Switching from blonanserin oral tablets/powders to transdermal patches alleviates extrapyramidal symptoms in patients with schizophrenia: A 52-week open-label study

Kazutaka Ohi a, b, *, Kentaro Takai a, Ayumi Kuramitsu a, Shunsuke Sugiyama a, Toshiki Shioiri a

a Department of Psychiatry, Gifu University Graduate School of Medicine, Gifu, Japan
b Department of General Internal Medicine, Kanazawa Medical University, Ishikawa, Japan

1. Introduction

Blonanserin (Lonasen®) is a relatively novel second-generation antipsychotic that is approved for the treatment of schizophrenia in East Asian countries, including South Korea, China and Japan (Deeks and Keating, 2010). Blonanserin has strong affinity for D2 and D3 dopamine and 5-HT2A serotonin receptors, while it has low or very low affinity for other neurotransmitter receptor subtypes, such as other dopamine and serotonin receptors; histamine H1 receptors; adrenoreceptors a1, a2, and b1; and muscarinic M1 and M3 receptors (Deeks and Keating, 2010). Blonanserin can improve positive and negative symptoms as well as cognitive impairments in patients with schizophrenia by blocking D2 and D3 dopamine and 5-HT2A serotonin receptors (Hori et al., 2014; Kishi et al., 2019).

Blonanserin is generally well tolerated and effective in patients with schizophrenia (Deepak et al., 2015; Garcia et al., 2009; Harvey et al., 2019; Li et al., 2015; Yang et al., 2010). Short-term, multicenter, randomized controlled clinical trials (RCTs) have demonstrated that blonanserin has a lower risk of extrapyramidal symptoms (EPS) and is more effective for the treatment of Positive and Negative Syndrome Scale (PANSS) negative symptoms than haloperidol (Garcia et al., 2009; Harvey et al., 2019) and has lower risks of hyperprolactinemia and weight gain than risperidone (Garcia et al., 2009; Li et al., 2015). A meta-analysis of RCTs demonstrated that blonanserin had a lower risk of hyperprolactinemia than a combination of risperidone and paliperidone and was more effective than aripiprazole in improving PANSS total scores (Garcia et al., 2009; Harvey et al., 2019; Li et al., 2015). Blonanserin is generally well tolerated and effective in patients with schizophrenia (Deepak et al., 2015; Garcia et al., 2009; Harvey et al., 2019; Li et al., 2015; Yang et al., 2010). Short-term, multicenter, randomized controlled clinical trials (RCTs) have demonstrated that blonanserin has a lower risk of extrapyramidal symptoms (EPS) and is more effective for the treatment of Positive and Negative Syndrome Scale (PANSS) negative symptoms than haloperidol (Garcia et al., 2009; Harvey et al., 2019) and has lower risks of hyperprolactinemia and weight gain than risperidone (Garcia et al., 2009; Li et al., 2015). A meta-analysis of RCTs demonstrated that blonanserin had a lower risk of hyperprolactinemia than a combination of risperidone and paliperidone and was more effective than aripiprazole in improving PANSS total scores (Garcia et al., 2009; Harvey et al., 2019; Li et al., 2015).
scores, while blonanserin had higher risks of EPS, akathisia, and agitation/excitement than the combination of risperidone and paliperidone (Kishi et al., 2019). EPS and akathisia were relatively frequent adverse reactions in patients taking oral blonanserin (Inoue et al., 2021), although the frequencies were lower than those in haloperidol.

Commonly used formulations of antipsychotics for the treatment of schizophrenia are oral tablets or powders. Long-acting injections (LAIs) are also available when poor adherence to antipsychotic medication is observed in patients with schizophrenia or when desired by the patients and/or caregivers. The LAI removes the need for daily pill-taking behaviors but has a disadvantage in dosage modification after an injection. Blonanserin is currently available as a transdermal patch (20 mg and 40 mg) formulation in addition to oral tablets and powders. Blonanserin transdermal patches were well tolerated, significantly improved PANSS total scores compared with placebo (Iwata et al., 2020a) and had long-term safety and efficacy in patients with schizophrenia (Iwata et al., 2020b).

