Recurrent tinea versicolor: treatment with itraconazole or fluconazole?

Report by

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A 14-year-old girl is seen in the paediatric outpatient department. She was referred by her general practitioner (GP) with persistent tinea versicolor. The GP had previously treated her with topical clotrimazole over the last few years with varying degree of success. The girl has recently returned from a trip to South America during which she experienced an exacerbation of her symptoms.

On examination you find multiple oval to round shaped lesions which are hypopigmented with superficial scaling, that appear particularly prominent in the axillary region and around the neck. The girl tells you that these areas had previously been darker than the surrounding skin, which was more obvious during the winter months. Under Wood's light examination the lesions appear fluorescent yellow. You obtain samples for microbiological confirmation but concur with the GP that this is tinea versicolor.

The girl expresses her distress about her external appearance and is very keen to finally get rid of this problem. You wonder whether oral antifungal agents may provide a more effective alternative to topical treatment and consult the British National Formulary for Children (BNFC 2006). The formulary states that oral itraconazole should be considered if topical treatment has failed. It also mentions that fluconazole may be used as an alternative. You wonder which of these treatment options is more effective in tinea versicolor.

Structured clinical question

In a child/adolescent with tinea versicolor [patient] is oral itraconazole more effective than oral fluconazole [intervention] as regards cure [outcome]?

Search strategy and outcome

Cochrane Library using the terms "pityriasis versicolor" and "tinea versicolor": no relevant reviews.

PubMed (1950–to date/no limits set) using the terms "Pityrosporum versicolor", "Pityrosporum orbiculare", "Malassezia furfur", "pityriasis versicolor" and "tinea versicolor" in combination with [AND] itraconazole [AND] fluconazole. Search date 19 November 2006. Results in the same order: 8, 11, 14, 18 and 16 articles. There was considerable overlap between the results produced by the different search terms. Only three articles were relevant which are summarised in table 3.^{1–3}

EMBASE database (1974–to date) using the same set of search terms employed in the PubMed search – results in the same order as above: 0, 4, 34, 28 and 20 articles. This search identified two further relevant publications. One report of an RCT comparing both drugs was published in Turkish only (abstract available in English) and had to be excluded since the details available to us were insufficient, while the second article is summarised in table 3.⁴

Search of multiple trials registers: UK National Research Register (NRR and MRC), ISRCTN, NIH: no relevant studies identified.

Search date: 9 December 2006.

Commentary

Tinea versicolor, also called pityriasis versicolor, is a common skin condition which is caused by a superficial cutaneous infection with the fungal agent *Malassezia furfur* (previously *Pityrosporum versicolor* or *Pityrosporum orbiculare*). The infection occurs worldwide, with prevalences from 0.5% in temperate climates up to 18% in humid tropical climates reported in the literature.^{5–6} Tinea versicolor predominately affects adolescents and adults, but infection as early as in infancy has been described.

The typical clinical finding consists of multiple, oval lesions with fine scaling, which are predominately distributed over the upper areas of the trunk, the upper arms and the neck. Facial involvement is particularly common in children. The lesions may be hypopigmented or hyperpigmented and are frequently associated with pruritus. The areas typically fail to tan during the summer and appear darker than the surrounding unaffected skin in the winter months when they appear yellow to brown in colour. The diagnosis can be confirmed by demonstrating fluorescence under Wood's light (ultraviolet light), microscopic examination of a potassium hydroxide (KOH) preparation or with fungal cultures of skin scrapings.

Although the infection does not pose a significant health risk to the affected individual, the psychological and social implications can be profound. Spontaneous remission is generally rare. Topical treatment as a first line intervention can be curative, for which purpose clotrimazole, econazole, ketoconazole, miconazole or terbinafine can be used. However, some patients do not respond satisfactorily or experience multiple relapses and may require systemic treatment, particularly when large areas are affected. In these circumstances "azole" antifungal drugs, which include fluconazole, itraconazole and ketoconazole, are considered to be the treatment of choice.

