EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 9
157-162
Year: 2018

TOPICAL ANTIFUNGALS FOR TREATMENT OF TINEA VERSICOLOR: CURRENT TREATMENT AND NEW HORIZONS

[1]*Sharma Jyoti, [2]Srivastava A. and [3]Kaushal Jyoti

[1]Senior Resident Department of Pharmacology PGIMS, Rohtak, Haryana.
[2]Senior Resident Department of Dermatology Government Medical College Kota.
[3]Rajasthan Professor Department of Pharmacology PGIMS, Rohtak, Haryana.

***Corresponding Author: Dr. Sharma Jyoti**
Senior Resident Department of Pharmacology PGIMS, Rohtak, Haryana.

Article Received on 10/07/2018 **Article Revised on 30/072018** **Article Accepted on 19/08/2018**

ABSTRACT
Tinea versicolor (TV), is one of the most common infectious skin diseases It is a chronic fungal disease where patients can present with symptoms ranging from hypopigmented to hyperpigmented macules associated with erythema, scaling and itching in characteristic areas of the body, including the chest, back, abdomen, and proximal extremities. Systemic antifungals (oral) e.g. fluconazole, ketoconazole etc are effective in treatment of TV but can be associated with serious adverse events. Topical treatment of Tinea versicolor can be divided into Specific antifungals and Non-specific antifungals. Non-specific antifungals include salicylic acid, selenium sulfide, sodium sulfacetamide, sodium thiosulphate, sulphur/salicylic acid, Whitfield's ointment etc. Specific antifungals include azoles and allylamines. Topical azoles are mostly imidazoles (bifonazole, econazole, flutrimazole, ketoconazole, miconazole, fenticonazole, clotrimazole, sulconazole, tioconazole) or triazoles (fluconazole). The main problem in the treatment of tinea versicolor with topical therapy can be the development of resistance which can lead to treatment failure and relapse. Newer azoles for the treatment of tinea versicolor include eberconazole, sertaconazole, luliconazole, dapaconazole which were found to be more efficacious with less chances of treatment failure and relapse and. Also, some newer formulations of older drugs such as nanoparticles, penetration enhancers are also being developed for better efficacy and less side effects.

KEYWORDS: Topical, azoles, tinea versicolor, nanoparticles.

INTRODUCTION
Tinea versicolor (TV) or Pityriasis versicolor (PV), also known as Peter Elam's disease, Dermatomycosis furfurácea and Tinea flava, is one of the most common infectious skin diseases that is seen in abundance during summer. It is a chronic fungal disease characterized by lesions varying in colour from red to hypopigmentation to hyperpigmentation.

It is one of the most common disorders of pigmentation in the world. Pityriasis versicolor is also known as tinea versicolar and less commonly as dermato mycosis furfurraceus, achromia parasitica and tinea flava.[1]

Pityriasis versicolor occurs when yeast converts to mycelial phase as result of certain predisposing factors. The development of Pityriasis versicolor may be related to altered immune response to the organism.[2,3] TV was first recognized as a fungal disease by Eichsedt in1846.[4] In 1853, Robin described the fungus in scales and named it Microsporum furfur.[5] The Malassezia genus was created by Baillon in 1889 and Malassezia furfur was the name given to the etiological agent of tinea versicolor.[6] Malassezia infections occur in the cornified layers of the epidermis. It is an opportunistic organism, which changes from the saprophytic phase to the pathogenic mycelian phase under certain conditions, such as increased temperature, greasy skin, sweating and immunosuppression.[7]

Yeasts of malassezia furfur usually start colonization at puberty. Through androgen stimulation, sebaceous glands reach their peak at this stage and therefore there is higher incidence of tinea versicolor in adolesence and adulthood. This incidence significantly drops at age extremes. It is rarely seen in elderly.[8]

