The Use of Tetracyclines for the Treatment of Sarcoidosis

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Background: To evaluate the safety and efficacy of minocycline in the treatment of sarcoidosis, a nonrandomized, open study was performed in patients with cutaneous sarcoidosis.

Observations: Twelve patients with cutaneous sarcoidosis were treated with minocycline, 200 mg/d, for a median duration of 12 months. Three patients had extracutaneous lesions at the time of the study. The median follow-up was 26 months. A clinical response was observed in 10 patients, consisting of complete responses in 8 patients and partial responses in 2 patients. A progression of skin lesions was observed in 1 patient, and lesions remained stable in another patient. Adverse effects were minimal, except in 1 patient, who developed hypersensitivity syndrome. A slight hyperpigmentation occurred in 2 patients at the site of previous lesions, which completely disappeared after minocycline use was discontinued. A relapse of skin symptoms occurred after minocycline withdrawal in 3 patients, who further received doxycycline, 200 mg/d, allowing a complete remission of lesions.

Conclusions: These results support that minocycline and doxycycline may be beneficial for the treatment of cutaneous sarcoidosis. Randomized controlled studies are warranted for the evaluation of the true efficacy of tetracyclines in these patients.

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SARCOIDOSIS is a granulomatous, multisystemic disorder of unknown cause that involves predominantly the skin, eye, lungs, and lymph nodes. Therapeutic difficulties originate from the chronic course of the disease and the lack of spontaneous regression of lesions. This chronicity raises the balance between the benefit and the long-term tolerance of therapy. Thus, oral corticosteroids, which have been recognized as the most effective therapy for sarcoidosis, are indicated as the first-line treatment only in cases presenting with severe visceral involvement. Oral steroids are not warranted in cases presenting with less severe involvement, since their long-term use is associated with many adverse effects and because relapses are common during reduction of daily dosage. In view of the toxicity of steroids, much interest has been recently devoted to the efficacy of corticosteroid-sparing agents in sarcoidosis. Indeed, several studies suggested that both chloroquine and hydroxychloroquine sulfate may be beneficial in patients affected with sarcoidosis involving the skin and extracutaneous organs. However, the efficacy of antimalarial agents is not a consistent finding, thus warranting the need for new alternative drugs. In the present work, we report the results of an open, prospective study of the efficacy of minocycline hydrochloride in 12 patients affected with chronic forms of sarcoidosis.

RESULTS

The median follow-up was 26 months (mean, 29 months; range, 12-45 months). A clinical response of sarcoïdal cutaneous lesions was documented in 10 of 12 patients receiving minocycline, with a duration of response ranging from 10 to 41 months (median, 17 months; mean, 21.6 months) (Table 2). A complete clearing of cutaneous lesions was observed in 8 patients (Figure 1 and Figure 2). The mean time to reach maximal response of cutaneous lesions from the date of onset of minocycline treatment was 3.2 months (median, 3 months; range, 1-6 months); clinical improvement was noticed as early as 1 month after the onset of minocycline treatment in 7 patients. No relapse occurred during treatment. The median duration of minocycline treatment was 12
PATIENTS AND METHODS

Between 1996 and 1998, 12 patients (9 women and 3 men) who presented with histologically proven sarcoidosis involving the skin were enrolled in the present study. Patients were eligible if they had 1 or more evaluable skin lesions that showed stability or progression for more than 3 months. Patients had no history of hypersensitivity to tetracyclines and were free of any anti-inflammatory, immunomodulatory, or immunosuppressive therapy for a minimum of 3 months before entering the study. Topical steroid treatment was stopped at least 1 month before the study. The essential clinical and demographic features of the 12 patients are listed in Table 1. The ages of the patients ranged from 16 to 63 years (median, 37.5 years; mean, 36.8 years). All patients had a complete physical examination, a chest x-ray examination, and complete laboratory analysis, including peripheral blood cell counts and serum levels of calcium, phosphate, and angiotensin-converting enzyme. Chest computed tomographic scan was performed in case of abnormal findings on x-ray examination. Eleven patients presented with multiple skin lesions of sarcoidosis at the onset of the study, and only patient 12 presented with a unique subcutaneous nodular lesion involving the frontotemporal area. The cutaneous lesions were typed as papulonodular in 8 cases (cases 1, 3, 5, 6, 7, 8, 10, and 11), as plaques in 2 cases (patients 2 and 9), and as lupus pernio in 1 case (case 4), while a unique hypodermal nodule was present in patient 12. Six patients (cases 1, 2, 8, 10, 11, and 12) had extracutaneous manifestations at the time of diagnosis of sarcoidosis. Three patients who belonged to this latter subgroup presented with evaluable extracutaneous lesions at the time of the study: case 1 presented with parenchymal lung involvement associated with enlarged mediastinal lymph nodes, case 8 was characterized by an involvement of paranasal sinuses and of cervical lymph nodes, and patient 12 presented with enlarged mediastinal lymph nodes (Table 1).

