Am J Clin Dermatol (2013) 14:413–419
DOI 10.1007/s40257-013-0031-y

SHORT COMMUNICATION

Efficacy, Tolerability and Consumer Acceptability of Terbinafine Topical Spray versus Terbinafine Topical Solution: A Phase IIa, Randomised, Observer-Blind, Comparative Study

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Published online: 6 June 2013

Abstract

Introduction Tinea pedis is one of the world's most prevalent dermatophyte infections. MedSpray™ tinea pedis 1 % w/w (topical spray) is a novel, easy-to-use propellant-based spray formulation containing 1 % w/w terbinafine, requiring no manipulation at the site of infection. This is in contrast to the only formulation currently approved in Europe for single application (none are approved in the USA for single use), which is Lamisil® Once 1 % w/w (topical solution), containing 1 % w/w terbinafine hydrochloride, which requires manipulation on the affected area.

Objective The aim of this study was to evaluate the efficacy, tolerability and consumer acceptability of a topical spray versus a topical solution in the treatment of tinea pedis.

Methods This study is a phase IIa, randomised, observer-blind, non-inferiority comparative study of the topical spray compared with the topical solution over a 12-week study period. The study was conducted at Bioskin GmbH, Hamburg and Berlin. Patients ($n = 120$) who presented with the presence of interdigital tinea pedis caused by dermatophytes on one or both feet were enrolled in the study. Patients were randomly assigned between the two treatment groups. Either the topical spray or the topical solution was administered by the study nurse and consisted of a single application (equivalent to 20 mg of terbinafine per foot) on day 1 of the study. No further applications were made for the duration of the study. The hypothesis formulated before commencement of the study was that the topical spray would prove to be non-inferior to the topical solution. Efficacy assessments, including clinical signs and symptoms, mycology and microscopy were performed at baseline and 1, 6 and 12 weeks after treatment.

Results The rate of mycological cure at week 1 was statistically equivalent for both treatments. There was a significant reduction in the overall clinical score as assessed by the Physician's Global Assessment of signs and symptoms for both treatment groups.

Conclusion The topical spray and the topical solution showed comparable anti-fungal activity. Furthermore, the non-inferiority of topical spray to the topical solution was confirmed as determined by the proportion of patients categorised as successfully treated at week 1. This confirms that a topical spray product, which can be applied once without touching the affected skin, is equally as effective in the treatment of tinea pedis and removes the risk of organism transfer associated with touching infected areas. Clinical Trial registration number: EudraCT-No. 2008-002399-92.

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1 Introduction

It is estimated that 10–15 % of general practice consultations are related to skin conditions, the majority of which can be managed in the community using over-the-counter (OTC) and prescription preparations [1]. Tinea pedis is described as one of the world's most prevalent dermatophytoses and is commonly diagnosed by primary care

physicians (particularly amongst adolescents) [2]. Dermatophyte fungi invade the superficial keratin of the skin, with the infection remaining limited to this layer [3]. The cutaneous presentation is dependent upon the host's immune system as well as the infecting dermatophyte. The most common causative organism is *Trichophyton rubrum*; others include *Trichophyton mentagrophytes* and *Epidermophyton floccosum* [2]. Tinea pedis can be complicated by opportunistic bacterial infections and subsequent cellulitis (owing to the breakdown of the skin barrier), as well as the recurrence of the disease if treatment is ineffective or incomplete [4].

A number of prescription and OTC products are routinely used for the treatment of tinea pedis [5, 6]. Terbinafine is one of the drugs incorporated in the products widely used to treat dermatophytes, including tinea pedis; it is fungicidal at low concentrations against dermatophytes and moulds and effectively promotes clinical and mycological cure of tinea pedis [7–10]. As such, although previous formulations have been approved on the basis of multiple applications over a period of up to 7 days, Lamisil® Once 1 % w/w has been approved in Europe for a once only application together with a new concept of application over the whole area of both feet [11] and has thus gained considerable market share, mainly because of its ease of use and patient compliance. However, this product is not approved in the USA, and a similar product could have significant patient benefit in this market. MedSpray™ tinea pedis 1 % w/w is a novel, easy-to-use propellant-based spray formulation containing 1 % w/w of terbinafine, which requires no manipulation at the site of infection. This reduces contact between hands and infected areas, thus reducing the risk of transfer of the organism to areas of healthy skin. The formulation was developed using various in vitro skin models [12–14] and has been optimised to ensure that, upon application, the propellant and volatile solvents evaporate, producing an invisible residual phase of drug at elevated thermodynamic activity, which delivers terbinafine to the stratum corneum. The formulation is retained in the stratum corneum for several days, with terbinafine levels well above the minimum inhibitory concentration for dermatophytes. This study reports the results of a phase IIa, randomised, observer-blind, non-inferiority comparative study of the efficacy, tolerability and consumer acceptability of topical MedSpray™ tinea pedis 1 % w/w (hereafter referred to as topical spray) versus Lamisil® Once 1 % w/w (hereafter referred to as topical solution) in the treatment of tinea pedis.

