ORIGINAL RESEARCH ARTICLE

Drugs R D 2008; 9 (6): 455-459
1174-5886/08/0006-0455/$48.00/0

Irsogladine is Effective for Recurrent Oral Ulcers in Patients with Behçet's Disease

An Open-Label, Single-Centre Study

Yuki Nanke,[1] *Naoyuki Kamatani*,[2] *Toshihiro Okamoto*,[2] *Hideki Ogiuchi*[1] and *Shigeru Kotake*[1]

1 Institute of Rheumatology, Tokyo Women's Medical University, Shinjuku-ku, Tokyo, Japan
2 Department of Oral and Maxillofacial Surgery, Tokyo Women's Medical University, Shinjuku-ku, Tokyo, Japan

Abstract

Background and objective: Behçet's disease (BD) is a polysymptomatic condition characterized by recurrent oral and genital ulceration and uveitis. Aphthous stomatitis, a common complication, is painful, recurrent and sometimes resistant to treatment. Topical or intralesional corticosteroids and local anaesthetics are used for palliative therapy. We investigated whether irsogladine, a drug for the treatment of gastritis and peptic ulcers, reduced aphthous stomatitis lesions in patients with BD.

Methods: Irsogladine 2–4 mg/day was administered orally to ten BD patients (cases 1–10), three men and seven women, with a mean age of 48.5 years, with recurrent aphthous stomatitis as the main symptom. Pre-existing treatments were not changed. All patients were followed up at our outpatient clinic once a month. The patients had no systemic neurological, gastrointestinal or vascular symptoms. Efficacy was evaluated on the basis of the macroscopic findings of aphthous lesions. We counted the number of aphthous lesions three times prior to administration of irsogladine and three times after treatment at the outpatient clinic, i.e. six times in total, and compared pre- and post-treatment mean numbers of lesions for each patient.

Results: Irsogladine was effective in all ten patients. The mean aphthous ulcer count decreased in all patients 3 months after administration ($p < 0.0003$). Cases 5 and 6 stopped taking irsogladine of their own accord when the stomatitis disappeared; however, the stomatitis reappeared, and in both patients, aphthous stomatitis healed completely soon after re-administration of irsogladine. In case 8, aphthous stomatitis reappeared 2 months after administration of irsogladine 2 mg/day. The dose of irsogladine in this patient was then increased to 4 mg/day, after which aphthous stomatitis resolved. Taking irsogladine continuously prevented recurrence of stomatitis in these three patients.

Conclusion: Irsogladine reduces aphthous stomatitis/oral ulcers in patients with BD. The improvement in gap-junctional intercellular communication by irsogladine may contribute to the treatment of aphthous stomatitis in patients with

BD. Increasing the dose of irsogladine may resolve ulcers resistant to low doses of irsogladine.

Background

Behçet's disease (BD) is a polysymptomatic condition characterized by recurrent oral and genital ulceration and uveitis.[1-4] Aphthous stomatitis, a common complication, is painful, recurrent and sometimes resistant to treatment. Topical or intralesional corticosteroids and local anaesthetics are used for palliative therapy. No standard therapy for aphthous stomatitis, however, has yet been established. Recently, rebamipide, a gastroprotective drug, was reported to show efficacy against oral ulcers.[5] Rebamipide stimulates release of endogenous prostaglandins in the gastric mucosa and inhibits free radicals, but is not always effective against aphthous stomatitis.[5]

Irsogladine (2,4-diamino-6-(2,5-dichlorophenyl)-s-triazine maleate), a drug used in the treatment of gastritis and peptic ulcers, reinforces gap-junctional intracellular communication.[6,7] In this study, we investigated whether irsogladine is effective against aphthous stomatitis in patients with BD.