Seven patients (cases 1, 3, 4, 5, 7, 8, and 12) had previously received hydroxychloroquine as first-line therapy for a mean of 4.6 months (range, 3-6 months), without noticeable regression of lesions. Patients 6 and 9 initially received chloroquine for 2 and 3 months, respectively, without efficacy. In patients 2 and 11, first-line therapy consisted of oral prednisone associated with hydroxychloroquine, allowing an initial remission. However, further withdrawal of prednisone was followed by a relapse of skin lesions, without evidence of extracutaneous involvement. In patient 10, minocycline was given as first-line therapy, since the patient was affected with myasthenia gravis and diabetes mellitus, 2 conditions that contraindicated antimalarials and oral corticosteroids, respectively. The median duration of sarcoidal cutaneous lesions at the onset of the study was 15 months (mean, 26.7 months; range, 6-72 months). Patients were given minocycline, 100 mg twice daily. The clinical response to therapy was evaluated by the same physician, according to the size and number of skin lesions. Patients were examined monthly during the initial 6 months of the study, then once every 2 months. The median follow-up was 26 months (mean, 29.1 months; range, 12-45 months). A complete response was considered when all initial lesions completely disappeared, and no occurrence of new lesions was observed. A partial response was defined by a regression of at least 50% of skin lesions. Either progression or stability or regression below 50% of lesions was considered a lack of response. In patients showing a clinical relapse after minocycline withdrawal, doxycycline monohydrate was further given at the daily dosage of 200 mg.

Table 1. Clinical and Demographic Features in 12 Patients With Sarcoidosis

<table>
<thead>
<tr>
<th>Case No./Sex/Age, y</th>
<th>Race</th>
<th>Type of Cutaneous Lesions</th>
<th>Extracutaneous Involvement at the Time of the Study</th>
<th>Duration of Sarcoidosis Before Study, mo</th>
<th>Previous Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/31</td>
<td>White</td>
<td>Papulonodular</td>
<td>Lungs, mediastinal lymph nodes</td>
<td>49</td>
<td>Hydroxychloroquine sulfate</td>
</tr>
<tr>
<td>2/M/23</td>
<td>White</td>
<td>Plaques</td>
<td>None</td>
<td>11</td>
<td>Prednisone and hydroxychloroquine</td>
</tr>
<tr>
<td>3/F/63</td>
<td>White</td>
<td>Papulonodular</td>
<td>None</td>
<td>10</td>
<td>Hydroxychloroquine sulfate</td>
</tr>
<tr>
<td>4/M/39</td>
<td>Black</td>
<td>Lupus pernio</td>
<td>None</td>
<td>54</td>
<td>Hydroxychloroquine sulfate</td>
</tr>
<tr>
<td>5/F/16</td>
<td>White</td>
<td>Papulonodular</td>
<td>None</td>
<td>6</td>
<td>Hydroxychloroquine sulfate</td>
</tr>
<tr>
<td>6/F/24</td>
<td>Black</td>
<td>Papulonodular</td>
<td>None</td>
<td>46</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>7/F/41</td>
<td>White</td>
<td>Papulonodular</td>
<td>None</td>
<td>17</td>
<td>Hydroxychloroquine sulfate</td>
</tr>
<tr>
<td>8/F/43</td>
<td>Black</td>
<td>Papulonodular</td>
<td>Paranasal sinuses, peripheral lymph nodes</td>
<td>72</td>
<td>Hydroxychloroquine sulfate</td>
</tr>
<tr>
<td>9/F/58</td>
<td>White</td>
<td>Plaques</td>
<td>None</td>
<td>26</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>10/F/41</td>
<td>Black</td>
<td>Papulonodular</td>
<td>None</td>
<td>9</td>
<td>None</td>
</tr>
<tr>
<td>11/M/36</td>
<td>White</td>
<td>Papulonodular</td>
<td>None</td>
<td>13</td>
<td>Prednisone and hydroxychloroquine</td>
</tr>
<tr>
<td>12/F/27</td>
<td>White</td>
<td>Subcutaneous nodule</td>
<td>Mediastinal lymph nodes</td>
<td>8</td>
<td>Hydroxychloroquine sulfate</td>
</tr>
</tbody>
</table>
of cutaneous lesions was observed after 1 to 3 months of doxycycline therapy, without occurrence of any adverse effect. Furthermore, a clearing of lung infiltrates was noticed on chest radiography performed in patient 1, who was being treated with doxycycline.