2 Methods

The study was conducted at the Bioskin sites in Hamburg and Berlin. Ethics approval was granted by the Ethics Committee of the Federal State Berlin. The selection of patients was in accordance with the requirements of Sections 40 and 41 of the German Drug Law (AMG) as well as the recommendations of the Helsinki Declaration and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guideline. The clinical trial was registered with EudraCT (authorization number 2008-002399-92).

2.1 Recruitment and Enrolment

Patients were screened and enrolled in the study following a standard procedure outlined in the CONSORT flow chart shown in Fig. 1. An up-to-date medical history was recorded and a physical examination performed on study day 1; patients were selected according to defined inclusion and exclusion criteria. Men and women aged over 18 years, displaying presence of interdigital tinea pedis caused by dermatophytes on one or both feet, characterized by a Physician's Global Assessment score of two ("notable signs and symptoms exist") or three ("prominent signs and symptoms exist") at baseline were included. Patients must have been willing to comply with the requirements of the trial protocol, and written consent was obtained. Exclusion criteria were any patients with hyperkeratotic chronic plantar tinea pedis (moccasin type); patients who were immunosuppressed; patients who had received active treatment in the last 2 weeks before entry; patients who had been treated with oral anti-fungal agents within the 12 weeks prior to study entry or had been treated with topical anti-fungal agents within the previous 2 weeks; and patients with known hypersensitivity to terbinafine or any of the test or topical solution excipients.

2.2 Study Protocol

Each volunteer was treated with the topical spray or comparator corresponding to its randomisation number. The random list and a list with the treatment codes were kept in the trial master file. The topical spray and topical solution were not blinded. Consequently, the application of study medication, which was supervised by the study nurse, was performed in the absence of the investigator or sub-investigator who did the clinical assessments. On study day 1, under the supervision of the study nurse, the patients applied either the topical spray (40 spray pumps per foot [20 mg of drug on each foot]) or topical solution (half the tube per foot [20 mg of drug on each foot]) dependant on the treatment group to which they were randomly assigned. Medication was applied to all interdigital spaces of the feet, and around all the toes as well as to the sole and sides of the foot. The products were left to dry to a film for

