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The successful use of minocycline in pyoderma gangrenosum - a report of seven cases and review of the literature

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We report seven cases in which minocycline was successfully used to treat pyoderma gangrenosum. This more than doubles the six previously reported cases. Minocycline is considerably safer than systemic steroids and may, therefore, represent a useful advance in the treatment of this disease.

Introduction

It is often stated that a disease with many remedies has no cure. Pyoderma gangrenosum (PG) might appear to be a prime example of such a disease. The established treatment consists of high doses of oral steroids - with or without 'steroid sparing agents'.[1] Among alternative treatments advocated are: topical steroids, clofazimine,[2] intra-lesional triamcinolone,[3] cyclosporin A,[4] topical disodium cromoglycate,[5] cyclophosphamide,[6] azathioprine,[7] sulphasalazine,[8] dapsone,[9] plasma exchange[10] and minocycline.[11-13]

Of all these agents minocycline is, in our experience, the safest, and appears currently to be the most widely used. We were therefore surprised to discover that the entire literature on the use of minocycline in PG consists of three reports of successful use of the drug in a total of six cases.[11-13]

This is presumably due to the relative rarity of PG and other inherent difficulties in performing a trial of any new treatment. Not least of these are the heterogeneity in the severity of PG and in the diseases associated with it.

We therefore wish to report our experience of the use of minocycline in a further seven cases of PG.

Case reports

Case 1

Mr AC first developed PG in June 1977, aged 24, as a complication of facial acne vulgaris. This remained active in spite of treatment with oral prednisolone in high doses (55–80 mg alt die) for 18 months, before resolving on prednisolone 80 mg every other day. Extensive investigation revealed no evidence of any associated disease.

Lesions of pyoderma recurred in May 1983 involving the right temple. Treatment was commenced with intralesional triamcinolone, but no response was obtained. Minocycline 100 mg bd was then commenced, and after one month of this treatment alone the lesion had almost healed. Three further injections of intralesional triamcinolone effected complete resolution. Minocycline was discontinued in July 1983.

A further recurrence developed in November 1983, involving the right scapular region. This responded completely within 3 months to minocycline 100 mg bd and two intralesional injections of triamcinolone. The minocycline was then continued at the dose of 100 mg bd until April 1985 when the dose was halved.

Two additional recurrences of PG developed following attempts to reduce the dose of minocycline, and resolved after the dose was restored. Two doses of intralesional steroid were injected on one occasion, and a single dose on the other. The dose of minocycline was then maintained at 100 mg tds and he remained free from pyoderma for 2 years.

Two subsequent minor recurrences have responded promptly to an increase in the dose of minocycline to 200 mg daily and intralesional steroid injections.

Case 2

Mr JB presented in July 1981 at the age of 69, with a 5 month history of weeping ulcers over the back, chest, and arms. The clinical appearances were considered diagnostic of PG, and histology was compatible. Investigations revealed no evidence of additional pathology.

He was treated with minocycline 100 mg bd and the lesions gradually improved. Three months later only two remained, although complete healing took 6 months. Minocycline was continued in the same dose for a further 6 months and then stopped. There was no evidence of recurrence after a further 9 months of follow-up.

Case 3

Mrs JM presented at the age of 58 in January 1986 with an ulcerated lesion over the lateral aspect of the right shin. This had been slowly enlarging since its first appearance 2 months earlier. Her previous medical history was unremarkable except for recurrent episodes of posterior uveitis.

Examination revealed a sloughy ulcer measuring 6 cm in width and 7 cm in length with an undetermined necrotic margin, the appearance being typical of PG.

Investigations were all normal except for the rheumatoid factor which was positive in low titre.

Treatment was commenced with minocycline 100 mg twice daily orally and 0.05 per cent fluocinonide cream applied daily to the ulcer under an occlusive dressing.

The lesion began to heal within 1 week and had totally resolved within 2 months. Attem
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Treatment was commenced with minocycline 100 mg twice daily orally and 0.05 per cent fluocinonide cream applied daily to the ulcer under an occlusive dressing.

The lesion began to heal within 1 week and had totally resolved within 2 months. Attempts to reduce the dose of minocycline were followed on two occasions by recurrences of the ulcer when the dose was reduced to below

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50 mg daily. She therefore remains on this dose at present as maintenance therapy. She requires no topical steroids.

Case 4

Mrs MC presented in January 1987 at the age of 63 with a 3 month history of a persistent ulcer on the abdomen and a similar lesion which had developed on the right shin 3 days earlier. The appearances were typical of PG. Investigations revealed mild ulcerative colitis for which no treatment was initially required. Treatment was commenced with minocycline 100 mg bd and definite improvement was noted in both lesions 2 weeks later. Triamcinolone was then injected into the lesions. Complete healing of the pyoderma had occurred by April. The dose of minocycline was maintained until June, then gradually tailed off.

In December 1987 the dose of minocycline was cut to 50 mg daily. After 1 month on this dose and during an episode of more active colitis, a recurrence of pyoderma developed on the abdomen. The dose of minocycline was doubled, and treatment with sulphasalazine 4 gm daily was commenced for her colitis. The abdominal lesion healed completely in approximately 6 weeks. Treatment was maintained with minocycline 100 mg daily and sulphasalazine 3 gm daily, and no further recurrence developed.

