

CONCISE REPORT

Treatment of cutaneous calcinosis in limited systemic sclerosis with minocycline

L P Robertson, R W Marshall, P Hickling

Ann Rheum Dis 2003;**62**:267–269

Objectives: To evaluate the effect of minocycline as treatment for cutaneous calcinosis in limited cutaneous systemic sclerosis (lcSSc).

Methods: Patients with lcSSc who had cutaneous calcinosis causing pain or ulceration, or both, were prescribed minocycline 50 or 100 mg daily regularly in an open label manner between November 1994 and April 2000. At routine clinical follow up the appearance of the calcinosis deposits was assessed clinically and radiographically, and the patients' assessment of the degree of discomfort, size, and frequency of ulceration was recorded. Demographic data, including disease duration, clinical features, and antinuclear antibody (ANA) titres, were also recorded.

Results: Nine patients have been treated to date. Eight of the nine patients were ANA positive, five of whom were positive for anticentromere antibodies. Eight patients have shown definite improvement and seven patients continue to receive treatment. The frequency of ulceration and inflammation associated with the calcinosis deposits decreased with treatment. The size of the calcinosis deposits also decreased but was less dramatic than expected. Improvement occurred at the earliest after one month of treatment with a mean (SD) of 4.8 (3.8) months. The mean (SD) length of treatment was 3.5 (1.9) years. An unexpected effect was the darkening of the calcinosis deposits to a blue/black colour.

Conclusions: Minocycline may be effective in the control of calcinosis in systemic sclerosis. A low dose only is required and appears to be generally well tolerated. The mechanism of action may be mainly through inhibition of matrix metalloproteinases and anti-inflammatory effects. Calcium binding properties and antibacterial actions may also have a role.

Minocycline is a broad spectrum antibiotic related to the tetracycline family. It has been appreciated for some time that the tetracyclines, including minocycline, have other actions and effects in addition to their antibacterial properties. They chelate calcium and iron,¹ can influence osteoclast function,² inhibit collagenases, and are potent inhibitors of neutrophil matrix metalloproteinase (MMP) function.³ Systemic sclerosis (SSc) is a connective tissue disease with an estimated prevalence of about 10–25/100 000. Calcinosis occurs in about 25% of patients, who usually have limited cutaneous systemic sclerosis (lcSSc). The calcinosis can cause local skin irritation, inflammation, ulceration and, therefore, considerable morbidity. Primarily because of its calcium chelating properties we have prescribed minocycline as treatment for painful, ulcerating dermal calcinosis in patients with lcSSc, with considerable success. We present a series of patients treated with minocycline and discuss the possible mechanisms of action.

METHODS

Patients with lcSSc who had cutaneous calcinosis causing pain or ulceration, or both, were prescribed minocycline 50 or 100 mg daily regularly in an open label manner between November 1994 and April 2000. Informed consent was obtained. At routine clinical follow up the appearance of the calcinosis deposits was assessed clinically and radiographically and the patients' assessment of the degree of discomfort, size, and frequency of ulceration was recorded. Demographic data, including disease duration, clinical features, and antinuclear antibody (ANA) titre were collected.

RESULTS

Nine patients have been treated to date (table 1), all female, with a mean (SD) age of 66.2 (13.8) years and mean (SD) disease duration of 11.9 (8.6) years. Eight of the nine patients were ANA positive, five positive for anticentromere antibodies. Seven patients continue to receive minocycline with no significant side effects. There has been no evidence that minocycline has changed the serology in our patients and none developed a lupus-like illness. No changes in renal function were seen. One patient who responded to treatment died of oesophageal carcinoma in June 2001. One patient was unable to tolerate the minocycline as it caused unacceptable nausea and dizziness. The most common improvement was a reduction in the incidence of ulceration and inflammation associated with the calcinosis deposits. A reduction in the size of the calcinosis deposits was also seen, particularly in one patient on x ray examination, but was perhaps less dramatic than expected if the main mechanism of action was calcium chelation.

Improvement occurred at the earliest after one month of treatment, with a mean (SD) of 4.8 (3.8) months. The mean length of treatment was 3.5 (1.9) years. An unexpected effect was that the calcinosis deposits turned a blue/black colour. Two patients discontinued the minocycline temporarily after improvement had occurred (fig 1), but within 2–3 months the calcinosis deposits became more prominent, painful, and inflamed (fig 2). Treatment was restarted and improvement again occurred. Some patients are now using minocycline cyclically rather than continuously. Treatment for 4–8 weeks keeps the calcinosis satisfactorily controlled for about 3–4 months. When the lesions start to become painful, inflamed, and enlarged again a further 4–8 weeks' course is started. Other patients have preferred to take a low dose of minocycline continuously.