The transdermal patch formulation is expected to provide several advantages over oral tablet/powder or LAI formulations. The transdermal patch can provide stable blood concentrations over long periods and avoid first-pass metabolism that can affect plasma levels of oral agents (Isaac and Holvey, 2012). The mean plasma blonanserin concentration with an 80 mg/day blonanserin patch was approximately double that with a 40 mg/day blonanserin patch (Iwata et al., 2020a). These findings suggest that the transdermal patch may easily modify the plasma blonanserin concentration and decrease the incidence of adverse events, such as EPS and akathisia, due to unstable high plasma concentrations. In addition, the transdermal patch is noninvasive and can be stopped immediately and easily compared with LAI if patch removal is required. Furthermore, the transdermal patch may improve the daily quality of life of patients because the patch may reduce embarrassment at being seen swallowing tablets/powder and can be hidden under clothing. In contrast, a recent network meta-analysis of RCTs conducted in Japan indicated that oral blonanserin had a lower incidence of an anticholinergic agent use than transdermal patch, although no differences exist in terms of the efficacy and acceptability between oral and transdermal patch formulations (Kishi et al., 2021). However, these findings were determined only by indirect comparisons.

To date, a multicenter, 52-week open-label study for blonanserin transdermal patches has been performed to evaluate the long-term safety and efficacy of the patches in patients with schizophrenia (Iwata et al., 2020b). We hypothesized that directly switching from blonanserin tablets/powders to transdermal patches would reduce EPS and/or the dose of antiparkinsonian drugs in patients with schizophrenia or when desired by the patients and/or caregivers. The LAI removes the need for daily pill-taking behaviors but has a disadvantage in dosage modification after an injection. Blonanserin is currently available as a transdermal patch (20 mg and 40 mg) formulation in addition to oral tablets and powders. Blonanserin transdermal patches were well tolerated, significantly improved PANSS total scores compared with placebo (Iwata et al., 2020a) and had long-term safety and efficacy in patients with schizophrenia (Iwata et al., 2020b).

The aim of cohort 1 (patients switched from blonanserin tablets to patch therapy) was to evaluate the safety and efficacy of blonanserin patches in patients who received blonanserin tablets prior to transdermal patches (Iwata et al., 2020b). In cohort 1, patients received blonanserin tablets twice daily (after breakfast and dinner) for 6 weeks (tablet treatment period), followed by blonanserin transdermal patches once daily for a year (patch treatment period). The initial dose of blonanserin tablets during the tablet treatment period was 8 mg/day, and then the dose was adjusted to a range between 8 and 16 mg/day. The starting dose of blonanserin patches was determined by the final dose of blonanserin tablets, i.e., patients (n = 97, 43 males/54 females; mean age ± SD: 44.1 ± 14.4 years) who had received 8, 12, and 16 mg/day blonanserin tablets received 40, 60, and 80 mg/day patches, respectively. Patients applied 40–80 mg blonanserin patches to their back, chest, or abdomen by combining 20 mg or 40 mg patches. The blonanserin patch was adjusted in a range between 40 and 80 mg during the patch treatment period.

The aim of cohort 2 (patients who received continuous blonanserin patch therapy despite previously receiving any antipsychotic treatments during the screening period) was to evaluate the safety and efficacy of the blonanserin transdermal patches in patients, including those who had previously received any antipsychotic treatments or had not received a treatment for schizophrenia before the screening period (Iwata et al., 2020b). However, we excluded patients (n = 45) who had previously received any antipsychotic treatments except for blonanserin or those who had not received treatment for schizophrenia before the screening period because the main purpose of this study was to evaluate EPS and/or the dose of antiparkinsonian drugs after switching from blonanserin tablets/powders to transdermal patches. Therefore, all patients received oral blonanserin tablets/powders before the patch treatment period.
treatment period. In cohort 2, patients (n = 58, 22 males/36 females; 43.7 ± 13.5 years) received blonanserin transdermal patches for one year. All patients started with 40 mg blonanserin patches. The blonanserin patch was adjusted in a range between 40 and 80 mg during the patch treatment period.

2.2. Clinical assessments

Clinical assessments were performed at the start of the transdermal patch treatment and at 3, 6, and 12 months after the initiation of blonanserin patch treatment until discontinuation. The presence and severity of EPS were evaluated using the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) total scores for individual symptoms, excluding overall severity (Inada et al., 2003). The individual symptom scores of the EPS ranged from 0 (normal) to 4 (severe). Current positive and negative symptoms were evaluated using the PANSS (Kay et al., 1987). The positive and negative symptom scores are rated from 7 to 49. Chlorpromazine equivalents of total antipsychotics (CPZ-eq) and biperiden equivalents of total antiparkinsonian drugs (BPD-eq) were calculated based on a previous study (Inada and Inagaki, 2015).