This cutaneous infection has a worldwide distribution, especially in tropical areas. Infection by pityriasis versicolor usually infects adults due to increase sebum secretion after puberty.[9] A prevalence of 30–40% has been reported in tropical areas worldwide.[10] The risk factors described are warm season, profuse sweating,

malnutrition, Cushing's disease, pregnancy, and the use of oral contraceptive pills.[11] The cosmetic effect of hypopigmented patches on the skin brings the patient to the dermatologist for a consultation.[1]

Tinea versicolor is responsible for morbidity mainly due to cosmetic reasons. The adverse cosmetic effect of lesions may lead to significant emotional distress, particularly in adolescents. Tinea versicolor frequently recurs despite adequate initial therapy. Even with adequate therapy, residual pigmentary changes may take several weeks to resolve. Although tinea versicolor usually is more apparent in darker-skinned individuals, the incidence of tinea versicolor appears to be the same in all races.[12]

Patients can present with symptoms ranging from hypopigmented to hyperpigmented macules associated with erythema, scaling and itching in characteristic areas of the body, including the chest, back, abdomen, and proximal extremities. The density of skin colonization with *Malassezia* depends on age, body site, and comorbid skin conditions, as well as the geographic area. Being lipophilic, *Malassezia* are found in the highest density in sebaceous areas such as the scalp, face, and upper trunk.

Systemic antifungals (oral) e.g. fluconazole, ketoconazole etc are effective in treating a variety of infections but can be associated with serious adverse events. Use of oral antifungals to treat TV is therefore considered as second line treatment and used for recalcitrant or severe infections.[13]

Effective topical treatment for TV includes creams, lotions, and shampoos. These are applied daily or twice daily for varying periods of time, quickly improving clinical symptoms. Patient compliance may be affected by multiple, laborious applications, or minor skin irritation.[13] Topical treatment of Tinea versicolor can be divided into Specific antifungals and Non-specific antifungals Non-specific antifungals (with keratolytic and other actions) include salicylic acid, selenium sulfide (2.5% lotion, cream, or shampoo for one week), sodium sulfacetamide, sodium thiosulphate, sulphur/salicylic acid, Whitfield's ointment (6% benzoic acid and 3% salicylic acid in an emulsifying ointment), tretinoin, adapalene, benzoyl peroxide (5% to 10% gel for three weeks), and propylene glycol.[14,15] They do not act specifically against Malassezia species. Rather, they physically or chemically remove dead infected tissue.[16] Laundry soaps, keratolytic herbal soaps (papaya, glycolic), and simply rubbing with a pumice stone or other rough and abrasive material have also been used, especially in developing countries. Other novel interventions include herbal preparations (akapulco, lemon grass), cycloserine, and nitric oxide-liberating cream.

Specific antifungals include azoles and allylamines. They are used as creams, lotions and a great variety of anti-dandruff shampoos. Presently many azoles are being used, the reason being their efficacy, broad spectrum, fungicidal nature at therapeutic doses, short duration of therapy for cure, nonirritating, availability in multiple formulations etc. Amongst the azoles, there are multiple topical medications, such as bifonazole, clotrimazole, and miconazole, that have direct fungistatic activity and are shown to be effective in treating TV.[14] Azoles are fungistatic because they inhibit fungal cell membrane formation. Topical azoles are mostly imidazoles (bifonazole, econazole, flutrimazole, ketoconazole, miconazole, fenticonazole, sulconazole, tioconazole) or triazoles (fluconazole). Topical imidazoles usually come in 1% to 2% concentration and in various formulations (shampoos, sprays, lotions, gels, creams, or powder). They may be used once or twice daily, as a single application, or up to as long as two to eight weeks. Triazoles are newer generation azoles, and consist of oral itraconazole and topical or oral fluconazole. Topical fluconazole is available as 2% shampoo and is used daily for five days. Apart from azoles, the other topical antifungals include allylamines (naftifine, terbinafine), benzyl amines (butenafine), and ciclopiroxolamine. Terbinafine is given as 1% solution, emulsion, or cream for one week. Ciclopiroxolamine is given as 0.1% solution for four to eight weeks or as a 1% cream twice daily for two weeks. Older non-prescription agents are haloprogin, nystatin, tolnaftate, and zinc pyrithione (1% shampoo for two weeks).

