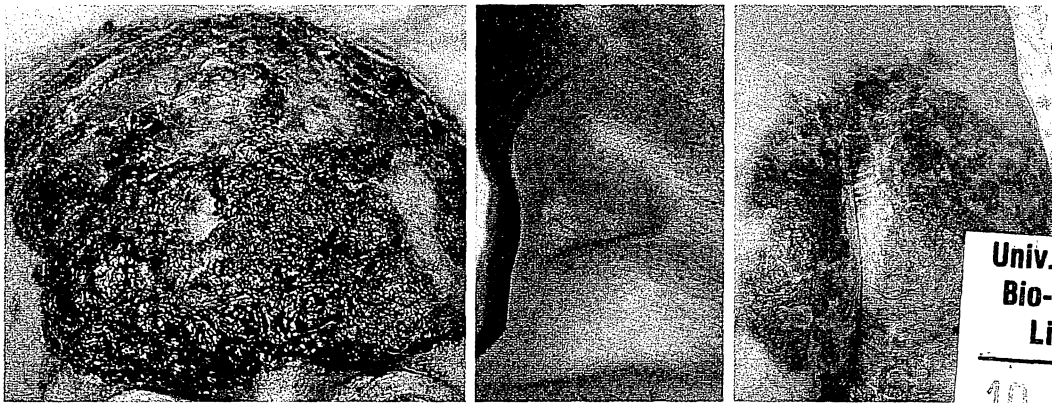


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Exhibit 1039

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Exh. 1039

# Comparative Safety of Tetracycline, Minocycline, and Doxycycline

Lori E. Shapiro, MD, FRCPC; Sandra R. Knowles, BScPhm; Neil H. Shear, MD, FRCPC

**Background:** Because minocycline can cause serious adverse events including hypersensitivity syndrome reaction (HSR), serum sicknesslike reaction (SSLR), and drug-induced lupus, a follow-up study based on a retrospective review of our Drug Safety Clinic and the Health Protection Branch databases and a literature review was conducted to determine if similar rare events are associated with tetracycline and doxycycline. Cases of isolated single organ dysfunction (SOD) attributable to the use of these antibiotics also were identified.

**Observations:** Nineteen cases of HSR due to minocycline, 2 due to tetracycline, and 1 due to doxycycline were identified. Eleven cases of SSLR due to minocycline, 3 due to tetracycline, and 2 due to doxycycline were identified. All 33 cases of drug-induced lupus were attribut-

able to minocycline. Forty cases of SOD from minocycline, 37 cases from tetracycline, and 6 from doxycycline were detected. Hypersensitivity syndrome reaction, SSLR, and SOD occur on average within 4 weeks of therapy, whereas minocycline-induced lupus occurs on average 2 years after the initiation of therapy.

**Conclusions:** Early serious events occurring during the course of tetracycline antibiotic treatment include HSR, SSLR, and SOD. Drug-induced lupus, which occurs late in the course of therapy, is reported only with minocycline. We theorize that minocycline metabolism may account for the increased frequency of serious adverse events with this drug.

*Arch Dermatol.* 1997;133:1224-1230

**M**INOCYCLINE HAS been reported to cause serious, rare adverse events including the hypersensitivity syndrome reaction (HSR), serum sicknesslike reaction (SSLR), and drug-induced lupus (DIL).<sup>1,2</sup> We conducted a review to determine if similar events are associated with other tetracycline antibiotics, namely, tetracycline and doxycycline. We also attempted to identify serious single organ dysfunction (SOD) attributable to these antibiotics.

## RESULTS

Review of the Drug Safety Clinic database, Health Protection Branch data, and MEDLINE search produced 19 reports of HSR, 11 reports of SSLR, 40 reports of SOD, and 32 reports of DIL attributable to minocycline (**Table 1**).<sup>2-34</sup> **Table 2** shows data on the mean patient age, mean interval to onset of the reaction, and sex distribution of these reactions. We found no difference in the average daily doses of minocycline in causing the different re-

action patterns. The most common patterns of internal organ involvement seen with minocycline HSR were hepatitis in 15 (79%), lymphadenopathy in 14 (74%), hematologic abnormalities in 13 (68%), and renal and pulmonary abnormalities in 5 (26%) patients each. Three case fatalities have been described.<sup>2,11</sup> Three patients who were rechallenged redeveloped symptoms within 48 hours.

