Clinical trial

Oral erosive/ulcerative lichen planus: preliminary findings in an open trial of sulodexide compared with cyclosporine (ciclosporin) therapy

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Abstract

Objective To study the effect of the heparinoid sulodexide systemically, compared with topical cyclosporine (ciclosporin), on chronic oral erosive/ulcerative lichen planus.

Study design An open nonrandomized trial was conducted in two groups of 10 Italian patients with lichen planus, with subjective assessment of pain and assessment of ulceration amelioration by nonblinded clinicians.

Results Comparable pain relief and amelioration of erosions/ulcers were seen in patients on sulodexide and in those on ciclosporin, but with faster healing in those on sulodexide.

Conclusions Sulodexide appears to be as effective, and perhaps more effective, than topical ciclosporin in the therapy of oral lichen planus, and is less expensive, but full double-blind placebo-controlled studies are required.

Introduction

Lichen planus is a chronic inflammatory disorder in which the keratinocyte is the main target of a T-lymphocyte immunologically mediated attack, with release of tumour necrosis factor alpha, and similarities to a delayed hypersensitivity response. The aetiology is unclear but, in a minority, identifiable precipitating factors can be identified, such as hepatitis C virus, in some persons from southern Europe or Japan.[1]

Therapy cannot therefore usually be targeted and is restricted largely to the use of immunomodulatory agents, particularly topical corticosteroids.[2–4] However, these are not reliably effective or without occasional adverse effects, and therefore other immunomodulatory agents are sometimes used, including systemic corticosteroids, azathioprine and ciclosporin (cyclosporine).[4]

Ciclosporin has also been used with some beneficial effect topically,[5–9] although not in all cases.[10–13]

Heparin is a novel therapy that has recently emerged: it is a sulfated glycosaminoglycan possessing immunomodulatory potential that is effective in inhibiting delayed hypersensitivity reactions.[14] Heparin also interacts with keratinocyte heparin-binding growth factors[15] and, more importantly, may inhibit tumour necrosis factor alpha.[16] It thus has the potential for modulating the course of lichen planus.

Preliminary trials have shown that a low-molecular-weight heparin (Enoxaparin), in doses low enough to be devoid of anticoagulant activity, may produce at least partial resolution of lichen planus with cutaneous[17,18] and oral[18] involvement.

Sulodexide is a low-molecular-weight product constituted from heparin (80%) and dermatan sulfate (20%) chains which has a number of heparin-like activities on immunocytes and tissues but extremely low anticoagulant activity.[19,20] The therapeutic action of sulodexide is related to the activity of plasmin with stimulation of cell proliferation and activation of cytokines (transforming growth factor β and epidermal growth factor). Sulodexide also has a protective action on endothelium,[21] and aids the repair of cell damage,[22,23] and may therefore also have the potential for controlling lichen planus.

We were thus interested to compare the efficacy of sulodexide with that of ciclosporin in the control of pain and ulceration in erosive oral lichen planus, underlining also the difference in cost between the two therapies.

Patients and methods

This was an open study to compare the efficacy of systemic sulodexide with that of topical ciclosporin in the control of pain and ulceration in erosive oral lichen planus. The study group consisted of 20 adult Italian patients with chronic oral erosive lichen planus, and no extraoral lesions, whose oral lesions had previous failed to respond to topical corticosteroid therapy, and all of whom had persistent oral pain and erosions/ulcers. In all patients there was histological and immunofluorescence confirmation of the diagnosis from lesional biopsy. None was taking other medication. The study had local ethical committee approval and all patients gave fully informed consent.

International Journal of Dermatology 2003, **42**, 308–311

Table 1 Study group characteristics of patients with chronic erosive oral lichen planus

Sulodexide study group			Ciclosporin study group		
Patient	**Gender**	**HCV**	**Patient**	**Gender**	**HCV**
FB	M	Yes	RG	M	No
CA	F	No	TA	M	No
RA	M	Yes	LV	F	Yes
NE	M	Yes	PG	M	Yes
GS	F	Yes	FC	F	No
RG	F	Yes	DS	M	Yes
AF	M	No	RN	M	Yes
EG	M	No	CF	M	Yes
SV	F	No	DDM	F	No
DN	M	Yes	ZL	F	Yes
Overall	60% M	60% HCV+	Overall	60% M	60% HCV+

The 20 patients were subdivided nonrandomly by gender and hepatitis C (HCV) status into two subgroups each of 10 subjects with oral lesions of comparable pain and lesion extent, each subgroup including six females and four males, and each containing six patients infected with HCV (Table 1). The HCV-positive subjects all had serum transaminase levels at least twice the normal levels. Patients with any haemorrhagic diathesis or peptic ulceration were excluded. Baseline assays of prothrombin (PT), partial thromboplastin (PTT) and thrombin (TT) times were established in all patients.

