Original Article

Ciclopirox gel in the treatment of patients with interdigital tinea pedis

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Abstract

Background Tinea pedis (athlete's foot) is the most common fungal infection in the general population. Ciclopirox, a broad-spectrum hydroxypyridone antifungal, has proven efficacy against the organisms commonly implicated in tinea pedis: *Trichophyton rubrum*, *T. mentagrophytes* and *Epidermophyton floccosum*.

Objective Two multicenter, double-blind, clinical studies compared the efficacy and safety of ciclopirox gel with that of its vehicle base in subjects with moderate interdigital tinea pedis with or without plantar involvement.

Methods Three hundred and seventy-four subjects were enrolled and randomized to one of two treatment groups: ciclopirox gel 0.77%, or ciclopirox gel vehicle, applied twice daily for 28 days, with a final visit up to day 50. The primary efficacy variable was Treatment Success defined as combined mycological cure and clinical improvement ≥ 75%. Secondary measures of effectiveness were Global Clinical Response, Sign and Symptom Severity Scores, Mycological Evaluation (KOH examination and final culture result), Mycological Cure (negative KOH and negative final culture results) and Treatment Cure (combined clinical and mycological cure).

Results At endpoint (final post-baseline visit), 60% of the ciclopirox subjects achieved treatment success compared to 6% of the vehicle subjects. At the same time point, 66% of ciclopirox subjects compared with 19% of vehicle subjects were either cleared or had excellent improvement. Pooled data showed that 85% of ciclopirox subjects were mycologically cured, compared to only 16% of vehicle subjects at day 43, 2 weeks post-treatment.

Conclusions Ciclopirox gel 0.77% applied twice daily for 4 weeks is an effective treatment of moderate interdigital tinea pedis due to *T. rubrum*, *T. mentagrophytes* and *E. floccosum* and is associated with a low incidence of minor adverse effects.

Introduction

Tinea pedis, also known as athlete's foot, is the most common fungal infection in the general population. It occurs most often in humid environments, and is related to sweating and warmth, and the use of occlusive footwear[1,2]. Men between the ages of 20 and 40 years are most frequently affected[1]. Pruritus, burning, scaling, interdigital maceration and fissuring are the usual clinical signs[2]. Dermatophytes, specifically *Trichophyton rubrum*, *T. mentagrophytes*, and *Epidermophyton floccosum* are the most common causative species[1].

The term tinea pedis is a general one that encompasses three clinically distinctive syndromes: interdigital toe web infections, scaly, hyperkeratotic moccasin-type infection of the plantar surface of the foot, and a highly vesicular/bullous variety[3]. Interdigital toe web infections may present as a relatively asymptomatic, mild scaling condition or as a painful, exudative, macerated inflammatory process that is frequently accompanied by a foul odor[3,4]. Although infections of the toe web space have been traditionally categorized as caused solely by invasion of the skin by dermatophyte organisms, in macerated, malodorous, highly symptomatic infected interspaces, there is an overgrowth of various bacterial species. Many of these bacteria are antibiotic resistant derivatives, and their proliferation may be caused by the production of penicillin- and streptomycin-like antibiotics by dermatophytes.

In the presence of a stratum corneum damaged by dermatophyte invasion, these bacteria proliferate and induce inflammation[3]. Leyden and Kligman have proposed the term 'dermatophytosis simplex' for the uncomplicated fungal type of scaling tinea pedis and 'dermatophytosis complex' for the condition of macerated, itchy, often foul smelling interspaces superinfected by bacteria[5]. When secondary bacterial infection is associated with tinea pedis the most common bacterial pathogens include *Staphylococcus aureus*, *Micrococcus sendantarius*, *Pseudomonas aeruginosa* and *Corynebacterium minutissimum*[6].

Another common problem with the treatment of tinea pedis is the frequency of recurrence – either relapse or reinfection – with relapse being the result of treatment discontinued before the point of eradicating the fungus, even though the clinical signs are absent[3]. Fungicidal activity, rather than fungistatic activity, is necessary in order to kill the fungal spores and eradicate the fungus[5].