Reports of SOD attributable to minocycline include 17 of pneumonitis,<sup>6,18-23</sup> 4 of hepatitis,<sup>3,24,25</sup> 2 of antineutrophil cytoplasmic antibody-positive polyarthritides,<sup>26,27</sup> 1 of nephritis,<sup>28</sup> 1 of both fulminant hepatic failure and necrotizing pancreatitis,<sup>29</sup> and 1 of severe cutaneous adverse reaction.<sup>30</sup>

The patients with minocycline-induced lupus erythematosus presented with malaise that was accompanied by myalgia, arthralgia, or arthritis. Eighty-eight percent of cases occurred in women. Ten patients developed elevated serum hepatic transaminase levels. Two patients had livedo reticularis and antineutrophilic cytoplasmic antibodies, and in 2 other patients, precise descriptions of their erup-

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## MATERIALS AND METHODS

### DEFINITIONS OF ADVERSE EVENTS

Specific reaction patterns were identified for inclusion. Hypersensitivity syndrome reaction was defined by fever, skin eruption, and internal organ involvement developing within 8 weeks of initiation of therapy; SSLR was defined by fever, skin eruption (most commonly urticarial or erythema multiforme), arthralgia with or without lymphadenopathy occurring within 6 weeks of treatment; and DIL was defined by the presence of antinuclear antibodies, the presence of at least 1 clinical feature of systemic lupus erythematosus (SLE) that resolves with drug discontinuation, and the absence of idiopathic SLE. Single organ dysfunction was defined as the presence of severe disease in a major organ, eg, pancreatitis, hepatitis.

### SOURCES OF CASES

#### Drug Safety Clinic

We reviewed the records of all patients referred to the Glaxo Wellcome-Sunnybrook Drug Safety Clinic, Toronto, Ontario, from January 1985 through October 1996 who possibly had adverse events attributable to the use of minocycline, tetracycline, or doxycycline.

#### Health Canada

Reports from the Adverse Drug Reaction Monitoring Division of the Health Protection Branch, Ottawa, Ontario, were requested regarding adverse events possibly attributable to the use of minocycline, tetracycline, or doxycycline from 1966 through October 1996. Cases were classified as HSR, SSLR, DIL, or isolated SOD.

#### Literature Search

A thorough computer-based MEDLINE search of articles published from 1966 to October 1996 was conducted. Search terms included drug hypersensitivity, tetracycline antibiotics, and liver, kidney, skin, and joint diseases. The reference lists of all pertinent articles also were reviewed to identify any additional articles that might have been missed or that predated the computer search.

#### Utilization Data

The Institute of Medical Statistics, Toronto, provided us with the most recent statistics from 1994 to identify prescribing patterns for tetracycline antibiotics.

symptoms developed with minocycline rechallenge remained asymptomatic after doxycycline exposure.<sup>31</sup>

Review of the Drug Safety Clinic database, Health Protection Branch data, and MEDLINE search produced 2 reports of HSR, 3 reports of SSLR, 37 reports of SOD, and no reports of DIL attributable to tetracycline.<sup>35-41</sup>

Review of the Drug Safety Clinic database, Health Protection Branch data, and MEDLINE search produced 1 report of HSR, 2 reports of SSLR, 6 reports of SOD, and no reports of DIL attributable to doxycycline.<sup>42-45</sup>

### PRESCRIBING DATA

The Institute of Medical Statistics provided the most recent (ie, 1994) Canadian national statistics regarding the use of tetracycline antibiotics. In 1994, 1 866 000 prescriptions for tetracycline antibiotics were filled (**Table 3**).

### COMMENT

Minocycline has been used as successful, safe, long-term therapy for patients with acne vulgaris. However, there are concerns about the safety of minocycline based on recent reports of serious adverse events.<sup>1,2</sup> These reports of minocycline-induced side effects prompted a complete review of the literature to determine whether these reactions occur with other tetracycline antibiotics.

