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Irsogladine maleate for the treatment of recurrent aphthous stomatitis in hepatitis C virus patients on pegylated-interferon and ribavirin: A pilot study

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Abstract

Background and Aim: Aphthous stomatitis is one of the adverse effects associated with interferon (IFN) that forces dose reduction of IFN and there is no established therapy. This study was aimed to investigate whether irsogladine maleate, which enhances the functions of intercellular communication through the gap junctions, is effective for the treatment of aphthous stomatitis developed in hepatitis C virus (HCV) patients on pegylated-interferon (PEG-IFN) and ribavirin.

Methods: Nineteen patients with HCV were treated with PEG-IFN and ribavirin for 48 weeks. Ten out of 19 patients developed aphthous stomatitis during treatment with PEG-IFN and ribavirin. Within 1–2 weeks after development of aphthous stomatitis, 4 mg irsogladine maleate was orally administered daily to all patients and the therapeutic and adverse effects of irsogladine maleate were examined on every week. The degree of aphthous stomatitis was evaluated by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Results: Out of 10 patients, aphthous stomatitis was evaluated as grade 3 in three patients (30%) and grade 2 in seven patients (70%) by CTCAE. CTCAE grade was improved to 0 after 1 week in six patients, after 2 weeks in two patients, and after 3 weeks in two patients after the start of administration of irsogladine maleate. Aphthous stomatitis has not recurred in patients who had been on irsogladine maleate continuously during treatment of PEG-IFN and ribavirin.

Conclusions: Irsogladine maleate is effective for the treatment of aphthous stomatitis developing during PEG-IFN and ribavirin administration in HCV patients.

Introduction

In recent years, combination therapy with pegylated-interferon (PEG-IFN) and ribavirin has been used for treatment of chronic hepatitis C virus (HCV) infection with positive response resulting in cure of HCV in more than 50% of treated patients. Sustained virologic response is achievable in nearly half of patients with genotype 1 and about 80% of those with genotype 2 and 3.[1] The primary adverse effect of ribavirin is hemolytic anemia. Adverse effects associated with PEG-IFNs include fatigue, influenza-like symptoms, gastrointestinal disturbances, hematological abnormalities, neuropsychiatric effects (particularly depression), and thyroid dysfunction.[2,3] Manufactures of PEG-IFN also suggest that mouth ulceration, gingival bleeding, stomatitis, dysphagia, and glossitis are considered adverse reactions of this medication.

Patients with aphthous stomatitis have recurrent ulcers that cause constant pain and discomfort. Although recurrent aphthous stomatitis is a common disease that affects oral mucosa, the ulcers heal spontaneously within 2–3 weeks; aphthous stomatitis caused from IFN is refractory. Recently, it was reported that irsogladine maleate prevented gastric mucosal damage in several experimental animal models without inhibiting gastric secretion.[4,5] Irsogladine maleate enhances the functions of intercellular communication through the gap junctions in vitro,[6] and this reinforcement of the gap junction between gastric mucosal epithelia is considered one of the major therapeutic effects of the drug. Hosokawa *et al.*[7] reported that irsogladine maleate was effective for the treatment of recurrent aphthous stomatitis. Subsequently, Hara *et al.*[8] also observed that oral pain was rapidly reduced and recurrent aphthous stomatitis lesions were healed within 7 days of oral administration of irsogladine maleate. In addition, continuous administration of irsogladine maleate prevented the recurrence of aphthous stomatitis for 4.3 years in patients with recurrent aphthous stomatitis.[8] These results suggest that irsogladine maleate could be effective for the treatment of aphthous stomatitis caused by interferon.

Table 1 Aphthous stomatitis was evaluated by Common Terminology Criteria for Adverse Events version 4.0

	Oral pain	Oral dysesthesia
Grade 1	Mild pain	Mild discomfort Not interfering with oral intake
Grade 2	Moderate pain Limiting instrument ADL	Moderate pain Interfering with oral intake
Grade 3	Severe pain Limiting self-care ADL	Disabling pain Tube feeding or TPN indicated
Grade 4	—	—
Grade 5	—	—

—, not available; ADL, activities of daily living; TPN, total parenteral nutrition.

This study was aimed to investigate whether irsogladine maleate is effective for the treatment of aphthous stomatitis caused from interferon therapy in HCV patients. We administrated irsogladine maleate orally to HCV patients who developed aphthous stomatitis during the combination treatment of PEG-IFN and ribavirin.

