Use of minocycline in rheumatoid arthritis: a district general hospital experience

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Double blind, randomised controlled trials have shown that minocycline is an effective disease modifying antirheumatic drug (DMARD) in rheumatoid arthritis (RA), compared with placebo1 or hydroxychloroquine.2 Minocycline was first used on the premise that RA may be caused by an infection but, subsequently, it was also shown to possess other properties such as matrix metalloproteinase inhibition and immunomodulation. Despite reported proof of its efficacy, most rheumatologists do not favour the use of minocycline in RA, possibly owing to availability of other “standard” DMARDs.

We performed a retrospective review of the case notes of 28 patients with RA who were prescribed minocycline. Treatment with minocycline in these patients began before the widespread availability of biological agents. Our aim was to assess the efficacy and safety of this drug in our hands compared with published trials. Our patients included 24 women and four men, aged between 43 and 80 years (mean 60). Their disease duration ranged from 2 to 48 years (mean 18). Rheumatoid factor status was known in 26 patients, of whom 21 were seropositive. Minocycline was used only after at least two to eight DMARDs (mean five drugs) had failed. None of these patients were receiving concomitant treatment with other DMARDs at the time of starting minocycline. We used minocycline in a dose of 100 mg twice daily.

As this was a retrospective review of case notes, improvement in disease activity could only be assessed from the information in clinic letters. Clinical improvement was assessed by factors such as improvement in joint pain and swelling, duration of early morning stiffness, function, physician’s global assessments, and general wellbeing of the patient, while improvement in laboratory measures was assessed by change in erythrocyte sedimentation rate (ESR) and haemoglobin.

In the opinion of the rheumatologist the drug was considered effective in 10 (36%) patients, of whom seven were still taking it at the time of performing this study. Three of these 10 patients had to stop taking minocycline because of side effects. Benefit was noted after a mean duration of 4 months (range 2–6) and was sustained for a mean duration of 14 months (range 8–24). Stopping treatment owing to a lack of efficacy occurred in only 7/28 (25%) patients and they had taken the drug for a mean duration of 6 months (range 3–11). No differences in disease duration, number of DMARDs tried before starting minocycline, or rheumatoid factor status were found between responders and non-responders (also including patients who stopped minocycline owing to toxicity, but had received the drug for at least 4 months).

There was documented improvement in clinical measures in all patients who responded. Laboratory data were available for 24 patients, of whom 18 had taken the drug for at least 4 months (eight responders, 10 non-responders). Among the eight responders, ESR values improved by more than 40 mm/1st h in four patients (reduced to 13, 25, 31, and 31 mm/1st h), while haemoglobin improved by more than 20 g/l in two patients. We did not note any deterioration of ESR or haemoglobin values in any of the other responders. However, the ESR and haemoglobin values either remained the same or deteriorated in all non-responders save for one patient.

Thirteen (46%) patients, including the three patients in whom the drug was considered effective, stopped taking the drug because of side effects. There were no serious or long term adverse effects. The side effects that were directly attributable to minocycline included dizziness (four patients), nausea (three patients), dizziness and nausea, allergic rash, and reversible grey pigmentation (one patient each). Three patients stopped the drug owing to problems not directly related to minocycline (atrial fibrillation, allergic skin rash to trimethoprim, and non-specific chest pain). The reason for stopping minocycline was not clear from the notes for one patient.

As far as we know, no one has reported their experience with the use of minocycline in patients with RA outside a research setting. If the fact that minocycline was only tried in our patients after they had failed to respond to other DMARDs is taken into account, it can be considered as a moderately efficacious drug. Studies in future should examine the role of minocycline in early RA either on its own or as part of combination DMARD treatment.

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REFERENCES
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Toxic myopathy induced by the ingestion of loquat leaf extract

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Loquat (Eriobotrya japonica) belongs to the trees of the Rosaceae family. Loquat leaves are widely used in the preparation of oriental herbal teas. In folk medicine, the loquat leaves are used against various skin diseases, cough, nausea, and itching.

