The Safety and Efficacy of Sertaconazole Nitrate Cream 2% for Tinea Pedis

Ronald Savin, MD; Joseph Jorizzo, MD

To determine the safety and efficacy of topical sertaconazole nitrate cream 2% in the treatment of tinea pedis, 2 randomized, multicenter, double-blinded, parallel group, vehicle-controlled studies were conducted. A total of 588 subjects were enrolled, and 383 subjects were randomized to treatment with sertaconazole or vehicle applied twice daily for 4 weeks. Improvements in symptoms were noted at week 1 in the active treatment group. At week 4, mycologic cure was seen in 70.3% of sertaconazole-treated subjects and 36.7% of vehicle-treated subjects (P<.0001). At week 6, 46.7% of sertaconazole-treated subjects had successful treatment outcomes compared with 14.9% of vehicle-treated subjects (P<.0001). No serious adverse events were reported, and rates of cutaneous adverse events were comparable between treatment groups. In conclusion, sertaconazole nitrate cream 2% was well-tolerated, offered rapid relief of symptoms, and achieved high rates of mycologic cure. The stability of the mycologic cure rates through weeks 5 and 6 (2 weeks after cessation of therapy) indicate that sertaconazole protects against reinfection.

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Approximately 10% to 20% of the US population has tinea pedis (athlete's foot).[1-5] In the United States, most cases of tinea pedis are caused by dermatophytes, primarily *Trichophyton rubrum* and *Trichophyton mentagrophytes*, and less commonly *Epidermophyton floccosum*.[2,6,7] Classic interdigital tinea pedis causes pruritus or burning and is characterized by fissuring, scaling, or maceration in the toe webs. The "moccasin" form of tinea pedis involves thickening and scaling of skin on the soles, heels, and sides of the feet.[8,9]

Drug classes available for treating tinea pedis include imidazoles, triazoles, benzylamines, allylamines, and hydroxypyridones. Although over-the-counter topical antifungal products such as clotrimazole, miconazole nitrate, terbinafine, and tolfanate are safe and generally effective, complete mycologic or clinical cures are difficult to achieve because relapses and chronic infection are common.[1,5,8,10,11]

Sertaconazole nitrate is a benzothiophene imidazole,[12,13] with broad-spectrum in vitro activity against dermatophytes, yeasts, filamentous fungi, and bacteria associated with cutaneous infections.[14-16] The drug has both fungistatic[17] and fungicidal activity.[18] Its antibacterial activity extends to the types of Gram-positive bacteria that typically colonize these fungal infections of the skin and contribute to the worsening of regional inflammation, lesion appearance, and clinical symptoms.[15,16] Of particular importance in treating tinea pedis, the sertaconazole molecule contains a highly lipophilic benzothiophene fragment that enhances penetration and long-term drug residency within the horny layer of the epidermis.[12,13,19] Systemic absorption of sertaconazole following topical application is not detectable.[19,20]

We report on combined results from 2 clinical trials that were identically designed to evaluate the safety and efficacy of sertaconazole in treating tinea pedis.

MATERIALS AND METHODS

Overall Study Design

Two 6-week, randomized, multicenter, double-blinded, parallel group, vehicle-controlled studies of sertaconazole were conducted at 35 clinical centers in the United States. The study protocol was designed in accordance with registration criteria established by the

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Dr. Savin is from the Department of Dermatology, Yale University School of Medicine, New Haven, Connecticut. Dr. Jorizzo is from the Department of Dermatology, Wake Forest University School of Medicine, Winston-Salem, North Carolina.

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Reprints: Ronald Savin, MD, Department of Dermatology, Yale University School of Medicine, 134 Park St, New Haven, CT 06511 (e-mail: savinderm@snet.net).

