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Griseofulvin vs. Terbinafine in the Treatment of Tinea Capitis

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ABSTRACT

Background: Two oral antifungal agents, griseofulvin and terbinafine, have regulatory approval but it is unknown whether one has superior overall efficacy. Genus-specific differences in efficacy are believed to exist for the two agents. It is not clear at what doses and durations of treatment these differences apply.

Purpose: The purposes of this meta-analysis were to determine whether a statistically significant difference in efficacy exists between these agents at a given dose and duration of each in tinea capitis infections overall and to determine whether a genus-specific difference in efficacy exists for these two treatments at a given dose and duration of each. We performed a literature search for clinically and methodologically similar randomized controlled trials comparing 8 weeks of griseofulvin (6.25–12.5 mg⁄kg⁄day) to 4 weeks of terbinafine (3.125–6.25 mg⁄kg⁄day) in the treatment of tinea capitis. A meta-analysis was performed using the Mantel–Haenszel method and random effects model; results were expressed as odds ratios with 95%.

Results: Meta-analysis of randomized controlled trials did not show a significant difference in the overall efficacy of the two drugs at the doses specified, but specific efficacy differences were observed based on the infectious species. For tinea capitis caused by Microsporumspp., griseofulvin is superior ($p = 0.04$), whereas terbinafine is superior for Trichophyton spp. infection ($p = 0.04$).

Conclusion:Our results support species-specific differences in treatment efficacy between griseofulvin and terbinafine and provide a clinical context in which this knowledge may be applied.

Keywords: Griseofulvin, Terbinafine, Tinea Capitis.

INTRODUCTION

Tinea capitis is a fungal infection of the hair and scalp with worldwide distribution, affecting commonly prepubertal children. It is caused by the dermatophyte genera Trichophyton and Microsporum. The mid-20th century saw a shift in main genus from Microsporum to Trichophyton following the introduction of griseofulvin and the availability of the Wood's lamp for diagnosing Microsporum infections [(1)]. After its introduction in 1958, griseofulvin became the treatment of select for tinea capitis and remained popular for decades. Terbinafine was first introduced to the U.S. market as a treatment for onychomycosis in the 1990s and subsequently gained popularity as an off-label treatment for tinea capitis. Lately a new formulation of the drug (oral granules) has gained marketing approval for tinea capitis in the United States. Griseofulvin and terbinafine have been shown to be safe and efficacious in the treatment of tinea capitis, but whether one of these agents has superior overall efficacy is unresolved.

A number of clinical trials comparing griseofulvin and terbinafine have been published, yielding mixed outcomes as to superiority [(2-7)]. Meta-analyses of these trials have consequently been performed in a challenge to synthesize the obtainable data into a clear conclusion [(6, 7)]. These analyses have accordingly far failed to detect a statistically significant difference between the two drugs, generally, while latest reviews presented that terbinafine is more effective for Trichophyton spp. and griseofulvin for Microsporum spp. [(8, 9)].Previous meta-analyses have assembled the outcomes from all available randomized controlled trials (RCTs) in an effort to boost statistical power. This forces the combining of data from studies that might be clinically and methodologically diverse. Study characteristics can impact efficacy results, so combining data in this manner might avoid detection of a real difference in efficacy.

This method can similarly be problematic if a difference is detected between the two treatment groups. The heterogeneity in the treatment procedures could make it difficult to define which dose and period is the most effective of the combined treatments. It can moreover be problematic because there might be a hierarchy of response in which certain doses and periods might not conform to the combined efficacy measures. At certain doses and durations of treatment, for

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instance, a difference between two drugs could cease to exist or even become reversed. This poses a challenge when attempting to apply the results of these studies to clinical practice.

The objectives of the present study were to determine, by meta-analysis, whether there is an overall difference in efficacy between griseofulvin and terbinafine administered at specific doses and durations in clinically and methodologically similar studies of tinea capitis and whether such a difference exists with regard to tinea capitis infections caused by particular dermatophyte genera.

