REVIEW ARTICLE

Drug Safety 2000 May; 22 (5): 405-414
0114-5916/00/0005-0405/$20.00/0

Benefits and Risks of Minocycline in Rheumatoid Arthritis

Pnina Langevitz, Avi Livneh, Ilan Bank and *Mordechai Pras*

Rheumatic Disease Unit, Chaim Sheba Medical Center, Tel Hashomer, Israel

Contents

Abstract

Rheumatoid arthritis is a chronic inflammatory disease affecting about 1% of the adult population. The pathophysiology of rheumatoid arthritis remains incompletely understood. An infectious aetiology of the disease has long been postulated, but not proved. Despite insufficient evidence for the infectious nature of this disorder, several antibacterials, such as sulfa compounds, tetracyclines and rifampicin, have been investigated in the treatment of rheumatoid arthritis.

In the last few years, minocycline, a semi-synthetic derivative of tetracycline, has been extensively studied as a therapeutic agent for rheumatoid arthritis. The antirheumatic effect of minocycline can be related to its immunomodulatory and anti-inflammatory, rather than to its antibacterial properties. Its efficacy in rheumatoid arthritis has been reported in 2 open trials and in 3 double-blind controlled studies. The first 2 double-blind studies, 1 in The Netherlands and 1 in the US, were performed in patients with advanced disease. Both studies showed a modest, but statistically significant improvement in the clinical parameters of disease activity and in the erythrocyte sedimentation rate in the minocycline-treated patients. The US study also reported that patients in the minocycline group developed fewer erosions than those in the placebo group. This finding supports the role of minocycline as a disease modifying agent. The common adverse effects of minocycline reported in these 2 studies included gastrointestinal adverse effects, dizziness, rash and headaches. Less common adverse effects were intracranial hypertension, pneumonitis, persistent skin and mucosal hyperpigmentation, lupus-like syndrome and acute hepatic injury.

The third double-blind study enrolled only seropositive rheumatoid arthritis

patients with early disease (less than 1 year duration), and showed very encouraging results of significant improvement in the disease activity parameters in the minocycline treated group of patients. The same authors later reported that about half of these patients were in or near remission after 3 years of follow up. No adverse effects were reported in this study.

Summarising the data of these 3 double-blind studies, we may conclude that minocycline may be beneficial in patients with rheumatoid arthritis, especially when given early in the disease course or in patients with a mild disease.

Rheumatoid arthritis is a chronic, potentially incapacitating disease that affects about 1% of the adult population. Various pharmacological agents are used to manage this condition. They include NSAIDs, low dose corticosteroids and so called disease-modifying antirheumatic drugs, such as antimalarials, sulfasalazine, gold salts, methotrexate, azathioprine, cyclosporin, various combination therapies, biological agents and others. Despite this considerable amount of pharmacological agents, about 10% of patients still experience a rapidly progressive disease, refractory to these therapies, with permanent joint destruction, physical incapacity and sometimes life-threatening complications.[1] In addition, although the short term efficacy of the disease-modifying antirheumatic drugs is well established, their long term efficacy is less optimal.[2,3] In fact, in most rheumatoid arthritis patients, each of these agents is discontinued after 2 to 5 years of therapy because of toxicity or lack of efficacy.[4,5] These findings justify the sustained search for new therapeutic modalities.

The precise aetiology of rheumatoid arthritis is unknown, as well as the exact role of T cells, autoantibodies and cytokines in the disease process. It has been proposed that rheumatoid arthritis may have an infectious aetiology. After a successful isolation of various mycoplasma species from patients with rheumatoid arthritis, mycoplasma was suggested as an aetiological agent in this disease.[6] Based on this theory, some rheumatologists have long advocated tetracyclines as an appropriate treatment for rheumatoid arthritis.[7,8] Unfortunately, the studies were not appropriately designed, the dose of tetracycline was low and the studies did not show positive results.

However, in the last decade, this issue was revived. Minocycline, a broad spectrum antibacterial of the tetracycline group, was suggested as a useful agent in the treatment of patients with rheumatoid arthritis.

In this article, we will review the current use of minocycline in rheumatoid arthritis, discuss risk-benefit issues arising from its use and present our own experience with this agent in rheumatoid arthritis.

1. Pharmacological Considerations

Minocycline is a semi-synthetic derivative of tetracycline with a large volume of distribution. 100% of the drug is absorbed from the gastrointestinal tract and 60 to 75% is bound to plasma proteins. Food does not interfere with the absorption of minocycline. The majority of minocycline is concentrated in the liver and excreted, by way of the bile, into the intestine from which the drug is partially reabsorbable. Because of the enterohepatic circulation, minocycline, as well as other tetracyclines, may be present in the blood for a considerable time after the cessation of therapy. Indeed, its half-life is long, about 18 hours. Only 11% of the drug is excreted by the kidneys.