Current Treatment

Allylamines (Terbinafine)

Terbinafine, an allylamine antifungal has also been used for the treatment of tinea versicolor. It is a synthetic antimycotic agent which is highly active against dermatophytes, but less active against moulds, dimorphic fungi and various yeasts. Terbinafine inhibits the enzyme squalene epoxidase in the fungal cell membrane, thereby blocking the biosynthesis of ergosterol. Squalene epoxidase catalyzes the first enzymatic step of ergosterol synthesis: the conversion of squalene into squalene epoxide.[17] On topical administration, it efficiently penetrates the stratum corneum, where it may persist for extended duration. It is highly lipophilic and keratophilic in nature and therefore is highly distributed throughout skin and adipose tissue. Terbinafine may persist at minimum inhibitory concentration (MIC) for upto 7 days after application.[18] However, terbinafine is not effective orally for the treatment of tinea versicolor, but twice daily application of topical terbinafine 1% solution, cream or gel, has been effective in randomized placebo-controlled trials.[17]

In one study Faergemann concluded that terbinafine 1% gel was more effective than placebo after a 7 day treatment course.[19] Multiple double blind, randomized, placebo-controlled studies have investigated the efficacy of 1% terbinafine solution applied twice daily for 7

days.[20,22] Seven weeks following a 7-day course of twice daily terbinafine solution, both Vermeer[21] et al and Savin[20] et al reported a mycological cure rate of 81% vs 41% and 81% vs 30% respectively which was significantly greater than placebo. When clinical effectiveness was evaluated as absence or nearly complete absence of physical symptoms combined with mycological cure, terbinafine was significantly more effective than placebo immediately following the completion of treatment (48% vs. 30%) and 7 weeks later (81% vs. 30%). Additionally, patient's ratings of treatment efficacy were significantly higher for terbinafine vs. placebo ($p < 0.001$).[20]

Chopra and his colleagues conducted a comparative clinical trial of topical terbinafine and ketoconazole and found a clinical and mycological clearance of 88% in ketoconazole group and 96% in terbinafine group.[23] In another study done by Rad et al, topical terbinafine was more effective than topical ketoconazole for the treatment of tinea versicolor.[24] In a study done by Jerajani et al in which terbinafine was compared with different azoles, the mean percentage reduction in total composite score (pruritus, erythema, vesicle and desquamation) was 91.2% with terbinafine suggesting good efficacy of terbinafine at the end of follow-up phase. However, better reduction in mean composite score (97.1% and 92.9% respectively) was seen in both sertaconazole and luliconazole group.[25]

Azoles

Ketoconazole

Ketoconazole, an imidazole, was the first broad-spectrum antifungal used in the treatment of superficial and systemic mycoses. Through inhibition of the enzyme lanosterol 14α-demethylase, ketoconazole disrupts ergosterol biosynthesis to limit cell function and growth. Multiple formulations have proved effective in treating PV, including cream, shampoo, and foam, with the most common regimen being once daily application of cream or foam for 14 days. Ketoconazole cream has been shown to be as effective as 1% clotrimazole and 1% terbinafine cream, whereas ketoconazole shampoo was shown to be as effective as 2.5% selenium sulphide and 1% flutrimazole shampoo.[13]

However, ketoconazole foam or cream applied once daily for 14 days appear to have some ability in maintaining complete cure 3–12 months post-treatment. Seventy nine percent of patients displayed complete cure at 12 months post-treatment with 2% ketoconazole cream, while 82% and 92% of patients displayed complete cure measured 3 months post-treatment with ketoconazole 1% foam and 2% cream, respectively. Potential advantages to using 1% ketoconazole foam include a shorter evaporation time and increased transcutaneous penetration for a longer time in the epidermis compared to creams or lotions.[13]