2.3. Statistical analyses

We analyzed cohort 1 and cohort 2 separately because detailed study protocols, e.g., blonanserin tablet/powder treatment period, the initial dose of blonanserin tablets during the tablet treatment period, and the initial dose of blonanserin transdermal patches during the patch treatment period, were different between cohorts 1 and 2. Statistical analyses were performed in each cohort, which included patients with at least one assessment at 3, 6, or 12 months during the patch treatment period. Missing data were not imputed, and our analysis in this study was limited to observed cases. For the observed value, changes from the start of the blonanserin transdermal patch in the DIEPSS total scores and BPD-eq in addition to the PANSS positive and negative symptom scores at 3, 6, and 12 months were analyzed using a paired t-test. Standardized effects were calculated using Cohen’s d method (https://memory.psych.mun.ca/models/stats/effect_size.shtml). The significance level was set at a two-tailed p < 0.05 for all statistical tests.

3. Results

3.1. The demographic variables in patients with schizophrenia (cohorts 1 and 2)

The demographic variables in patients with schizophrenia (cohorts 1 and 2) at study enrollment and at baseline of blonanserin patch treatment are summarized in Table 1. Patient characteristics were similar between the two cohorts. A total of 155 patients with schizophrenia in cohort 1 (n = 97) and cohort 2 (n = 58) started blonanserin transdermal patch treatment (Fig. 1). Of 97 patients in cohort 1, forty patients (41.2%) discontinued treatment with blonanserin transdermal patches by one year. Of 58 patients in cohort 2, twenty-six patients (44.8%) discontinued treatment with blonanserin transdermal patches by one year. The percentage of discontinuation resulting from EPS during a transdermal patch treatment period was 41% (n = 4) in cohort 1 and 0% (n = 0) in cohort 2. There were no specific larger reasons for discontinuations among periods by 3, 6, and 12 months (Fig. 2). The doses of blonanserin transdermal patches during the treatment period are summarized in Table 2. Overall, the mean daily dose of blonanserin transdermal patches was 56.0 ± 17.0 mg/day, and the maximum daily dose was 59.2 ± 18.4 mg/day.

3.2. Changes from baseline in EPS at 3, 6, and 12 months of transdermal patch treatment

In both cohorts, the DIEPSS total score significantly decreased after switching treatment from blonanserin tablets/powders to transdermal patches at any point (Fig. 3). In cohort 1, the mean ± SD change from baseline in the DIEPSS total score at 3, 6, and 12 months was −0.44 ± 1.50 (n = 75, Cohen’s d = −0.29, t = −2.54, p = 0.013), −0.07 ± 1.78 (n = 67, d = −0.04, t = −0.34, p = 0.73), and −0.14 ± 1.37 (n = 57, d = −0.10, t = −0.77, p = 0.44), respectively. In cohort 2, the mean ± SD change from baseline in the DIEPSS total score at 3, 6, and 12 months was −0.16 ± 1.32 (n = 51, d = −0.12, t = −0.85, p = 0.40), −0.74 ± 1.92 (n = 39, d = −0.39, t = −2.42, p = 0.020), and −0.81 ± 2.22 (n = 32, d = −0.37, t = −2.07, p = 0.047), respectively.

3.3. Changes from baseline in the dose of concomitant antiparkinsonian drugs at 3, 6, and 12 months of transdermal patch treatment

Overall, 21.9% (34/155) of patients used concomitant antiparkinsonian drugs at the start of patch treatment, while 25.8% (23/89) of patients used concomitant antiparkinsonian drugs at one year after patch treatment initiation. BPD-eq did not significantly decrease or increase after switching treatment from blonanserin tablets/powders to transdermal patches at any point in either cohort (Fig. 3). In cohort 1, the mean ± SD change from baseline in BPD-eq at 3, 6, and 12 months was 0.08 ± 1.16 (n = 75, d = 0.07, t = 0.60, p = 0.55), 0.12 ± 1.35 (n = 67, d = 0.09, t = 0.72, p = 0.47), and 0.10 ± 1.09 (n = 57, d = 0.09, t = 0.68, p = 0.50), respectively. In cohort 2, the mean ± SD change from baseline in BPD-eq at 3, 6, and 12 months was 0.09 ± 1.54 (n = 51, d = 0.06, t = 0.41, p = 0.68), −0.12 ± 1.34 (n = 39, d = −0.09, t = −0.54, p = 0.60), and 0.06 ± 1.56 (n = 32, d = 0.04, t = 0.23, p = 0.82), respectively.

