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ORIGINAL RESEARCH

# Evaluation of the Effect of Patient–Initiated Antiviral Therapy on the Frequency of the Recurrent Herpes Simplex Viral Infection: A Single Center, Retrospective Study

Junichi Sugai[1], Tomoyoshi Takeshita[2]

[1]Sugai Dermatology Park Side Clinic, Tochigi, Japan; [2]Medical Affairs Department, Maruho Co., Ltd., Osaka, Japan

Correspondence: Tomoyoshi Takeshita, Medical Affairs Department, Maruho Co. Ltd., Osaka, Japan, Tel +81 663 718 913, Fax +81 663 718 927, Email takeshita_emk@mii.maruho.co.jp



**Purpose:** Although recurrent herpes simplex (RHS) is usually self–limiting, it can significantly impair quality of life due to frequent recurrences and associated symptoms. Patient–initiated therapy (PIT) enables patients with RHS to initiate high–dose antiviral medication at their own discretion as soon as prodromal symptoms appear. While famciclovir–based PIT offers the convenience of a single–day treatment and has shown efficacy comparable to low–dose, long–term regimens such as 5–day treatment, no reports have evaluated its impact on the annual recurrence rate. To investigate this further, we conducted a single–center, chart–based retrospective study to assess the effect of PIT on annual recurrence rate.

**Patients and Methods:** Patients who visited a medical institution for RHS and who had their recurrence frequency recorded over the preceding year were included. Annual recurrence number, adherence, treatment efficacy, and other relevant factors were assessed through interviews and questionnaires. The effectiveness and safety of PIT were compared with conventional 5–day oral anti–herpesvirus treatment.

**Results:** Sixty patients who were prescribed famciclovir for PIT were enrolled, of whom 43 with recurrent episodes were included in the efficacy analysis population. The mean number of recurrences during the first year of PIT was 2.8 (SD: 2.1), representing a significant reduction compared to 5.3 (SD: 2.9) during 5–day treatment ($p < 0.001$). Patient questionnaires indicated high adherence, treatment efficacy, and preference for PIT. Regarding safety, no increase in adverse events was observed compared to 5–day treatment.

**Conclusion:** Famciclovir–based PIT significantly reduced the recurrence rate of RHS, demonstrated high adherence and treatment efficacy, was preferred by patients, and was well tolerated. These results support PIT as a promising therapeutic approach for management of recurrent herpes simplex.

**Keywords:** herpes simplex virus, recurrence rate, patient–initiated treatment, 5–day treatment, famciclovir, real–world clinical practice

## Introduction

Recurrent herpes simplex is a disease in which a latent herpes simplex virus (HSV) in the neuronal cells of the sensory ganglia is reactivated after immunocompromise, trauma, exposure to UV light, or other triggering factors. Following primary infection, patients repeatedly develop lesions with vesicles, erosions, and sores on the skin and mucous membranes.[1,2] HSV–1 typically causes infections around the mouth and face, while HSV–2 is more commonly associated with infections of the genital area and surrounding regions. HSV–1 is highly prevalent, affecting 64% of people under the age of 50, while HSV–2 affects 13% of individuals aged 15 to 49.[2] Although recurrent herpes simplex is usually self–limiting, it can significantly impair quality of life due to frequent recurrences and associated symptoms.[3,4] HSV infection warrants clinical attention, as it can lead to severe complications in some cases.[2,5] HSV–1 is also a major cause of meningoencephalitis, Kaposi's varicelliform eruption, and other related conditions. HSV–2 can occasionally



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result in serious conditions such as neonatal herpes or meningitis. HSV infections also tend to be more severe and frequent in individuals with weakened immune systems, such as those with advanced HIV infection.

Japanese treatment guidelines recommend oral antiviral drugs as treatment for recurrent herpes simplex.[6] The most common episodic antiviral treatment involves taking the prescribed anti–herpes drug for 5 days after onset.[7,8] However, recurrent herpes simplex rapidly worsens after patients recognize the initial symptoms such as discomfort, burning sensation, and pruritus in the affected area, so early intervention is crucial.[9] When high doses of anti–viral treatment were initiated soon after infection in a mouse model of latent HSV infection, a reduction in the numbers of latently infected neurons and a significant reduction in the frequency of reactivation were observed.[10] Nevertheless, in humans, few patients can visit a medical institution as soon as early symptoms appear.[11] To address this issue, patient–initiated therapy (PIT) allows patients to initiate high–dose medication at their own discretion. It completes treatment in one or two days and has been reported to be as effective as low–dose long–term courses.[12–14] Therefore, it is recommended as first–line treatment for recurrent herpes simplex in Western countries.[15–17] In Japan, the dosage and administration (BID) of famciclovir as PIT were finally approved in 2019.[18,19] In 2023, the helicase–primase inhibitor amenamevir was newly approved for PIT.[20–22] This drug completes treatment with just a single dose, raising expectations for improved convenience. Despite these advantages, recognition of PIT remains low, and the 5–day treatment is still the standard approach.