Clotrimazole

Clotrimazole has fungistatic effect inhibiting the biosynthesis of ergoserol and thus disrupting the formation of fungal cell wall. It is a broad spectrum immidazole reported to be effective against the pityriasis versicolar in both open and controlled double blind trials.[26,29] In a study done by Ravindranath et al, 15 patients were treated with topical therapy of clotrimazole cream alone for a period of one month. 4 patients reported with 100% clinical cure, 3 patients reported with 70 and 3 patients reported with 80% clearance of the lesions while 5 patients reported with 50% clinical cure. There was an average clinical cure of 73%.[30]

Miconazole

It is the azole used for the treatment of tinea versicolor. In a study done by Tanenbaum et al, miconazole was compared with sulconazole in the treatment of tinea versicolor. The medications were applied twice daily for three weeks. Of 181 patients analyzed for efficacy at the end of the treatment trial, 93% of sulconazole-treated patients and 87% of miconazole-treated patients had become KOH negative. The complete clearing of tinea versicolor lesions occurred in 89% of sulconazole-treated patients and 82% of miconazole-treated patients. Both drugs were well tolerated with no systemic reactions reported.[31]

The main problem in the treatment of tinea versicolor with topical therapy can be the development of resistance which can lead to treatment failure and relapse. So, there is need of newer antifungals which are more efficacious, less chances of treatment failure, relapse and less side effects.

Newer Antifungals

Luliconazole

Luliconazole is a novel, optically active imidazole antifungal.[32] The compound has a unique chemical structure, which is augmented by introduction of a ketone dithioacetate structure in the imidazole moiety. It has high potency inhibitory action against filamentous fungi, including dermatophytes. Preliminary studies suggested that luliconazole could also be effective against Malassezia species.[33]

In a study by Kishore Kumar et al, topical luliconazole 1% cream was compared with topical ketoconazole 2% cream in the treatment of Pityriasis versicolor. A total of 70 patients with skin lesions of Pityriasis versicolor were selected to this study. These patients were divided into two groups (A and B) randomly with 35 patients in each group. The group A patients were treated with topical luliconazole 1% cream twice daily and group B patients were treated with topical ketoconazole 2% cream twice daily for 28 days. Clinical assessment and mycological (by KOH mount) assessment was done to all the patients in both the groups at the beginning and at the two follow up visits, first follow up on the 14th day and second follow up on the 28th day of this study to evaluate the

comparative therapeutic efficacy of both these drugs. Both topical luliconazole 1% cream and topical ketoconazole 2% cream had nearly equal therapeutic efficacy in the treatment of Pityriasis versicolor when treated for 2 weeks (81.82% and 69.70%), but topical luliconazole 1% cream was found to be more therapeutically efficacious over topical ketoconazole 2% cream when treated for 4 weeks (96.77% and 72.41%) in the treatment of Pityriasis versicolor.[34]

In another study by Sarkar et al, which was carried out over three months among 86 consecutive patients of pityriasis versicolor. Patients were randomly allocated to two groups by coin flipping method. The first group was advised to apply ketoconazole 2% cream twice daily and second group were asked to apply topical luliconazole 1% cream twice daily. On the 14^{th} and 28^{th} day, the therapeutic response was evaluated and KOH preparation of skin scrapings was repeated. At baseline, KOH mount was positive in 80% case in the ketoconazole group and 85% in the luliconazole group. At first follow up (day 14), KOH mount negativity among the ketoconazole group was 67.50% and in the luliconazole group it was 80.00%. At the second follow up (day 28), KOH mount was negative in 72.50% in the ketoconazole group and 92.50% in the luliconazole group. Comparison between two groups showed that there was no statistically significant difference between two groups at first follow up (P= 0.2178). However, at the second follow up the improvement in luliconazole-treated group was better than in the ketoconazole-treated group (P= 0.0367), which is statistically significant.[35]