Minocycline is highly lipid soluble and easily penetrates the CNS, eye, and prostate, and is found in high concentration in the tears, saliva and milk. Drug interactions with minocycline, as with other tetracyclines, include various antacids, calcium, iron supplements, and cholestyramine which can impair absorption of the drug. Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are receiving anti-

coagulant therapy may require downward adjustment of their anticoagulant usage.[9]

2. Mechanism of Action of Tetracyclines in Arthritis

As mentioned before, the initial enthusiasm for the use of antibacterials in the treatment of rheumatoid arthritis, came from the recognition of a possible role of mycoplasma in the aetiology of rheumatoid arthritis. However, an infectious process cannot be demonstrated by microbiological investigation. Furthermore, a group of tetracyclines that had no antimicrobial activity, were proven to be efficacious in rats with adjuvant arthritis.[10] This suggests that other factors are involved in the mechanism of action of tetracyclines.

It has become clear that tetracyclines have anti-inflammatory and immunomodulatory activities. One of the proposed mechanisms of action of tetracyclines in rheumatoid arthritis is their ability to inhibit matrix metalloproteinases. Matrix metalloproteinases are a group of enzymes that play an important role in the destruction of cartilage and bone. Mammalian matrix metalloproteinases can be inhibited *in vivo* and *in vitro* by tetracyclines (especially minocycline and doxycycline), by mechanisms independent of their antimicrobial activity.[11-15]

Minocycline and doxycycline inhibit excessive activity of epiphyseal cartilage collagenase and partially, bone resorption.[16] It was shown that the inhibitory activity of doxycycline may be partially reversed by addition of calcium and zinc.[17] Minocycline also inhibits collagenase activity in synovial tissue in humans. Greenwald et al.[13] compared the collagenase activity in 2 joints removed from a rheumatoid arthritis patient during total joint replacement. Collagenase activity was found to be much higher in the first joint removed, before the patient received minocycline compared with the other joint which was removed after the patient was treated with the drug. Minocycline and doxycycline also inhibit phospholipase A2 which plays an important role in the inflammatory process of arthritis.[18-20]

Tetracyclines have been investigated for their inhibitory anti-inflammatory action *in vivo*. Minocycline suppressed collagen- and freund's adjuvant-induced types of experimental arthritis.[21,22] This effect was mediated by alteration of T cell-derived collagen-binding proteins.[23]

Minocycline, given with flurbiprofen, synergistically completely inhibits collagenase activity, suppresses gelatinase activity and inhibits bone resorption, while flurbiprofen given alone, suppresses only joint swelling without affecting bone damage.[24]

Extensive research has proved the anti-inflammatory action of tetracyclines in periodontal disease which is expressed by inhibition of collagenase activity and prostaglandin synthesis in the gingiva, and by activation of the regeneration of periodontal tissue.[14-16,25]

Furthermore, tetracyclines were shown to suppress the immunological functions of polymorphonuclear cells by modulating their chemotactic activity and by reducing their capacity for delayed-type hypersensitivity responses to sheep red blood cells.[26,27] Minocycline was shown to affect synovial T cell proliferation and cytokine production after stimulation with anti-CD3 monoclonal antibodies, effectively suppressing the activation and function of these T cells.[28] Suppression of a T cell activation antigen (gp 26) in patients treated with minocycline was also shown in our study.[29] In addition, tetracyclines inhibit nonbacterial inflammatory reactions associated with antioxidant activity.[30,31]

3. Efficacy of Minocycline in the Treatment of Rheumatoid Arthritis

For many years tetracyclines were used for the therapy of rheumatoid arthritis. Forty years ago, an American rheumatologist, TMP Brown, published his long term but uncontrolled experience with tetracyclines in patients with rheumatoid arthritis,[32] and about 10 years later, Sanchez published his observation about the effectiveness of tetracyclines in rheumatoid arthritis.[33] However, a double-blind, placebo-controlled study of 250 mg/day of tetracycline published in 1971 failed to show a beneficial

Table I. Clinical and demographic data of minocycline-treated patients with rheumatoid arthritis in 3 double-blind, placebo-controlled studies

	Kloppenberg et al.[40]	Tilley et al.[41]	O'Dell et al.[42]
No. of patients	80	219	46
Mean age (y)	56	54	41
Mean disease duration (y)	13	9	0.4
Study duration (wk)	26	48	26
Other DMARDs taken during study	Yes	No	No
Response rate (%) minocycline *vs* placebo in the no. of inflamed joints (p-value)	38/18 (0.05)	55/40 (≤0.023)	65/13 (0.001)
No. of swollen joints (maximum: 20): minocyclines *vs* placebo (p-value)	0.008	0.023	0.18
Duration of morning stiffness: minocycline *vs* placebo (p-value)	0.14	>0.2	0.03

DMARDs = disease-modifying antirheumatic drugs.

effect, probably because of a low dose of the tested drug.[34] Nevertheless, during the following decades, tetracyclines proved themselves as useful and well tolerated agents in the long term treatment of severe acne, Reiter's syndrome, reactive arthritis and other conditions.[35-38] This experience and the favourable laboratory data lead to the revived interest in tetracyclines, particularly minocycline, in the treatment of rheumatoid arthritis.

