Drug-Induced Lupus Associated With COL-3

Report of 3 Cases

Jayashri V. Ghate, MD; Maria L. Turner, MD; Michelle A. Rudek, BS; William D. Figg, PharmD; William Dahut, MD; Valerie Dyer, RN; James M. Pluda, MD; Eddie Reed, MD

**Background:** Anti-angiogenesis is an exciting new approach to anticancer therapy. COL-3, a tetracycline derivative, is a novel anti-angiogenesis agent with potent preclinical anticancer activity. During the conduct of a phase 1 clinical trial for refractory metastatic cancer at the National Institutes of Health, we observed 3 individuals who developed phototoxicity followed by clinical and laboratory features of drug-induced lupus.

**Observations:** Three of 35 patients treated with COL-3 developed sunburnlike eruptions accompanied by fever and a positive antinuclear antibody titer within 8 to 29 days of starting treatment. Two of 3 had positive anti-histone antibody levels and arthralgia. One patient had marked systemic manifestations including pulmonary infiltrates and elevated erythrocyte sedimentation rate remittent for more than 1 year after discontinuing COL-3 treatment. The other 2 patients’ symptoms and rash abated within 2 weeks of discontinuing therapy although the serologic markers remained abnormal for the duration of follow-up.

**Conclusions:** COL-3 is the second tetracycline derivative to be implicated in the development of drug-induced lupus. A sunburnlike eruption immediately preceded or accompanied the systemic and serologic changes in these 3 patients. The rapid onset and the phototoxic appearance of the accompanying eruptions might suggest that damage to the keratinocytes caused the formation of neoantigens to which autoantibodies formed.

*Arch Dermatol.* 2001;137:471-474

---

**T**he inhibition of angiogenesis, invasion, and metastasis is an important area for the development of new anticancer agents. COL-3 (6-demethyl-6-deoxy-4-dedimethylaminotetracycline) is a nonantimicrobial derivative of tetracycline that has been shown to inhibit matrix metalloproteinases (MMPs). The MMPs are involved in angiogenesis, invasion, and metastasis. We conducted an approved experimental phase 1 study at the National Institutes of Health for patients with refractory metastatic cancer, using COL-3, an orally administered medication. Patients received a test dose followed by 7 days of pharmacokinetic testing followed by daily dosing. Herein, we describe 3 patients who developed drug-induced lupus while receiving COL-3. Patients with drug-induced lupus develop clinical manifestations and serologic markers similar to those for systemic lupus erythematosus (SLE), albeit milder, in association with particular drugs. Several agents have been reported to cause this, including procainamide, hydralazine, antithyroid drugs, and minocycline, a tetracycline derivative.

**REPORT OF CASES**

**CASE 1**

A 63-year-old man with metastatic prostate cancer had failed combined androgen blockade and chemotherapy. He was enrolled in this phase 1 trial using COL-3 in March 1998. He presented to the clinic 29 days after beginning therapy and was hospitalized with complaints of fever, chills, joint swelling around the ankles and wrists, and photosensitivity. Table 1 presents dosing schedules and relation of cumulative dose to onset of each symptom. A chest x-ray film showed bilateral infiltrates.

Pertinent skin findings included periungual telangiectasias as well as erythematous and purpuric papules and plaques on the dorsal aspect of the hands, especially on the interphalangeal regions (Figure 1). The initial skin biopsy from the dorsum of the left hand revealed a superficial perivascular lymphocytic infiltr-
mained positive at 1:640. However, his antinuclear antibody (ANA) titer has re-

tation of COL-3. Each episode responded to short courses of prednisone (5 mg/d) and clobetasol propionate cream. 

The patient has had 2 milder recurrences of rash, fever, and joint pains 6 and 12 months after discontinu-

colchicine and amlodipine besylate. A skin biopsy of this area revealed necrotic keratinocytes, basal vacuolar degeneration, and a superficial perivascular lymphocytic infiltrate with eosinophils consistent with a drug eruption. The patient continued taking COL-3 while a lupus panel was drawn. After 2 weeks of COL-3 treatment, the patient had mild arthralgia but denied fevers. The patient continued taking COL-3 while a lupus panel was drawn. After 2 weeks of COL-3 treatment, the patient had mild arthralgia but denied fevers. 

Table 1. Dose of Drug at Onset of Symptoms

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Dose, mg/d</th>
<th>Dose at Onset of Phototoxicity, mg</th>
<th>Dose at Onset of Fever, mg</th>
<th>Dose at Onset of Arthralgia, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>850</td>
<td>1150</td>
<td>1150</td>
</tr>
<tr>
<td>2</td>
<td>110</td>
<td>990</td>
<td>330</td>
<td>. . .</td>
</tr>
<tr>
<td>3</td>
<td>130</td>
<td>1690</td>
<td>1950</td>
<td>650</td>
</tr>
</tbody>
</table>

*Patient denied arthralgia.