Subjects in the first subgroup (the sulodexide group) were given intramuscular sulodexide 600 units (one vial) followed by oral doses of 250 units twice daily for 1 month. The other subgroup (the ciclosporin group) used oral ciclosporin (Sandimmun, Novartis SPA, Origgio, Italy), 1 mL (100 mg/mL) 3 times daily as an oral rinse for 3 min, for 1 month.

All patients were submitted to clinical assessment (the patient assessed the level of pain relief as "no relief" or "full/partial relief", and a clinician assessed the presence of oral ulceration/erosion) and laboratory testing of PT, PTT and TT on the 7th, 14th and 30th days. Clinical assessment was carried out by one of two senior clinicians (FF or FG) who had been calibrated for their assessment of the presence of oral erosion/ulceration: the outcomes recorded were the number of days to either pain relief, and/or healing of erosions/ulcers. At 3 and 5 months after the completion of the course of therapy, all patients were reviewed. The times to ulcer healing were analysed by Fisher's method.

Results

Nine of the 10 patients in the first subgroup (sulodexide) reported resolution of pain by 6–7 days (mean 6.4 days) and had total clinical resolution of oral erosion/ulceration after 20–25 days (mean 23 days) of treatment. The other patient showed intolerance, reporting vertigo, vomiting and hot flushes by the 2nd day (Table 2), and was withdrawn from the study.

No patients in this sulodexide subgroup had significant changes in the results of their laboratory tests.

The cost of pharmacological therapy for the whole period of study was US$130 for the sulodexide group against US$400 for the ciclosporin group.

In the ciclosporin subgroup, all patients tolerated the agent and the ulcer pain abated after 7–10 days (mean 8 days), but the clinical resolution of erosion/ulceration was slower than with sulodexide (Table 2) at a mean of 36 days (27–44 days; $P < 0.004$).

At follow-up 3 and 5 months after the completion of the course of therapy, the patients of both subgroups maintained remission of pain and erosion/ulceration in the absence of continued drug therapy.

Discussion

This open trial compared the effects of systemic sulodexide, a new heparin-related molecule, in 10 patients with chronic erosive/ulcerative oral lichen planus unresponsive to topical corticosteroids with those of topical ciclosporin in another 10 subjects. Positive therapeutic effects from both agents were found. Both sulodexide and ciclosporin showed benefits in terms of subjective pain relief and resolution of clinical erosion/ulceration. Healing was significantly faster with sulodexide, but one patient could not tolerate the drug and withdrew from the trial.

The time to resolution of pain with sulodexide therapy was about 6.5 days (6–7 days) and erosion/ulceration resolved within 20–25 days (mean 23 days). In the ciclosporin-treated group, pain abated after 7–10 days (mean 8 days), but clinical resolution of the erosions/ulcerations was significantly slower, taking 36 days (27–44 days).

At follow-up 3 and 5 months later, however, the patients of both treatment groups maintained remission in the absence of continued drug therapy. Both groups had a high rate of HCV positivity, as is typical for Italian lichen planus patients.[1]

Table 2 Results of use of sulodexide and ciclosporin in oral erosive lichen planus

	Mean no. of days (range)		
Therapy	**Pain resolution**	**Ulcer resolution**	**Significance regarding resolution of ulceration**
Sulodexide	6.5 (6–7)	23 (20–25)	$P < 0.004$
Ciclosporin	8 (6–10)	36 (27–44)	

Sulodexide is a low-molecular-weight heparin-related product constituted from heparin (80%) and dermatan sulfate (20%) chains extracted from pig intestine.[24,25] There is very little antithrombotic effect[20,25] but there is fibrinolytic activity, with increases in tissue plasminogen activator (tPA) and reductions in plasminogen activator inhibitor (PAI) levels.[26,27] tPA and urokinase (uPA) are produced by keratinocytes also responsible for the synthesis of the uPA epithelial receptor and for inhibiting both enzymes tPA and uPA as well as PAI-1 and PAI-2. The tPA and uPA enzymes are principal activators of the conversion of plasminogen to plasmin, resulting in proteolytic action on fibronectin, laminin and fibrin-like natural constituents of the extracellular matrix.[28–31] These activities can assist the recovery of damaged epithelium.[15,32,33] PAI-2 is present in the extracellular matrix of the epithelial granular layer, can inhibit proteolysis, and therefore blocks cellular proliferation.[34,35]

This was an open nonrandomized trial with subjective assessment of pain and assessment of ulceration amelioration by nonblinded clinicians. Thus, although these results appear promising, full double-blind placebo-controlled studies are required to establish the true value of sulodexide in the therapy of erosive oral lichen planus, and its merits relative to systemic cyclosporine.

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