

Leg Ulcers Treated with Topical Tacrolimus in Patients with Rheumatoid Arthritis

Johanna M. Mandelin¹, Kari K. Eklund² and Sakari Reitamo¹

Departments of ¹Dermatology, and ²Medicine, Division of Rheumatology, Helsinki University Central Hospital, Meilahdentie 2, FIN-00250 Helsinki, Finland. E-mail: johanna.mandelin@hus.fi

Accepted June 4, 2010.

Patients with rheumatoid arthritis (RA) are at increased risk of developing leg ulcers. A history of leg ulcer has been reported by 9% of RA patients (1), compared with only 1% of the total adult population in UK (2). The aetiology of leg ulcers in patients with RA appears to be multifactorial; venous insufficiency, vasculitis, and arterial disease are often contributory factors, either alone or together (3). Venous disease seems to be the most important factor and plays a role in up to 78% of cases (4).

In patients with RA, the mean duration of chronic leg ulcers is from 5 to 15 months, which means that they are often long-lasting and resistant to treatment (5). The treatment commonly used is similar to that used for other chronic leg ulcers, i.e. compression therapy, if there are indications of venous disease, and different dressings. Other treatments commonly used include antibiotics, immunosuppressive therapy, skin grafting, and other surgical options (2). However, the slow healing tendency and high morbidity create a need for new, efficient, and cost-effective treatments.

Tacrolimus ointment (0.1% and 0.03%) is approved for treatment of atopic dermatitis. Apart from one case report (6), there are, to our knowledge, no other reports on the efficacy of topical tacrolimus in the treatment of leg ulcers in patients with RA. As the management of chronic leg ulcers in patients with RA is unsatisfactory, we treated leg ulcers that were unresponsive to standard therapy with tacrolimus ointment and report here the results of five patients.

CASE REPORTS

Five patients, referred to our dermatological department for management of refractory rheumatic leg ulcers, were treated with topical tacrolimus. All patients fulfilled the revised American College of Rheumatology criteria for RA (7). No other

ulcer aetiology than RA and venous insufficiency was found. We describe here two of the successfully treated patients in detail and present all patients in Table I.

Patient 1 was a 84-year-old woman, who had had seropositive RA for 24 years. Her medication consisted of prednisone 5 mg/2.5 mg on alternate days. Her 3 months previously opened leg ulcer was initially treated with intensive local wound care and periodic debridement of necrotic tissue. A skin graft operation was performed, which was not successful. After 8 months of unsuccessful treatment, treatment with 0.1% tacrolimus ointment was started. It was applied into, and around, the ulcer every other day and covered with dressings (Unitulle[®], Roussel Uxbridge, England and Ete[®], Mölnlycke Healthcare, Göteborg, Sweden). After 6 weeks the ulcer was clearly healing, and after 16 weeks it was completely healed. During treatment, no local adverse events occurred, but the patient had one episode of cystitis and one episode of acute bronchitis, which were thought not to be related to tacrolimus treatment.

Patient 2 was a 69-year-old woman who had had RA for 49 years. She was referred to our clinic because of several leg ulcers on each leg that had been treated at the primary healthcare level for 4 months. Her anti-rheumatic treatment was prednisolone 5 mg twice daily. Due to the large number ($n = 16$) and total area (18.8 cm²) of the ulcers, tacrolimus ointment therapy was started at the first consultation. After one week of treatment, the ulcer area was only half of the area at baseline. The ulcer was completely healed after 13 weeks of treatment.

Whole-blood tacrolimus concentration

The whole-blood tacrolimus concentration during treatment was measured in 2 patients. Patient 4, with the largest ulcer area, showed the highest through-blood level of 1.7 ng/ml. Four months later the through-blood level was below the limit of detection (<1.5 ng/ml), as was the case for patient 3. These levels indicate that systemic exposure is low even when tacrolimus ointment is applied into a leg ulcer. Serum creatinine levels showed no signs of elevation with a mean value before treatment of 95 (SD ± 29, $n = 5$), and after treatment of 84 (SD ± 31, $n = 5$). No local adverse events that clearly related to tacrolimus ointment therapy were recorded. Interestingly, no burning or itch was reported, although this is the most common adverse event when treating atopic dermatitis (8).

Table I. Demographics of rheumatoid arthritis (RA) and ulcer healing in five patients treated with tacrolimus ointment

	Patient number				
	1	2	3	4	5
Sex/age, years	F/84	F/69	F/69	F/74	F/55
Duration of RA, years	24	49	20	50	30
DMARDs and corticosteroids	PRE	PRE	MPRE, HCQ	PRE, MTX, HCQ	PRE, MTX
Duration of ulcer, months	11	4	13	3	24
Ulcer size before tacrolimus, cm ²	6.00	18.75	12.75	52.88	3.75
Ulcer size after tacrolimus, cm ²	0.00	0.00	6.75	20.50	5.00
Treatment time, weeks	16	13	33	45	22

DMARDs: disease-modifying-anti-rheumatic drugs; PRE: prednisolone; MPRE: methylprednisolone; HCQ: hydroxychloroquine; MTX: methotrexate.

DISCUSSION

Complete healing of chronic leg ulcers in RA patients treated with tacrolimus ointment was observed in 2 of the 5 patients. Prior to tacrolimus treatment these patients (patients 1 and 2) had been treated for several months with standard treatments without any significant healing of the ulcers. Response to tacrolimus treatment was relatively rapid. In patients 3 and 4 healing was initially good, but stopped before the ulcers were completely healed. The reason for this, and for the increase in the ulcer area in patient 5, is not clear, but we suspect that bacterial infections may play a role.