Ciclopirox, a broad-spectrum hydroxypyridone antifungal, has proven efficacy against the organisms commonly implicated in tinea pedis: *T. rubrum*, *T. mentagrophytes* and *E. floccosum*. Ciclopirox has been shown in both *in vitro* and *in vivo* studies to possess some inherent anti-inflammatory activity[7–10]. Investigators have reported on the antibacterial activity of ciclopirox[6], as well as its sporicidal action (unpublished data, on file at Medicis, The Dermatology Company®). Ciclopirox gel differs from the other ciclopirox formulations in that it contains ciclopirox as the free acid rather than the olamine salt. Studies indicate that the microbiologic and toxicological profiles are similar to those of the olamine salt.

We describe the results of two similar clinical studies comparing the efficacy and safety of ciclopirox gel with that of its vehicle base in subjects with moderate interdigital tinea pedis, with or without plantar involvement.

Materials and Methods

Study design

Two similar studies were conducted using identical variables and methods of evaluation. A total of 11 investigators participated in these multicenter, randomized, double-blind, vehicle controlled studies. Three hundred and seventy-four subjects were enrolled and randomized to one of two treatment groups: ciclopirox gel 0.77% or ciclopirox gel vehicle. For enrollment in the study, all subjects were required to have clinically diagnosed, stable or exacerbating interdigital tinea pedis, with or without mild-to-moderate plantar involvement, and a clearly positive KOH examination, consistent with the diagnosis. To be included in the efficacy analysis, subjects were also required to have a positive culture (a dermatophyte isolated from skin specimens taken from the affected interdigital area) at baseline. Three hundred and seventeen subjects were evaluated for efficacy.

A target foot was designated for efficacy evaluations. Safety evaluations were made on both feet, if treated. The primary efficacy variable was Treatment Success defined as combined mycological cure and clinical improvement ≥ 75%. Secondary measures of effectiveness were Global Clinical Response (evaluated on a 0–5 scale, where: 0 = cleared (100% clearance); 1 = excellent improvement (75% to < 100% clearance); 2 = moderate improvement (50% to < 75% clearance); 3 = slight improvement (< 50% clearance); 4 = no change; and 5 = exacerbation), Sign and Symptom Severity Scores, Mycological Evaluation (KOH examination and final culture result), Mycological Cure (negative KOH and negative final culture results), and Complete Cure (combined clinical and mycological cure, referred to as 'Treatment Cure' in the original studies).

The treatment period consisted of 28 consecutive days with evaluations for clinical response on days 8, 15, 22, 29 and 43 (14 days post-treatment) and at endpoint. Endpoint is defined as the final post-baseline visit, up to day 50, allowing capture of data for patients who lack the day 43 visit. Evaluations for mycological response were done only on study visit days 15, 29 and 43 and at endpoint.

Subjects being treated with any medication that could affect the course of the disease were excluded. Subjects were also excluded if they had a fungal infection elsewhere on the body. A 14-day washout period was imposed if a subject was using any topical medication for the treatment of tinea pedis. Prior use of systemic antimicrobials or corticosteroids carried a 28-day washout period before a patient could be enrolled as a subject in the study. All subjects gave informed consent.

Subjects

Of the 374 enrolled subjects, 77% were male and 23% female. Their mean age was 42 years with a range of 16–80 years. Caucasians made up 77% of the subject base, while 23% were non-Caucasian. There were no significant differences between studies or between groups for demographic data. Furthermore, there were no significant differences in baseline demographic data or disease state comparing all subjects to efficacy subjects.

The 317 subjects evaluated for efficacy (160 ciclopirox and 157 vehicle) were both KOH and interdigital culture positive for dermatophyte at baseline. The majority of these subjects (61%) were rated as having moderate clinical disease. Mild or severe disease was recorded for 25% and 14%, respectively. Almost all (96%) subjects had suffered with the disease for at least 6 months. One quarter of subjects (24%) had continuous disease involvement with 76% reporting intermittent episodes. Duration of the subjects' current episode was greater than 6 months for 35% of subjects, less than 6 weeks for 24% of subjects and between 6 weeks and 6 months for 41% of subjects. Seventy-one percent reported stable disease condition, while 29% described their condition as exacerbating. Of the 317 efficacy subjects, 115 (36%) had plantar as well as interdigital involvement, either mild (43%) or moderate (57%). Subjects with severe plantar involvement were excluded from the study.