None of the studies we identified in our search was conducted in paediatric patients. However, previous studies in children using itraconazole and fluconazole for other purposes have demonstrated that both drugs are generally safe and well tolerated in this age group.^{7–8} Side effects mainly consist of transient, mild elevation of liver function tests and gastrointestinal symptoms.

There is little consensus regarding the optimal dosing regimen and duration of treatment with systemic antifungal agents. The BNFC suggests a 7-day course with itraconazole or a 2–4-week course with fluconazole for the treatment of tinea versicolor. Interestingly, a randomised controlled trial in adults has demonstrated that single high dose (400 mg) fluconazole treatment can be as effective as a prolonged 4-week course with lower doses with regard to clinical cure.⁹

All of the studies, with the exception of the report by Silva *et al*, were rather small and therefore may have been insufficiently powered to demonstrate a significant difference between treatment groups. Regarding clinical cure and improvement, all of the studies included have reported marginally better results with fluconazole, with the exception of the article by Montero-Gei *et al*. However, in all four studies the difference between both treatment groups was small and statistically not significant. Similarly, none of the studies demonstrated a statistically significant difference between the two treatment options regarding mycological cure or eradication rates. Nevertheless, the study by Partap *et al*, in which single dose itraconazole was compared with single dose fluconazole, showed that 65% of patients who had received fluconazole became culture negative at 8 weeks (ie, mycological cure), while this was achieved in only 20% of patients treated with itraconazole.

Table 3 Itraconazole versus fluconazole in the treatment of tinea versicolor

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Partap <i>et al</i> (2004) ¹	40 consecutive patients with >15% skin surface area involvement Case definition: culture positive for <i>Malassezia furfur</i> +skin changes All patients >16 years (mean age 26.7 years, range 17–55 years) Patients randomly assigned to treatment with fluconazole (400 mg single dose) or itraconazole (400 mg single dose)	Individual RCT (level 1b)	Resolution of hypo-/hyperpigmentation at 8 weeks Mycological cure: defined as culture negative at 2 and 8 weeks Relapse: defined as reappearance or worsening of clinical signs and symptoms or positive culture after initial improvement	Fluconazole group: 20% pigmentation changes resolved, 80% mild residual hypochromia Itraconazole group: 5% pigmentation changes resolved, 95% mild residual hypochromia (not statistically significant) Cultures at 2 and 8 weeks: fluconazole group 10% and 65% negative, respectively, itraconazole group 30% and 20% negative Relapse rate: fluconazole 35%, itraconazole 60% (statistically significant, $p<0.05$)	Exclusion criteria: patient used antifungal treatment less than 3 weeks prior to the study No blinding of patients or investigators Full blood count, liver and renal function tests were monitored: no abnormalities detected Clinical side effects: only one patient developed headache and loose stools (likely unrelated to medication)
Kose (1995) ²	64 consecutive patients with recurrent and/or extensive tinea versicolor (age range: 19–42 years). Patients received either fluconazole (300 mg bd) or itraconazole (200 mg bd) for 2 weeks	Individual RCT (level 1b)	Clinical cure: defined as resolution of scaling, pigmentation changes and pruritus Mycological cure: defined as negative microscopy and Wood's light examination Relapse: not explicitly defined, assessed at 12 weeks	Clinical cure: 80% of patients treated with fluconazole, 74% with itraconazole (not statistically significant) Mycological cure: 88% in fluconazole group, 80% in itraconazole group (not statistically significant) Relapse rate: 14% in fluconazole group, 20% in itraconazole group	Process of randomisation not described No blinding of patients or investigators 12 patients excluded from analysis (reasons not given): 5 in fluconazole and 7 in itraconazole group Full blood count, liver and renal function tests were monitored: no abnormalities detected Reported side effects: only mild gastrointestinal upset (2 cases in the fluconazole and 3 in the itraconazole group)
Montero-Gei <i>et al</i> (1999) ³	90 patients with tinea versicolor (ages not given). Patients received fluconazole 450 mg single dose (SD), or fluconazole 300 mg two doses 1 week apart (TD), or itraconazole 200 mg daily for 7 days	Multicentre open label RCT (level 1b)	Assessments carried out at day 14, 30 and 60 Clinical signs: erythema, scaling, pigmentation changes scored by investigators on a scale of 0–3 (not present–severe) Mycological efficacy assessed by microscopy of skin scrapings and classified as eradication, persistence or eradication with re-infection	Clinical cure at day 60: 52% with fluconazole SD, 70% with fluconazole TD, 74% with itraconazole (no statistically significant difference between the latter 2 groups) Mycological eradication at day 60: 55% with fluconazole SD, 77% with fluconazole TD, 78% with itraconazole	Process of randomisation not described No blinding of patients or investigators No clinical side effects were reported by the participants
Silva <i>et al</i> (1998) ⁴	388 patients with mycologically proven tinea versicolor (age 16–86 years) Case definition: presence of <i>M furfur</i> on microscopic examination and positive Wood's light test. Patients were randomised to receive either fluconazole (104 patients, 300 mg od, 2 doses 1 week apart; 90 patients, 3 doses total), or itraconazole (200 mg for 7 days) or ketoconazole (200 mg for 10 days) or 1% clotrimazole cream (bd for 21 days)	Three open label RCTs, multicentre (level 1b) Each part of the study evaluated the response to fluconazole vs one of the "comparators" (itraconazole, ketoconazole, clotrimazole)	Assessments carried out at day 14, 30 and 60 Clinical cure: defined as resolution of scaling and pruritus Clinical relapse: cure followed by reappearance or worsening of signs and symptoms Mycological cure: disappearance (eradication) of <i>M furfur</i> on microscopy Reinfection: complete eradication with subsequent reappearance of the organism	Clinical cure+improvement at day 60: fluconazole 86%, itraconazole 83.5% (not statistically significant) Clinical relapse at day 60: fluconazole 2.3%, itraconazole 5.9% (not statistically significant) Mycological cure at day 60: fluconazole 77.6%, itraconazole 76.5% Reinfection at day 60: fluconazole 5.9%, itraconazole 15.3% (? no significance calculated)	No blinding of patients or investigators Criteria for decision to give third dose of fluconazole not sufficiently described Fluconazole group was composed of patients who have received either 2 or 3 doses Five patients reported side effects consisting of mild gastrointestinal upset Full blood count, liver and renal function tests were monitored: no abnormalities detected

