as "conscientious and altruistic"; Godlee, adding insult to injury, prefers to label WHO staff as "demoralised."

What is truly demoralising is the tendency of the *BMJ* to recycle again and again a negative image of WHO, while denying credit where it is due. This doesn't hurt just WHO staff; it hurts the people WHO is trying to help. In devoting so many thousands of words to WHO, the *BMJ* had a real chance to reach the same high standards that it seeks of us and to enrich

the debate over the future of global health. Instead, the *BMJ* cheapened it, and we are left to wonder why.

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Lesson of the Week

Minocycline and pulmonary eosinophilia

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Pulmonary eosinophilia due to minocycline is a potentially serious complication of a commonly used drug

Minocycline hydrochloride, a semisynthetic tetracycline derivative, is often prescribed by general practitioners and dermatologists for acne vulgaris in young people. It is also useful in treating bronchopulmonary and urinary tract infections. Longstanding familiarity with the drug has established its relative safety.¹ Adverse effects that have been reported are nausea, fever, blood eosinophilia, vestibular symptoms, skin rashes, photosensitivity, and hyperpigmentation. Minocycline is known to cause tooth discoloration in the fetus and is contraindicated during pregnancy and in childhood up to the age of 8 years.

We report on four patients who became unwell with fevers and pulmonary eosinophilia while receiving minocycline for acne.

Case reports

CASE 1

One week after starting Minocin MR (Lederle Laboratories, UK) 100 mg once a day for facial acne, a 36 year old woman presented with fevers, cough, shortness of breath on exertion, and weight loss. A chest radiograph showed bilateral infiltration, and her blood eosinophil count was $1.3 \times 10^9/l$ (14%). IgE in the blood measured 807 IU/l, with specific IgE against house dust mite only. Tests for antinuclear factor, antineutrophil cytoplasmic antibody, and aspergillus precipitins had negative results. The sputum contained large clumps of eosinophils with numerous Charcot-Leyden crystals. The patient was treated with 30 mg prednisolone once a day for 10 days, and minocycline was discontinued. After three weeks the patient was asymptomatic with a normal chest radiograph and eosinophil count. Rechallenge (with informed consent) resulted in a prompt recurrence of symptoms, chest radiograph changes, and blood eosinophilia ($1.9 \times 10^9/l$; 24%) after three doses of Minocin MR 100 mg. Again these resolved after discontinuation of the drug.

CASE 2

A 29 year old woman with facial acne who had been taking Minocin MR 100 mg once a day for six weeks reported a four week history of effort dyspnoea. A chest radiograph showed opacities peripherally in the right upper and lower zones (fig). The blood eosinophil count was $0.8 \times 10^9/l$ (12%). Aspergillus precipitins were positive (single line). Transbronchial biopsy showed chronic inflammation in the presence of eosinophils. During the investigations the patient's minocycline had been discontinued and her symptoms and radiological results had improved, but when

the drug was restarted (minocycline had not been identified as the aetiological agent at this stage), the symptoms recurred, to resolve again after discontinuation.

CASE 3

A 25 year old woman became unwell within three days of starting Minocin MR 100 mg once a day for facial acne; she had nocturnal fever, non-productive cough, lethargy, and anorexia. Examination revealed a temperature of $37.6^\circ C$ and acne vulgaris but was otherwise unremarkable. A chest radiograph showed patchy infiltrates peripherally in the middle and upper zones bilaterally. Her eosinophil count was $1.12 \times 10^9/l$ (10.7%); erythrocyte sedimentation rate was 96 mm/h; antinuclear factor was weakly positive with a nucleolar fluorescence pattern; total IgE was raised (260 IU/l). Tests for aspergillus precipitins and antineutrophil cytoplasmic antibody had negative results. Minocycline was discontinued and oral amoxycillin and erythromycin were prescribed; abnormalities resolved within seven days.

