ClinicalEvidence

Fungal toenail infections

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ABSTRACT

INTRODUCTION: Fungal infections are reported to cause 23% of foot diseases and 50% of nail conditions in people seen by dermatologists, but are less common in the general population, affecting 3–5% of people. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of oral treatments for fungal toenail infections? What are the effects of topical treatments for fungal toenail infections? We searched: Medline, Embase, The Cochrane Library, and other important databases up to May 2008 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 11 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: amorolfine, butenafine, ciclopirox, fluconazole, griseofulvin, itraconazole, ketoconazole, mechanical debridement, terbinafine, and tioconazole.

QUESTIONS

INTERVENTIONS

ORAL TREATMENTS

Beneficial

Likely to be beneficial

Unknown effectiveness

TOPICAL TREATMENTS

Likely to be beneficial

Unknown effectiveness

Key points

- Fungal toenail infection (onychomycosis) is characterised as infection of part or all of the toenail unit, which includes the nail plate, the nail bed, and the nail matrix. Over time, the infection causes discoloration and distortion of part or all of the nail unit.

  Fungal infections are reported to cause 23% of foot diseases and 50% of nail conditions in people seen by dermatologists, but are less common in the general population, affecting 3–5% of people.

  Infection can cause discomfort in walking, pain, or limitation of activities.

- People taking oral antifungal drugs reported greater satisfaction, and fewer onychomycoses-related problems, such as embarrassment, self-consciousness, and being perceived as unclean by others, compared with people using topical antifungals.

  Oral antifungals have general adverse effects including gastrointestinal complaints (such as diarrhoea), rash, and respiratory complaints. It was rare for people to withdraw from an RCT because of adverse effects.

- Both oral itraconazole and oral terbinafine effectively increase cure rates of fungal toenail infection; terbinafine seems slightly more effective.

  Adverse effects unique to terbinafine include sensory loss, such as taste, smell, or hearing disturbance.

- Alternative oral antifungal treatments include fluconazole, which seems to modestly improve cure rates, and ketoconazole and griseofulvin, which may be effective; but the evidence is insufficient to allow us to say for certain.

- Topical ciclopirox seems to modestly improve symptoms of fungal toenail infection compared with placebo.

  We found no evidence examining the effectiveness of other topical agents such as ketoconazole, fluconazole, amorolfine, terbinafine, tioconazole, or butenafine.

We don't know whether mechanical debridement has any effect on fungal toenail infection, as we found no adequate studies.

DEFINITION

Fungal toenail infection (onychomycosis) is characterised as infection of part or all of the nail unit, which includes the nail plate, the nail bed, and the nail matrix. [1] [2] [3] Over time, the infection causes discoloration and distortion of part or all of the nail unit. [4] The tissue under and around the nail may also thicken. This review deals exclusively with dermatophyte toenail infections (see aetiology) and excludes candidal or yeast infections.

INCIDENCE/ PREVALENCE

Fungal infections are reported to cause 23% of foot diseases and 50% of nail conditions in people seen by dermatologists, but are less common in the general population, affecting 3–5% of people. [3] The prevalence varies among populations, which may be due to differences in screening techniques. In a large European project (13,695 people with a range of foot conditions), 35% had a fungal infection diagnosed by microscopy/culture. [5] One prospective study in Spain (1000 adults aged over 20 years) reported a prevalence of fungal toenail infection as 2.7% (infection defined as clinically abnormal nails with positive microscopy and culture). [6] In Denmark, one study (5755 adults aged over 18 years) reported the prevalence of fungal toenail infection as 4.0% (determined by positive fungal cultures). [7] The incidence of mycotic nail infections may have increased over the past few years, perhaps because of increasing use of systemic antibiotics, immunosuppressive treatment, more advanced surgical techniques, and the increasing incidence of HIV infection. [8] However, this was contradicted by a study in an outpatient department in Eastern Croatia, which compared the prevalence of fungal infections between two periods (1986–1988, 47,832 people; 1997–2001, 75,691 people). [9] It found that the prevalence of fungal infection overall had increased greatly over the 10 years, but that the percentage of fungal infections affecting the nails had decreased by 1% (fungal infections overall: 0.26% in 1986–1988 *v* 0.73% in 1997–2001; nail: 10.31% in 1986–1988 *v* 9.31% in 1997–2001).