Table 2. Clinical and Serologic Data*

<table>
<thead>
<tr>
<th>Case No./Sex/Age, y</th>
<th>ESR, mm/h</th>
<th>Antihistone Antibodies</th>
<th>Antinuclear Antibody Titer</th>
<th>Follow-up (Duration)</th>
<th>ANCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/63</td>
<td>143</td>
<td>Negative</td>
<td>1:1280, speckled</td>
<td>1:640, speckled (1.5 y)</td>
<td>Negative</td>
</tr>
<tr>
<td>2/F/46</td>
<td>133</td>
<td>3.5</td>
<td>1:160, homogeneous</td>
<td>1:80, homogeneous (2 wk)</td>
<td>Not done</td>
</tr>
<tr>
<td>3/M/73</td>
<td>Not done</td>
<td>2.2</td>
<td>1:320, speckled</td>
<td>1:640, speckled (2 mo)</td>
<td>Not done</td>
</tr>
</tbody>
</table>

*Reference values are as follows: erythrocyte sedimentation rate (ESR), 0–25 mm/h; antihistone antibodies <1 unit; and antinuclear antibody titer, 1:80.

ANCA indicates antineutrophil cytoplasmic antibody.

†Done at onset of phototoxicity.

Figure 1. Grayish-purple papules with some scale crust coalescing into plaques on the dorsal surface of the hand of patient 1. Histologic examination revealed necrotic keratinocytes, basal vacuolar degeneration, and a superficial perivascular lymphocytic infiltrate with eosinophils consistent with a drug eruption.

Figure 2

Figure 3

CASE 2

A 46-year-old woman with colon cancer metastatic to the liver and lungs was enrolled in the phase 1 trial using COL-3 in June 1999 after failing multiple chemotherapy regimens. COL-3 dosing is shown in Table 1. After 15 doses of COL-3, the patient presented with a sunburn that started after her ninth dose. This occurred while driving short distances, despite using a titanium dioxide–containing sunblock. She had no personal or family history of connective tissue diseases including lupus erythematosus and she was taking no other medications. There were erythematous plaques on the anterior neck,ears, V area of the chest, cheeks, brachio-radial areas, and the dorsa of the hands. She denied arthralgia. She had fevers after the third dose. A skin biopsy from the right forearm revealed focal vacuolar degeneration of the basal layer, necrotic keratinocytes within the epidermis, and a mild superficial and deep perivascular lymphocytic infiltrate consistent with lupus erythematosus (Figure 3). Serologic studies are summarized in Table 2. Her liver function tests, routine chemistry panel, urinalysis, and complete blood cell count were all within normal limits except for mild anemia. Another skin biopsy from a plaque on the left thumb 1 month later revealed vacuolar degeneration of the basal layer with necrotic keratinocytes, a superficial perivascular lymphocytic infiltrate, and papillary dermal edema consistent with lupus erythematosus. Drug-induced lupus was diagnosed, and COL-3 was discontinued. Treatment consisted of prednisone, clobetasol propionate cream, sun avoidance, and a micronized titanium dioxide–containing sunblock.

A 73-year-old man with androgen-independent metastatic prostate carcinoma began the COL-3 protocol in July 1999. COL-3 dosing is shown in Table 2. After 5 doses, the patient had mild arthralgia but denied fevers. The patient continued taking COL-3 while a lupus panel was drawn. After 2 weeks of COL-3 treatment, the patient presented with erythematous patches and plaques involving the left side of the face and the dorsa of the hands, a flaccid bulla on the dorsum of the left thumb, and erosions and crusting of the lower lip despite using a titanium dioxide–containing sunscreen. He reported increased arthralgia in his hands and low-grade fevers. He had no personal or family history of connective tissue diseases and his only medications were benazepril hydrochloride and amiodipine besylate. A skin biopsy of his left hand revealed basilar vacuolar degeneration with a superficial perivascular lymphocytic infiltrate consis-
tent with lupus erythematosus. Serologic tests are summarized in Table 2. Serum chemistry panel, urinalysis, and complete blood cell counts were normal except for mild anemia. COL-3 was discontinued. He was treated with clobetasol propionate cream and a milder corticosteroid for his face, resulting in marked improvement within 2 weeks. Two months after discontinuing COL-3, the patient was asymptomatic despite an antihistone antibody level of 3.0 and ANA titer of 1:640.