There is also suppressive therapy, where patients take a low–dose of an antiviral drug every day as a treatment to reduce recurrence frequency.[6,16,17] Patient satisfaction with this form of treatment is reported to be high.[23] However, suppressive therapy has limited utility in genital herpes patients who suffer recurrence more than six times a year[24,25] and adherence is a challenge because of the need to take medication daily over the long term.[26,27] In addition, antiviral drugs cannot eliminate latent infectious viruses, and once treatment is discontinued, the severity and frequency of recurrence have been confirmed to return to pre–treatment levels.[15,28] In clinical trials, the time to the next recurrence after medication has been evaluated in both PIT and 5–day treatment;[13] however, the evaluation periods were short and not sufficient to assess changes in annual recurrence frequency. Moreover, in the 5–day treatment, medication was prescribed in advance and taken promptly or within 12 hours at the onset of initial symptoms. This differs from real–world clinical practice, where only 8.1% of patients are able to visit within 12 hours after symptoms onset.[11] As there are no other reports related to the recurrence frequency of PIT, the impact of PIT on recurrence rate in real–world clinical practice remains unclear. Therefore, we conducted a retrospective study using medical records with the aim of assessing the impact on the frequency of herpes simplex recurrence when treatment was switched from conventional 5–day treatment to PIT with famciclovir.

# Materials and Methods

## Study Design

This study is a single–center, chart–based, retrospective cohort study to evaluate the effectiveness of patient–initiated therapy (PIT) in reducing the recurrence rate of recurrent herpes simplex. The study design is shown in Figure 1.

Patients who visited Sugai Dermatology Parkside Clinic between January 1, 2018, and December 31, 2023, were eligible for inclusion if they were diagnosed with recurrent herpes simplex, prescribed famciclovir for PIT, and had the number of recurrences over the preceding year recorded by the principal investigator. Recurrence was defined not only as the presence of skin lesions but also as the recognition of prodromal symptoms by the patient, regardless of the presence of lesions or the use of medication.

The period after the enrollment date was considered the period of PIT with famciclovir, which was set at a minimum of one year. During the PIT period, the number of recurrences in the most recent year was collected annually by asking each patient during an interview conducted by the principal investigator, “How many times have you had herpes simplex outbreaks in the past year?”. In addition, a questionnaire was administered on PIT adherence, the comparison of symptom severity between PIT and 5–day treatment, and other related factors (Supplementary Figure 1).

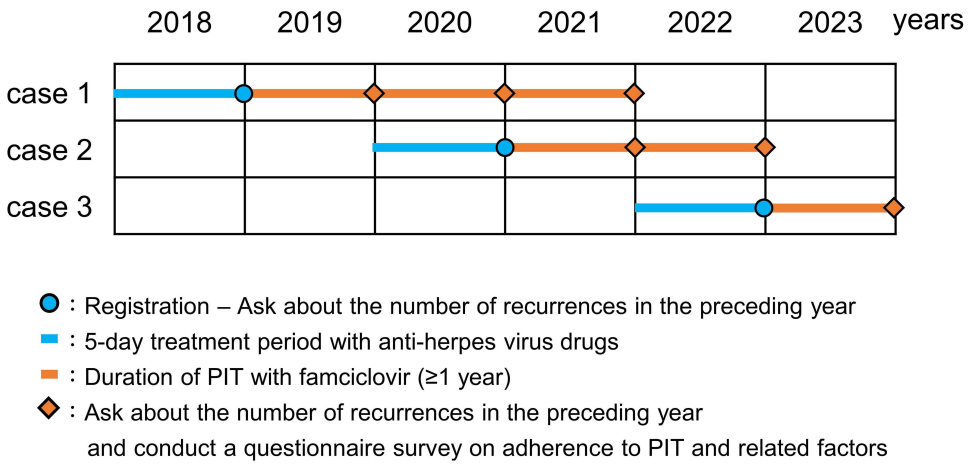


**Figure 1** Study design.

## Subjects, Inclusion Criteria and Exclusion Criteria

Study subjects were patients who met the following inclusion criteria, while those deemed inappropriate by the investigator were excluded.