Two short term open studies published in the early 1990s, one in The Netherlands and the other in Israel by our group, showed the beneficial effect of minocycline on almost all clinical parameters of rheumatoid arthritis. Minocyline was given either as a single second-line agent in our study or in combination with other disease-modifying antirheumatic drugs in The Netherlands.[29,39] Following the open trials, 3 large, well conducted double-blind, placebo-controlled studies were performed in The Netherlands and in the US over the last 5 years (table I).[40-42] Two of the studies included patients with a long-lasting rheumatoid arthritis,[40,41] and the third included patients with early rheumatoid arthritis.[42]

All 3 studies showed minocycline 200 mg/day to be superior to placebo in several clinical and laboratory parameters, including joint swelling and tenderness, erythrocyte sedimentation rate and haemoglobin levels in the intention-to-treat cohort of patients (table I). The Dutch study included 80 patients with an advanced rheumatoid arthritis and with a disease duration of 13 years. These patients were allowed to remain on concurrent disease-modifying antirheumatic drugs. The study lasted 26 weeks. The clinical parameters of disease activity (Ritchie articular index, number of swollen joints) improved significantly in these patients ($p = 0.007$ and 0.008, respectively), while morning stiffness improved only slightly, and pain and fatigue scores did not improve (table I).

The change in laboratory parameters of disease activity (erythrocyte sedimentation rate, haemoglobin level, platelet count, C-reactive protein level) was clinically significant. In the minocycline group, no premature discontinuations were observed for lack of efficacy and no failures occurred, while in the placebo group, 10 premature discontinuations, 8 for lack of efficacy, 1 because of adverse effects and 1 because of the development of breast cancer, were reported.[40]

The Minocycline in Rheumatoid Arthritis trial (MIRA) included 219 patients with rheumatoid arthritis with a mean disease duration of 9 years. The patients stopped previous disease-modifying antirheumatic drugs and were treated with minocycline 100mg twice daily or placebo for 48 weeks. At week 48, the same percentage of patients in the minocycline and placebo group continued to receive the study medication, however more patients in the minocycline group showed improvement in joint tenderness and swelling ($p < 0.023$). The laboratory parameters of disease activity also changed significantly in the minocycline group ($p = 0.001$).[41] However, no differences were found in the rate of disease progression in terms of radiological findings in the minocycline versus placebo groups in this study.[43]

Encouraging results were reported from the double-blind study involving patients with early rheumatoid arthritis. In this study lasting 26 weeks, 46 patients with seropositive rheumatoid arthritis of less than 1 year duration were included. Among them, 15 of the 23 patients (65%) treated with minocycline, and only 3 of 23 patients (13%) treated with placebo, achieved at least 50% improvement criteria at 3 months of treatment and maintained it during the study period.[42] The same authors also published their long term experience with this drug, showing a favourable response in most patients who restarted minocycline following a flare of their rheumatoid arthritis after stopping the drug.[44]

Although there are no studies comparing the efficacy and tolerability of minocycline in patients with early rheumatoid arthritis with other second line agents, including hydroxychloroquine, the results of the above double-blind study appear promising. We also reported beneficial results in rheumatoid arthritis patients treated with minocycline for up to 6 years.[45] Thus, based on these studies and recently published editorials and reviews,[46-51] we may conclude that minocycline is beneficial in the treatment of patients with rheumatoid arthritis. Further studies comparing minocycline with other disease-modifying antirheumatic drugs are needed to provide the practising rheumatologist with precise indications for minocycline use in different subsets of rheumatoid arthritis patients, and to elucidate its real place in the therapeutic scheme of treatment of such patients.

4. Adverse Effects of Minocycline in Patients with Rheumatoid Arthritis

Adverse effects of minocycline have been reported in both open trials and in 2 of the double-blind studies.[29,39,40,41] They included mainly rashes, dizziness, headache, nausea and gastrointestinal adverse effects (table II). The adverse effects resulted in discontinuation of therapy in some of the patients. In the Dutch study, 57% of patients treated with minocycline experienced gastrointestinal adverse effects compared with only 15% of patients in the placebo group. 40% of patients in the minocycline group complained of dizziness versus 15% in the placebo group, and 6 of 40 patients stopped medication because of adverse effects in the minocycline group compared with only 1 of 40 patients in the placebo group.[40]

In the MIRA study, adverse effects were less frequent, probably because the study allowed for dose reduction for adverse effects. Only 26% of patients experienced gastrointestinal adverse effects in the minocycline group and 25% in the placebo group. Of those receiving minocycline, 21% had dizziness compared with 11% in the placebo group, and 6 out of 103 patients in the minocycline group but none in the placebo group stopped therapy because of adverse effects.[41] All of the adverse effects disappeared after stopping therapy and did not result in serious morbidity. No relationship was found between the serum concentrations of minocycline and its toxicity in the Dutch

Table II. Toxicity of minocycline in patients with rheumatoid arthritis

	Breedveld et al.[39]	Langevitz et al.[29]	Kloppenburg et al.[40]	Tilley et al.[41]
No. of patients treated with minocyline	10	18	40	103
Adverse effects [no. (%) of patients][a]				
gastrointestinal	2 (2)	1 (5.5)	23 (57)	27 (26)
rash				15 (14.5)
pneumonitis			1 (2.5)	
headache			1 (2.5)	20 (19)
dizziness/vertigo/light-headedness	4 (4)	2 (11)	16 (40)	22 (21)
leucopenia		1 (5.5)		
skin hyperpigmentation		4 (22)		
candidiasis		2 (11)		

a More than 1 adverse effect per patient may have occurred.