Contaminated chronic ulcers often heal poorly (2). The two patients with a response to tacrolimus treatment had no, or minor, bacterial colonization of the ulcers when tacrolimus therapy was initiated, and had no significant ulcer infections during treatment. Patients 3, 4 and 5 had bacterial colonization of the ulcers with *Staphylococcus aureus*, and *Pseudomonas spp.*, *Enterococcus faecalis*, or *Enterococcus cloacae* at the time of initiation of treatment. At the time of treatment discontinuation these patients had clinically evident infections with either *S. aureus* or *Pseudomonas spp.* Bacterial colonization of the ulcer at treatment initiation seemed to predict a less favourable outcome, and thus thorough clearing of the ulcer base and antimicrobial treatment should be considered before starting treatment with tacrolimus, even in the absence of clinical infection.

The main mechanism of action of tacrolimus is the suppression of early activation of T lymphocytes. Interestingly, T-cell activation due to staphylococcal enterotoxins occurs via this same pathway (8). In infected ulcers the suppression of T-lymphocyte activation could result in increased manifestation of infection.

As the T cell is the cell type most likely to be affected by tacrolimus, the present study suggests a role for T cells in rheumatoid ulcers. Topical tacrolimus inhibits cytokine production, and is locally immunomodulating (8), which could suppress the vasculitic component likely to be involved in the ulcers associated with RA and thus promote healing. Other possible mechanisms include inhibition of other pro-inflammatory cells, such as tissue mast cells, which are a rich source of cytokines and serine proteases (9). TGF- β seems to be important for wound healing (10). Tacrolimus upregulated the release of TGF- β in keratinocytes (11). On the other hand, both an *in vitro* and *in vivo* study have suggested that tacrolimus inhibits the enhanced effects of TGF- β on wound healing (10). One-year treatment with tacrolimus ointment in patients with atopic dermatitis is associated with an increase in collagen synthesis (12). This may be a major advantage in ulcer healing compared with topical corticosteroids, which are widely used for the treatment of dermatitis surrounding ulcers.

The patient material described here is small and uncontrolled, but nevertheless, the results are promising

and a prospective, controlled, double-blinded study is warranted. Further studies should attempt to define the subgroup of patients that benefits from tacrolimus treatment and to establish the role of ulcer infections in the treatment response.

ACKNOWLEDGEMENTS

This study was supported by grants from Finska Läkaresällskapet, and Suomen Ihotautilääkäriyhdistys (SILY ry) and they are gratefully acknowledged.

Conflict of interest: Drs Mandelin and Reitamo have received funding for clinical studies on atopic dermatitis from Astellas Pharma. Dr Reitamo has had an advisory role for Astellas Pharma.

REFERENCES

1. Thurtle OA, Cawley MI. The frequency of leg ulceration in rheumatoid arthritis: a survey. *J Rheumatol* 1983; 10: 507–509.
2. McRorie ER, Jobanputra P, Ruckley CV, Nuki G. Leg ulceration in rheumatoid arthritis. *Br J Rheumatol* 1994; 33: 1078–1084.
3. Öien RF, Håkansson A, Hansen BU. Leg ulcers in patients with rheumatoid arthritis – a prospective study of aetiology, wound healing and pain reduction after pinch grafting. *Rheumatology* 2001; 40: 816–820.
4. McRorie ER, Ruckley CV, Nuki G. The relevance of large-vessel vascular disease and restricted ankle movement to the aetiology of leg ulceration in rheumatoid arthritis. *Br J Rheumatol* 1998; 37: 1295–1298.
5. Espinoza LR, Espinoza CG, Vasey FB, Germain BF. Oral methotrexate therapy for chronic rheumatoid arthritis ulcerations. *J Am Acad Dermatol* 1986; 15: 508–512.
6. Schuppe H, Richter-Hinz D, Stierle HE, Homey B, Ruzicka T, Lehmann P. Topical tacrolimus for recalcitrant leg ulcer in rheumatoid arthritis. *Rheumatology* 2000; 39: 105–106.
7. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315–324.
8. Reitamo S, Remitz A, Kyllönen H, Saarikko J. Topical non-corticosteroid immunomodulation in the treatment of atopic dermatitis. *Am J Clin Dermatol* 2002; 3: 381–388.
9. Sengoku T, Kishi S, Sakuma S, Ohkubo Y, Goto T. FK506 inhibition of histamine release and cytokine production by mast cells and basophils. *Int J Immunopharmacol* 2000; 22: 189–201.
10. Hasegawa T, Sumiyoshi K, Tsuchihashi H, Ikeda S, Nakao A, Ogawa H. FK506 inhibits the enhancing effects of TGF- β on wound healing in a rabbit dermal ulcer model. *J Dermatol Sci* 2007; 47: 37–40.
11. Lan CC, Kao YH, Huang SM, Yu HS, Chen GS. FK506 independently upregulates transforming growth factor beta and downregulates inducible nitric oxid synthase in cultured human keratinocytes: possible mechanisms of how tacrolimus ointment interacts with atopic skin. *Br J Dermatol* 2004; 151: 679–684.
12. Kyllönen H, Remitz A, Mandelin JM, Elg P, Reitamo S. Effects of one-year intermittent treatment with topical tacrolimus monotherapy on skin collagen synthesis in patients with atopic dermatitis. *Br J Dermatol* 2004; 150: 1174–1181.