AETIOLOGY/ RISK FACTORS

Fungal nail infections are most commonly caused by anthropophilic fungi called dermatophytes. The genera *Trichophyton*, *Epidermophyton*, and *Microsporum* are typically involved, [1] specifically *T rubrum*, *T mentagrophytes* var *interdigitale*, and *E floccosum*. Other fungi, moulds, or yeasts may be isolated, such as *Scopulariopsis brevicaulis*, *Aspergillus*, *Fusarium*, and *Candida albicans*. [3] *T rubrum* is now regarded as the most common cause of onychomycosis worldwide. [10] Several factors that increase the risk of developing a fungal nail infection have been identified. One survey found that 26% of people with diabetes had onychomycosis, and that diabetes increased the risk of infection, but the type and severity of diabetes was not correlated with infection (OR 2.77, 95% CI 2.15 to 3.57). [11] Another survey found that peripheral vascular disease (OR 1.78, 95% CI 1.68 to 1.88) and immunosuppression (OR 1.19, 95% CI 1.01 to 1.40) increased the risk of infection. These factors may explain the general increase in prevalence of onychomycosis in the elderly population. [12] Environmental exposures such as occlusive footwear or warm, damp conditions have been cited as risk factors, as has trauma. [2] [12] Fungal skin infection has been proposed as a risk factor. [3] [10] [12] However, one large observational study, which included 5413 people with positive mycology, found that only a small proportion (21.3%) had both skin and toenail infections. [12]

PROGNOSIS

Onychomycosis does not have serious consequences in otherwise healthy people. However, the Achilles project (846 people with fungal toenail infection) found that many people complain of discomfort in walking (51%), pain (33%), or limitation of their work or other activities (13%). [5] Gross distortion and dystrophy of the nail may cause trauma to the adjacent skin, and may lead to secondary bacterial infection. In immunocompromised people, there is a risk that this infection will disseminate. Quality-of-life measures specific to onychomycosis have recently been developed. Studies using these indicators suggest that onychomycosis has negative physical and psychosocial effects. [13] [14] [15]

AIMS OF INTERVENTION

To eradicate fungal spores from the nail unit (nail bed, matrix, or plate); to allow a normal nail to regrow if permanent damage to the nail matrix has not occurred.

OUTCOMES

Negative microscopy and culture; satisfaction with treatment; adverse effects of treatment, especially liver failure.

METHODS

Clinical Evidence search and appraisal May 2008. The following databases were used to identify studies for this review: Medline 1966 to May 2008, Embase 1980 to May 2008, and The Cochrane Library, Issue 2, 2008. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE clinical guidelines. Abstracts of the studies retrieved were assessed independently by two information specialists using

predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 people of whom more than 80% were followed up. The minimum length of follow-up required was 3 months to include studies. We excluded all studies described as "open", "open label", or not blinded unless the interventions could not be blinded. RCTs of treatment in fingernails and of infections related to candidal and yeast infections were also excluded. We considered systematic reviews, RCTs, and observational studies for the harms because of the potentially serious nature of the harms (liver failure). In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are continually added to the review as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 14). To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs.

QUESTION What are the effects of oral treatments for fungal toenail infections?

OPTION ITRACONAZOLE (ORAL)

Cure rate
Compared with placebo Oral itraconazole may be more effective at curing fungal toenail infection (very low-quality evidence).

Compared with oral griseofulvin Oral itraconazole and oral griseofulvin may be equally effective at curing fungal toenail infection after 24–72 weeks (very low-quality evidence).

Compared with oral terbinafine Oral itraconazole may be less effective at curing fungal toenail infection after 12–16 weeks' treatment (very low-quality evidence).

Pulsed oral itraconazole compared with continuous oral itraconazole Pulsed oral itraconazole for 3–4 months and continuous oral itraconazole may be equally effective at curing fungal toenail infection (low-quality evidence).

Compared with topical treatments Oral antifungal treatment may lead to greater patient satisfaction after 9 months (very low-quality evidence).

Note
We found no clinically important results about the effects of oral itraconazole compared with oral ketoconazole or oral fluconazole.

For GRADE evaluation of interventions for fungal toenail infections, see table, p 14 .

Benefits:

Oral itraconazole versus placebo:
We found one systematic review (search date 2000). [16] It found that 12 weeks of itraconazole 200 mg daily significantly increased cure rates at the end of treatment compared with placebo (3 RCTs, 433 people with fungal toenail infection; AR: 63% with itraconazole *v* 4% with placebo; ARI 60%, 95% CI 54% to 67%).

Oral itraconazole versus oral griseofulvin:
See benefits of oral griseofulvin, p 7 .

