

COMPARISON OF SAFETY AND EFFICACY OF LALICONAZOLE AND OTHER ANTIFUNGAL AGENTS

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Abstract

Aims: The main aim of the study is to compare the efficacy of newer antifungals like Luliconazole, Amorolfine, eberconazole, sertaconazole and terbinafine cutaneous mycoses (commonest presentation- tinea corporis). The study also aims to evaluate the effectiveness and safety of these newer topical antifungals. **Study Design:** Prospective parallel study and is a randomized, open-label, comparative study to evaluate the efficacy of newer antifungal drugs. Study population as a total 150 patients, needed to be enrolled in the study based on the inclusion and exclusion criteria. All the patients are aged between 18 to 80 years. Patients will receive the newer antifungals randomly and the test product needed be applied once daily for 1 week in patients with Tinea cruris/ Tinea corporis and for 2 weeks in patients with Tinea pedis. Follow up as the first follow up will be at 1 week and all the patients will be evaluated for clinical parameters and global clinical response. The second follow up is at 4 weeks and all the patients are again needed to be assessed for the parameters. Adverse events were recorded at each visit. Place and Duration of Study: Omni Hospitals, Kothapet, Hyderabad approvals , 4 weeks. Conclusions in this study, the efficacy was higher in Sertaconazole (93.3%) group followed by Luliconazole, Amorolfine, Terbinafine and Eberconazole(86.6%, 83.3%, 80.0% and 73.3% respectively). And the Adverse events order as follows Eberconazole>Luliconazole>Terbinafine>Amorolfine>Sertaconazole.

Introduction

Dermatophyte infections are one of the earliest known fungal infections of mankind and are very common throughout the world (Venkatesan et al, 2007). Although dermatophytoses does not cause mortality, it does cause morbidity and poses a major health problem (Emmons and Binford et al, 1974) especially in tropical countries like India due to the hot and humid climate. No race in any geographical location is totally free from dermatophytoses (Rippon et al, 1988). Given that, the degree of immunosuppression and the number of immunosuppressed patients are increasing at an unprecedented pace, the management of dermatophytoses would be a definite challenge to mankind in the years to come. Most modern broad-spectrum antifungal agents act by blocking specific steps in the synthesis of fungal cell membrane components. Although the choice of an antifungal agent should be based on an accurate diagnosis. (Diehl et al, 1996). Currently, topical azoles and allylamines are used for the treatment of Cutaneous mycoses with disadvantages like long duration of therapy, which leads to poor compliance and a high relapse rate. Some of the newer agents require only once-daily application and shorter courses of treatment, and are associated with lower relapse rates (Palacio et al 1995).

Within the past few years, new extended-spectrum triazoles and allylamines have been introduced into market among such are Luliconazole, Sertaconazole, Eberconazole which belong to triazoles and Amorolfine which belong to Allyamine group. This report will summarize the studies evaluating new antifungal agents that are approved by the US Food and Drug or that have completed phase 3 clinical trials Administration. (Spanakis et al, 2006). Dermatophytes constitutes a group of about 40 fungal species that are members of the Trichophyton, Microsporium, and Epidermophyton genere and cause superficial infection called dermatophytosis, ringworm, or tinea (Ajello, 1968; David H.Stein et al 1998). Clinical fungal infection are generally divided into four types 1) superficial, including Tinea versicolor, Tinea piedra, Tinea nigra; 2) Cutaneous, including Onchomycosis, Tinea capitis, Tinea corporis, Tinea barbae, Tinea pedis, Candidiasis of skin, mucosa and nails; 3) subcutaneous including Mycetema, Sporotrichosis, and Chromoblastomycosis; and 4) systemic including North American blastomycosis and cryptococcosis. Superficial infections are defined as infection which a pathogen is restricted to the stratum corneum, with little or no tissue reaction.

Superficial mycoses are common worldwide. They are believed to affect 20% to 25% of the world's population, and the incidence continues to increase (Griffith et al., 1986). They are predominantly caused by dermatophytes,

and the causative species vary with geographic region and dermatophyte infections do not result in significant mortality, but they can greatly affect quality of life (Dahl, 1979).