1. Men or women aged 18 years or older at the time enrollment;
2. Individuals with a history of outpatient visits to the research institution for the treatment of recurrent herpes simplex;
3. Individuals who had continued 5–day treatment for more than one year;
4. Individuals who had switched their treatment method from 5–day treatment to PIT at the research institution;
5. Individuals who had continued PIT with famciclovir at the research institution for more than one year;
6. Individuals whose treatment periods under criteria 3 and 5 were consecutive;
7. Individuals who could provide the number of recurrences in the year prior to registration;
8. Individuals who could provide the annual number of recurrences during the period of PIT;
9. Individuals did not express refusal through opt–out.

## Data Set Creation

From January 1, 2018, to December 31, 2023, the investigator selected the cases for inclusion. A questionnaire regarding patient characteristics, number of recurrences, treatment, and efficacy, and safety–related information were collected from patients' medical records (electronic medical records, physician–generated case cards, and patient questionnaires), transcribed to a coded case report form (CRF) that did not disclose the patient's name, and mailed to the contract institution (WDB COCO Co., Ltd). The contract institution entered and checked the data on the basis of the CRF and prepared the data set for analysis.

## Data Collection

Age, sex, height and weight, history of recurrent herpes simplex (age of onset, site of onset), creatinine clearance, the number of recurrences of recurrent herpes simplex prior to enrollment (prior to PIT initiation), and annual number of recurrences after PIT initiation were collected.

In addition, the investigator administered a questionnaire to patients at annual follow–up visits for PIT. The content of the questionnaire addressed adherence, convenience, preference, degree of severity, irritation and discomfort, and improvement in rash.

In terms of safety, the names of adverse events occurring within 2 weeks after drug administration, the causal relationship between adverse events and medication, date of onset, outcome, and seriousness were collected. Adverse events were any unfavorable medical events observed in patients who took antiviral drugs during the evaluation period.


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## Endpoints

The primary endpoint was the number of recurrences prior to PIT compared to the number of recurrences in the first year of PIT. The main secondary endpoint was the number of recurrences during the first year of PIT compared to the second year of PIT. The number of recurrences prior to PIT compared to the second year onwards of PIT was evaluated as sensitivity analysis for the primary endpoint. In addition, annual questionnaires regarding adherence, convenience, effectiveness, etc., were administered and evaluated. Finally, the presence and type of adverse events during the respective treatment periods prior to and after PIT initiation were determined.

## Treatment

For 5–day treatment, the following medications were prescribed: acyclovir tablets (200 mg orally administered 5 times a day), valacyclovir tablets (500 mg orally administered twice a day), or famciclovir tablets (250 mg orally administered 3 times a day). For PIT, famciclovir tablets (1,000 mg orally administered twice a day) were prescribed.

## Analysis Set

All enrolled cases were included in the safety analysis set (SAS). Among the enrolled cases, those with a missing number of recurrences in the first year of PIT excluding were included as the full analysis set (FAS). Among the FAS, cases that did not meet any of the inclusion criteria or fell under any of the exclusion criteria were excluded from the per protocol set (PPS). In this study, the primary efficacy analysis was based on the FAS and the secondary analyses were based on the PPS.

## Statistical Analysis

Differences in the number of recurrences between prior to PIT and first year of PIT were used, and paired t–tests were performed. A paired *t*–test was also performed to compare the secondary endpoints and differences in the number of recurrences for other endpoints. Correlation analyses were performed to calculate Pearson's correlation coefficients for the number of recurrences in the year preceding PIT and the change in the number of recurrences in the first year of PIT. Questionnaires were aggregated by year for the frequency of responses to each question. Analysis of the primary endpoint and secondary endpoints was performed using the following subgroups.

Age: $< 30$ years, $\geq 30$ years $< 50$ years, $\geq 50$ years.

The number of recurrences: 3–5 times/year, 6 times/year or more.

Morbidity duration: $< 10$ years, $\geq 10$ years.

Site of lesion: lips or face, genitalia or buttocks.

Investigator–reported adverse events were classified using MedDRA/J ver. 27.0 and the frequency of adverse events that occurred prior to PIT and during PIT was calculated.

No imputation was performed for missing data. Outliers were not excluded from the analysis unless there was a clear reason. The level of significance was set at 5% two–sided. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, USA).

## Ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, as revised in 2013, and all applicable Japanese clinical study regulations. This study was approved by the Institutional Review Board (IRB) of the external institution, Shiba Palace Clinic Ethics Review Committee, as the research institution does not have its own IRB (approval number: 153877_rn–36508). As this was a retrospective study using medical chart data, written informed consent was not required; instead, an opt-out method was used in accordance with Japanese ethical guidelines for medical research involving human subjects. Information and opt–out documents for this study were publicized on in–house postings and on the research institution's official website to ensure that patients had the opportunity to refuse to participate in the study. The study content was registered in the Japan Registry of Clinical Trials with the identifier jRCT1031230671. This study was conducted between February 2024 and March 2025 in compliance with the Japanese ethical guidelines for medical research involving people.