DISCUSSION

Calcinosis occurs in about 25% of patients with lcSSc and can compound the problems of poor peripheral circulation,

Abbreviations: ANA, antinuclear antibody; lcSSc, limited cutaneous systemic sclerosis; MMP, matrix metalloproteinase; PMN, polymorphonuclear neutrophil

Table 1 Clinical characteristics of patients with lcSSc receiving minocycline for calcinosis and response to treatment

Patient	Age (years)	Sex	Disease duration (years)	Clinical features	Autoantibodies	Date starting minocycline	Improvement
1	55	F	17	Raynaud's Calcinosis Telangiectasia Arthritis Oesophageal	Anticentromere +ve	Nov 1994	Within 1 month
2	85	F	27	Sclerodactyly Calcinosis Arthritis	ANA +ve 1/320	Jun 1996	Over 1 year
3	74	F	5	Raynaud's Calcinosis Telangiectasia Sclerodactyly Oesophageal Arthritis	Anticentromere +ve	Apr 1996	Within 5 months
4	72	F	17	Raynaud's Calcinosis Telangiectasia Sclerodactyly Oesophageal	Negative	Sep 1999	Within 7 months
5	58	F	15	Raynaud's Calcinosis Pulmonary fibrosis Sclerodactyly	ANA +ve 1/160	Nov 1999	Over 1 year
6	70	F	1	Raynaud's Calcinosis Telangiectasia Sclerodactyly	ANA +ve 1/640	Apr 2000	Within 5 months
7	70	F	1.5	Raynaud's Calcinosis Telangiectasia Sclerodactyly	Anticentromere +ve	Feb 2000	Within 6 months. Died of oesophageal carcinoma June 2001
8	74	F	8	Raynaud's Calcinosis Telangiectasia Sclerodactyly	Anticentromere +ve	Aug 1992	Minimal – poorly tolerated
9	38	F	16	Raynaud's Calcinosis Telangiectasia Sclerodactyly Oesophageal	Anticentromere +ve	May 1995	Within 1 month

**Figure 1** Patient No 2: November 1998 after two years of minocycline treatment. There are severe flexor contractures at the metacarpophalangeal and proximal interphalangeal joints. The calcinosis deposits are blue/black in colour.

causing local skin irritation, inflammation, and ulceration and encouraging secondary infection. The appearance of the calcinosis deposits can also be distressing for patients. They most often occur on the digits but can develop more proximally on the knees and at the elbows.

Cutaneous calcification also occurs in dermatomyositis and lupus panniculitis. Various treatments have been reported as successful, including warfarin,⁴ probenecid,⁵ colchicine,⁶ diltiazem,⁷ intralesional corticosteroids,⁸ and carbon dioxide lasers.⁹ There are obvious problems with the above treatments. Long term anticoagulation is associated with an increased risk of potentially serious bleeding. Probenecid, colchicine, and diltiazem may be difficult drugs for patients to tolerate long term. Intralesional steroids are painful to receive and repeated

injections are not ideal for already atrophied, sclerodermatous skin. Carbon dioxide lasers are not widely available and need appropriate expertise to operate.

Most of our patients with lcSSc taking minocycline experienced a slow decrease in the size of their calcinosis deposits, healing of associated ulceration, and improvement in discomfort. The treatment was well tolerated, with only one patient discontinuing owing to nausea and dizziness. These side effects appear to be dose dependent. Dizziness is particularly associated with the lipophilic tetracyclines (for example, minocycline, doxycycline). The less lipophilic tetracycline and oxytetracycline are more prone to cause gastrointestinal side effects so may not be tolerated any better. The calcinosis deposits became discoloured turning a blue/black colour, suggesting that the minocycline had become incorporated into



Figure 2 Patient No 2: October 1999, 11 months after minocycline treatment was withdrawn. The calcinosis deposits are enlarged with increased surrounding inflammation particularly at the left third and fourth fingers.

the lesions. The precise mechanisms by which the minocycline causes these effects are not completely understood. It is a relatively poor chelator of calcium compared with iron and therefore the mechanisms involved are likely to be more complex than calcium chelation.

Minocycline is well known to cause the discolouration of various tissues, including teeth, bone, skin, and thyroid. Evidence from dental publications looking at the dental and oral discolourations associated with minocycline suggests that the colour change of minocycline is a result of oxidation either within the tissues or by exposure to bacterial processes.¹⁰ Haemosiderin has been detected in minocycline pigmented skin and it may be responsible for the colour change. However iron is not a constituent of minocycline or its metabolites. The haemosiderin may be derived from extravasated erythrocytes. None of our patients found this discolouration unacceptable as their calcinosis became less painful and smaller.

Over the past decade it has become apparent that tetracyclines have non-antimicrobial properties which may also be of therapeutic use. They have anti-inflammatory actions and suppress polymorphonuclear neutrophil (PMN) activity, inhibit the cyclo-oxygenase pathway, and scavenge for reactive O₂ metabolites produced by PMNs that play a part in tissue destruction.³ Tetracyclines also directly inhibit collagenolytic enzymes including matrix MMPs, elastase and cathepsins.³ These properties have been of interest in conditions which are characterised by overproduction of these enzymes, and there has been some success in treating non-infected corneal ulcers,¹¹ blistering skin disorders,¹² rheumatoid arthritis,¹³ and scleroderma.¹⁴ We propose that one of the main actions of minocycline in our patients with lcSSc is through its MMP inhibitory activity, thus reducing the inflammation and ulceration associated with calcinosis deposits.

