Diagnosis and Treatment of Tinea Versicolor

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Tinea versicolor (pityriasis versicolor) is a common superficial fungal infection of the stratum corneum. Caused by the fungus *Malassezia furfur*, this chronically recurring disease is most prevalent in the tropics but is also common in temperate climates. Treatments are available and cure rates are high, although recurrences are common. Traditional topical agents such as selenium sulfide are effective, but recurrence following treatment with these agents is likely and often rapid. Currently, therapeutic interest is focused on synthetic "-azole" antifungal drugs, which interfere with the sterol metabolism of the infectious agent. Ketoconazole, an imidazole, has been used for years both orally and topically with great success, although it has not been approved by the Food and Drug Administration for the indication of tinea versicolor. Newer derivatives, such as fluconazole and itraconazole, have recently been introduced. Side effects associated with these triazoles tend to be minor and low in incidence. Except for ketoconazole, oral antifungals carry a low risk of hepatotoxicity.

Key Words: Tinea versicolor; pityriasis versicolor; antifungal agents.

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Normal skin flora includes two morphologically discrete lipophilic yeasts: a spherical form, *Pityrosporum orbiculare*, and an ovoid form, *Pityrosporum ovale*. Whether these are separate entities or different morphologic forms in the cell cycle of the same organism remains unclear.[1] In the mycelial phase, *P orbiculare* is known as *Malassezia furfur*, the fungal agent that causes tinea versicolor.

Tinea versicolor manifests as a superficial, chronically recurring infection of the stratum corneum. It occurs principally on the trunk and proximal extremities and is characterized by scaly hypopigmented or hyperpigmented salmon pink, red, brown, or white macules, most often producing patches of white skin that are often referred to as "spotty body" (Figure). The hypopigmentation of tinea versicolor is thought to be due to inhibition of tyrosinase by dicarboxylic acids that the fungus releases.[2]

The incidence of tinea versicolor in children is low but recently was demonstrated to be higher than formerly thought. In one study, children under age 14 represented nearly 5% of confirmed cases of the disease.[3] In many of these cases, the face was involved, a rare manifestation of the disease in adults.[4] The condition is most prevalent in tropical and semitropical areas, where up to 40% of some populations are affected. In temperate areas, tinea versicolor is also quite common, representing 3% of patients presenting to dermatologists during the summer months.[5] The disease is rare in cold climates.

Tinea versicolor can be regarded as an opportunistic infection, although the biochemical defect that enhances this opportunity has not been defined. It is several times more common in persons infected with the human immunodeficiency virus (HIV), in whom the condition tends to be more severe.[6] The disease can be induced experimentally by inoculation under an occlusive dressing. In this experimental situation, self-healing occurs when the occlusion is terminated. The fungus is still present in the skin at the sites of clinical resolution, but the delicate balance has been restored between host and resident flora. Tinea versicolor is not contagious. The organism is ubiquitous and infection is related to host susceptibility rather than exposure.

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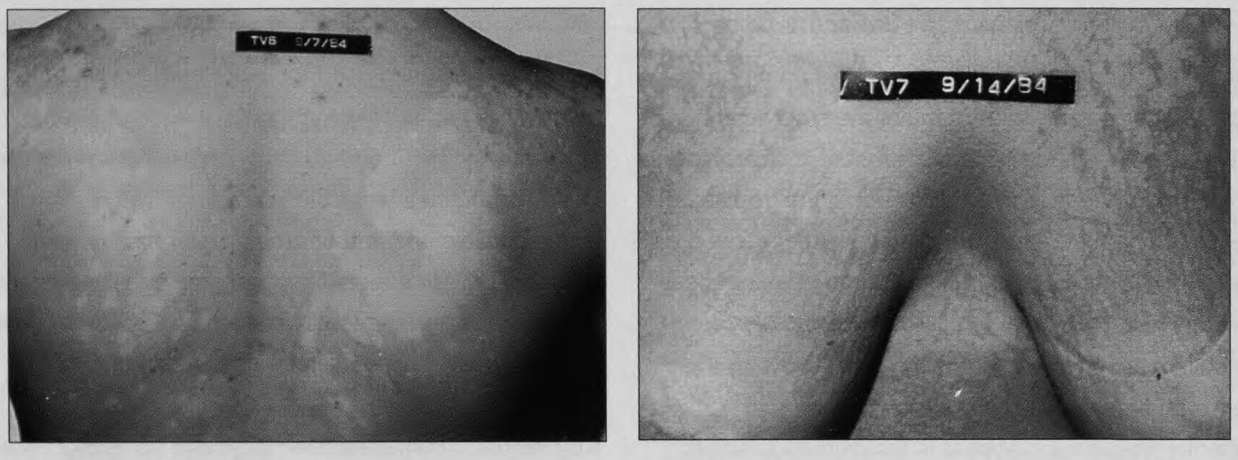
FIGURE