3.4. Changes from baseline in psychotic symptoms at 3, 6, and 12 months of transdermal patch treatment

Although determining the efficacy after switching treatment from blonanserin tablets/powders to transdermal patches was not the main

| Cohort | (n = 97) | Cohort 2 | (n = 58) | Total | (n = 155) |
|--------|---------|---------|---------|-------|-----------|
| Sex (male/female) | 43/54 | 22/36 | 65/90 |
| Age (years) | 44.1 ± 14.4 | 43.7 ± 13.5 | 43.9 ± 14.1 |
| Outpatients/inpatients | 89/9 | 48/10 | 137/18 |
| Duration of illness (years) | 14.9 ± 12.7 | 15.6 ± 11.1 | 14.9 ± 12.1 |
| Number of psychotic episodes at 3, 6, and 12 months | 104.7 ± 102.3 ± 103.8 |
| Blonanserin tablet/powder of the previous day (mg/day) | 10.7 ± 3.5 | 10.2 ± 4.2 | 10.5 ± 3.8 |
| CPZ-eq (mg/day) | 268.0 ± 87.3 | 262.8 ± 109.1 | 266.1 ± 95.7 |
| PANSS total score | 63.6 ± 21.2 | 69.5 ± 21.2 | 65.8 ± 21.4 |
| PANSS positive symptoms | 13.4 ± 5.5 | 15.1 ± 5.7 | 14.0 ± 5.6 |
| PANSS negative symptoms | 17.5 ± 6.9 | 19.0 ± 7.8 | 18.1 ± 7.3 |
| DIEPSS total score | 0.9 ± 1.8 | 1.0 ± 1.8 | 1.0 ± 1.8 |

CPZ-eq, chlorpromazine equivalents of total antipsychotics; BPD-eq, biperiden equivalents of total antiparkinsonian drugs; PANSS, Positive and Negative Syndrome Scale; DIEPSS, Drug-Induced Extrapyramidal Symptoms Scale.
purpose of this study, we additionally investigated changes from base-
line in psychotic symptoms at 3, 6, and 12 months of transdermal patch
treatment. In cohort 1, the PANSS negative symptom scores significantly
decreased over 12 months after switching treatment from blonanserin
tablets/powders to transdermal patches: −0.7 ± 2.1 (n = 75, d = −0.36,
t = −3.13, p = 0.003), −1.0 ± 3.1 (n = 67, d = −0.31, t = −2.54, p = 0.013), and −1.3 ± 2.8 (n = 57, d = −0.46, t = −3.50, p = 0.001) at 3, 6,
and 12 months, respectively (Fig. 3). In contrast, the PANSS positive
symptom scores did not change after switching at any point: −0.2 ± 2.1
(n = 75, d = −0.09, t = −0.79, p = 0.44), 0.1 ± 3.0 (n = 67, d = 0.03, t = 0.29, p = 0.78), and −0.5 ± 2.7 (n = 57, d = −0.18, t = −1.37, p = 0.18)
at 3, 6, and 12 months, respectively (Fig. 3). In cohort 2, the PANSS
positive and negative symptom scores significantly decreased over 12
months after switching treatment from blonanserin tablets/powders to
transdermal patches (Fig. 3). The mean ± SD change from baseline in the
PANSS positive symptom scores at 3, 6, and 12 months was −1.6 ± 3.2
(n = 51, d = −0.52, t = −3.69, p = 0.001), −2.3 ± 4.0 (n = 39, d = −0.57, t = −3.54, p = 0.001), and −2.4 ± 5.3 (n = 32, d = −0.46, t = −2.61, p = 0.014), and the mean ± SD change from baseline in the
PANSS negative symptom scores at 3, 6, and 12 months was −1.4 ± 3.3
(n = 51, d = −0.44, t = −3.12, p = 0.003), −2.7 ± 4.7 (n = 39, d = −0.58, t = −3.64, p = 0.001), and −2.8 ± 5.6 (n = 32, d = −0.50, t = −2.85, p = 0.008, respectively.

