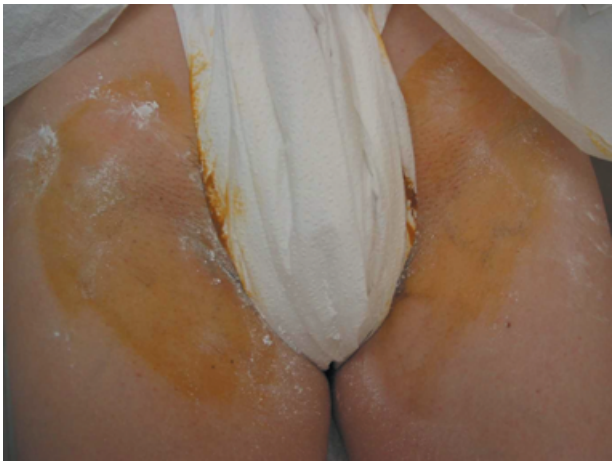

**Figure 3** Inguinal starch-iodine test two weeks following treatment

toxin type A (BOTOX) in humans for hyperhidrosis only came about since 1996.[2,3]

Botulinum toxin is a safe and effective treatment for hyperhidrosis, and has been shown to improve the quality of life in affected patients.[4] The toxin works by inhibiting the release of acetylcholine at the neuromuscular junction, and affecting the postganglionic sympathetic innervation of sweat glands.[5]

Axillary and palmar hyperhidrosis have thus far been the most studied affected areas with regards to the beneficial effects of botulinum toxin type A (BOTOX). Using a PubMed search, only one reference was found with mention to the use of botulinum toxin for inguinal or groin hyperhidrosis. Goldman reports his personal experience with the use of botulinum toxin for several areas, and experience with inguinal hyperhidrosis in two patients.[6]

Our case report of the use of botulinum toxin for inguinal hyperhidrosis corroborates the findings of Goldman. More work should be done in this area to find the optimal dose for treating this area, and patients should be made aware that this is another area of the body that can benefit from botulinum toxin therapy.

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### Oral lichen planus: clinical and histological evaluation in an open trial using a low molecular weight heparinoid (sulodexide)

Lichen planus (LP) is a relatively common disorder affecting stratified squamous epithelia, often in multiple sites.[1,2] Although often presenting as symptomless white lesions, oral lichen planus (OLP) may be painful – especially in the atrophic and erosive forms or where there is desquamative gingivitis.[2] In contrast to cutaneous LP, the oral disease tends to be chronic.[2–4] Therefore, in some of LP patients, systemic therapy is indicated.

Therapy of OLP includes mainly the use of various immunosuppressive agents, especially corticosteroids,[2,5,6] or more recently, tacrolimus;[7,8] but the adverse effects of several of the immunosuppressive agents used systemically, especially in elderly patients, means that safer alternatives are sought.

The aim of this study was to determine the clinical effectiveness of a new low molecular weight heparinoid molecule (sulodexide) used systemically, but which has immunosuppressive activity with minimal adverse effects.

Twenty Italian patients with chronic erosive or reticular-erosive oral lichen planus (LP) (13 female and 7 males, age range 3874 years; median 59 years) were studied (Fig. 1). Informed consent and approval of the local district ethical committee was obtained.

All patients were submitted to oral lesional biopsy and had LP confirmed in accordance with World Health Organization (WHO) parameters and all had positive immunostaining for fibrinogen along the epithelial basal membrane zone. Four of the patients had LP affecting skin but none had LP in other sites. All had normal blood count, PT, PTT, fibrinogen, and blood glucose levels. Of the 20 LP patients, six had active viral