Tinea versicolor in a 23-year-old man (left) and a 27-year-old woman (right). Patients such as these may perceive their skin to be disfigured.



Spontaneous cure of tinea versicolor is not common, and the disease will persist for many years if left untreated. It usually presents in adolescence and seldom presents beyond middle age.

DIAGNOSIS

The outstanding clinical feature of tinea versicolor is patches of whitish skin—a partial leukoderma. Closer examination reveals a fine scale that can be "brought out" by gently scraping the involved skin with a scalpel blade. The scale is limited to the area of leukoderma. Alternatively, the infection may present as a tan or fawn-colored scale that can be similarly "raised up." This uniform fine scaling characteristic of tinea versicolor is rarely found in other forms of tinea or seborrheic dermatitis. Vitiligo can be ruled out because, whereas tinea versicolor is a partial leukoderma, vitiligo is complete and scaling is absent. Wood's light produces a yellow fluorescence in one third of cases but is not necessary for diagnosis.[7] The organism resides principally in the stratum corneum and can be conveniently removed for identification purposes by scraping the skin lightly or stripping it using cellophane tape. Then, a simple, inexpensive test, the potassium hydroxide (KOH) preparation, can be used to confirm the presence of the organism. Scales can be easily examined using special staining techniques,[8] and the morphologic characteristics usually permit a definitive diagnosis.

The leukoderma of tinea versicolor is due to the inhibitory effect of the organism on pigmentation and tanning. The presence of the active scale acts like a cover on the skin limiting the degree of tanning that can occur. When the scale is removed, the occluded area is white and remains so, even after successful therapy, until the skin is retanned or the surrounding tanned skin "wears off" months later. The condition truly produces a "spotty body."

TREATMENT

A wide range of antifungal drugs has been shown to be effective in the treatment of tinea versicolor.[9] In a broad sense, all these medications are at least transiently "effective" if used appropriately, and follow-up evaluation is limited to only a 2- to 6-week period. Some of the agents are far more effective in producing prolonged cures. Although several of these agents are not currently approved in the United States for the treatment of tinea versicolor, they serve as a basis for discussion about current and past therapeutic strategies and the development of future treatments (Table).

Traditional Topical Agents

Traditionally, the most frequently used topical treatment has been a 2.5% selenium sulfide shampoo applied once a day, usually after showering, over the entire affected area. After 10 minutes, it is washed off.[10] Alternatively, the shampoo can be

applied, left on overnight, and washed off the following morning. Typically, treatment is continued for 7 to 14 days or longer, sometimes indefinitely.

All the topical "-azoles," including econazole nitrate, ciclopirox olamine, and oxiconazole nitrate, appear to be equally effective in the treatment of tinea versicolor, although none has been studied as thoroughly as ketoconazole cream.

In one study, application of a 2% ketoconazole cream from the neck to the knees produced clearing in 98% of the 51 treated patients, compared with a response in 28% of the 50 patients who received placebo.[11] The overall mycologic cure rate was 84% in the ketoconazole group and 10% in the placebo group. In follow-up, 80% of treated patients remained clear after 1 year and 33% were still clear 2 years later.

