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ORIGINAL RESEARCH

A 1-Year Survey of Zoster-Associated Pain after Amenamevir Treatment

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ABSTRACT

Introduction: Amenamevir is a new anti-varicella-zoster virus drug that inhibits the helicase–primase complex involved in viral replication. Amenamevir has the same effect as valaciclovir on acute pain and skin eruption, but no studies have examined the presence of long-term zoster-associated pain (ZAP) or postherpetic neuralgia (PHN) after amenamevir treatment.

Methods: A total of 785 herpes zoster patients treated with amenamevir were followed up for 12 months. Patients recorded their pain status on a questionnaire once a month.

Results: The proportion of patients with pain was 20.8% at 90 days, 8.0% at 180 days, 3.8% at 270 days, and 2.7% at 360 days after treatment. The median residual pain duration was 48 days. ZAP resolution rate slowed between 90 and 120 days, suggesting that the main feature of ZAP is a shift from nociceptive pain to neuropathic pain. Older age and more severe skin symptoms at the first visit were associated with a higher risk of developing PHN. Median ZAP duration was high for the head, face, and upper back and chest. Regarding the nature of pain, sudden pain attacks that felt like electric shocks, sensation of numbness, burning sensation, and cold/heat pain tended to remain as PHN.

Conclusions: Although conclusions must remain tentative without further comparative studies, amenamevir seems to have a similar effect on PHN as conventional nucleoside analogs, despite having a different action mechanism.

Clinical Trial Registration: UMIN000035938.

Keywords: Amenamevir; Postherpetic neuralgia; Zoster-associated pain; 12-Month survey

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13555-022-00727-9.

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Key Summary Points

Why carry out this study?

A previous clinical trial showed that amenamevir effectively treats acute pain in Japanese patients with herpes zoster.

Zoster-associated pain (ZAP) and neuropathic pain changes over time during the transition from acute to prolonged pain have not been fully examined.

What was learned from the study?

Amenamevir is an anti-varicella-zoster virus drug that has a novel action mechanism and is a helicase–primase inhibitor.

Patients with residual pain after treatment with amenamevir were more likely to be older and to have more severe eruption at the start of treatment.

Although not directly comparable, the course of ZAP and postherpetic neuralgia (PHN) after amenamevir treatment was similar to that for previous treatments such as conventional nucleoside analogs.

INTRODUCTION

Several nucleoside analogs that inhibit the replication of the varicella-zoster virus (VZV) have been developed to treat herpes zoster, and their effectiveness for skin symptoms has been well evaluated. However, there is insufficient evidence for the effectiveness of these treatments for acute pain and postherpetic neuralgia (PHN), which are collectively termed zoster-associated pain (ZAP).

Amenamevir (Amenalief; Maruho Co., Ltd., Osaka, Japan) exerts an antiviral effect by inhibiting the activity of helicase–primase, an enzyme involved in VZV DNA replication [1]. This mechanism of action differs from that of conventional nucleoside analogs. Amenamevir shows greater antiviral activity against VZV than aciclovir [1]. One comparative study that compared amenamevir and valaciclovir showed that they had the same effect on acute pain and skin eruption [2, 3]; however, no studies have conducted long-term patient follow-ups of ZAP and PHN after amenamevir treatment.

Therefore, we conducted a 12-month survey of ZAP in patients with herpes zoster treated with amenamevir. In this paper, we report the results from 785 of 1021 patients who received amenamevir treatment and for whom we were able to confirm the resolution of pain or investigate ZAP for 12 months or longer.

METHODS

Patients

The inclusion criteria were patients with herpes zoster aged 20 years or older who were prescribed Amenalief. Patients who were selected for treatment with amenamevir after herpes zoster diagnosis were given an explanation of the study and of informed consent. Patients whose consent was obtained were asked to participate in a questionnaire survey. The exclusion criteria were patients with complications (such as cognitive disease or back pain) that prevent accurate assessment of ZAP and PHN, and patients deemed inappropriate for participation by the attending physician owing to complications that necessitated additional systemic treatments (e.g., meningitis, Hunt syndrome, keratitis, severe generalized herpes zoster). If such complications were confirmed, they were excluded because additional treatments were required or the pain could not be assessed accurately.

Study Design

This was a prospective, observational, multicenter study that was conducted from December 2018 to December 2020 at 48 dermatology institutions. Patients who visited the outpatient clinic and were diagnosed with herpes zoster on

medical examination, and who received amenamevir and were able to attend the outpatient clinic, were included in the study.