study.[52] Interestingly, only hyperpigmentation was seen in the third double-blind study in early rheumatoid arthritis patients.[44] However, several case reports have described a number of serious adverse effects of minocycline therapy such as autoimmune hepatitis, hypersensitivity pneumonitis and other autoimmune disorders.[53-70]

4.1 Gastrointestinal Adverse Effects

Nausea, vomiting, diarrhoea and taste disturbances were the most commonly reported adverse effects in the studies of minocycline use in rheumatoid arthritis (table II). However, other gastrointestinal adverse effects have also been reported in patients taking minocycline. Autoimmune hepatitis (early and acute, or late and chronic), sometimes associated with a lupus-like disease, and acute hepatic failure have been reported in patients treated with minocycline.[53-58] Oesophageal injury on endoscopic examination was also found in patients on minocycline therapy.[59] Furthermore, pancreatitis has been reported in patients treated with minocycline.[55]

4.2 Hypersensitivity Reactions

Urticarial skin rash appeared in 15 patients in the MIRA study (table II). A few patients in our study also experienced an allergic skin rash.[29] Moreover, serum sickness (sometimes severe), has been relatively frequently reported in patients receiving minocycline.[60-62]

Hypersensitivity pneumonitis and eosinophilic pneumonia (table II) may be a serious complication of minocycline therapy in a few patients with rheumatoid arthritis, requiring not only discontinuation of the drug, but often treatment with corticosteroids.[63-70] In an attempt to try to identify the cause of hypersensitivity pneumonitis in a patient treated with minocycline, sequential bronchoalveolar lavages were performed and an immunological analysis of the phenotype and function of alveolar lymphocytes was done. The results confirmed the central role of T lymphocytes in the pathogenesis of the hypersensitivity pneumonitis.[63]

4.3 Minocycline-Induced Hyperpigmentation

Minocycline-induced hyperpigmentation is an often observed adverse effect of therapy, although it was not mentioned in the double-blind trials.[40-42] Three types of minocycline-induced skin hyperpigmentation have been described.[71,72] Type I occurs as blue-black pigmentation at sites of inflammation, usually in pre-existing scars, and consists of iron-containing compounds in the dermis; haemosiderin or iron chelates of minocycline. Type II appears on normal skin as circumscribed hyperpigmented macules or as diffuse hyperpigmentation, usually on the shins. Deposition of melanin and iron in the dermis are found in the hyperpigmented macules. Type III hyperpigmentation is muddy brown, occurs mostly in sun-exposed skin and contains melanin deposits in the epidermis and in the papillary dermis, probably because of stimulation of melanin production in the sun-exposed skin by minocycline.

Hyperpigmentation associated with minocycline therapy may also occur in the mouth, on the tongue, teeth, lips, sclera, thyroid, bone and breast milk.[73-87] In addition, a hyperpigmentation is described in postacne osteoma cutis, venous ectasia of the extremities and in basal cell carcinomas.[88-90]

Minocycline-induced hyperpigmentation is gradual in onset and can be photo-sensitive. In our experience, minocycline-induced skin hyperpigmentation of different types occurred in about 70% of patients. In most of these patients, some discolouration of the sclera, teeth, gingiva, lips and nails also appeared. In a 75-year-old patient treated with minocycline for 3 years for rheumatoid arthritis who died from acute myocardial infarction, severe hyperpigmentation was found in his aorta, thyroid and other tissues at post mortem (unpublished observation).

This hyperpigmentation, when not very severe and widespread, seems to be at least partially reversible, over time. Recently, treatment with neodymium YAG laser was suggested for this adverse condition.[91]

4.4 Autoimmune Disorders

Drug-induced lupus with arthralgia, leucopenia, thrombocytopenia lung infiltrates, and a positive antinuclear antibody is sometimes reported in minocycline treated patients.[92-103] In addition, an autoimmune disorder with arthritis, fever and antineutrophil cytoplasmic antibodies has been mentioned in a few reports in association with minocycline therapy given for patients with arthritis and acne.[104-106] The symptoms usually resolved after stopping the drug.

4.5 Intracranial Hypertension

Intracranial hypertension is a common adverse effect associated with minocycline therapy and presents as headache, nausea, vomiting, visual disturbances and dizziness.[107,108] The symptoms disappear completely after discontinuation of therapy. In addition, a high incidence of vestibular symptoms has been reported in the open and double-blind studies (table II).

5. Conclusions

Minocycline, a semi-synthetic derivative of tetracycline, has many beneficial effects independent of its antimicrobial action. The antirheumatic effect of minocycline is based on its anti-inflammatory and immunomodulatory properties. It has been shown that minocycline inhibits matrix metalloproteinases, a group of enzymes that play an important role in the destruction of cartilage and bone. Minocycline suppresses collagen- and freund's adjuvant-induced types of experimental arthritis, an effect mediated by the alteration of T cell-derived collagen-binding proteins. Minocycline also inhibits gelatinase activity, suppresses bone resorption, and affects synovial T cell proliferation and cytokine production.

