Minocycline-Induced Hyperpigmentation in Patients With Pemphigus and Pemphigoid

David M. Ozog; Darin S. Gogstetter, MD; Glynis Scott, MD; Anthony A. Gaspari, MD

Background: Immunosuppressive medications typically used to treat the immunobullous disorders pemphigus vulgaris, pemphigus foliaceus, and bullous pemphigoid can have serious adverse effects. The tetracycline family of antibiotic drugs has been shown to be effective in the treatment of these conditions with a more favorable side effect profile. Minocycline hydrochloride use has been associated with various forms of hyperpigmentation, and its incidence is well reported in acne vulgaris and rheumatoid arthritis. We examined a series of 9 patients treated with minocycline for pemphigus or pemphigoid, most of whom have developed cutaneous hyperpigmentation.

Observations: Seven of 9 patients treated with minocycline, 50 mg daily (1 patient) or 100 mg twice daily (8 patients), for pemphigus vulgaris, pemphigus foliaceus, or bullous pemphigoid developed hyperpigmentation, which necessitated discontinuing therapy. Five of these patients had experienced notable clinical improvement of their immunobullous disease with minocycline therapy. The average duration of treatment was 8.2 months (range, 1-25 months). The second most common adverse effect in our group was oral candidiasis, which occurred in 2 patients.

Conclusions: We found a favorable response to minocycline therapy in 5 of 9 patients. However, 7 patients developed localized hyperpigmentation as early as 1 month after starting medication use. This incidence of minocycline-induced hyperpigmentation is significantly higher in immunobullous disease than in acne vulgaris or rheumatoid arthritis. This increased incidence may be related to an increase in pigment deposition complexed with collagen during the remodeling process, subclinical inflammation, or glucocorticosteroid-induced skin fragility. The hyperpigmentation process was reversible, as most of our patients had fading of their pigmentation after minocycline cessation.

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USE OF minocycline, a semi-synthetic derivative of tetracycline,1 can induce tissue pigmentation in a variety of organs, including skin,2,4 teeth,3,6 bone,7,8 thyroid,9,10 and sclera.11 In patients with acne treated with minocycline, the incidence of cutaneous hyperpigmentation is uncommon, ranging from 2.4% to 14.8%.4,12 The incidence of alveolar oral pigmentation has been reported8 to be as high as 20% after 4 years of minocycline therapy. Hyperpigmentation after treatment of rheumatoid arthritis occurred in 2.75% of patients in one series.13 There is limited information regarding the incidence of hyperpigmentation in patients with immunobullous disorders treated with minocycline (Table 1). We report a series of 9 consecutive patients with pemphigus or pemphigoid treated with minocycline, 7 of whom developed minocycline-induced hyperpigmentation.

RESULTS

Nine patients, 5 women and 4 men, with PV, PF, or BP had been or were currently being treated with minocycline for their immunobullous disease. Their ages ranged from 19 to 79 years, with a mean age of 53 years. Six patients had PV, 2 had BP, and 1 had PF. Six patients had a favorable response to minocycline treatment, with 3 having a marked response (Table 2). Seven patients developed localized minocycline-induced hyperpigmentation (Table 3). One patient developed subungual pigmentation (Figure 1, C) and another (patient 3) developed pigmentation on the dorsum of his hands and forearms. One patient with early pigmentation on the legs had a prominent perifollicular pigment distribution (not shown).

Hematoxylin-eosin–stained sections (patient 2) showed numerous pig-
PATIENTS AND METHODS

PATIENTS

Analysis of all patients with immunobullous disorders treated with minocycline in our office between January 1, 1997, and December 31, 1999, was conducted. The diagnosis of pemphigus vulgaris (PV), pemphigus foliaceous (PF), or bullous pemphigoid (BP) was made on the basis of clinical findings, diagnostic histopathologic analysis, and direct immunofluorescence testing.11 Response to treatment was based on clinical improvement and/or a reduction in immunosuppressive drug use (Table 2). The diagnosis of minocycline-induced hyperpigmentation was made on clinical grounds.

HISTOLOGICAL ANALYSIS OF CUTANEOUS PIGMENTATION

Skin biopsy specimens were taken from the lower anterior leg of patient 2 (a site of minocycline-induced hyperpigmentation), fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin-eosin. In addition, staining for iron (Perls Prussian blue stain) and melanin (Masson-Fontana amniocal silver stain) with and without bleach was performed.

STATISTICAL ANALYSIS

Using spreadsheet software (Excel; Microsoft, Redmond, Wash), a single-sample binomial analysis was conducted on our patient population using the highest previously reported8 incidence of minocycline-induced hyperpigmentation of 20%.