Patients and Methods

Patients

Irsogladine 2–4 mg/day was administered orally to ten BD patients, three men and seven women, mean age 48.5 years, with recurrent aphthous stomatitis. All patients attended the Institute of Rheumatology, Department of Oral and Maxillofacial Surgery, Tokyo Women's Medical University, Shinjuku-ku, Tokyo, Japan. Pre-existing treatments were not changed. BD was diagnosed according to both International Study Group criteria[3] and the Behçet's Disease Research Committee of Japan criteria.[4] All patients were followed up at our outpatient clinic once per month. Informed consent was obtained from all patients, and received institutional approval.

The patients had no systemic neurological, gastrointestinal or vascular symptoms. Efficacy was evaluated on the basis of the macroscopic findings of aphthous lesions. We counted the number of aphthous lesions three times prior to administration of irsogladine and each time the patients visited the clinic after irsogladine treatment at the outpatient clinic, i.e. six times in total, and compared pre- and post-treatment mean numbers of lesions.

Statistical Analysis

Data were analysed by the Mann-Whitney U test. A significant difference was defined as $p < 0.05$.

Results

Table I summarizes the clinical features of the patients. All patients fulfilled both the International Study Group criteria[3] and the Behçet's Disease Research Committee of Japan criteria.[4] Seven of the ten patients had been taking rebamipide for oral ulcers without effect (table II). Irsogladine was effective against oral ulcers in all ten patients, although the other symptoms of BD such as uveitis or skin lesions were not affected. No adverse effects were noted. At the first visit (1 month post-treatment) after the administration of irsogladine, all lesions had resolved or decreased. The mean aphthous ulcer count had decreased in all patients 3 months after drug administration ($p < 0.0003$) [figure 1]. Figure 2 shows the clinical course of three patients, cases #5, #6 and #8. Cases #5 and #6 stopped taking irsogladine of their own accord when the stomatitis disappeared; however, the stomatitis reappeared, and in both patients, aphthous stomatitis healed completely soon after re-administration of irsogladine. In case #8, aphthous stomatitis reappeared 2 months after administration of irsogladine 2 mg/day. The dose of irsogladine in this patient was then increased to 4 mg/day, after which the ulcers resolved. Taking irsogladine continuously prevented recurrence of stomatitis in these three patients.

Table I. Clinical features of patients in the study

Case no.	Sex/age (y)	Type of BD	Duration (y)	Feature	GU	Eye	Skin	CRP (mg/dL)	IgD (mg/dL)	HLA
1	M/28	C	5	(–)	+	U	Acne	0.0	2.5	B51, A26
2	F/36	IC	2	(–)	+	No uveitis	Acne	0.0	<1.0	B51
3	F/45	IC	15	Entero	+	PU	EN, acne	0.3	4.7	Negative for HLA B51, A26
4	M/62	C	16	(–)	–	AU	Acne	0.22	2.4	B51
5	F/54	IC	6	(–)	–	IR	EN	0.22	0.6	Negative for HLA B51, A26
6	F/41	IC	7	(–)	–	IR	Acne	0.0	1.7	Negative for HLA B51, A26
7	F/43	IC	5	(–)	+	IR	No acne, no EN	0.0	2.8	A26
8	F/64	IC	22	Entero	+	IR	EN	1.7	2.6	A26
9	F/61	IC	1	(–)	–	IR	No acne, no EN	0.1	<1.0	Negative for HLA B51, A26
10	M/29	C	5	Neuro	+	IR	EN, acne	0.07	<1.0	B51

AU = anterior uveitis; **BD** = Behçet's disease; **C** = complete type (Behcet's Disease Research Committee of Japan criteria[4]); **CRP** = C-reactive protein; **EN** = erythema nodosum; **entero** = enterological BD; **F** = female; **GU** = genital ulcer; **HLA** = human leukocyte antigen; **IC** = incomplete type (Behcet's Disease Research Committee of Japan criteria[4]); **IgD** = immunoglobulin D; **IR** = iritis; **M** = male; **neuro** = neurological BD; **PU** = panuveitis; **U** = uveitis; + indicates present; – indicates absent; (–) indicates no enterological, neurological or vascular BD.