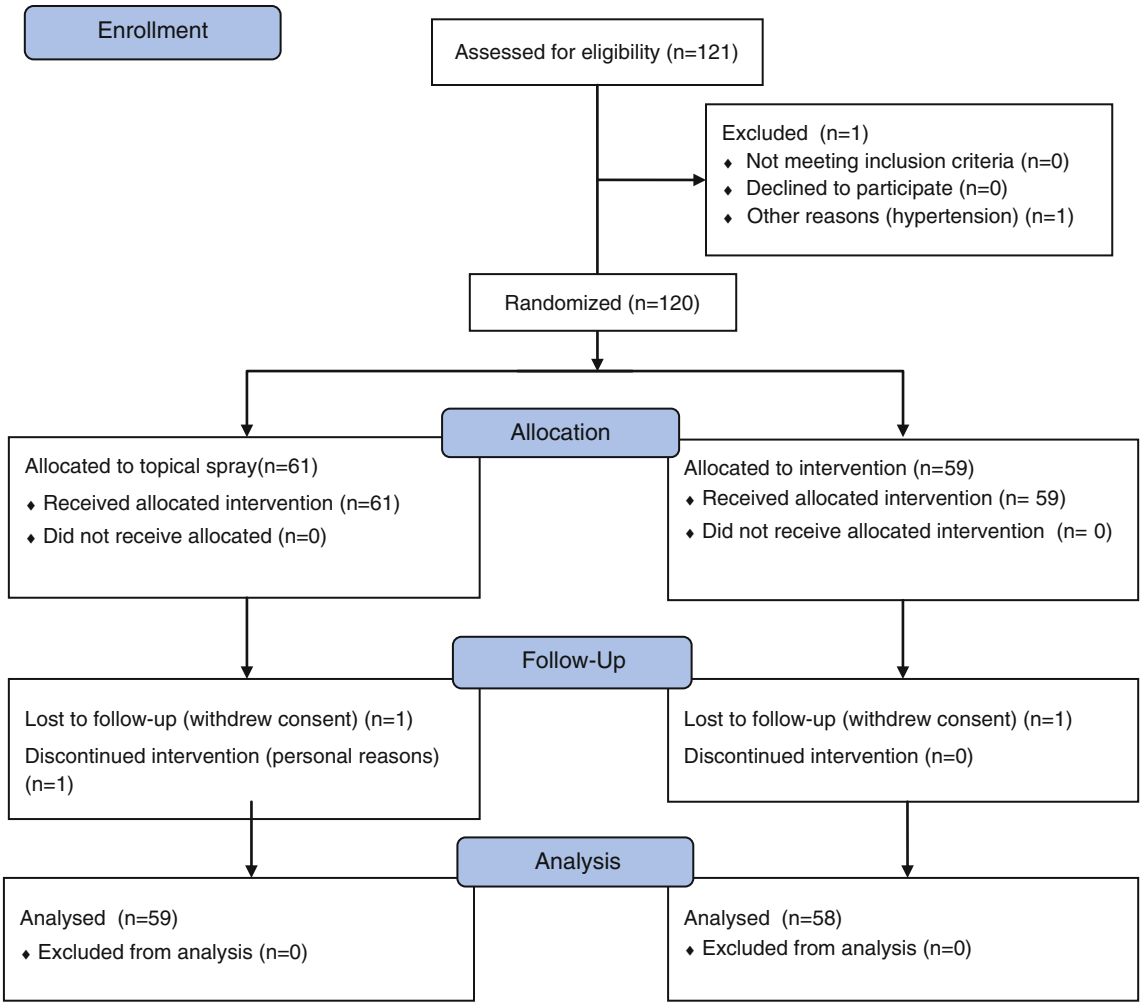

Fig. 1 CONSORT flow chart summarising participant recruitment, enrolment, treatment, follow-up and completion rates

1–2 min, after which patients washed their hands. This study was based upon a single application; no further treatment applications were made either by the study nurse or by the individual participants throughout the duration of the study. Patients were evaluated at baseline, and 1, 6 and 12 weeks after treatment. These time points were considered to reflect clinically important timings [3, 15].

For this initial proof of principle pilot study, diagnosis and efficacy measures were based primarily on visual inspection and evidence of signs and symptoms (erythema, scaling, vesicles, pustules, crusting, fissuring and maceration), assessed by the investigator according to a four-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe), which was representative of day-to-day identification and management of tinea pedis in the community.

Additionally, all enrolled patients had a lesion sample taken at baseline (pre-treatment) and at the 1-week follow-up visit for microscopy (KOH test)/mycology (identification and culture of fungi). The mycological assessment was performed on samples taken from all interdigital spaces of the affected foot/feet. The mycological assessment by microscopy (KOH test) and species identification/culture was performed by the Laborfuer Klinische Forschung GmbH (LKF), Raisdorf/Kiel, Germany. In so far as practicable, the same lesion was sampled within a patient at baseline and week 1. Mycological cure at week 1 was defined as KOH negative and culture negative, or KOH positive and culture negative. A positive KOH and positive culture were classed as no mycological cure.

Follow-up evaluations were conducted 1, 6 and 12 weeks after treatment; at each visit, a visual observation was made by an assessor (normally the same assessor for each patient at each visit), who was blinded to the patient's treatment group. The observation was scored using the Physician's Global Assessment scale, which was performed according

Table 1 Determination of treatment success rates at follow-up visits

	Week 1		Week 6		Week 12	
	Topical spray ($n = 60$)	Topical solution ($n = 58$)	Topical spray ($n = 60$)	Topical solution ($n = 58$)	Topical spray ($n = 60$)	Topical solution ($n = 58$)
Success	14 (23.3 %)	12 (20.7 %)	34 (56.7 %)	31 (53.4 %)	32 (53.3 %)	34 (58.6 %)
Failure	46 (76.7 %)	46 (79.3 %)	26 (43.3 %)	27 (46.6 %)	28 (46.7 %)	24 (41.4 %)
Difference in SRs[a]	2.64 %		3.22 %		−5.29 %	
One-sided lower CI[b]	−7.13 %		−8.51 %		−16.98 %	

Treatment success or failure determined according to mycology testing and the Physician's Global Assessment score for clinical signs and symptoms

[a] SR (topical spray) − SR (topical solution)

[b] One-sided lower 90 % CI determined by asymptotic normality approximation for the difference in SRs

CI confidence interval, *SR* success rate

to the following four-point scale: 0 = clinical cure/clear; 1 = almost clear; 2 = notable signs and symptoms exist; 3 = prominent signs and symptoms exist. Finally, an overall clinical score was calculated by summing up all individual score values for the clinical signs and symptoms (erythema, scaling, vesicles, pustules, crusting, fissuring and maceration). Laboratory parameters (e.g. haematology/biochemistry values) were not measured during the course of the study.

