotine (Neupro[®]) patch is administered transdermally resulting in stable plasma levels over 24 hours [8]-[10]. In a clinical trial, RECOVER (rotigotine effects on early morning motor function and sleep in Parkinson's disease: a double-blind, randomized, placebo-controlled study), rotigotine patch demonstrated significant improvements in sleep disorders in PD patients [11].

Reviewing RECOVER and other reports, we tried to evaluate safety and efficacy of a transdermal rotigotine for the treatment of fatigue and quality of life in PD patients.

2. Patients and Methods

We conducted a multi-sites open-label study. 58 PD patients (male 26, female 32, **Table 1**) who met a Japanese PD diagnosis criterion [12] were enrolled in this study. They received a transdermal rotigotine 4.5 mg/day for 8 weeks. We added a transdermal rotigotine on the previous anti-Parkinson's agents. All previous agents prescribed before the observation were required to be at stable doses for at least 8 weeks prior to baseline, and were to remain stable for the duration of the observation.

Clinical signs and severity were evaluated by Hoehn-Yahr (H-Y) stage [2], Unified Parkinson's Disease Rating Scale (UPDRS) Parts III (motor examination; in the "on" state) [13], fatigue severity scale (FSS) [14] and Euro quality of life (Euro QOL) [15]. We evaluate all patients before and 8 weeks after prescribing rotigotine. Clinical evaluations were conducted regular outpatiently admission and almost all patients were on-conditions.

Efficacy variables were summarized with univariate statistics (mean \pm SD), and 95% confidence intervals (CI) were calculated for changes from baseline (*i.e.*, before and after rotigotine add-on). The ethical committee in our institution approved this study.

3. Results

There were no adverse side effects and all patients were fulfilled 8 weeks observation period. Concerning severity of motor symptoms, the total scores of UPDRS improved from 35.2 ± 8.0 (mean \pm SD) to 31.8 ± 8.3 (**Figure 1**, $P = 0.14$), but this was not statistically significant. There was no significant improvement or worsening of the H-Y stages. Concerning severity of non-motor symptoms, the scores of FSS improved from 57.3 ± 12.7 (mean \pm SD) to 50.1 ± 11.8 (**Figure 2**, $P = 0.061$) but this was not statistically significant. The scores of QOL improved from 38.1 ± 11.1 to 48.3 ± 10.0 (**Figure 3**, $P = 0.068$), but this also was not statistically significant.

4. Discussions

PD has been classified as "Movement Disorders" and its clinical diagnosis requires existences of tremor, bradykinesia, muscle rigidity, and loss of right reflex. Thus clinicians have tried mainly to improve these motor

Table 1. Baseline characteristic of patients.

Age, years	70.6 \pm 10.6 (mean \pm SD)
Female/Male	32/26
Duration, years	7.1 \pm 2.6 (mean \pm SD)
Levodopa Equivalent Doses (LED), mg	723 \pm 416 (mean \pm SD)

UPDRS (Part III) Changes from Baseline

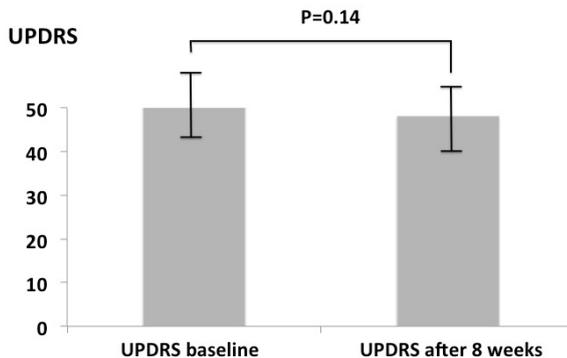


Figure 1. PDRS (Part III) changes from baseline after 8 weeks prescribing a transdermal rotigotine. There were no significant differences ($P = 0.14$) between before and after prescribing a transdermal rotigotine.