T. rubrum was isolated from 80% of the subjects' baseline cultures, *T. mentagrophytes* from 13%, *E. floccosum* from 6%, and other dermatophytes or nondermatophytes from 3%. More than one organism was isolated from some subjects' cultures.

Thirteen individual signs and symptoms were evaluated as a clinical measure of efficacy: erythema, pruritus, scaling, maceration, fissures, hyperkeratosis, vesiculation, edema, exudation, papules, burning, pain and pustules. At baseline, overall mean scores for these signs and symptoms were indicative of mild-to-moderate clinical disease.

Baseline disease characteristics and the prevalence of pathogens were similar between treatment groups and between the two studies.

Two hundred and eighty-seven of the 317 efficacy subjects (90%) completed the entire 28 day treatment. Of the 30 who did not complete the 28 day treatment period, 15 vehicle and two ciclopirox subjects discontinued for lack of efficacy. One ciclopirox subject discontinued due to a nondrug related adverse event. The rest were lost to follow-up or failed to meet protocol criteria.

Conduct of the study

Ciclopirox gel or vehicle base was applied topically to lesions twice daily, in the morning and at bedtime, for 28 consecutive days. Subjects applied the study medication by lightly and uniformly rubbing it into and around all affected designated treatment areas, including approximately one inch of normal-appearing skin surrounding the lesions. All interdigital web spaces, whether or not they were infected, and all infected plantar areas on the target foot were to be treated. They continued to apply the medication to the target areas even if all the signs and symptoms of disease were cleared. Occlusive dressings were not permitted. Subjects were instructed to bathe or wash the treatment areas immediately before applying the study medication and were restricted from bathing or washing the treatment areas for at least eight hours after application.

Efficacy was based on mycological and clinical improvement in interdigital disease at endpoint, as determined from the derived variable, Treatment Success. Clinical evaluations were performed at baseline, and at days 8, 15, 22, 29 and 43, and at endpoint. Mycological evaluations (KOH) and cultures were performed at days 15, 29 and 43, and at endpoint. The final visit was on day 43, 14 days post-treatment.

Thirteen signs and symptoms directly attributable to tinea pedis at the interdigital site on the target foot were evaluated before start of treatment and at each study visit. Additionally, each study visit incorporated a global evaluation of change in overall severity of the disease, which included an evaluation of change in both the area involved and in the signs and symptoms.

Subjects were questioned at each visit on the occurrence of adverse events. Adverse events were recorded and evaluated by the investigator for severity and relationship to the study drug. Clinical laboratory tests were obtained at baseline and the last treatment visit, for one of the two studies. They included blood and urine specimens for hematology, serum chemistry and urinalysis. Subjects' evaluations of the cosmetic acceptability of the study drug were carried out at the final treatment visit.

Statistical analysis

Demographic and background characteristics were compared between treatments using analysis of variance (ANOVA) for continuous variables, and the Mantel-Haenszel test for categorical variables. Post-baseline efficacy data were analyzed using the Mantel-Haenszel test. Two-tailed tests were used; test results were considered statistically significant if $P \leq 0.05$.

All treated subjects (374) were included in the safety analysis, while only 317 subjects were eligible for inclusion in the efficacy analysis.

Results

The key visit analyzes include the final treatment visit (day 29), the visit 2 weeks post-treatment (day 43) and endpoint. Endpoint was considered to be the primary time point. Outcomes of the individual studies and the two studies combined were identical in all cases at all key visits and for all key efficacy parameters (percentage of subjects with Treatment Success and percentage of subjects with Treatment Cure). Analyses of the pooled data included only the key visits.

The overall results were similar between subjects with or without plantar disease. Therefore, the data that combines subjects with and without plantar involvement are presented.