Materials and methods

This study was conducted in the Department of Gasteroenterology and Hepatology, Kanazawa Medical University Hospital from January 2011 to October 2012. The clinical trial protocol was approved by the Kanazawa Medical University ethics committee and followed principals of the Declaration of Helsinki. Informed consent was obtained from all patients who participated in the study. From January 2011 to September 2012, 19 patients (age, 59.6 ± 10.8 years, male/female, 11/8) with chronic HCV were treated with PEG-IFN (α2a/α2b, 7/12) and ribavirin for 48 weeks. Ten out of 19 patients developed aphthous stomatitis during the treatment. The patients were selected for the study based on the oral symptoms and pain. Patients with other causal or associated conditions of aphthous stomatitis such as inflammatory bowel disease, Behcet's disease, iron or folic acid deficiency, or HIV infection were not included in the study. Within 1–2 weeks after development of aphthous stomatitis, we administered 4 mg of irsogladine maleate daily to all patients orally and examined the therapeutic and adverse effects of irsogladine maleate on every week. Administration of irsogladine maleate was continued during the entire treatment period of PEG-IFN and ribavirin, except those patients who wanted to discontinue after healing the ulcer. Administration of irsogladine maleate was started again if the ulcer recurred.

The aphthous stomatitis was evaluated by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 which is widely accepted throughout the oncology community as the standard classification and severity grading scale for adverse events in cancer therapy clinical trial (Table 1).

The results were expressed as mean ± standard error. Statistical analysis was carried out using Student's *t*-test and chi-square test. A value of $P < 0.05$ was considered as significant.

Results

In this study, we evaluated the effects of irsogladine maleate for the treatment of aphthous stomatitis developed in HCV patients on PEG-IFN and ribavirin regimen. Out of 19 patients included in the study, 10 patients developed aphthous stomatitis. The development of aphthous stomatitis was independent of age, sex, and type of PEG-IFN (α2a or α2b) administered in HCV patients. The time of the development of aphthous stomatitis after starting treatment with PEG-IFN and ribavirin was variable from 4–40 weeks.

Aphthous stomatitis is diagnosed with subjective symptoms such as redness, inflammation, swelling with pain, and difficulty in chewing and swallowing.[9] Aphthous stomatitis developed in 10 patients (number 2–3, size 1–2 mm) and was evaluated using CTCAE criteria as grade 3 in three patients (30%) and grade 2 in seven patients (70%) (mean 2.3 ± 0.1). In the three patients with grade 3, subjective symptoms such as pain, and difficulty in chewing and swallowing were completely improved within 1 week in two patients. In another patient, CTCAE grade was improved to 1 within 1 week and to 0 within 2 weeks after the start of administration of irsogladine maleate. In four out of seven patients (57%) with grade 2, CTCAE grade was improved to 0 within 1 week after the start of treatment with irsogladine maleate. In one patient with grade 2, CTCAE grade was improved to 1 within 1 week and to 0 within 2 weeks after the start of treatment. Although in the other two patients with grade 2, CTCAE grade was improved to 1 within 1 week, they still had mild pain for another 2 weeks after the start of irsogladine maleate administration. However, within 3 weeks after the start of administration of irsogladine maleate, subjective symptoms related to aphthous stomatitis disappeared completely. Figure 1 summarizes aphthous stomatitis score evaluated by CTCAE version 4.0. The score, 2.3 ± 0.1, before administration of irsogladine maleate was improved to 0.3 ± 0.1 at the end of 1 week, 0.2 ± 0.1 at the end of 2 weeks, and 0 at the end of 3 weeks after the start of administration of irsogladine maleate.

In 8 out of 10 patients who had been on irsogladine maleate continuously during the entire treatment with PEG-IFN and ribavirin, aphthous stomatitis did not recur. Two patients discontinued taking irsogladine maleate of their own accord when aphthous stomatitis disappeared. However, aphthous stomatitis recurred at 8 weeks in both patients after discontinuing irsogladine maleate. In both patients, aphthous stomatitis disappeared completely within 1 week after the start of re-administration of irsogladine maleate (Fig. 2).

Administration of irsogladine maleate did not produce any specific side effects or adverse effects during the entire period of treatment. However, the known toxicities related to interferon and ribavirin treatment were present.