Twenty-two patients with HSRs attributable to the 3 tetracycline antibiotics were identified, of which minocycline was implicated in 86%. Reports of hepatotoxic effects from excessive serum levels of tetracycline are not included in this report as the mechanism of these reactions is associated with suprapharmacologic doses.<sup>49-53</sup>

Of note are additional references in the literature pertaining to tetracycline antibiotic-induced severe isolated SOD. These cases may represent a forme fruste of HSRs. For example, critical detailed information in case reports is often lacking so that the defining criteria of an HSR may not be fulfilled (eg, presence of fever). Another shortcoming with extracting data from case reports is that patients are often taking multiple medications and exact details of timing are missing. Therefore, an accurate assessment of drug causation is more difficult and less reliable.<sup>54</sup>

Isolated SOD attributable to tetracycline and doxycycline is manifest most commonly as severe cutaneous adverse reaction (30% and 71%, respectively), whereas SOD related to minocycline most commonly is manifest as pneumonitis (45%).

Based on the available information, there are more reports of serious adverse events from minocycline use than from the use of other tetracycline antibiotics. We acknowledge that the sources from which we collected our data rely on voluntary reporting, and therefore only a fraction of the true number of reactions are known. Although it is unclear why there are more serious adverse events reported with the use of minocycline, we theorize that this may relate to its unique metabolism.

Tetracycline antibiotics all possess the same basic

tion were lacking. No patient had renal, neurologic, or vasculitic involvement. All patients' symptoms had improved after discontinuation of the minocycline. Twenty-one patients who were rechallenged with minocycline developed a recrudescence of their DIL. One patient in whom

Table 1. Summary of Adverse Events to Tetracycline Antibiotics

	Tetracycline			Minocycline			Doxycycline		
	Drug Safety Clinic	Health Protection Branch	Literature	Drug Safety Clinic	Health Protection Branch	Literature	Drug Safety Clinic	Health Protection Branch	Literature
No. referred	166	976	...	17	160	...	39	145	...
Mild									
Rash	66	406	0	1	52	0	15	38	0
Urticaria	35	138	0	6	7	0	11	0	0
Angioedema	11	8	0	1	8	0	3	1	0
Photosensitivity	4	10	0	0	0	0	3	4	0
Vomiting/diarrhea	23	159	0	2	53	0	3	17	0
Severe									
Hypersensitivity syndrome reaction	0	1	1 <sup>46</sup>	2	4	13 <sup>2,6-10,42,47</sup>	0	0	1 <sup>42</sup>
Serum sicknesslike syndrome	0	3	0	2	4	5 <sup>4,34</sup>	1	1	0
Drug-induced lupus	0	0	0	1	0	32 <sup>2,3,5,12-17,27,31,32</sup>	0	0	0
Single organ dysfunction	2	26	9	0	14	26	0	3	3
Severe cutaneous adverse reaction	1	9	1 <sup>35</sup>	0	2	1 <sup>30</sup>	0	1	3 <sup>43-45</sup>
Hepatitis	1	7	0	0	7	4 <sup>3,24,25</sup>	0	0	0
Pneumonitis	0	0	1 <sup>38</sup>	0	0	17 <sup>6,18-23,33</sup>	0	0	0
Pancreatitis	0	3	4 <sup>36,41,48</sup>	0	1	1 <sup>29</sup>	0	1	0
Nephritis	0	2	0	0	0	1 <sup>28</sup>	0	1	0
Hematologic	0	4	2 <sup>39,40</sup>	0	4	0	0	0	0
Parotitis	0	1	0	0	0	0	0	0	0
Myocarditis	0	0	1 <sup>37</sup>	0	0	0	0	0	0
Arthritis	0	0	0	0	0	2 <sup>26,27</sup>	0	0	0

4-ring carbocyclic structure but differ in the substituents on the ring<sup>55</sup> (**Figure**). Doxycycline has a hydroxyl side chain distinguishing this congener from tetracycline.<sup>56</sup> Minocycline shares the basic 4-ring structure of the other commonly used tetracyclines having a substitution of a dimethylamino group in the 7 position.<sup>57</sup> Whether minocycline metabolism produces a reactive metabolite is unknown, although an iminoquinone derivative may be generated that is a potential reactive electrophilic intermediate. Neither tetracycline nor doxycycline contains this amino acid side chain that has the potential to form this reactive metabolite.