Historically, medical mycology, specifically relating to human disease, began with the discovery of the fungal etiology of favus and centered around three European physicians in the mid-19th century: Robert Remak, Johann L. Schonlein, and David Gruby. According to Seeliger (Seeliger et al, 1985), However, Remak established that the etiologic agent of favus was infectious, cultured it on apple slices, and validly described it as *Achorion schoenleinii*, in honor of his mentor and his initial discovery (Weitzman et al, 1995). David Gruby on the basis of his discoveries during 1841 to 1844 has been described ectothrix invasion of the beard and scalp, naming the etiologic agent of the latter *Microsporum* (referring to the small spores around the hair shaft) *audouinii*, and described endothrix hair invasion by *Herpes (Trichophyton) tonsurans*. In addition to his observations on dermatophytes, he also described the clinical and microscopic appearance of thrush in children. (Weitzman et al, 1995). Sabouraud's treatment of tinea capitis by a one-dose, single-point roentgenologic epilation achieved cures in 3 months as opposed to the then current therapy of manual epilation and topical application of medications (Borello et al., 2010).

The main aim of the study is to compare the efficacy of newer antifungals like Luliconazole, Amorolfine, eberconazole, sertaconazole and terbinafine cutaneous mycoses (commonest presentation- tinea corporis). The study also aims to evaluate the effectiveness and safety of these newer topical antifungals. Dermatophytosis, commonly referred to as ringworm (Baran et al., 2007). Infection is generally cutaneous and restricted to the nonliving cornified layers because of the inability of the fungi to penetrate the deeper tissues or organs of immunocompetent hosts (Dei Cas et al, 1986).

Study design

It is a multicentric, randomized, open-label, comparative study to evaluate the efficacy of newer antifungal drugs. Study population as a total 150 patients needed to be enrolled in the study based on the inclusion and exclusion criteria. All the patients are aged between 18 to 80 years.

Patient selection

Patients above the age of 18 with clinical evidence of cutaneous mycoses (commonest presentation- tinea corporis) were clinically evaluated and a potassium hydroxide (KOH) preparation of scrapings from a selected lesion was examined microscopically. The symptoms and signs of erythema, scaling and pruritus were scored on a scale of 1 (Nil) to 3 (severe). Patients were eligible for the study if they had a combined score of at least 5. Age group between: 18-80 years; Gender: Both; No healthy volunteers and study was started after Institutional Ethics Committee of Omni Hospitals, Kothapet, Hyderabad approvals.

a. Inclusion criteria

1. Male and non-pregnant, non-lactating/ non-breast feeding female above 18 years of age, as confirmed by a medical history and physical examination and who are willing to give informed consent. 2. All patients with symptoms of cutaneous mycoses with the target site characterized by at least 2 of the 3 major symptoms of Erythema, Desquamation, Pruritis. Patients were eligible for the study if they had a combined score of at least 5

b. Exclusion criteria

1. Age less than 18 years, 2. Pregnant and lactating women, 3. Patients with a known history or clinical evidence of severe cardiac, pulmonary, gastrointestinal, renal, hepatic or neurological disease and uncontrolled diabetes mellitus, 4. Patients with a known hypersensitivity to allylamine/benzylamine agents, 5. Previous treatment with antifungal, antibiotic or immunosuppressant agents, 6. Patients with contact dermatitis, atopic dermatitis, psoriasis or any other disease

c. Drug administration

After recruitment, patients were randomly assigned to receive Luliconazole, Sertaconazole, Amorolfine, Eberconazole, Terbinafine cream in blocks of 25 patients. On the first presentation each patient's demographic data including age, sex, baseline clinical parameters such as erythema, desquamation, pruritis, vesicles, and encrustation needed to be noted. The individual scores were added and total score was reported. A KOH (10%) preparation of the scraping was examined to confirm the presence of hyphae.

Treatment: Patients will receive the newer antifungals randomly and the test product needed be applied once daily for 1 week in patients with Tinea cruris/ Tinea corporis and for 2 weeks in patients with Tinea pedis. Follow up as the first follow up will be at 1 week and all the patients will be evaluated for clinical parameters and global clinical response. The second follow up is at 4 weeks and all the patients are again needed to be assessed for the parameters. Adverse events were recorded at each visit.

Clinical assessment

The clinical efficacy was assessed on signs and symptoms severity score of the target lesion. These signs and symptoms were scored as: 0=absent (none), 1= mild (barely perceptible), 2=moderate (distinctive presence), and

3= severe (marked, intense). The signs and symptoms that were evaluated were erythema, desquamation, pruritis, vesicles, and encrustation.

Global clinical response was also evaluated by the investigator using the following 6 point scale: -1= exacerbation (flareup at the site of treatment), 0=unchanged, 1= mild improvement (<50% clearance), 2= moderate improvement (50% to 75% clearance), 3= excellent improvement (75% to 100% clearance), 4= cleared (100% clearance).