MATERIALS AND METHODS

We performed a PubMed search using the term tinea capitis, limiting our search to English-language RCTs involving human subjects, followed by a hand search of the bibliographies of relevant identified articles. This approach yielded six RCTs that directly compared griseofulvin with terbinafine [2–7]. Two reviewers reviewed all the titles and abstracts unconventionally. Data was extracted from eligible full-text studies. The doses and periods of treatment used in these studies are listed in Table 1. Three studies made identical or nearly identical comparisons in terms of the dose and duration of studied drugs [3,5,6], comparing 4 weeks of daily terbinafine (3.125– 6.25 mg⁄kg⁄day) with 8 weeks of daily griseofulvin (6.25–12.5 mg ⁄kg ⁄day [5,6] or 10 mg ⁄kg ⁄day [3]). These articles were chosen for our meta-analysis. The three remaining studies differed significantly from the selected studies and from each other in dose, duration, or one or both drugs and were consequently excluded from further analysis.

To analyse efficacy in a consistent manner across studies, we chose clinical and mycologic cure at the end of griseofulvin treatment (week 8) as our efficacy result. Clinical cure was defined as a total signs and symptoms score of 2 or less and mycologic cure as negative outcomes from fungal culture. Results other than clinical and mycologic cure were counted as failures.

The rate of complete clinical and mycologic cure was calculated using the modified intention to treat (mITT) population; this included all patients who had a confirmed diagnosis of tinea capitis from fungal culture who had undergone randomization into their treatment group. Missing values for patients who did not complete treatment for any reason were ascribed utilizing a last observation carried forward (LOCF) method. If these data were not delivered, they were calculated from the number of patients randomized to each treatment group and the number of complete clinical and mycological cures at the end of griseofulvin treatment. Three studies were evaluable using our protocol [3,5,6]; patient and disease characteristics of these studies are listed in Table 2.

Table 1. Treatment details of identified studies

	Terbinafine		Griseofulvin	
Study	Dose, mg ⁄kg⁄ day	Duratio ı, weeks	Dose, mg ⁄kg⁄ day	Duratio , weeks
Elewski *et al.*	5–7.5	6	6.5–21.6	6
Fuller *et al.*	3.125–6.25	4	10	8
Caceres-Rios *et al.*	3.125–6.25	4	6.25–12.5	8
Gupta *et al.*	3.125–6.25	2–3	20	6
Lipozencic *et al.*	3.125–6.25	6, 8, 10, 12	20	12
Memisoglu *et al.*	3.125–6.25	4	6.25–12.5	8

The participants used in the meta-analysis fulfilled the inclusion criteria: positive baseline culture and randomization into their group. Patients who had recently used oral or topical antimycotic agents were excluded in all studies, and all studies included cases of Trichophyton sp. and Microsporum sp. infection. Table 3 provides the efficacy analysis details and results of the selected studies.

Review Manager 5 software (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen and Denmark) was utilized to do a meta-analysis of dichotomous efficacy data (cure vs failure) at week 8, using the Mantel–Haenszel method and random effects model. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Heterogeneity was investigated using the chi-square test with p-value and I^2 for significance, and overall effect was determined according to the Z-value and corresponding p-value. ORs greater than 1 favored griseofulvin, and ORs less than 1 favored terbinafine. If significant differences were detected, they were re-expressed as the number fewer per 1,000 (absolute risk reduction [ARR]) and the number needed to treat (NNT).

These were calculated from the ORs and estimated intervention effects (assumed control risk [ACR]) for each treatment. Subgroup analyses using the same methods were performed for cases as a result of Trichophyton spp. and Microsporum spp.

TABLE 2. Patient and disease characteristics of included studies

Characteristic	Caceres-Rios *et al.*	Memisoglu *et al.*	Fuller *et al.*
Clinical diagnosis of tinea capitis	+	+	+
100% positive baseline fungal culture	+	+	+
Randomized to treatment group	+	+	+
Excluded recent use of oral or topical antifungals	+	+	+
Organisms isolated	Mixed	Mixed	Mixed

TABLE 3. Efficacy analysis details of included studies

	Caceres-Rios *et al.*	Memisoglu *et al.*	Fuller *et al.*
Randomized to terbinafine, n	25	39	76
Randomized to griseofulvin, n	25	39	68
Terbinafine cure rate at week 8, n (%)	18 (72)	20 (51)	42 (55.3)
Griseofulvin cure rate at week 8, n (%)	19 (76)	23 (59)	32 (47.1)

The study was done according to the ethical board of King Abdulaziz university.