Eberconazole

Eberconazole, an imidazole derivative is a newer antimycotic agent. It is a broad spectrum antifungal agent used as a topical preparation in the management of cutaneous mycoses. It is distinct from other imidazoles as it has been shown to have anti-inflammatory activity, which is attributed to the inhibition of 5-lipooxygenase; it is also known to inhibit cyclooxygenase-1. This property favours its use in the management of inflammed dermatophytic infections. Eberconazole exerts fungicidal or fungistatic activity depending upon concentration, being fungicidal at higher concentration and fungistatic at lower concentrations. It prevents fungal growth by inhibiting ergosterol synthesis, an essential component of the fungal cytoplasmic membrane leading to structural and functional changes.[36]

In a comparative study with clotrimazole, eberconazole 1% cream has been shown to be efficacious in the treatment of dermatophytoses, candidiasis, and pityriasis, with higher efficacy than clotrimazole cream in the case of dermatophytoses.[37] Another study by Fonseca Capdevila showed that eberconazole 1% cream is more efficacious than clotrimazole 1% cream for the treatment of skin mycoses produced by dermatophytes, but with similar efficacy for candidiasis and tinea versicolor treatment, with a good safety and tolerability profile.[38]

In another study done by Sharma et al, 60 patients were randomly divided into two study groups. In Group A, Eberconazole 1% cream once daily was given and in Group B, Terbinafine 1% cream once daily for 2 weeks was given. Both the treatment groups, i.e., eberconazole and terbinafine were found to be safe and efficacious at the end of 2 weeks, and no statistically significant difference was observed between the two groups regarding complete cure, i.e., mycological and clinical cure (80% vs. 63.33%), respectively. However, early response (at the end of week 1) was observed with eberconazole.[39]

Sertaconazole

Sertaconazole, one of the newer azoles, is structurally unique due to a benzothiophene ring. It is the only azole with a fungicidal action due to its ability to cause direct fungal cell membrane damage. The available topical formulation of sertaconazole (2%) attains fungicidal concentration in the stratum corneum as the lipophilic property of the benzothiophene ring enables prolonged dermal retention. This permits just once-daily application contrary to most other topical azoles.[40] Sertaconazole act as fungistatic at low concentration and fungicidal at high concentration. At higher concentrations, sertaconazole binds directly to nonsterol lipids in the fungal cell wall, which leads to increased permeability and subsequent lysis of the mycelium. Henceforth sertaconazole out scores the clotrimazole because of its direct membrane damaging effect leading to persistent action. Sertaconazole also has antibacterial, antiinflammatory, antitrichomonal, antipruritic actions in addition. Sertaconazole achieves high epidermal concentrations following cutaneous application.[41,43]

In a study done by Tatavarthi et al, 110 patients who were diagnosed clinically and microscopically as pityriasis versicolor and fulfilling the criteria were enrolled, of which 55 were treated with 2% sertaconazole cream and 55 with 1% clotrimazole cream twice daily for 4 weeks, 42(82.3%) of the sertaconazole group, 30(61.2%) of the clotrimazole group were improved clinically. Mycological examination at the same time was negative in 44(86.3%), 33(67.4%) respectively. Comparing the results obtained in this trial showed that sertaconazole was more efficacious than clotrimazole in the treatment of pityriasis versicolor because of its direct membrane damaging effect.[44]

Dapaconazole

Dapaconazole tosylate is a new imidazole antifungal that has been shown to have a good tolerability and safety profile for topical administration in healthy volunteers. The efficacy of dapaconazole tosylate 2% cream was compared with ketoconazole 2% cream in a non-inferiority design clinical trial. Sixty patients with clinical and mycological diagnosis of PV were randomly assigned to receive either 1 g dapaconazole tosylate 2% cream or 1 g ketoconazole 2% cream. Treatments were applied once a day for 28 days. Clinical and mycological

cure was achieved in 84.6% (22/26) and 92.6% (25/27) of patients treated with ketoconazole and dapaconazole, respectively. Dapaconazole tosylate was found to be non-inferior to ketoconazole when used at a dose of 20 mg/day for 28 consecutive days for the treatment of PV. Dapaconazole also demonstrated a good safety profile.[45]