Loquat leaves contain ursolic acid and oleanolic acid, which both have hypoglycaemic and antihyperlipidaemic effects in test animals.1,2

CASE REPORT

We present a patient with hypertriglyceridaemia, who after ingestion of loquat leaf extract had a remarkable decrease in triglycerides and an increase in high density lipoprotein (HDL). However, this benefit was accompanied by toxic myopathy, resembling the effect of HMG-CoA reductase inhibitors and fibrac acid derivatives.

A 39 year old man was found to have a high fasting triglyceride level on routine blood testing. The total cholesterol level was normal, and the HDL cholesterol was low. He was otherwise healthy and smoked one packet of cigarettes a day for 5 years. He did not take any drugs, and denied habitual alcohol intake. The patient was advised to stop smoking, and he started a low fat and sugar diet.

Three months after this regimen his triglyceride level remained high (9.38 mmol/l), total cholesterol 4.30 mmol/l, and HDL 0.80 mmol/l. The patient was prescribed bezafibrate 400 mg daily. After 3 months on this regimen, the triglyceride level diminished to 3.88 mmol/l, but the creatine kinase (CK) was 1400 IU/l (6 months earlier the CK level was normal). The man had not reported myalgia; he denied fall or any trauma within the past weeks. He also denied intramuscular drug injection and strenuous exercise. Bezafibrate was stopped and the CK level returned to normal after 2 weeks.

During the following year the patient had blood tests every 2 months, the triglyceride level during this period ranged from 6.20 to 18.06 mmol/l, the total cholesterol from 3.69 to 5.10 mmol/l, the HDL from 0.80 to 1.05 mmol/l, and the CK was normal. The man refused to take lipid lowering agents, and he decided to try herbal medicines.

He had heard that an extract of loquat leaves (obtained by boiling the leaves in water) would be effective for his problem. During the following 2 weeks he drank about 2 litres daily of this extract until he presented with severe myalgia, particularly of the proximal muscles of the arms and legs. On examination he was afebrile, his body mass index was 22 kg/m². The proximal part of his limbs was tender, no erythema was detected. Blood tests showed: triglyceride 2.20 mmol/l, total cholesterol 4.50 mmol/l, HDL cholesterol 1.10 mmol/l, CK 5950 IU/l, lactic dehydrogenase 412 IU/l, aspartate aminotransferase 113 IU/l, alanine aminotransferase 85 IU/l. A complete blood count, serum electrolytes, kidney, and thyroid function tests were normal. An electrocardiogram showed sinus rhythm without signs of ischaemia.

The patient was admitted and treated with intravenous fluids. On the third day the transaminases returned to normal, the CK level decreased to 1102 IU/l, and the patient was discharged. Blood tests taken after 2 weeks showed a normal CK level and a triglyceride level of 4.14 mmol/l. During the following 5 months the patient underwent three blood tests that showed a triglyceride level of 4.74–10.18 mmol/l and an HDL level of 0.85–1.00 mmol/l; he decided to take the loquat leaf extract at reduced doses. Blood tests taken three weeks later showed: triglyceride 1.98 mmol/l, HDL 1.15 mmol/l, and CK 1330 IU/l; the transaminases were normal.

DISCUSSION

The decreased triglyceride level, in addition to the myopathy, represented by myalgia and a rise in CK, in the absence of other apparent causes, strongly suggests that these effects are related to the ingestion of loquat leaf extract. This assumption is supported by the recurrence of the same effects after rechallenge by the patient himself. Whether the antihyperlipidaemic effect and toxic myopathy are related to the action of one or more constituents of the loquat leaves is not clear.

Only a minority of patients develop myopathy in response to lipid lowering agents,++ with an incidence ranging from 0.1 to 0.3%. There are strong indications that other (endocrine, metabolic, genetic) factors may have a role in the pathophysiology of the myopathy.7

In our patient the CK level increased significantly after 3 months’ treatment with bezafibrate. This patient might have been particularly sensitive to this type of treatment, and may have a predisposing factor, probably genetic.

The pronounced difference of CK level on the two occasions after ingestion of loquat leaf extract, suggests that this extract has a dose dependent toxic effect. However, this toxic effect may occur only in predisposed patients as is the case for myopathy related to lipid lowering agents.

Ingestion of loquat leaves should be included in the differential diagnosis of myopathy. The potential effect of