TABLE

Treatment Approaches for Tinea Versicolor

Agent	Suggested Dosing
Topical	
Ciclopirox olamine 1% cream*	Twice daily for 2 weeks
Ketoconazole 2% cream*	Twice daily until clinical improvement
Miconazole 2% cream*	Once daily for 2 weeks
Oxiconazole nitrate1% cream	Once to twice daily until clinical improvement
Selenium sulfide 2.5% shampoo*	Once daily for 7 days
Terbinafine 1% cream	Twice daily for 2 weeks
Systemic	
Ketoconazole	200 mg/d for 10 days
Fluconazole	400 mg/d for 3 days
Itrraconazole	200 mg/d for 7 days

*Currently approved by the Food and Drug Administration for the treatment of tinea versicolor.

Systemic Agents

Ketoconazole

An early double-blind study of oral ketoconazole at doses of 200 mg/day for 4 weeks demonstrated complete healing in 97% of patients.[12] Only 9% of patients in the placebo group responded. Follow-up 1 year later showed that 64% remained clear. These findings compare favorably with a recurrence rate of 89% with casual use of miconazole nitrate.[12] Multiple open and double-blind studies of systemic ketoconazole have been conducted in various regions of the world.[13] The optimum dosage is 200 mg/day for 10 days. Cure rates have been high, often 90% to 100%, even in studies in which patients previously failed to respond to various topical therapies.

Because the overall rate of hepatic toxicity with oral ketoconazole is about 1:10,000, many dermatologists are uncomfortable using this agent. The incidence of hepatotoxicity, however, has been calculated to be only 1:500,000 in patients who are receiving short-term (10-day) oral ketoconazole therapy for tinea versicolor. Oral ketoconazole is not currently approved by the Food and Drug Administration (FDA) for the treatment of tinea versicolor in the United States.

Fluconazole

Oral fluconazole, a triazole, is currently approved in the United States for oral, esophageal, vaginal, and systemic candidiasis and relapsed cryptococcal meningitis. Although the oral formulation has not been approved by the FDA for the treatment of tinea versicolor, it appears to be quite effective. In a pilot study of the oral formulation, patients were given a single dose of 400 mg of fluconazole and monitored after 3 and 6 weeks.[14] Of 23 patients, 17 (74%) were free from lesions after 3 weeks, and no recurrence was observed 3 weeks thereafter. In the author's experience, a regimen of fluconazole 400 mg/day for 3 consecutive days has been found to be effective; however, definitive studies have not been conducted to confirm the value of this regimen.

Itraconazole

Concern about the toxicity of ketoconazole led to the development of other azoles, such as itraconazole, which is available in capsule form. Animal studies showed that itraconazole is 5 to 10 times more potent in vivo than ketoconazole against *Pityrosporum* spp. Initial studies demonstrated cure rates of greater than 90%, confirming the efficacy of 50- or 100-mg daily doses.[15] Since then,

much developmental work has been done to establish optimum dosing regimens. A double-blind, placebo-controlled study demonstrated that itraconazole 100 mg/day for 15 days produced a mycologic cure rate in seven of eight patients (88%) vs none out of five (0%) in the placebo group.[16] When the latter group received itraconazole in an open phase of the study, all responded. A dosage of 200 mg/day for 7 days was also reported to be effective.[15]

The time of assessment was found to be critical to the outcome rating. After the organism dies, it takes the body 3 to 4 weeks to slough the involved epidermis. At the end of short-term treatment, the skin continues to scale and leukoderma persists; therefore, follow-up sooner than 3 to 4 weeks after therapy is inappropriate.

One double-blind, placebo-controlled study[17] examined patients at baseline and 5 weeks after treatment with itraconazole 200 mg/day for 7 days. All 13 patients in the itraconazole group showed a clinical response, and 9 of the 13 were mycologically clear at the end of the 6-week study period. In contrast, only 1 of 14 patients in the placebo group showed a clinical response; that patient was mycologically clear 5 weeks after treatment. Adverse events were reported in five treated and three placebo patients. The author's usual treatment schedule is 200 mg of itraconazole in one daily dose for 7 days.