Mycological cure

Mycological cure was defined as negative KOH and negative final culture. Differences between treatments for mycological cure were both numerically large and significant by day 15, in the individual studies, and mycological cure increased with time in the ciclopirox group. Analyses of pooled data at key time points (day 29, 43 and endpoint) reflect these significant differences in favor of ciclopirox (Fig. 1). Since statistical analysis for the combined studies was only performed for the

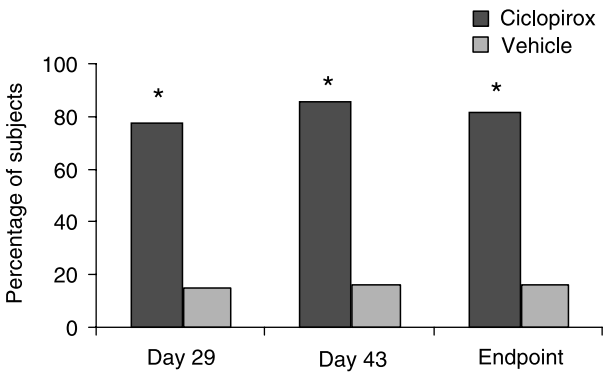

Figure 1 Percentage of subjects with mycological cure. (*P = 0.05 compared to vehicle.)

key time points of days 29, 43 and endpoint, the significance at day 15 (present in both studies) is not shown in Fig. 1. At day 43, 2 weeks post-treatment, the pooled data showed that 85% of ciclopirox subjects were mycologically cured, compared to only 16% of vehicle subjects.

Analysis by organism demonstrated ciclopirox to be significantly better than vehicle, at all key visits, in affecting mycological cure in subjects with *T. rubrum*. Because most of the subjects were infected with *T. rubrum*, the analysis for this pathogen mirrors the overall analysis for Treatment Cure by organism. Too few subjects were infected with other organisms to permit meaningful evaluations. However, there was a strong trend toward superiority of ciclopirox in the treatment of *T. mentagrophytes* and *E. floccosum*.

In order to assess the validity of the individual measures involved in mycological cure, KOH and culture results were compared. The results of KOH and culture tests were highly correlated, i.e. the majority of negative results in one test were associated with negative results in the other.

Treatment success

Treatment success, the primary efficacy variable, was defined as mycological cure with ≥ 75% clinical improvement (a global evaluation score of 0 or 1). The studies showed significant differences between ciclopirox and the vehicle in favor of ciclopirox at all key time points. When plotted vs. time, in each study there was an impressive upward trend after day 15 in the percentage of ciclopirox subjects who were treatment successes, whereas the vehicle response was almost flat. Analyses of pooled data at key time points showed significant differences in favor of ciclopirox. (Fig. 2) At endpoint, 60% of the ciclopirox subjects were treatment successes compared to 6% of the vehicle subjects.

Complete cure

Complete Cure was defined as mycological cure plus clinical cure (100% clinical improvement, indicated by a global evaluation score of 0). Again, significant differences favored ciclopirox over vehicle at days 29, 43 and endpoint. (Fig. 3) At endpoint, 40% of the ciclopirox subjects were completely cured compared with only 4% of those using vehicle.

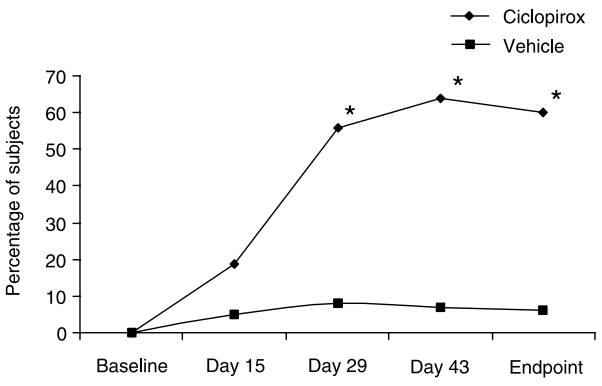

Figure 2 Percentage of subjects with treatment success mycological cure and > 75% clearance of interdigital signs and symptoms. (*P = 0.05 compared to vehicle.)