Discussion

Aphthous ulcers are a common disease of the oral mucosa affecting 20% of the general population.[9] It is a common disease of unknown etiology and most cases are idiopathic. The term "aphthous stomatitis" has been used interchangeably with "aphthous ulcers," but at present, the term aphthous stomatitis is more widely accepted.[10] Relapsing aphthous stomatitis includes the secondary stomatitis induced by systemic disease such as Behcet's syndrome[11] and drug-induced stomatitis, as a side effect of the anticancer drug[12] and IFN.[13] Although various modalities have been used for the treatment of aphthous stomatitis, there is no established therapy. We also tried topical treatments such as

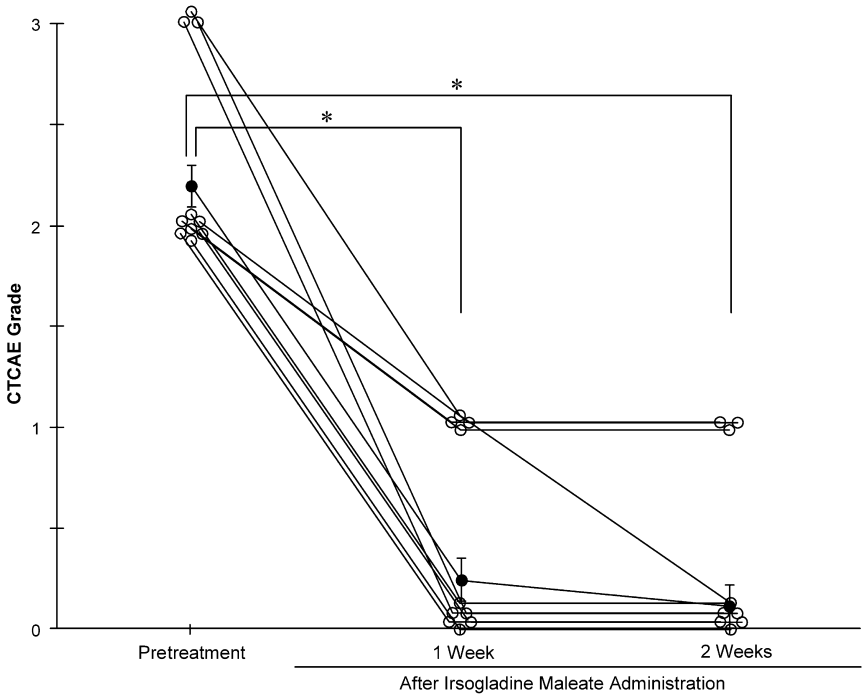

Figure 1 The grade of aphthous stomatitis evaluated by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 before and after the start of treatment with irsogladine maleate. Three patients were grade 3 and seven patients were grade 2 before the treatment. Out of 10 patients, CTCAE grade was improved to 0 at the end of 1 week in six patients, at the end of 2 weeks in two patients, and at the end of 3 weeks in two patients after the start of the administration of irsogladine maleate. Closed circles show the mean of CTCAE grade. *$P < 0.001$ versus pretreatment.

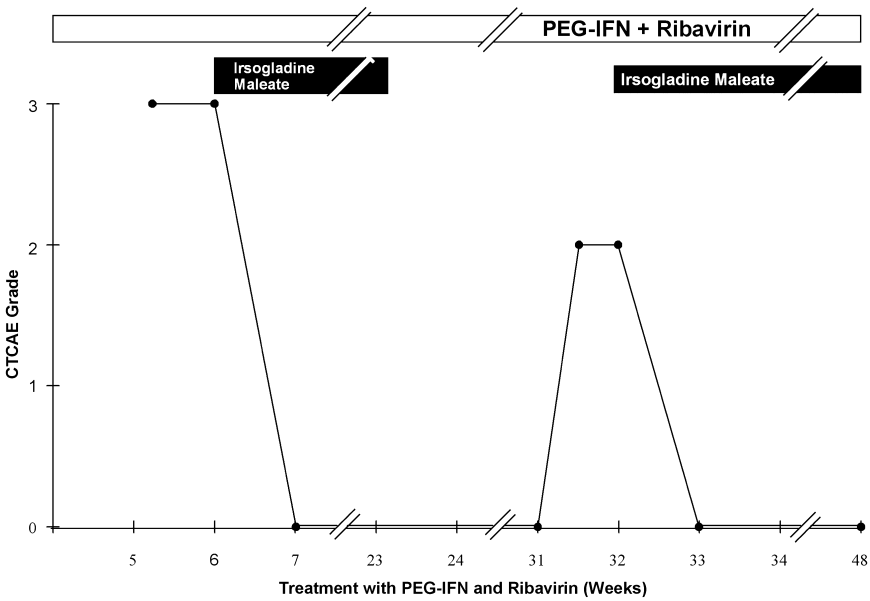

Figure 2 A case treated with irsogladine maleate. A 61-year-old man had aphthous stomatitis (grade 3) at 5 weeks after the start of treatment with pegylated-interferon (PEG-IFN) and ribavirin. Aphthous stomatitis completely disappeared within 1 week after the start of administration of irsogladine maleate. During the 15-week intake period of irsogladine maleate, he did not develop aphthous stomatitis. Therefore, he discontinued intake of irsogladine maleate. Eight weeks after discontinuation, aphthous stomatitis (grade 2) recurred. However, the symptoms completely disappeared within 1 week after the start of re-administration of irsogladine maleate.