**COMMENT**

COL-3 is an oral MMP inhibitor. The MMPs are a class of membrane-bound enzymes that are involved in the degradation of the extracellular matrix and have been associated with progression of tumors. It is hypothesized that tumor angiogenesis and metastasis may be inhibited through MMP inhibitors such as COL-3. COL-3 is a nonantimicrobial derivative of tetracycline (Figure 4A) with spectrophotometric absorption at wavelengths of 264 nm, which falls within the UV-C range, and 350 nm, which falls within the UV-A range. Tetracycline derivatives such as doxycycline and demeclocycline are well-known causes of phototoxicity. However, these drugs have not been implicated in drug-induced-lupus. In a retrospective review of drug safety databases, Shapiro and colleagues found that minocycline is the only tetracycline derivative that has been recognized to cause drug-induced lupus despite the fact that it is not a known photosensitizer. They propose that this propensity to cause drug-induced lupus may be due to the presence of a functional group in the structure of minocycline that is easily oxidized to a reactive metabolite. COL-3 lacks these functional groups (Figure 4B).

In a recent review of relevant American and European literature, 4 minocycline-induced autoimmune syndromes were described in 82 patients, all occurring in young patients treated for acne. Except for serum sickness, which occurred on average within 16 days of starting treatment, drug-induced lupus, hepatitis, and vasculitis occurred after protracted use (mean, 23.3 months). Hepatitis and drug-induced lupus occurred in 66 of the 82 cases. Arthralgia, arthritis, fever, and rash occurred in 73, 45, 38, and 28 patients, respectively. Presence of ANA was found in 63 of the 68 patients who were tested and peripheral antineutrophil cytoplasmic antibody was positive in 20 of the 24 who were assayed. Antihistone antibodies were infrequently seen (4 of 31 tested).
Although there are no specific diagnostic criteria for drug-induced lupus, patients generally present with clinical symptoms and laboratory results consistent with a mild form of SLE while taking the drug. The most common symptoms are fever, arthritis, and serositis. Abnormal hematologic findings and central nervous system and renal involvement are rare in drug-induced lupus. About 25% of patients present with a skin rash, which is histologically nondiagnostic, although consistent with cutaneous lupus erythematosus. In general, most patients have a positive ANA titer and meet at least 1 of the criteria for SLE. A positive antihistone antibody level is thought to be very suggestive though not specific, as it is also seen in 20% of patients with SLE. Discontinuing the drug usually leads to rapid improvement of the clinical symptoms, whereas clearing of the serologic abnormalities occurs more gradually.

The prevalence of skin manifestations in drug-induced lupus varies according to the offending agent. Approximately 25% of patients with hydralazine-induced lupus develop skin manifestations. Patients with drug-induced lupus related to thiazide diuretics and calcium channel blockers often present with photosensitivity and subacute cutaneous lupus erythematosus-like skin lesions. However, in procainamide-induced lupus, skin manifestations are said to be absent.

Our patients developed several features of drug-induced lupus while taking COL-3. All had phototoxic skin eruptions despite sun avoidance and the use of a titanium dioxide–based sunblock. The histologic features of the skin rash were consistent with cutaneous lupus erythematosus. All had positive ANA titers and 2 of 3 had elevated antihistone antibody levels. All had fever at some time during the course of their disease and 2 of 3 had arthralgia, one of whom had joint swelling. Within a few weeks of discontinuing COL-3, the symptoms and skin eruptions cleared in 2 patients and have been recurrent in 1. As in other reported cases of drug-induced lupus, the serologic markers decreased but had not completely cleared at last follow-up.

The pathogenesis of this syndrome remains unknown although it is proposed to be multifactorial, involving genetic predisposition, drug or metabolite interaction with nuclear antigens, and immunologic alterations. The rapidity of onset and the phototoxic appearance of the accompanying eruption suggest the possibility that ultraviolet damage to the keratinocytes generated neoantigens to which autoantibodies formed.

A total of 35 patients were enrolled in the COL-3 protocol at the time of this report. Approximately 8% of the COL-3 patients in this National Institutes of Health protocol have developed drug-induced lupus. At present, no new patients have been enrolled. COL-3 is the second tetracycline derivative implicated in the development of drug-induced lupus.

Accepted for publication November 9, 2000.

Corresponding author: Maria L. Turner, MD, Dermatology Branch, National Institutes of Health, Bldg 10, Room 12N238, Bethesda, MD 20892-1908 (e-mail: mlturner@box-m.nih.gov).

Reprints: William D. Figg, PharmD, Clinical Pharmacokinetics Section, Medicine Branch, National Cancer Institute, Bldg 10, Room 5A-01, Bethesda, MD 20892.

REFERENCES