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REVIEW ARTICLE

# Adverse Effects Associated with Long-Term Administration of Azole Antifungal Agents

**Lydia L. Benitez**[1] · **Peggy L. Carver**[2]

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## Abstract

Azole antifungals are first-line options in the prophylaxis and treatment of invasive fungal infections. They are often used for prolonged (weeks to months) periods of time, particularly in patients with hematologic malignancies, or in those who have received a solid organ or hematopoietic stem cell transplant. Long-term use of azoles is associated with hepatotoxicity and hormone-related effects, including gynecomastia, alopecia, decreased libido, oligospermia, azoospermia, impotence, hypokalemia, hyponatremia, and (rarely) adrenal insufficiency. Voriconazole and posaconazole have been associated with peripheral neuropathies, and itraconazole and voriconazole with pancreatitis. In addition, voriconazole has been associated with periostitis, phototoxic reactions, and squamous cell carcinoma. Since many at-risk patients are commonly receiving multiple medications, it can be difficult for care providers to identify antifungal agent causality or contribution to patient symptoms. Knowledge and recognition of adverse events caused by azoles, leading to dose reduction or discontinuation, can generally reverse these adverse events.

**Key Points**

Liver toxicity, generally reversible, is common with all azoles.

Hormone-related adverse effects are observed with select azoles; these include hair loss, breast enlargement, decreased libido, impotence, and (rarely) adrenal insufficiency.

Patients on voriconazole should use liberal amounts of broad spectrum UV protectants and wear sun protective clothing, avoid excess sunlight, and undergo frequent monitoring of skin as phototoxic reactions progressing to development of skin cancer has been associated with long-term use.

Therapeutic drug monitoring may be utilized to prevent neuropathies in specific patient populations on voriconazole; its role in preventing other long-term toxicities is less clear.

✉ Peggy L. Carver
peg@umich.edu

[1] Michigan Medicine, 1540 East Medical Center Dr. CW7-521B, Ann Arbor, MI 48109, USA

[2] University of Michigan College of Pharmacy, 428 Church St., Ann Arbor, MI 48109-1065, USA

## 1 Introduction

Azoles are commonly used as first-line agents in the prophylaxis and therapy of invasive fungal infections in patients with hematologic malignancies, autoimmune diseases, and in those undergoing solid organ or stem cell transplantation [1]. Often, azoles must be administered for long periods of time (weeks to months), followed by long-term suppressive therapy [2–4]. The oral availability of these agents as well as their good tolerability profile as compared with alternative agents makes this drug class preferred in many clinical scenarios where long-term treatment is necessary. The adverse effects associated with short-term use of azoles are well described, and have been summarized in several recent reviews [5–7]. However, the long-term use (defined throughout this review as > 4 weeks) of antifungal agents has raised concerns regarding cost, the development of resistance, and the risk of treatment-related toxicities. In order to identify and manage adverse effects, clinicians must be cognizant of adverse effects associated with prolonged courses of azole antifungals. This review summarizes currently available information describing adverse effects associated with long-term azole use, and provides recommendations for management, when available. Experience with long-term exposure to isavuconazole (approved in 2015) is limited at this time. As such, there are limited data to allow assessment of potential chronic toxicities.

## 2 Methods

A literature search was conducted via the PubMed search engine. Search terms and keywords included the generic and brand name of each individual azole evaluated, any adverse events reported in clinical trials and/or package inserts for the agents, and combinations of terms (e.g., 'voriconazole periostitis', 'azole alopecia', etc.). Additional articles were identified by reviewing the references of the articles obtained via PubMed.

## 3 Results

### 3.1 Fluoride Excess and Periostitis

The development of periostitis and exostoses in patients receiving voriconazole has been reported in a number of case reports [8–20] and small case series [21–27], and were recently summarized [28, 29]. Characteristic signs and symptoms of periostitis generally include initial complaints of myalgias or diffuse pain in one or more skeletal sites, most often including the ribs, forearm, leg, shoulder, wrist, hip, or arm, associated with elevations of serum alkaline phosphatase (but not of alanine aminotransferase or total bilirubin), and nodular growths (exostoses) on radiographs or radionuclide bone imaging scans [23]. Multiple areas of periosteal ossification generally occur; the most commonly affected sites include the ulna and thoracic ribs, followed by the arms and forearms, clavicle, including phalanges of the hands, consistent with typical findings observed in periostitis deformans of subacute fluoride poisoning [21, 23]. Less commonly, the hips or lower extremities are affected [23]. In a large case series of 195 patients, of whom 28 underwent bone scans, periostitis was located in the ulna or rib; 48% of patients had disease involving both sites [23]. On bone scans, bilateral and diffuse bony changes with dense undulating or feathery periosteal reaction may be observed, with a presentation similar to that of hypertrophic osteoarthropathy (HOA); however, patients with HOA usually demonstrate symmetric polyarthralgia, periostitis of the long tubular bones, and digital clubbing, while bone scans demonstrate diffuse features [21, 25].

The onset of symptoms varies widely, from 100 days to 4/2 years after the start of voriconazole therapy [21, 22, 24–26]. Reversal of symptoms, including radiological findings, generally occurs upon discontinuation of therapy. Bone pain and elevated plasma fluoride and alkaline phosphate levels generally resolve within 2–5 months upon discontinuation of voriconazole [22, 23, 27]. No studies have assessed whether patients who experienced voriconazole-associated periostitis experience the same symptoms upon rechallenge with voriconazole or a different fluorinated azole. Of note, itraconazole does not contain a fluorine atom, and patients in whom voriconazole was changed to itraconazole following the development of periostitis have experienced rapid resolution of bone pain [11, 12, 22, 27]. The rapid resolution of pain upon discontinuation of voriconazole has led several investigators to speculate a dominant inflammatory rather than a mechanical nociceptive pathogenesis for this adverse effect [8, 21, 27].

The clinical findings of voriconazole-associated periostitis appear similar to those of skeletal fluorosis, a condition resulting from excess fluoride intake; thus, several investigators have postulated that periostitis results from increased circulating levels of fluoride following metabolism of voriconazole, or from direct effects of the fluoride component of voriconazole [12, 21–23, 27]. Fluconazole, posaconazole, and the recently approved isavuconazole all contain two fluoride atoms; as yet, no case reports have described periostitis with these agents [30]. Whether the lack of reports reflects a difference in the metabolism of fluoride in voriconazole, differences in cumulative fluoride 'dosages', or other mechanisms, is unknown. Voriconazole contains three fluorine atoms, and a 400-mg dose contains 65 mg of fluoride; however, its metabolism results in minimal release of free fluoride ion (approximately 5% of the dose) [13, 15, 31]. Posaconazole contains two fluorine atoms, and a 400-mg dose contains 21.7 mg of fluoride [15]. To put this quantity in perspective, the typical daily exposure of fluoride in municipal tap water is 2–4 mg, since the concentration of fluoride is ~1 mg/L. In a cohort of patients undergoing long-term (defined by the authors as > 6 months) therapy with antifungal agents, patients treated with posaconazole, fluconazole, or itraconazole had plasma fluoride levels of 4.06, 2.98, and 1.74 μmol/L, respectively, as compared with levels of 9.17 μmol/L in patients receiving voriconazole [26].