Amenamevir was administered at an ordinary dosage of 400 mg once daily for 7 days, as recommended. The duration of amenamevir treatment was < 2 days for 1 case (0.1%), 3–-6 days for 24 cases (3.1%), 7 days for 748 cases (95.3%), and > 8 days for 12 cases (1.5%). The start of this observational study was after medication completion. The end of the study was defined as complete resolution of pain or 1 year from beginning of follow-up. We evaluated changes in ZAP over 1 year. The required number of cases was calculated as 724, in accordance with a previous study [4]. Assuming a dropout rate of approximately 30% owing to the mail questionnaire survey design, the target number of registered cases was set at 1000.

The attending doctor recorded each patient's background, the nature of the eruption at the time of diagnosis, and the current state of pain on the first examination day, at each subsequent visit, and at the last visit. After outpatient treatment, patients completed a mailed questionnaire survey form at home. Patients recorded their pain status on the survey form, which was mailed from the research secretariat once a month, and returned the form by mail. The study was scheduled to continue for 12 months regardless of whether patients experienced pain. The questionnaire survey form used was the Japanese version of the painDETECT [5], which assesses the level of pain (numerical rating scale (NRS) score), course of the pain, and nature of the pain.

Ethical Issues

This study was reviewed and approved by the institutional review board of the NPO Health Institute Research of Skin (committee no. 19000025), and it allowed all institutions to participate in. This study was performed in accordance with the ethical principles of the Declaration of Helsinki and the ethical guidelines for medical research on humans. The study was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry. Written informed consent was obtained from all participants.

Survey Items

Sex, age, medical history, and complications were recorded to assess patients' background characteristics. Skin symptoms were investigated at the start of the study according to the day of onset, severity of eruption, and site of onset. Skin lesion severity was considered mild if the lesions comprised 1/3 or less of the involved innervated area, moderate if 1/3 to 2/3 of the area was involved, and severe if $\geq$ 2/3 of the area was involved. Concomitant medications and pain therapies at the first visit were also recorded.

Pain level was evaluated by the attending doctor according to the patient's assessment during outpatient treatment, and was evaluated by the patient at home using an NRS score range of 0–10. The nature of the pain was investigated using the Japanese version of the painDETECT questionnaire. Overall pain was evaluated, regardless of the location or type of pain. Possible responses on the painDETECT questionnaire are "never," "hardly noticed," "slightly," "moderately," "strongly," and "very strongly." Patients with responses of "slightly," "moderately," "strongly," and "very strongly" were considered to be experiencing pain. To evaluate changes in patients' pain over the course of the study, the proportion of patients with pain was determined using Kaplan–Meier estimation. Changes in NRS score over time and residual pain duration were also determined.

Furthermore, changes in pain were evaluated for a subpopulation stratified by age, eruption severity, level and nature of the pain, and site of onset. We also evaluated changes in pain by the number of days from the onset of herpes zoster to the start of treatment. The date of ZAP resolution was defined as the first study day with two consecutive NRS scores of 0.

Safety was assessed by recording the occurrence of adverse events during outpatient treatment. Adverse events were defined as any undesired or unintended signs, symptoms, or illnesses that occurred between provision of

consent and finishing the medication, regardless of whether there was a causal relationship between the adverse event and the therapeutic drug.

We excluded patients who failed to complete all questionnaires or who withdrew consent. Among the evaluation target population, we analyzed data for subpopulations stratified by age, level of pain, eruption severity, involved site, and nature of the pain. The significance level in the comparative (two-tailed) tests was 5%, and test multiplicity was not considered. We used the analysis software JMP, version 14.3.0 (SAS Institute, Cary, NC, USA). Missing value imputation was not performed.

The median residual ZAP time and 95% confidence interval were calculated using Kaplan–Meier estimates, with pain resolution as an event. The number of residual cases and the proportion of patients with pain at 90, 180, 270, and 360 days after treatment initiation were determined.

We analyzed changes in NRS score over time in the evaluation target group. Pain level was categorized according to NRS scores of 0, 1–3, 4–6, and 7–10. Scores were obtained at the first visit, after finishing amenamevir therapy, and at each questionnaire collection. If duplicate questionnaires were collected within the same aggregation time, the questionnaire with the date closer to the aggregation time was used. In addition, data from the questionnaires collected over 360 days were included in the total at the end of 1 year.

The subpopulations were stratified according to age, the period from onset to the start of amenamevir treatment (0–2 days, 3–5 days, and $\geq$ 6 days), rash severity at onset (mild, moderate, and severe), and NRS scores, as described above.

We also created subpopulations according to the nature of the pain that each patient experienced at the start of treatment. The number of residual cases and the proportion of patients with pain 90, 180, 270, and 360 days after treatment initiation were analyzed.

To evaluate pain by onset site, a subpopulation was created for each herpes zoster onset site, and the number of patients with residual pain and the proportion of patients with pain 90, 180, 270, and 360 days after treatment initiation were determined.

