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Liver Damage Associated with Minocycline Use in Acne

A Systematic Review of the Published Literature and Pharmacovigilance Data

Ross A. Lawrenson,[1] *Helen E. Seaman*,[2] *Anders Sundström*,[2] *Timothy J. Williams*[2] and *Richard D.T. Farmer*[2]

1 Primary Care Research Unit, Postgraduate Medical School, University of Surrey, Guildford, Surrey, England

2 Department of Pharmacoepidemiology and Public Health, Postgraduate Medical School, University of Surrey, Guildford, Surrey, England

Abstract

Objective: Minocycline is an antibacterial drug used in the treatment of acne. Concern has been expressed over the possibility of severe adverse reactions to minocycline, including hepatitis. This study set out to identify and characterise reported cases of hepatotoxicity associated with the use of minocycline.

Methods: A systematic review of the literature including a search of computerised databases and analysis of data from the Uppsala Monitoring Centre (WHO Collaborating Centre for International Drug Monitoring) was conducted. The review involved a search for original case reports involving liver damage in people using minocycline. Patients taking minocycline for reasons other than acne or those given intravenous minocycline were excluded. The search strategy involved an enquiry of computerised databases and a search for secondary references. Cases were then classified appropriately.

Results: 65 reported cases of hepatitis or liver damage in association with minocycline from either case reports or case series were identified from the literature review. 58% of cases occurred in females and 94% were aged under 40 years. For 20 case reports there was insufficient information to classify the type of event, but for the remaining 45, 2 types of hepatic reaction were recognised: autoimmune hepatitis associated with lupus-like symptoms occurring after a median duration of exposure to minocycline of 365 days in females (n = 20) and 730 days in males (n = 9), hypersensitivity reaction associated with eosinophilia and exfoliative dermatitis occurring within 35 days of therapy (n = 16).

Reports to the WHO of hepatic adverse drug reactions associated with minocycline accounted for 6% (493) of all minocycline-related adverse drug reactions (8025). The pattern of distribution in relation to exposure demonstrated 2 groups, similar to that described by the case reports.

Conclusions: Severe cases of minocycline-associated hepatotoxicity appear to be a hypersensitivity reaction and occur within a few weeks of commencing therapy. An autoimmune hepatitis usually presents after exposure to minocycline

of a year or more, is more common in women and is sometimes associated with lupus-like symptoms.

The tetracyclines are a group of antibacterials that have been widely accepted for many years as effective systemic treatment for acne. Minocycline is a semisynthetic tetracycline, licensed for a broad range of indications, including urinary tract and ear, nose and throat infections, pneumonia and bronchitis. In the UK, once daily modified release minocycline (Minocin MR®) is specifically licensed for the treatment of acne.

The superior efficacy of minocycline over other anti-acne therapies, including other tetracyclines, has been demonstrated in clinical trials.[1-7] The benefits of minocycline treatment for acne include good oral absorption, enhanced tissue penetration, slow elimination and improved patient compliance through once daily dosage. The drug can be effectively taken with food,[8] is highly lipophilic becoming rapidly concentrated in the target sebaceous follicles after oral administration,[2,3,8] and has been demonstrated to have superiority over other tetracyclines in overcoming the growing problem of bacterial resistance.[6,7,9,10] These advantages often favour the use of minocycline over other therapies.

The safety of minocycline in the treatment of acne has been widely reported.[3,4,7,11,12] Adverse effects are generally transient, though hyperpigmentation of tissues may occur and may persist. None of the observational studies or clinical trials have identified patients with minocycline-induced liver damage.

The parent drug of minocycline, tetracycline, was first noted to be hepatotoxic in hospital inpatients who received high doses of tetracycline intravenously. Serious hepatitis developed with a histological picture of microvesicular steatosis or 'fatty liver'. Fatty liver in response to minocycline exposure is considered rare.[13]

In 1983 a case of a severe leukaemoid reaction in association with minocycline therapy was reported in the literature,[14] and further cases of pneumonitis,[15,16] pancreatitis[17] and myocarditis[18,19] have been reported. The development of lupus-like symptoms has also been described in patients taking minocycline. Such drug-induced lupus, specifically attributed to minocycline, was first described by Matsuura et al. in 1992[16] and subsequently described in a number of other case reports.[20-27] Sturkenboom et al.[28] demonstrated that the risk of developing a lupus-like condition in people with acne exposed to minocycline was significantly raised [odds ratio 8.5; 95% confidence interval (CI) 2.1 to 35.0] compared with nonuse and higher than the risk associated with other tetracyclines. The findings of this study indicate that minocycline may well be responsible for promoting drug-induced lupus and also support previous observations that drug-induced lupus is reported most frequently in young women. In this respect the pattern of drug-induced lupus occurrence reflects the propensity of several autoimmune diseases to affect predominantly women (e.g. systemic lupus erythematosus, rheumatoid arthritis, scleroderma). Drug-induced lupus may involve the liver, provoking symptoms akin to those of autoimmune hepatitis and a liver histology similar to that of chronic active hepatitis.

Case reports of autoimmune hepatitis associated with minocycline generally describe a long period of exposure to the drug prior to the onset of disease.[22,23,26,29] Other adverse reports associated with minocycline describe a hypersensitivity-type reaction typified by fever, rash and internal organ involvement after about 12 weeks of exposure.[18,19,23,30]

It has been proposed that the risk of adverse reactions involving the liver and associated with minocycline is higher than that associated with other tetracyclines.[31] One explanation may be that whilst the primary route of elimination for most tetracyclines is the kidney, minocycline is extensively metabolised by the liver and renal clearance is low.[32] Another important factor to consider is that unlike some other tetracyclines, minocycline has the potential to form reactive metabolites that serve as antigens and may incite an immune reaction.[23]

In the UK, the popularity of minocycline has

waned since the mid 1990s.[33] The paper on minocycline-associated hepatotoxicity published by Gough et al.[22] in January 1996 had a significant effect on prescribing practice in the UK. Dispensing data for the first quarter of 1996, presented by Ferguson et al.,[33] show that the use of minocycline (in terms of defined daily doses) dropped to less than 70% of figures for the previous quarter, and then further to 62%.