Minocycline is most commonly used to treat refractory acne vulgaris. In addition to their antimicrobial properties, tetracyclines have been found to have antichemotactic18,19 and collagenase inhibitory20 activities. After treatment with minocycline, keratinocytes demonstrate a clear increase in interleukin 1α activity and a decrease in tumor necrosis factor α production at protein and messenger RNA levels.21 This might decrease the extent and duration of the inflammatory stage in damaged follicular epithelium and inhibit granuloma formation. It has been postulated22 that the ability of minocycline to inhibit neutrophil and eosinophil chemotaxis could downgrade the afferent and efferent limbs of humoral immune response.

Because of these anti-inflammatory properties, long-term use of tetracyclines, as a corticosteroid-sparing agent, often combined with niacinamide, has expanded to include rheumatoid arthritis13 and immunobullous diseases.18,19,23-26 In PV and BP, most authors16,18,19,23-26 report efficacy at least equal to that of previous immunosuppressive therapies, and some suggest use of tetracyclines as a first-line agent in light of their favorable side effect profile. Although most studies focus on the efficacy and adverse effects of tetracycline therapy, minocycline has been used often as an initial agent or as an alternative if tetracycline adverse effects develop.14,15

Observations that our patients with immunobullous disease had a significantly higher incidence of minocycline-induced hyperpigmentation suggests that this phenomenon in PV and BP is more common than in acne vulgaris or rheumatoid arthritis. There have been several long-term studies14,18,12 regarding hyperpigmentation in patients with acne vulgaris treated with minocycline. Therefore, it seems unlikely that the incidence in this population is underestimated because of underreporting.

In immunobullous diseases, autoantibody deposition in the epidermis or the basement membrane zone results in complement activation, which in turn results in chemotactic factors, leukocyte migration into the skin, and production of other mediators of inflammation.17,27 However, the immunobullous disorders, which include PV, FF, and BP, are systemic autoimmune diseases, which are frequently accompanied by circulating autoantibodies. It is possible that subclinical areas of skin or mucous membrane damage secondary to immunoglobulin and complement activity would facilitate an increased deposition of minocycline in immunobullous disorders.

Cutaneous minocycline hyperpigmentation has been observed to have 3 distinct morphologic characteriza-

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tions: a diffuse blue-gray pigmentation involving normal skin, a localized blue-gray or black pigmentation at sites of previous inflammation or trauma,2-4,28 and a diffuse muddy brown hyperpigmentation involving the entire body.2-4 Our patients developed 2 types of minocycline-induced hyperpigmentation: the postinflammatory type at sites of previous lesions and the diffuse blue-gray pigmentation in other skin areas (Table 3).

With the exception of the series presented by Gaspar et al,16 results of other studies of minocycline-induced hyperpigmentation are rare. From the limited number of studies that have been published, it is evident that minocycline can cause hyperpigmentation in patients with a variety of immunobullous diseases. The presence of hyperpigmentation may be related to the dose of minocycline or the duration of therapy and the type of immunobullous disease. The severity of the hyperpigmentation may be modest or severe. The skin areas most commonly involved include the face, upper eyelids, and chest, with a variable involvement of the trunk, extremities, and oral mucosa.

Table 1. Studies of Minocycline-Induced Hyperpigmentation in Immunobullous Disorders

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, %</th>
<th>Diagnosis</th>
<th>Age, y/Sex</th>
<th>Dose, −g</th>
<th>Color and Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altman et al14</td>
<td>100 (2/2)</td>
<td>BP</td>
<td>90/F</td>
<td>16</td>
<td>Gray-black pigmented coalescent macules on the anterior surfaces of lower legs in areas of previous bullae</td>
</tr>
<tr>
<td>Reiche et al15</td>
<td>50 (4/8)†</td>
<td>CP</td>
<td>71/F</td>
<td>NR</td>
<td>Lower legs</td>
</tr>
<tr>
<td>Gaspar et al16</td>
<td>10 (1/10)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Slate gray pigmentation of lower legs</td>
</tr>
</tbody>
</table>

*BP indicates bullous pemphigoid; CP, cicatricial pemphigoid; and NR, not reported.
†The fourth patient was described separately but was included in the original study.27