Discussion

In this study, we found that irsogladine is effective for aphthous stomatitis in patients with BD. Rebamipide, a gastroprotective drug, has been reported to show efficacy for recurrent aphthae in patients with BD.[5] However, in the seven out of ten patients who had been taking rebamipide for oral ulcers in our study, rebamipide was ineffective. Surprisingly, irsogladine was effective in all seven of these patients.

It is possible that the oral ulcers of patients in this study healed spontaneously because the present study was not a randomized case-control study. Nevertheless, we still believe that the oral ulcers were, at least in part, healed by administration of irsogladine. First, there is an extremely low probability that these recurrent oral ulcers in all ten patients decreased spontaneously at the same time. Second, as shown in figure 2, cases #5 and #6 can be considered 'challenge tests'. In cases #5 and #6, rebamipide 300 mg was not effective against the patients' oral ulcers. Conversely, administration of irsogladine stopped the pain caused by the patients' ulcers and completely healed them. Cases #5 and #6 also stopped taking irsogladine of their own accord after 5 and 6 months, respectively, after which their oral ulcers reappeared. Soon after re-administration of irsogladine, their ulcers disappeared again.

In case #8, the oral ulcers were not healed by administration of irsogladine 2 mg/day. However, they resolved completely after administration of irsogladine 4 mg/day. In this case, increasing the dose of irsogladine was effective against resistant oral ulcers. Thus, a higher dose of irsogladine may resolve ulcers resistant to low doses of irsogladine.

Irsogladine has been used as an antigastric ulcer agent in Japan, with the relevant mechanism of action being up-regulation of the function of intercellular gap junctions.[6,7] This may be modulated by phosphorylation of connexins (gap junction proteins) induced by cyclic adenosine monophosphate (cAMP)-dependent kinase.[6] Irsogladine has also been shown to reinforce the function of gap junctions through an increase in intercellular pH mediated by Na^+/H^+ exchangers and phosphorylation of

Table II. Pretreatment received by patients in the study

Case no.	Rebamipide	Effect	Treatment for Behçet's disease				
			colchicine	prednisolone	sulfasalazine	mizoribine	NSAID
1	+	−	+	+	−	−	−
2	−		+	−	−	−	−
3	−		+	+	−	−	−
4	+	−	+	−	−	−	−
5	+	−	+	−	−	−	−
6	+	−	−	−	+	−	−
7	+	−	+	−	−	−	+
8	+	−	+	+	+	−	−
9	−		−	−	−	−	−
10	+	−	−	+	−	+	−

+ indicates receiving the drug; − indicates not receiving the drug.

connexin by cAMP *in vitro*.[6] In addition, irsogladine increases intracellular cAMP levels and regulates gap junctional intercellular communication via the protein kinase A pathway.[6] Treatment with irsogladine for pancreatic cancer was found to move the localization of connexin 43 immunoreactive spots from the cytoplasm to boundary lesions with neighbouring cells, and to increase intercellular cAMP levels.[7] Thus, we speculate that irsogladine may heal oral ulcers through the same mechanism.

In addition, irsogladine has cytoprotective effects. Pretreatment with irsogladine prevents desquamation and exfoliation of gastric mucosal epithelial cells and inhibits the expansion of intracellular space induced by intragastric infusion of 0.2 N HCl.[6,7] Pretreatment with irsogladine also prevents the desquamation and exfoliation of gastric epithelial cells induced by oral administration of absolute ethanol (alcohol).[6,7] We speculate that irsogladine may prevent oral ulcers through the same mechanisms.

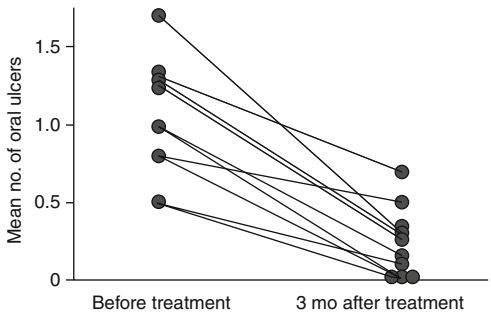

Fig. 1. Effect of irsogladine on mean number of oral ulcers (aphthous stomatitis lesions) in patients with Behçet's disease.