Efficacy parameters

The efficacy is assessed based on the following parameters: 1) KOH test: A negative KOH preparation at the end of the study period was considered as mycological cure. 2) Change in the signs and symptoms score.

Statistical analysis

The last observation carried forward (LOCF) method was used to analyze the data. Patients who had completed at least 2 weeks of therapy were included in the analysis. The data obtained was represented as mean \pm SEM and percentages, as applicable. Appropriate statistical tests (One way Analysis of Variance, ANOVA) were used for determining association between variables. A difference was considered as significant if the P value was less than 0.05.

Results:

Baseline demographics and disease characteristics of the patients included in this study results represented as in total 150 patients were included into the study population, divided into five groups of 30 patients and received Terbinafine(A), Eberconazole(B), Luliconazole(C), Sertaconazole (D), Amorolfine (E), and compared five symptoms they were Erythema, Desquamation, Pruritus, Vesicles, and Encrustation. A study population included 93 (62.0%) male patients and 57 (38.0%) female patients, the youngest patient was 18 years and the oldest was 58 years. Baseline characteristics of the IIT population are summarized in table 1. The mean changes in signs and symptoms at each week in different drug treatment groups that is Amorolfine group the mean changes for Erythema, Desquamation, Pruritus, Vesicles, and Encrustation were 0.74 ± 0.71 , 1.02 ± 0.75 , 0.75 ± 0.53 , 0.22 ± 0.38 and 0.09 ± 0.16 respectively. In Sertaconazole group the mean changes for Erythema, Desquamation, Pruritus, Vesicles and Encrustation were 0.67 ± 0.78 , 0.93 ± 0.8 , 0.74 ± 0.69 , 0.20 ± 0.39 and 0.06 ± 0.13 respectively. In Luliconazole group the mean changes for Erythema, Desquamation, Pruritus, Vesicles and Encrustation were 0.78 ± 0.72 , 0.93 ± 0.69 , 0.77 ± 0.62 , 0.19 ± 0.35 and 0.08 ± 0.16 respectively. In Eberconazole group the mean changes for Erythema, Desquamation, Pruritus, Vesicles and Encrustation were 0.96 ± 0.65 , 1.13 ± 0.62 , 0.77 ± 0.41 , 0.24 ± 0.28 and 0.06 ± 0.11 respectively. In Terbinafine group the mean changes for Erythema, Desquamation, Pruritus, Vesicles and Encrustation were 0.79 ± 0.68 , 1.08 ± 0.64 , 0.84 ± 0.58 , 0.22 ± 0.29 and 0.05 ± 0.09 respectively were given in Figures 2 to 6. Overall Mean changes in signs and symptoms of different treatment groups were given in Figure 7. Mean of Signs and Symptoms at four weeks durations compared to baseline are given Figure 8. The efficacy is assessed by the number of patients who has maximum improvement in signs and symptoms and those who has complete cure and the results were presented in Figure 9. Safety is assessed by the number of adverse events and the results were presented in Figure 10.

In Amorolfine group, Terbinafine group, Eberconazole group Sertaconazole and Luliconazole group, the mean change in sign and symptom score at week 4 was significantly ($P<0.0001$) reduced compared to baseline, whereas at week 2 there is significant ($P<0.001$) difference compared to baseline and at week 1 there is no significant difference compared to baseline.

The efficacy is assessed by the number of patients who has maximum improvement in signs and symptoms and those who has complete cure. The efficacies of different treatments are given in figure 9. Sertaconazole is showing higher efficacy with 93.3% followed by Luliconazole, Amorolfine, Terbinafine and Eberconazole with efficacy 86.6%, 83.3%, 80.0% and 73.3% respectively.

Efficacy order: Sertaconazole>Luliconazole>Amorolfine>Terbinafine>Eberconazole

Safety is assessed by the number of adverse events noted at each visit. A total of 25 patients that is 16.6% of cases had adverse events after the treatment. Out of these maximum were Burning, Irritation, Peeling of skin, Itching and Hyperpigmentation. Not a single patient discontinued the treatment because of adverse events. The safety of different treatments is given in figure 10. Eberconazole is having maximum adverse events with 26.6% followed by Luliconazole, Terbinafine, Amorolfine and Sertaconazole.

Adverse events order: Eberconazole>Luliconazole>Terbinafine>Amorolfine>Sertaconazole

Discussions:

All the drugs were well tolerated, but Sertaconazole proved to be significantly more effective in terms of clinical improvement and in the eradication of fungal pathogens. In the present study Sertaconazole is having higher

clinical symptom cure with 93.3%, in a study of Sharma et al., 2009 & 2011 comparing sertaconazole with miconazole, Sertaconazole showed 62.3% of clinical cure ($P < 0.05$) compared with 44.6% in miconazole users.