Fatigue severity scale (FSS) Changes from Baseline

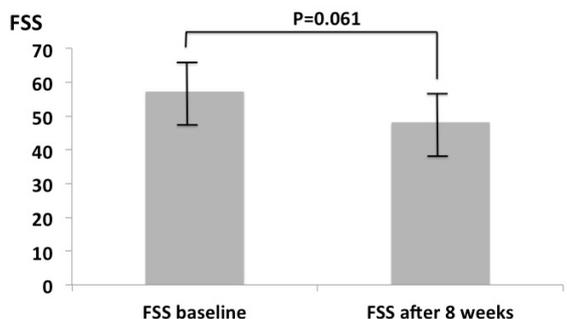


Figure 2. Fatigue severity scale (FSS) changes from baseline after 8 weeks prescribing a transdermal rotigotine. There were no significant differences ($P = 0.061$), but tendencies of improvements between before and after prescribing a transdermal rotigotine.

Quality of life (QOL) Changes from Baseline

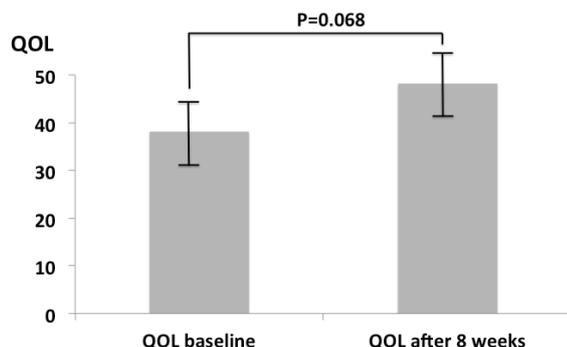


Figure 3. Quality of life (QOL) changes from baseline after 8 weeks prescribing a transdermal rotigotine. There were no significant differences ($P = 0.068$), but tendencies of improvements between before and after prescribing a transdermal rotigotine.

symptoms [1] [16]. Advent of drug therapy for PD can improve motor symptoms, but some researchers consider that non-motor symptoms are also initial signs and symptoms in PD [17] [18].

Chaudhuri, *et al.* investigated overall frequency of non-motor symptoms and signs using a newly developed questioner sheet to inquire existence of neuropsychological signs (depression, apathy, anxiety, anhedonia, cognitive dysfunction, attention deficit, hallucination, delusion, dementia, delirium, panic disorder), sleep disorders (restless leg syndrome, abnormal behavioral disorders in REM period, insomnia, excessive day time sleep, sleep apnea), dysautonomia (orthostatic hypotension, dysuria, impotent), digestion disorders (drooling, incontinence, dysphagia, dysosmia, visual disorder), behavioral disorder (hyper-sexuality, compulsive behavior, pathological shopping, pathological gambling), and others (fatigue, weight loss, weight gain) [17]-[19]. Reviewing these studies, non-motor symptoms in PD patients may affect their QOL.

Although we examined with a small sample size and did not optimize doses, our data demonstrate that administration of a transdermal rotigotine was associated with few side effects and was modestly effective for the treatment of fatigue and QOL in patients with PD. Although there were no significant differences ($P = 0.14$) between before and after motor symptoms evaluated by UPDRS, there were tendencies of improvement comparing between before and after in fatigue ($P = 0.061$) and in QOL ($P = 0.068$). This means that improvement in fatigue and QOL did not depend on improvement in motor symptoms.

Among non-motor symptoms in PD patients, fatigue was considered one of the most non-motor symptoms that were associated with signify QOL worsening [20] [21]. Thus, drugs to improve fatigue in PD patients have possibility also to improve their QOL. Transdermal agents have advantage not to be affected by digestive problems that also are non-motor symptoms in PD patients. We demonstrated that a transdermal rotigotine treatment was safe and effective for fatigue in PD patients, and improved their QOL.

We prescribed rotigotine of 4.5 mg/day and this is a minimum dose of rotigotine patches in Japan. However, it is notable that this minimum dose showed effect for non-motor symptoms in PD patients. Our study also has limitation in a small number of patients. We also plan to seek optimal doses in a future study.