US Food and Drug Administration.[21] At the pretreatment assessment (week 0) and each subsequent visit, investigators assigned a severity score (0=absent [healthy appearing skin], 1=mild [barely abnormal], 2=moderate [distinctly present abnormality], 3=marked [intense involvement or marked abnormality]) to the interdigital area most affected with tinea pedis. They also took scrapings for microbiologic examination and culture. Eligible subjects were randomized (1:1 ratio) to receive sertaconazole nitrate cream 2% or vehicle cream (control) at the first visit. The subjects used the cream twice daily for 4 consecutive weeks, followed by a 2-week period with no treatment. Evaluations of safety, disease severity, and mycologic eradication were conducted at weeks 1, 2, 3, 4, and 6.

The primary efficacy endpoint was assessed at week 6 and was defined as the percentage of subjects who demonstrated successful treatment outcome.

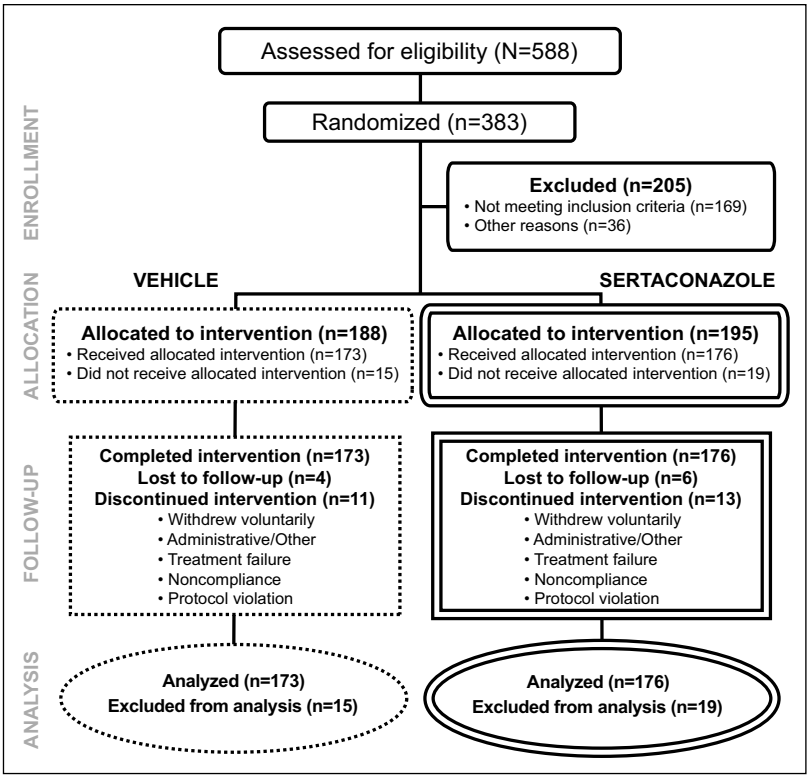

Figure 1. Study schema of clinical trials evaluating the safety and efficacy of sertaconazole nitrate cream 2% for tinea pedis.

Entry Requirements

The studies enrolled immunocompetent subjects 12 years and older (males or nonpregnant nonnursing females). All subjects had a clinical diagnosis of interdigital tinea pedis on 1 or both feet, confirmed by laboratory evaluation (microscopic examination confirmed by a positive potassium hydroxide [KOH] test).

Exclusion Criteria

Specifically excluded from the studies were individuals with extensive moccasin-type tinea pedis; extremely severe tinea pedis; widespread dermatophytoses; onychomycosis (on the evaluated foot); oral, vaginal, or chronic mucocutaneous candidiasis; or bacterial skin infection. Also excluded were subjects who had applied topical antifungal therapy to the feet within 14 days of study entry (30 days for terbinafine, butenafine, and naftifine hydrochloride) or had been treated with oral antifungal therapies within 3 months of study entry (8 months for oral terbinafine). Other exclusion criteria included a variety of prespecified skin disorders, diseases, drug sensitivities, and laboratory abnormalities.

Treatment

After screening and enrollment, subjects were randomized to sertaconazole nitrate cream 2% or its vehicle. The creams were supplied in 30-g tubes. Beginning on day 0 and for 4 consecutive weeks, subjects rubbed a thin film of the cream onto the skin twice daily (morning and evening). Subjects were asked not to make any additional changes to their daily routines.