2.3 Safety and Adverse Effects

Safety parameters included the recording of medical history, clinical examination and recording of 'adverse events'. Adverse events (AEs), either reported by the patient or observed by the investigator, were recorded with duration, intensity and probability of a correlation with the study preparation. The nature of the AE was described in precise, standard medical terminology and, if known, a specific diagnosis was stated (e.g. allergic contact dermatitis). The intensity of the AE was described in terms of mild, moderate or severe according to the investigator's clinical judgment. The location for cutaneous AEs was described as at or just around the application area (≤2 cm from the application area) or distant (>2 cm from the application area).

2.4 Data Analysis

All statistical processing was performed using SAS®. The sample size determination was based on the expected treatment success rate of 70 % in the reference product group. The required non-inferiority margin of 20 % was considered a minimum clinically important difference (MCID).

The primary objective was the demonstration of the non-inferiority of the topical spray versus the topical solution with respect to the treatment success rate at the week 1 visit, with a non-inferiority margin of 20 % and was

Table 2 Physician's Global Assessment score

	Baseline (day 1)		Week 1		Week 6		Week 12	
	Topical spray ($n = 60$)	Topical solution ($n = 58$)	Topical spray ($n = 60$)	Topical solution ($n = 58$)	Topical spray ($n = 60$)	Topical solution ($n = 58$)	Topical spray ($n = 60$)	Topical solution ($n = 58$)
0 = clinical cure/clear	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	9 (15.0 %)	4 (6.9 %)	17 (28.3 %)	10 (17.3 %)
1 = almost clear	0 (0.0 %)	0 (0.0 %)	14 (23.3 %)	12 (20.7 %)	25 (41.7 %)	27 (46.6 %)	15 (25.0 %)	24 (41.4 %)
2 = notable signs and symptoms exist	46 (76.7 %)	40 (69.0 %)	39 (65.0 %)	37 (63.8 %)	23 (38.3 %)	26 (44.8 %)	24 (40.0 %)	22 (37.9 %)
3 = prominent signs and symptoms exist	14 (23.3 %)	18 (31.0 %)	7 (11.7 %)	9 (15.5 %)	3 (5.0 %)	1 (1.7 %)	4 (6.7 %)	2 (3.4 %)
Median	2.00	2.00	2.00	2.00	1.00	1.00	1.00	1.00
Minimum–maximum	2–3	2–3	1–3	1–3	0–3	0–3	0–3	0–3

Table 3 Physician's assessment of signs and symptoms score and overall clinical score

	Baseline (day 1)		Week 1		Week 6		Week 12	
	Topical spray ($n = 60$)	Topical solution ($n = 58$)	Topical spray ($n = 60$)	Topical solution ($n = 58$)	Topical spray ($n = 60$)	Topical solution ($n = 58$)	Topical spray ($n = 60$)	Topical solution ($n = 58$)
Median erythema score[a]	1.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00
Minimum–maximum	0–3	0–3	0–2	0–2	0–2	0–2	0–2	0–2
Median scaling score[a]	2.00	2.00	2.00	1.00	1.00	1.00	1.00	1.00
Minimum–maximum	1–3	1–3	1–3	1–3	0–3	0–3	0–3	0–2
Median vesicle score[a]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Minimum–maximum	0–1	0–1	0–0	0–0	0–0	0–0	0–0	0–0
Median pustule score[a]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Minimum–maximum	0–0	0–0	0–0	0–0	0–0	0–0	0–0	0–0
Median crusting score[a]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Minimum–maximum	0–2	0–2	0–2	0–3	0–1	0–1	0–0	0–1
Median fissuring score[a]	1.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00
Minimum–maximum	0–2	0–3	0–3	0–3	0–2	0–2	0–1	0–1
Median maceration score[a]	1.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00
Minimum–maximum	0–3	0–3	0–3	0–3	0–3	0–3	0–3	0–3
Overall median clinical score[b]	5.0	4.5	4.0	4.0	2.0	2.0	2.0	2.0
Minimum–maximum	2–8	2–10	1–8	1–9	0–6	0–6	0–7	0–5

[a] Physician's assessment of signs and symptoms score: 0 = absent (normal); 1 = mild (barely abnormal); 2 = moderate (distinctly abnormal); 3 = severe (intense involvement or marked abnormality)

[b] Overall clinical score calculated by summing up all individual score values for the clinical signs and symptoms (erythema, scaling, vesicles, pustules, crusting, fissuring and maceration)

evaluated by the confidence interval method. Using the asymptotic normality-approximation, a one-sided lower 90 % confidence interval for the difference in success rates π (topical spray) $-$ π (topical solution) was determined. The primary null-hypotheses were rejected if the lower limit of the confidence interval fell above 0.2.