# Results

## Disposition of Cases

Sixty patients diagnosed with recurrent herpes simplex and prescribed famciclovir for PIT were included in the SAS (Figure 2). The FAS comprised 43 patients, excluding 17 patients for whom efficacy data were not available, including cases without recurrence during the period of PIT. Patients who did not meet the inclusion criteria were excluded, and 26 patients were included in the PPS.

## Patient Characteristics

The mean age (SD) was 45.7 (15.6) years, and the most common age group in the FAS comprised patients aged ≥ 30 years and < 50 years (23/43 patients, 53.5%) (Table 1). Women accounted for the majority, with a mean age of onset of 24.0 (18.3) years. The mean number of recurrences was 5.3 (2.9), with more patients experiencing 3–5 recurrences in a year. The mean disease duration was 21.5 (12.2) years, with 31 patients (73.8%) being affected for more than 10 years. Among all patients, 32 cases (74.4%) presented with oral–facial herpes, while 10 cases (23.3%) presented genital or buttock herpes. Of the oral–facial herpes cases, 2 affected the perinasal area and 30 affected the lips. Among the genital or buttock herpes cases, 2 involved the genitalia and 8 the buttocks. The mean creatinine clearance was 86.6 (16.5) mL/min. Analysis of the PPS showed a tendency similar to that of the FAS, but none of the patients were younger than 30 years. The median age at onset was 29.0 years, which was higher than the age in the FAS of 15.0.

## Annual Number of Recurrences

The annual number of recurrences is shown in Figure 3. The mean number of recurrences in the first year of PIT was 2.8 (2.1), a significant reduction compared to 5.3 (2.9) prior to PIT initiation ($p < 0.001$) (Table 2). The number of recurrences in the second year and third year during PIT was also significantly reduced compared with that prior to PIT initiation ($p = 0.011$, 0.004) (Table 2). The results for the PPS were similar to those of the FAS (Table 2). The proportion of individuals whose rate of recurrence decreased from the first to the third year of PIT compared to before PIT was 86.0%, 76.2%, and 75.0%, respectively (Supplementary Table 1). There was no significant change in the number of recurrences between the first year and second year after PIT initiation ($p = 0.634$,) (Table 2). There was a negative association between the number of recurrences prior to PIT initiation and the change in the number of recurrences before

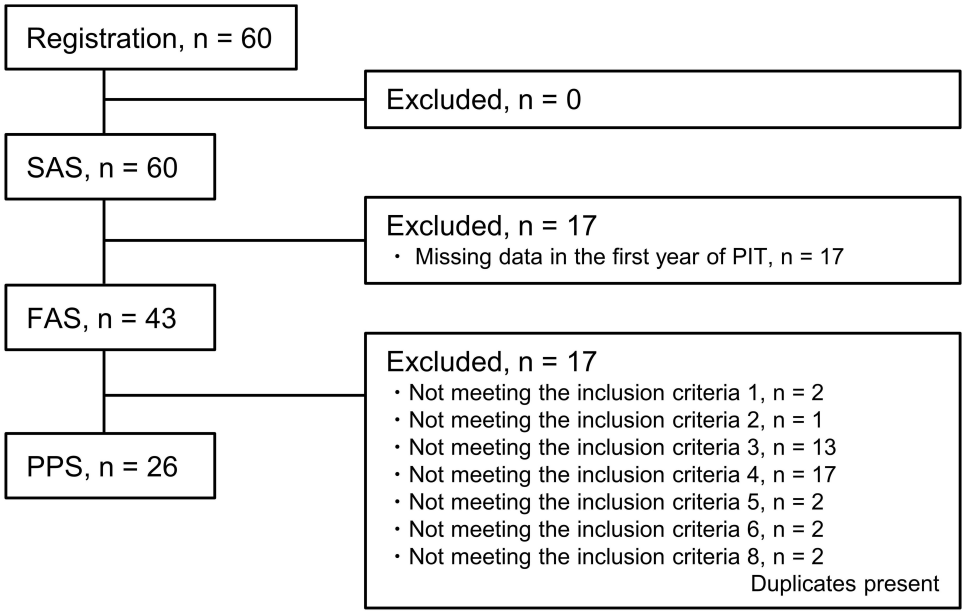


**Figure 2** Patient disposition.


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**Table 1** Patient Characteristics