Concern over the incidence of severe adverse reactions to minocycline, particularly acute hepatic failure, has prompted some general practitioners and dermatologists to advocate prescribing minocycline only as a second line treatment for acne.[34] Cautions relating to autoimmune hepatotoxicity after longer term (>6 months) exposure to minocycline have been given in the datasheets since 1998. It is apparent that the 1996 article was particularly influential over UK prescribing patterns, although the authors do acknowledge later that '. . . it was impossible to definitely attribute (the adverse events) to the drug'.[35]

This study investigates the reported association between minocycline and hepatitis in order to evaluate and characterise the type of liver disease that has been associated with oral minocycline in the treatment of acne.

Methods

Systematic Literature Review

Original studies reporting liver damage associated with minocycline therapy were sought in the following databases: Medline, CINAHL, Cochrane, Embase, Current Contents and Toxline. Publications from the earliest years available on the databases to December 1998 were included. Patients taking minocycline for reasons other than acne or those given intravenous minocycline were excluded.

The following terms for liver damage were used to identify relevant papers: (i) liver diseases (fatty liver, liver failure, liver function tests, liver transplantation, hepatic dysfunction); (ii) hepatitis (hepatitis, autoimmune hepatitis, chronic hepatitis, chronic drug-induced hepatitis, toxic hepatitis) and; (iii) jaundice.

Further searches excluding either minocycline or acne were performed and reviewed to ensure that no relevant material was missed. The search criteria sought to include papers in English as well as French, German, Swedish and Spanish. We did not review papers in other languages as we did not have the capacity to translate them.

For full evaluation of minocycline-associated hepatotoxicity, similar searches were performed to identify cases of hepatitis in association with all tetracyclines.

An extensive review of the papers identified from the database searches was carried out to find relevant secondary references, and where applicable tertiary references were sought. A citation search was also carried out using the Bath Information and Data Services database (BIDS) for those papers recognised to be particularly pertinent to the subject. The reference list of this study does not list all of the references identified but notes key references to case reports and other papers which were considered relevant.

'Grey' literature (theses, internal reports, nonpeer reviewed journal articles, etc.) was also acquired for the review. Reporting data for adverse drug reactions associated with minocycline were supplied by John Wyeth & Brother, UK, and additional data relating to specific patient case histories were obtained directly from the *Lancet* to supplement 1 published report (Bénéton et al.[19]).

The selection of published reports citing cases of minocycline-related hepatotoxicity was based on a critical appraisal of the medical histories presented. Those listing the findings of laboratory investigations indicating liver dysfunction were included, as were those where specific reference was made to liver dysfunction by the authors. Relevant case histories could then be identified from a firm indication of hepatic dysfunction post administration of minocycline.

Having identified case reports from the literature, patient details and medical histories were entered into an Access database. The interpretation and

Table I. Criteria used in the study for classification of hepatitis from case reports

Autoimmune hepatitis (n = 29)	Hypersensitivity reaction (n = 16)	Unspecified hepatitis (n = 20)
Altered liver enzyme levels	Altered liver enzyme levels	Altered liver enzyme levels
Positive ANA (and/or other auto-antibodies)	Negative ANA	No further diagnostic information
Histological evidence of chronic active hepatitis	Eosinophilia (> 5%)	Did not fit clearly criteria for autoimmune hepatitis or hypersensitivity reaction
	Exfoliative dermatitis	

ANA = antinuclear antibodies.

recording of details was further reviewed by 2 independent researchers [one medically qualified (RL)] to ensure accurate assessment of clinical symptoms/investigations from the given data. The possibility of reporting duplication was recognised, and all case reports were compared by age, gender, country of domicile of the patient and year of occurrence wherever possible. Cases without age and/or gender of the patient were excluded (accounting for 3 cases[22]), as were those cases where administration of minocycline was other than oral (1 patient[36]).

Decisions on the appropriateness of cases for inclusion were reached by consensus and cases were then classified into 1 of the 3 groups described in table I. A diagnosis of hepatitis was made, qualified by evidence of raised liver enzyme levels (twice the upper limit of normal) and/or a firm indication of liver dysfunction by the authors of the particular case report. The classification criteria for autoimmune hepatitis defined by Alvarez et al.[37] (table II) were applied to aid definition of the cases as were the characteristics of hypersensitivity reactions (fever, rash and internal organ involvement within 12 weeks of drug initiation) described in the literature.[18,19,23,30]

Review of WHO Data

The Uppsala Monitoring Centre (WHO Collaborating Centre for International Drug Monitoring) provided us with data on minocycline-associated adverse reactions. The Centre collates data gathered from national centres within 53 countries worldwide. Notifications of adverse reactions within each country may be made via regulatory bodies or through voluntary sources and, as such, figures obtained are of limited value in estimating the true incidence of specific reactions.[38] This said, the data obtained are valuable in that they provide information on the types of reactions reported, the duration of treatment before the event and also changes in reporting frequency by year and country.

In addition to reporting the type of reaction, the WHO information usually states the age and gender of individuals affected and the route of drug administration. Fields are also available on the database to define indications for use, time of treatment and outcome subsequent to the reaction.