4. Discussion

This was the first study to evaluate the EPS and dose of anti-
parkinsonian drugs in schizophrenia patients who switched to the
blonanserin transdermal formulation from blonanserin oral tablets/
powders in a long-term open-label multicenter study (two cohorts). In
both cohorts, the EPS were significantly reduced at any point (3, 6, or 12
months) after switching. In addition, switching was significantly asso-
ciated with improvements in positive and negative symptoms. As
blonanserin-induced EPS could be caused by higher drug concentrations
antagonizing dopamine D2 receptors in the central nervous system
(CNS), and diurnal variability in striatal dopamine D2 receptor occupa-
cy was higher during tablet treatment than during transdermal patch
treatment (Nishibe et al., 2021), the stabilization of plasma blonanserin
levels, instead of “fluctuation”, with transdermal patches compared with
the oral formulation could prevent patients from suffering from EPS.
Furthermore, less fluctuation in blood levels (Kitamura et al., 2021) and
less chances of pharmacokinetic drug interactions with transdermal
patch formulation of blonanserin (Tomita et al., 2020) might have
affected the improvements in EPS at least in part even though central
dopamine blockade with the doses used appears similar (Nishibe et al.,
2021). These findings suggest that the blonanserin transdermal formu-
lation could be safer and more effective than blonanserin oral for-
mulations.

The dose of antiparkinsonian drugs was not significantly decreased
at any point after switching. The dose of antiparkinsonian drugs is
dependent on prescription behaviors by psychiatrists. Unfortunately,
some patients who are receiving antipsychotics are regularly given
anticholinergic agents, such as biperiden, in Japan despite the relative
absence of neurological side effects. Psychiatrists care too much about
cholinergic rebound following the withdrawal of biperiden to reduce the
dose of antiparkinsonian drugs. In contrast, the harmful effects of anti-
parkinsonian drugs on cognitive functions in patients with schizo-
phrenia were substantial, and cognitive impairments were improved
after tapering long-term antiparkinsonian drugs (Desmarais et al., 2012;
Ogino et al., 2011). Therefore, the use of antipsychotics without anti-
parkinsonian drugs could be recommended as a treatment for cognitive
impairments in patients with schizophrenia (Ohi et al., 2020). Our

Fig. 2. Patient flowchart and reasons for discontinuation during the current study. EPS, extrapyramidal symptoms.

Table 2

| Dose of the blonanserin transdermal patch (mg/day) during a treatment period. | Cohort 1 | Cohort 2 | Total |
|---|---|---|---|
| (n = 97) | (n = 58) | (n = 155) |
| Initial dose (mg/day) | 53.6 ± 17.5 | 40.0 ± 15.3 | 48.5 ± 15.3 |
| 40 mg (n) | 57 | 58 | 115 |
| 60 mg (n) | 14 | 0 | 14 |
| 80 mg (n) | 26 | 0 | 26 |
| Mean dose (mg/day) | 55.2 ± 17.2 | 57.5 ± 16.8 | 56.0 ± 17.0 |
| Maximum dose (mg/day) | 57.7 ± 18.2 | 61.7 ± 18.5 | 59.2 ± 18.4 |
| Modal dose (mg/day) | 54.8 ± 17.9 | 59.0 ± 18.5 | 56.4 ± 18.2 |
| 40 mg (n) | 54 | 26 | 80 |
| 60 mg (n) | 14 | 9 | 23 |
| 80 mg (n) | 29 | 23 | 52 |
| Last dose (mg/day) | 55.5 ± 17.9 | 59.0 ± 18.1 | 56.8 ± 18.0 |

Means ± SD are shown.

Fig. 3. Changes from the beginning of transdermal patch treatment in the
dIEPSS overall severity score, BPD-eq and PANSS positive and negative
symptom scores. Means ± standard errors are shown. *p < 0.05 and **p < 0.01
vs at the start of the transdermal patch treatment. DIEPSS, Drug-Induced
Extrapyramidal Symptoms Scale; BPD-eq, biperiden equivalents of total anti-
parkinsonian drugs; PANSS, Positive and Negative Syndrome Scale.
findings indicate the possibility of decreasing the dose of anti-parkinsonian drugs after switching from blonanserin tablets/powders to blonanserin transdermal patches.