Fluoride, when ingested, is distributed to a number of body sites, including a small amount (< 1%) to soft tissues, where an equilibrium between intra-and extracellular fluids is maintained. However, > 99% becomes associated with mineralized tissues, including bone, enamel, and dentin. Bone concentrations of fluoride tend to increase with age, and to concentrate in the periosteal and endosteal region of long bones, and in cancellous versus compact bone. The binding of fluoride to bone is reversible; when plasma fluoride levels decline, primarily via excretion in the urine, fluoride is released back into plasma. Plasma fluoride levels are not homeostatically regulated; levels vary based upon fluoride intake, deposition and removal into soft and hard tissues, and urinary excretion [32]. Ionic fluoride is not bound to plasma proteins, and its concentration in glomerular filtrate is the same as in plasma. However, 10–90% of the ionic fluoride is reabsorbed into the systemic circulation, and not excreted in urine, resulting in a net renal clearance of

fluoride of ~ 35 mL/minute in healthy adults, depending on the glomerular filtrate rate, urinary pH (with alkaline urine promoting urinary excretion), and flow rate. Since fluoride is eliminated renally, patients with renal failure are expected to have higher plasma fluoride levels. Gerber et al. [22] noted that in 20 patients receiving voriconazole, plasma fluoride levels were inversely correlated to the glomerular filtration rate, and all patients with proven voriconazole-induced skeletal disease had moderate to severe chronic renal failure. However, not all patients with renal failure showed evidence of fluoride toxicity. Conversely, in a multivariate analysis, Wermers et al. [27] failed to identify impaired renal function as a predictor of serum fluoride levels despite inclusion of a control group of patients with serum creatinine levels ≥ 1.4 mg/dL.

In a prospective evaluation of fluoride levels in solid organ transplant patients, of ten patients who had received voriconazole for ≥ 6 months (mean 21.0 ± 13.3 months), five (50%) developed periostitis, and two (20%) developed exostoses. Patients treated with voriconazole demonstrated significantly higher plasma fluoride levels than did the ten post-transplant patients who did not receive voriconazole (14.32 ± 6.41 vs 2.54 ± 0.67 μmol/L, respectively) [27].

Several comparative studies have assessed the incidence of elevated fluoride levels and bone pain with voriconazole versus other azoles [22, 23, 26]. Gerber et al. [22] compared 32 patients with hematologic malignancies who were receiving voriconazole, posaconazole, or itraconazole, versus control patients who had not received an azole. Clinically significant skeletal disease was observed in 3/20 patients receiving voriconazole, but in none of the 12 patients receiving other azoles, or in the control group. Serum fluoride levels were significantly higher in patients receiving voriconazole, compared with levels in patients receiving posaconazole ($n = 8$), and itraconazole ($n = 4$), or the control group ($n = 11$). Similarly, in a prospective cohort study, Thompson et al. [26] compared 29 patients with coccidioidomycosis receiving long-term (> 6 months) treatment with a fluorinated azole (fluconazole, posaconazole, or voriconazole; $n = 9$, 5, and 9, respectively) with a control group of patients ($n = 6$) receiving a non-fluorinated azole, itraconazole. Patients treated with voriconazole had significantly higher fluoride levels (mean 9.17 μmol/L) than those treated with either itraconazole or fluconazole ($p = 0.002$) but not versus patients receiving posaconazole ($p = 0.24$). No relationship was found between serum fluoride levels and the dosing, duration of therapy, or serum drug levels of azoles. Intriguingly, no patients had clinically or radiographically apparent periostitis or exostoses (although imaging was performed in only 5/9 voriconazole patients and 7/20 patients receiving other azoles), despite having a voriconazole sample size similar to that of Wermers et al. [27]. In a large study [23] of 195 patients who received long-term, high-dose voriconazole therapy as treatment for fungal infections acquired as a result of contaminated methylprednisolone injections, the correlation between plasma fluoride and bone scan results was evaluated in 28 patients in whom fluoride levels and whole-body bone scans were obtained to assess skeletal pain. Patients with periostitis demonstrated higher plasma fluoride levels (12.78 ± 0.96 vs 3.61 ± 1.29 μmol/L; $p < 0.001$), alkaline phosphatase (273 ± 35.6 vs 117 ± 15.7, respectively; $p = 0.020$), and had received higher daily and cumulative doses of voriconazole than those who did not experience periostitis. The daily, but not the cumulative, voriconazole dose was positively correlated with plasma fluoride levels: patients with periostitis had received higher daily (780 ± 43 mg vs 450 ± 82 mg; $p < 0.001$) and cumulative (130.5 ± 7.3 g vs 94.7 ± 9.5 g; $p = 0.024$) doses of voriconazole than those who did not experience periostitis. A voriconazole dosage reduction was successful in reducing symptoms in two out of six (33%) patients in whom it was attempted, consistent with previous literature reports of the reversibility of periostitis in patients with excessive fluoride intake [23].

In children, the higher metabolic activity, rich vascularity, and comparatively large surface area of bone crystallites of younger bones results in more rapid accumulation of fluoride than in adults. Thus, caution is warranted in the long-term use of voriconazole in children. A recent report described elevated serum fluoride levels in five pediatric hematopoietic stem cell transplant (HSCT) recipients who had received voriconazole for ≥ 3 months, one of whom was symptomatic and had confirmed skeletal fluorosis [24].

Fluoride-independent mechanisms may also play a role in the development of voriconazole-induced periostitis. The development of new bone extracellular matrix results from the differentiation and maturation of osteoblasts into mature osteocytes [33]. In mouse osteoblasts, exposure to very high concentrations of voriconazole (up to 20,000 μg/mL) results in reversible cytotoxicity to osteoblasts and fibroblasts [34]. In a recent study evaluating the in vitro effects of sodium fluoride, voriconazole, and fluconazole on the proliferation and differentiation of human osteoblasts, only voriconazole exposure resulted in increased osteogenic activity. Exposure to voriconazole and sodium fluoride, but not fluconazole, resulted in significant increases in the expression of the soluble cytokines, vascular endothelial growth factor and platelet-derived growth factor, by human osteoblasts; however, neither voriconazole- nor fluconazole-exposed osteoblasts displayed significant elevations of fluoride ion in the culture supernatants [33]. Thus, while free fluoride may contribute to the stimulatory effects of voriconazole on osteoblast activity, the lack of a similar response with fluconazole suggests that this effect is specific to voriconazole [33].

#### 3.1.1 Summary

Periostitis should be considered in patients undergoing long-term therapy with voriconazole who present with diffuse myalgias or bone pain and an elevated alkaline phosphatase, without clubbing. The reported frequency of this adverse effect is 5–10% (Table 1). Elevated serum levels of fluoride or voriconazole-induced direct stimulation of osteoblasts may lead to periostitis and exostoses. Given these potential mechanisms of toxicity, the daily and cumulative dosage of voriconazole (and thus, indirectly, the duration of therapy with voriconazole), may provide the best predictor of the development of this adverse effect, rather than voriconazole serum levels. Although serum fluoride levels are significantly elevated with voriconazole therapy, including those patients with periostitis, since elevated fluoride levels may also be observed in patients without periostitis, and are not consistently predictive of the development of skeletal disease, they are unlikely to be a useful routine monitoring parameter in patients receiving voriconazole [23]. In patients who complain of bone pain while receiving voriconazole, a serum fluoride level provides an inexpensive, non-invasive assessment tool; in patients with elevated fluoride levels, a bone scan can be utilized to confirm the diagnosis of periostitis. Fortunately, discontinuation of voriconazole generally results in a rapid reduction of pain symptoms; however, dosage reduction is a reasonable alternative in patients unable to discontinue the drug. Larger observational studies will likely further elucidate additional risk factors for skeletal disease with voriconazole treatment. In particular, further studies in children are warranted, given the likelihood of higher bone retention of fluoride in young children.

### 3.2 Neuromuscular Effects

A variety of neuromuscular symptoms have been reported in patients taking azole antifungals, leading to the inclusion of these in product labeling [35–38]. In many cases, these adverse effects may have a multifactorial etiology involving concomitant medications and pharmacokinetic drug interactions, while in other reported cases no other explanatory causes for these adverse events were found.