Frequency tables are presented for the treatment success by treatment group. Each sign and symptom of the physician's assessment and the Physician's Global Assessment are presented using frequency tables and descriptive statistics covering number of patients, median and minimum to maximum range. The overall clinical score sum is presented by treatment group and visit using descriptive statistics only.

3 Results

The recruitment and assignment of patients to treatment groups are summarized in the CONSORT flow chart in Fig. 1.

At baseline, the mycological results for the two treatment groups were comparable (80 % positive KOH microscopy with 58.3 % positive fungal culture for the

topical spray group vs. 80.5 and 67.2 %, respectively, for the topical solution group). In both cases, an increase in mycological cure as defined in the methods section was seen throughout the duration of the trial. There was no statistically significant difference in mycological cure rate between the two treatment groups as determined by calculation of the one-sided lower 90 % confidence interval determined by asymptotic normality-approximation for the difference in success rates (Table 1).

Re-infection rates were comparable between both treatment groups, with re-infection reported in one patient (7.1 %) after 6 weeks and in four patients (28.6 %) after 12 weeks in the topical spray group and re-infection noted in four patients (33.3 %) after 12 weeks in the topical solution group. In the statistical comparisons (Fisher's exact test), no statistical differences were found between the two treatment groups at both test points (weeks 6 and 12) in terms of re-infection rates.

A continuous and comparable improvement was seen in the Physician's Global Assessment for both the topical spray and the topical solution over the entire study period (Table 2). The score decreased from 2 at baseline and week 1 follow-up to a score of 1 by weeks 6 and 12 for both treatment groups. Treatment success rates were comparable and the lower confidence interval confirmed non-inferiority of the topical spray product.

The physician's assessment scores for the individual signs and symptoms are summarized in Table 3. Comparable improvements in scores were observed for both treatment groups and no statistically significant difference between the performance of the topical spray or topical solution was observed for any of the signs and symptoms assessed.

Twenty-nine patients reported a total of 42 AEs; 12 of these patients were from the topical spray treatment group (18 AEs) and 17 patients were from the topical solution treatment group (24 AEs). Three AEs from each treatment group were assessed as moderate; all other AEs were classified as mild. The relationship to study medication was considered unlikely in all AEs for the patients treated with topical solution and in 16 AEs for the patients treated with the topical spray; two AEs were considered as not classifiable. There were no safety concerns in this study.

4 Discussion

The topical spray and topical solution showed statistically equivalent anti-fungal activity. Furthermore, the non-inferiority of the topical spray compared with the topical solution was confirmed. An improvement was seen in the Physician's Global Assessment for both preparations. The intensity of signs and symptoms of tinea pedis continuously decreased over the entire study period in both treatment groups. A comparable clear improvement was also seen in the overall clinical scores. A re-infection rate of four was noted in both treatment groups at the end of the study.

In Europe, the market-leading product for the topical treatment of tinea pedis (topical solution) requires patients to apply a solution to the affected area using their hands; this exposes the patient to the risk of transferring the infective organism to areas of healthy skin. This study has shown that a topical spray product that needs to be applied only once and without touching the affected skin is equally as effective in the treatment of tinea pedis and removes the risk of organism transfer associated with touching infected areas. It is anticipated that this dosing regimen is likely to improve patient compliance with the treatment and thus lead to an increase in cure rates for the treatment of tinea pedis.

Acknowledgments The authors would like to thank BioSkin® for designing and conducting the study and carrying out the initial analysis and interpretation of the data. This study was funded by MedPharm Ltd who also approved the manuscript.

Conflict of interest M.B. Brown is a part owner of MedPharm Ltd. and holds a patent for the technology used in the test product. C. Evans is employed by MedPharm Ltd. A. Muddle is part owner of MedPharm Ltd. R. Turner is employed by MedPharm Ltd. S. Lim is employed by MedPharm Ltd. J. Reid has no conflicts of interest to declare. M. Traynor has received research grant funding from MedPharm Ltd.

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