Global evaluation scores

Improvement or clearing of tinea pedis, reflected by a decrease in the global evaluation score, showed mean global evaluation scores for the ciclopirox group decreasing throughout the study, including the post-treatment period, while there was little change for vehicle. In both studies, differences in mean global evaluation scores significantly favored ciclopirox beginning at day 8. Analyses of pooled data at key time points showed significant differences in favor of ciclopirox. (Fig. 4)

The percentage of subjects with clinical cure (global evaluation score = 0) or excellent improvement (global evaluation

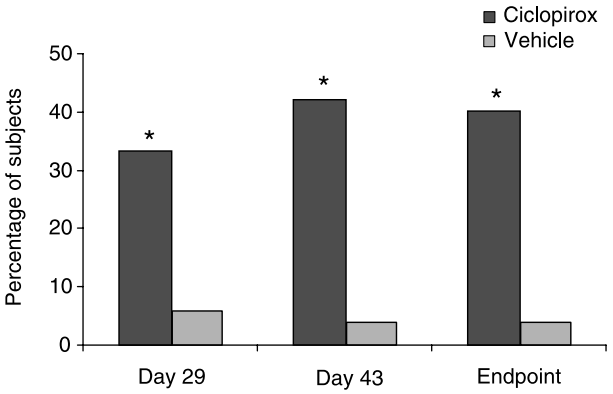

Figure 3 Percentage of subjects with complete cure (negative KOH and culture, and 100% clearance of interdigital signs and symptoms). (*P = 0.05 compared to vehicle.)

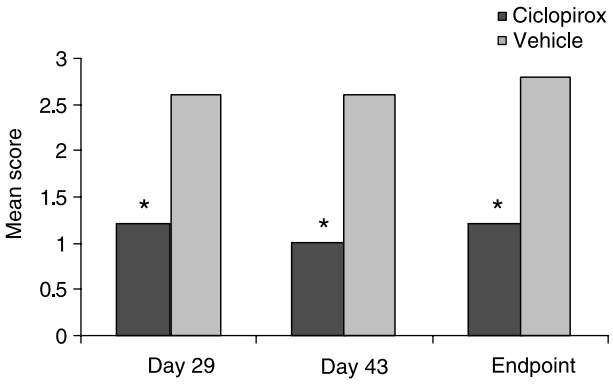

Figure 4 Mean global evaluation scores. Cleared = 0 (100% clearance); excellent improvement = 1 (75% to 99% clearance); moderate improvement = 2 (50% to 74% clearance); slight improvement = 3 (< 50% clearance); no change = 4; exacerbation = 5. (*P = 0.05 compared to vehicle.)

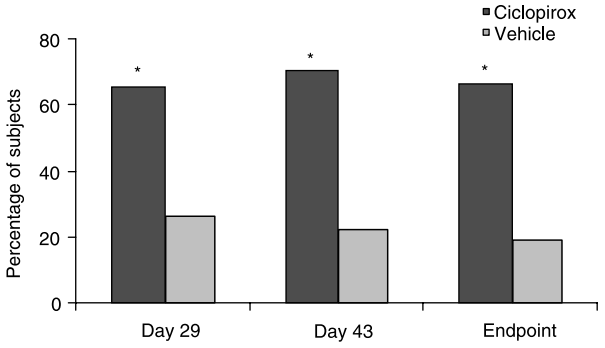

Figure 5 Percentage of subjects with clinical cure or excellent improvement. (*P = 0.05 compared to vehicle.)

score of 0 or 1) was significantly higher in the ciclopirox group than in the vehicle group for days 29, 43 and endpoint. At endpoint, 66% of ciclopirox subjects compared with 19% of vehicle subjects were either cleared or had excellent improvement. (Fig. 5)

At the other extreme, 32% of vehicle subjects vs. 5% using ciclopirox showed either no improvement or exacerbations (global evaluation scores of 4 or 5) at endpoint.

Signs and symptoms

The severity of 13 signs and symptoms of disease were rated on a 0–3 scale where 0 = none and 3 = severe. Change from baseline mean sign and symptom scores were analyzed including only subjects who had the sign/symptom at baseline or any subsequent visit. Subjects without signs or symptoms were excluded from the analysis to avoid dilution of the mean scores.