In a direct comparative test of oral itraconazole and selenium sulfide shampoo,[18] 20 patients took itraconazole 200 mg/day for 5 days, and another 20 patients used the shampoo daily for 7 days. Similar cure rates were obtained: 85% (17 patients) and 80% (16 patients), respectively. Follow-up was limited to 3 weeks. Both treatments were found to be acceptable and were well tolerated, but the majority of patients expressed a preference for the oral medication. Generally, patients who have experienced the simplicity of oral therapy for tinea versicolor prefer it to cream or shampoo.

In general, itraconazole is well tolerated. Therapy lasting more than 7 days for indications requiring longer term therapy may be accompanied by minor gastrointestinal side effects. The worldwide incidence of side effects such as headache, nausea, and abdominal pain is, however, less than 7%.[19] Few of these symptoms occur with short-term (1-week) courses of treatment, as used to treat tinea versicolor. Only rarely do side effects necessitate the interruption of therapy.

Ongoing studies are reporting a favorable efficacy and safety profile for itraconazole, and the incidence of associated hepatotoxicity is thought to be much lower than that for ketoconazole.

Terbinafine

Terbinafine is a broad-spectrum antifungal agent of the allylamine class. Although oral terbinafine is very effective against many dermatophyte infections, it is *not* effective against tinea versicolor, perhaps because it may not achieve high enough concentrations in the stratum corneum to be effective.[20] In contrast, topical terbinafine is effective. Several studies[20] have reported that a 1% cream formulation produced mycologic cure rates of from 80% to 90% with short-term follow-up.[20]

Topical vs Systemic Therapy

For the optimum treatment of tinea versicolor, the clinician must weigh the relative efficacy, safety, compliance, and cost of topical vs systemic therapy. From a pharmacotherapeutic point of view, superficial infections would seem ideally suited to topical treatment. The fungal overgrowth that causes tinea versicolor is largely restricted to the stratum corneum and is theoretically readily accessible to drugs in the appropriate vehicle. Realistically, the organism is usually so widespread over the body that the best possible means of treating all affected areas would be to dip the patient in the prescribed medication. Topicals such as selenium sulfide employ keratolytics, which mechanically remove the keratinized layer of skin and the infection therein. If the organism has penetrated less accessible layers, however, this form of treatment will be incomplete and recurrence is likely.

From the patient's point of view, topical agents have several disadvantages. It is difficult and time-consuming to apply a topical agent to a large affected area, especially the back. Furthermore, topical treatments are messy, and some have unpleasant odors. For these reasons, adherence to topical regimens is frequently inadequate, which increases the likelihood of recurrence.

Topical regimens are generally less effective than oral ones, and recurrence rates with topical

agents are 60% to 80%.[21] Oral medications, which appear to have few side effects when used as recommended in short-term regimens, are preferred by many patients.

Oral itraconazole and fluconazole are both good choices for systemic therapy. Itraconazole is lipophilic and accumulates in the skin in amounts 3 to 10 times greater than simultaneous plasma concentrations.[19] A total dosage of more than 1000 mg is necessary and can be conveniently administered over a period of 7 days. Fewer data are available on fluconazole, but treatment regimens are likely to be similar to those for itraconazole.

In today's health care environment, the cost of treatment is an important factor. The cost of therapies for tinea versicolor can vary widely depending on the agent used, route of administration, dosage schedule, and duration of administration. The newer oral antifungals have been shown to be effective following short-term regimens, reducing costs compared with traditional long-term antifungal dosages. Similarly, short-term topical treatments appear to offer significant clinical promise while keeping drug administration costs low. In all cases, the assessment of total therapeutic costs should be based not only on drug acquisition cost but also on the cost of repeat drug administration in the event of therapeutic failure or nonadherence.