Oral itraconazole versus oral terbinafine:
We found one systematic review (search date 2000, 4 RCTs) [16] and one subsequenl RCT. [17] The first and second RCTs identified by the review found that 12 weeks of itraconazole 200 mg daily produced significantly lower cure rates compared with 12 weeks of terbinafine 250 mg daily at about 1 year (501 people with fungal toenail infection; AR: 69% with terbinafine *v* 48% with itraconazole; ARR 21%, 95% CI 13% to 29%). The third RCT identified by the review compared three treatments given for 16 weeks: pulsed itraconazole (400 mg/day for 1 week in every 4 weeks); pulsed terbinafine (500 mg/day for 1 week in every 4 weeks); and continuous terbinafine 250 mg daily. It found no significant difference in cure rates between pulsed itraconazole and continuous terbinafine at 43 weeks (60 people with fungal toenail infection; AR: 75% with itraconazole *v* 84% with continuous terbinafine; ARR +9%, 95% CI –34% to +16%). The fourth RCT identified by the review compared four treatments: pulsed itraconazole for 12 weeks (400 mg/day for 1 week in every 4 weeks); pulsed itraconazole for 16 weeks (regimen as for 12-week treatment); continuous terbinafine for 12 weeks 250 mg daily; and continuous terbinafine 250 mg daily for 16 weeks. It found that pulsed itraconazole produced significantly lower cure rates compared with continuous terbinafine, regardless of duration, at 72 weeks (250 people with fungal toenail infection; AR after

12 weeks' treatment: 33% with itraconazole *v* 65% with terbinafine; ARR 33%, 95% CI 21% to 44%; 246 people with fungal toenail infection; AR after 16 weeks' treatment: 42% with itraconazole *v* 67% with terbinafine; ARR 25%, 95% CI 13% to 37%).

The subsequent RCT (70 people with diabetes and dermatophyte toenail distal and lateral subungual onychomycosis) compared oral pulsed itraconazole (200 mg twice daily, 1 week on/3 weeks off for 12 weeks) versus oral terbinafine (250 mg/day for 12 weeks). [17] The RCT found no significant difference in cure rates between groups at 48 weeks (30/35 [88%] with pulsed itraconazole *v* 23/29 [77%] with continuous terbinafine; ARR 11.5%, 95% CI –5.2% to 28.2%). [17]

Oral itraconazole versus oral ketoconazole:
We found one systematic review (search date 2000), which found no RCTs.

Oral itraconazole versus oral fluconazole:
We found one systematic review (search date 2000), which found no RCTs. [16]

Pulsed versus continuous oral itraconazole:
We found one systematic review (search date 2000, 3 RCTs). [16] The first RCT identified by the review found no significant difference in cure rates between 12 weeks of continuous itraconazole (200 mg/day) and 12 weeks of pulsed itraconazole (400 mg/day for 1 week in every 4 weeks) at 52 weeks (121 people with fungal toenail infection; AR: 66% with continuous itraconazole *v* 69% with pulsed itraconazole; ARR +3%, 95% CI –10% to +20%). The second RCT identified by the review found no significant difference in cure rates between 3 and 4 months of pulsed itraconazole (400 mg/day for 1 week in every 4 weeks) at 24 weeks (50 people with fungal toenail infection; AR: 64% with 3 months and 72% with 4 months; ARR +8%, 95% CI –20% to +30%). The third RCT identified by the review found no significant difference in cure rates between 12 or 16 weeks of continuous itraconazole (200 mg/day) and 12 or 16 weeks of pulsed itraconazole (200 mg/day for 1 week in every 4 weeks) at 48 weeks (64 people with fungal toenail infection; AR after 12 weeks' treatment: 68% with continuous itraconazole *v* 50% with pulsed itraconazole; ARI +18%, 95% CI –50% to +40%; AR after 16 weeks' treatment: 64% with continuous itraconazole *v* 64% with pulsed itraconazole; ARR 0%, 95% CI –34% to +34%).

Oral itraconazole versus topical treatments:
We found no systematic review or RCTs. We found one longitudinal study comparing oral antifungals versus topical treatments (see comment on oral griseofulvin, p 7).

Harms:

Oral itraconazole versus oral griseofulvin:
See harms of oral griseofulvin, p 7 .

Oral itraconazole versus oral terbinafine:
The RCT of pulsed itraconazole versus continuous terbinafine in people with diabetes mellitus reported that only one person in the itraconazole group withdrew due to gastic pain. [17] There were no other serious adverse events or interactions with normal medications. [17]

Re-infection rates:
One open-label RCT comparing oral itraconazole (400 mg/day for 1 week in every 4 for 12 weeks) versus oral terbinfine (250 mg/day for 12 weeks) recorded the number of people initially considered cured (mycological cure) and who then became re-infected with either the same or a different fungal species during the course of the study (relapsed). [18] At the final follow-up (96 weeks), 21% of people in the itroconazole group versus 14% of the terbinafine group were found to have a further infection. This was reported to be non-significant (P greater than 0.05). [18]

Comment:

See comment on oral griseofulvin, p 7 .

Oral itraconazole versus placebo:
Outcomes were measured at 12 weeks. It is more clinically relevant to measure outcomes after at least 9 months, because it takes at least 6 months for the toenail to regrow completely.