#### 3.2.1 Myositis and Rhabdomyolysis

The 3-hydroxy-3methylglutaryl coenzyme A (HMG-C0A) reductase inhibitor drug class has been widely implicated in development of myositis with progression to rhabdomyolysis. While not completely understood, the mechanism of toxicity is thought to be related to the decreased production of coenzyme Q10, which is important in muscle synthesis [39]. Several reports of myositis and myalgias with progression to rhabdomyolysis have been reported in patients receiving azole antifungals in combination with statins [40–42]. The increased risk of these toxicities with use of azole agents in patients taking statins is related to the cytochrome P450 (CYP) mediated metabolism and P-glycoprotein efflux of the statins and the inhibition of these enzymes and efflux pumps by azole antifungals. The extent of the metabolism by CYP3A4 and efflux through P-glycoprotein pumps of the statin in combination with the extent of inhibition by the different azole antifungals dictates the risk incurred in using the combination of agents [43]. Nonetheless, there are case reports of myositis and rhabdomyolysis occurring after exposure to ketoconazole, itraconazole, and voriconazole without concomitant statins [44–46]. The onset of symptoms reported was variable—1 week with ketoconazole, 2 weeks

**Table 1** Summary of long-term adverse effects

| Azole | Fluoride excess and periostitis | Myositis and peripheral neuropathies | Alopecia | Xerosis | Hormone-related: gynecomastia, breast tenderness, adrenal insufficiency, hyponatremia, hypokalemia | Phototoxicity | Irreversible hepatotoxicity | Pancreatitis |
|---|---|---|---|---|---|---|---|---|
| Ketoconazole | NR | NR | ++(5–10%) | NR | ++(5–10%) | NR | +(<5%) | NR |
| Fluconazole | +(<5%) | +(<5%) | ++(5–10%) | ++ | +(<5%) | NR | +(<5%) | NR |
| Itraconazole | NR | +++ | NR | NR | +(<5%) | NR | +(<5%) | +(<5%) |
| Voriconazole | ++(5–10%) | ++(5–10%) | ++(5–10%) | NR | +(<5%) | ++(5–10%) SOT/aHSCT (>10%) | +(<5%) | +(<5%) |
| Posaconazole | +(<5%) | +(<5%) | +(<5%) | NR | +(<5%) | NR | +(<5%) | NR |
| Isavuconazole | NR | NR | NR | NR | NR | NR | NR | NR |

*aHSCT* allogeneic hematopoietic cell transplant population, *NR* not reported, *SOT* solid organ transplant population

with itraconazole, and 2 months with voriconazole. In all cases, the patients developed weakness and diffuse myalgia with concomitant elevations in creatine phosphokinase ranging from mild to severe (379–5200 IU/L). The patient receiving voriconazole was also receiving tacrolimus after renal transplant, and this drug has been reported to cause myositis, but this is a dose-dependent adverse event and the tacrolimus plasma levels were not elevated at symptom onset [44]. The most severe form of this adverse effect reported was in the patient taking itraconazole [45]. In this case, the symptoms progressed to rhabdomyolysis over a period of 4 weeks, culminating in an inability to walk, heme positive brown urine, and renal failure. In all cases reviewed, symptoms and lab abnormalities improved with discontinuation of azole antifungals.

#### 3.2.2 Peripheral Neuropathy

In patients with hematologic malignancies, exposure to the vinca alkaloids is the most common risk factor for the development of peripheral neuropathies. Due to the dose-dependent nature of vinca toxicity, concomitant use of vinca alkaloids and azole antifungals increases a patient's risk of developing peripheral neuropathies. This interaction with the triazoles voriconazole, itraconazole, and posaconazole is well documented, and is generally ascribed to strong inhibition of CYP3A4-mediated metabolism of the chemotherapeutic agents by azoles, and by inhibition of P-glycoprotein-mediated efflux of the vinca alkaloids vincristine and vinblastine by itraconazole or posaconazole [47–50]. Given the long terminal half-life of vincristine (median 85 hours), the risk of neuropathies is high even without concurrent administration with CYP3A4 inhibitors [51]. Similarly, in patients undergoing transplantation, calcineurin inhibitors (CNIs) used as immunosuppressants (including tacrolimus and cyclosporine) cause neuropathies, including tremors, neuralgias, paresthesias, and peripheral mononeuritis and polyneuritis. Predisposing factors for these CNI toxicities include elevated plasma concentrations of the agents, the use of drugs known to cause neuropathies, or inhibition of CNI metabolism via CYP inhibition (such as the azole antifungals), and the presence of type 1 diabetes mellitus [52–55]. However, neuropathies have also been reported in the absence of elevated CNI levels, and may be potentiated with the addition of azoles, despite maintenance of CNI levels in the therapeutic range [56, 57].

Boussaud et al. [56] described 27 lung transplant patients treated over a period of 3 years for *Aspergillus* colonization or infection, of whom nine (30%) developed painful neuromuscular disorders. These disorders developed 2 weeks to > 1 year after initiation of voriconazole despite maintenance of therapeutic tacrolimus trough concentrations ($11 \pm 1.5$ ng/mL). Symptoms experienced by these patients included muscular pain and/or weakness, numbness, sensory loss, and other deficiencies. In four of five patients who underwent nerve conduction and needle electromyography studies, a demyelinating neuropathy of toxic origin with motor predominance was found. Interestingly, significantly higher doses of voriconazole ($735 \pm 218$ mg/day) were required in order to achieve goal trough levels, as compared with dosages in patients without symptoms ($560 \pm 162$ mg/day). While not supratherapeutic, trough voriconazole levels were significantly higher in patients with side effects at the onset of symptoms, than in those without symptoms ($2.1 \pm 0.8$ vs $1.31 \pm 0.77$ mg/L; $p < 0.02$) [56]. In two of these patients, voriconazole use prior to the introduction of tacrolimus had been well tolerated, suggesting a correlation between concomitant use of tacrolimus and voriconazole and these toxicities. Discontinuation of voriconazole led to rapid and complete recovery within 1–2 weeks. Given their findings, the authors changed their practice to maintain voriconazole trough levels at ≤ 1.5 mg/mL, after which no further neuromuscular complications were observed.

Development of peripheral neuropathies in the absence of other neuropathy-inducing medications or underlying diseases has been observed following administration of fluconazole, itraconazole, voriconazole, and posaconazole [58–62]. While the mechanism for this toxicity is not well understood, it is hypothesized to be caused by the azole moiety, since peripheral neuropathies have been reported for other azole ring-containing medications, including metronidazole [63]. Glove and stocking-type hypoesthesia, low-amplitude peroneal and median nerve compound motor action potential, and sural sensory action potential were reported in three patients following exposure to voriconazole. A case report of bilateral axonal sensorimotor polyneuropathy of the hands and feet, with ankle edema developing over a period of weeks to months with a time to onset of ~ 2 weeks to 3 months has been reported with itraconazole [64, 65]. Tremor, occurring 1–12 months following initiation of itraconazole therapy, has also been described in five cases. In each case, symptoms were reversible with discontinuation of itraconazole [59]. In the largest cohort of cases reported to date, the National Aspergillosis Center in the United Kingdom conducted a retrospective observational study of 222 patients who received an azole antifungal for the treatment of aspergillosis [60]. Peripheral neuropathies were reported in 26 patients (11.7%), of which 15 (6.6%) were confirmed by nerve conduction studies. Neuropathies were described in 7/75 (9.3%) patients receiving voriconazole, 1/40 (2.5%) patients receiving posaconazole, and in 18/107 (16.8%) patients receiving itraconazole. Symptoms were usually bilateral, symmetrical, and developed over 1–4 weeks, with a median time to onset of symptoms of 3 months. In most patients, the neuropathy presented as numbness or tingling

of the extremities, and were axonal, length-dependent neuropathies. In four patients, the predominant symptom was leg weakness. Of the 26 patients who discontinued azole therapy, 24 (92%) recovered sensation; two patients experienced non-progressive but irreversible peripheral neuropathies. Supratherapeutic plasma concentrations had been observed in 11 of the 26 patients: ten episodes with itraconazole, and one with posaconazole; however, drug levels below the maximum target therapeutic level were observed in all seven patients receiving voriconazole. The potential contribution of other neuropathy-producing drugs to the development of symptoms is unclear, but the authors comment that through their analysis they could not implicate drugs or medical history in the development of symptoms.