A favorable course of intrathoracic involvement correlated with the one of skin lesions in cases 1 and 12. In case 1, a partial regression of pulmonary infiltrates was noticed after 12 months of minocycline use, and a chest x-ray examination performed 6 months after the onset of second-line treatment with doxycycline showed no abnormal findings. In patient 12, enlarged mediastinal lymph nodes resolved with minocycline therapy (Figure 3). In 3 patients who presented with lymphopenia (white blood cell count <1.0×10^9/L) at the time of inclusion, an increase of blood lymphocyte count was observed with minocycline therapy (Table 3). Furthermore, the angiotensin-converting enzyme serum level was markedly reduced in 4 patients after 3 months of minocycline therapy (Table 3). No evidence of minocycline toxicity was found in 9 patients. Patient 5 complained of mild dizziness, which completely resolved after reduction of the daily dosage of minocycline to 100 mg. Another patient (case 10) who presented with myasthenia gravis and diabetes was considered as a complete responder after 1 month of minocycline use but developed a drug hypersensitivity syndrome 6 weeks after the onset of minocycline treatment. This severe adverse effect was characterized by a general malaise with fever, a generalized itching rash, a superficial lymphadenopathy, and an interstitial pneumopathy. Biological investigations revealed eosinophilia and elevated serum levels of transaminases. All these abnormalities resolved following treatment with prednisone, 1 mg/kg daily. A slight grayish hyperpigmentation involving the sites of previous sarcoid lesions was observed in another patient and completely resolved 2 months after minocycline withdrawal (Figure 2B).

Chronic forms of sarcoidosis raise the issue of the long-term tolerance of the treatment, since individual patients may require lifetime maintenance therapy to avoid relapses of skin lesions. Although it is widely admitted that severe forms of the disease, ie, neurosarcoidosis, severe uveitis, and forms with cardiac involvement, require high-dose corticosteroids, the optimal therapeu-
tomic regimen for cases without severe visceral involvement has not been clearly delineated. Indeed, the balance between benefit and toxicity is of primary importance in cases that may be associated with a severe functional and/or esthetic prejudice. Although corticosteroids used at intermediate dosage, ie, 0.5 mg/kg daily, may bring a short-term benefit in these patients, their prolonged use is associated with significant toxic effects. Consequently, several agents that show potential corticosteroid-sparing properties have been recently investigated in patients affected with sarcoidosis. Among these drugs, both chloroquine and hydroxychloroquine have also been beneficial in patients affected with cutaneous or extracutaneous sarcoidosis. However, responses to antimalarial therapy may be incomplete, and resistance is not a rare finding, thus warranting the need for alternative non-steroidal therapies. More recently, the efficacy of methotrexate has been reported in disseminated forms of the disease. However, taking into account the risk-benefit ratio of this drug, its use in cutaneous forms of the disease has to be questioned.

