Introduction

Minocycline is a semi-synthetic tetracycline with improved anti-bacterial activity, oral availability and longer half-life. It is commonly used to treat acne vulgaris and rosacea which often requires months to years' therapy. Apart from this, it is also recognized as having anti-inflammatory, immunomodulatory, and inhibitory effects on matrix metalloproteinases. In recent years, it has been used as a disease modifying agent in rheumatoid arthritis (RA). Its role is established by three randomized double-blinded placebo-controlled trials. It is found to be more effective than hydroxychloroquine in early seropositive RA. Moreover, it is also used in treating Lyme disease and reactive arthritis.

Minocycline is generally considered a safe drug. Reported adverse effects include gastrointestinal toxicity, nephritis, vestibular symptoms, skin hyperpigmentation, intracranial hypertension, photosensitivity, rashes, eosinophilia, fever, hypersensitivity pneumonitis and toxic hepatitis.

Case Report

A 47-year-old Chinese lady presented in May 2000 with 3-day history of fleeting polyarthralgia of the small and large joints. She had a long history of rosacea with regular follow up by the dermatologists and was maintained on 100 mg minocycline daily for 10 years. In the recent year, she noticed to have reticular skin rash over her limbs with Raynaud's phenomenon and numbness over her ankles. Apart from livedo reticularis (Figure 1), physical examination was unremarkable. She was afebrile with no signs of active arthritis.

Initial investigations showed normochromic normocytic anaemia with hemoglobin (Hgb) level of 10.6 g/dL and erythrocyte sedimentation rate (ESR) of 64 mm/hr. Albumin was 33 g/dL and globulin was 57 g/dL with a polyclonal increase in globulin. Renal and liver functions were normal. Urine protein was negative. Rheumatoid factor was negative and antinuclear antibody (ANA) was 1:160. Anti-dsDNA and anti-extractable nuclear antigen (anti-ENA) were negative. Complements (C3 and C4) were normal. Perinuclear-antineutrophil cytoplasmic antibody (p-ANCA) was positive.
with elevated anti-myeloperoxidase (anti-MPO) level of 30 U/ml (normal <5). Cryoglobulin was negative. Anti-cardiolipin antibodies (aCL) were elevated with IgG 34 GPL/ml (normal <15) and IgM 33 MPL/ml (normal <12.5). Lupus anticoagulant was negative.

Minocycline was stopped. Non-steroidal anti-inflammatory drug was given for arthralgia. Skin biopsy performed on her right thigh showed features of leucocytoclastic vasculitis. Immunofluorescence was negative. She was put on aspirin and persantin as suggested by the dermatologist.

On follow up 4 weeks later, she had no more arthralgia but still complained of numbness of her feet. Physical examination reviewed loss of pinprick sensation on the dorsum of her feet. Propioception was intact. Diminished muscle power was noted on dorsiflexion and plantar flexion of both feet.

Nerve conduction study showed combined motor and sensory peripheral neuropathy. Sural nerve biopsy was performed and showed demyelination and axonal degeneration with no definite vasculitis. She started to develop Raynaud's phenomenon of her toes and an increase in the extent of livedo reticularis. As minocycline had been stopped for 4 months and there were persistent symptoms, prednisolone was commenced at a dose of 0.5 mg/kg/day.

She responded partially to steroid treatment with an improvement in ankle movement. Steroid dose was gradually tailed down. The biochemical and serological markers gradually normalized (ESR 7 mm/hr, Hgb 12.1 g/dL, albumin/globulin 46/36 g/dL and anti-MPO turned negative). Her neuralgic pain improved slowly but numbness of the feet and livedo reticularis persisted.

**Discussion**

Our patient illustrates a case of minocycline-induced vasculitis with polyarthralgia, livedo reticularis, peripheral neuropathy, positive ANA, anti-MPO and aCL antibodies.

Minocycline-induced autoimmune syndromes can be categorized into 4 types, namely minocycline-induced serum sickness, minocycline-induced lupus, minocycline-induced autoimmune hepatitis (AIH) and minocycline-induced vasculitis. The clinical and serological features of the separate syndromes may overlap. Minocycline-induced lupus and hepatitis are the most common events. On reviewing the literature, over 60 cases of minocycline-induced lupus and 24 cases of minocycline-induced AIH have been reported. In 13 cases, both syndromes coexist. Except for serum sickness, which presents shortly (mean 16 days) after minocycline, the other autoimmune syndromes manifest after prolonged use (mean 25.3 months).

**Minocycline-induced Serum Sickness**

Clinical features include fever, arthralgia, lymphadenopathy and urticarial rash a few days after starting minocycline. This condition is self-limiting and symptoms subside soon after drug cessation.

**Minocycline-induced Lupus**

This is the commonest entity. It is defined as a syndrome with at least one clinical feature of systemic lupus erythematosus (SLE), positive ANA together with circumstantial association between the use of drug and development of clinical and
serological features. It has been estimated that minocycline is associated with an 8.5 fold increased risk of developing a lupus-like syndrome. It can cause disease exacerbation in cases of probable SLE. It occurs more frequently in female (female to male ratio = 8:1) suggesting that male sex might possess protective factor. Most patients remit within few days after drug withdrawal, a few need a short course of corticosteroid. There was a case report of death from pancytopenia.

Minocycline-induced Autoimmune Hepatitis (AIH)

Patients develop variable degree of elevated serum transaminases (2-10 fold) which usually normalize within 3 months after drug cessation. Serum level of alkaline phosphatase is usually normal. In the literature, one patient died with severe hepatitis and another required liver transplantation.

Minocycline-induced Vasculitis

Common presentations include fever, arthralgia, symmetrical polyarthralgia/polyarthritis. More than half had fever, weight loss, malaise and rash. Two had extra-articular/extra-hepatic involvement with Hashimoto thyroiditis and peripheral neuropathy. All patients had positive ANA predominantly homogenous pattern. Acute phase reactants were elevated. Majority of them had rapid remission after drug cessation but one patient required a 2-year course of immunosuppressive therapy.

Use of minocycline for treatment of RA was established in randomized controlled trials. There was no report of minocycline-induced autoimmune syndrome among the 345 RA patients in the trials. In a small study, two out of 30 RA patients developed unexplained hepatitis that resolved on withdrawal of treatment. There was one case report of minocycline-induced lupus-like syndrome in RA patient.
It is difficult to diagnose drug-induced autoimmune phenomenon in RA patients as elevated ESR and polyarthralgia/polyarthritis may reflect disease activity. New rheumatic symptoms, newly emerged ANA and the absence of elevated C-reactive protein warrant a high suspicion for patients taking long-term minocycline. To make the issue more complicated, minocycline was found to be effective in treating RA-related leucocytoclastic vasculitis. Additional clinical research is needed to document the long-term efficacy: toxicity ratio of minocycline in RA.

Conclusions

Minocycline is increasingly used in the treatment of rheumatic diseases and side effects are going to be encountered more frequently. It is advisable to perform periodic liver function tests and ANA accompanied with clinical surveillance for patients on long-term minocycline. Patients should be informed of these rare but potentially serious adverse effects, and if happen, they should be advised to avoid all tetracycline since information on potential cross-reactivity is not available. Rechallenge of the drug is not recommended given a large number of alternative treatment options available.

References