The safety evaluation comprised analyzing the number and incidence rate of adverse events for which an association with amenamevir could not be ruled out.

RESULTS

Patients' Composition and Background Characteristics

Figure 1 shows the flow of study participants. There were 1021 enrolled cases. After excluding patients who withdrew consent, 954 eligible patients remained. In this study, pain resolution was defined as two consecutive NRS scores of 0. We were unable to obtain pain assessment responses for 169 patients, so these patients were excluded from the analysis. A final total of 785 patients confirmed resolution of pain or completed observation for 12 months or longer.

Patients' background characteristics and herpes zoster-related information are presented in Table 1. The 785 patients surveyed comprised 314 males (40.0%) and 471 females (60.0%); most were in their sixties (22.5%), and the median age was 56 years. The period from onset of herpes zoster to treatment initiation was within 2 days for 33.2%, 3–5 days for 42.5%, and $\geq$ 6 days for 24.2%. The severity of eruption was mild in 53.9% of participants, moderate in 39.1%, and severe in 7.0%. Regarding the level of pain, 4.6% of participants had NRS scores of 0, 40.9% had scores of 1–3, 31.7% had scores of 4–6, and 22.8% had scores $\geq$ 7. Regarding the nature of the pain, a tingling or prickling sensation was most common (78.0%). The site of onset was the upper back for 28.3% of participants and the lower back and abdomen for 23.4%. In terms of skin symptoms, erythema/papules were observed in 83.6% of participants and blisters/pustules in 71.3%.

Changes in NRS Scores over Time

NRS scores were categorized into three groups: 1–3, 4–6, and 7–10. Scores were obtained at the

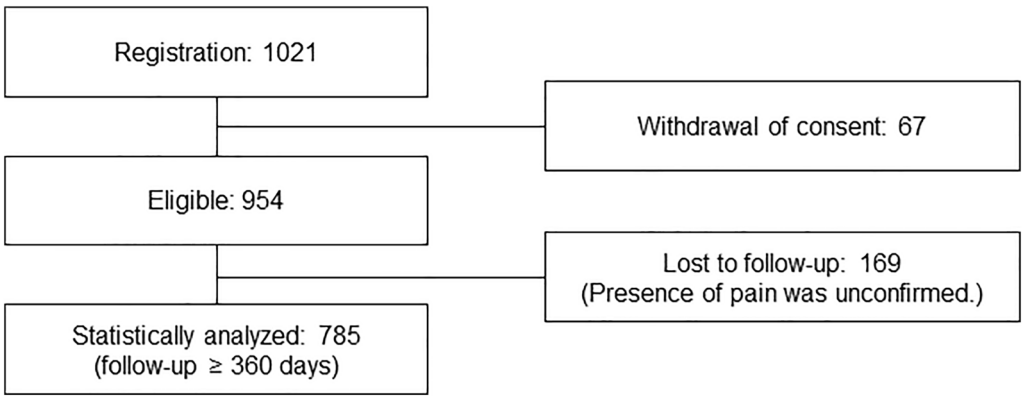


Fig. 1 Patient flow diagram

first visit, after finishing the medication, and every 30 days thereafter. Pain rate changes are shown in Fig. 2. At the start of treatment, more than 50% of patients had severe (NRS: 7–10) pain or moderate (NRS: 4–6) pain; however, these pain scores declined over time, and after 90 days, the pain had almost resolved. In contrast, pain in the NRS 1–3 group declined gradually to 2.7% by 360 days.

ZAP Duration and Rate in the Stratified Subpopulations

Figure 3 shows the proportion of patients with pain and its change over time. The median duration of pain was 48 days. The residual pain duration and proportion of patients with pain stratified by age were also examined. A stratified analysis was conducted to compare patients aged < 50 years and ≥ 50 years. The median residual pain duration was 29.5 days for patients aged < 50 years and 52 days for those aged ≥ 50 years. A significant difference was observed between patients aged < 50 and ≥ 50 years.

The period from the onset of herpes zoster symptoms to treatment initiation was stratified into three groups: within 2 days, within 3–-5 days, and ≥ 6 days from symptom onset. The changes over time are shown in Fig. 4. The median pain duration was 50 days in the within 2 days group, 47.5 days in the within 3–5 days group, and 44 days in the ≥ 6 days group. There were no differences between the groups.

Residual pain duration and the proportion of patients with pain stratified by eruption severity were categorized into mild, moderate, and severe groups. The associated changes over time are shown in Supplementary Fig. S1. The median residual pain duration was 31 days for mild cases, 50 days for moderate cases, and 141 days for severe cases, showing a clear difference. There was no difference between mild and moderate cases, but there was a significant difference between mild or moderate and severe cases, demonstrating a high residual frequency of pain in severe cases of rash.

