Alopecia and Nail Changes Associated With Voriconazole Therapy

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Background. Voriconazole was 1 of 2 antifungal agents recommended for treatment of fungal infections associated with injection of contaminated methylprednisolone. Alopecia and nail changes are not commonly reported side effects of voriconazole. Having noted increasing hair loss among our patients treated with voriconazole, we sought to determine the prevalence and characteristics of alopecia associated with this agent.

Methods. Patients who received voriconazole for at least 1 month for probable or confirmed fungal infection were eligible to complete a survey regarding alopecia and nail changes. For those patients who reported alopecia, additional questions about reversal of hair loss were asked after voriconazole had been stopped for at least 3 months.

Results. A total of 152 of 175 eligible patients (87%) completed the survey. One hundred twenty-five (82%) reported alopecia. Hair loss on the scalp was noted in 120 (96%), arms and legs in 52 (42%), and eyebrows and eyelashes in 47 each (38%). Nineteen patients (15%) reported wearing a wig or hat because of extensive hair loss. Alopecia developed a mean (standard deviation) of 75 (54) days after initiation of voriconazole. Of 114 patients who were off voriconazole for at least 3 months, hair loss had stopped in 94 (82%) and regrowth had begun in 79 (69%), including those who were changed to either itraconazole or posaconazole. Nail changes or loss occurred in 106 (70%) patients.

Conclusions. Alopecia and nail changes were common adverse effects associated with voriconazole therapy during the multistate fungal outbreak.

Keywords. voriconazole; alopecia; nail changes; multistate meningitis outbreak; fungal infections.

In September 2012, a multistate outbreak of fungal infections, mostly meningitis and spinal/paraspinal infection, was linked to injection of contaminated methylprednisolone that had been manufactured by the New England Compounding Center [1–8]. By October 2013, 751 cases had been identified, making this the largest healthcare-associated outbreak in US history [9].

The predominant pathogen identified was the brown–black mold, Exserohilum rostratum, an environmental mold that rarely causes human infection [10, 11]. Voriconazole was 1 of 2 first-line antifungal agents recommended by the Centers for Disease Control and Prevention (CDC) to treat the E. rostratum infections [12]. The dosage recommended (6 mg/kg every 12 hours) was higher than normal because of concern about achieving adequate concentrations in the cerebrospinal fluid and tissues of the nervous system. Combination therapy with liposomal amphotericin B was recommended for those patients with severe or refractory disease.

Several months into therapy, many patients commented that their hair was thinning, some noticed large amounts of hair on their hairbrushes, and others noticed changes in their nails. Alopecia has been described with fluconazole in 2 small retrospective series [13, 14], but voriconazole has been reported to cause alopecia in only 1 child [15]. The US Food and Drug Administration (FDA) prescribing information for
voriconazole mentions alopecia among a list of all side effects occurring in <2% of patients [16]. Nail changes have not been described with voriconazole. We sought to determine the prevalence and characteristics of alopecia and changes in nails in patients who were treated with voriconazole during this outbreak of healthcare-associated fungal infections.

METHODS

Patients and Setting
This is a cross-sectional survey of patients who received voriconazole for at least 1 month for probable or confirmed fungal infection associated with contaminated steroid injection. Patients were excluded if they did not receive voriconazole for at least 1 month or if they had died. All patients were cared for at St. Joseph Mercy Hospital (SJMH), Ann Arbor, MI, a 537-bed, nonuniversity-affiliated, community teaching hospital. The institutional review board at SJMH reviewed and approved the study protocol and informed consent.

Survey Protocol
A questionnaire was developed by study personnel and piloted for clarity by 5 patients who were different genders and ages. Their comments and suggestions were incorporated into the final questionnaire. Prior to administration of the questionnaire, all eligible patients were sent a letter outlining the study. The questionnaire was administered between July 2013 and October 2013 by the fungal outbreak clinic pharmacist either face-to-face for patients who had a clinic visit or by phone for those who did not have an appointment in that time frame. Questions included whether hair loss had occurred; if so, in what body area; the time they first noticed hair loss; whether they shaved less; and whether the loss was severe enough that they wore a wig or hat. Additional questions in regard to regrowth of hair were asked of patients who reported alopecia and who had been off voriconazole for at least 3 months. Patients were also asked questions about changes and appearance of fingernails and toenails, but the time this occurred was not queried.

Definitions
Using the CDC case definitions, probable fungal meningitis was defined as signs or symptoms of meningitis (with cerebrospinal fluid white blood cells ≥5/µL, accounting for presence of red blood cells) of unknown etiology or posterior circulation stroke without a cardioembolic source following epidural or paraspinal injection with contaminated methylprednisolone [17]. Probable spinal or paraspinal infection was defined as magnetic resonance imaging evidence of osteomyelitis, abscess, or other infection (eg, soft tissue infection) of unknown etiology in the spinal or paraspinal structures or at or near the site of epidural or paraspinal injection with contaminated methylprednisolone. Probable peripheral joint infection was defined as osteomyelitis or worsening inflammatory arthritis of unknown etiology following joint injection. Confirmed cases were defined as patients who had the above findings plus microbiological, molecular, or histopathological evidence of a fungal pathogen [17].