Three double-blind studies reported the efficacy of minocycline in patients with rheumatoid arthritis. Of these studies, 2 were performed on patients with an advanced disease and showed a modest but statistically significant improvement in the clinical parameters of disease activity in the group of patients treated with minocycline. The third double-blind study, performed on rheumatoid arthritis patients with an early seropositive disease, reported very promising results with minocycline treatment. The same authors published their long term experience with minocycline and also demonstrated a favourable response in most patients. Thus, although the effects of minocycline in rheumatoid arthritis depend on when it is given in the clinical course of the disease, these 3 studies provide unquestionable evidence of the efficacy of this drug.

However, minocycline has quite a significant toxicity profile, including gastrointestinal adverse effects, hyperpigmentation, and intracranial hypertension. One should be especially aware of the relatively infrequent, but more serious adverse effects of therapy such as pneumonitis, hepatitis and autoimmune disorders.

Thus, based on the available data, minocycline would appear to have a positive benefit–risk ratio in the treatment of patients with rheumatoid arthritis, especially in patients with early disease.

References

1. Wollheim FA. Rheumatoid arthritis. In: Maddison PJ, Isenberg DA, Woo P, et al., editors. Oxford textbook of rheumatology. 2nd ed. Oxford; Oxford Medical Publications, 1998: 1018-31
2. Felson DT, Anderson JJ, Meenan RF. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis: results of two metaanalyses. Arthritis Rheum 1990; 33: 1449-61
3. Felson DT, Anderson JJ, Meeman RF. Use of short-term efficacy-toxicity trade-offs to select second-line drugs in rheumatoid arthritis: a metaanalysis of published clinical trials. Arthritis Rheum 1992; 35: 1117-25
4. Morand EF, McCloud PI, Littlejohn GO. Life table analysis of 879 treatment episodes with slow acting antirheumatic drugs in community rheumatology practice. J Rheumatol 1992; 19: 704-8
5. Wolfe F, Hawley DJ, Cathey MA. Termination of slow acting antirheumatic therapy in rheumatoid arthritis: a 14-year prospective evaluation of 1017 consecutive starts. J Rheumatol 1990; 17: 994-1002
6. Bartolomew IE. Isolation and characterization of mycoplasma (PPLO) in patients with rheumatoid arthritis, systemic lupus erythematosus and Reiter's syndrome. Arthritis Rheum 1965; 8: 376-88
7. Brown T, Bush SW, Felts WR. In: Wohl MG, editor. Long-term illness: management of the chronically ill patient. Philadelphia: WB Saunders, 1959: 93-125
8. Sanchez I. Tetracyclines treatment in rheumatoid arthritis and other rheumatic diseases. Brazil Med 1968; 82: 22-31