Luliconazole is having clinical symptom cure of 86.6% there is no much percentage difference compared to a previous study with different concentrations like 0.5%, 1% and 0.1% the rates of improvement in skin lesions were 90.5%, 91.0% and 95.8%, respectively showing greater efficacy rates. (Watanabe et al, 2007) In a study comparing Amorolfine and terbinafine, the Amorolfine-terbinafine combination showed higher response compared with the terbinafine group (66.7% vs. 53.5%, respectively; $P < 0.04$). In the present study Amorolfine and Terbinafine is having clinical symptom cure percentage of 83.3% and 80%. According to the results of (Sudip das et al., 2010; Bonifaz et al., 2000)

Adverse events reported were mild and did not report in the discontinuation of the drug. In a study of Borello et al., 2010. Sertaconazole reported AEs was low (8.7% [8/92]), and none were considered serious. In the present study the adverse event reported with Sertaconazole was 6.6% which was very mild (Carrillo-Munoz et al., 2005). In a study of palacio et al., 2006, with Amorolfine the adverse event reporting was 13% which was comparable to that of present study which resulted in 13.3%. In another study of Eberconazole resulted withdrawal of two patients due to side effects, in the present study it accounted for 26.6% but didn't result in the withdrawal of patients (palacio et al., 2009).

In the present study the order of improvement in signs and symptoms in the Sertaconazole group was with pruritus followed by erythema and desquamation which is comparable to the study of Borelli et al, (2010) substantial improvement in signs and symptoms after 4 weeks of treatment 63.7% (58/91) were free of erythema, 33.0% (30/91) were free of desquamation, and 91.2% (83/91) were free of itch.

Conclusion

A total of 150 patients were included in the study to find the efficacy and safety of new antifungals. Tinea corporis and Tinea cruris accounted for 57.3% and 43.0% of the three infections (viz., Tinea corporis, Tinea cruris and Tinea pedis). Mean changes in signs and symptoms showed patients with improvement in erythema, was higher in Sertaconazole group followed by Amorolfine, Terbinafine, Luliconazole and Eberconazole group. Likewise the mean changes in Desquamation and Pruritus, was higher in sertaconazole group followed by Luliconazole, Amorolfine, Terbinafine and Eberconazole. The efficacy was higher in Sertaconazole (93.3%) group followed by Luliconazole, Amorolfine, Terbinafine and Eberconazole (86.6%, 83.3%, 80.0% and 73.3% respectively). The adverse events were highest with Eberconazole (26.6%) followed by Luliconazole, Terbinafine, Amorolfine and Sertaconazole (20.0%, 16.6%, 13.3% and 6.6% respectively). Sertaconazole is having greater efficacy and safety compared with other antifungals. Even though Luliconazole is having greater efficacy it has reported to have more adverse events.

Results

Table 1. Baseline demographics and disease characteristics (intent-to-treat population) of this study.

	A group	B group	C group	D group	E group	Total
Sex, n(%)						
Male	19(62.0)	24(80.0)	21(70.0)	22(73.3)	21(70.0)	93(62.0)
Female	11(36.6)	6 (20.0)	9 (30.0)	8 (26.6)	9 (30.0)	57(38.0)
Age, years						
Mean \pm SD	28.5 \pm 8.64	28.6 \pm 6.48	32.8 \pm 10.7	30.9 \pm 10.4	30.8 \pm 7.79	30.4 \pm 8.99
Median	25.5	27.5	31.0	29.5	29.0	28.0
Type of Infection, n(%)						
T.corporis	19(63.3)	17(56.6)	15(50.0)	17(56.6)	18(60.0)	86(57.3)
T.cruris	11(36.6)	13(43.3)	15(50.0)	13(43.3)	11(36.6)	63(42.0)
T.pedis	–	–	–	–	1(0.03)	1(0.006)

Mycological examination

positive^a, n(%) 30(100.0) 30(100.0) 30(100.0) 30(100.0) 30(100.0) 150(100.0)

Total diseased surface (cms)^b

Mean ± SD 24.0±14.4 26.0±14.9 28.7±15.9 24.6±5.4 26.2±5.9 35.9(15.2)