The calcium binding actions of tetracyclines are well known and in view of the reduction in size of the calcinosis deposits with minocycline treatment, it is likely that this action is also

relevant. Tetracycline has been shown to be a potent anticalcification agent in an in vitro ectopic anticalcification model. Tetracycline reduced the calcification of bioprosthetic heart valve cusps implanted subdermally in rats by 55% compared with controls.¹ Another possibility is that the minocycline through binding to calcium may reduce local PMN activity by preventing the entry of calcium into PMNs. There is evidence that an increase in intracellular calcium is a trigger for O₂ free radical production by PMNs.¹⁵ Therefore the calcium binding and PMN suppressing properties of minocycline may not be entirely mutually exclusive.

The antibiotic actions of minocycline may also have had a role in the improvement seen. The calcinotic deposits were often ulcerated. Associated secondary infection, contributing to the local inflammatory process and impaired healing, is therefore possible.

In conclusion we believe that minocycline is a potentially useful drug in the treatment of calcinosis in patients with lcSSc. Its mechanisms of action are probably multiple but we suspect the MMP inhibition activity may be predominant. Further studies on the actions of the tetracyclines will be helpful in improving our understanding of these effects.

Finally, a double blind placebo controlled study of minocycline for the treatment of calcinosis is warranted in view of the substantial benefits seen in this case series.

Authors' affiliations

L P Robertson, Department of Rheumatology, Royal Cornwall Hospital, Truro, UK

R W Marshall, Academic Rheumatology, University of Bristol, UK

P Hickling, Department of Rheumatology, Derriford Hospital, UK

Correspondence to: Dr L P Robertson, Department of Rheumatology, Royal Cornwall Hospital, Truro TR1 3LJ, UK; rwmlpr@eurobell.co.uk

Accepted 3 July 2002

REFERENCES

- Cohen H**, Solomon V, Alferiev IS, Breuer E, Ornoy A, Patlas N, *et al*. Bisphosphonates and tetracycline: experimental models for their evaluation in calcium related disorders. *Pharm Res* 1998;15:606–13.
- Donahue HJ**, Iijima K, Goligorsky MS, Rubin CT, Rifkin BR. Regulation of cytoplasmic calcium concentration in tetracycline treated osteoclasts. *J Bone Min Res* 1992;7:1313–18.
- Gabler WL**, Creamer HR. Suppression of human neutrophil functions by tetracyclines. *J Periodontol Res* 1991;26:52–8.
- Yoshida S**, Torikai K. The effects of warfarin on calcinosis in a patient with systemic sclerosis. *J Rheumatol* 1993;20:1233–5.
- Skuterud E**, Sydnes OA, Haavik TK. Calcinosis in dermatomyositis treated with probenecid. *Scand J Rheumatol* 1981;10:92–4.
- Fuchs D**, Fruchter L, Fishel, Holtzman M, Yaron M. Colchicine suppression of local inflammation due to calcinosis in dermatomyositis and progressive systemic sclerosis. *Clin Rheumatol* 1986;5:527–30.
- Dolan AL**, Kassimos D, Gibson T, Kingsley GH. Diltiazem induces remission of calcinosis in scleroderma. *Br J Rheumatol* 1995;34:576–8.
- Lee SS**, Felsenstein J, Tanzer FR. Calcinosis cutis circumscripta: treatment with intralesional corticosteroid. *Arch Dermatol* 1978;114:1080–1.
- Bottomley WW**, Goodfield MJ, Sheehan-Dare RA. Digital calcification in systemic sclerosis: effective treatment with good tissue preservation using the carbon dioxide laser. *Br J Dermatol* 1996;135:302–4.
- Cheek CC**, Heymann HO. Dental and oral discolourations associated with minocycline and other tetracycline analogues. *J Esthet Dent* 1999;11:43–8.
- Perry HD**, Golub LM. Systemic tetracycline in the treatment of non-infected corneal ulcers. *Ann Ophthalmol* 1985;17:742–4.
- Berk MA**, Lorincz AL. The treatment of bullous pemphigoid with tetracycline and niacinamide. *Arch Dermatol* 1986;122:670–4.
- O'Dell JR**, Blakely KW, Mallek JA, Eckhoff PJ, Leff RD, Wees SJ, *et al*. Treatment of early seropositive rheumatoid arthritis: a two-year, double-blind comparison of minocycline and hydroxychloroquine. *Arthritis Rheum* 2001;44:2235–41.
- Le CH**, Morales A, Trentham D. Minocycline in early diffuse scleroderma. *Lancet* 1998;352:1755–6.
- Hallett MB**, Campbell AK. Is intracellular calcium the trigger for oxygen radical production by polymorphonuclear leucocytes? *Cell Calcium* 1984;5:1–19.