RESULTS

Table 4 shows that, at week 8, the studies were not heterogeneous (p = 0.45) and that no statistically significant difference was detected between the two interventions (p = 0.81) when considering all cases regardless of organisms.

Table 4. Cure rates of included studies at week 8

	Griseofulvin		Terbinafine			Odds Ratio
Study	Events	Total	Events	Total	Weight	M-H, Random, 95%, CI
Memisoglu *et al.*	23	39	20	39	29.8%	1.37 [0.56, 3.34]
Fuller *et al.*	32	68	42	76	55.3%	0.72 [0.37, 1.39]
Caceres-Rios *et al.*	19	25	18	25	14.9%	1.23 [0.35, 4.37]
Total (95%, CI)		132		140	100%	0.94 [0.58, 1.54]
Total events	74		80			

The results in Table 5 indicate that, at week 8, the two studies were not heterogeneous (p = 0.89). For Trichophyton spp., terbinafine administered at 3.25– 6.5 mg⁄kg⁄day for 4 weeks is significantly more efficacious than griseofulvin given for 8 weeks (combined results from 6.25 to 12.5 and 10 mg⁄kg⁄day) assessed at this time point (OR = 0.50, 95% CI = 0.26–0.98; p = 0.04). Estimating the griseofulvin ACR to be 46.6% (the cure rate that Fuller *et al.* [3] provided) predicts an average ARR of 162, representing a predicted average of 162 fewer cures per 1,000 patients treated with griseofulvin than terbinafine at these doses and durations. The corresponding NNT, indicating the number of patients who would have to receive terbinafine rather than griseofulvin to produce one additional cure, was 7. If the ACR is estimated at 76% (the cure rate that CaceresRios *et al.* (2) provided), 147 fewer cures per 1,000 (ARR) are predicted for griseofulvin than for terbinafine, with the NNT remaining at 7.

Table 5. Cure rates for Trichophyton spp. at week 8

	Griseofulvin		Terbinafine			Odds Ratio
Study	Events	Total	Events	Total	Weight	M-H, Random, 95%, CI
Fuller *et al.*	27	58	41	65	86%	0.51 [0.25, 1.05]
aceres-Rios *et al.*	16	21	14	16	14%	0.46 [0.08, 2.74]
Total (95%, CI)		79		81	100%	0.50 [0.26, 0.98]
Total events	43		55			

The results in Table 6 indicate that, at week 8, the two studies were not heterogeneous (p = 0.59). For Microsporum spp., griseofulvin administered for 8 weeks (combined results from 6.25 to 12.5 and 10 mg⁄kg ⁄day) is significantly more efficacious than terbinafine administered for 4 weeks (3.125–6.25 mg⁄kg⁄day) (OR = 6.39, 95% CI = 1.09–37.47; p = 0.04).

An ACR of 50% (the griseofulvin cure rate that Fuller *et al.* (4) provided) predicted an average of 365 fewer cures per 1,000 with terbinafine than griseofulvin (NNT = 3). An ACR of 75% (the griseofulvin cure rate that Caceres-Rios *et al.* (2) provided) predicted 200 fewer (NNT = 5).

	Griseofulvin		**Terbinafine**			**Odds Ratio**
Study	Events	Total	Events	Total	Weight	M-H, Random, 95%,
Fuller *et al.*	5	10	1	11	54.3%	10.00 [0.91, 110.28]
Caceres-Rios *et*	3	4	4	9	45.7%	3.75 [0.27, 51.37]
Total (95%, CI)		14		20	1	6.39 [1.09, 37.47]
)tal events						

Table 6. Cure rates for Microsporum spp. at week 8.