The Uppsala Monitoring Centre provided us with data on all hepatic reactions associated with minocycline use for all indications from its inception in 1968 to October 1998 – a timespan which covers the first licensed therapeutic use of minocycline in the early 1970s. This subset of the database, along with sales figures obtained from Intercontinental Medical Statistics, was entered onto a local database, reviewed and analysed within our department.

Results

Systematic Literature Review

65 case reports of liver disease associated with minocycline were identified from the literature (see tables III, IV and V). More adverse hepatic reactions have been reported in women (58%) and 94% of patients were below 40 years of age.

Autoimmune hepatitis was attributed to 29 patients, 20 (69%) of whom were female (table III). The mean age of females was 22 years, and males 23 years. Cases of autoimmune hepatitis were generally associated with a prolonged course of minocycline therapy (median = 365 days for females, 730 days for males), the presence of autoantibodies [a positive titre for antinuclear antibodies was recorded in 26 patients (90%)], and symptoms of arthritis and/or arthralgia in 21 (72%). The ethnicity

of all but 1 patient (a 19-year-old Columbian) was unknown and no deaths as a consequence of this reaction were recorded. Recovery on complete cessation of the drug was apparent for all patients in a mean of 14 days (range 4 to 38 days). Five patients had experienced a recurrence of symptoms in response to re-challenge with minocycline. Diagnosis was supported by liver histology in 13 patients.

16 cases of hepatic damage attributable to a hypersensitivity reaction were identified, 10 (63%) of these patients were female (table IV). The condition was typically associated with eosinophilia (69% patients) and desquamation of the skin (63%). The mean age of females was 25 years, and males 18 years. The duration of treatment with minocycline before onset of symptoms was less than 35 days in all cases. Six of the 16 cases of hypersensitivity reaction were recorded in patients of African-Caribbean origin – data on the ethnicity of the other patients were not available. Three patients died from what appeared to be a hypersensitivity reaction. An account of these 3 deaths is given below. Another young male who was 16 years old survived his illness following liver transplantation. There was 1 patient with a hypersensitivity reaction who demonstrated a positive response to re-challenge with minocycline. Liver histology was presented for only 1 patient.

An unspecified hepatitis was attributed to the remaining 20 patients (table V). Eight (40%) of these patients were female with a mean age of 28 years, while for the males the mean age was 25 years. 14 of the patients were under the age of 30 years. The duration of treatment with minocycline before onset of symptoms ranged between 8 to 360 days for females (median 30 days) and 9 to 840 days for males (median 63 days). One female patient aged 17 years survived her illness after liver transplantation whilst another female aged 22 years died from an illness associated with pancytopenia (see below). One case from this group experienced a resumption of symptoms on re-exposure to minocycline. Liver histology was reported in only 1 case and revealed a normal architecture.

Figure 1 presents the proportional distribution of hepatic reactions by duration of exposure to minocycline. All the cases of hypersensitivity reaction reported occurred within 35 days of starting minocycline, whilst the autoimmune hepatitis occurred usually after 1 year of treatment.

A total of 4 deaths have been cited in the literature in association with minocycline hepatotoxicity. Three of the deaths appeared to be from a hypersensitivity reaction. One occurred in a 17-year-old girl who presented with pyrexia, myalgia, arthralgia and a pruritic erythematous rash.[22,47,54,55] Her past medical history was complicated. She had been taking minocycline for 29 days (100 mg/day to treat acne) before the onset of her illness and just prior to presentation she had returned from a visit to Kenya for which she had taken antimalarials and received various vaccinations. After 2 failed liver transplantations, she died, death being attributed to gastrointestinal and abdominal haemorrhage. At postmortem, her liver and the first donor liver were found to be infected with an arbovirus, possibly transmitted by a biting insect whilst on holiday.

The second death from a hypersensitivity reaction was that of a West Indian boy of 16 years who presented with grossly abnormal liver function af-

Table II. Diagnostic criteria for autoimmune hepatitis [37]

Diagnostic criteria for autoimmune hepatitis	
Liver histology	Chronic active hepatitis: piecemeal necrosis ± lobular hepatitis or central-portal bridging necrosis
Serum biochemistry	Raised levels of serum aminotransferases. Alkaline phosphatase may be normal
Serum immunoglobulins	Raised total globulin, γ-globulin or immunoglobulin G levels
Serum autoantibodies	Seropositivity for ANA, smooth muscle antibodies or liver-kidney microsomal antibodies
Viral markers	Negative viral serology
Other	No excessive alcohol consumption
	No exposure to known hepatotoxic drugs

ANA = antinuclear antibodies.

Table III. Patient details recorded from published case reports: autoimmune hepatitis–type reactions