#### 3.2.3 Summary

Patients receiving vinca alkaloids or calcineurin inhibitors are at an increased risk of developing neuropathies when on concomitant triazole antifungals. The reported risk varies by agent (Table 1) but the mechanism of increased risk is pharmacokinetic for all azoles. Based upon the above data, the benefit of therapeutic drug monitoring for prevention of neuropathies with long-term triazole therapy is unclear. For patients receiving voriconazole and tacrolimus, maintaining a voriconazole trough level below 1.5 mg/mL may be considered. Pre-emptive dose reductions and careful monitoring of CNI plasma levels are recommended upon initiation of azole antifungal therapy to lower the risk of developing neurologic adverse effects. In the case of patients receiving other offending agents, monitoring and careful attention to interactions with azole antifungals is important. In particular, in patients receiving vincristine chemotherapy, concurrent prophylaxis or treatment with strong CYP3A4 inhibiting azole antifungals should be avoided. More generally, careful clinical monitoring for the development of symptoms consistent with peripheral neuropathies is of significant value, as dose reductions or discontinuation of offending agents is likely to result in reversibility of symptoms.

### 3.3 Hair Loss, Alopecia, and Nail Changes

Until recently, the development of alopecia had been reported mainly in patients receiving long courses of fluconazole or with high-dose ketoconazole therapy for invasive fungal infections [62, 66–74]. Pappas et al. conducted a retrospective evaluation of patients treated with fluconazole as part of the National Institute of Allergy and Infectious Diseases mycoses study group (MSG) [71]. Thirty-three patients in the MSG 13 study were reported to have developed alopecia during treatment with fluconazole, 12.5% of whom were non-human immunodeficiency virus (HIV) patients being treated for histoplasmosis, blastomycosis, or sporotrichosis; and 20% of patients in the MSG 23 study developed alopecia, which included acquired immunodeficiency syndrome patients receiving therapy for histoplasmosis. The adverse event seemed to affect males and females equally. In most cases, the dose given was at least 400 mg daily and the median time to onset of alopecia was 3.2 months. In 32/33 cases (97%), alopecia was reversible upon discontinuation or dose reduction of at least 50% of the original dose of fluconazole and in the remaining case, alopecia resolved without the need for dose reduction. The mean time to resolution of alopecia was 6 months [71]. Patients had variable degrees of scalp hair loss and 30% of patients also experienced substantial non-scalp body hair loss.

A single case report of alopecia in a child receiving voriconazole, and several case reports of alopecia associated with posaconazole therapy have been reported [75, 76]. However, more recently, the development of alopecia was reported in 125/152 (82%) patients receiving high-dose voriconazole for > 1 month. Although the investigators were unable to detect a correlation between drug levels and the incidence of alopecia, most patients had received large (6 mg/kg) daily doses of voriconazole to ensure adequate penetration into the cerebrospinal fluid for the treatment of fungal meningitis. Symptoms developed a mean of 2.5 months after initiation of voriconazole, and involved the scalp (96%), arms and legs (42%), and eyebrows (38%). In 15% of patients, hair loss was extensive enough to result in the need to wear a wig. Hair loss stopped and regrowth of hair was observed in 94 (82%) and 79 (69%) of patients, respectively, once voriconazole had been discontinued for > 3 months, and alopecia resolved in patients switched to posaconazole or itraconazole. Nail changes (new splitting, thinning, and development of brittle nails) occurred in 106 (70%) patients, and nail loss in 15 (10%) patients [77].

The proposed mechanism by which azoles cause alopecia is not fully understood. It has been proposed that inhibition of the P450-dependent metabolism of retinoic acid leads to the development of dystrophic anagen hairs, which cannot progress in the hair follicle cycle [69]. While all azoles inhibit retinoic acid metabolism to some extent, via inhibition of CYP344 (Fig. 1), alopecia has only been reported with voriconazole, fluconazole, and posaconazole but not with ketoconazole, a potent inhibitor of CYP3A4. In fact, ketoconazole topical products are used to treat male androgenetic alopecia (MAGA). While the mechanism for ketoconazole-induced hair growth is not fully understood, its inhibition of 17-α-hydroxylase (CYP17A1) is thought to disrupt the dihydrotestosterone pathway, which is implicated in MAGA. Alopecia related to azole antifungals may be overlooked in certain patient populations that are likely to receive long-term therapy with these agents, such as patients with hematological malignancies and in HIV-infected patients with progressive disease, who might have additional risk factors for this adverse effect.

#### 3.3.1 Summary

Alopecia has been associated with long-term fluconazole (reported frequency 5–10%) and voriconazole (reported frequency 5–10% with high doses) use, and rarely with posaconazole, and nail changes have been reported with voriconazole. The mechanisms for these toxicities are not fully understood. In certain patient populations, these adverse effects may be attributed to other causes and, thus, the offending agent is not appropriately identified. Clinician awareness of this adverse effect is important as it may help in determining the etiology of alopecia in these patient populations. For patients receiving voriconazole, doses of 6 mg/kg were associated with the toxicity, but there was no correlation found with higher serum plasma levels. Reversibility of symptoms is likely to occur months after discontinuation of the offending azole.

### 3.4 Hormone-Related Adverse Effects

In humans, all azole antifungals block steroidogenesis, via inhibition of the CYP450-dependent enzyme 14-α-demethylase (CYP51A1), which is responsible for the conversion of lanosterol to ergosterol (Fig. 2) [67, 78–91].

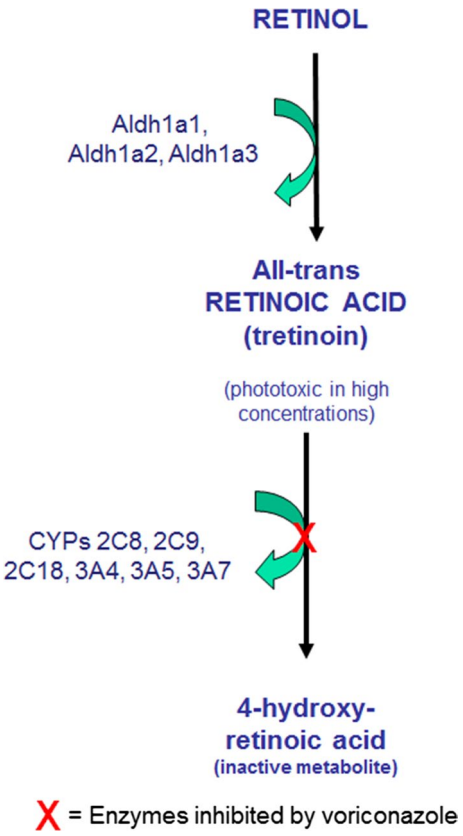


**Fig. 1** Retinoic acid metabolism. *CYP* cytochrome P450

Ergosterol is an essential starting component for many human glucocorticoid, mineralocorticoid, and gonadal hormones. However, since azoles exhibit different binding affinities to human CYP51A1, the magnitude of these effects differs between azole antifungals [67, 82, 84, 87]. Administration of ketoconazole also results in reversible, dose-dependent inhibition of CYP17A1, 11-β-hydroxylase (CYP11B1), and 18-hydroxylase (CYP11B2) [86, 90, 92–98]. Azoles also exhibit varying potency with respect to their ability to inhibit CYP3A4: ketoconazole is the most potent inhibitor, followed by itraconazole and voriconazole (roughly equipotent), and then fluconazole [87].