DISCUSSION

Overall we were unable to detect a significant difference in efficacy between the two interventions for the treatment of tinea capitis (3.125–6.25 mg⁄kg⁄day terbinafine administered for 4 weeks and 6.25–12.5 mg⁄kg ⁄day of griseofulvin managed for 8 weeks). This finding relates to mycologically confirmed cases of tinea capitis evaluated using equal definitions of cure, with cure rates resolute using equivalent analyses (mITT, LOCF). The effectiveness of these managements was statistically significant for specific dermatophyte genera. Terbinafine (3.125–6.25 mg⁄kg⁄day for 4 weeks) was found to be greater to griseofulvin (6.25–12.5 mg ⁄kg ⁄day for 8 weeks) for treating infections owing to Trichophyton spp. In infections due to Microsporum spp., griseofulvin was found to be superior. It would be remarkable to compare the two drugs at equal treatment periods, nonetheless griseofulvin and terbinafine are usually in use for 8 and 4 weeks, respectively, so insufficient data are obtainable to compare the two treatments at equal periods. As of late an alternative meta-analysis contrasting griseofulvin and terbinafine for the treatment of tinea capitis was published [(10)]. The authors distinguished a similar arrangement of clinical trials utilized for the present investigation, yet picked distinctive scientific parameters to contrast efficacy. Where we picked with utilize clinical trials with coordinating doses and treatment spans, these creators selected to expand the quantity of studies. This implies that the examinations included by Tey *et al.* [(10)] are more heterogeneous than the investigations included here. Both meta-examinations arrived at a similar conclusion; the information don't bolster a distinction in viability amongst griseofulvin and terbinafine. They additionally distinguish similar species-particular impacts for Trichophyton rubrum and Candida albicans.

We have exhibited favorable position of terbinafine (3.125– 6.25 mg⁄kg⁄day) over griseofulvin (6.25– 12.5 mg⁄kg⁄day) in instances of tinea capitis because of Trichophyton spp. as far as general adequacy and length of treatment (a month for terbinafine versus two months for griseofulvin). Griseofulvin has already been accounted for to require bigger measurements for fruitful treatment (13,14), however we have additionally demonstrated that two months of a low dosage of griseofulvin (6.25– 12.5 mg⁄kg⁄day) has better adequacy than a month of terbinafine (3.125– 6.25 mg⁄kg⁄day) in instances of tinea capitis because of Microsporum spp. It would be clinically valuable to look at high-and low-measurements regimens of each medication, however there are inadequate clinical trials information accessible to perform such an investigation. Here we reach a reasonable determination that the choice to treat tinea capitis with terbinafine or griseofulvin ought to be founded on the mycologic analysis of the contamination, given that neither one of the regimens is prevalent in all instances of tinea capitis. Nowadays clinical practice, griseofulvin and terbinafine are endorsed at higher measurements and longer spans than the clinical trials broke down in this investigation. Griseofulvin is frequently recommended at higher dosages (up to 25 mg⁄kg ⁄day), sometimes for longer lengths (up to four months) than the regimens researched here [(11, 12)]. The endorsed dosage of terbinafine oral granules is somewhat

higher (5– 7.5 mg⁄kg⁄day) and the length is marginally more (a month and a half) [13] than the tablet measurements examined here, which might be connected to the disclosure of a more prominent rate of terbinafine freedom in kids [14, 15]. Despite the fact that there are deficient investigations of the two medications at higher dosages or longer lengths to allow meta-analysis, one huge trial [7] has searched at higher-measurements of griseofulvin (6.5– 21.6 mg⁄kg⁄day) with the mark dosage of terbinafine oral granules (5– 7.5 mg⁄kg⁄day). Not at all like prior examinations contrasting longer-length of griseofulvin (two months) with shorter-span of terbinafine (a month), this trial searched at the two medications when given for break even with treatment terms (a month and a half each). The trial revealed the same factually critical, species-particular contrasts as we report here (terbinafine indicated essentially more noteworthy adequacy for Trichophyton spp.; griseofulvin demonstrated fundamentally more prominent viability for Microsporum spp.), yet the examination additionally detailed altogether more noteworthy viability with terbinafine for tinea capitis contaminations by and large.