Reference	Gender	Age (y)	Dosage (mg/day)	Duration[a] (days)	↑ AST/ ALT levels	ANA titre	Other AA	Altered serum IG levels	Viral serology	Eosinohilia	Re-challenge	Other manifestations	Liver histology	Outcome
Akin et al.[27] (Case 2)	F	16	100	365	Yes	+ve	Yes		-ve		Yes	Arthralgia, fatigue, fever	Not done	Recovered
Akin et al.[27] (Case 3)	F	17		42	Yes	+ve	Yes		-ve			Arthritis/myalgia, fatigue, fever, rash	Not done	Recovered
Akin et al.[27] (Case 4)	F	14		365	Yes	+ve			-ve			Arthritis, fatigue, fever	Not done	Recovered
Angulo et al.[39]	F	22		365	Yes	+ve	Yes		-ve			Arthritis, jaundice	CAH	Recovered
Bhat et al.[29]	M	18	100	60	Yes	+ve	Yes	Yes	-ve			Jaundice	Moderately active hepatitis with piecemeal necrosis	Recovered
Crosson & Still-man[25]	F	22		730	Yes	+ve	Yes	Yes	-ve		Yes	Arthritis/arthralgia	Not done	Recovered
Elkayam et al.[40] (Patient 6)	M	22	50-100	730	Yes	-ve	Yes		-ve			Arthralgia, fever, subcutaneous nodules	CAH (periportal inflammation and minimal piece-meal necrosis)	Recovered
Elkayam et al.[40] (Patient 7)	M	17	50-100	730	Yes	+ve	Yes		-ve			Arthritis/arthralgia, fever, subcutaneous nodules	CAH (periportal inflammation and minimal piece-meal necrosis)	Recovered
Golstein et al.[26]	M	19	100	750	Yes	+ve	Yes	Yes	-ve			Anorexia, asthenia	Not done	Recovered
Gorard[41]	M	37	50	360	Yes	-ve	Yes		-ve		Yes	Arthralgia/myalgia, fever, malaise	Normal	Recovered
Gough et al.[22] (Case 1)	F	26	100	730	Yes	+ve		Yes	-ve			Arthritis	CAH	Recovered
Gough et al.[22] (Case 3a)[b]	F	23	100	42	Yes			Yes	-ve			Arthralgia, fever	Not done	Recovered
Gough et al.[22] (Case 3b)[b]	F	25	100	90		+ve		Yes			Yes	Arthralgia, malaise	Not done	Recovered
Gough et al.[22] (Case 4)	M	36	100	730	Yes	+ve		Yes	-ve			Arthralgia, jaundice, rash	Acute hepatitis with confluent necrosis	Recovered

Gough et al.[22] (Case 5)	F	16	100	730	Yes	+ve		Yes	-ve			Arthralgia, jaundice, malaise	CAH with bridging and piecemeal necrosis	Recovered
Gough et al.[22] (Case 6)	F	16	100	730	Yes	+ve		Yes	-ve			Arthralgia, jaundice, malaise	CAH	Recovered
Gough et al.[22] (Case 7)	F	20	200	240	Yes	+ve	Yes	Yes	-ve			Arthralgia, fever, jaundice, malaise, rash	Not done	Recovered
Herzog et al.[42]	F	16	50	540	Yes	+ve			-ve			Arthralgias	Chronic portal inflammation and piecemeal necrosis	Recovered
Knowles et al.[23] (Case 13)	F	43		10	Yes	+ve					Yes	Arthritis, fever		Recovered
Malcolm et al.[43] (Case 1)	F	15	100	360	Yes	+ve						Abdominal pain, anorexia, pruritus	Not done	Recovered
Malcolm et al.[43] (Case 2)	M	17	200	120	Yes	+ve			-ve	Yes	Yes	Arthralgia	CAH	Recovered
Malcolm et al.[43] (Case 4)	F	20	200	28	Yes	+ve			-ve			Fever, rash	Not done	Recovered
Malcolm et al.[43] (Case 5)	F	48	200	180	Yes	+ve			-ve			Malaise	Mild lobular hepatitis	Recovered
Matteson et al.[44]	M	20	200	1825	Yes	+ve			-ve			Arthralgia/myalgia, fatigue/asthenia, fever	Not done	Recovered
Pavese et al.[45]	F	19	50	730	Yes	+ve	Yes	Yes	-ve			Arthralgia, fatigue, pruritus	Not done	Recovered
Teitelbaum et al.[46] (Case 1)	F	15	100	540	Yes	+ve		Yes	-ve			Arthralgia, fatigue, fever, rash	Not done	Recovered
Teitelbaum et al.[46] (Case 2)	F	15	200	365	Yes	+ve	Yes	Yes	-ve			Abdominal pain, anorexia, diarrhoea, jaundice	CAH	Recovered
Teitelbaum et al.[46] (Case 3)	M	16	100-200	540	Yes	+ve	Yes	Yes	-ve	Yes		Anorexia, fatigue, fever, jaundice, myalgias	CAH	Recovered
Teitelbaum et al.[46] (Case 4)	F	17	0	365	Yes	+ve							Not done	Recovered

a Duration of therapy prior to onset of reaction.

b Case presented on 2 separate occasions.

AA = autoantibodies; **ANA** = antinuclear antibodies; **ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **CAH** = chronic active hepatitis; **F** = female; **IG** = immunoglobulin; **M** = male; +**ve** = positive laboratory result; -ve = negative laboratory result; ↑ = raised.

ter taking minocycline for acne, 100 mg/day, for 30 days.[19] He was treated with corticosteroids for 6 months but died 15 days after stopping this therapy. Postmortem revealed eosinophilic myocarditis. Another young boy of 15 presented with altered liver enzyme levels after taking minocycline, 100 mg/day, for 30 days, possibly for acne.[18] Minocycline therapy was discontinued immediately and despite treatment with corticosteroids for 8 weeks, he died. Postmortem examination revealed myocardial necrosis and marked eosinophilia. Biochemical investigations before his death had revealed antibodies against parvovirus 19.

The fourth death was associated with an unspecified hepatitis and 'pancytopenia' and was reported to the UK Committee on Safety of Medicines (CSM) in 1990. A detailed picture of this patient's illness has not been published, although we know from the CSM report referred to by Gough et al.[22] that she had been receiving minocycline therapy, 100 mg/day, for about 5 months.

