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Q / Which oral antifungal works best for toenail onychomycosis?

EVIDENCE-BASED ANSWER

A / TERBINAFINE, 250 mg daily for 12 to 16 weeks, produces higher clinical cure rates than either pulsed-dose itraconazole or weekly fluconazole (strength of recommendation [SOR]: **A**, multiple randomized controlled trials [RCTs]).

Daily oral dosing is more effective than pulsed-dose terbinafine (SOR: **A**, multiple RCTs).

No long-term or large studies have

evaluated terbinafine's safety. However, patients who have diabetes or are older than 65 years who take terbinafine along with antihypertensives, lipid-lowering agents, or "diabetic medications," don't manifest abnormal serum liver enzymes, creatinine, or glucose levels in the short term (SOR: **C**, 2 small cohort studies with disease-oriented outcomes).

Evidence summary

Multiple head-to-head RCTs of oral treatments for toenail onychomycosis demonstrate that terbinafine 250 mg per day for at least 12 weeks is superior to pulse itraconazole, weekly fluconazole, or pulse terbinafine (TABLE).¹⁻⁵ In these studies the number needed to treat (NNT) favoring daily terbinafine ranged from 2 to 12.

Recurrence is less common in patients who take terbinafine daily. In a prospective cohort study of 73 patients (21-81 years of age) followed for 5 years after clinical and mycological cure, onychomycosis recurred in 7 of 59 (12%) patients treated with daily terbinafine and 5 of 14 (36%) treated with pulse itraconazole ($P=.046$; $NNT=4.2$).⁶

No interactions in patients with diabetes, the elderly

A prospective open study of 89 diabetic patients with longstanding toenail onychomycosis, treated with terbinafine 250 mg/d for 12 weeks (mean age 56 years, 42% with insulin-dependent diabetes mellitus), showed a clinical cure rate of 57% at 48 weeks. No hypoglycemic episodes were reported during the treatment phase, and no changes in liver

enzymes or creatinine levels occurred.⁷

An open-label trial of 75 patients older than 65 years compared terbinafine alone (34 patients) with terbinafine and nail debridement (41 patients). Subjects took 250 mg terbinafine per day for 12 weeks; 73 (97.3%) took concomitant medications, including antihypertensives (64%), diabetic medications (25%), and lipid-lowering agents (47%).⁸ No clinically significant drug interactions or elevations in liver function tests occurred. Three patients (4%) withdrew from the study because of drug-related adverse effects (nausea, headache, or flank pain).

Recommendations

No major American medical organization has published guidelines addressing treatment of onychomycosis. The British Association of Dermatologists' guidelines (2003) recommend terbinafine as first-line treatment for fungal toenail infections, with itraconazole as the next best alternative.⁹

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References

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TABLE

Oral treatments for onychomycosis: RCTs reveal how they compare

Total subjects	Mean age, y (range); sex	Follow-up (wk)	Drug	Duration (wk)	Dose (mg)	Frequency	Clinical cure* %	NNT (95% CI)	
151 ¹	48 (18-75); 66% male	Median 234 (range 35-251)	Terbinafine	12-16	250	Daily	42	4 (3-11) [†]	
			Itraconazole	12-16	400	Pulsed: 7 of 28 days	18	—	
496 ²	46 (NA); 58% male	72	Terbinafine	12	250	Daily	54	4 (3-11) [†]	
			Terbinafine	16	250	Daily	60	3 (2-7) [†]	
			Itraconazole	12 or 16	400	Pulsed: 7 of 28 days	32	—	
137 ³	50 (18-75); 48% male	60	Terbinafine	12	250	Daily	67	2 (2-4) [‡]	
			Fluconazole	24	150	Weekly	32	9 (NS) [‡]	
			Fluconazole	12	150	Weekly	21	—	
306 ⁴	64.5 (NA); 96% male	78	Terbinafine	12	250	Daily	45	6 (4-18) [§]	
			Terbinafine	12	350	Pulsed: 14 of 30 days	29	—	
2005 ⁵	50.8 (18-90); 67% male	48	Trial 1	Terbinafine	12	250	Daily	40	10 (6-38) [§]
				Terbinafine	12	350	Pulsed: 14 of 30 days	30	—
			Trial 2	Terbinafine	12	250	Daily	40	12 (7-85) [§]
				Terbinafine	12	350	Pulsed: 14 of 30 days	32	—

CI, confidence interval; NA, not available; NNT, number needed to treat to effect one cure when compared with alternate therapy (see below); NS, not statistically significant; RCT, randomized controlled trial.

*Defined as 100% normal-appearing toenails.

[†]NNT when compared with itraconazole 400 mg pulsed dosing 7 of 28 days.

[‡]NNT when compared with fluconazole 150 mg weekly for 12 weeks.

[§]NNT when compared with terbinafine 350 mg pulsed dosing 14 of 30 days.

^{||}Two studies in reference 5 were run as identical parallel group RCTs; 979 patients completed trial 1, and 1026 patients completed trial 2 (90% completion rate).

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