Which drug is most effective in treating childhood tinea capitis caused by *Microsporum* species?

Trial: Lipozencic J, Skerlev M, Orofino-Costa R, et al, and the Tinea Capitis Study Group.
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Question

What is the optimum duration for oral terbinafine therapy when treating children with tinea capitis caused by *Microsporum* species? How do these terbinafine dose schedules compare in effectiveness to griseofulvin?

Trial details

Design: Four double-blind duration-finding terbinafine arms were compared with an unblinded griseofulvin arm. Each arm was parallel, and patients were randomly allocated. The study duration was 12 weeks with a 4-week follow-up. Mycological assessment and clinical assessment were performed at entry, every 2 weeks, and at follow-up.

Clinical signs assessed were erythema, scaling, papules, pustules and pruritis. Each was rated on a scale of 0 (absent) to 3 (severe), and individual scales were summed at each assessment.

Direct mycological microscopy was performed at each visit to the local centre. Cultures were taken at the initial and all subsequent visits, and referred to a central laboratory. The study was sponsored by the manufacturer of terbinafine.

Setting: 22 centres in Europe and South America.

Patients: 165 children with *Microsporum* tinea capitis proven by culture. Their mean age was 7.7 years, 67% weighed 20–40 kilograms, and 77% of patients were white. Patients in each arm seemed similar.

Interventions: The 4 terbinafine arms were double blinded. Terbinafine dosage was based on a patient bodyweight formula (62.5 mg/day if < 20 kg, 125 mg/day if 20–40 kg and 250 mg/day if > 40 kg bodyweight). Patients in Arm 1 had 6 weeks terbinafine treatment plus 6 weeks placebo; those in Arm 2 had 8 weeks terbinafine plus 4 weeks placebo; those in Arm 3 had 10 weeks terbinafine plus 2 weeks placebo; those in Arm 4 had 12 weeks terbinafine treatment; and those in Arm 5 had 12 weeks griseofulvin (oral suspension) at 20 mg/kg/day, and this arm was unblinded.

Main outcome measure: Complete cure (CC) was assessed as negative results on mycological studies and no clinical signs at the finish. Effective treatment (ET) was assessed as negative culture and a clinical score of < 2 at the finish; clinical cure was absence of signs and symptoms; mycological cure was negative microscopy and negative culture. The primary efficacy was CC rate at the end of the study.

Main results: In 134 intention-to-treat patients, 6 weeks of terbinafine therapy gave 62% CC and 62% ET, 8 weeks gave 60% CC and 63% ET, 10 weeks gave 48% CC and 59% ET, and 12 weeks gave 43% CC and 52% ET. This compared with 84% CC and 88% ET for 12 weeks of therapy with griseofulvin.

Conclusion: Terbinafine treatment for 6 or 8 weeks seemed more effective than 10 or 12 weeks. Terbinafine therapy for 6 weeks could represent an alternative to griseofulvin. There might be some correlation between the daily dose of terbinafine (mg/kg) and complete cure.

Commentary

Rationale for the trial

Tinea capitis is infectious and caused by a variety of fungi. *Trichophyton* species predominate in Australia, but *Microsporum* species predominate in other parts of the world.[1] *Microsporum* species are mainly acquired from pets (cats and dogs). Fungal infection of hair requires oral treatment as topical therapy is rarely sufficient.

Griseofulvin is the most commonly prescribed treatment. It is cheap, relatively safe, effective and fungistatic. In contrast, terbinafine is fungicidal, but more expensive.[2] Terbinafine seems more effective against *Trichophyton* infections than *Microsporum* infections,[3] and, in this trial, the terbinafine manufacturer sought to determine the optimum duration of terbinafine treatment in *Microsporum* tinea capitis.

Microsporum tinea capitis occurs primarily in children, so information on efficacy and dose duration of terbinafine from adult studies may not be applicable. It might be predicted that longer courses of terbinafine would be more effective than shorter courses, as this has been the experience when treating fungal infections of the nails with terbinafine. There was therefore a need to examine this issue by means of a randomised controlled trial.

Therapeutic studies in children present particular ethical questions about informed consent and study design. The drug industry has been criticised for seeming to be unwilling to run trials in children.[4] The manufacturer of terbinafine is to be congratulated for attempting to redress this situation and for ensuring publication in spite of equivocal results.

Trial methods

This was a multicentre trial in Europe and South America. Conducting a trial of 165 patients in 22 centres does raise questions on the rigour of ensuring the trial requirements are met equally by all the participants. It is not clear whether the centres were private or public institutions. If any financial payments were made, these were not made explicit.

Both the clinical and microscopic assessments at the 22 centres may have had problems of standardisation and reliability. In the assessment of all arms of the trial, the rate of clinical cure was 20% higher than the cure rate based on the results of the fungal tests, suggesting that clinical assessment of tinea capitis may have significant reliablity problems. Direct fungal microscopy was performed at each centre, while culturing was performed at a central laboratory. It was not specified whether direct microscopy was of scale or hair or both, nor how independent the laboratory was from the trialists or the pharmaceutical company.

The terbinafine arms were blinded while the griseofulvin arm was not, presumably because the appearance of the tablets would have made it obvious what was being given. The participants in all arms, including the griseofulvin arm, were randomly allocated according to a predetermined computer-generated randomisation code produced by Novartis Pharma AG (Basel, Switzerland), with what seems appropriate concealment and an equivalent spread of patients. Inclusion criteria and exclusion criteria were equalised and reasonable. The dropout rate was smaller than I would have expected, and highest in the 12-week terbinafine arm (12 discontinued, 20 completed). A similar previous trial involving six centres in the United Kingdom had a higher dropout rate.[2]

Griseofulvin therapy is the present standard practice for most patients with tinea capitis. The recommended dose of griseofulvin is 10–25 mg/kg/day for 8–10 weeks, so the dosage used in this study does reflect clinical practice.[5] Griseofulvin was significantly more effective than terbinafine in this study.

It could be argued that a larger number of patients would have generated more powerful and reliable statistical evidence, but there are practical and ethical restrictions in conducting a study in children. By choosing 165 patients, it was hoped to allow 25 evaluable patients in each arm, to provide 79% power to detect a cure trend ranging from 30% to 70% with various terbinafine arms. Surprisingly, the 10-week and 12-week duration arms were much less effective than the 6-week and 8-week arms.

The logistic regression analysis of terbinafine therapies suggested a tendency to a higher cure rate at higher daily doses, and a lower cure rate with longer duration of treatment.

Safety

Adverse events such as fever, pharyngitis and influenza-like symptoms occurred in 18%–42% of patients in the terbinafine groups and 17% in the griseofulvin group. The 12-week terbinafine arm had 12 patients (of 32) who did not complete the study. Tolerability and laboratory profiles were similar between terbinafine and griseofulvin. Two significant adverse events (reversible neutropenia in one patient and urticaria in another) were assessed as being caused by terbinafine.

New information

This study has shown that griseofulvin is a more effective therapy than terbinafine in children with tinea capitis caused by *Microsporum* infection. Surprisingly, a prolonged course of terbinafine does not increase the effectiveness of this therapy. This is an important observation.

Implications for clinical practice

Long-term terbinafine therapy cannot be recommended on the evidence of this trial. Griseofulvin remains the treatment of choice for *Microsporum* tinea capitis, and is certainly more cost effective.

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Competing interests

None identified.

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