antimicrobial mouthwash and corticosteroids including triamcinolone acetonide and dexamethasone to patients with aphthous stomatitis caused by IFN. However, there was no positive response except temporary relief of pain. Recently, it has been reported that irsogladine maleate, a drug used for the treatment of gastritis and peptic ulcer, was effective for the treatment of aphthous stomatitis.[14] In the present study, for the first time, we demonstrated that irsogladine maleate is also effective for aphthous stomatitis developed in patients with chronic HCV who are treated with PEG-IFN and ribavirin.

Irsogladine maleate is absorbed from the small intestine after oral administration and its plasma levels reach a maximum at 4 h in monkeys.[15] The half-life of non-metabolized irsogladine maleate is about 50 h in monkeys and about 60% and 30% of the dose is excreted through urine and feces, respectively.[15] Irsogladine maleate enhances the functions of intercellular communication through the gap junctions in vitro,[6] and this reinforcement of the gap junction between gastric mucosal epithelia is considered as one of the major therapeutic effects of this drug. Recently, Hara *et al.*[8] reported existence of connexin 26 and 32 in the oral

mucosa in both healthy controls and patients with relapsing aphthous stomatitis. Although they could not find significant differences in the expression of connexin 26 and 32 in oral mucosa between the patients and controls, the evidence of the existence of gap junctions in human oral mucosa could have potential therapeutic effects from agents which could modify the function of gap junctions in patients with aphthous stomatitis. Irsogladine maleate reinforces the function of gap junctions through a rise in intercellular pH mediated by Na^+/H^- exchangers and through phosphorylation of connexin by cyclic adenosine monophosphate, in vitro.[16] It is assumed that the potent effect of irsogladine maleate is due to the enhancement of gap junctional intercellular communication in connexin 26-positive oral mucosal squamous cells and/or connexin 32-positive oral mucosal glands.[8] These results suggest that irsogladine maleate could be effective for the treatment of aphthous stomatitis as well as the treatment of gastritis and peptic ulcer.

Although in the present study, the number of patients treated with PEG-IFN and ribavirin was only 19, aphthous stomatitis was developed in more than 50% of patients, suggesting that aphthous stomatitis is a common adverse effect associated with PEG-IFN such as fatigue, influenza-like symptoms, gastrointestinal disturbances.[2,3] Manufacturers of interferon α2a (Roferon-A) (Roche Laboratories, Tokyo, Japan) reported that IFN treatment produces mild inflammation of oral mucosa, such as mouth ulceration, stomatitis, dysphagia, and glossitis frequently. Recently, it was reported that severe aphthous stomatitis was developed in HCV patients taking PEG-IFN or interferon-α[13,17,18] and due to this adverse side effect, patients did not take their medication properly. Although aphthous stomatitis is not a serious condition, severe pain from aphthous stomatitis affects daily activities of patients. Therefore, it is very important to continue the combination therapy with PEG-IFN and ribavirin in order to reduce the symptoms of aphthous stomatitis such as pain, and difficulty in chewing and swallowing.

Serious adverse effects were not reported with the administration of irsogladine maleate. Recently, Nomura *et al*.[12] used irsogladine maleate to treat the oral mucositis induced during 5-fluorouracil-based chemotherapy. They did not observe any specific adverse effects related to irsogladine maleate treatment. However, adverse effects such as gastric cancer, abdominal distention, constipation, diarrhea, ischemic enteritis, stomatitis, reflux esophagitis, drug eruption, and reduced white blood cell counts were observed in 11 patients (7.3%) out of 150 patients treated with irsogladine maleate. However, these symptoms were not attributed to the administration of irsogladine maleate.[19] In the present investigation, administration of irsogladine maleate did not produce any side effects or adverse effects during the entire period of study.

In conclusion, in the present study, we demonstrated that irsogladine maleate is effective for the treatment of aphthous stomatitis caused by PEG-IFN and ribavirin administration in HCV patients. Therefore, irsogladine maleate could be used for the successful treatment of aphthous stomatitis developing in HCV patients during the combination treatment with IFN and ribavirin. However, there is no information about any potential drug interactions of irsogladine maleate with the new protease inhibitor treatments for hepatitis C.

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