References

- [1] Parkinson, J. (2002) An Essay on the Shaking Palsy. *Journal of Neuropsychiatry and Clinical Neurosciences*, **14**, 223-236. <http://dx.doi.org/10.1176/jnp.14.2.223>
- [2] Hoehn, M.M. and Yahr, M.D. (1967) Parkinsonism: Onset, Progression and Mortality. *Neurology*, **17**, 427-442. <http://dx.doi.org/10.1212/WNL.17.5.427>
- [3] Jankovic, J. (2008) Parkinson's Disease: Clinical Features and Diagnosis. *Journal of Neurology, Neurosurgery & Psychiatry*, **79**, 368-376. <http://dx.doi.org/10.1136/jnnp.2007.131045>
- [4] Chaudhuri, K.R. and Schapira, A.H. (2009) Non-Motor Symptoms of Parkinson's Disease: Dopaminergic Pathophysiology and Treatment. *Lancet Neurology*, **8**, 464-474. [http://dx.doi.org/10.1016/S1474-4422\(09\)70068-7](http://dx.doi.org/10.1016/S1474-4422(09)70068-7)
- [5] Antonini, A., Barone, P., Marconi, R., Morgante, L., Zappulla, S., Pontieri, F.E., *et al.* (2012) The Progression of Non-Motor Symptoms in Parkinson's Disease and Their Contribution to Motor Disability and Quality of Life. *Journal of Neurology*, **259**, 2621-2631. <http://dx.doi.org/10.1007/s00415-012-6557-8>
- [6] Rey, C.K., Angero, S., Kapil, S.D., Anthony, S.H.V., Richard, B., Angelo, A., Fabrizio, S., Per, O., Kristy, B., Yoshio, T., Kazuo, A., Alexandra, R., Carmen, R.-B. and Pablo, M.-M. (2015) The Burden of Non Motor Symptoms in Parkinson's Disease Using a Self-Completed Non-Motor Questionnaire: A Simple Grading System. *Parkinsonism & Related Disorders*, **21**, 287-291. <http://dx.doi.org/10.1016/j.parkreldis.2014.12.031>
- [7] Barone, P. (2010) Neurotransmission in Parkinson's Disease: Beyond Dopamine. *European Journal of Neurology*, **17**, 364-376. <http://dx.doi.org/10.1111/j.1468-1331.2009.02900.x>
- [8] Naidu, Y. and Chaudhuri, K.R. (2007) Transdermal Rotigotine: A New Non-Ergot Dopamine Agonist for the Treatment of Parkinson's Disease. *Expert Opinion on Drug Delivery*, **4**, 111-118. <http://dx.doi.org/10.1517/17425247.4.2.111>
- [9] Elshoff, J.P., Braun, M., Andreas, J.O., Middle, M. and Cawello, W. (2012) Steady-State Plasma Concentration Profile of Transdermal Rotigotine: An Integrated Analysis of Three, Open-Label, Randomized, Phase I Multiple Dose Studies. *Clinical Therapeutics*, **34**, 966-978. <http://dx.doi.org/10.1016/j.clinthera.2012.02.008>
- [10] Baldwin, C.M. and Keating, G.M. (2007) Rotigotine Transdermal Patch. *CNS Drugs*, **21**, 1039-1066. <http://dx.doi.org/10.2165/00023210-200721120-00007>
- [11] Trenkwalder, C., Kies, B., Rudzinska, M., Fine, J., Nikl, J., Honczarenko, K., *et al.* (2011) Rotigotine Effects on Early Morning Motor Function and Sleep in Parkinson's Disease: A Double-Blind, Randomized, Placebo-Controlled Study