Efficacy and Safety Assessments

At all visits, investigators used a 4-point scale to grade interdigital web spaces for severity. The investigator also performed global evaluations of clinical responses at weeks 1, 2, 3, 4, and 6 using 3 definitions of efficacy as outlined in the physician global assessment of clinical response scale: successful treatment outcome, clinical success, and clinical failure. *Successful treatment outcome* was defined as either effective clinical treatment (mycologic cure in addition to marked improvement over baseline signs and symptoms of interdigital tinea pedis) or clinical cure (mycologic cure in addition to normal appearance of skin). *Clinical success* was defined as either effective clinical treatment (marked improvement over pretreatment in signs and symptoms; at most, mild residual erythema and/or scaling in all treated interdigital web spaces without other signs of interdigital tinea pedis) or clinical cure (normal appearance of skin in all treated interdigital web spaces with signs

Table 1.

Analysis of Baseline Disease Severity

	Study 1		Study 2	
	Vehicle (n=148)	Sertaconazole Nitrate Cream 2% (n=151)	Vehicle (n=143)	Sertaconazole Nitrate Cream 2% (n=146)
Lesions, n (%)				
One foot	29 (19.6)	33 (21.9)	33 (23.1)	29 (19.9)
Both feet	119 (80.4)	118 (78.1)	110 (76.9)	117 (80.1)
Duration of current episode, n (%)				
<1 mo	16 (10.8)	19 (12.6)	20 (14.0)	27 (18.5)
1–3 mo	35 (23.6)	40 (26.5)	37 (25.9)	45 (30.8)
3–6 mo	17 (11.5)	21 (13.9)	17 (11.9)	8 (5.5)
>6 mo	80 (54.1)	71 (47.0)	69 (48.3)	66 (45.2)
Mean no. of previous episodes	8.5	10.9	9.7	11.9

and symptoms of interdigital tinea pedis completely resolved). *Clinical failure* was defined as either a worsening of clinical status (some pretreatment signs and symptoms of interdigital tinea pedis are more severe or new symptoms are present); mild clinical improvement or no change (pretreatment signs and symptoms have decreased or significant evidence of disease remains); or moderate clinical improvement (pretreatment signs and symptoms have shown a definite decrease).

Mycologic cure was defined as negative tests (both KOH preparation and culture) at weeks 4 and 6; *mycologic failure* was defined as a positive test (either KOH or culture) at either week 4 or 6. Adverse event data were collected at each study visit using an open-ended question format. Subjects also were asked by nonclinic personnel to evaluate treatment effectiveness and cosmetic acceptability at week 4.

Statistical Analysis

The primary variable, the percentage of subjects who demonstrated successful treatment outcome with sertaconazole compared with vehicle, was analyzed using the Cochran-Mantel-Haenszel χ^2 test adjusted for the investigator. All statistical tests were 2 tailed with a significance level of less than .05 unless otherwise stated. Discrete variables such as sex, race, number of feet with infection, history of infection, and adverse events were compared using the χ^2 or Fisher exact test.

RESULTS

Study Participants

A total of 588 subjects were enrolled between September 1997 and March 1998. This intent-to-treat (ITT) group, with an average duration of treatment of 21 days, formed the basis of the safety analysis. The modified ITT population included all randomized subjects who had a positive baseline culture, received study treatment, returned for at least one postbaseline treatment, and had no major protocol violations. This modified ITT population was the basis for all primary efficacy analyses. In all, 349 subjects completed the study (Figure 1). Demographic characteristics and incidence of disease factors (Table 1) were comparable in the treatment groups. The mean age in the modified ITT group was 35 years (range, 12–86 years). Causative pathogens included *T rubrum* (78.9%), *T mentagrophytes* (14.1%), and *E floccosum* (10.7%).

Table 2.