Pain level at the first visit was stratified into four NRS score ranges: 0, 1–3, 4–6, and 7–10. The associated changes in the proportion of patients with pain are shown in Fig. 5. Of the 36 patients with NRS scores of 0 at the time of diagnosis, some developed pain after amenamevir treatment. The median pain duration was 12 days for the 0 group, 32 days for the 1–3 group, 51 days for the 4–6 group, and 57 days for the 7–10 group. Pain reduction tended to be slower in the NRS 7–10 group, but there was no difference between the three groups after 360 days.

Table 2 shows the residual pain duration and the proportion of patients with pain stratified by onset site. The median pain duration was 52 days for the head and 51.5 days for the face and upper back, but there was almost no difference between the areas. At 360 days after the start of treatment, the residual rate did not differ according to onset site; the highest rate was for the lower back and abdomen at 3.8%,

Table 1 Patients' baseline demographics and characteristics

	Male		Female		Total	
	n	%	*n*	%	*n*	%
Age (years)	314	40.0	471	60.0	785	100
20–29	19	2.4	32	4.1	51	6.5
30–39	50	6.4	54	6.9	104	13.2
40–49	57	7.3	72	9.2	129	16.4
50–59	60	7.6	100	12.7	160	20.4
60–69	66	8.4	111	14.1	177	22.5
70–79	48	6.1	83	10.6	131	16.7
≥ 80	14	1.8	19	2.4	33	4.2
Median (range) age: 56 (20–95) years						

Clinical feature	*n*	%
Interval between rash onset and start of treatment (days)		
≤ 2	261	33.2
3–5	334	42.5
≥ 6	190	24.2
Severity of eruption		
Mild	423	53.9
Moderate	307	39.1
Severe	55	7.0
Duration of amenamevir treatment (days)		
≤ 2	1	0.1
3–6	24	3.1
7	748	95.3
≥ 8	12	1.5
NRS		
0	36	4.6
1–3	321	40.9
4–6	249	31.7
7–10	179	22.8
Nature of pain		
Burning sensation	436	55.5
Tingling or prickling sensations	612	78.0

Table 1 continued

Clinical feature	*n*	%
Pain upon light touch	541	68.9
Sudden pain attacks that felt like electric shocks	204	26.0
Cold/heat pain	149	19.0
Sensation of numbness	186	23.7
Slight pressure-triggered pain	520	66.2
Onset site		
Head	76	9.7
Face	114	14.5
Neck	44	5.6
Upper back and chest	222	28.3
Upper extremities	81	10.3
Lower back and abdomen	184	23.4
Lumbar pelvic	141	18.0
Lower extremities	120	15.3
Skin symptoms		
No skin symptoms	4	0.5
Erythema/papules	656	83.6
Blisters/pustules	560	71.3
Erosions/ulcers	53	6.8
Crusting	52	6.6

NRS numerical rating scale

followed by the upper back at 3.6%. In addition, nearly 70% of patients who had residual pain after 90 days reported that "pain sometimes became paroxysmal" and that they were "otherwise painless" (data not shown). Table 3 presents the residual pain duration and proportion of patients with pain stratified by the nature of the pain at the first visit. Long-duration median residual pain was reported as sudden pain attacks that felt like electric shocks (55.5 days), sensation of numbness (54 days), burning sensation (52 days), and cold/heat pain (52 days). At 360 days after treatment initiation, sensation of numbness was reported most frequently, at 3.2%, with all other types of pain reported at a rate of < 3%.

Concomitant Medications and Concomitant Therapies

Supplementary Table S1 presents the drugs for the treatment of herpes zoster used in combination during outpatient treatment. Of patients, 34.4% received mecobalamin/