Table 2. Patients Treated With Minocycline for Pemphigus or Pemphigoid

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y/Sex</th>
<th>Diagnosis</th>
<th>Date of Diagnosis, mo/y</th>
<th>Laboratory Study Results</th>
<th>Previous or Current Immunosuppressive Drug Therapy</th>
<th>Treatment Period (Minocycline, 100 mg BID)</th>
<th>Response to Minocycline Therapy†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48/M</td>
<td>PV</td>
<td>3/98</td>
<td>Bx+, DIF+</td>
<td>Prednisone, chlorambucil (for CLL)</td>
<td>11/2/98-8/99</td>
<td>Partial</td>
</tr>
<tr>
<td>2</td>
<td>65/F</td>
<td>BP</td>
<td>8/98</td>
<td>Bx+, DIF+</td>
<td>Niacin, 0.05% chlorobetasol cream</td>
<td>8/98-2/5/99</td>
<td>Partial</td>
</tr>
<tr>
<td>3</td>
<td>79/M</td>
<td>BP</td>
<td>1984</td>
<td>Bx+, DIF+</td>
<td>Prednisone, erythromycin, methotrexate, dapsone, niacinamide, azathioprine</td>
<td>8/16/99-9/20/99</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>67/F</td>
<td>PV</td>
<td>7/92</td>
<td>Bx+, DIF+, IIF+</td>
<td>Prednisone, cyclophosphamide, intraleSIONAL triamcinolone, erythromycin</td>
<td>2/99-3/15/99</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>65/F</td>
<td>PV</td>
<td>3/64</td>
<td>Bx+, DIF+, IIF+</td>
<td>Prednisone, azathioprine, oral gold, cyclophosphamide, intraleSIONAL triamcinolone acetonide (3 mg/mL)</td>
<td>2/1/99-present</td>
<td>Marked</td>
</tr>
<tr>
<td>6</td>
<td>48/F</td>
<td>PV</td>
<td>1993</td>
<td>Bx+, DIF+, IIF+</td>
<td>Prednisone, azathioprine, tetracycline, clobetasol propionate, intraleSIONAL triamcinolone acetonide (3 mg/mL)</td>
<td>7/98-7/26/99</td>
<td>Marked</td>
</tr>
<tr>
<td>7</td>
<td>19/F</td>
<td>PV</td>
<td>6/98</td>
<td>Bx+, DIF+</td>
<td>Prednisone</td>
<td>8/20-10/98, 10/14-11/98</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>33/M</td>
<td>PV</td>
<td>3/95</td>
<td>Bx+, DIF+, IIF+</td>
<td>Prednisone, azathioprine, tetracycline, clobetasol propionate</td>
<td>7/97-8/97‡; 8/97-8/99</td>
<td>Marked</td>
</tr>
<tr>
<td>9</td>
<td>49/M</td>
<td>PF</td>
<td>Unknown</td>
<td>Bx+, DIF+</td>
<td>Prednisone, dapsone, clobetasol, propionate</td>
<td>3/99-present</td>
<td>Partial</td>
</tr>
</tbody>
</table>

*BID indicates twice daily; PV, pemphigus vulgaris; BP, bullous pemphigoid; PF, pemphigus foliaceous; formalin-fixed, paraffin-embedded, hematoxylin-eosin–stained skin biopsy specimens (Bx); DIF, direct immunofluoresence; IIF, indirect immunofluorescence; plus sign, positive; and CLL, chronic lymphocytic leukemia.
†Marked response indicates a decreased requirement for immunosuppressive medications and/or diminution of clinical symptoms; partial response, some decreased requirement for immunosuppressive agents and/or minimal decrease in clinical symptoms.
‡Fifty milligrams twice daily.

Table 3. Patients Who Developed Minocycline-Induced Hyperpigmentation

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Duration of Therapy, mo</th>
<th>Cumulative Dose, −g</th>
<th>Inflammatory Areas During Disease Course</th>
<th>Sites of Pigmentation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>54</td>
<td>Dorsum of tongue/buccal mucosa</td>
<td>++ – – ++ –</td>
</tr>
<tr>
<td>2‡</td>
<td>6</td>
<td>30</td>
<td>Face, lower legs, arms</td>
<td>+++ ++ – – –</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>6</td>
<td>Face, back, arms, inguinal</td>
<td>– + – + –</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>8</td>
<td>Erosions of gingiva, nasal mucosa, buccal mucosa, esophagus, lip</td>
<td>– – ++ – –</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>72</td>
<td>Erosions of tongue, buccal mucosa, gums, posterior palate, nares</td>
<td>– + – + –</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>12</td>
<td>Erosions of oral mucosa, forehead, cheeks, chin, back, chest, abdomen</td>
<td>– – + – +</td>
</tr>
<tr>
<td>8</td>
<td>25</td>
<td>147</td>
<td>Buccal mucosa gums at base of teeth, scalp</td>
<td>++ + – – –</td>
</tr>
</tbody>
</table>