9. Sande MA, Mandell GL. Antimicrobial agents. Tetracyclines. In: Gilman A, Goodman LS, Rall TW, editors. Goodman and Gilman's the pharmacological basis of therapeutics. 7th ed. New York (NY): Macmillan Publishing Co, 1980: 1170-9
10. Golub LM, McNamara TF, D'Angelo G, et al. A non-antibacterial, chemically-modified tetracycline inhibits mammalian collagenase activity. J Dent Res 1987; 66: 1310-4
11. Golub LM, Ramamurthy NS, McNamara TF, et.al. Tetracyclines inhibit tissue collagenase activity: a new mechanism in the treatment of periodontal disease. Periodontal Res 1984; 19: 651-5
12. Golub LM, Suomalainen K, Sorsa T, et al. Host modulation with tetracyclines and their chemically modified analogues. Curr Opin Dent 1992; 2: 80-90
13. Greenwald RA, Golub LM, Lavietes B, et al. Tetracyclines inhibit human synovial collagenese in vivo and in vitro. J Rheumatol 1987; 14: 28-32
14. Golub LM, Lee HM, Lehrer G, et al. Minocycline reduces gingival collagenonic activity during diabetes: preliminary observations and a proposed new mechanism of action. J Periodontal 1983; 18: 516-24
15. Golub LM, Wolf M, Lee HM, et al. Further evidence that tetracyclines inhibit collagenase activity in human crevicular fluid and from other mammalian sources. J Periodontal Res 1985; 20: 12-23
16. Rifkin RB, Colub LM, Sanavi R, et al. Effects of tetracyclines on rat osteoblast collagenase activity and bone resorption in vitro. In: Davidovich Z, editor. The biological mechanisms of tooth movement and craniofacial adaptation. Birmingham: EBSCO, 1992: 85-90
17. Yu LPJ, Smith GNJ, Hasty KA, et al. Doxycycline inhibits type XI collagenolytic activity of extracts from human osteoarthritic cartilage and of gelatinase. J Rheumatol 1991; 18: 1450-2
18. Pruzanski W, Greenwald RA, Street IP, et al. Inhibition of enzymatic activity of phospholipases A2 by minocycline and doxycycline. Biochem Pharmacol 1992; 44: 1165-70
19. Vadas P, Pruzanski W, Kim J, et al. The proinflammatory effect of the intraarticular injection of soluble venom and human phospholipase A2. Am J Pathol 1988; 134: 807-11
20. Bomalski JS, Lawton P, Browning JL. Human extracellular recombinant phospholipase A2 induces an inflammatory response in rabbit joints. J Rheumatol 1991; 146: 3904-10
21. Breedveld FC, O'Brien JM, Brinckerhoff CE, et al. Suppression of collagen and adjuvant arthritis by a tetracycline [abstract]. Arthritis Rheum 1988; Suppl. 31: 588
22. Sewell KI, Furrie E, Trentham DE. The therapeutic effect of minocycline in experimental arthritis: mechanism of action [abstract]. Arthritis Rheum 1991; Suppl. 33: S106
23. Sewell KL, Fury E, Dynesius-Trentham R, et al. Evidence that minocycline suppress collagen and adjuvant arthritis by altering the expression of T cell derived , collagen-binding proteins [abstract]. Arthritis Rheum 1989; Suppl 32: S134
24. Greenwald RA, Moak SA, Ramamurthy NSD, et al. Tetracyclines suppress metalloproteinase activity in adjuvant arthritis and, in combination flurbiprofen, ameliorate bone damage. J Rheumatol 1992; 19: 927-38
25. El Attar TMA, Lin HS, Schulz R. Effect of minocycline on prostaglandin formation in gingival fibroblasts. J Periodontal Res 1988; 23: 285-6
26. Martin RR, Warr GA, Couch RB, et al. Effects of tetracyclines on leukotaxis. J Infect Dis 1974; 129: 110-6
27. Thong YH, Ferrante A. Effect of tetracycline treatment on immunological responses in mice. Clin Exp Immunol 1980; 39: 728-32
28. Kloppenburg M, Miltenburg AMM, Vendonk MYA, et al. Minocycline inhibits T-cell proliferation and interferon gamma (IFN-gamma) production after stimulation with anti CD3 monoclonal antibodies [abstract]. Br J Rheumatol 1992; 31 Suppl.: 41
29. Langevitz P, Bank I, Zemer D, et al. Treatment of resistant rheumatoid arthritis with minocycline: an open study. J Rheumatol 1992; 19: 1502-4
30. Wasil M, Halliwell B, Moorhouse CP. Scavenging of hypochlorous acid by tetracycline, rifampicin and some other antibiotics: a possible antioxidant action of rifampicin and tetracycline. Biochem Pharmacol 1988; 37: 775-8
31. Van Barr HM, van de Kerkhop PC, Mier PD, et al. Tetracyclines are potent scavengers of the superoxide radical. Br J Dermatol 1987; 117: 131-2
32. Brown TMcP, Bush SW, Felts WR. In: Wohl MG, editor. Long-term illness: management of the chronically ill patient. Philadelphia: WB Saunders, 1959: 93-125
33. Sanchez I. Tetracycline treatment in rheumatoid arthritis and other rheumatic diseases [in Portuguese]. Brasil Med 1968; 82: 22-31
34. Skimer M, Cathcart ES, Mills YA, et al. Tetracycline in the treatment of rheumatoid arthritis. Arthritis Rheum 1971; 14: 727-32
35. Wright AL, Colver GB. Tetracyclines: how safe are they? Clin Exp Dermatol 1988; 13: 57-61
36. Bardin T, Erel C, Cornelis F, et al. Antibiotic treatment of venereal disease and Reiter's syndrome in Greenland population. Arthritis Rheum 1992; 35: 190-4
37. Bardin T, Schumacher HR. Should we treat postvenereal Reiter's syndrome by antibiotics? J Rheumatol 1991; 18: 1780-2
38. Lauhio A, Leirisalo-Repo M, Lahdevirta J, et al. Double-blinded, placebo-controlled study of three-month treatment with lymecycline in reactive arthritis with special reference to chlamidia arthritis. Arthritis Rheum 1991; 34: 6-14
39. Breedveld FC, Dijkmans BAC, Mattie H. Minocycline treatment for rheumatoid arthritis: an open dose finding study. J Rheumatol 1990; 17: 43-6
40. Kloppenburg M, Breedveld FC, Terwiel JPH, et al. Minocycline in active rheumatoid arthritis: a double-blind, placebo-controlled trial. Arthritis Rheum 1994; 37: 629-36
41. Tilley BC, Alarcon GS, Heyse SP, et al., for the MIRA trial group. Minocycline in rheumatoid arthritis: a 48-week, double-blind, placebo-controlled trial. Ann Int Med 1995; 122: 81-9
42. O'Dell JR, Haire CE, Palmer W, et al. Treatment of early rheumatoid arthritis with minocycline or placebo. Arthritis Rheum 1997; 40: 842-8
43. Bluhm GB, Sharp JT, Tilley B, et al. Radiographic results from the minocycline in rheumatoid arthritis trial (MIRA). J Rheumatol 1997; 24: 1295-302
44. O'Dell JR, Paulsen G, Haire LE, et al. Treatment of early seropositive rheumatoid arthritis with minocycline. Four year follow up of a double-blind, placebo controlled study. Arthritis Rheum 1999; 42: 1691-5
45. Langevitz P, Bank I, Livneh A, et al. Long-term experience with minocycline in patients with resistant rheumatoid arthritis (RA) [abstract]. Rheumatol Eur 1995; 24 Suppl.: D100