| Characteristics | Summary Statistics | FAS (n = 43) | PPS (n = 26) |
|---|---|---|---|
| Age | Mean (SD)<br>Median (IQR)<br>< 30 years, n(%)<br>≥ 30 years < 50 years, n(%)<br>≥ 50 years, n(%) | 45.7 (15.6)<br>44.0 (37.0–53.0)<br>5 (11.6)<br>23 (53.5)<br>15 (34.9) | 50.5 (15.3)<br>47.0 (39.0–55.0)<br>0 (0.0)<br>16 (61.5)<br>10 (38.5) |
| Gender | Male, n(%)<br>Female, n(%) | 16 (37.2)<br>27 (62.8) | 8 (30.8)<br>18 (69.2) |
| Age at onset | Mean (SD)<br>Median (IQR) | 24.0 (18.3)<br>15.0 (10.0–34.0) | 29.6 (20.0)<br>29.0 (15.0–36.0) |
| Recurrences (number /year) | Mean (SD)<br>Median (IQR)<br>3–5 times, n(%)<br>6 times or more, n(%) | 5.3 (2.9)<br>5.0 (3.0–6.0)<br>30 (69.8)<br>13 (30.2) | 5.4 (2.9)<br>5.0 (3.0–6.0)<br>19 (73.1)<br>7 (26.9) |
| Disease duration in years | Mean (SD)<br>Median (IQR)<br>< 10 years, n(%)<br>≥ 10 years, n(%) | 21.5 (12.2)<br>22.0 (9.0–31.0)<br>11 (26.2)<br>31 (73.8) | 20.8 (12.6)<br>22.0 (8.0–31.0)<br>8 (32.0)<br>17 (68.0) |
| Site of lesion | Lips or face, n(%)<br>Genital or buttock, n(%)<br>Other, n(%) | 32 (74.4)<br>10 (23.3)<br>1 (2.3) | 18 (69.2)<br>8 (30.8)<br>0 (0.0) |
| CCr (mL/min) | Mean (SD) | 86.6 (16.5) | 84.2 (19.0) |

**Notes**: Recurrences (number / year), the number of recurrent prior to patient-initiated therapy; age at onset: age at onset of herpes simplex; Disease duration: difference in age from age of onset to date of enrollment.
**Abbreviations**: FAS, full analysis set; PPS, per protocol set; SD, standard deviation; IQR, interquartile range; Ccr, creatinine clearance.

and after PIT initiation, with a higher number of recurrences associated with a greater reduction in the number of recurrences (Supplementary Figure 2, $r = -0.723$, $p < 0.001$).

## Subgroup Analysis

The results of subgroup analysis in the FAS are shown in Table 3. A significant reduction in the number of recurrences was observed in the first year of PIT compared with prior to PIT initiation except in those subgroups with < 10–year morbidity or genital herpes. In the second and third year of PIT, compared with the period prior to PIT initiation, there was a significant reduction in recurrence among women, as well as in the group that experienced recurrence six times/year or more, those who had ≥ 10–year morbidity, and those with oral–facial herpes. Comparing the number of recurrences in the first year and the second year during PIT, the number of recurrences was significantly reduced in the group that had 6 or more recurrences before PIT.

## Questionnaire

The questionnaire–based survey administered to the PPS is shown in Table 4. Regarding adherence, three patients (11.5%) in the first year and one patient (7.1%) in the second year of PIT answered, “not on time”, but more than 80% of the patients selected “well maintained” or “almost complete” throughout the first to third year after the initiation of PIT.

In terms of convenience, all patients selected “very convenient” or “somewhat useful”. Regarding preference for treatment, all patients except for two (92.3%) in the first year selected “Receiving medicine beforehand and take oral

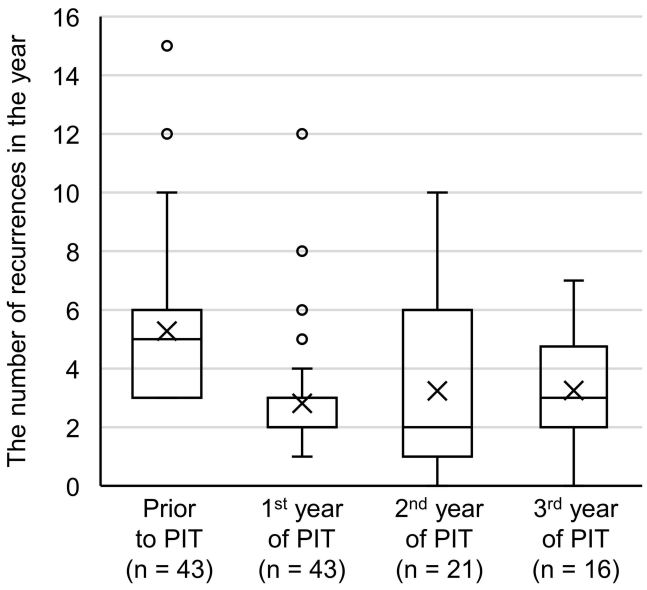


**Figure 3** Change in the number of recurrences per year (FAS) Box-and-whisker plot of the number of recurrences per year by assessment period.

administration twice a day as PIT". The results for the other items, the degree of severity, irritation and discomfort, and improvement in rash, were used to compare PIT and 5–day treatment (Supplementary Table 2). Although there was one patient who gave the negative answer "heal apparently slower" for improvement in rash, in reply to all questions, most patients answered that PIT was better than 5–day treatment.