Study Limitations

The limitations of this study are that the number of patients studied was small, the study was not a randomized case-control study, and the endpoint

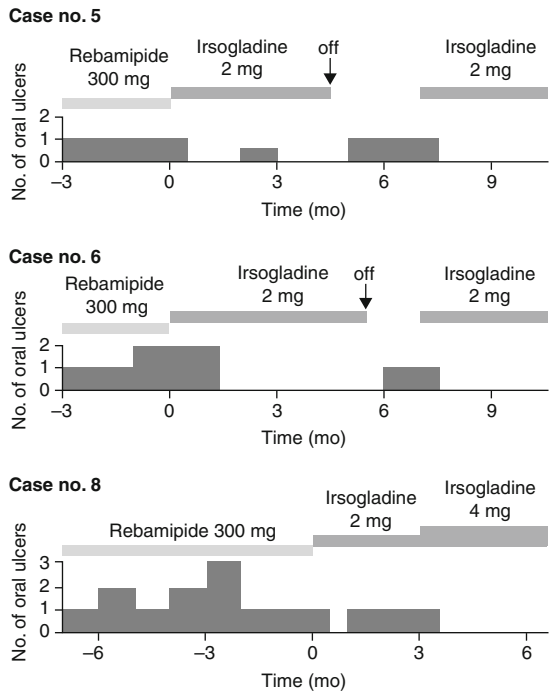

Fig. 2. Clinical course of cases #5, #6 and #8 who were administered rebamipide prior to treatment with irsogladine.

was numbers of macroscopic lesions without histological evaluation.

Conclusion

Iirsogladine reduced aphthous stomatitis/oral ulcers in patients with BD. The study did not investigate the mechanism of action of irsogladine, so this arguably could not form part of the main conclusion of the study. Suggest this be reworded)) The improvement in gap-junctional intercellular communication by irsogladine may contribute to the treatment of aphthous stomatitis in patients with BD. Irsogladine could be a treatment choice for recurrent aphthous stomatitis when treatment with rebamipide is not successful. Further studies are needed to clarify the pathogenesis of aphthous stomatitis in BD and the functions of gap junction in the oral mucosa.

Acknowledgements

No sources of funding were used to assist in the preparation of this study. The authors have no conflicts of interest that are directly relevant to the content of this study.

References

1. Nanke Y, Kotake S, Ogasawara K, et al. Raised plasma adrenomedullin level in Behcet's disease patients. Mod Rheumatol 2003; 13: 139-42
2. Nanke Y, Kotake S, Tateishi M, et al. Synovial histology in three Behcet's disease patients with orthopedic surgery. Clinical Exp Rheum 2002; 20: 35-44
3. International Study Group for Behcet's Disease. Criteria for diagnosis of Behcet's disease. Lancet 1990; 335: 1078-80
4. Behcet's Disease Research Committee of Japan. Behcet's disease: a guide to diagnosis of Behcet's disease. Jpn J Ophthalmol 1974; 18: 291-4
5. Matsuda T, Ohno S, Hirohata S, et al. Efficacy of rebamipide as adjunctive therapy in the treatment of recurrent oral aphthous ulcers in patients with Behcet's disease. Drugs R&D 2003; 4: 19-28
6. Hara A, Murata T, Uemura R, et al. Identification of connexins in human oral mucosa and therapeutic effect of irsogladine maleate on aphthous stomatitis. J Gastroenterol 1999; 34: 1-6
7. Kawasaki Y, Tsuchida A, Sasaki T, et al. Irsogladine maleate up-regulates gap junctional intercellular communication between pancreatic cancer cells via PKA pathway. Pancreas 2002; 25: 373-7

Correspondence: Dr *Yuki Nanke*, Institute of Rheumatology, Tokyo Women's Medical University, 10-22 Kawadacho, Shinjuku-ku, Tokyo, 162-0054, Japan.
E-mail: ynn@ior.twmu.ac.jp