#### 3.4.1 Gynecomastia, Decreased Libido, Oligospermia, Azoospermia, and Impotence

As noted previously, ketoconazole, and to a lesser extent, itraconazole, inhibit a number of the CYP enzymes involved in steroidogenesis, including estradiol and testosterone [67, 78–91]. Ketoconazole causes transient inhibition of testosterone synthesis, as well as a selective displacement of dihydrotestosterone and estradiol from sex hormone-binding globulin, which may result in a decreased androgen/estrogen ratio and the development of gynecomastia. Gynecomastia, decreased libido, oligospermia, azoospermia, and impotence have been reported in 2–14% of men treated with high (> 600 mg) daily doses of ketoconazole, and during prolonged administration of lower (400–600 mg daily) dosages, secondary to the anti-androgenic effects of decreased testosterone synthesis [73, 82–84, 99–101]. Dose-related gynecomastia was observed in 25 of 160 patients (21%) enrolled in a prospective multicenter study of ketoconazole 400–2000 mg once daily for coccidioidomycosis. Gynecomastia appeared as early as 1 month and as late as 32 months after initiation of therapy, and was reversible upon discontinuation of the drug. Similarly, gynecomastia was observed in 6 of 42 (14%) and 2 of 55 (4%) men receiving high- (800 mg daily) or low-dose (400 mg daily) ketoconazole, respectively ($p < 0.05$) for blastomycosis or histoplasmosis [99]. Gynecomastia has also been observed in 1% of patients following therapy with itraconazole 400 mg daily for systemic mycoses [101].

#### 3.4.2 Adrenal Insufficiency

Adrenal insufficiency is a well-recognized adverse effect of ketoconazole, but has also been reported in patients treated with itraconazole, fluconazole, voriconazole, and posaconazole [97, 102–110]. Administration of a single 400-mg or 600-mg dose of ketoconazole produces a significant decrease in the cortisol response to adrenocorticotropic hormone (ACTH) for 4–6 hours [82]; larger doses cause more prolonged blockade. In one case report, the patient had been

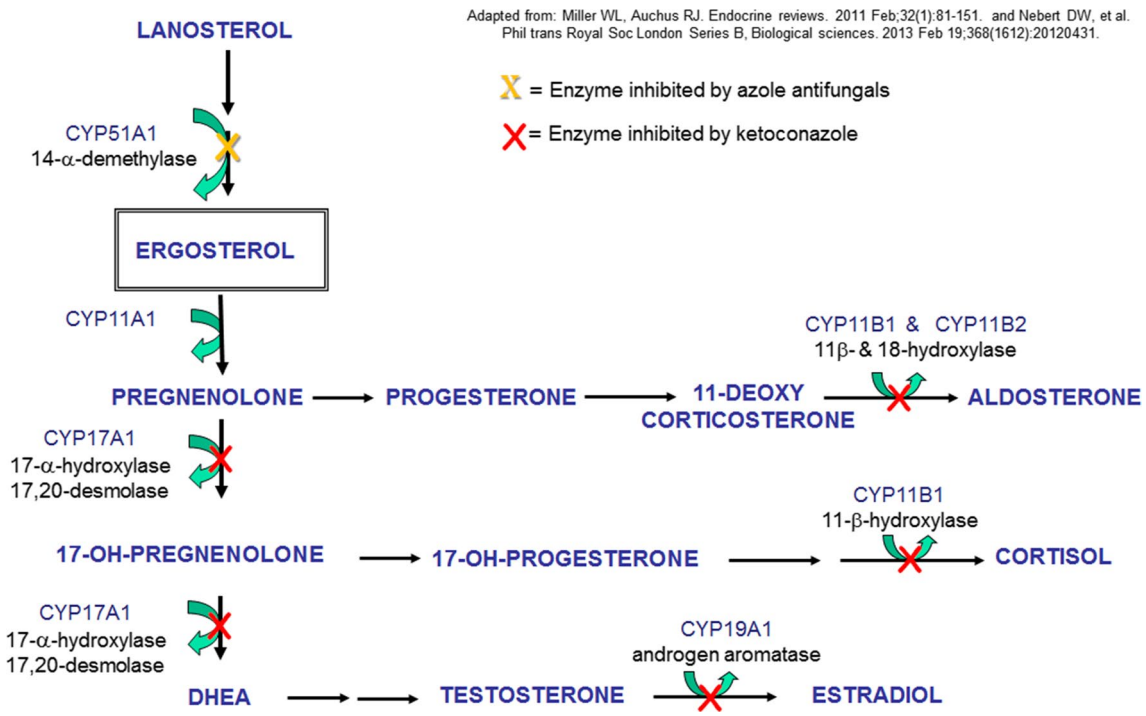


**Fig. 2** Steroid hormone synthesis pathways. *CYP* cytochrome P450, *DHEA* dehydroepiandrosterone

administered a high dose (600 mg daily) of itraconazole for 5 months [107]. Although early studies suggested that fluconazole did not alter cortisol levels in vitro, in healthy volunteers, or hospitalized patients [111, 112], several studies have since reported that even low doses can result in adrenal insufficiency [97, 102, 108]. A recent in vitro study demonstrated fluconazole dose-dependent suppression of cortisol production and 17-α-hydroxylase activity in several human cell culture lines, although at a lower level than that observed for ketoconazole [97]. Acute adrenal insufficiency was reported in a male patient receiving fluconazole 200 mg during high-dose cyclophosphamide therapy. An ACTH test revealed mild cortisol suppression, which normalized when the patient was switched to amphotericin B and given supplemental prednisone 10 mg daily. However, a repeat ACTH during rechallenge with fluconazole 400 mg daily demonstrated significant cortisol suppression [108]. Similarly, reversible adrenal insufficiency was reported in two patients following initiation of therapy with high-dose fluconazole. ACTH stimulation tests normalized 11 and 5 days following discontinuation of fluconazole [102].

Adrenal suppression or insufficiency may also result from azole-mediated inhibition of CYP3A4 during concomitant administration of azole antifungals with oral, intravenous, or inhaled corticosteroids [113–132]. For example, suppression of the hypothalamic-pituitary-adrenal axis was observed in 12 cystic fibrosis patients undergoing therapy with inhaled fluticasone, with or without concomitant oral itraconazole. In patients receiving the combination therapy, median basal cortisol levels were significantly lower (219 nmol/L vs 348 nmol/L; $p = 0.02$), as were peak cortisol levels (404 nmol/L vs 672 nmol/L; $p < 0.001$) [118].

### 3.4.3 Hyponatremia

Hyponatremia, and salt-losing nephropathy in association with elevated plasma renin and antidiuretic hormone have been occasionally observed with long-term therapy with voriconazole [132–137], and, in several case reports, following long-term use of ketoconazole [138]. Hyponatremia has been observed to occur as early as early as 6 days, and as late as 26 days after the start of voriconazole therapy, and is usually reversible after dose reduction or discontinuation of voriconazole [133, 135]. In most cases, voriconazole-associated hyponatremia appeared to be concentration-dependent, with an increased risk of hyponatremia occurring in patients with elevated (> 7 mg/L) trough concentrations. Of note, the majority of case reports with voriconazole have involved Asians (in whom poor metabolizers with homozygous mutation of CYP2C19 alleles are more common [15–20%] than in Caucasian or African American populations [3–5%]) or elderly (> 60 years old) patients [133]. Whether these constitute risk factors for increased levels or toxicity is unclear; however, it has been suggested that these patients may warrant monitoring of serum electrolytes while on voriconazole therapy [5]. Adrenal sufficiency, as a cause of hyponatremia,

was ruled out since it occurred in patients on maintenance doses of corticosteroids or progressed despite replacement doses [133]. While the symptoms and morbidity of voriconazole-induced hyponatremia appear similar to those of the syndrome of inappropriate antidiuretic hormone (SIADH), the pathophysiology appears to differ [134]. Patients with SIADH usually present with decreased plasma osmolality, increased urinary osmolality and uricemia, euvolemia, increased urinary sodium, and normal renal, thyroid and adrenal function and no recent use of diuretics [132].