OPTION ORAL TERBINAFINE (ORAL)

Cure rate
Compared with placebo Oral terbinafine for 12–24 weeks may be more effective at curing fungal toenail infection (very low-quality evidence).

Compared with oral itraconazole Oral terbinafine may be more effective at curing fungal toenail infection after 12–16 weeks' treatment (very low-quality evidence).

Compared with oral griseofulvin Oral terbinafine may be more effective at curing fungal toenail infection after 24–52 weeks' treatment (low-quality evidence).

Compared with oral terbinafine plus topical ciclopirox Continuous terbinafine alone for 12 weeks and pulsed or continuous terbinafine for 12 weeks plus topical ciclopirox for 48 weeks may be equally effective at curing fungal toenail infection (moderate-quality evidence).

Adverse effects
Terbinafine has been associated with hepatotoxicity, but serious adverse effects are rare.

Note
We found no clinically important results about the effects of oral terbinafine compared with ketoconazole or fluconazole.

For GRADE evaluation of interventions for fungal toenail infections, see table, p 14 .

Benefits:

Oral terbinafine versus placebo:
We found one systematic review (search date 2000, 5 RCTs). [16] The review found that 12 weeks of terbinafine 250 mg daily significantly increased cure rates at the end of treatment compared with placebo (3 RCTs, 337 people with fungal toenail infection; AR: 63% with terbinafine *v* 20% with placebo; ARI 43%, 95% CI 34% to 53%). The review identified two further RCTs, which could not be included in the meta-analysis because they examined different terbinafine regimens. The first of these RCTs found that 12 and 24 weeks of terbinafine 250 mg daily significantly increased cure rates at 48 weeks compared with placebo (353 people with fungal toenail infection; AR after 12 weeks' treatment: 70% with terbinafine *v* 8% with placebo; ARI 62%, 95% CI 52% to 72%; AR after 24 weeks' treatment: 87% with terbinafine *v* 8% with placebo; ARI 79%, 95% CI 70% to 87%). The second of these RCTs found that 12, 16, and 24 weeks of terbinafine 250 mg daily significantly increased cure rates at 72 weeks compared with placebo (109 people with fungal toenail infection; AR after 12 weeks' treatment: 38% with terbinafine *v* 0% with placebo; ARI 38%, 95% CI 20% to 50%; AR after 16 weeks' treatment: 37% with terbinafine *v* 0% with placebo; ARI 37%, 95% CI 21% to 56%; AR after 24 weeks' treatment: 65% with terbinafine *v* 0% with placebo; ARR 65%, 95% CI 46% to 81%).

Oral terbinafine versus oral griseofulvin:
See benefits of oral griseofulvin, p 7 .

Oral terbinafine versus oral itraconazole:
See benefits of oral itraconazole, p 3 .

Oral terbinafine versus oral ketoconazole:
We found one systematic review (search date 2000), which found no RCTs. [16]

Oral terbinafine versus oral fluconazole:
We found one systematic review (search date 2000), which found no RCTs. [16]

Oral terbinafine versus topical treatments:
We found one RCT comparing three treatments: topical ciclopirox daily for 48 weeks plus pulsed terbinafine for the initial 12 weeks (250 mg daily for 4 weeks daily/4 weeks rest/4 weeks daily); topical ciclopirox plus continuous terbinafine for 12 weeks followed by topical ciclopirox alone for 36 weeks; and continuous terbinafine alone for 12 weeks. [19] The RCT found no significant difference between the three treatments in mycological cure rates at 48 weeks (73 people; 14/21 [67%] with ciclopirox plus pulsed terbinafine *v* 19/27 [70%] with ciclopirox plus continuous terbinafine *v* 14/25 [56%] with continuous terbinafine alone; P value for overall comparison reported as not significant). We found also one longitudinal study comparing oral antifungals versus topical treatments (see comment on oral griseofulvin, p 7).

Harms:

Adverse events unique to terbinafine include sensory loss such as taste, smell, or hearing disturbance (see harms of oral griseofulvin, p 7 and harms of oral itraconazole, p 3).

Oral terbinafine versus topical treatments:
The RCT found that the incidence of adverse events (including gastrointestinal effects, and subcutaneous tissue and skin disorders) was similar between the three treatment groups (20.5% with ciclopirox plus pulsed terbinafine *v* 21.4% with ciclopirox plus continuous terbinafine *v* 22.0% with continuous terbinafine alone; significance not reported). No participants withdrew because of adverse events. One open-label RCT (249 people) compared amorolfine hydrochloride (5% nail lacquer for 12 months) plus oral terbinafine (250 mg/day for 3 months) versus terbinafine alone (250 mg/day for 3 months). [20] The study reported adverse effects in 15/103 (12%) people with terbinafine alone versus 19/105 (16%) people with combination treatment (no significance assessment between

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