Subjects Free of Clinical Signs and Symptoms

	Vehicle, n (%) (n=188)	Sertaconazole Nitrate Cream 2%, n (%) (n=195)	*P* value
Erythema			
Week 2	20 (10.6)	28 (14.4)	
Week 4	48 (25.5)	91 (46.7)	<.0001
Week 6	48 (25.5)	105 (53.8)	<.0001
Pruritus			
Week 2	65 (34.6)	93 (47.7)	
Week 4	103 (54.8)	145 (74.4)	.0001
Week 6	96 (51.1)	149 (76.4)	<.0001
Scaling			
Week 2	9 (4.8)	8 (4.1)	
Week 4	28 (14.9)	41 (21.0)	.0046
Week 6	26 (13.8)	60 (30.8)	<.0001

Efficacy

Clinical Success—Based on the investigator's periodic global evaluation of clinical signs and subjective symptoms, the subjects treated with sertaconazole achieved a statistically higher percentage of overall clinical success versus vehicle at weeks 4 (57.9% vs 39.9%; $P<.0009$) and 6 (64.6% vs 37.8%; $P<.0001$). These findings indicate that significantly more subjects treated with sertaconazole had marked improvement, if not complete resolution of signs and symptoms, along with normal or at most mild residual erythema and/or scaling.

Clinical Signs and Symptoms—In terms of specific symptoms, investigator ratings for erythema, pruritus, and scaling showed that a significantly greater number of subjects treated with sertaconazole versus vehicle were free of clinical signs and symptoms of erythema ($P<.0001$), pruritus ($P=.0001$), and scaling ($P=.0046$) by week 4 (Table 2). Subject evaluations also indicated rapid relief of symptoms. After one week of treatment, 77% of subjects using sertaconazole reported either mild or no itching, compared with only 20% pretreatment. By week 3, significantly more subjects using sertaconazole were completely itch free compared with the vehicle group (64% vs 44%, respectively; $P=.0001$), and this statistical superiority was sustained for 2 weeks posttreatment (week 6)(76.4% vs 51.1%, respectively; $P<.0001$).

Mycologic Cure—Significantly more sertaconazole-treated subjects achieved mycologic cure versus vehicle-treated subjects throughout the studies ($P<.0001$)(Figure 2). After 2 weeks with no treatment (week 6), the sertaconazole mycologic cure rate of 66.2% was 3 times the mycologic cure rate in the control group ($P<.0001$). The results of the culture tests alone (ie, without reference to KOH wet mount results) reveal an even more marked ability for sertaconazole to clear infections and prevent relapses. Two weeks after treatment cessation, 89% of subjects using sertaconazole had negative cultures versus 38% of subjects using vehicle ($P<.0001$).

Successful Treatment Outcome—In terms of this combined clinical-mycologic endpoint, sertaconazole was more effective than vehicle cream

at all time points past week 2 (Figure 3). At week 6, sertaconazole subjects had significantly higher rates (46.7%) of successful treatment outcomes than control subjects (14.9%), an advantage also evident in each study (study 1: 36.5% vs 13.6%, $P=.0006$; study 2: 56.6% vs 16.0%, $P<.0001$). This finding indicates that subjects randomized to sertaconazole were about 3 times as likely as those receiving vehicle to attain complete mycologic cure and to show marked or complete improvement of skin appearance.

The relapse rate (defined as the number of subjects with a successful treatment outcome at week 4 but a clinical failure at week 6) was significantly higher in the control group than in the sertaconazole group (66.7% vs 29.5%; $P<.0001$). Time to successful treatment outcome based on both mycologic clearing and clinical cure at week 4 (and excluding relapsed subjects) also was significantly shorter in the sertaconazole group than in the control group ($P=.0001$). Vehicle group relapse rates were 70.6% (study 1) and 64.0% (study 2). Sertaconazole relapse rates were 37.5% (study 1) and 20.8% (study 2).