Newer Formulations

Fluconazole-loaded solid lipid nanoparticles topical gel- Solid lipid nanoparticles (SLNs) are very potential formulations for topical delivery of antifungal drugs. A randomized controlled clinical trial (RCT) of potential batches was carried out on 30 well diagnosed PV patients comparing to market product Clotrimazole 1% cream. Clinical studies registered significant improvement ($p < .05$) in therapeutic response (1.4-fold; healing%, 4-fold; complete eradication) in terms of clinical cure and mycological cure rate from PV against marketed cream.[46]

Penetration enhancers- Nanovesicles containing different skin penetration enhancers 'PEVs' were prepared and loaded with sertaconazole. Selected formulae were preliminary tested for clinical efficacy on patients suffering from tinea corporis and tinea versicolor. It was concluded that the nanosize of the vesicles, their content of penetration enhancer and their deformable nature are three cornerstones which positively influence the therapeutic outcome of topical antifungal therapy.[47]

CONCLUSION

Tinea versicolor is a tropical disease that is very common in our country. Tinea versicolor evolves in outbreaks, with improvement and aggravation of the symptoms, becoming relapsing or chronic. The rise in fungal infections due to increase in incidence of immunocompromised states, change in socioeconomic and cultural states is demanding an effective antimycotic agent for the treatment and cure. Hence, newer antimycotic agents as well as newer formulations having good safety profile and better efficacy with less chances of developing drug resistance are being introduced.

REFERENCES

1. Sunenshine P, Schwartz RA, Janniger CK. Tinea versicolor. Int J Dermatol, 1998; 37: 648-55.
2. Shuttleworth D, Philpot CM, Salaman JR. Cutaneous fungal infection following renal transplantation: a case control study Br J Dermatol, 1987; 117: 585-90.
3. Schechtman RC, Midgley G, Hay RJ. HIV disease and Malussesia yeasts a quantative study of patients presenting with seborrheic dermatitis Br J Dermatol., 1995; 133: 694- 8.
4. Baillon H. Traite de Botanique Medicale Cryptogamique. Paris. Octave Doin., 1889: 234.
5. Robin C. Historie Naturelle des Vegeaux Parasites. London. Balliere., 1853: 438.
6. Janik M, Heffernan M. Yeast infections: Candidiasis & Tinea (Pityriasis) infections. In: Wolff K, Goldsmith L, Katz S, Gilchrest B, Paller A, Leffel D, editors. Fitzpatrick's Dermatology in General Medicine. 7th ed. New York: McGraw Hill, 2007; 1822-30.
7. Roberts SOB. Pityriasis versicolor: A clinical and mycological investigation. Br J Dermatol., 1996; 81: 315–26.
8. Roberts SOB. Pityrosporum orbiculare: Incidence and distribution on clinically normal skin. Br Dermatol., 1969; 81: 264-9.
9. DiSilverio A, Mosca M, Gatti M, Brandozzi G. Pityriasis versicolor in the aged: A clinical investigation and epidemiological survey in 190 elderly hospitalized patients. Mycopathologia, 1989; 105: 187-90.
10. Borelli M, Jacobs PH, Nall L. Tinea versicolor: Epidemiologic, clinical and therapeutic aspects. J Am Acad Dermatol, 1991; 25: 300-5.
11. Hay RJ, Moore M. Mycology. In: Champion RH, Burton JL, Burns DA, Breathnach SM editors. Textbook of Dermatology. Vol. 6. Oxford: Blackwell Science, 1998; 1277-376.
12. Rajashekhar N. Oral fluconazole in Tinea versicolor. Indian J Dermatol Venereol Leprol., 1997; 63: 166-7.
13. Gupta AK, Foley KA. Antifungal Treatment for Pityriasis Versicolor. J Fungi., 2015; 1: 13-29.
14. Gupta AK, Kogan N, Batra R. Pityriasis versicolor: a review of pharmacological treatment options. Expert Opin Pharmacother, 2005; 6: 165–78.
15. Gupta AK, Batra R, Bluhm R, Faergemann J. Pityriasis versicolor. Dermatol Clin., 2003; 21: 413–29.
16. Gupta AK, Bluhm R, Summerbell R. Pityriasis versicolor. J Eur Acad Dermatol Venereol., 2002; 16: 19–33.
17. Lee-Bellantoni M, Konnikov N. Oral antifungal agents. In: Wolff K, Goldsmith L, Katz S, Gilchrest B, Paller A, Leffel D, editors. Fitzpatrick's dermatology of General Medicine. 7th ed. New York: McGraw Hill, 2007; 2211-7.
18. High W, Fitzpatrick J. Topical antifungal agents. In: Wolff K, Goldsmith L, Katz S, Gilchrest B, Paller A, Leffel D, editors. Fitzpatrick's dermatology of General Medicine. 7th ed. New York: McGraw Hill, 2007; 2116-21.
19. Faergemann J, Hersle K, Nordin P. Pityriasis versicolor: clinical experience with lamisil cream and lamisil dermgel. Dermatology, 1997; 194(1): 19–21.
20. Savin R, Eisen D, Fradin MS. Lebwohl M. Tinea versicolor treated with terbinafine 1% solution. Int J Dermatol., 1999; 38: 863-5.
21. Vermeer BJ, Staats CC. The efficacy of a topical application of terbinafine 1% solution in subjects with pityriasis versicolor: A placebo-controlled study. Dermatology., 1997; 194: 22–4.

