Review: Oral antifungal therapy has low risk for adverse events in superficial dermatophytosis and onychomycosis

Chang C, Young-Xu Y, Kurth T, Orav JE, Chan AK. **The safety of oral antifungal treatments for superficial dermatophytosis and onychomycosis: a meta-analysis.** Am J Med. 2007;120:791-8.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Infectious Disease ★★★★★☆☆ Dermatology ★★★★★★☆

QUESTION

In patients with superficial dermatophytosis or onychomycosis, what is the absolute risk for termination of oral antifungal therapy (OAT) because of adverse events?

METHODS

Data sources: MEDLINE, EMBASE/Excerpta Medica, Cochrane Library, and bibliographies of relevant studies.

Study selection and assessment: English-language, randomized, controlled trials (RCTs); non-RCTs; case series; and cohort studies of patients > 18 years of age who had superficial dermatophytosis (tinea pedis, tinea manus, tinea corpora, and tinea cruris) or onychomycosis and were receiving continuous or intermittent OAT (terbinafide [TBF], itraconazole [ITR], or fluconazole [FLU]) for ≥ 2 weeks. Studies of pharmacokinetics; drug–drug interactions; patients with HIV or AIDS, hematologic or other types of cancer, tinea versicolor, or tinea capitis; or patients receiving bone marrow or organ transplantation or immunosuppressive therapy were excluded. 122 studies met the selection criteria, including 77 RCTs (n = 6640, mean age range 27 to 72 y). 2 reviewers independently assessed individual study quality.

Outcomes: Treatment termination because of adverse events or elevated serum transaminase level (liver injury), and liver injury without treatment termination.

MAIN RESULTS

The pooled absolute risks for treatment termination because of adverse events ranged from 1.5% to 4.2% for continuous OAT and 2.0% to 5.8% for intermittent OAT (Table). OAT and placebo did not differ for incidence of adverse events (Table). The risk for treatment termination because of liver injury and risk for liver injury without treatment termination was < 2% for both continuous and intermittent OAT (Table).

CONCLUSION

Oral antifungal therapy has low risk for adverse events in patients with superficial dermatophytosis or onychomycosis.

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For correspondence: Dr. A.K. Chan, Harvard School of Public Health, Boston, MA, USA. E-mail kachan@hsph.harvard.edu.

Comparisons of continuous or intermittent oral antifungal therapy with placebo in superficial dermatophytosis or onychomycosis*

Oral antifungal therapy	Number of RCTs (n)	Pooled absolute risk (95% CI)		
		TT because of adverse events	TT because of liver injury	Liver injury without TT
Continuous				
TBF, 250 mg/d	41 (3135)	3.4% (2.3 to 4.6)	0.3% (0.09 to 0.6)	0.7% (0.08 to 1.3)
ITR, 100 mg/d	19 (1002)	2.0% (0.4 to 3.6)	0.1% (0 to 0.3)	1.2% (0 to 2.6)
ITR, 200 mg/d	12 (2145)	4.2% (2.3 to 6.1)	0.7% (0.3 to 1.1)	1.9% (0.1 to 3.7)
FLU, 50 mg/d	3 (235)	1.5% (0 to 4.0)	1.2% (0 to 5.3)	1.6% (0 to 5.0)
Intermittent				
TBF, 500 mg/d × 0.25 wk	5 (359)	2.1% (0 to 4.4)	0.6% (0 to 1.3)	0.9% (0 to 2.2)†
ITR, 400 mg/d × 0.25 wk	15 (766)	2.6% (1.2 to 4.0)	0.4% (0 to 0.9)	1.0% (0 to 2.3)
FLU, 150 mg/wk	7 (514)	2.0% (0.1 to 3.9)	0.4% (0 to 0.9)	0.8% (0 to 2.0)
FLU, 300 to 450 mg/wk	3 (468)	5.8% (2.4 to 9.1)	0.8% (0.02 to 1.7)	–
Placebo	15 (891)	3.2% (1.5 to 5.0)	1.0% (0 to 2.2)	1.2% (0 to 3.5)

*FLU = fluconazole; ITR = itraconazole; RCT = randomized controlled trial; TBF = terbinafine; TT = treatment termination; CI defined in Glossary.
†Based on the adjusted Wald method.

COMMENTARY

Fungal infections of the skin, hair, and nails are common in all age groups worldwide. The most common causes are dermatophytes (*Trichophyton* and *Microsporum*) and yeast (*Candida* and *Pityrosporum*). Dermatophytoses, superficial fungal infections called tinea and onychomycosis, respond well to TBF and triazoles (ITR and FLU). Yeast infections respond only to oral triazoles.

The review by Chang and colleagues focused on dermatophytoses and the safety of 3 OATs. Often, patients with dermatophytoses are relatively asymptomatic, so risk aversion is a clinical concern; however, most cases treated with topical therapies do well. This is not true for tinea corporis, hyperkeratotic tinea pedis (moccasin foot), and onychomycosis, where OAT is usually the only treatment that leads to clearance. The results of the review are reassuring for clinicians and patients—the risk for harm to the liver from OAT in most common regimens is low, and severe reactions in the liver and other organs are rare.

Relevant patient groups excluded from the review include those with tinea capitis, a scourge in children. Nail infections with yeast or other nondermatophyte fungi or in diseased nails (e.g., psoriasis) may require longer treatment periods and have higher rates of treatment failure than dermatophytoses. Elderly persons, who are often infected for decades, can have extensive infection of the feet and lower legs, resulting in loss of function and poor wound healing. Studies on the efficacy and safety of antifungal treatments in these groups are lacking.

Drug–drug interactions are important with each OAT. TBF is a potent inhibitor of cytochrome P450 (CYP) 2D6, an enzyme that metabolizes > 40 drugs. ITR inhibits CYP 3A4 and P-glycoprotein, resulting in increased levels of statins and other drugs, such as cyclosporine and benzodiazepines. FLU affects CYP 2C9, an enzyme that metabolizes losartan. Given that patients on concomitant drugs may have the highest clinical need for OAT, management of potential drug–drug interactions is the primary safety concern. For otherwise-healthy adult patients with dermatophytoses of the skin and nails, this review adds to the reassuring evidence about the relative safety of OAT.

Neil H. Shear, MD, FRCPC
University of Toronto
Toronto, Ontario, Canada