Black pigmentation in the thyroid gland has been seen in patients receiving long-term minocycline treatment and is not seen with other tetracyclines. One explanation for this effect of minocycline is that its strongly electron-donating dimethylamino group possibly increases its reactivity to oxidation. In support of this theory, treatment of minocycline-induced black pigmentation with thyroid peroxidase resulted in the formation of a black product, whereas other members of the tetracycline family were not oxidized to dark products by the same system.<sup>58</sup>

In vitro studies have demonstrated the presence of a minocycline-glutathione conjugate when minocycline is incubated with hypochlorous acid, as is found in neutrophils. This in vitro system serves as a surrogate for oxidation reactions that take place in the liver. These reactions are most commonly mediated by the cytochrome P450 family of heme-containing enzymes. When a reac-

tive metabolite is generated, there are several cellular mechanisms that detoxify this product. One such system is glutathione transferase; therefore, the presence of minocycline-glutathione conjugates implies the formation of potentially toxic metabolites. When tetracycline or doxycycline were incubated in the same system, no glutathione conjugates were detected (J. Uetrecht, personal communication, 1996).

The potential reactive metabolites generated by minocycline may bind to tissue macromolecules thereby causing cell damage directly, or they may act as haptens, eliciting an immune response secondarily.<sup>59</sup> This "hapten hypothesis" is thought to explain HSRs seen with aromatic anticonvulsants, sulfonamide antibiotics, allopurinol, and dapsone, as well as SSLRs due to cefaclor.<sup>60</sup>

Minocycline causes DIL and appears to be most common in young women. We found no reports of either tetracycline- or doxycycline-induced lupus. There has been a misperception that tetracycline causes DIL based on a misinterpretation of the 1959 article by Domz et al.<sup>61</sup> In that article, 1 of the 3 case reports describes aminoglutethimide-induced lupus erythematosus and another describes positive lupus erythematosus cells without clinical symptoms after tetracycline and penicillin were separately administered. The third case report describes a patient with active SLE whose underlying disease continued to progress after tetracycline was prescribed and in whom a severe cutaneous adverse reaction, possibly from tetracycline, developed. These cases do not support the concept of tetracycline causing DIL.

Table 2. Descriptive Data

Group	Mean±SE Patient Age, y	Mean±SE Interval to Onset, d (Range)	Sex, No.
<b>Hypersensitivity Syndrome Reaction</b>			
Tetracycline	54	11 (1-21)	2 M
Minocycline	21.2±1.8	24.4±1.5 (4-30)	13 F, 6 M
Doxycycline	18	15 (2-37)	1 F
<b>Serum Sicknesslike Reaction</b>			
Tetracycline	...	11±3 (8-14)	1 F, 1 M
Minocycline	25±3	16.2±2.7 (8-35)	6 F, 5 M
Doxycycline	35.3±12.3	24.5 (21-28)	2 F, 1 M
<b>Drug-Induced Lupus</b>			
Tetracycline	...	...	...
Minocycline	21.9±1.5	632.6±104.8 (3-2190)	28 F, 4 M
Doxycycline	...	...	...
<b>Single Organ Dysfunction</b>			
Tetracycline	41.8±8.0*	5±1.8 (1-90)*	17 F, 18 M
Minocycline	42.9±4.7†	18.3±6.6 (1-720)†	18 F, 9 M
Doxycycline	39.8±10.3‡	13.8±8.5 (1-10)‡	3 F, 3 M

\*Denotes values for tetracycline-induced severe cutaneous adverse reactions.

†Denotes values for minocycline-induced pneumonitis.

‡Denotes values for doxycycline-induced severe cutaneous adverse reactions.