Review of WHO Data

The WHO has recorded 8025 reactions to minocycline overall. Of these, 493 (6%) were reactions involving the liver, representing reporting for 393 individuals.

Information on both age and gender of individuals was available for 346 of the 393 reports (88%) and on the route of administration for 370 reports (94%). Fields available to define indications for use, time of treatment and outcome subsequent to the reaction were seldom complete.

22 different hepatic reactions were recorded. Groupings of like reactions produced 4 principal categories – 'hepatic dysfunction' (32%), 'hepatitis' (26%), 'abnormal liver function tests' (24%), and 'hyperbilirubinaemia/jaundice' (14%). There were a small number of other reactions including 11 cases of hepatic damage/necrosis, 7 cases of fatty liver and 9 other unspecified reactions.

Gender distribution was almost even (51% females *vs* 49% males) and the mean age was 31 years for females and 30 for males. An indication for use (ICD code) was given for 78 of the 393 reports (20%). Of these reports, 61 (78%) patients had been prescribed minocycline to treat acne or rosacea, whilst a further 5 reports cited a different dermatological indication.

Minocycline was administered orally to 355 (96%) with information on dosage available for 228 (64%). The mean daily dosage of minocycline for these cases was 127mg (range 10 to 500mg). The duration of treatment with minocycline was available for 216 of the 393 reports (55%) with a mean of 269 days (95% CI 208 to 330). Reactions occurring within 35 weeks of exposure accounted for 42% of the total, whilst over half (53%) occurred within 10 weeks.

Of the 393 individuals experiencing a hepatic reaction to minocycline, 14 also had drug-induced lupus-like symptoms. The precise nature of the symptoms was not specified. 12 females (mean age 23) and 2 males (mean age 22) demonstrated a reaction of this type, and for those where the information was available (n = 5), the mean duration of exposure was 593 days.

The outcome of the reactions was reported in less than half the cases. Three deaths were evident. One report from Japan recorded the death of a 31-year-old man who had taken 200mg of minocycline by mouth for only 1 day. The notes accompanying this report state that the drug 'may have been contributory'. Two other deaths where minocycline was considered to be responsible for the patient's illness were reported from the UK in 1989. Both these deaths occurred in females, one aged 17 and the other aged 20. The 20-year-old had been exposed to minocycline for 154 days.

Table VI shows the reporting of minocycline-associated adverse drug reactions from each country identified from the WHO database. The majority of reports (63%) came from the US and the UK.

Since 1990, more than 20 cases per year of minocycline-associated adverse drug reactions have been reported to WHO. In the UK, the highest annual count of adverse drug reactions was received in the same year that the greatest number of cases was published. At the same time, the number of units sold reached its lowest figure. In the USA, how-

Table IV. Patient details recorded from published case reports: hypersensitivity result–type reactions

Reference	Gender	Age (y)	Dosage (mg/day)	Duration[a] (days)	↑AST/ ALT levels	ANA titre	Other AA	Altered serum IG levels	Viral serology	Eosinophilia	Re-challenge	Other manifestations	Liver histology	Outcome
Bénéton et al.[19] (Case 1)	M	16		30	Yes					Yes		Lymphadenopathy		Patient died
Bénéton et al.[19] (Case 2)	F	17		12	Yes					Yes (weak)		Lymphadenopathy		Recovered
Bénéton et al.[19] (Case 6)	F	24		23	Yes					Yes		Lymphadenopathy		Recovered
Bénéton et al.[19] (Case 7)	F	32		31	Yes					Yes		Lymphadenopathy		Recovered
Chatham & Ross[14]	M	24	200	28	Yes		Yes		-ve	Yes	Yes	Erythema, fever, jaundice, lymphadenopathy		Recovered
Davies & Kersey[47] (Case 1)	M	16	200	32	Yes				-ve	Yes		Exfoliative rash, fever, lymphadenopathy, malaise		Recovered
Gough et al.[22] (Case 22)[b] [Davies & Kersey[47] (Case 2)]	F	17	100	29	Yes					Yes		Anaemia, exfoliative dermatitis, fever	Toga-like virus particles	Patient died despite transplant
Kaufmann et al.[30]	F	35	100	21	Yes			Yes	-ve	Yes		Arthralgia/myalgia, fever, lymphadenopathy, rash		Recovered
Knowles et al.[23] (Case 1)	M	16		29	Yes							Exfoliative dermatitis[c], fever, lymphadenopathy		Recovered (transplant)
Knowles et al[23] (Case 2)	F	14		30	Yes							Exanthema, fever, lymphadenopathy		Recovered
Knowles et al.[23] (Case 3)	F	25		30	Yes							Exfoliative dermatitis, fever, lymphadenopathy		Recovered
Knowles et al.[23] (Case 5)	M	21		28	Yes							Erythema, fever, lymphadenopathy		Recovered
Knowles[23] (Case 6)	F	16		21	Yes							Erythema, fever, lymphadenopathy		Recovered

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Table IV cont.

ever, a peak in reporting frequency occurred earlier and the sales increased. These findings are presented in figures 2 and 3.

Discussion

This systematic review of the literature has indicated that minocycline therapy has been implicated in several instances of severe hepatic dysfunction,[14,17-19,22,23,25-27,29,30,39-48,50-53] including 4 deaths.[18,19,22,47,54,55]

Our investigation into the cases cited in the medical literature supported the previous division of the most severe adverse reactions into 2 groups. First, those that appear to be attributable to a hypersensitivity reaction (with rapid onset usually within 1 month of treatment) and second, those that can be classed as an autoimmune hepatitis or 'late onset hepatitis' (generally after a year or more of therapy). A characterisation of the 20 cases of 'unspecified hepatitis' was not attempted because of the sparsity of evidence from the medical histories. The onset of illness in 9 of those patients with an unspecified hepatitis, however, was within 35 days of commencing therapy whilst for the remaining 11 cases, data on duration of exposure to minocycline was available for 8 patients, giving a mean of 376 days.