#### 3.4.4 Hypokalemia and Hypertension

Hypokalemia during administration of azole antifungals has been reported with all azoles [101, 107, 139–164], although the majority of case reports have focused on posaconazole, despite it being a more recently approved azole [110, 139, 142, 154–156, 162, 163]. The package insert for posaconazole notes that it was observed in 22% of patients, while a phase Ib study noted an incidence of 9% during prophylactic use of the tablet formulation of posaconazole [145]. While generally appearing within the first 2 weeks of azole therapy, and in association with other hepatotoxic agents, patients have also presented later in the course of long-term therapy. Higher doses and (when tested) higher serum levels of the drug are often implicated as contributing factors. For posaconazole, hypokalemia and hypertension appear to result from inhibition of 11-β-hydroxylase [139, 140, 154, 162, 163]. The resulting increases in 11-deoxycorticosterone (a mineralocorticoid receptor activator) and 11-deoxycortisol production (Fig. 2), lead to water and sodium retention, hypokalemia, and hypertension [139]. In addition, posaconazole may stimulate adrenal cells, increasing metanephrines and catecholamines and contributing to the hypertension observed in these patients [139].

#### 3.4.5 Summary

Hormone-related adverse effects, most notably adrenal insufficiency, hyponatremia, and hypokalemia, have been noted with prolonged use of azole antifungals (frequency < 5 to 10% varying by agent, Table 1). Adrenal insufficiency is related to azole inhibition of CYP51A1. Ketoconazole also inhibits CYP17A1, which is involved in androgen synthesis, leading to additional sex hormone-related adverse effects. Patients with hematologic malignancies as well as transplant recipients may be receiving concomitant long-term or high-dose steroids and azole antifungals, and it is important to understand that both agents can cause adrenal insufficiency and that azoles may alter steroid metabolism. In these patients, careful monitoring should be performed during steroid tapers. In patients receiving only azole antifungals, the risk of hormone-related adverse effects is also present and these patients should also be carefully monitored for signs and symptoms of these adverse effects.

### 3.5 Hepatotoxicity and Drug-Induced Liver injury

The annual incidence of drug-induced liver injury (DILI) has been estimated to be roughly 19 cases per 100,000 persons, of which 11% are ascribed to idiosyncratic injuries, meaning that there is no predictable pattern or mechanism of injury [165]. Azole antifungals have been implicated in idiosyncratic DILI, accounting for 2.9% of all DILI (including acute liver failure events) reported to international adverse event reporting databases from 2011 to 2014, although the incidence and pattern of injury varies between agents [166–168]. In addition, it is important to remember risk for the development of hepatotoxicity includes a number of other factors, including the presence of pre-existing liver disease, use of concomitant hepatotoxic medications, genetic factors, azole dosage and plasma concentrations, and infection of the liver by fungal pathogens [169].

Hepatotoxicity is often defined as an increase in aspartate transaminase (AST) to > 3-fold the upper limit of normal (ULN), or an elevation in total bilirubin to > 2 times the ULN, and less often, as elevations in alanine aminotransferase or alkaline phosphatase (ALP); alterations in total or direct bilirubin are often not evaluated [6, 168, 169].

Exact mechanisms of toxicity have not been elucidated and there are varying levels of evidence correlating azole doses or serum concentrations with the development of toxicity. All antifungals have been associated with hepatotoxicity; generally, these are reported as minor abnormalities in liver function. However, while uncommon, reactions can be serious and life-threatening hepatitis and hepatic necrosis can occur [170, 171]. In a recent study, the risk of hepatotoxicity following parenteral antifungal agent therapy was similar in patients who were propensity-score matched for clinical characteristics, other treatments, procedures, and hospital service where antifungal treatment was initiated [172]. However, similar comparisons following higher dosages or long-term therapy are not available [169].

Although hepatotoxicity can occur at any time after initiation of azole antifungals, most cases occur within the first month of therapy. Liver damage is generally reversible within ~ 2 weeks upon dosage reduction or discontinuation of the drug. However, fulminant hepatotoxicity, with hepatic necrosis, has (rarely) been reported, and may recur upon rechallenge [173]. Despite their structural similarities, several reports support limited cross-reactivity between azoles, and that substitution of azole antifungals in the setting of azole-induced liver damage can occur without adversely affecting resolution of symptoms [169, 174–179]. Furthermore, in cases where the liver function test (LFT) abnormalities are deemed not to be deleterious to the patient,

continuing offending azole therapy with careful monitoring may result in spontaneous resolution [180]. The hepatotoxic profiles of currently available azole antifungals are summarized in Table 2.

#### 3.5.1 The Relationship Between Azole Dosage or Serum Concentrations and Liver Function Test Abnormalities

All azoles have been implicated in producing elevations in LFT abnormalities. The relationship between azole dosage or serum concentrations and LFT abnormalities have been evaluated for several azoles, with the level of evidence supporting conclusions varying by agent. Ketoconazole hepatotoxicity has not been found to be related to either the dose or duration of therapy [73, 181]. Fluconazole hepatotoxicity has been described as a dose-dependent toxicity in two case reports, while other reports and reviews have not found a relationship between dose and toxicity [170, 182–184]. Itraconazole hepatotoxicity has been found to be related to long-term, continuous use as well as prolonged pulse therapy (> 12 weeks), but it is unknown whether this is a dose-dependent or duration of therapy effect [165, 171]. Very limited information is currently available evaluating the dose dependence of the newest agents, posaconazole and isavuconazole, on hepatotoxicity, but small studies seem to suggest increases in serum concentration seen with newer formulations of posaconazole have not been correlated with increased incidence of hepatotoxicity [30, 185].

Several retrospective studies, including data from phase II and III clinical trials, have evaluated the relationship between voriconazole doses and serum concentrations on the development of hepatotoxicity. The overall rate of LFT abnormalities was 13.4%, and each 1-μg/mL increase in voriconazole serum concentration was predictive of increases in AST, ALP, and bilirubin of 13.1%, 16.5%, and 17.2%, respectively [186, 187]. However, investigators have been unable to determine a threshold voriconazole concentration at which the risk of voriconazole-induced LFT abnormalities occur, and voriconazole serum concentrations are a weak predictor of the development of LFT abnormalities. A higher risk of increases in ALP may be associated with higher mg/kg doses and longer durations of voriconazole therapy [188]. Furthermore, in patients with impaired liver function it is possible that the elevated serum levels of voriconazole are a result of impaired metabolism, as opposed to the agent being the cause of the toxicity. In addition, specific patient populations may be at increased risk of voriconazole-induced hepatotoxicity. For example, In lung transplant recipients, the overall rate of LFT abnormalities is ~ 30%, and several studies have found voriconazole therapy to be an independent risk factor for the development of hepatotoxicity [189, 190]. Similarly, in Japanese patients, LFT abnormalities are observed in 28% of patients, perhaps due to the higher likelihood of genetic polymorphisms in CYP2C19, leading to decreased metabolism (and elevated serum concentrations) of voriconazole [191, 192].