Conclusion

There is an increasing evidence signifying superior efficacy of griseofulvin over terbinafine for treating tinea capitis due to Microsporum spp. and for terbinafine over griseofulvin for treating Trichophyton spp., which are the main organisms responsible for tinea capitis in the United States, Canada, and the United Kingdom [11,16]. According to our meta-analysis, these findings apply to doses of griseofulvin of 6.25 to 12.5 mg ⁄kg ⁄day given for 8 weeks and 3.125 to 6.25 mg ⁄kg ⁄day of terbinafine given for a shorter period of 4 weeks. The safety of the two agents in tinea capitis is beyond the scope of this publication and has been discussed elsewhere [8,17]. There are other factors as well that may determine physician and patient preference, including the cost of the agent and the availability of griseofulvin as a liquid formulation.

REFERENCES

1. **Gupta AK and Summerbell RC (2000):** Tinea capitis. Med Mycol.,38:255–287.
2. **Elewski BE, Caceres HW, DeLeon L *et al.*. (2008):** Terbinafine hydrochloride oral granules versus oral griseofulvin suspension in children with tinea capitis: results of two randomized, investigator-blinded, multicenter, international, controlled trials. J Am Acad Dermatol., 59:41–54.
3. **Fuller LC, Smith CH, Cerio R *et al.*.(2001):** A randomized comparison of 4 weeks of terbinafine vs. 8 weeks of griseofulvin for the treatment of tinea capitis. Br J Dermatol.,144:321–327.
4. **Gupta AK, Adam P, Dlova N *et al.*. (2001):**Therapeutic options for the treatment of tinea capitis caused by Trichophyton species: griseofulvin versus the new oral antifungal agents, terbinafine, itraconazole, and fluconazole. Pediatr Dermatol., 18:433–438.
5. **Caceres-Rios H, RuedaM, Ballona R *et al.*. (2000):**Comparison of terbinafine and griseofulvin in the treatment of tinea capitis. J Am Acad Dermatol.,42:80–84.
6. **Memisoglu HR, Erboz S, Akkaya S *et al.*.(1999):** Comparative study of the efficacy and tolerability of 4 weeks of terbinafine therapy with 8 weeks of griseofulvin therapy in children with tinea capitis. J Dermatol Treat , 10:189–193.
7. **Lipozencic J, Skerlev M, Orofino-Costa R *et al.*.(2002):** A randomized, double-blind, parallel-group, duration-finding study of oral terbinafine and open-label, high-dose griseofulvin in children with tinea capitis due to Microsporum species. Br J Dermatol., 146:816–823.
8. **Gonzalez U, Seaton T, Bergus G *et al.*.(2007):** Systemic antifungal therapy for tinea capitis in children. Cochrane Database Syst Rev .,17:CD004685.
9. **Fleece D, Gaughan JP, Aronoff SC(2004):** Griseofulvin versus terbinafine in the treatment of tinea capitis: a meta-analysis of randomized, clinical trials. Pediatrics, 114: 1312–1315.
10. **Tey HL, Tan AS, Chan YC(2011):** Meta-analysis of randomized, controlled trials comparing griseofulvin and terbinafine in the treatment of tinea capitis. J Am Acad Dermatol.,64:663–670.
11. **Elewski BE(2000):** Tinea capitis: a current perspective. J Am Acad Dermatol.,42:1–20; quiz 21–24.
12. **Roberts BJ, Friedlander SF(2005):** Tinea capitis: a treatment update. Pediatr Ann., 34:191–200.
13. **http://www. pharma.us.novartis.com/product/pi/pdf/Lamisil_Oral_ Granules.pdf.**
14. **Abdel-Rahman SM, Herron J, Fallon-Friedlander S *et al.*.(2005):** Pharmacokinetics of terbinafine in young children treated for tinea capitis. Pediatr Infect Dis J.,24:886–891.
15. **Nejjam F, Zagula M, Cabiac M *et al.*.(1995):** Pilot study of terbinafine in children suffering from tinea capitis: evaluation of efficacy, safety and pharmacokinetics. Br J Dermatol .,132:98–105.
16. **Higgins EM, Fuller LC, Smith CH(2000):** Guidelines for the management of tinea capitis. British Association of Dermatologists. Br J Dermatol.,43:53–58.
17. **Gupta AK, Cooper EA(2008):** Update in antifungal therapy of dermatophytosis. Mycopathologia,66:353–367.