46. Pruznaski W, Vadas P. Should tetracyclines be used in arthritis? J Rheumatol 1992; 19: 1495-6
47. Trentham DE, Disenius-Trentham RA. Antibiotic therapy for rheumtoid arthritis: scientific and anecdotal appraisals. Rheum Dis Clin North America 1995; 21: 817-34
48. Langevitz P, Livneh A, Bank I, et al. Minocycline in rheumatoid arthritis. Isr J Med Sci 1996; 32-4
49. Alarcon GS. Minocycline for the treatment of rheumatoid arthritis. Rheum Dis Clin North Am 1998; 24: 489-99
50. Paulus EH. Minocycline treatment of rheumatoid arthritis. Ann Int Med 1995; 122: 147-8
51. Breedveld FC. Minocycline in rheumatoid arthritis. Arthritis Rheum 1997; 40: 794-6
52. Kloppenburg M, Mattie H, Dauwes N, et al. Minocycline in the treatment of rheumatoid arthritis: the relationship of serum concentrations to efficacy. J Rheumatol 1995; 22: 611-6
53. Malcolm A, Heap TR, Eckstein RP, et al. Minocycline induced liver injury. Am J Gastroenterol 1996; 91: 1641-3
54. Golstein PE, Deviere J, Gremer M. Acute hepatitis and drug-related lupus induced by minocycline treatment. Am J Gastroenterol 1997; 92: 143-6
55. Beudreaux JP, Hayes DK, Mizrahi S, et al. Fulminant hepatic failure, hepatorenal syndrome and necrotizing pancreatitis after minocycline hepatotoxicity. Transplant Proceed 1993; 25: 1873
56. Sorbi D, Thistle JR. Minocycline, an unusual cause of drug-induced lupus and autoimmune hepatitis. Am J Gastroenterol 1997; 92: 1732
57. Hewak J, Teuyses G, Hunt RH. Minocycline induced hepatotoxicity presenting as autoimmune hepatitis: report of three cases [abstract]. Canadian J Gastroenterol 1996; 10 Suppl.: 57
58. Min DY, Burke PA, Lewis D. Acute hepatic failure associated with oral minocycline: a case report. Pharmacother 1992; 12: 68-71
59. Ovartlarnporn B, Kuluichit, Hiranniramal S. Medication induced esophageal injury: report of 17 cases with endoscopic determination. Ann J Gastroenterol 1991; 86: 748-50
60. Puyana J, Urena V, Quirce S, et al. Serum sickness-like syndrome associated with minocycline therapy. Allergy 1990 45: 313-5
61. Levenson T, Masood D, Patterson R. Minocycline-induced serum sickness. Allergy Asthma Proceed 1996; 17: 79-81
62. Harel L, Amir J, Livni E. Serum sickness-like reaction associated with minocycline therapy in adolescents. Ann Pharmacother 1996; 30: 481-3
63. Guillon JM, Joly P, Autran B, et al. Minocycline-induced cell-mediated hypersensitivity pneumonitis. Ann Int Med 1992; 117: 476-81
64. Dupont C, Rouveix E, Chinet T, et al. Loffler's syndrome in a minocycline-treated woman. Ann Med Intern 1993; 14: 76
65. Bentur L, Bar Kana Y, Livni E, et al. Severe minocycline-induced-eosinophilic pneumonia: extrapulmonary manifestations and the use of in vitro immunoassays. Ann Pharmacother 1994; 31: 733-5
66. Sitbon O, Bidel N, Dussport C, et al. Minocycline pneumonitis and eosinophilia: report on eight patients. Arch Int Med 154: 1633-40
67. Dykhuizen RS, Zaidi AM, Golden DJ, et al. Minocycline and pulmonary eosinophilia. BMJ 1995; 310: 1520-1
68. Toyoshima M, Sato A, Hoyakawa H. A clinical study of minocycline-induced pneumonitis. Int Med 1996; 35: 176-9
69. Bando T, Fujimura M, Noda Y, et al. Minocycline-induced pneumonitis with bilateral hilar lymphadenopathy and pleural effusion. Int Med 1994; 33: 177-9
70. Dykhuizen RS, Legge JS. Minocycline induced pulmonary eosinophilia. Resp Med 1995; 89: 61-2
71. Eisen D, Hakim MD. Minocycline-induced pigmentation: incidence, prevention and management. Drug Saf 1998; 18: 431-40
72. Basler RSW. Minocycline-related hyperpigmentation. Arch Dermatol 1985; 121: 606-8
73. Dwyer CM, Guddihy AM, Keer REI. Skin pigmentation due to minocycline treatment of facial dermatoses. Br J Dermatol 1993; 129: 158-62
74. Okada N, Sato S, Sasou T, et al. Characterization of pigmented granules in minocycline-induced cutaneous pigmentation: observations using fluorescence microscopy and high performance liquid chromatography. Br J Dermatol 1993; 129: 403-7
75. Schofield JK, Tatnall FM. Minocycline induced skin pigmentation. Br J Gen Pract 1993; 43: 173-4
76. Katz J, Barak S, Shemer J, et al. Black tongue associated with minocycline therapy [letter]. Arch Dermatol 1995; 131: 620
77. Hunt MJ, Salisbury ELC, Grace J, et al. Black breast milk due to minocycline therapy. Br J Dermatol 1996; 134: 943-4
78. Sabrae RA, Archer CB, Harlow D, et al. Minocycline-induced discoloration of the sclerae. Br J Dermatol 1996; 135: 314-6
79. Eedy DJ, Burrows D. Minocycline-induced pigmentation occurring in two sisters. Clin Exp Dermatol 1991; 16: 55-7
80. Pepine M, Flowers FP, Ramas-Caro FA. Extensive cutaneous hyperpigmentation caused by minocycline. J Am Acad Dermatol 1993; 28: 292-5
81. Hung PK, Caldwell JB, James WD. Minocycline-induced hyperpigmentation. J Fam Pract 1995; 41: 183-5
82. Fraunfelder FT, Randall JA. Minocycline induced scleral pigmentation. Ophthalmol 1997; 104: 936-8
83. Purdue B. An incidental autopsy finding of black thyroid associated with minocycline therapy. Med Sci Law 1992; 32: 148-50
84. Meyerson MA, Cohen PR, Hymes JR. Lingual hyperpigmentation associated with minocycline therapy. Oral Surg Oral Med Oral Phathol Oral Radiol Endodontics 1995; 79: 180-4
85. Parkins FM, Furnish G, Bernstein M. Minocycline use discolors teeth. J Am Dent Assoc 1992; 123: 87-9
86. Eisen D. Minocycline-induced oral hyperpigmentation [letter]. Lancet 1997; 349: 400
87. Rumback MJ, Pitcock JA, Palmieri GMA. Black bones following long-term minocycline treatment. Arch Pathol Lab Med 1991; 115: 939-41
88. Moritz DL, Elewski B. Pigmented postacne osteomacutis in a patient treated with minocycline: a report and review of the literature. J Am Acad Dermatol 1991; 24: 851-3
89. Leffell DJ. Minocycline hydrochoride hyperpigmentation complicating treatment of venous ectasia of the extremities. J Am Acad Dermatol 1991; 24: 501-2
90. Butt A, Statham BN. Minocycline-induced hyperpigmentation of basal cell carcinomas. J Dermatol Treat 1998; 9: 39-42
91. Wilde LJ, English III JC, Finley EM. Minocycline-induced hyperpigmentation: treatment with neodymium: YAG laser. Arch Dermatol 1997; 133: 1344-6
92. Matsumura T, Shimizu Y, Fujimoto H, et al. Minocycline induced lupus [letter]. Lancet 1992; 340: 1553
93. Farver DK. Minocycline-induced lupus. Ann Pharmacother 1997; 31: 1160-3
94. Masson C, Pascaretti C, Capon F, et al. Minocyline-related lupus: a review of 23 definite cases [abstract]. Arthritis Rheum 1996; 39 Suppl.: 60