## Safety

No adverse events were observed in the period prior to the initiation of PIT, and one event of cardiac disorder and palpitations was observed in one out of 60 patients (1.7%) included in the safety analysis during the period of PIT, but a causal relationship to the drug was ruled out.

**Table 2** Comparison of the Number of Recurrences per year Between Prior to PIT and During PIT

| Items | Prior to PIT | During PIT | | |
|---|---|---|---|---|
| | | 1st year | 2nd year | 3rd year |
| FAS | | | | |
| No. of patients | 43 | 43 | 21 | 16 |
| Recurrences, Mean no. (SD) | 5.3 (2.9) | 2.8 (2.1) | 3.2 (3.3) | 3.3 (1.9) |
| p-value (vs Prior to PIT) # | - | < 0.001** | 0.011* | 0.004** |
| p-value (vs 1st year of PIT) # | - | - | 0.634 | - |
| PPS | | | | |
| No. of patients | 26 | 26 | 17 | 13 |
| Recurrences, Mean no. (SD) | 5.4 (2.9) | 3.3 (2.5) | 3.2 (3.4) | 3.1 (2.0) |
| *p*-value (vs Prior to PIT) # | - | < 0.001** | 0.020* | 0.007** |
| *p*-value (vs 1st year of PIT) # | - | - | 0.445 | - |

**Notes**: #Paired *t*-test; *$p<0.05$; **$p<0.01$.
**Abbreviations**: PIT, patient-initiated therapy; FAS, full analysis set; SD, standard deviation; PPS, per protocol set.

**Table 3** Subgroup Analysis (FAS)

| Category | | | Prior to PIT | During PIT | | |
|---|---|---|---|---|---|---|
| | | | | 1st year | 2nd year | 3rd year |
| Age | < 30 years | No. of patients | 5 | 5 | 2 | 2 |
| | | Recurrences, Mean no. (SD) | 5.6 (2.7) | 2.0 (1.2) | 3.0 (2.8) | 4.0 (2.8) |
| | | *p* (vs Prior to PIT) # | – | 0.015* | 0.258 | 0.344 |
| | | *p* (vs 1st year of PIT) # | – | – | 1.000 | – |
| | ≥ 30 years | No. of patients | 23 | 23 | 12 | 9 |
| | < 50 years | Recurrences, Mean no. (SD) | 5.2 (2.7) | 2.4 (1.3) | 3.2 (3.2) | 3.2 (2.3) |
| | | *p* (vs Prior to PIT) # | – | <0.001** | 0.110 | 0.085 |
| | | *p* (vs 1st year of PIT) # | – | – | 0.777 | – |
| | Age ≥ 50 years | No. of patients | 15 | 15 | 7 | 5 |
| | | Recurrences, Mean no. (SD) | 5.3 (3.4) | 3.7 (2.9) | 3.4 (4.0) | 3.0 (1.0) |
| | | *p* (vs Prior to PIT) # | – | 0.049* | 0.151 | 0.083 |
| | | *p* (vs 1st year of PIT) # | – | – | 0.211 | – |
| Gender | Male | No. of patients | 16 | 16 | 5 | 5 |
| | | Recurrences, Mean no. (SD) | 4.8 (2.6) | 2.3 (0.9) | 3.4 (3.5) | 2.4 (2.7) |
| | | *p* (vs Prior to PIT) # | – | 0.001** | 0.697 | 0.294 |
| | | *p* (vs 1st year of PIT) # | – | – | 0.683 | – |
| | Female | No. of patients | 27 | 27 | 16 | 11 |
| | | Recurrences, Mean no. (SD) | 5.6 (3.1) | 3.1 (2.5) | 3.2 (3.3) | 3.6 (1.5) |
| | | *p* (vs Prior to PIT) # | – | <0.001** | 0.011* | 0.009** |
| | | *p* (vs 1st year of PIT) # | – | – | 0.406 | – |
| The number of recurrences | 3–5 times/year | No. of patients | 30 | 30 | 13 | 10 |
| | | Recurrences, Mean no. (SD) | 3.7 (0.9) | 2.3 (1.0) | 3.4 (3.3) | 2.9 (2.2) |
| | | *p* (vs Prior to PIT) # | – | <0.001** | 0.484 | 0.290 |
| | | *p* (vs 1st year of PIT) # | – | – | 0.397 | – |
| | 6 times/year or more | No. of patients | 13 | 13 | 8 | 6 |
| | | Recurrences, Mean no. (SD) | 8.8 (2.7) | 4.1 (3.1) | 3.0 (3.5) | 3.8 (1.5) |
| | | *p* (vs Prior to PIT) # | – | <0.001** | 0.004** | <0.001** |
| | | *p* (vs 1st year of PIT) # | – | – | 0.011* | – |
| Morbidity Term | < 10 years | No. of patients | 11 | 11 | 6 | 4 |
| | | Recurrences, Mean no. (SD) | 5.2 (2.2) | 3.5 (3.2) | 4.0 (4.0) | 2.8 (2.2) |
| | | *p* (vs Prior to PIT) # | – | 0.052 | 0.273 | 0.029* |
| | | *p* (vs 1st year of PIT) # | – | – | 0.272 | – |
| | ≥ 10 years | No. of patients | 31 | 31 | 15 | 12 |
| | | Recurrences, Mean no. (SD) | 5.4 (3.1) | 2.5 (1.5) | 2.9 (3.0) | 3.4 (1.9) |
| | | *p* (vs Prior to PIT) # | – | <0.001** | 0.028* | 0.046* |
| | | *p* (vs 1st year of PIT) # | – | – | 0.929 | – |
| Site of lesion | Lips or face | No. of patients | 32 | 32 | 15 | 12 |
| | | Recurrences, Mean no. (SD) | 4.6 (2.1) | 2.2 (0.9) | 2.3 (2.4) | 2.8(1.8) |
| | | *p* (vs Prior to PIT) # | – | <0.001** | 0.005** | 0.011* |
| | | *p* (vs 1st year of PIT) # | – | – | 0.649 | – |
| | Genital or buttock | No. of patients | 10 | 10 | 6 | 4 |
| | | Recurrences, Mean no. (SD) | 6.7 (3.8) | 4.8 (3.4) | 5.7 (4.0) | 4.8 (1.7) |
| | | *p* (vs Prior to PIT)# | – | 0.112 | 0.569 | 0.238 |
| | | *p* (vs 1st year of PIT)# | – | – | 0.844 | – |