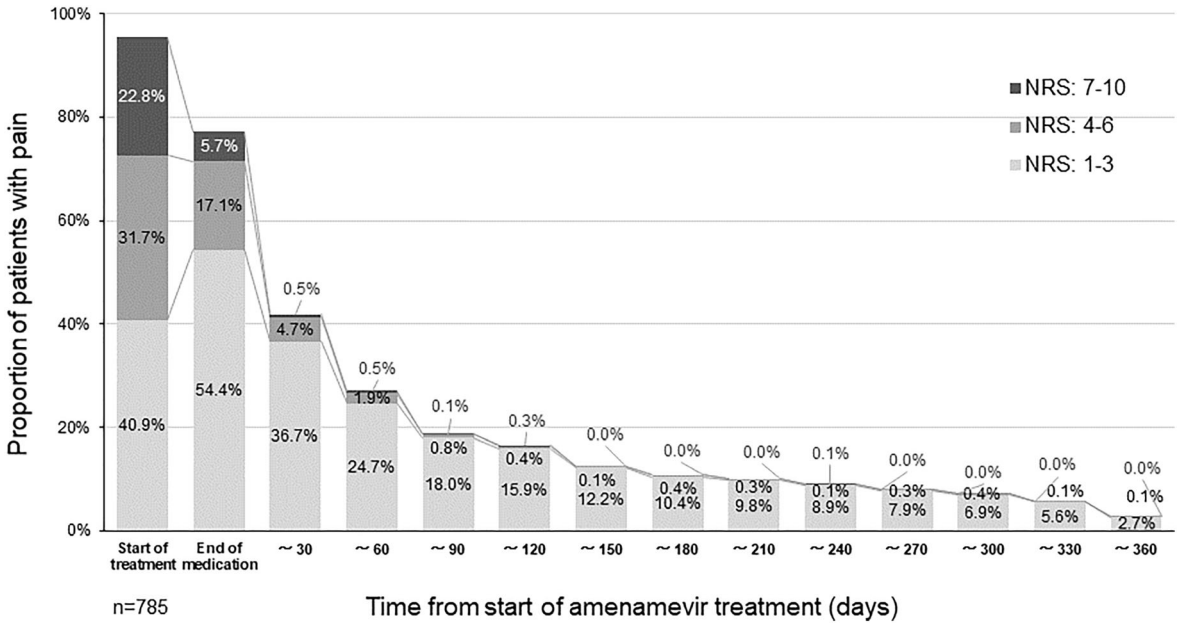
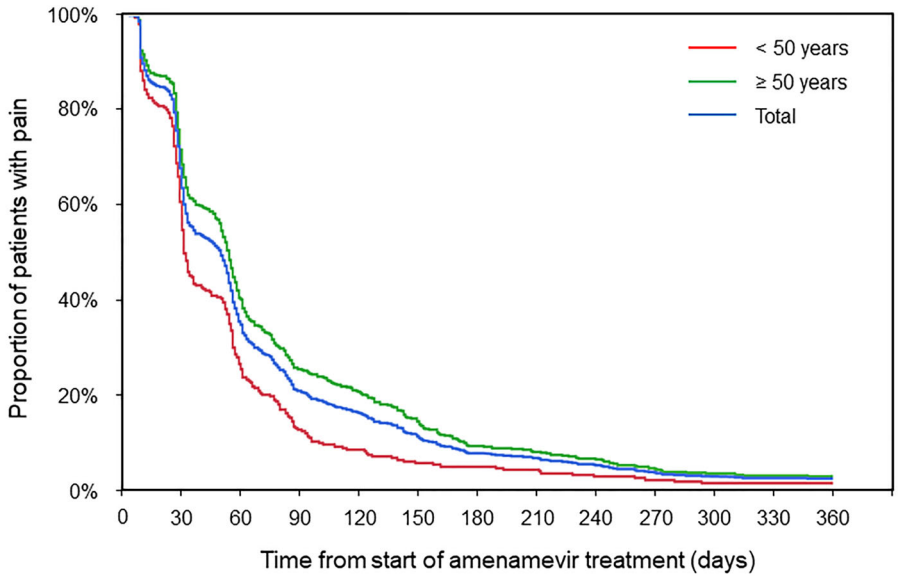


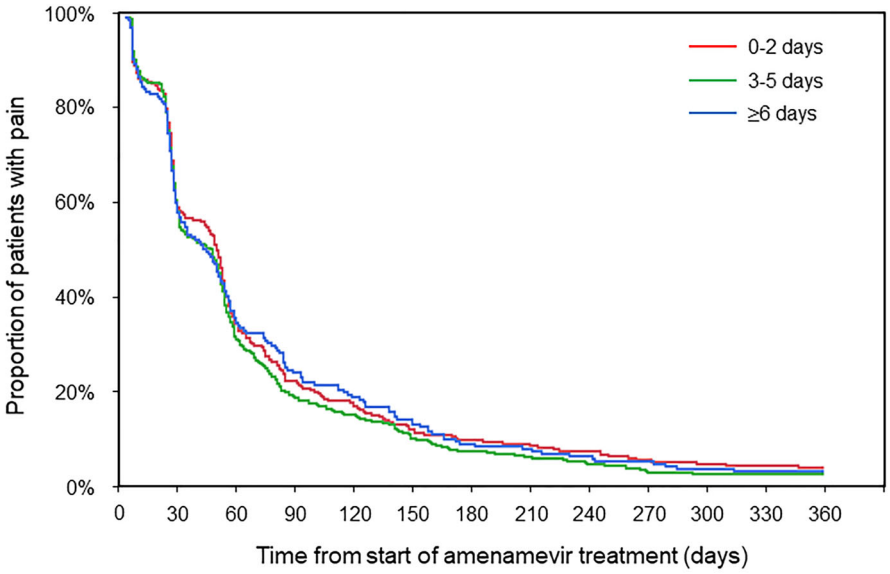
Fig. 2 Proportion of patients with pain in the three different NRS categories. *NRS* numerical rating scale