*Investigators' subjective assessment of severity of pigmentation: – indicates no pigmentation; +, mild hyperpigmentation (pale gray); ++, moderate hyperpigmentation (slate gray); and ++++, severe hyperpigmentation (black).
†Other sites of pigmentation were the dorsum of the hands and forearms (patient 3) and the back (patient 7).
‡Patient also taking imipramine, which has been reported to cause hyperpigmentation; however, her lesions were clinically and histologically consistent with minocycline-induced hyperpigmentation.
induced pigmentation in immunobullous disease are consistent with our findings (Table 1). Patients in the series by Gaspar et al16 and Reiche et al15 were receiving 100 mg of minocycline daily, and our patients and those in the series by Altman et al14 were receiving 100 mg twice daily. Reports of pigmentation location in these series were confined to the pretibial areas. We found that other areas of pigmentation, including the oral cavity, arms, and subungual area, are less likely to be appreciated unless specifically examined for this phenomenon.

Minocycline is a yellow crystalline material that turns black on oxidation.3 Pigment formation probably occurs through polymerization in a process analogous to melanogenesis from dopa.10 Ultraviolet light has the ability to convert minocycline to a dark pigment in vitro; however, none of our patients developed pigmentation...
in sun-exposed skin. Most authors believe that the pigment complex is unique in each subtype. Electron paramagnetic resonance spectroscopy on thyroid pigment revealed it to be a unique melanin-like compound bound tightly to iron.\textsuperscript{10} This finding is supported by previous x-ray energy spectroscopic findings\textsuperscript{28} in a patient with localized blue-gray pigmentation of the forearms. Minocycline, in contrast to the other tetracyclines, chelates less with calcium but forms insoluble complexes with iron. Diverse light microscopic findings might be explained by the chelation of the unique melanin-like pigment to iron, hemosiderin, or ferritin and complexed with various proteins.\textsuperscript{3,10,29}

Minocycline is lipid soluble, thus facilitating intestinal absorption, resulting in a lower incidence of gastrointestinal tract adverse effects than tetracycline, and increased penetration into body tissues, including skin.\textsuperscript{1,30,31} In vitro protein binding studies have shown minocycline to bind collagen. Collagen-rich areas such as scars, bone, and dental pulp may act as reservoirs for minocycline before its transformation into a pigment.\textsuperscript{5,32} This collagen-minocycline binding may help explain the distribution of pigment in vivo. Pigment location varies by subtype but has been found in cells of the epidermis, upper dermis, subcutis, and macrophages and in association with collagen bundles.\textsuperscript{23,33}

In patient 2, histological analysis revealed diffuse pigment distributed in the macrophages as well as extracellularly. The pigment consisted of iron and melanin and thus resembled the staining pattern described in diffuse (“muddy”) brown minocycline-induced pigmentation. Many of our patients with anterior shin pigmentation recalled a previous trauma to their leg. Nearly all of our patients had previously taken systemic corticosteroids for their immunobullous disorder, predisposing them to easy bruising. Eccymotic areas consist of iron-containing hemosiderin and melanin. The source for iron and melanin in minocycline pigmentation may be via tissue injury, with inflammation-induced melanin incontinence and extravasated red blood cells from capillary fragility.

Minocycline has been shown to inhibit thyroidal peroxidase, allowing a local buildup of hydrogen peroxide\textsuperscript{10} and presumably an accelerated oxidation of minocycline. Whether a similar reaction occurs in the skin has yet to be shown. This effect was inhibited by vitamin C in vivo, possibly through its antioxidant qualities.\textsuperscript{3} Similarly, receiving high doses of ascorbic acid (75 mg/kg per day) prevented development of thyroidal pigmentation in rats.\textsuperscript{22} We found no correlation in our patients between use of ascorbic acid (60-100 mg/d) and development of pigmentation. However, this dose is 1% to 2% of the protective dose used in rats.\textsuperscript{32}

In conclusion, we found a favorable response to minocycline therapy in patients with immunobullous disorders. However, 7 of 9 patients developed localized hyperpigmentation as early as 1 month after starting medication use. The incidence of this adverse effect was significantly higher than has been reported in patients with acne vulgaris or rheumatoid arthritis. The higher incidence in immunobullous disease may be related to a variety of factors, including increased pigment deposition complexed with collagen and other proteins during the remodeling response of pemphigus and pemphigoid, subclinical inflammation, or increased skin fragility due to concurrent systemic corticosteroid use. After discontinuing minocycline therapy, our patients experienced gradual fading of their skin discoloration. Patients with pemphigus or pemphigoid should be advised that hyperpigmentation can be a common adverse effect of minocycline therapy, regardless of treatment duration. However, they can be reassured that this drug-induced hyperpigmentation is reversible, in most cases, and is less troublesome than many of the adverse effects of long-term corticosteroid therapy.

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