There were no significant differences between treatment groups or between studies in the incidence of signs and symptoms at baseline. (Table 1)

Scaling was the most common sign or symptom (present in all but one ciclopirox subject at baseline) and was relatively resistant to treatment. Nevertheless, ciclopirox subjects experienced steady improvement in this symptom through day 29. The differences between ciclopirox and vehicle were significant from day 29 onward. At the post-treatment time point (day 43), there was a notable improvement in the ciclopirox group vs. the vehicle group. The baseline mean scores were 1.92 for ciclopirox and 1.96 for vehicle; at endpoint, these scores were 0.86 and 1.51, respectively. At endpoint, 34% ciclopirox and 12% vehicle subjects were free of scaling.

Erythema responded readily to treatment. Scores for erythema declined in a consistent pattern throughout both studies showing significant differences from day 22 onward. By endpoint the mean baseline ciclopirox score of 1.4 had significantly decreased to 0.32, while vehicle scores showed only a modest change from 1.39 at baseline to 0.91. At endpoint 85% of ciclopirox subjects and 36% of vehicle subjects, who had exhibited erythema at baseline, were clear of erythema.

Table 1 Frequency* and mean severity score† of signs and symptoms at baseline: combined studies

	Ciclopirox			Vehicle		
	n	%	Mean Score	*n*	%	Mean Score
Scaling	159	99	1.92	157	100	1.96
Erythema	138	86	1.48	138	88	1.39
Pruritus	131	82	1.86	130	83	1.70
Maceration	109	68	1.58	90	57	1.36
Fissures	89	56	1.14	92	57	1.02
Hyperkeratosis	79	49	1.24	68	43	1.30
Burning	54	34	1.49	58	37	1.27
Exudation	31	19	1.20	30	19	0.68
Pain	29	18	1.38	28	18	1.16
Edema	25	16	1.14	19	12	0.65
Papules	17	11	0.94	16	10	0.48
Vesiculation	11	7	1.10	8	5	0.80
Pustules	2	1	1.00	1	1	0.25

*Number of subjects with a sign or symptom score of 1–3 evaluated on a 0–3 scale where 0 = none; 1 = mild; 2 = moderate; 3 = severe.
†only for subjects with signs or symptoms.

The differences between treatment groups, in change-from-baseline pruritus mean scores, were significant at all time points after baseline. The mean scores at endpoint were 0.14 for ciclopirox, a decrease of 1.72, and 0.91 for vehicle, down only 0.79 from baseline. At endpoint, most ciclopirox subjects (89%) were clear of pruritus, regardless of baseline severity while less than half (45%) of vehicle subjects were clear of pruritus at endpoint.

Mean ciclopirox maceration scores declined rapidly and steadily through day 43. In both studies, differences between ciclopirox and vehicle were significantly in favor of ciclopirox from day 15 onward. At endpoint, mean scores were 0.32 for ciclopirox and 1.0 for vehicle. For ciclopirox subjects with maceration at baseline, 81% were cleared vs. 47% of the vehicle group. Clearing of maceration in ciclopirox subjects was independent of its baseline severity.

Fissures responded well to treatment with ciclopirox. There were significant differences between groups, in favor of ciclopirox from day 22 through the end of the study. At endpoint, the mean fissure score was 0.25, a significant change from baseline of 0.89, with most of the ciclopirox subjects cleared of fissures, regardless of baseline severity. Comparatively, the mean endpoint fissure score for vehicle subjects was 0.7, a change from baseline of only 0.32.

Ciclopirox scores for hyperkeratosis fell rapidly and consistently throughout the study, in contrast to the small reductions in vehicle scores. Mean scores for ciclopirox subjects decreased by 0.76 while vehicle subjects' mean scores decreased by approximately half that amount (0.4).

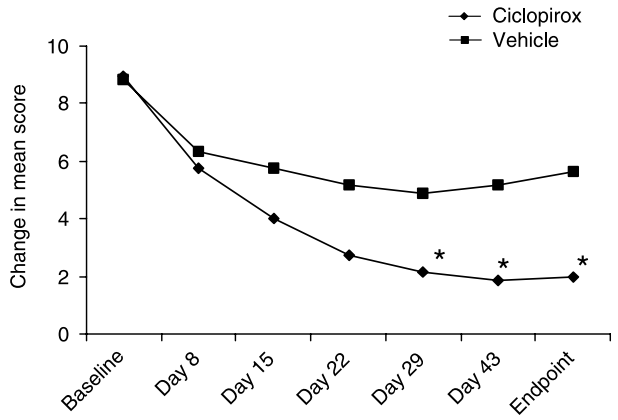

Figure 6 Change in TSS3 (Total of all 13 signs and symptoms scores) in the ciclopirox gel and vehicle groups. (*P = 0.05 compared to vehicle.)