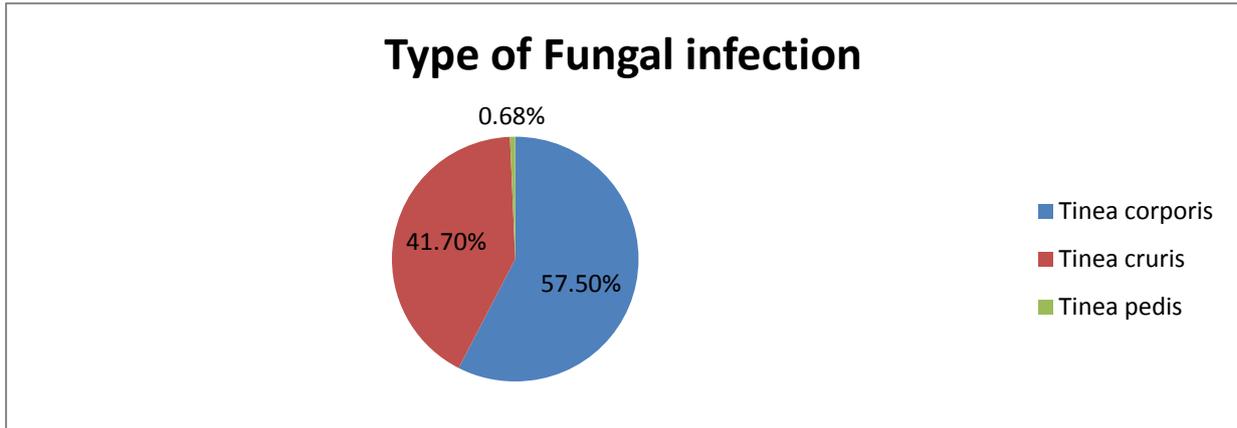


Figure 1: Percentages of the type of fungal infection

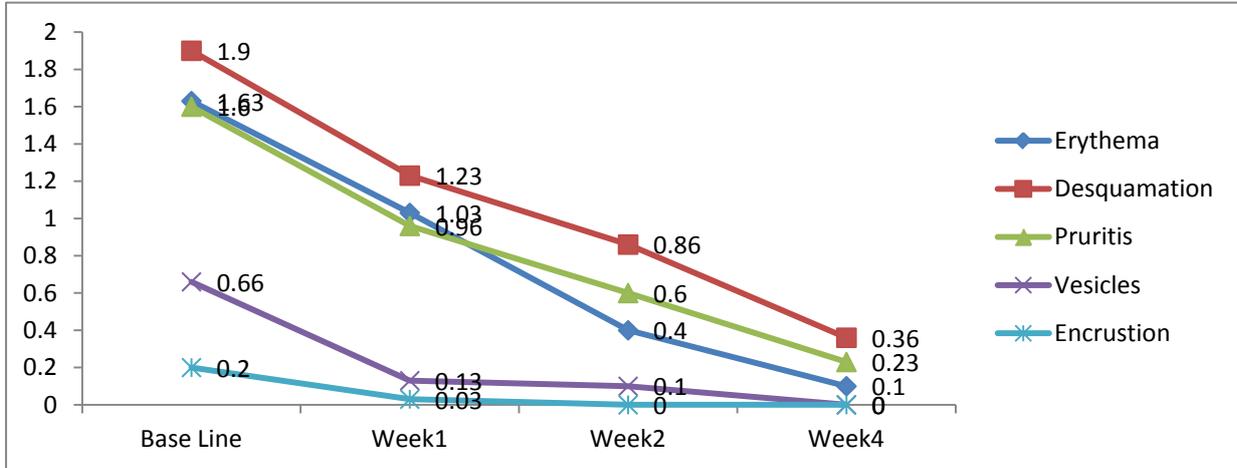


Fig 2: Changes in mean symptom score in Terbinafine treatment group for 4 weeks

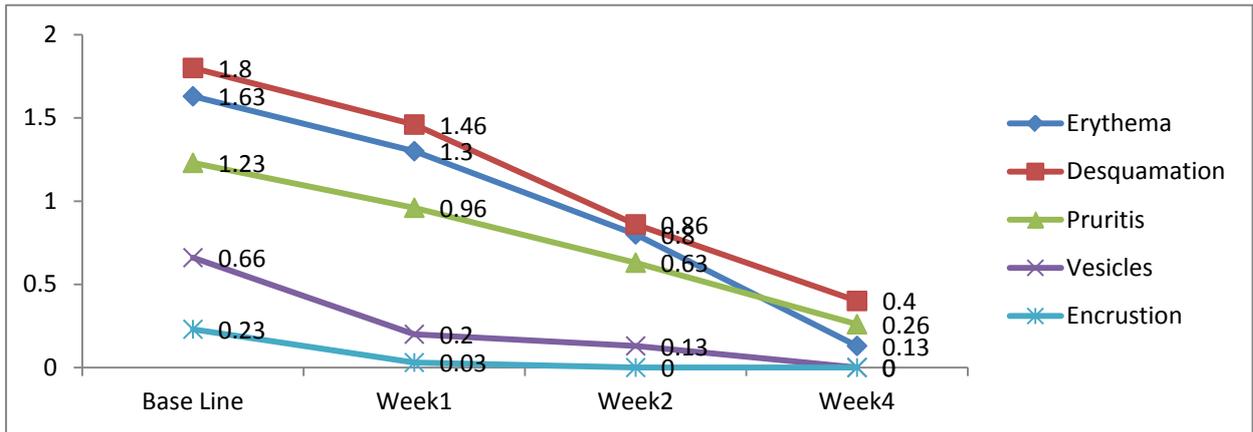