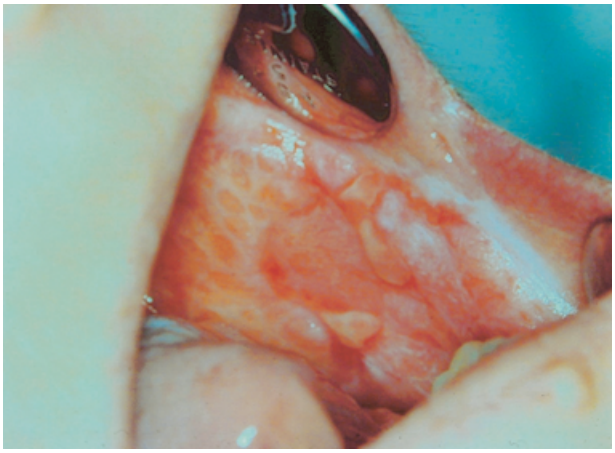

**Figure 1** Erosive lichen of cheek before therapy

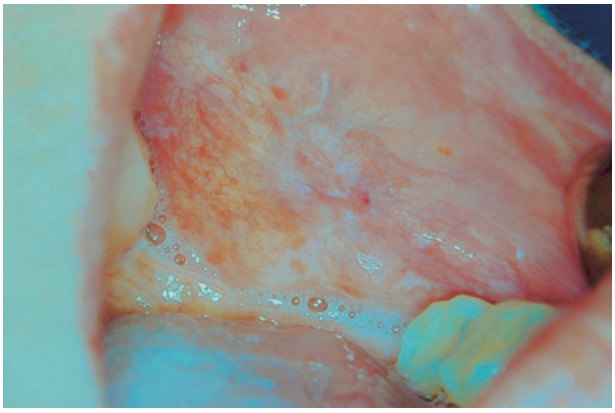

**Figure 2** Clinical resolution of erosive lichen after sulodexide therapy and at end of follow-up at 1 year

**Table 1** Characteristics of study group

| Patients N° | Age and sex | Duration of lesions prior to therapy (months) | Cutaneous manifesations | Viral hepatitis |
|---|---|---|---|---|
| 1 | 38/F | 8 | NO | NO |
| 2 | 59/F | 12 | YES | NO |
| 3 | 65/M | 4 | NO | HCV+ |
| 4 | 46/F | 12 | NO | HCV+ |
| 5 | 73/M | 24 | YES | NO |
| 6 | 74/F | 18 | NO | NO |
| 7 | 66/F | 24 | NO | NO |
| 8 | 52/F | 8 | NO | NO |
| 9 | 64M | 12 | NO | NO |
| 10 | 61/F | 24 | YES | HBV+ |
| 11 | 44/F | 36 | NO | NO |
| 12 | 63/F | 18 | NO | NO |
| 13 | 55/M | *12* | NO | NO |
| 14 | 56/F | 10 | NO | HCV+ |
| 15 | 49/M | 14 | YES | NO |
| 16 | 64/F | 36 | NO | HCV+ |
| 17 | 56/F | 18 | NO | NO |
| 18 | 67/F | 24 | NO | NO |
| 19 | 74M | 12 | NO | HCV+ |
| 20 | 68/M | 8 | NO | NO |

hepatitis with serum transaminase levels at least double the norm and positive polymerase chain reaction (PCR) (5 HCV+ and 1 HBV+) (Table 1).

Therapy was with oral sulodexide (250 units) twice each day between meals for 40 days and then once a day for a further 40 days. Patients were reviewed weekly with laboratory investigations (blood count, PT, PTT, fibrinogen, blood glucose, GOT, GPT).

Results were analyzed by the Student's *t*-test.

Two subjects taking systemic sulodexide showed intolerance, reporting dizziness, vomiting, and hot flushes by the second day, and therefore treatment was aborted. The remaining 18 patients responded positively to therapy with a notable subjective reduction of symptomatology within 9–12 days and subjective improvement with clinical recovery within 20–25 days. They had previously been recalcitrant. Laboratory parameters remained substantially unchanged all throughout (Table 2). Histopathological examination of biopsy of previous lesional tissue at the end of the study confirmed return to normality with resolution of the chronic inflammatory infiltrate and epithelial changes.

At follow-up, two patients had recurrences by 3 months and four patients had recurrences by 4 months. Follow-up at 1 year confirmed resolution in 12 of the 18 patients (55%) who had responded positively to sulodexide without recurrence (Table 3) (Fig. 2).

Sulodexide is a glucosaminoglycan (GAG) similar to low molecular weight heparin (LMWH)[9] except that it has low anticoagulant activity despite being of equal antithrombotic effect, as it inhibits antithrombin III (ATIII) complex that inhibits the coagulation cascade and it also inhibits factor Xa.[10] The risk of undesirable bleeding is thus small.[11]

Interestingly, heparin and heparin-like molecules (heparinoids) also activate macrophages and the migration of B lymphocytes, inhibit B and T lymphocytes, and inhibit histamine and bradykinin.[12,13] Sulodexide also alters blood vessel permeability, and regulates smooth muscle proliferation and angiogenesis.[14] Low doses of heparin also suppress the activity of heparinase in T lymphocytes and, thus, the migration of T cells with consequent inhibition of delayed-type hypersensitivity reactions.[15] The ability of activated T lymphocytes to cross vascular barriers and to penetrate the extracellular matrix to reach target tissues is modulated by heparinase, which degrades the heparan-sulfate molecules of the proteoglycan of the extracellular matrix.[16]

The ability of LMWH molecules to inhibit immune reactions has been correlated with the suppression of heparinase