22. Budimulja U, Paul C. One-week terbinafine 1% solution in pityriasis versicolor: Twice-daily application is more effective than once-daily. J Dermatol Treat., 2002; 13: 39–40.
23. Chopra V, Jain VK. Comparative study of topical terbinafine and topical ketoconazole in pityriasis versicolor. Ind J Dermatol Venereol Leprol., 2000; 66: 299-300.
24. Rad F, Nik-Khoo B, Yaghmaee R, Gharibi F. Terbinafine 1% Cream and Ketoconazole 2% Cream in the Treatment of Pityriasis Versicolor: A randomized comparative clinical trial. Pak J Med Sci., 2014; 30(6): 1273–6.
25. Jerajani HR, Janaki C, Kumar S, Phiske M. Comparative Assessment of the Efficacy and Safety of Sertaconazole (2%) Cream Versus Terbinafine Cream (1%) Versus Luliconazole (1%) Cream in Patients with Dermatophytoses: A Pilot Study. Indian J Dermatol, 2013; 58(1): 34–8.
26. Gip L. The topical therapy of pityriasis versicolor with clotrimazole. Postgrad Med J., 1974; 50: 59-60.
27. Polemann G; Clinical experience in the local treatment of Dermatomycoses with clotrimazole. Postgrad Med J., 1974; 50: 54-6.
28. Zias N, Battistini F Superficial mycoses; treatment with a new broad spectrum antifungal agent. 1% clotrimazole. solution; Postgrad. Med J., 1974; 50: 54-6.
29. Spierkmann PH. Young MD. Clinical evaluation of clotrimazole. A broad – spectrum antifungal agent; Arch. Dermatol., 1976; 112: 350-2.
30. Ravindranath S. Pityriasis Versicolor: Therapeutic Efficacy of Various Regimes of Topical 2% Clotrimazole Cream, Oral Flucanazole and Ketoconazole. International Journal of Contemporary Medical Research, 2016; 3(8): 2393-915X.
31. Tanenbaum L, Anderson C, Rosenberg MJ, Akers W. 1% sulconazole cream v 2% miconazole cream in the treatment of tinea versicolor. A double-blind, multicenter study. Arch Dermatol, 1984; 120(2): 216-9.
32. Niwano Y, Kuzuhara N, Kodama H, Yoshida M, Miyazaki T, Yamaguchi H. In vitro and invivo antidermatophyte activities of NND-502, a novel optically active imidazole antimycotic agent. Antimicrob Agents Chemother, 1998; 42: 967-70.
33. Uchida K, Nishiyama Y, Tanaka T, Yamaguchi H. In vitro activity of novel imidazole antifungal agent NND-502 against Malassezia species. Int J Antimicrob Agents., 2003; 21: 234-8.
34. Kishore Kumar V. A study of comparative assessment of the therapeutic efficacy of topical luliconazole versus topical ketoconazole in the treatment of pityriasis versicolor. J Evid Based Med Healthc., 2018; 5(1): 53-6.
35. Sarkar S, Sengupta D, Basak S, Damji SA, Shukla DK, Anurag D. Comparative assessment of the efficacy of topical ketoconazole and topical luliconazole in cases of pityriasis versicolor at a tertiary care hospital in eastern India: A prospective, open, randomized controlled trial. Indian Dermatology Online Journal., 2016; 7(4): 335-6.