95. Breedveld FC. Minocycline induced autoimmune disease: reply. Arthritis Rheum 1998; 41: 563-4
96. Gordon PM, White MI, Herriot R. Minocycline-associated lupus erythematosus. Br J Dermatol 1995; 132: 120-1
97. Gendi NST, Bawman SJ, Mowat AG. Lupus-like syndrome in patients treated for acne. Br J Rheumatol 1995; 34: 584-5
98. Quilty B, McHugh N. Lupus-like syndrome associated with the use of minocycline. Br J Rheumatol 1994; 33: 1197-8
99. Byrne PAC, Williams BD, Pritchard MH. Minocycline-related lupus. Br J Rheumatol 1994; 33: 674-6
100. Lauwerys B, Martin F, Mahri A, et al. Minocycline: a common cause of drug-induced lupus. Clin Rheumatol 1997; 16: 520
101. Gresson J, Stillman MT. Minocycline-related lupus erythematasus with associated liver disease. J Am Acad Dermatol 1997; 36: 867-8
102. Masson C, Chevailler A, Pascoretti C. Minocycline related lupus. J Rheumatol 1996; 23: 2160-1
103. Alain E, Miller LC, Tucker LB. Minocycline-induced lupus in adolescents. Pediatrics 1998; 101: 926-8
104. Elkayam O, Yaron M, Caspi D. Minocycline induced arthritis associated with fever, livedo reticularis and P-ANCA. Ann Rheum Dis 1996; 55: 769-71
105. Alain E, Miller LC, Tucker CB, et al. Minocycline related lupus-like syndrome: possible association with antineutrophil cytoplasmic antibodies. Arthritis Rheum 1997; 40 Suppl.: 191
106. Elkayam O, Levartovsky D, Brautbar Ch, et al. Clinical and immunological study of 7 patients with minocycline- induced autoimmune phenomena. Am J Med 1998; 105: 484-7
107. Boyd I. Benign intracranial hypertension induce by minocycline. Curr Ther 1995; 36: 70-1
108. Weller M, Klockgether T. Minocycline-induced benign intracranial hypertension [letter]. J Neurol 1988; 245: 55

Correspondence and offprints: Dr *Pnina Langevitz*, Heller Institute of Medical Research, Chaim Sheba Medical Center, Tel Hashomer 52621, Israel.