**Table 2** Lichen planus: results of sulodexide therapy

| Patient N° | Time to abatement of symptoms (days) | Variation in symptomatology | Time to clinical resolution of lesions (days) | Skin improvements |
|---|---|---|---|---|
| I | 9 | ++ | 20 | |
| 2 | 10 | + | 22 | ++ |
| 3 | 9 | + | 20 | |
| 4 | 12 | + | 23 | |
| 5 | 11 | ++ | 25 | ++ |
| 6 | Treatment abandoned | ------- | ------ | ------ |
| 7 | 10 | ++ | 20 | |
| 8 | 9 | + | 21 | |
| 9 | 12 | ++ | 22 | |
| 10 | 11 | + | 24 | ++ |
| 11 | 11 | + | 21 | |
| 12 | 9 | ++ | 20 | |
| 13 | 12 | + | 22 | |
| 14 | Treatment abandoned | ------- | -------- | ------- |
| 15 | 11 | ++ | 25 | |
| 16 | 12 | + | 24 | ++ |
| 17 | 9 | ++ | 21 | |
| 18 | 11 | + | 22 | |
| 19 | 12 | ++ | 24 | ++ |
| 20 | 10 | + | 20 | |

Legend: + = reduction in symptomatology.
++ = total improvement.
*t*-test $P < 0.0001$.

**Table 3** Follow-up for 1 year

| | Recurrence | | |
|---|---|---|---|
| Patients | Necessitating treatment at 3 months | Necessitating treatment at 4 months | Necessitating treatment at 12 months |
| 1 | YES | – | – |
| 2 | | | |
| 3 | | | |
| 4 | | YES | – |
| 5 | | | |
| 6 | – | – | – |
| 7 | | | |
| 8 | YES | | – |
| 9 | | YES | – |
| 10 | | | |
| 11 | | | |
| 12 | | | |
| 13 | | | |
| 14 | – | – | – |
| 15 | | YES | – |
| 16 | | | |
| 17 | | YES | – |
| 18 | | | |
| 19 | | | |
| 20 | | | |

expression on activated T lymphocytes.[17] Additionally, both chains of sulodexide (heparin and dermatan) synergistically promote endothelial fibrinolytic activity by increasing tissue plasminogen activator (tPA) and reducing plasminogen activator inhibitor (PAI) thus stimulating cell proliferation, favoring the repair of epithelial damage.[18]

This open trial suggests that sulodexide may offer a valid safe alternative systemic therapy for oral lichen planus. Two patients (10%) showed adverse effects significant enough to warrant medical attention. Whether this therapy is superior to topical tacrolimus, however, remains to be tested.

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### The therapeutic effect of combined cryotherapy, paramomycin, and intralesional meglumine antimoniate in treating lupoid leishmaniasis and chronic leishmaniasis

Chronic or recurrent leishmaniasis (also called lupoid leishmaniasis) is one of the least common clinical presentations of cutaneous leishmaniasis. In contrast to the self-healing oriental sore, chronic leishmaniasis is characterized by persistent lesions and the parasite is thought to be maintained inside the macrophages. This chronic condition typically follows acute cutaneous leishmaniasis (CL), and in the majority of cases, *Leishmania tropica* is the causative agent.[1,2] It has a broad range of clinical presentation, including brown to red papules or yellowish-brown papules that are characteristically present at the margin of the scarred area. These papules gradually coalesce to produce a plaque, which is very much similar to cutaneous lesions of lupus vulgaris (even the apple-jelly nodules are similar in both lesions). These lesions usually aggravate in the summer and may even produce crusts or concentric rings.

Lupoid leishmaniasis is most prevalent in the endemic areas of leishmaniasis, particularly in the Middle East and Afghanistan,[3] with reported incidence of 0.5–6.2% of all CL cases. It strongly resembles lupus vulgaris, both clinically and histologically, and is therefore not usually diagnosed immediately but after a certain period of time. The amastigote forms are rare or absent.[4] Macrophages cannot kill the organism. These findings suggest that certain leishmanial strains, which induce chronic disease, may have the capacity to evade intracellular destruction by activated macrophages or there is a defect in the T-cell activation process by the amastigots.[5,6] Therefore, lupoid leishmaniasis may persist over a long time (even years) and aggravate gradually.

Many therapeutic regimens with different efficacies have been proposed for these two forms of leishmaniasis (i.e., lupoid and chronic). Some of these therapeutic modalities are combined intramuscular injection of meglumine antimoniate (MA) and allopurinol,[7] local injection of amphothericin B,[8] levamizole,[9] dapsone,[10] cryotherapy,[11] and intravenous injection of sodium stibogluconate.[12]

el Darouti has shown the effectiveness of intralesional injection of MA accompanied with local cryotherapy in the treatment of acute cutaneous leishmaniasis.[13] Also, we have reported the effectiveness of the triple-therapy regimen (local administration of paramomycin, cryotherapy, and intralesional injection of MA) for the treatment of acute leishmaniasis.[14] This study was designed to assess the therapeutic effectiveness of a proposed nonsystemic triple-drug therapy for the treatment of both types of lupoid and chronic leishmaniasis.

It ran as a descriptive clinical trial at the Skin Disease and Leishmaniasis Research Center, Isfahan, Iran.

The target population was those who had chronic or lupoid leishmaniasis. Among these cases, those with any concomitant systemic disease, those with lesions located in a 3 cm range distance from the eyelid, and those with concomitant pregnancy or lactation were excluded from the study.