Eight years previously this patient had been extensively investigated for a similar illness characterised by high fevers, dry cough, raised erythrocyte sedimentation rate (120 mm/h), eosinophilia ($1.4 \times 10^9/l$), and fleeting peripheral shadowing on chest radiography. At that time she had been treated for acne with minocycline for three months. She was treated with high dose oral corticosteroids for presumed polyarteritis nodosa and recovered completely within

Chest radiograph shows opacifications in upper and lower zones of the right lung

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one month. There had been no subsequent exposure to tetracyclines.

CASE 4

A 26 year old beauty consultant treated without adverse effect on several occasions in previous years for facial acne with Minocin R 50 mg once a day was given Minocin MR 100 mg once a day. After one week she developed a non-productive cough, night sweats, and dyspnoea. The chest radiograph showed inflammatory changes in both upper zones. The blood eosinophil count was $1.7 \times 10^9/l$ (26%). Pulmonary function testing showed both obstructive and restrictive lung defects with reduced gas transfer. Minocycline was discontinued, and chest radiograph abnormalities and blood eosinophilia resolved within three weeks. Lung volumes returned to normal, but the gas transfer factor remained low at 60% of the predicted value two months after discontinuation of the drug.

Discussion

We are confident that drug hypersensitivity, with minocycline as the aetiological agent, was the cause of the syndrome of pulmonary infiltrates and eosinophilia reported in these cases. In all four patients, Minocin MR 100 mg once a day was the only medication. There was a definite temporal association between respiratory symptoms and minocycline in each case. Rechallenge testing was carried out with informed consent in case 1; cases 2 and 3 were rechallenged inadvertently, and in case 4 all abnormalities resolved after simple discontinuation of the drug. None of the patients had a history of atopy.

The syndrome of pulmonary infiltrates and eosinophilia has been associated with systemic illnesses such as the Churg-Strauss syndrome, parasitic infestations, allergic bronchopulmonary aspergillosis, and exposure to a variety of drugs. Pneumonitis due to minocycline was first reported by Ho *et al* in 1979.² Since then a further 29 cases of reversible pneumonitis during treatment with minocycline have been described, mostly in Japan.³⁻²⁰ The typical presentation with biapical subpleural opacities on the chest radiograph and eosinophilia in the blood²¹ is by no means always encountered in pulmonary eosinophilia induced by minocycline. In our cases, as in others in the literature, infiltration developed anywhere in the lungs. Blood eosinophilia ($>0.6 \times 10^9/l$) occurred in all of our cases but was present in only 17 of the 27 cases of minocycline pneumonitis for which adequate information has been reported.

The pathogenesis of minocycline induced pneumonitis is unknown. A central role of T lymphocytes was suggested by Guillon *et al*,¹⁵ who found a lymphocyte mediated specific cytotoxicity against minocycline-bearing alveolar macrophages in vitro. The hypersensitivity reaction seems to be specific to minocycline; a patient given doxycycline after pneumonitis induced by minocycline did not have a relapse,¹⁹ and only one case has been associated with the use of tetracycline.² IgE titres were measured in two of our four cases and

found to be raised (807 and 260 IU/l). Possibly an IgE mediated immune response against minocycline itself or one of the constituents of its formulation is involved in the formation of pulmonary infiltrates in the presence of blood eosinophilia.

The prognosis of minocycline induced pneumonitis after discontinuation of the drug seems good. No mortality and no residual sequelae have been reported. However, severe transient respiratory failure necessitating ventilatory support has been reported,¹⁹ and corticosteroid therapy was required to control symptoms in several cases.^{3,7,11,17-19} Residual lung damage may have resulted from minocycline ingestion in our fourth case.

Three of these four cases presented in one centre within one year, all with the new formulation Minocin MR 100 mg. We wish to raise awareness among prescribing clinicians of this uncommon complication of a commonly used drug—there are 900 000 prescriptions a year in Britain—so that with early recognition and appropriate action potential lung damage is avoided.

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