Residual pain duration (days)			
Age	n	Median	95% CI
Total	785	48	(39-51)
< 50 years	284	29.5	(28-34)
≥ 50 years	501	52	(49-54)
Log-rank	P<0.0001		
Wilcoxon	P<0.0001		

Proportion of patients with pain (%)			
90 days	180 days	270 days	360 days
20.8	8.0	3.8	2.7
12.7	5.3	2.5	1.8
25.4	9.6	4.6	3.2

Fig. 3 Proportion of patients with pain after amenamevir treatment during the 360-day follow-up according to age (red line: < 50 years, green line: ≥ 50, blue line: total). *CI* confidence interval



Residual pain duration (days)

Initiation of therapy	n	Median	95% CI
0-2 days	261	50	(42-53)
3-5 days	334	47.5	(31-52)
≥6 days	190	44	(31-53)
Total	785		

Log-rank P=0.4716
Wilcoxon P=0.7707

Proportion of patients with pain (%)

90 days	180 days	270 days	360 days
21.8	9.2	5.0	3.5
18.3	6.9	2.4	2.1
23.7	8.4	4.7	2.6

Fig. 4 Proportion of patients with pain after amenamevir treatment during the 360-day follow-up according to the timing of initiation of therapy (red line: 0–2 days, green line: 3–5 days, blue line: ≥ 6 days). *CI* confidence interval

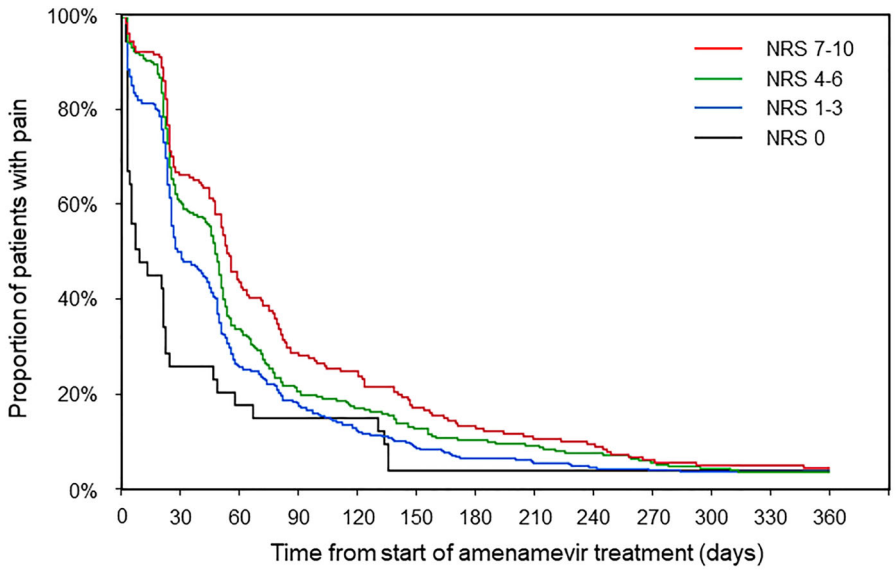
peripheral neuropathy therapeutic agents, 30.7% received acetaminophen/antipyretic analgesic, 26.1% received loxoprofen/oral nonsteroidal antiinflammatory drugs (NSAIDs), and 15.9% received vidarabine/anti-herpes virus external preparation. Acetaminophen was widely used regardless of pain level and rash severity, but loxoprofen or naproxen was prescribed more frequently as pain intensity or rash severity increased.

Safety Evaluation

Four patients experienced adverse events for which an association with amenamevir could not be ruled out (seven events: diarrhea, headache, general malaise, cold limbs, limb weakness, numbness, and light-headedness). The frequency of adverse events was 0.42%, and none of the events were serious. In all four cases, the outcome was judged to be recovery or no need for follow-up.

DISCUSSION

In this 12-month prospective observational study, we investigated ZAP in 785 patients with herpes zoster who were followed up for more than 1 year after treatment with amenamevir. In preparation for the study, we published an interim report of data to 6 months after the start of treatment [6]. In the study, the first survey date with two consecutive NRS scores of 0 was set as the pain resolution date. Therefore, according to the information collected at 6 months, cases that did not meet the definition of pain resolution were treated as nonresolution of pain. Additionally, there was a delay of approximately 1–2 months in obtaining the patients' questionnaires. Thus, the number of patients with residual ZAP and the residual rate were slightly higher in the interim report than in this report. However, because the trend was similar, the present paper reports the results for the final 785 cases.