Fig 3: Changes in mean symptom score in Eberconazole treatment group for 4 weeks

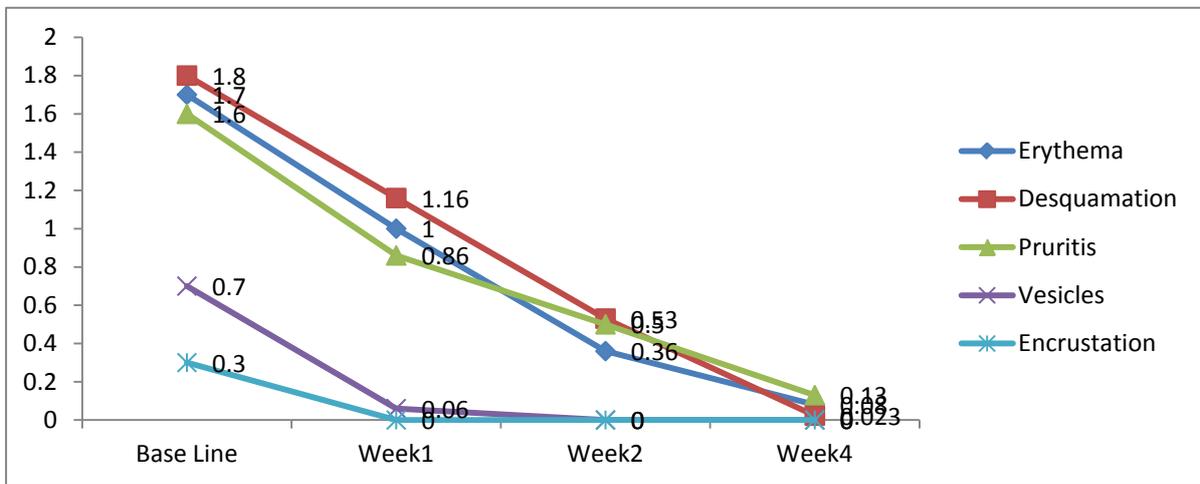


Fig 4: Changes in mean symptom score in Luliconazole treatment group for 4 weeks

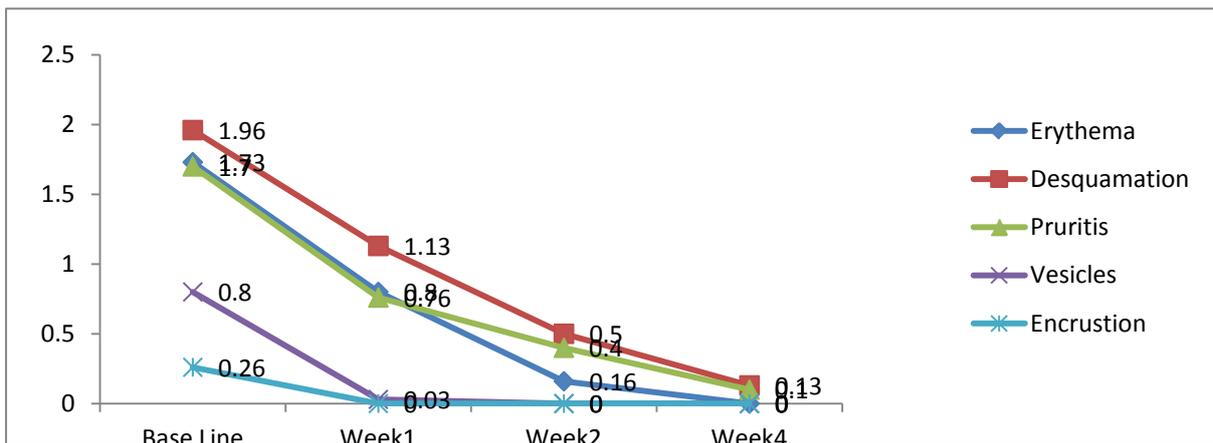


Fig 5: changes in mean symptom score in Sertaconazole treatment group for 4 weeks