#### 3.5.2 Cholestasis

Cholestasis has rarely been reported following administration of itraconazole and voriconazole [165, 193–195]. Although in vitro, posaconazole and itraconazole significantly inhibit multidrug resistance protein 3-mediated phosphatidylcholine secretion; case reports of cholestasis resulting from posaconazole are not available [196, 197]. However, the lack of case reports may reflect the often polypharmacy nature of severely ill patients prescribed posaconazole [196]. However, itraconazole is often used as long-term therapy for onychomycosis in otherwise healthy individuals, and several case reports have described the development of jaundice and elevated bilirubin > 1 month after initiation of therapy. In one case, prolonged cholestasis was noted; a peak bilirubin of 32 mg/dL was observed ~ 2 months after discontinuation of itraconazole [194].

The use of a daily regimen of fluconazole has been associated with the development of cholestasis in very low-weight infants in whom daily administration of fluconazole is utilized as prophylaxis against invasive fungal infections [198, 199]. In a retrospective study comparing the effectiveness and safety of daily versus three times daily dosing, the severity of conjugated hyperbilirubinemia was reduced with use of a three-times-weekly regimen, while maintaining the same level of efficacy for infection prophylaxis [199]. At this time, the use of fluconazole prophylaxis in this patient population is not a uniform practice. Nevertheless, evidence suggests that three-times-weekly dosing regimens may decrease the risk of developing adverse effects while maintaining efficacy.

#### 3.5.3 Summary

LFT abnormalities and hepatotoxicity have been noted with all azoles, with the frequency of adverse effects varying by agent and patient population (Table 2). It is recommended that baseline LFTs be obtained for patients at the time azole therapy is initiated and monitored periodically. Given data to support lack of cross reactivity between agents, it is likely safe to continue azole therapy with a different agent for patients where discontinuation or switch to a different antifungal class is not preferred. Patients who develop hepatotoxicity on voriconazole may have elevated trough serum levels; however, high serum levels are not predictive of hepatotoxicity. Patients of Japanese descent may have a higher incidence of LFT abnormalities, possibly due to CYP2C19 genetic polymorphisms.

**Table 2** Hepatotoxicity of azole antifungals [6, 168, 169, 173, 181, 270–273]

| Azole | Pattern of hepatic injury | Approximate incidence of elevations in LFTs (%) | Toxicity requiring discontinuation of drug | Comments |
|---|---|---|---|---|
| Ketoconazole | Hepatocellular[a] | 3–17.5 | ~1 in 1000–3000 patients experience LFT elevations serious enough to warrant discontinuation of drug | Most LFT elevations are transient and resolve upon discontinuation of drug but risk of serious hepatotoxicity appears to be the highest among azoles |
| Itraconazole | Cholestatic[b] | 1–17.4 | ~1.5% of patients experience LFT elevations serious enough to warrant discontinuation of drug | LFT elevations may require 4–10 weeks. Hepatocellular pattern of toxicity may indicate serious toxicity. Dose or duration dependence of hepatotoxicity unclear |
| Fluconazole | Cholestatic | 1–10 | ~0.7% of patients experience LFT elevations serious enough to warrant discontinuation of drug | Most LFT elevations are transient and resolve upon discontinuation of drug. Mixed data regarding dose-dependence of hepatotoxicity |
| Voriconazole | Mixed[c] hepatocellular and cholestatic | 12–19 | Fulminant hepatic failure rare | Toxicity usually occurs within the first 10–28 days of therapy, and may be drug concentration related |
| Posaconazole | Hepatocellular | 1–10 | LFT elevations serious enough to warrant discontinuation of drug are rare | LFT elevations generally resolve within 2 weeks after drug discontinuation |
| Isavuconazole | Varied | < 5 | Limited data | Hepatoxicity may be dose related (minimal data) |

The pattern of injury is characterized by [a]hepatocellular: predominantly by an increase in ALT; [b]cholestatic: by an initial or predominant increase in ALP; [c]mixed: the pattern resembles both cholestatic and hepatocellular injury

*ALP* alkaline phosphatase, *ALT* alanine transaminase, *LFT* liver function test

### 3.6 Pancreatitis

Itraconazole use has been associated with pancreatitis in clinical trials and in phase IV studies [173]. The Netherlands Pharmacovigilance Centre Lareb reported a series of four cases of documented pancreatitis in the period from 1999 to 2000 [200]. The time frame to development of symptoms ranged from 7 days to 7 weeks. In three of the four cases, itraconazole was the only drug that could be correlated to pancreatitis, whereas in the fourth case it is plausible that the interaction between itraconazole and simvastatin leading to increased levels of simvastatin in the blood could have been the cause of the event. In all cases, the regimen prescribed resulted in a greater drug exposure to itraconazole than recommended for treatment of the patient's condition (i.e., greater daily doses and/or longer duration of therapy). A single case report has implicated voriconazole use with the development of pancreatitis in a 16-year-old patient with acute myeloid leukemia who was being treated for aspergillosis [201]. Although the patient was receiving a cytarabine-containing chemotherapeutic regimen, which can also be associated with the development of pancreatitis, the patient experienced multiple episodes of epigastric pain and associated increases in amylase that correlated with the first introduction and later re-introduction of voriconazole. Of note, the patient was taking double the prescribed dose of voriconazole when she presented with signs and symptoms of pancreatitis. Voriconazole blood levels were not reported for this patient.

Given the small number of cases described in the literature, there is limited data to support a dose or duration-of-therapy relation to pancreatitis. Nevertheless, prescribers should be cognizant of the increased potential for adverse effects with any additional exposure to medication and should adhere to established regimens for the treatment of infection when available in order to minimize potential patient harm. The relationship between serum drug levels of itraconazole or voriconazole and the development of pancreatitis is unknown.

### 3.7 Dermatological Effects: Xerosis, Phototoxic Dermatoses, and Skin Cancer

Xerosis is common (16.9%) in patients receiving long-term therapy with fluconazole [62]. Phototoxic reactions and the development of various skin cancers, including squamous cell carcinoma (SCC), have been associated with the duration of therapy, and with cumulative high-dose exposure to voriconazole [21–27, 202–255]. To date, there have been no reports with other azoles. The median time to development of phototoxic lesions is 3.5–7 months, while the time to development of SCC lesions is longer, with median time to event reported as 19–43.2 months after initiation of voriconazole [220, 229, 233, 256, 257] (Fig. 3). In a French nationwide retrospective study, voriconazole-associated skin manifestations were reported in 61 patients with long-term exposure to voriconazole, including 19 (31%) cases of SCC. In SCC patients, the mean duration of voriconazole therapy was shorter in transplant versus non-transplant recipients (39 versus 45 months; $p < 0.05$) [226].

Phototoxic reactions include acute and chronic skin lesions including severe, painful erythema with or without blistering of sun-exposed areas and cheilitis, that appear as an exaggerated sunburn appearing within minutes to hours following light exposure [257, 258]. Pseudoporphyria, an uncommon photosensitive blistering with clinical and histologic features similar to porphyria cutanea tarda but lacking the serum and urine abnormalities in porphyrin metabolism, has also been reported in several patients [206, 247, 259–261]. Phototoxicity and the development of SCC due to exposure to voriconazole appears to be a multi-step process, with acute phototoxicity occurring during the first year of voriconazole use, actinic keratosis of the same sun-exposed skin during the next 2–3 years of therapy, followed by SCC in patients treated for 3 or more years. It is important to note that patients with non-malignant skin lesions in whom voriconazole is discontinued generally experience rapid improvement of lesions [226].