**Notes**: #Paired *t*-test; *$p<0.05$; **$p<0.01$.

**Abbreviations**: PIT, patient-initiated therapy; FAS, full analysis set; SD, standard deviation.

**Table 4** Questionnaire Results: Adherence, Convenience, and Preference (PPS)

| Question item | Alternative | During PIT | | |
|---|---|---|---|---|
| | | 1st year | 2nd year | 3rd year |
| | | N = 26 | N = 14 | N = 8 |
| | | Number of responses (%) | | |
| Adherence* | Well maintained | 12 (46.2) | 7 (50.0) | 3 (37.5) |
| | Almost complete | 10 (38.5) | 5 (35.7) | 5 (62.5) |
| | Unable to take at the appropriate timing | 3 (11.5) | 1 (7.1) | 0 (0.0) |
| | Sometimes not have on hand | 2 (7.7) | 2 (14.3) | 0 (0.0) |
| | Gradually improving | 1 (3.8) | 0 (0.0) | 1 (12.5) |
| Convenience (vs 5-day treatment) | Very convenient | 21 (80.8) | 9 (64.3) | 6 (75.0) |
| | Somewhat useful | 5 (19.2) | 5 (35.7) | 2 (25.0) |
| | Not very different | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | I do not find it very useful | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | I'd like to return to the 5-day treatment | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Preference | Take oral administration twice a day for 5 days after visiting for symptoms | 2 (7.7) | 2 (14.3) | 1 (12.5) |
| | Take oral administration three times a day for 5 days after visiting for symptoms | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Take oral administration five times a day for 5 days after visiting for symptoms | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Receiving medicine beforehand and take oral administration twice a day as PIT | 24 (92.3) | 12 (85.7) | 7 (87.5) |

**Notes**: *Multiple responses were accepted.
**Abbreviations**: PPS, per protocol set; PIT, patient-initiated therapy.

## Discussion

This study evaluated the impact of switching from 5–day treatment with antiviral drugs to PIT with famciclovir on the annual recurrence frequency of herpes simplex in real–world clinical practice. For the primary endpoint, the number of recurrences during the first year of PIT was significantly reduced compared to before PIT initiation, with 37 of 43 patients (86.0%) experiencing a decrease in recurrence frequency. The recurrence frequency was also significantly reduced in the second and third years after PIT initiation for sensitivity analysis, suggesting that switching from conventional treatment such as 5–day treatment to PIT may reduce the rate of recurrence in recurrent herpes simplex. The characteristic feature of PIT is that patients can take a high dose of medication promptly upon recognizing the initial symptoms. Since the clinical effectiveness of antiviral drugs is generally influenced by the timing of administration, PIT, which allows for early treatment initiation, is considered an important treatment option.