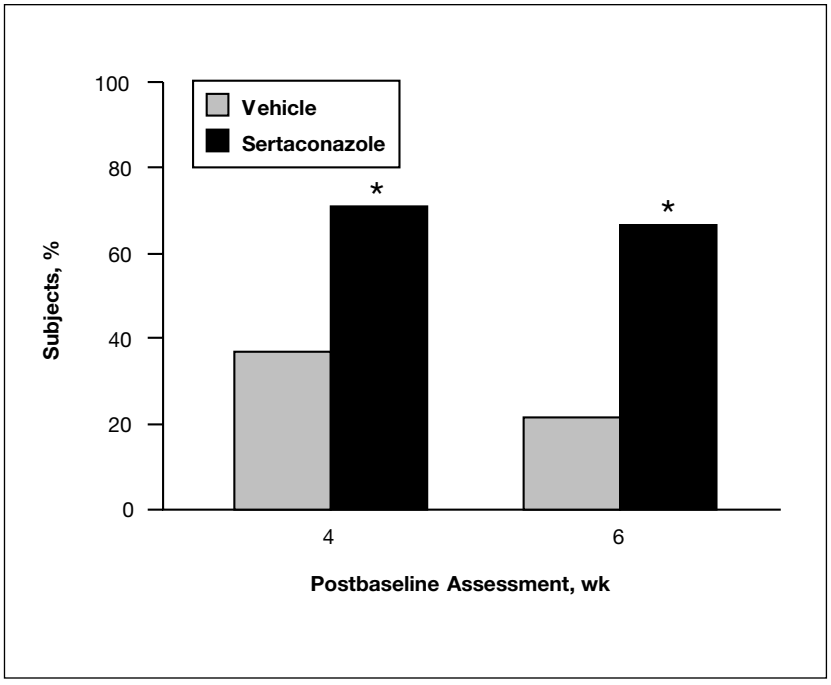

Figure 2. Percentage of subjects treated with sertaconazole nitrate cream 2% (n=195) and vehicle (n=188) with mycologic cure at weeks 4 and 6. Asterisk indicates $P<.0001$.

Subgroup Analyses—Examination of results by subject subgroups of age, sex, and race revealed no conflicting trends, with all statistically significant treatment effects favoring the sertaconazole subgroups.

Safety and Tolerability

Overall, 50 of 291 (17.2%) vehicle-treated ITT subjects reported 67 adverse events, and 58 of 297 (19.5%) sertaconazole-treated ITT subjects reported 81 adverse events. Cutaneous adverse events, including contact dermatitis, dry skin, burning skin, application site reaction, and skin tenderness, occurred in 7 of 291 (2.4%) vehicle-treated subjects and 7 of 297 (2.4%) sertaconazole-treated subjects. Four of the 14 cutaneous adverse events were considered severe (2 in each treatment group). Nonserious and non–drug-related adverse events included, in order of frequency, headache, upper respiratory infection, and common cold. Significantly more subjects in the sertaconazole group (88.1%) than the vehicle group (77.1%) said they would use the treatment again if the condition returned ($P=.0007$).

COMMENT

Sertaconazole nitrate cream 2% had greater efficacy than the vehicle cream in the treatment of interdigital tinea pedis. Subjects receiving sertaconazole had statistically significant improvements in the composite primary outcome (successful treatment outcome), as well as in a range of important secondary outcomes such as clinical cure, mycologic cure, and relapse rate ($P<.0001$ for all). Physician tracking of erythema, pruritus, and scaling also revealed rapid and significant reductions in disease severity with sertaconazole ($P<.001$ at week 6 for all). The safety profiles of sertaconazole cream and its vehicle are comparable.

Some dermatologists may perceive the absolute cure rates for both control and active treatment groups in these trials to be low by historical standards. For example, the vehicle cure rates in this study were only 5% to 20%, though placebo cure rates of 30%, 40%, or even 50% are more typical in tinea pedis trials.[22] However, critical differences in study design and subject populations preclude any direct cross-study comparisons of efficacy rates. In this regard, 2 unique features of this new sertaconazole study are worth mentioning.