Transplant recipients are at an increased risk of malignancies. Skin cancer (primarily SCC) is the most common malignancy occurring after solid organ transplantation and patients experience a > 65-fold increased risk of developing SCC compared with the general population [203]. This increased risk is explained by the relationship between immunosuppression to prevent graft rejection and resulting decreased immune surveillance and activity against cancerous cells. Specifically, functional T cells are paramount to the regulation of dermatologic cancers. CNIs inhibit T-cell activation, which results in a decreased ability of the immune system to keep developing cancers in check. Overall, the risk of developing SCC and other skin cancers in this population is related to the choice of immunosuppression, the intensity (serum levels of the CNIs and addition of steroids and antimetabolites or other types of immunosuppressants), and duration of suppression [262]. The risk of developing SCC increases with the time after transplantation [213]. However, the time to onset of SCC appears to be shorter in voriconazole-exposed patients, perhaps due to synergistic effects with voriconazole [226, 263]. Voriconazole exposure has been reported by some (but not all [224]) investigators as an independent risk factor for the development of cutaneous SCC in lung transplant recipients [227, 229, 233, 237, 264]. The rates of SCC in heart, lung, and HSCT patients receiving voriconazole surpass those of kidney and liver transplant patients, who are not routinely exposed to voriconazole for fungal prophylaxis, are typically younger in age at the time

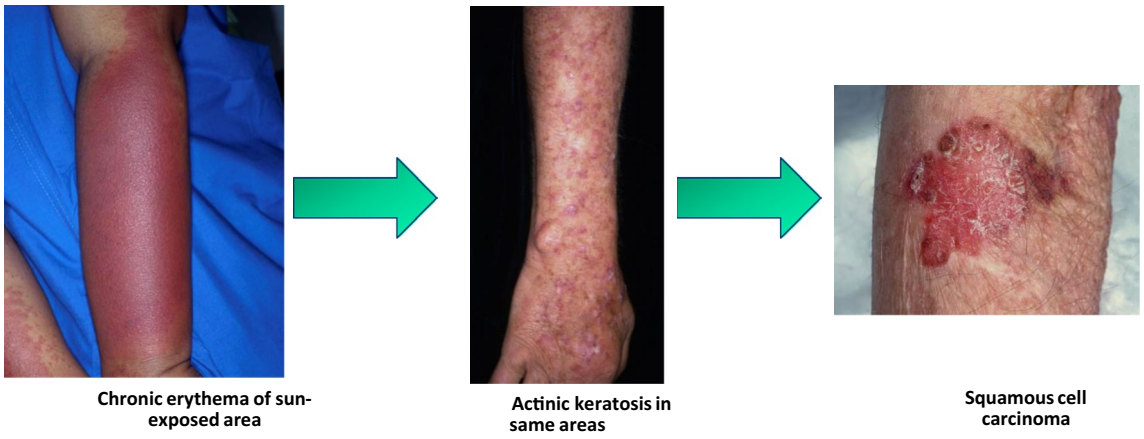


**Fig. 3** Progression of skin toxicity as described with chronic voriconazole exposure (images reproduced with permission from VisualDx©)

of transplantation, and experience less intense immunosuppression at time of transplant and more intense immunosuppression [226, 265, 266]. Similar rates of SCC development have been described in allogeneic HSCT (allo-HSCT) transplant patients: in a retrospective study of patients undergoing allo-HSCT, 25/281 (6.6%) patients exposed to voriconazole after transplant developed SCC, with a cumulative incidence of cutaneous SCC 5 years post-transplant of 19%. Additional risk factors for voriconazole-induced phototoxic reactions (in both transplant and non-transplant populations) include the duration of voriconazole exposure, geographical location, older age at time of transplant, skin cancer pre-transplant, Fitzpatrick skin type, and (in cystic fibrosis patients) the presence of the ΔF508/ΔF508 genotype [203, 207, 208, 212, 216, 224, 228, 230, 237]. Notably, chronic graft versus host disease was not found to be a risk factor for the development of SCC [205].

No significant correlation was found between the incidence of photosensitivity and voriconazole serum levels in six of eight children with allergic bronchopulmonary aspergillosis; however, trough voriconazole concentrations were variable and very low (< 1000 ng/mL in 80% of patients) [231]. The use of voriconazole has also been associated with more numerous and aggressive SCC lesions [267]. A single retrospective study of lung transplant patients receiving voriconazole for fungal prophylaxis found increased risk with higher cumulative doses of voriconazole, while a separate study evaluating this factor did not find congruent results [229, 233]. The main limitation of the retrospective analyses conducted in these studies is the lack of evaluation of intensity of immunosuppression, a known risk factor for the development of SCC, into the risk factor assessment models.

The mechanism of phototoxicity with voriconazole has not been elucidated; currently, there are two main hypotheses. Voriconazole's N-oxide metabolite may serve as a chromophore (a molecule that absorbs photons during ultraviolet [UV] light exposure), which triggers skin changes such as tanning, sunburn, and oxidative damage including aging and carcinogenesis when the skin of a patient taking the drug is exposed to UV radiation [257, 268], and may possibly be enhanced by vitamin A supplementation [244]. Voriconazole undergoes metabolism by CYP2C19, CYP2C9, and CYP3A4 to a variety of inactive metabolites, include the N-oxide form, which constitutes 72% of circulating metabolites and absorbs UVB and UVA more strongly than the parent drug. It has been hypothesized that the N-oxide metabolite localizes in skin epidermis and act as a chromophore, sensitizing keratinocytes to UVA [268, 269]. A competing hypothesis is that voriconazole inhibits the CYP3A4-mediated metabolism of tretinoin (vitamin A), a known phototoxic compound (Fig. 1) [257]. It is likely that both of these factors play a role in the development of the toxicity. In addition, the lack of SCC development in hematology-oncology patients receiving long-term therapy with voriconazole may support an etiological role for immunosuppressive therapies targeting lymphocyte activation in the development of skin cancer [242].

### 3.7.1 Summary

Phototoxic reactions and the development of skin cancers, including SCC, have been associated with exposure to voriconazole. The frequency of this adverse event is reported to be 5–10% in the general population and > 10% in the solid organ and allogeneic hematopoietic cell transplant populations. Patients on voriconazole should use liberal amounts of broad-spectrum UV protectants with SPF30 or higher, as recommended by the American Academy of Dermatology, and wear sun-occluding clothing (e.g., long-sleeved shirts, pants, hats), avoid excess sunlight, and undergo frequent monitoring of skin. Voriconazole should be discontinued when possible if erythema of sun-exposed areas or actinic

keratosis develops during the course of treatment [268]. While there is limited evidence regarding the relationship between serum drug levels and skin toxicities, it appears that duration of exposure, rather than drug levels, is related to the development of this toxicity.

## 4 Conclusion

Azole antifungals are commonly used over periods of weeks to months for the prophylaxis and treatment of invasive fungal infections. Since these patients are often receiving other medications, it may be difficult for care providers to identify the antifungal agent's causality or contribution to patient symptoms. Long-term use of azoles is associated with hepatotoxicity and hormone-related effects, including gynecomastia, alopecia, decreased libido, oligospermia, azoospermia, impotence, hypokalemia, hyponatremia, and (rarely) adrenal insufficiency (Tables 1, 2). Voriconazole and posaconazole have been associated with peripheral neuropathies. In addition, voriconazole has been associated with periostitis, phototoxic reactions, and squamous cell carcinoma (Table 1). Knowledge and recognition of adverse events caused by azoles, leading to their prompt discontinuation, can reduce symptoms and reverse toxic processes. For the majority of the adverse events described, there are no known or hypothesized genetic profiles that increase the risk of development. More research is needed in order to determine whether specific patient populations are at increased risk. Furthermore, the cost of newer triazole antifungals is high, and the financial implications of the medical management of adverse events and switching therapies is not well described in the literature and remains an additional area of future research.

### Compliance with Ethical Standards

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**Conflict of interest** Peggy L. Carver, PharmD, FIDP has served as a consultant for Astellas. Lydia L. Benitez, PharmD, BCOP has no conflicts to disclose.

**Research involving human participants and/or animals** This article does not contain any studies with human participants or animals performed by any of the authors.

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