The most striking difference between the two treatment options seems to occur in relation to clinical and mycological relapses. Three of the studies assessed the clinical relapse rate. The study by Partap *et al* demonstrated a statistically significant ($p<0.05$) higher proportion of relapses in the itraconazole treatment group (60% vs 35% in the fluconazole group). A similar trend, although this did not achieve statistical significance, was observed by Kose *et al*. Silva *et al* reported that reinfection had occurred in 15.3% of

patients treated with itraconazole in comparison to only 5.9% of patients in the fluconazole group, but did not state whether this was statistically significant. Using the data provided in the publication, we have calculated that the reinfection rate was in fact significantly higher in the itraconazole group ($p = 0.041$ in χ^2 test, Pearson uncorrected; $p = 0.048$ in Fisher exact, two tailed).

Although it appears likely that the data from these adult studies can be directly extrapolated to children, a sufficiently

powered study comparing fluconazole with itraconazole in paediatric patients suffering from tinea versicolor, with a long follow-up period that would allow the evaluation of relapse rates, would be desirable. Since there is evidence from adult studies that a single high-dose antifungal treatment can be as successful as a prolonged course, such a study should ideally re-evaluate the dosing and duration of treatment for both agents. Ultimately, a shorter treatment course would reduce costs and potentially minimise the risk of adverse events.

CLINICAL BOTTOM LINE

- There are no published paediatric studies which have compared the efficacy of itraconazole versus fluconazole for the treatment of tinea versicolor.
- Evidence from adult studies suggests that the initial cure rates with both drugs are comparable. (Grade A)
- There is some evidence from adult studies that relapses are less frequent with fluconazole treatment. (Grade A)

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