The classification of 29 case reports as an autoimmune hepatitis in association with minocycline, using the criteria set out in tables I and II, demonstrated that this type of reaction generally occurs after exposure of at least a year. The medical summaries of 20 cases (69%) revealed a history of exposure of a year or more. Of the remaining 9 cases, the duration of exposure ranged between 10 and 240 days (median 60 days). The most notable outlier in this pattern of distribution is the case of a 43-year-old woman presented by Knowles et al.[23] (their case 13). The authors of this report describe a drug-induced lupus-like reaction with hepatic involvement after only 10 days' exposure to minocycline. Over the previous 10 years, however, the woman had been exposed to minocycline intermittently. This would be a significant factor in her illness and may explain the development of autoimmune hepatitis

Table IV. Contd

Reference	Gender	Age (y)	Dosage (mg/day)	Duration[a] (days)	↑AST/ ALT levels	ANA titre	Other AA	Altered serum IG levels	Viral serology	Eosinophilia	Re-challenge	Other manifestations	Liver histology	Outcome
MacNeil et al.,[48] Knowles et al.[23] (Case 4) and Shapiro et al.[49]	F	17	100	21	Yes	-ve		Yes	-ve	Yes		Exfoliative dermatitis, fatigue, fever, lymphadenopathy, malaise, pruritus, bodyweight loss	Not done	Recovered
Min et al.[50]	F	39	200	28	Yes				-ve	Yes		Fever/malaise, maculopapular rash, myalgia, lymphadenopathy		Recovered
Parneix-Spake et al.[18] (Case 1)	M	15	100	30	Yes					Yes		Fever, diffuse pustular eruption, lymphadenopathy		Patient died

a Duration of therapy prior to onset of reaction.

b Case reported to the Committee on Safety of Medicines, UK.

c Stevens-Johnson syndrome.

AA = autoantibodies; **ALT** = alanine aminotransferase; **ANA** = antinuclear antibodies; **AST** = aspartate aminotransferase; **F** = female; **IG** = immunoglobulin; **M** = male; +**ve** = positive laboratory result; **-ve** = negative laboratory result; ↑ = raised.

Table V. Patient details recorded from published case reports: unspecified hepatic reactions

Reference	Gender	Age (y)	Dosage (mg/day)	Duration[a] (days)	↑AST/ ALT levels	ANA titre	Other AA	Altered serum IG levels	Viral serology	Eosinohilia	Re-challenge	Other manifestations	Liver histology	Outcome
Bénéton et al.[19] (Case 3)	F	30		10	Yes									Recovered
Bénéton et al.[19] (Case 5)	F	21		21	Yes							Lymphadenopathy		Recovered
Boudreaux et al.[17]	F	17												Recovered (transplant)
Bruguera & Padros[51]	M	18	100	21	Yes	-ve			-ve					Recovered
Castex et al.[52]	F	30	200	8	Yes	-ve	Yes (weak)		-ve			Asthenia, jaundice		Recovered
Gough et al.[22] (Case 18)[b]	M	39	100	10										Recovered
Gough et al.[22] (Case 21)[b]	F	39	200	30								Dizziness, headache, taste disturbance		Unknown
Gough et al.[22] (Case 23)[b]	M	17	100	90										Recovered
Gough et al.[22] (Case 24)[b]	M	18	100	30					-ve		Yes	Jaundice		Unknown
Gough et al.[22] (Case 25)[b]	M	22	100	840										Recovered
Gough et al.[22] (Case 26)[b]	F	22	100	150								Pancytopenia		Patient died
Gough et al.[22] (Case 27)[b]	M	18	100	210										Recovered
Gough et al.[22] (Case 28)[b]	M	22	100						-ve					Recovered
Gough et al.[22] (Case 29)[b]	M	20	100	360					-ve			Arthritis		Recovered
Gough et al [22] (Case 31)[b]	M	73	50	9										Unknown
Gough et al.[22] (Case 32)[b]	M	23	100			-ve	Yes		-ve			Jaundice		Recovered

Continued on next page

Table V cont.

after the unusually short exposure period quoted in the case-report.

In a review of this nature, an appraisal of causation in reported deaths is important. As mentioned previously, 4 deaths have been cited in the literature in association with minocycline hepatotoxicity. The case of the 17-year-old girl who died after taking minocycline[22] is complicated by her recent exposure to multiple drugs and the presence of an arbovirus. Postmortem findings from her liver and the first donor liver indicated both intra- and extrahepatic infection with the arbovirus and the role of minocycline exposure in her death is unclear.[47,54,55]

Postmortem examination of the 16-year-old boy who died from an apparent hypersensitivity reaction revealed eosinophilic myocarditis.[19] Generally, in cases of hypersensitivity myocarditis, the condition regresses upon discontinuance of the drug, so any association with minocycline exposure, which in this instance was withdrawn immediately at the onset of illness, is unsubstantiated.

Evidence of antibodies to parvovirus 19 and postmortem findings of myocardial necrosis and marked eosinophilia on the 15-year-old boy who died from a hypersensitivity reaction[18] also raises some doubt over the causative role of minocycline. Antibodies against parvovirus 19 have previously been implicated in deaths from myocarditis with associated mononuclear infiltrates.[18] The opinion of the authors of this case report was that minocycline was implicated in the boy's death but, in the light of evidence they themselves present of parvovirus infection and also because of evidence for myocarditis at postmortem, the association with minocycline is arguable.