A total of 21.9% (34/155) of patients took concomitant anti-parkinsonian drugs at the start of the patch treatment. Although the number of patients who took concomitant antiparkinsonian drugs at the start of patch were quite limited (n = 34), we further examined whether the EPS, dose of antiparkinsonian drugs and psychotic symptoms in these patients were improved at any point after the switch to the blonanserin transdermal formulation from the oral tablet/powder formulations (Supplementary Fig. 1). In the limited patients who took concomitant antiparkinsonian drugs at the start of patch treatment, the EPS, dose of antiparkinsonian drugs and psychotic symptoms were also gradually reduced. These findings further support that the transdermal formulation could be safer and more effective than oral formulations.

The prior antipsychotic dose was gradually decreased to <12.0 mg/day in haloperidol equivalents during a dose reduction period of <4 weeks if patients had been taking antipsychotics at a dose of >12.0 mg/day in haloperidol equivalents. Only three patients (two patients in cohort 1 and a patient in cohort 2) had been taking antipsychotics at a dose of >12.0 mg/day in haloperidol equivalents, and the antipsychotic dose was gradually decreased to <12.0 mg/day in haloperidol equivalents during the dose reduction period. Therefore, we can exclude the possibility that the prior decrease in antipsychotic dose during the dose reduction period could affect improvements in the DIEPSS total score after the start of patch treatment.

A multicenter, 52-week open-label study for oral blonanserin (8–24 mg/day) in Kanagawa, Japan, was performed over a decade to evaluate the long-term safety and efficacy of oral blonanserin in 61 patients with schizophrenia (Murasaki, 2007). A total of 62.3% (38/61) of patients completed the 52-week trial. The study demonstrated that oral blonanserin is well tolerated and effective in patients with schizophrenia because significant improvements in the DIEPSS total score from the start of oral blonanserin treatment (mean ± SD change, −0.7 ± 2.1) and PANSS positive (−1.7 ± 6.1) and negative (−2.9 ± 3.9) symptom scores at 52 weeks were observed. In the study, most patients switched from first-generation antipsychotics (FGAs), including haloperidol, to oral blonanserin. Because of the difference in the timing between the study and the current study, an exact comparison cannot be made, but our findings suggest that switching from oral blonanserin to blonanserin patches might lead to further improvements in DIEPSS and PANSS scores.

There are some limitations to the interpretations of our findings. Since this study was an open-label trial, we cannot exclude the possibility that patients’ expectations of the formulation changes may have affected their improvements in DIEPSS and PANSS scores. We examined changes in EPS and the dose of antiparkinsonian drugs over time in schizophrenia patients who switched to the blonanserin transdermal formulation from blonanserin tablets/powders; however, we did not examine crossover changes in schizophrenia patients who switched to blonanserin tablets/powders from blonanserin transdermal patches or examine the therapeutic drug monitoring between the two formulations. Furthermore, we did not include any control groups to compare the effects of the time-course differences in EPS and the dose of antiparkinsonian drugs.

In conclusion, we demonstrated that direct switching from blonanserin tablets/powders to transdermal patches reduced EPS and psychotic symptoms in patients with schizophrenia in a multicenter, 52-week open-label study. We suggest that transdermal patches have better acceptability and efficacy than oral medication in patients with schizophrenia.

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The authors have declared that there are no conflicts of interest in relation to the subject of this study.

Contributors

K. Ohi supervised the entire project, collected the data, wrote the manuscript and was critically involved in the design, analysis and interpretation of the data. All authors were responsible for performing the literature review. K. Takai, A. Kuramitsu, S. Sugiyama and T. Shioiri intellectually contributed to data interpretation. All authors contributed to and approved the final manuscript.

Data availability statement

Our data are not publicly available due to them containing information that could compromise research participant privacy/consent.

Ethical statement

This study was performed in accordance with the ethical principles stated in the Declaration of Helsinki and with the Good Clinical Practice (GCP) guidelines and other relevant Japanese regulations. The study protocol was approved by the institutional review boards of all participating institutions. Written informed consent was obtained from all participants and their legal guardian if the patient was <20 years old or was hospitalized for medical care and protection prior to the study.

Declaration of Competing Interest

All authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2021.110470.

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