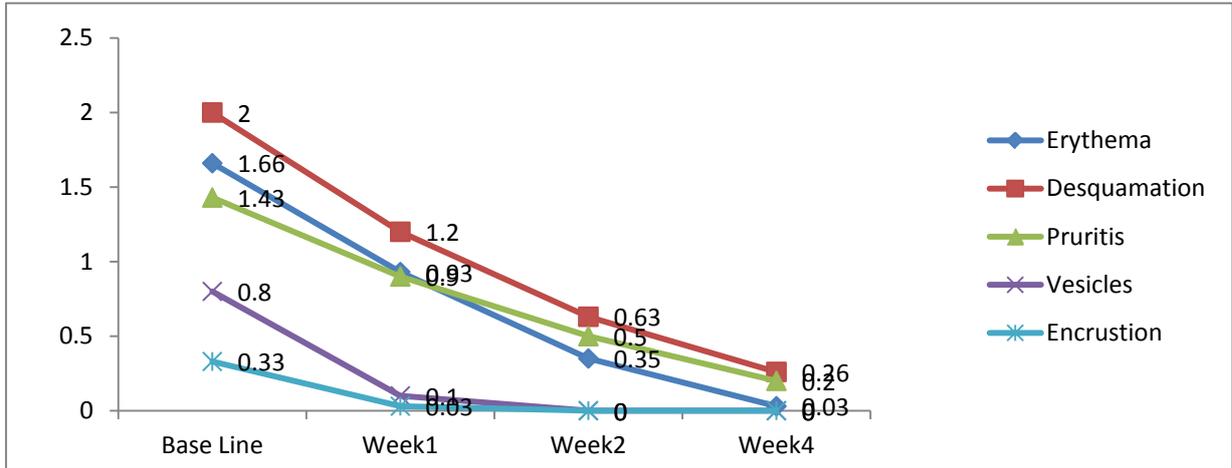


Fig 6: changes in mean symptom score in Amorolfine treatment group for 4 weeks

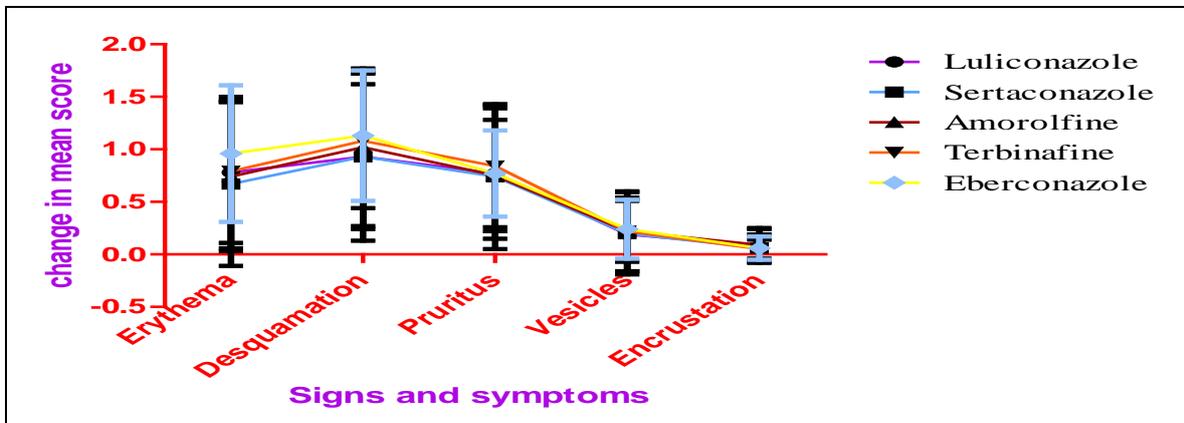


Fig 7: Overall Mean changes in signs and symptoms in different drug treatment groups.