Table 3. Prescribing Data for Tetracycline Antibiotics, 1994\*

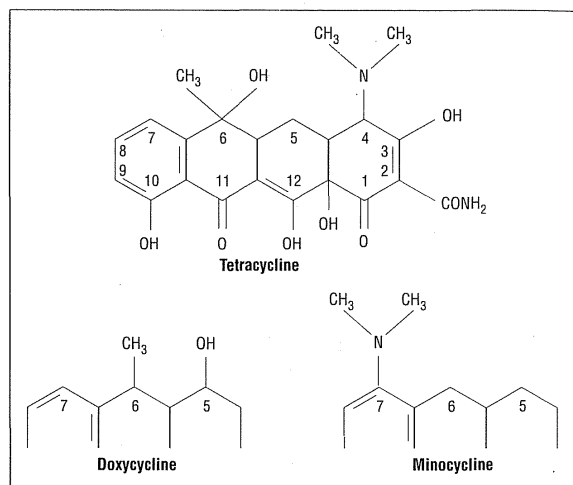
No.	Tetracycline	Minocycline	Doxycycline
Total No. prescriptions (% of total)	855 000 (45.8)	369 000 (19.8)	642 000 (34.4)
New prescriptions, %	68.2	37.2	91.3
Repeated prescriptions, %	31.8	62.8	8.7

\*From the Institute of Medical Statistics, Toronto, Ontario.

Several mechanisms for DIL have been suggested and include the possibility that a reactive metabolite binds to the class II major histocompatibility antigen and induces an autoimmune reaction analogous to a graft vs host reaction.<sup>62</sup> A drug or its potentially reactive metabolites may bind directly to histones and act as haptens, producing an antigenic complex capable of stimulating autoantibody formation.<sup>63</sup> Factors that have been implicated in causing DIL include the use of the drug for long-term therapy, dose dependency, and the presence of a functional group that is easily oxidized to a reactive metabolite such as what we hypothesized occurs with minocycline.

The frequency of these reactions attributable to tetracycline antibiotics remains unknown. The incidence or prevalence cannot be estimated without knowing the denominator, ie, the number of patients receiving each of the tetracycline antibiotics. However, the risk of developing symptomatic hepatotoxic effects from tetracyclines has been estimated to be between 1.6 per million and 2.1 per 100 000 treated patients.<sup>64-66</sup>

In Canada, tetracycline has been licensed since 1959, doxycycline since 1969, and minocycline since 1972. Review of the Institute of Medical Statistics data reveals that although minocycline is the least frequently prescribed



Structure of tetracycline antibiotics.

of the 3 tetracycline congeners, it is the tetracycline antibiotic with the largest fraction of repeated prescriptions. This prescribing pattern likely reflects the fact that minocycline is more commonly used as long-term therapy, particularly in the treatment of acne vulgaris. This may help explain the sole association of minocycline with DIL. Doxycycline and tetracycline are more likely to be prescribed for acute infections in which the duration of treatment is relatively brief. This assumes that prescribing patterns in Canada reflect patterns in other geographic locales. It also assumes that the reason for the long-term use of minocycline is not explained by better tolerance compared with tetracycline and doxycycline.

The diagnosis of these specific reaction patterns rests largely on the presence of a symptom complex. In a recent report of minocycline-induced SSLRs, a migration inhibitory factor assay and mast cell degranulation test were positive in 4 of 5 patients.<sup>4</sup> No skin, patch, or lymphocyte transformation testing was documented in any of the published reports.

To evaluate the safety of high-dose long-term minocycline therapy, researchers in England studied 700 patients with acne vulgaris treated with 100 mg/d or more of minocycline for a mean of 10.5 months.<sup>67</sup> Although no laboratory abnormalities were noted, the study population was too small to detect the severe but rare reactions that can occur. A study sample would need to be 3 to 4 times larger to detect hepatitis and DIL that occur in less than 1 in 10 000 patients.<sup>68</sup>

Blood samples from more than 3000 patients receiving minocycline showed no abnormalities in hepatic transaminase levels.<sup>69</sup> In the United Kingdom, 6.5 million patients have been treated with minocycline on average for 9 months during the last 26 years, and in 1996, 28 million tablets a year of minocycline were taken. The conclusion is that these serious side effects are extremely rare.

Risk management strategies can be applied to various phases of prescribing. These include pretreatment identification of risk factors, risk communication of potential adverse events to patients when the medication is prescribed, monitoring and ascertainment of adverse

**Table 4. Risk Management Strategy for Tetracycline Antibiotics\***

#### Minocycline

Common and dose-dependent side effects: gastrointestinal upset, vestibular dysfunction, headache, localized pigmentary disturbances  
Serious, rare side effects†: HSR; SSLR; isolated SOD, most commonly manifest as pneumonitis; DIL; and hepatitis

Early reaction patterns: HSRs, SSLRs, and SOD occur on average within 2 mo of treatment and are characterized by fever, malaise, arthralgia with or without major organ involvement.