Case 5

Mr PR presented with PG in September 1987 at the age of 56. Typical PG lesions had developed on the left temple and perineum over the previous 2 months. Investigations revealed no evidence of any associated illness. Treatment was commenced with minocycline 100 mg bd and within 1 week a marked improvement had been noted.

The lesions subsequently continued to heal, but rather slowly, and the dose of minocycline was therefore increased to 100 mg tds 1 month later. During December 1987 the perineal lesion resolved. The lesion over the temple improved but did not completely heal, and a single intralesional injection of triamcinolone was performed in February 1988. Three weeks later this lesion had also healed, leaving a fragile scar over the temple, which broke down occasionally when traumatized. The dose of minocycline was gradually reduced, and the drug was finally stopped in October 1988.

Case 6

Mr JB first developed PG in November 1987, aged 62, in association with an IgA monoclonal band, which has so far behaved in a benign manner. The initial episode responded to systemic steroids, but the disease recurred at the same site on the left leg 8 months later. On this occasion the patient was treated with minocycline 200 mg bd. One week after commencing treatment the lesion had noticeably reduced in size. It subsequently resolved completely over the following 4 weeks, and the dose was reduced to 100 mg daily. The patient has remained in remission to date.

Case 7

Mr DG had suffered from rheumatoid disease for 26 years. He presented in December 1988 at the age of 60, with a 1 month history of multiple ulcers over the trunk. The appearances were typical of PG. The largest lesion, in the right inguinal region, measured 18 cm in length by 8 cm in width at presentation.

Treatment commenced in hospital with minocycline 200 mg bd. Healing was clearly evident within 4 days of starting treatment, and progressed rapidly, so that at the time of discharge, 3 weeks later, all of the ulcers on his trunk had healed and the lesion in the right groin had reduced in size to 8 cm × 4 cm. On review in outpatients 1 month later healing had progressed further.

Discussion

The term pyoderma gangrenosum was first used by Brunsting, Goeckerman and O'Leary in 1930.[14] Under this title these authors reported a series of five patients suffering from cutaneous ulcers of an unusual and distinctive appearance. These were surrounded by a blue zone, consisting of an oedematous boggy strip from 5 to 8 mm wide, in which there developed extensive undermining and necrosis of the subcutaneous tissue. Four of these patients suffered from ulcerative colitis. In early reports the disease was considered to be caused by a variety of infections with bacteria or amoebae.[15] Treatment was therefore directed towards eradication of these organisms using a variety of measures including antiseptics, vaccines, X-rays, carbon dioxide snow, cautery,[14] hyperimmune steptococcic serum,[16] and, when they became available, sulphonamides.[17,18,8] However, further investigation failed to implicate any consistent association with a specific organism,[19] and it was noted that if early pustular lesions were sampled, cultures always proved to be sterile.[20–22]

More significantly, associations were increasingly recognized with a number of diseases considered to be linked with immune dysfunction. These included rheumatoid disease, chronic active hepatitis, inflammatory bowel disease, leukaemias, and dysproteinaemias.[1] Paradoxically, therefore, the treatment approach in general use changed from methods directed towards eradicating infection, to the use of systemic steroids and immunosuppressants. These proved highly effective.[1]

The use of systemic steroids and immunosuppressants is, of course, associated with significant morbidity and mortality,[23] and the ensuing years have seen a search for effective safer alternatives. There has been a return to the use of antibiotics and, in particular, minocycline.

The mechanism of action of these agents in PG remains obscure, but it has been suggested that it may be related to alterations in neutrophil polymorph function. Infiltration by neutrophils is a consistent histological feature of PG,[24] and tetracyclines inhibit the chemotactic responsiveness of neutrophils.[25]

Side-effects of minocycline are rarely serious. They include pigmentation of the face or extremities, (especially at high dose),[26] exanthematous, urticarial, bullous and fixed drug eruptions.[27] Photosensitive eruptions also occur.[27] Nausea, vertigo and infections with candida albicans may occur.[27] All tetracyclines are contraindicated in children under the age of 12 as they cause staining of the teeth. More seriously, episodes of headache and visual disturbance associated with raised intracranial pressure have been reported.[28,29] This can also occur with tetracycline but appears to be a rare

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phenomenon.[28] This effect is not dose-related, and is reversible on stopping treatment.

The use of minocycline in PG was first reported by Lynch and Bergfeld in 1978,[11] following an initial chance observation. They reported four cases which responded to a dose of 300 mg daily. These were associated in one case each with rheumatoid disease, dysproteinaemia and ulcerative colitis. Davies and Piper[12] described a further case, associated with rheumatoid disease, which responded to a dose of 100 mg tds. In the French literature a single case showing a favourable response was reported by Bernard *et al.*[13]

In all our cases there was improvement of the PG following treatment with minocycline. Several cases also showed a marked tendency to relapse when the minocycline was reduced in dose or stopped. It therefore appears highly likely that minocycline is of real value in this condition. Furthermore, both in previous reports and in our cases, response to minocycline appears to occur regardless of disease severity or the coexistence of other associated conditions such as paraproteinaemias, rheumatoid disease, or ulcerative colitis.

Our cases bring to a total of 13 the number of cases of PG reported to have been treated successfully with minocycline. Although the results of the use of minocycline sound very promising, further studies of the use of this treatment are required before it can really be established as a first-line modality.

PG is a difficult disease to investigate and a double-blind trial of minocycline against either placebo or prednisolone is probably impossible. It might, however, be possible to perform an open study of a large group of patients on a multi-centre basis.

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