Good evidence to support the role of minocycline exposure in the death of a 22-year-old woman from an unspecified hepatitis and 'pancytopenia' is not available. The case was notified to the CSM[22] but the published case history does not provide enough clinical evidence to substantiate the role of minocycline in her illness. Therefore, minocycline-related hepatotoxicity cannot be established firmly as the cause of death.[12]

Table V. Contd

Reference	Gender	Age (y)	Dosage (mg/day)	Duration[a] (days)	↑AST/ ALT levels	ANA titre	Other AA	Altered serum IG levels	Viral serology	Eosinohilia	Re-challenge	Other manifestations	Liver histology	Outcome
Gough et al.[22] (Case 32)[b]	M	23	100			-ve	Yes		-ve			Jaundice		Recovered
Gough et al.[22] (Case 33)[b]	F	23	100	270										Recovered
Hardman et al.[53]	F	42		360	Yes	-ve			-ve			Arthralgia, rash	Normal architectur	Recovered
Malcolm et al.[43] (Case 3)	M	17	100	730	Yes				-ve			Abdominal pain, fatigue	Not done	Recovered
Malcolm et al.[43] (Case 6)	M	17	200	35	Yes	-ve			-ve			Anorexia, jaundice	Not done	Recovered

a Duration of therapy before onset of reaction.

b Case reported to the Committee on Safety of Medicines, UK.

AA = autoantibodies; **ALT** = alanine aminotransferase; **ANA** = antinuclear antibodies; **AST** = aspartate aminotransferase; **F** = female; **IG** = immunoglobulin; **M** = male; +**ve** = positive laboratory result; **-ve** = negative laboratory result; ↑ = raised.

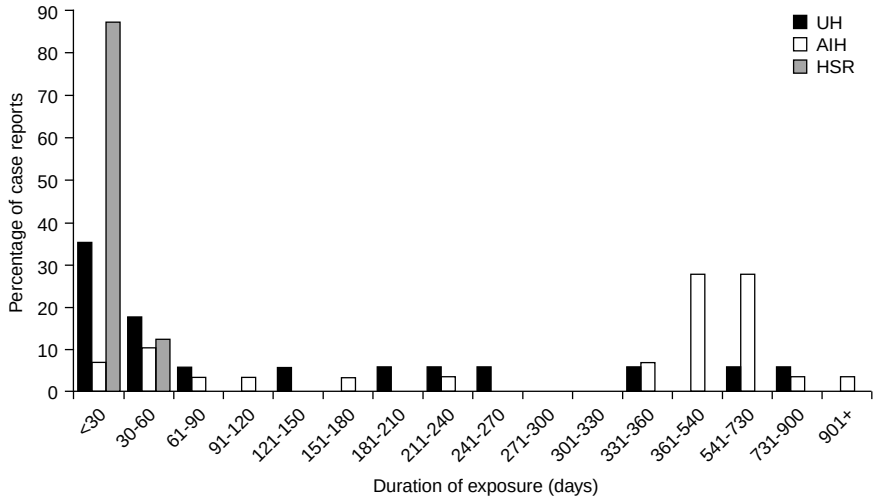

Fig. 1. Proportional distribution over time of hepatic reactions associated with minocycline from published case reports. **AIH** = autoimmune hepatitis; **HSR** = hypersensitivity reaction; **UH** = unspecified hepatitis.

In an investigation of causality such as addressed in this paper, evidence from re-challenge is particularly important. From our series, 7 cases demonstrated a positive re-challenge to minocycline, all of whom recovered from the illness. Given the potential seriousness of reactions, however, and the reported cross-sensitivity between the tetracyclines[32] physicians should not prescribe tetracyclines to patients in whom an adverse reaction has been suspected previously.

There were 3 deaths associated with minocycline recorded on the WHO database. One was reported by Japan but apparently was not published as a case report in the specialist journals. The 2 other deaths, however, present similarities to those CSM reports cited in the literature (see table IV, Gough et al.,[22] case 22 and table V, Gough et al.,[22] case 26), and are thus likely to be duplications.

It is apparent from the cases identified from the literature that 6 of the 16 cases of hypersensitivity reaction were recorded in people of African-Caribbean origin. A genetic predisposition to hypersensitivity reaction has previously been suggested[56-58] and this may be important to consider when prescribing minocycline.

The population which experienced an hepatic adverse drug reaction to minocycline as identified from the WHO database has shown an almost equal male:female distribution with a mean age of 30 years, whilst 58% of cases of hepatic injury drawn from the literature are female, and the mean age of the population is younger at 24 years.

Around 22% of the WHO data for hepatic reactions was recorded for patients aged ≥40 years, compared with only 6% for this age group in the literature case reports. Part of the explanation for the discrepancy in the age profile of the 2 populations may be associated with different utilisation of minocycline in reporting countries. From Japan, for example, of the 23 reported adverse drug reactions, 16 (70%) were in patients over the age of 40 years and in 11 cases minocycline was administered intravenously. An indication for use was given for only 2 cases, neither of which specified acne. No case reports in the literature originating from Japan would have been relevant to this study as none was found where hepatic dysfunction was associated with minocycline administered orally.