In addition, total signs and symptoms were analyzed using three derived efficacy variables: TSS1 (the sum of the most common signs and symptoms: erythema, pruritus and scaling scores), TSS2 (the sum of maceration, fissures, hyperkeratosis and TSS1 scores), and TSS3 (the sum of scores for all 13 signs and symptoms). Slopes of the TSS1 and TSS2 curves mirrored that of the TSS3 curve and all showed ciclopirox-treated infections to improve continually, even through the post-treatment period. Differences between ciclopirox and vehicle were significant at days 29, 43 and endpoint in both studies. The combined scores for all 13 signs and symptoms are presented. (Fig. 6)

Cosmetic acceptability

Subjects rated cosmetic acceptability on a 0–3 scale where: 0 = Excellent, and 3 = Poor. Their ratings were generally favorable. At the end of treatment, 46% of ciclopirox and 24% of vehicle subjects rated the cosmetic acceptability of their treatment as excellent. At the final treatment, the mean acceptability score for ciclopirox was 0.7 and 1.0 for vehicle.

Clinical laboratory evaluations

Laboratory data were collected in only one of the two studies. Descriptive statistics were used to evaluate the data. There were no clinically noteworthy, abnormal laboratory findings.

Treatment emergent signs and symptoms – local adverse effects

All subjects who were treated were included in the safety evaluations. In both treatment groups, all treatment emergent signs and symptoms, possibly or probably related to the study drug, were localized reactions. The most common adverse event occurring in either treatment group was burning sensation of the skin, reported by 14 ciclopirox subjects and 13 vehicle subjects. Many of the subjects who reported burning had fissures. Three ciclopirox subjects and one vehicle subject reported pruritus. No subjects discontinued therapy for safety reasons.

Discussion

Ciclopirox gel was found to be significantly more effective than vehicle in the above studies. This is similar to the results reported in other studies involving the use of ciclopirox for treating tinea pedis. In two double-blind trials, Kligman *et al.*[11] reported that ciclopirox cream was significantly more effective clinically ($P < 0.001$) and mycologically ($P < 0.05$) when compared to vehicle. Ciclopirox lotion was found to be significantly more effective than vehicle in treating common presentations of tinea pedis, with very few side-effects[12]. Ciclopirox 0.77% gel was evaluated in a recent placebo-controlled, randomized, double-blind study involving patients with dermatophytosis complex (A. Gupta *et al.*, submitted for publication). Subjects in this trial applied ciclopirox twice daily, and it was reported that ciclopirox was significantly more effective than placebo for reducing total signs and symptoms of tinea pedis ($P < 0.01$), and improving global evaluation scores and subject evaluation ($P < 0.05$). More subjects obtained mycological cure and complete cure in the ciclopirox groups, than those who applied placebo (A. Gupta *et al.*, submitted for publication). All of these trials had subjects apply ciclopirox for 28 days, which seems to be an appropriate length of time for good efficacy to be obtained.

Because the gel contains isopropyl alcohol, mild-to-moderate burning sensations when the gel formulation is applied to acutely inflamed skin are not unexpected. The intensity of the burning experienced by patients in this trial was generally considered mild. Most cases of burning occurred very early in treatment and upon application of the study drug; the reaction lasted from two to 18 days. In no case did the condition persist throughout treatment. Similar side-effects were reported in a recent study using ciclopirox gel to treat interdigital tinea pedis (A. Gupta *et al.*, submitted for publication).

Conclusion

These studies demonstrate that ciclopirox gel applied twice daily for 4 weeks is effective in the treatment of interdigital tinea pedis due to *T. rubrum*, *T. mentagrophytes* and *E. floccosum* and is associated with a low incidence of minor adverse effects.

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