The primary efficacy analysis targeted the FAS, excluding 17 cases from the SAS for which efficacy data could not be obtained. Most cases excluded from the PPS did not meet inclusion criteria 3 or 4, had an unclear treatment history before enrollment, or had not continued 5–day treatment for one year. Therefore, the PPS was defined as a population that had continued 5–day treatment for one year before enrollment. A significant reduction in the number of recurrences before and after PIT initiation was observed not only in the FAS but also in the PPS. A study that observed the recurrence frequency of genital herpes patients over the past five years showed that, in the group with primary infection, the recurrence rates decreased from the first to the second year, whereas in the recurrent infection group, no such decrease was observed.[29] However, by the fifth year, both groups showed a reduction in recurrence rates. In clinical practice, there are patients who suffer from frequent recurrences over long periods. In the present study, 73.8% of the patients had a history of herpes for more than 10 years, and a decrease in recurrence rates was observed immediately after switching to PIT. Furthermore, in patients who showed a reduction in recurrence rates, it was confirmed during clinical visits that they themselves recognized a decrease in the number of recurrences. Considering these points, this study is valuable in that it presents a different perspective from previous reports suggesting a decrease in the frequency of recurrences.[29–31]

A strong correlation was observed between the number of recurrences before PIT initiation and the reduction in the number of recurrences during the first year of PIT, suggesting that PIT may be more effective in patients who experience

a higher number of recurrences. Additionally, subgroup analysis showed that in the group with six or more recurrences in the year preceding PIT, the number of recurrences significantly decreased across all three years after PIT initiation. In Japan, it has been reported that approximately 6% of patients with recurrent labial or facial herpes and about 27% of patients with genital herpes experience six or more recurrences per year.[6] Therefore, PIT is considered a particularly useful treatment option for those with a high frequency of recurrence.

In a survey on treatment content and effectiveness after PIT initiation, compared to the previous 5–day treatment, most patients reported better outcomes with PIT in terms of degree of severity, irritation and discomfort, and improvement in rash. Regarding treatment preference, it was found that approximately 90% of patients preferred PIT. On the other hand, a small number of patients responded that they were unable to take the medication at the appropriate timing or did not have the medication on hand when needed. These patients preferred the 5–day treatment due to concerns about medication adherence. For such cases, it is important for physicians to carefully interview patients about the reasons for difficulties in taking medication at the appropriate timing and provide appropriate guidance to improve adherence such as using a case for carrying medicines.

The results of this study suggest that PIT enables patients to initiate treatment more quickly than conventional 5–day treatment through self–management, thereby promptly suppressing viral replication, preventing progression to severe symptoms, and reducing the frequency of recurrence. Additionally, considering that PIT has been found to be superior in terms of convenience and patient preference compared to 5–day treatment, it is expected to be a promising new approach for reducing the frequency of recurrence in labial and genital herpes.

## Limitation

This study has several limitations. First, the recurrence rate before the initiation of PIT was higher than previously reported,[32] and it is also possible that, for each individual, the recurrence rate happened to be high by chance in that particular year. Since recurrence frequency is influenced by fatigue and stress related to various life events, the number of recurrences can vary from year to year. One report has suggested that when cases with higher recurrence rates than the general population are gathered, their subsequent recurrence rates may appear to decline due to regression to the mean.[31] To address this issue, it is necessary to observe not only the period after PIT initiation but also the period prior to PIT over multiple years.

Second, as a single–center, chart–based study, the number of subjects was limited, and validation through prospective, multi–center studies is necessary for generalization.

Third, the evaluation of recurrence frequency and symptoms relied on patient self–reported outcomes, highlighting the need for more objective assessments.

Finally, it has been reported that the amount of latent virus at the time of primary infection is a significant factor influencing the frequency of reactivation the host experiences going forward.[33] However, this study did not conduct a detailed evaluation supported by measurements of latent viral load.

## Conclusion

The results of this study suggest that PIT with famciclovir may contribute to a reduction in recurrence frequency compared to 5–day treatment. Additionally, its usefulness from a patient perspective was demonstrated in terms of symptom severity, improvement, adherence, and patient preference. Furthermore, since no safety concerns were identified, the findings indicate that PIT should be considered for first–line treatment in Japan, as recommended in foreign guidelines.

## Abbreviations

BID, bis in die; CRF, case report form; FAS, full analysis set; HSV, herpes simplex virus; PPS, per protocol set; PIT, patient-initiated therapy; RHS, recurrent herpes simplex; SAS, safety analysis set.

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