First, the sertaconazole trial focused only on clinical responses that were either complete or marked improvements, but many trials involving imidazoles or other topical antifungals have defined cases of moderate or even mild clinical improvement as effective or a cure.[10,22,23] Such broad definitions of

clinical efficacy were common in the 1980s and 1990s before the US Food and Drug Administration issued revised guidelines on the study design for skin infection.[21]

A second possible explanation for a dampened cure rate in both treatment groups is the study protocol's lack of direction to subjects on improved foot hygiene. In fact, subjects were specifically asked to avoid changing any bathing habits, types of clothing, or footwear, and to refrain from use of foot or shoe powders—all basic strategies that, in other trial settings, boost baseline healing rates. Furthermore, most subjects in the sertaconazole trials had tinea pedis episodes of more than 3 months' duration; a typical subject had already experienced 10 previous episodes. Thus, given the stubborn and recurring nature of the tinea pedis infections in this study population, withholding of basic foot hygiene counseling may have helped maintain a challenging local environment for cure. Relapse rates of 70.6% and 64.0% in the study 1 and 2 vehicle groups, respectively, reflect this difficult treatment environment, just as the sharply reduced relapse rates in the sertaconazole-treated subjects (37.5% [study 1] and 20.8% [study 2]) attest to the lingering protective effect of this benzothiophene imidazole agent.

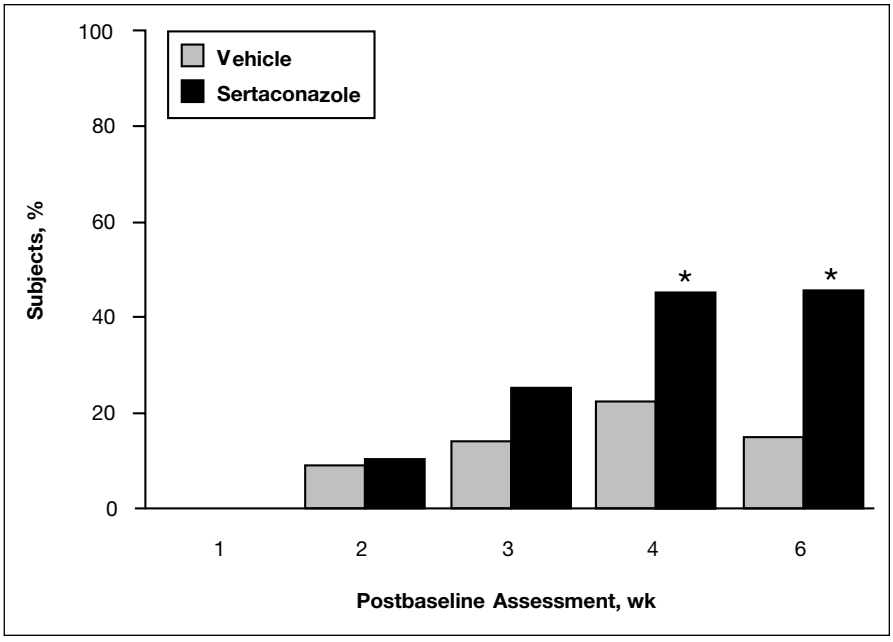

Figure 3. Percentage of subjects with successful treatment outcomes (weeks 1–6) in 2 identical placebo-controlled clinical trials evaluating sertaconazole nitrate cream 2% versus vehicle cream. Asterisk indicates $P<.0001$.

Previous European comparative studies of sertaconazole in various dermatomycoses indicate that sertaconazole may offer efficacy advantages over some currently employed topical imidazoles.[24-26] In infections with *T rubrum*, an organism common in tinea pedis that has a propensity to develop resistance,[27] sertaconazole cured all infections and miconazole was effective in only 23 of 27 cases (85%). The relapse rate at day 35 also was significantly lower with sertaconazole (13/294, 4.4%) compared with miconazole (33/277, 11.9%)($P=.001$). These reports shed light on the potential enhanced efficacy profile of sertaconazole related to its broad-spectrum fungicidal activity and its high stratum corneum penetration and retention.

Conclusion

Two US-based, randomized, multicenter, double-blinded, parallel group, vehicle-controlled clinical trials have demonstrated that sertaconazole nitrate cream 2% is a safe, well-tolerated, and effective treatment for subjects with interdigital tinea pedis. These studies involving 588 subjects show that sertaconazole used twice daily for 4 weeks is safe, as well as clinically and microbiologically effective, in treating the most common form of tinea pedis.

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