Late reaction pattern: DIL occurs on average after 2 y of therapy but may be delayed up to 6 y. Occurs predominantly in females, presents with a symmetrical polyarthritis or polyarthralgia in the small joints of the hands and wrists. Some of these patients have concomitant liver disease with biopsy specimens disclosing chronic active hepatitis. Phototoxicity is rare. Benign intracranial hypertension is rare.

#### Recommendations

- Minocycline should be avoided in patients with systemic lupus erythematosus (SLE) or in those with a history of SLE in a first-degree relative.
- Relative contraindications to the use of minocycline include underlying hepatic or renal disease.
- Patients receiving chronic minocycline therapy should have antinuclear antibody and hepatic transaminase levels assessed only if symptoms develop during the course of treatment.
- Routine monitoring of patients receiving chronic minocycline therapy is not recommended.
- Any patient with a serious adverse event such as HSR, SSLR, or DIL should be advised to avoid the class of tetracycline antibiotics.
- First-degree relatives of patients with a tetracycline-induced HSR may be at higher risk for similar reaction patterns and should avoid tetracycline antibiotics.
- In patients presenting with an early reaction pattern, the following laboratory values should be assessed: complete blood cell count, hepatic transaminases, urinalysis, urea and creatinine, chest radiograph, thyroid function tests at 3 mo
- There is no standardized treatment for early reaction patterns. Discontinuation of the offending drug is mandatory. Symptomatic treatment with nonsteroidal anti-inflammatory drugs or corticosteroids may be required.
- In patients presenting with a late reaction pattern, the following laboratory values should be assessed: antinuclear antibody, hepatic transaminases
- Treatment of DIL includes discontinuation of the offending drug. Symptomatic treatment with nonsteroidal anti-inflammatory drugs or corticosteroids may be required.
- Severe adverse reactions should be reported to the appropriate agency such as the US Food and Drug Administration or Canadian Health Protection Branch.

events during therapy, and management of adverse events when they occur (**Table 4**).

Before physicians prescribe tetracyclines, identification of patients who are at risk for adverse reactions is required. The recent publications of minocycline-induced lupus have prompted a change in the US product labeling adverse reactions section from "transient lupus-like syndrome" to "lupus-like syndrome."<sup>70</sup> Because minocycline is clearly associated with DIL, prudence would dictate avoidance in patients with underlying SLE or a history of SLE in a first-degree relative. Few data are available to support or negate the use of drugs known to cause DIL in patients with spontaneous lupus.<sup>71</sup> There are no data to support that the natural history of lupus erythematosus is worsened by use of such a drug even if symptoms develop; however, the standard of practice for

**Table 4. Risk Management Strategy for Tetracycline Antibiotics\* (cont)**

#### Tetracycline

Common and dose-dependent side effects: nausea, vomiting, epigastric burning, photosensitivity, vaginal candidiasis  
Serious, rare side effects: HSR, SSLR, benign intracranial hypertension  
Recommendations

- No baseline or periodic investigations are required.
- Investigations should be done if symptoms develop.
- Any patient with a serious adverse event such as HSR or SSLR should be advised to avoid the class of tetracycline antibiotics.

#### Doxycycline

Common and dose-dependent side effects: nausea, vomiting, epigastric burning, photosensitivity, vaginal candidiasis  
Serious, rare side effects: HSR, SSLR, benign intracranial hypertension  
Recommendations

- Warn patients about phototoxic potential.
- No baseline or periodic investigations are required.
- Investigations should be done if symptoms develop.
- Any patient with a serious adverse event such as HSR or SSLR should be advised to avoid the class of tetracycline antibiotics.

\*Appropriate risk communication for each drug requires (1) informing patients about minor side effects if they are relatively common (>2% of exposed patients) or may be dose dependent; and (2) warning patients about rare side effects that are serious, such as hypersensitivity syndrome reaction (HSR), serum sicknesslike reaction (SSLR), single organ dysfunction (SOD), and drug-induced lupus (DIL).