Residual pain duration (days)

NRS	n	Median	95% CI
7-10	179	57	(51-64)
4-6	249	51	(46-54)
1-3	321	32	(29-45)
0	36	12	(7-25)
Total	785		
Log-rank	P<0.0001		
Wilcoxon	P<0.0001		

Residual pain rate (%)

90 days	180 days	270 days	360 days
27.9	12.3	5.0	3.4
20.9	9.2	4.4	2.4
17.5	5.3	2.8	2.5
13.9	1.1	0.3	0.3

Fig. 5 Proportion of patients with pain after amenamevir treatment during the 360-day follow-up according to four NRS categories. *CI* confidence interval, *NRS* numerical rating scale

The median time to pain resolution in all cases was 48 days, and the proportion of patients with pain 90, 180, and 360 days after the start of treatment was 20.8%, 8.0%, and 2.7%, respectively. The number of patients who experienced pain resolution decreased after 90 days. Regarding the level of pain intensity, more than half of patients experienced pain and had NRS scores ≥ 4 at the start of amenamevir treatment; however, this proportion reduced rapidly after treatment, and almost no patients had NRS pain scores ≥ 4 after 90 days. In addition, nearly 70% of patients who had residual pain after 90 days reported that "pain sometimes became paroxysmal and otherwise painless." These findings may indicate that the change from persistent pain in the acute phase to PHN occurred approximately 90 days after treatment initiation. Most clinical studies on drugs for PHN have been carried out in patients with pain remaining at 3 months after the onset of herpes zoster [2, 4]. Our finding supports the validity of this target selection.

In a survey of famciclovir-treated patients conducted by Imafuku et al. [4], the proportion of patients with pain 90, 180, and 360 days after the start of treatment was 12.4%, 7.1%, and 4.0%, respectively. In our study, the rate after amenamevir treatment was slightly higher (20.8%) after 90 days but slightly lower (2.7%) after 360 days. Imafuku et al. assessed pain through regular telephone interviews; however, in the present study, the first survey date with two consecutive NRS scores of 0 was set as the pain resolution date. This may have led to resolution being evaluated up to 1 month later than the true resolution date. Furthermore, 4.6% of the patients in this study had an initial pain NRS score of 0, whereas more than 20% of the patients investigated by Imafuku et al. had no pain or negligible pain. This suggests that the level of initial pain also affected the proportion of patients with persistent pain. The

Table 2 Residual pain duration and proportion of patients with pain by onset site

Onset site	Residual pain duration (days)			Proportion of patients with pain, *n* (%)			
	n	Median	95% CI	90 days	180 days	270 days	360 days
Head	76	52	(31–57)	15 (19.7)	5 (6.6)	3 (4.0)	1 (1.3)
Face	114	51.5	(31–57)	29 (25.4)	10 (8.8)	4 (3.5)	2 (1.8)
Neck	44	49	(29–58)	6 (13.6)	4 (9.1)	4 (9.1)	1 (2.3)
Upper back and chest	222	51.5	(47–56)	53 (23.9)	20 (9.0)	12 (5.4)	8 (3.6)
Upper extremities	81	49	(29–54)	19 (23.5)	7 (8.6)	2 (2.5)	2 (2.5)
Lower back and abdomen	184	48	(31–53)	36 (19.6)	17 (9.2)	8 (4.4)	7 (3.8)
Lumbar pelvic	141	48	(39–51)	30 (21.3)	13 (9.2)	5 (3.6)	4 (2.8)
Lower extremities	120	45.5	(28–52)	24 (20.0)	8 (6.7)	2 (1.7)	1 (0.8)
Total	785						

CI confidence interval

Table 3 Residual pain duration and proportion of patients with pain according to the nature of pain at the first visit

Nature of pain	Residual pain duration (days)			Proportion of patients with pain, *n* (%)			
	n	Median	95% CI	90 days	180 days	270 days	360 days
Burning sensation	436	52	(50–54)	98 (22.5)	42 (9.6)	17 (3.9)	11 (2.5)
Tingling or prickling sensations	612	51	(47–52)	137 (22.4)	52 (8.5)	24 (3.9)	16 (2.6)
Pain upon light touch	541	50	(43–52)	111 (20.5)	48 (8.9)	21 (3.9)	14 (2.6)
Sudden pain attacks that felt like electric shocks	204	55.5	(52–60)	47 (23.0)	24 (11.8)	9 (4.4)	5 (2.5)
Cold/heat pain	149	52	(40–57)	37 (24.8)	12 (8.1)	7 (4.7)	4 (2.7)
Sensation of numbness	186	54	(50–59)	56 (30.1)	21 (11.3)	8 (4.3)	6 (3.2)
Slight pressure-triggered pain	520	49	(39–52)	111 (21.4)	43 (8.3)	18 (3.5)	11 (2.1)
Total	785						