The literature search sought to identify all patients experiencing an adverse drug reaction with

Table VI. Reporting to the WHO by country

Country	No. of reports
UK	143
US	105
France	37
Australia	33
Japan	23
Germany	21
Canada	10
Belgium	7
New Zealand	7
Spain	3
The Netherlands	2
Eire	1
Switzerland	1
Total Reports	**393**

liver involvement after ingestion of minocycline. We know from our preliminary analysis of utilisation data from the UK General Practice Research Database (GPRD) that around 90% of minocycline prescribed in the UK is used to treat acne, and evidence from the case reports on indication for use supports this finding. Because acne occurs mainly in people under 40, this would account for the high proportion of younger patients in case reports. 78% of cases recorded from the literature review had a record of acne. A specific reason for treatment was available for only 20% of individuals on the WHO database, of whom 65% had received minocycline for acne.

An interesting aspect of the present material is the relationship between reporting frequency, published cases in the literature and the sales of minocycline. Worldwide reporting of adverse drug reactions to the WHO have shown a gradual increase since 1978.[38] Figures 2 and 3 show the relationship between the 2 countries most frequently reporting adverse drug reactions, the UK and the US, in terms of the reporting frequency per number of units sold and the number of published hepatic cases in the literature. In the UK, the reporting frequency of hepatic reactions reached its peak in the same year that the highest number of cases was published. At the same time, the number of units sold reached its lowest figure. In the US, however, a peak in reporting frequency occurred earlier and the sales increased. The 1996 paper published in the *British Medical Journal* by Gough et al.[22] alerted doctors internationally to the possibility of serious adverse drug reactions associated with minocycline but apparently only influenced subsequent prescribing practice in the UK.

The characteristics of patients reported to have an autoimmune liver disease associated with minocycline use include an excess incidence in women (69%).[26,27] Over three-quarters of patients are under the age of 40. Utilisation data from the GPRD would suggest that much of the excess in young people is because they are the age group most affected by acne and who thus consume most of the minocycline prescribed. This raises the question as to whether this excess occurrence in younger patients is because they are predominantly the users or whether they truly have an increased risk. The apparently higher risk of autoimmune hepatitis in women may reflect gender-specific differences in drug metabolism. Without long term observational studies, it is difficult to predict the attributable risk of autoimmune hepatitis, especially for young women in whom autoimmune hepatitis is already more common.[37]

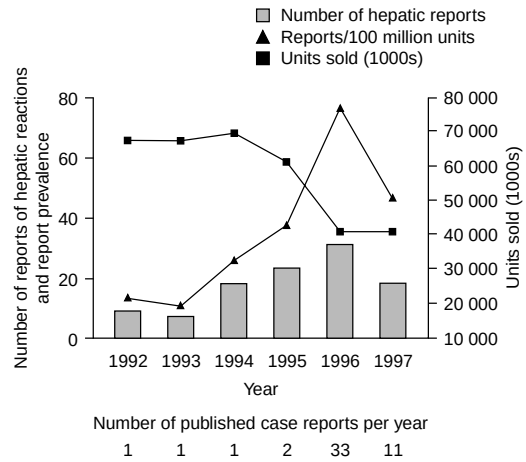

Fig. 2. Sales of minocycline in the UK versus worldwide reports of adverse hepatic reactions sent to the WHO.

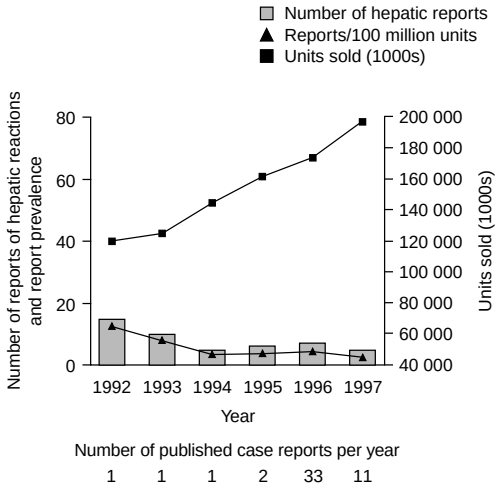

Fig. 3. Sales of minocycline in the US versus worldwide reports of adverse hepatic reactions sent to the WHO.

Conclusions

To determine if minocycline is likely to be causally related to the occurrence of hepatitis, we need to establish whether there is a strong association when compared with the general population or more importantly when compared with the population that have acne. The temporal relationship is well documented, evidence of positive re-challenge and the fact that patients get better after the removal of the minocycline adds weight to there being a causal relationship. However, transient hepatitis can occur in some patients and it is possible that some of these patients would have recovered without stopping the medication. From our preliminary unvalidated analysis of incidence rates for nonviral hepatitis in the general GPRD population compared with the acne population, people with acne appear more likely to experience an hepatic illness. There is no obvious explanation for this finding, and whilst various ideas could be discussed regarding the role of exposures, lifestyle or predisposing factors, more research is required to elucidate exactly why this should be so.

Despite the reported cases, we do not have any clear information about the absolute and relative risks of hepatitis, whether hypersensitivity reaction or autoimmune hepatitis, in patients receiving minocycline therapy for varying lengths of time. The WHO data show that whilst in the UK the utilisation has fallen, the reporting of adverse events has increased. The converse is true in the US. This suggests that there are considerable biases in using spontaneous reports to assess risk. There does however seem to be an association between hepatitis and the use of minocycline. A review of this nature cannot quantify the absolute or attributable risk of liver dysfunction associated with minocycline exposure and we think it inappropriate to make comment on whether monitoring of patients is worthwhile. A study of the comparative rates of hepatitis in people exposed to minocycline compared with those not exposed is required.

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Correspondence and offprints: Professor *Ross Lawrenson*, Primary Care Research Unit, Postgraduate Medical School, University of Surrey, Stirling House, Surrey Research Park, Guildford, Surrey, GU2 7DJ, England.
E-mail: r.lawrenson@surrey.ac.uk