In recent years, interest has been focused on some classes of antibiotics, such as tetracyclines, that, beside their anti-infectious effects, exhibit potent immunomodulating properties. Thus, minocycline has been shown to inhibit T-cell proliferation in vitro. Furthermore, both minocycline and doxycycline have been shown to inhibit granuloma formation in vitro. These results obtained in vitro have been the rationale basis for the successful use of minocycline and doxycycline in granulomatous dermatoses, such as silicone-induced subcutaneous granulomas and granulomatous cheilitis. The results of the present study support the efficacy of both minocycline and doxycycline in patients affected with cutaneous sarcoidosis following a long-term course. Furthermore, since lesions involving the lung parenchyma and mediastinal lymph nodes remitted in 2 patients, it is likely that minocycline and doxycycline are also efficient in treating extracutaneous lesions. In patients affected with sarcoidosis, it remains to be determined whether therapeutic efficacy of minocycline and doxycycline result either from an anti-infectious mechanism acting on a putative microbial agent or from anti-inflammatory or immunomodulatory properties. The changes of angiotensin-converting enzyme serum level and peripheral blood lymphocyte counts observed with minocycline therapy support the latter hypothesis. Interestingly, immunomodulatory effects and/or anti-infectious effects of minocycline have been advocated to explain the therapeutic efficacy of this drug in inflammatory disorders other than sarcoidosis, mostly rheumatoid arthritis. However, supporting the hypothesis that anti-infectious effects of tetracyclines might be involved in their efficacy on cutaneous lesions of sarcoidosis, recent publications reported the presence in sarcoidal lymph nodes of DNA products specific for

Table 3. Follow-up of Biological Variables in 4 Patients With Complete Remission of Sarcoidosis With Minocycline Treatment

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Angiotensin-Converting Enzyme Serum Level, U/L *</th>
<th>Blood Lymphocyte Absolute Count, ×10⁹/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At Onset of Minocycline</td>
<td>After 3 mo of Minocycline</td>
</tr>
<tr>
<td>2</td>
<td>89</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>110</td>
<td>44</td>
</tr>
<tr>
<td>7</td>
<td>106</td>
<td>62</td>
</tr>
<tr>
<td>11</td>
<td>120</td>
<td>72</td>
</tr>
</tbody>
</table>

*Normal values are 0 to 52 U/L.
mycobacterial and propionibacterial acnes, this latter bacterial species being known for its sensitivity to tetracyclines. On the other hand, we have recently reported striking remissions of noninfectious granulomatous disorders with minocycline therapy, such as silicone-induced cutaneous granulomas, showing that the anti-inflammatory properties of tetracyclines documented in vitro may be relevant in vivo.

Minocycline toxicity was minimal in the present study, except in 1 black patient with myasthenia gravis and insulin-requiring diabetes mellitus, who developed a drug hypersensitivity syndrome. Since the incidence of minocycline-related hypersensitivity has been claimed to be higher in patients with autoimmune disorders than in control patients and in black patients than in white patients, it would be warranted to exclude these conditions from future trials using minocycline.23,24 Indeed, the incidence of the main adverse effects related to minocycline therapy, such as drug hypersensitivity syndrome, hyperpigmentation, and dizziness, appears to be much lower in patients who receive doxycycline.23,24 Thus, in future trials, it will be of great interest to evaluate more extensively the therapeutic efficacy of doxycycline in patients who present with granulomatous cutaneous disorders.

It is noteworthy that among 9 patients who received single-agent therapy with chloroquine or hydroxychloroquine for sarcoidosis before entering into the minocycline study, 7 did not show any response, suggesting that tetracyclines should be considered an alternative therapy in cases that show a resistance of sarcoidal lesions to antimalarial drugs. However, because sarcoidosis lesions may be self-resolving, and the results of the present study were obtained in a limited, open trial, caution should be used when making conclusions concerning the true efficacy of tetracyclines in sarcoidosis. Indeed, prospective placebo-controlled studies are warranted to comparatively evaluate the efficacy and toxicity of minocycline and doxycycline in patients affected with chronic forms of sarcoidosis.

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REFERENCES