†These reactions can be divided into 2 groups according to the average time to onset after initiation of therapy, early and late.

rheumatologists is avoidance of drugs that can cause a lupuslike reaction in patients with definite SLE.<sup>72</sup>

Appropriate risk communication imparts information to the patient about minor side effects that are common and about rare side effects that are serious. It is clear that the serious reaction patterns to tetracycline antibiotics can be categorized into 2 groups—early and late. Early reactions include HSRs, SSLRs, and isolated SOD that occur on average within 2 months of treatment. They are characterized by fever, malaise, and arthralgia with or without major organ involvement. Late reactions include DIL, which occurs on average 2 years after initiation of therapy but may be delayed even up to 6 years. These patients, predominantly female, present with a symmetrical polyarthritis or polyarthralgia in the small joints of the hands and wrist. It is important to recognize this group as it is believed that there is no sex predilection to DIL when compared with idiopathic SLE. This belief comes from earlier reports of antiarrhythmic-induced lupus erythematosus where the population treated reflects the population afflicted with the disease in question.<sup>63</sup> Minocycline-induced lupus erythematosus afflicts the same population as idiopathic lupus, and there may be a long interval before onset. Some of these patients had concomitant liver disease with biopsy specimens disclosing chronic active hepatitis.<sup>2</sup> In these patients, all symptoms and signs promptly resolved with drug discontinuation. To avoid unnecessary interventions, such as liver biopsy or immunosuppressive therapy, this reaction pattern must be promptly recognized.

Appropriate investigations of an early reaction include complete blood cell count to identify an atypical lymphocytosis or eosinophilia, hepatic transaminase lev-



els, urinalysis, urea and creatinine levels, chest radiograph, and thyroid function test 3 months after the acute event.<sup>59,73</sup> Further evaluation of internal organ involvement will be determined by the patient's history and physical examination findings.

Extrapolating from the literature pertaining to aromatic anticonvulsant HSRs, we suggest that patients with a tetracycline antibiotic-induced HSR and their first-degree relatives avoid the class of tetracycline antibiotics.<sup>59</sup> A medical alert bracelet should document allergy to the tetracycline antibiotics.

For late reactions, tests for antinuclear antibody and hepatic transaminase levels are appropriate. Based on the rarity of DIL and the lack of large prospective trials, it is not justified to routinely monitor patients receiving long-term minocycline therapy. In one prospective study, 11 patients treated with minocycline showed no difference between pretreatment hepatic transaminase levels and those measured 6 months later.<sup>74</sup> A recent literature review did not support the practice of routine laboratory monitoring in healthy young patients with acne treated with oral tetracycline or minocycline.<sup>75</sup> Prospective trials to assess liver function in a large cohort of patients receiving minocycline for acne are under way.<sup>3</sup> Patients receiving long-term minocycline therapy should have an antinuclear antibody test and hepatic transaminase levels assessed only if symptoms develop during their course of treatment.

Treatment for these serious adverse reactions is not standardized. Corticosteroid therapy has been widely used without confirmation of its efficacy by controlled studies. Anecdotal experience suggests that treatment with systemic corticosteroids in doses of 0.5 to 1.0 mg/kg improves symptoms and laboratory measurements.<sup>76</sup> A slow taper over several weeks is suggested as relapses of HSR are common.<sup>76</sup> Severe adverse reactions should be reported to the appropriate agency such as the Canadian Health Protection Branch or the US Food and Drug Administration.

Reports of idiosyncratic adverse events with tetracycline, doxycycline, and minocycline are infrequent. Although there are published reports stating that patients with serious adverse reactions to minocycline can be subsequently treated with tetracycline, there is minimal evidence to support this claim.<sup>77</sup> One patient who developed a minocycline-induced pneumonitis on 2 occasions was able to tolerate doxycycline with no relapse.<sup>6</sup> Another patient who developed minocycline-induced lupus was able to tolerate doxycycline without an adverse event.<sup>31</sup> Because of the severity of these reactions, patients who experience a serious adverse event while receiving 1 of these tetracycline antibiotics should be advised to avoid all tetracyclines until more information regarding potential cross-reactivity is known.

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The interpretation of the results does not reflect the opinions or policies of Health Canada. The reproduced information from the Health Protection Branch is raw information and has not been scientifically verified.

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