Data Analysis
SAS 9.3 (SAS Institute Inc., Cary, NC, USA) was used for data analysis. We performed double data entry and a comparison procedure to ensure accurate transcription from the data collection forms to the spreadsheet. Demographic information, other clinical information, and survey results were summarized using means or percentages, as appropriate. In a post hoc analysis, a 2-sample t test was used to determine whether the average daily dose of voriconazole (assessed for the first 3 months of voriconazole therapy) was different in patients with alopecia and those without hair loss.

RESULTS

Patients
Of the 195 patients who met the CDC case definition for probable or confirmed fungal meningitis, spinal or paraspinal infection, or peripheral joint infection and who were cared for at SJMH, 175 were eligible for the study. 8 had been treated with voriconazole for <1 month, and 12 had died. Of the 175 eligible patients, 152 (87%) completed the questionnaire and 23 (13%) refused to participate. Of the 152 patients who completed the survey, there were 39 cases of fungal meningitis, 31 of whom subsequently developed concomitant spinal or paraspinal infections; 102 spinal/paraspinal infections; and 11 peripheral joint infections. The mean (standard deviation [SD]) age of the patients was 64.7 (12.3) years, and 96 (63%) were women. Hypertension, hyperlipidemia, and diabetes were common; few patients had immunosuppressive conditions, and none were taking chemotherapeutic agents (Table 1).

Survey Results
Of the 152 patients who completed the questionnaire, 125 (82%) reported alopecia. Hair loss on the scalp was noted in 120 (96%), the arms and legs in 52 (42%), the eyebrows in 47 (38%), and the eyelashes in 47 (38%; Table 2; Figure 1). Of the 120 patients who lost scalp hair, 114 noted thinning, 89 reported finding hair in the sink, and 86 noted that their hair came out in clumps. Nineteen patients (15%) reported wearing a wig or hat because of extensive hair loss. Fifty-nine patients (50 women, 9 men) reported shaving less due to alopecia. The mean (SD) time to onset of alopecia in the 114 patients for whom these data were available was 75 (54) days after...
initiation of voriconazole therapy. Nine patients reported development of alopecia within 14 days of initiation of voriconazole.

Of the 125 patients with alopecia, 114 (91%) had been off voriconazole for at least 3 months when they answered the follow-up questionnaire. Among these patients, hair loss had stopped in 4 (82%) and regrowth of hair had begun in 3 months in 79 (69%). There was no difference in the number of patients who experienced regrowth of hair in the subgroup of 32 whose therapy had been changed to either itraconazole or posaconazole. In this group, hair loss had stopped in 27 (84%) and regrowth of hair had started in 22 (69%), which was similar to the 82 patients whose antifungal therapy was completely stopped (hair loss stopped in 67 [82%] and regrowth occurred in 57 [70%]).

To evaluate whether there was an association between alopecia and the daily dose of voriconazole, we calculated the average daily dose of voriconazole for the first 3 months of voriconazole therapy. For the 125 patients with alopecia, the mean (SD) daily dose of voriconazole was 733 (192) mg compared with 681 (201) mg for the 27 patients without hair loss \((P = .21)\). The development of alopecia also did not correlate with serum voriconazole concentrations that are generally considered in the toxic range (>5.5 µg/mL). After steady state was reached within the first week, 53 (42%) of the 125 patients who manifested alopecia had 1 or more voriconazole serum levels >5.5 µg/mL compared with 19 (70%) of the 27 patients who did not develop alopecia. Of 24 patients who had 3 or more levels >5.5 µg/mL, 14 developed alopecia and 10 had no hair loss.

Nail changes were reported in 106 (70%) patients, including loss of nails in 15 (10%). Of the 89 patients who described nail changes, the most common findings were development of brittle nails in 21 patients, split nails in 20, and thinning nails in 16. Of the 125 patients with alopecia, 98 (78%) also reported changes in their nails. Eight patients had nail changes without hair loss.

**DISCUSSION**

Alopecia associated with voriconazole therapy has been previously described in only 1 patient, a child with cystic fibrosis, but few details were given in that case \[15\]. Alopecia is listed as an infrequent event without proof of causation in the FDA prescribing information for voriconazole and has not been reported in postmarketing surveillance data for voriconazole \[16\].

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**Table 1. Demographic and Clinical Characteristics of Survey Participants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
<th>(n = 152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>64.7 (29–90)</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>96 (63)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>150 (99)</td>
<td></td>
</tr>
<tr>
<td>Body mass index ≥ 35</td>
<td>38 (25)</td>
<td></td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>7 (5)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>21 (14)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>28 (18)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>64 (42)</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>52 (34)</td>
<td></td>
</tr>
<tr>
<td>Immunosuppression(^a)</td>
<td>12 (8)</td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>22 (15)</td>
<td></td>
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</tbody>
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\(^a\) Immunosuppression defined as human immunodeficiency virus/AIDS, chronic immunosuppressive drug therapy, connective tissue disorder, malignancy (solid or hematopoietic), or transplant.