HEPATIC EFFECTS OF ANTIFUNGAL THERAPY

Hepatotoxicity is a rare side effect that may be associated with any of the oral antifungals.[8] While idiosyncratic hepatic events have been reported within 2 to 3 days of initiating systemic antifungal therapy,[22] hepatic events are usually associated with long-term (ie, 2- to 4-week) use of these agents.[23] For example, hepatotoxicity with itraconazole, which has a short course of treatment, is generally uncommon: only three cases of reversible idiosyncratic hepatitis have been reported among more than 2500 patients treated with this agent. Similarly, mild, transient asymptomatic elevations in liver function tests have been reported in <5% of patients treated with fluconazole. This side effect appears to be largely an idiosyncratic reaction for which concomitant use of certain medications may be a predisposing factor.[23] The rare reports of hepatotoxicity associated with ketoconazole appear to be more common in women who are older than age 50 and have been taking the drug for prolonged periods (51 to 60 days); elevations in liver function tests during therapy with most systemic antifungals generally normalize when the drug is discontinued.[23]

Because the progression of most serious hepatic reactions can be limited if the offending antifungal is discontinued before the patient becomes symptomatic, the patient must be instructed on the signs of potential hepatic involvement (ie, chills, fever, discolored urine, pale stools). Many of the hepatic events associated with systemic antifungal therapies appear to be idiosyncratic, and therefore may be unpredictable during short-term therapy.[23] The value of monitoring liver function tests to identify patients who may be at risk for hepatic damage during short-term systemic therapy remains unclear; however, it is advisable to monitor liver function periodically during long-term treatment.

DRUG INTERACTIONS

Azole antifungals can play a part in both pharmacokinetic and pharmacodynamic interactions.[24] Ketoconazole is a base with limited solubility; therefore, agents that decrease gastric acidity will impair its dissolution and gastrointestinal absorption. Agents that increase gastric acidity will have the converse effect. Itraconazole is better absorbed when taken with food. Compounds that increase the activity of P-450–dependent enzymes, such as phenytoin, will stimulate the metabolism of ketoconazole. In turn, ketoconazole is a potent inhibitor of certain hepatic P-450 isozymes, and its administration can increase the concentrations of such drugs as cisapride, triazolam, and the antihistamines astemizole and terfenadine, and alter the pharmacokinetics of such drugs as erythromycin, cyclosporine, and coumadin.

Itraconazole has similar solubility properties to those of ketoconazole, whereas fluconazole is water-soluble and its absorption is largely unaffected by gastric acidity. Both itraconazole and fluconazole inhibit P-450 and, like ketoconazole, prolong the metabolism of drugs such as cyclosporine and digoxin. Serum concentrations of these drugs should be monitored when the patient is receiving

doses of itraconazole greater than 100 mg/day or doses of fluconazole greater than 100 to 200 mg/day. Fluconazole has also been shown to cause wide fluctuations in the bioavailability of ethinyl estradiol, which is a consideration in female patients using oral contraceptives, patients with diabetes or seizure disorders, and patients using anticoagulants.

Itraconazole and fluconazole are both contraindicated with astemizole and terfenadine, and itraconazole is also contraindicated with cisapride and triazolam.

SUMMARY

Several good therapeutic choices exist for the treatment of tinea versicolor: topical agents are effective to some degree; however, oral itraconazole and oral fluconazole offer many advantages. Patients may be given the option of topical or systemic medication. Topical ketoconazole, although inconvenient, is safer and probably just as effective as the systemic agents when used properly, ie, applied widely from ear lobes to knees for 2 weeks.

For systemic therapy, ketoconazole is effective at 200 mg/day for 10 days. Although tinea versicolor has been treated with a single dose of fluconazole 400 mg, pharmacokinetic studies indicate that two doses given 1 week apart may be more effective.[25] Itraconazole has been demonstrated in a variety of studies to be effective at a dosage of 200 mg/day for 7 days. [15,17]

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