- (RECOVER). *Movement Disorders*, **26**, 90-99. <http://dx.doi.org/10.1002/mds.23441>
- [12] Mizuno, Y. (1997) Concept and Diagnostic Criteria of Parkinson's Disease and Parkinsonism. *Nihon Rinsho. Japanese Journal of Clinical Medicine*, **55**, 16-20.
- [13] Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease (2003) The Unified Parkinson's Disease Rating Scale (UPDRS): Status and Recommendations. *Movement Disorders*, **18**, 738-750. <http://dx.doi.org/10.1002/mds.10473>
- [14] Abe, K., Takanashi, M. and Yanagihara, T. (2000) Fatigue in Patients with Parkinson's Disease. *Behavioral Neurology*, **12**, 103-106. <http://dx.doi.org/10.1155/2000/580683>
- [15] Martinez-Martin, P., Schapira, B.R. and The EuroQol Group (1996) EuroQol: The Current State of Play. *Health Policy*, **37**, 53-72. [http://dx.doi.org/10.1016/0168-8510\(96\)00822-6](http://dx.doi.org/10.1016/0168-8510(96)00822-6)
- [16] Coelho, M. and Ferreira, J.J. (2012) Late-Stage Parkinson Disease. *Nature Reviews Neurology*, **8**, 435-442. <http://dx.doi.org/10.1038/nrneurol.2012.126>
- [17] Chaudhuri, K.R., Martinez-Martin, P., Brown, R.G., Sethi, K., Stocchi, F., Odin, P., Ondo, W., Abe, K., MacPhee, G., MacMahon, D., Barone, P., Rabey, M., Bonnucelli, U., Forbes, A., Breen, K., Tluk, S., Naidu, Y., Olanow, C.W., Thomas, S., Rye, D., Bowron, A., Williams, A.J. and Schapira, A.H.V. (2007) The Metric Properties of a Novel Non-Motor Symptoms Scale for Parkinson's Disease: Results from an International Pilot Study. *Movement Disorders*, **22**, 1901-1911. <http://dx.doi.org/10.1002/mds.21596>
- [18] Martinez-Martin, P., Rodriguez-Blazquez, C., Bkurtis, M.M., Chaudhuri, K.R. and The NMSS Validation Group (2011) The Impact of Non Motor Symptoms on Health-Related Quality of Life of Patients with Parkinson's Disease. *Movement Disorders*, **26**, 399-406. <http://dx.doi.org/10.1002/mds.23462>
- [19] Martinez-Martin, P., Rodriguez-Blazquez, C., Abe, K., Bhattacharyya, K.B., Bloem, B.R., Carod-Artal, J., Dill, B., Esselink, R., Falup-Pecurariu, C., Gallardo, M., Mir, P., Naidu, Y., Nicoletti, A., Sethi, K., Tsuboi, Y., van Hilten, J.J., Visser, M., Zappia, M. and Chaudhuri, K.R. (2009) International Validation of the Non-Motor Symptoms Scale: Comparison with the Pilot Study. *Neurology*, **73**, 1584-1591. <http://dx.doi.org/10.1212/WNL.0b013e3181c0d416>
- [20] Stocchi, F., Abbruzzese, G., Ceravolo, R., Cortelli, P., D'Amelio, M., De Pandis, M.F., Fabbrini, G., Pacchetti, C., Pezzoli, G., Tessitore, A., Canesi, M., Iannaccone, C., Zappia, M. and FORTE Study Group (2014) Prevalence of Fatigue in Parkinson's Disease and Its Clinical Correlates. *Neurology*, **83**, 215-220. <http://dx.doi.org/10.1212/WNL.0000000000000587>
- [21] Barone, P., Antonini, A., Colosimo, C., Marconi, R., Morgante, L., Avarello, T.P., Bottacchi, E., Cannas, A., Ceravolo, G., Ceravolo, R., Cicarelli, G., Gaglio, R.M., Giglia, R.M., Iemolo, F., Manfredi, M., Meco, G., Nicoletti, A., Pederzoli, M., Petrone, A., Pisani, A., Pontieri, F.E., Quatralo, R., Ramat, S., Scala, R., Volpe, G., Zappulla, S., Bentivoglio, A.R., Stocchi, F., Trianni, G., Dotto, P.D. and PRIAMO Study Group (2009) The PRIAMO Study: A Multicenter Assessment of Nonmotor Symptoms and Their Impact on Quality of Life in Parkinson's Disease. *Movement Disorders*, **24**, 1641-1649. <http://dx.doi.org/10.1002/mds.22643>