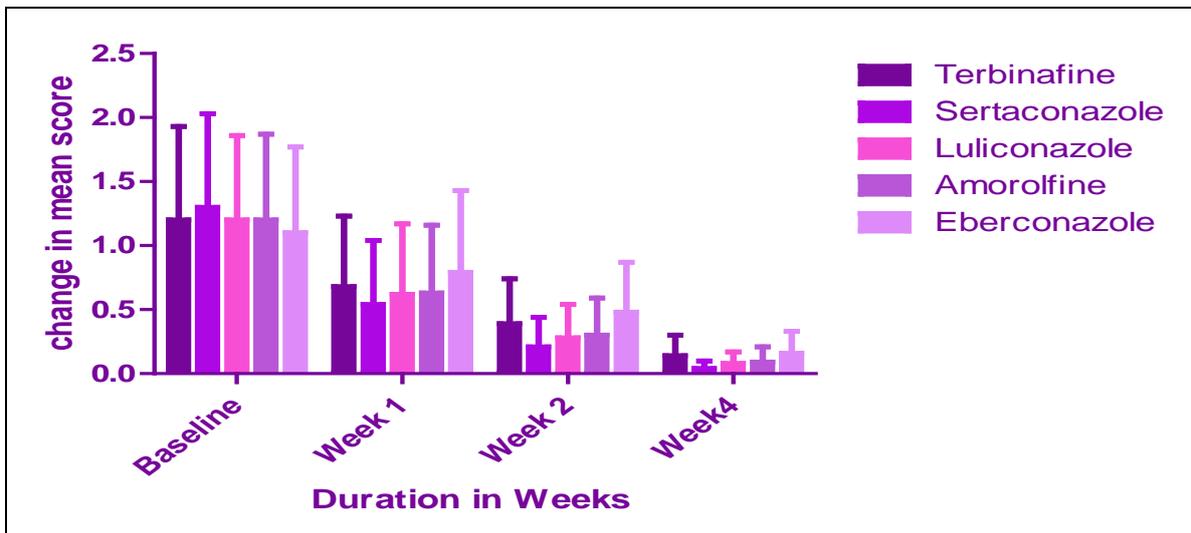


Fig 8: Mean changes of Signs and Symptoms in different treatment groups for 4 weeks duration comparison of Terbinafine with other drugs.

Efficacy

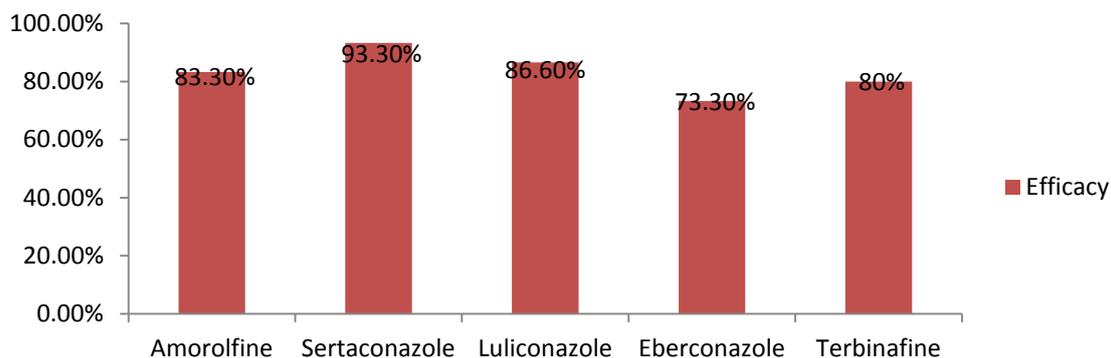


Fig 9: Efficacy comparison between treatment groups

Adverse Events

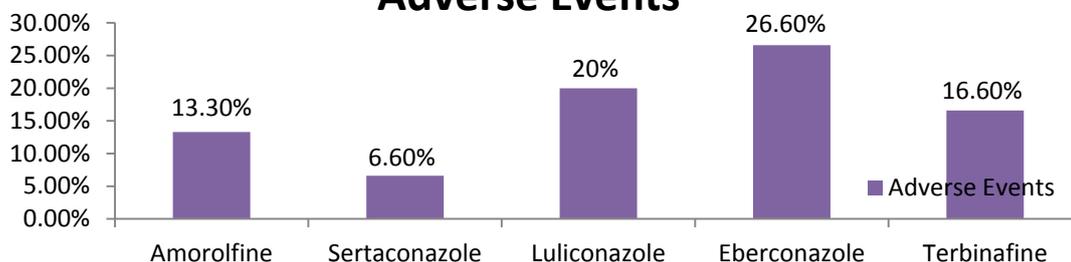


Fig 10: Adverse events percentages in treatment groups

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