36. Moodahadu-Bangera LS, Martis J, Mittal R, Krishnankutty B, Kumar N, Bellary S, et al. Eberconazole- pharmacological and clinical review. Indial J Dermatol Venereol Leprol., 2012; 78(2): 217-22.
37. Font E, Freixes J, Julve J. Profile of a new antimycotic, eberconazole. Revista iberoamericana De Micologia., 1995; 12: 16-7.
38. Fonseca Capdevilla E. Effectiveness of Eberconazole 1% cream as opposed to Clotrimazole 1% cream in patients with cutaneous mycoses. Skin., 2004; 19: 480-4.
39. Sharma J, Kaushal J, Aggarwal K. A comparative study of efficacy and safety of eberconazole versus terbinafine in patients of tinea versicolor. Indian J Dermatol, 2018; 63: 53‑6.
40. Chatterjee D, Ghosh SK, Sen S, Sarkar S, Hazra A, De R. Efficacy and tolerability of topical sertaconazole versus topical terbinafine in localized dermatophytosis: A randomized, observer-blind, parallel group study. Indian J Pharmacol, 2016; 48(6): 659-64.
41. Del Rosso JQ, Bikowski J. Topical management of superficial fungal infections: Focus on sertaconazole. Cosmet Dermatol, 2007; 20: 705-10.
42. Liebel F, Lyte P, Garay M, Babad J, Southall MD. Anti-inflammatory and anti-itch activity of sertaconazole nitrate. Arch Dermatol Res., 2006; 298: 191-9.
43. Carrillo-Munoz AJ, Giusiano G, Ezkurra PA, Quindos G. Sertaconazole: updated review of a topical antifungal agent. Expert Rev Anti Infect Ther., 2005; 3(3): 333-42.
44. Tatavarthi NBL, Ramachandra BV, Rao DS, Shrinivasulu G. Clinical evaluation of efficacy of sertaconazole 2% cream in treatment of pityriasis versicolor and a comparison with that of clotrimazole 1% cream. Journal of Evolution of Medical and Dental Sciences, 2015; 4(27): 4668-75.
45. Gobbato AA, Babadópulos T, Gobbato CA, Ilha Jde O, Gagliano-Jucá T, De Nucci G. A randomized double-blind, non-inferiority Phase II trial, comparing dapaconazole tosylate 2% cream with ketoconazole 2% cream in the treatment of Pityriasis versicolor. Expert Opin Investig Drugs., 2015; 24(11): 1399-407.
46. El-Housiny S, Shams Eldeen MA, El-Attar YA, Salem HA, Attia D, Bendas ER, et al. Fluconazole-loaded solid lipid nanoparticles topical gel for treatment of pityriasis versicolor: formulation and clinical study. Drug Deliv., 2018; 25(1): 78-90.
47. Bsieso EA, Nasr M, Moftah NH, Sammour OA, Abd El Gawad NA. Could nanovesicles containing a penetration enhancer clinically improve the therapeutic outcome in skin fungal diseases? Nanomedicine (Lond)., 2015; 10(13): 2017-31.