**Table 2. Alopecia and Nail Findings Associated With Voriconazole Therapy**

<table>
<thead>
<tr>
<th>Finding</th>
<th>Number (%)</th>
<th>(n = 152)</th>
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</thead>
<tbody>
<tr>
<td>Presence of alopecia</td>
<td>125 (82)</td>
<td></td>
</tr>
<tr>
<td>Scalp</td>
<td>120 (96)</td>
<td></td>
</tr>
<tr>
<td>Extremities</td>
<td>52 (42)</td>
<td></td>
</tr>
<tr>
<td>Eyebrows</td>
<td>47 (38)</td>
<td></td>
</tr>
<tr>
<td>Eyelashes</td>
<td>47 (38)</td>
<td></td>
</tr>
<tr>
<td>Underarms</td>
<td>42 (34)</td>
<td></td>
</tr>
<tr>
<td>Pubic region</td>
<td>36 (29)</td>
<td></td>
</tr>
<tr>
<td>Face</td>
<td>23 (18)</td>
<td></td>
</tr>
<tr>
<td>Chest(^b)</td>
<td>15 (27)</td>
<td></td>
</tr>
<tr>
<td>Shaved less while taking voriconazole</td>
<td>59 (47)</td>
<td></td>
</tr>
<tr>
<td>Required wig/hat</td>
<td>19 (15)</td>
<td></td>
</tr>
<tr>
<td>Changes in nails</td>
<td>106 (70)</td>
<td></td>
</tr>
<tr>
<td>Loss of nails</td>
<td>15 (10)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Most patients had more than 1 site involved.

\(^b\) Only men were asked about loss of chest hair (n = 56).
We were surprised to see the large number of patients who came to the clinic commenting on hair loss. Our survey found that 125 of 152 (82%) patients who had taken voriconazole for at least 1 month experienced alopecia; in some, it was severe enough that they wore a wig or hat.

Our survey also found that 106 of 152 (70%) patients who had taken voriconazole for at least 1 month experienced changes in their nails. Ninety-eight (78%) patients with alopecia experienced nail changes. Nail changes have not been previously described with voriconazole or other azoles. Unfortunately, we did not specifically define further the effect on nails, and additional study is needed to elucidate the relationship between voriconazole and nail changes.

The only other antifungal agent reported to cause alopecia in more than an occasional patient is fluconazole, which is similar in structure to voriconazole [13,14]. Many similarities are noted between the results of a retrospective survey by investigators caring for patients enrolled in several early Mycoses Study Group trials with fluconazole and the data presented here [13]. In that report of 33 patients, alopecia began as early as 14 days after starting therapy in a few patients, and the mean time until hair loss was first noted was 3 months, similar to our patients. Three patients (9%) required a wig or hat compared with 15% of our patients. Hair loss reversed when fluconazole was stopped or the dose decreased, and the time to complete resolution of alopecia was usually within 6 months, again similar to what our patients reported. It would appear that alopecia is not a class effect of azoles, as most of our patients whose therapy was changed to itraconazole or posaconazole had reversal of alopecia.

It is perplexing that alopecia and nail changes have not been described before. This may be related to the higher dosages that were used for a longer period of time to treat our patients, almost all of whom had meningitis or spinal/paraspinal infections. However, our post hoc analysis did not show significant differences between average daily dose of voriconazole and high serum voriconazole concentrations for patients who did or did not experience alopecia. One could postulate that alopecia has not been described before because the stress of having a fungal infection following contaminated methylprednisolone injection or the illness itself was the cause. However, at the time alopecia was prominent, most patients were feeling better, and the hair loss did not improve until after voriconazole was stopped. It is also possible that the patients for whom voriconazole has been most commonly prescribed have hematological malignancies and/or have received a hematopoietic cell transplant and frequently have alopecia from prior chemotherapy. The patients or their physicians may not notice additional hair loss due to voriconazole.

The mechanism of development of alopecia and nail changes is not known. Voriconazole has been associated with many different effects on skin, including photosensitivity that can be severe and development of skin cancers [18, 19]. Further study should explore whether some common pathogenetic mechanism underlies these disparate skin and skin structure manifestations.

The strengths of this study include the high response rate and the fact that the same person administered all questionnaires. However, there are several limitations to our study. This is a single-center experience, and we did not administer the questionnaire prospectively or to a group of control patients. Thus, results may be subject to survey bias. We did not have patients keep a log recording exact dates when they developed hair loss, but instead relied on patients recollecting dates in order to answer the survey questions.

Based on our findings, we feel that it is important for clinicians to recognize that voriconazole therapy can be associated with alopecia and changes in nails and to counsel their patients that these side effects may occur.

Notes

Financial support. There was no financial support given for this study.

Potential conflicts of interest. A. M. serves on the speaker’s bureau for Cubist Pharmaceuticals and is a shareholder of Pfizer. L. K. is a shareholder of Merck and Johnson & Johnson. C. K. is on the New England Research Institute Data Adjudication Panel for National Heart, Lung, and Blood Institute Transfusion Medicine/Hemostasis Clinical Trials Network. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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