CI confidence interval

slightly low proportion of patients with pain after 360 days in the present study may have contributed to the assumed effect of amenamevir in suppressing the transition to PHN; however, this was impossible to confirm from our results. A comparative study matching the level of pain, the patient's background (e.g., the presence or absence of underlying disease), and the timing of treatment initiation is needed to examine differences in the incidence of PHN according to the therapeutic agent.

Regarding the number of days from symptom onset to treatment initiation, Imafuku et al. reported that the proportion of patients with pain 90 days after the start of treatment was high in the group treated within 2 days

after onset. This is because more severe symptoms of herpes zoster or ZAP were associated with earlier visits. This tendency was also observed in our study; however, there was no significant difference in the proportion of patients with pain according to the number of days until treatment initiation. Compared with valaciclovir, amenamevir has a higher rate of arrest of new eruption within 24 h [2], suggesting that amenamevir has a more immediate effect. It is possible that amenamevir had an immediate effect on ZAP as well as on rash, but further confirmation of this is needed.

Our analysis of residual pain duration, stratified according to eruption severity at the start of treatment, showed no difference between mild and moderate cases, and resolution of pain was confirmed over time. In contrast, in more severe cases, pain remained and tended to easily shift to PHN. In the analysis stratified by pain level, higher pain levels at the first visit were associated with higher proportions of patients with pain at 90 and 180 days after the start of treatment; however, there was no difference at 360 days. These results indicate that early rash severity can predict residual pain, and it is important to inform patients of the potential for PHN.

After 90 days, a high proportion of patients had pain in the face (i.e., the trigeminal ganglion region); however, after 360 days, the residual rate was high in the upper back and chest (3.6%) and the lower back and abdomen (3.8%). This finding was expected considering the large number of ganglia in these areas.

As presentations of ZAP pain, burning sensation, tingling or prickling sensations, and pain upon light touch or slight pressure-triggered pain were seen frequently at symptom onset; however, 90 days after treatment initiation, the residual rate of cold/heat pain and sensation of numbness was high, and after 180 days, the residual rate of sensation of numbness remained high. Even after 360 days, sensation of numbness was present in 3.2% of patients, showing the highest duration of all types of pain, at $< 3\%$. Sensation of numbness appears to be the most common symptom of PHN.

In the treatment of herpes zoster, antiviral agents and drugs for pain relief are often used in combination. The use of peripheral neuropathy therapeutic agents was high (46.6%); mecobalamin was used for 34.4% of patients and pregabalin for 8.8% of patients. NSAIDs were used in combination for 44.1% of patients; loxoprofen was used for 26.1% of patients. The antipyretic analgesic acetaminophen was used in combination for 30.7% of patients. These drugs tended to be used more frequently with more intense pain or with more severe eruptions. Topical NSAIDs were frequently prescribed for patients with severe eruptions.

Amenamevir has a different mechanism of action from conventional anti-herpes virus drugs. It inhibits the early stages of viral synthesis by suppressing helicase–primase, and is sufficiently effective at low doses. There is little concern about the safety of amenamevir in patients with impaired renal function; therefore, the drug is frequently used in clinical practice in Japan. According to the mechanism of action of early viral replication, amenamevir should provide both early improvement for eruptions and early reduction of ZAP, as well as having a preventive effect on PHN.

Regarding the study limitations, this was a prospective observational study that used real-world data. The final survey sample size reflected the fact that some participants provided incomplete questionnaire responses and some dropped out of the study.

CONCLUSIONS

This large-scale survey of 785 cases showed that, regarding pain intensity at the first visit, there was no difference in the proportion of patients with pain at any point during the year after treatment with amenamevir. However, it is difficult to compare our results with surveys involving other drugs owing to differences in survey methods and target patients. A more accurate comparative study is required for a more in-depth evaluation of the superiority of amenamevir in ZAP treatment.

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Declarations

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Compliance with Ethics Guidelines This study was reviewed and approved by the institutional review board of the NPO Health Institute Research of Skin (committee number: 19000025), and it allowed all institutions to participate in. This study was performed in accordance with the ethical principles of the Declaration of Helsinki and the ethical guidelines for medical research on humans. The study was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry. Written informed consent was obtained from all participants.

Data Availability The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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