KETOCONAZOLE

shampoo 2%

All redactions under Section 41 and Section 43 of the Freedom of Information Act.

2.7.3 Summary of clinical efficacy

Summary of clinical efficacy

Indication: Prevention and treatment of Malassezia (previously called Pityrosporum) yeast infections

Seborrheic Dermatitis and Dandruff

Seborrheic Dermatitis (SD) and dandruff are of a continuous spectrum of the same disease that affects the seborrheic areas of the body. Dandruff is restricted to the scalp, and involves itchy, flaking skin without visible inflammation (Djunaidi, 2020). SD can affect the scalp as well as other seborrheic areas, and involves itchy and flaking or scaling skin, inflammation and pruritus. It is estimated that SD and dandruff combined affect half of the adult population. Despite such high prevalence, their etiology is not well understood. Various intrinsic and environmental factors, such as sebaceous secretions, skin surface fungal colonization, individual susceptibility, and interactions between these factors, all contribute to the pathogenesis of SD and dandruff (Borda and Wikramanayake, 2015). Multiple topical agents are effective therapies for the treatment of dandruff. These agents include pyrithione zinc, selenium sulfide, salicylic acid, sulfur, coal tar, hydrocortisone and ketoconazole. A common mechanism of most effective actives is their antifungal activity against *Malassezia.* In vitro fungistatic and fungicidal tests of ketoconazole, pyrithione zinc, and selenium disulfide have demonstrated low inhibitory concentrations of growth (MICs) against *Malassezia furfur* (Schwartz, et al 2006).

Both systemic and topical applications of ketoconazole have been found effective in seborrheic dermatitis (Elewski, 2009; Borgers, et al 2007; Goldenberg, 2013; Mokos, et al 2012; Herrera-Arellano, et al., 2004).

There are reports of better efficacy of 2% formulations as compared to the ones with 1% ketoconazole. Absorption of ketoconazole through the skin is insignificant, with no ketoconazole detected in plasma after topical application of ketoconazole cream or shampooing. Approximately 5% of the drug is found to penetrate into the hair keratin 12 hours after a single shampoo (Chowdhry and Gupta, 2016).

<u>Systematic reviews</u>

The Cochrane Skin Group conducted a meta-analysis for studies published by 2015 year, on the use of topical antifungals for SD. Okokon, et al searched the following databases up to December 2014: the Cochrane Skin Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 11), MEDLINE (from 1946), EMBASE (from 1974) and LatinAmerican Caribbean Health Sciences Literature (LILACS) (from 1982). Authors also searched trials registries and checked the bibliographies of published studies for further trials. Randomised controlled trials of topical antifungals used for treatment of seborrhoeic dermatitis in adolescents and adults, with primary outcome measures of complete clearance of symptoms and improved quality of life. Authors included 51 studies with 9052 participants. Of these, 45 trials assessed treatment outcomes at five weeks or less after commencement of

treatment, and six trials assessed outcomes over a longer time frame. Authors believe that 24 trials had some form of conflict of interest, such as funding by pharmaceutical companies.

Among the included studies were 12 ketoconazole trials (N = 3253), 11 ciclopirox trials (N = 3029), two lithium trials (N = 141), two bifonazole trials (N = 136) and one clotrimazole trial (N = 126) that compared the effectiveness of these treatments versus placebo or vehicle. Nine ketoconazole trials (N = 632) and one miconazole trial (N = 47) compared these treatments versus steroids. Fourteen studies (N = 1541) compared one antifungal versus another or compared different doses or schedules of administration of the same agent versus one another.

Topical ketoconazole 2% treatment showed a 31% lower risk of failed clearance of rashes compared with placebo (risk ratio (RR) 0.69, 95% confidence interval (CI) 0.59 to 0.81, eight studies, low-quality evidence) at four weeks of follow-up, but the effect on side effects was uncertain because evidence was of very low quality (RR 0.97, 95% CI 0.58 to 1.64, six studies); heterogeneity between studies was substantial (I^2 = 74%). The median proportion of those who did not have clearance in the placebo groups was 69%.

Ketoconazole treatment resulted in a remission rate similar to that of steroids (RR 1.17, 95% CI 0.95 to 1.44, six studies, low-quality evidence), but occurrence of side effects was 44% lower in the ketoconazole group than in the steroid group (RR 0.56, 95% CI 0.32 to 0.96, eight studies, moderate-quality evidence).

Ketoconazole yielded a similar remission failure rate as ciclopirox (RR 1.09, 95% CI 0.95 to 1.26, three studies, low-quality evidence). Most comparisons between ketoconazole and other antifungals were based on single studies that showed comparability of treatment effects.

Based on the results, it was concluded that Ketoconazole was more effective than placebo at four weeks of follow-up and possibly at three months of follow-up, but few longer-term studies have been conducted. Evidence for this was of low quality. Evidence was insufficient to suggest a dose effect. The most often applied dose was 2%, but the frequency of application of treatments varied between studies from once or twice daily to once or three times weekly for varying lengths of time, and it is unclear which regimen works best.

Ketoconazole did not cause more side effects than were observed with placebo. Topical ketoconazole showed similar efficacy when compared with steroids, but steroids showed a two-fold greater risk of side effects than was seen with ketoconazole. Compared with other antifungals, we cannot say that ketoconazole consistently resulted in a more or less effective outcome because most of these comparisons involved single studies.

Ciclopirox was more effective than placebo but with a comparable incidence of side effects. Evidence was insufficient to reveal an effect of increased dose. Evidence was of moderate quality. Ciclopirox showed effects similar to those of ketoconazole. No comparisons of ciclopirox versus steroids were reported. Bifonazaole was also found to be more effective than placebo. Outome variables in this review were stratified according to site (scalp, face or scalp and face). Treatment outcomes were fairly consistent for ketoconazole and other antifungals across different application sites. Studies provided insufficient evidence that the mode of delivery accounted for consistent differences in treatment effect (Okokon, et al, 2015).

Another meta-analysis was conducted to investigate the effects of topical pharmacological interventions with established anti-inflammatory action for seborrhoeic dermatitis occurring in

adolescents and adults. Authors searched the following databases up to September 2013: the Cochrane Skin Group Specialised Register, CENTRAL in *The Cochrane Library* (2013, Issue 9), MEDLINE (from 1946), Embase (from 1974), LILACS (from 1982), and the GREAT database. We searched five trials databases and checked the reference lists of included studies for further references to relevant randomised controlled trials (RCTs).

RCTs in adults or adolescents (> 16 years) with diagnosed seborrhoeic dermatitis of the scalp or face, comparing topical anti-inflammatory treatments (steroids, calcineurin inhibitors, and lithium salts) with other treatments were included in the search.

Results: Authors included 36 RCTs (2706 participants), of which 31 examined topical steroids; seven, calcineurin inhibitors; and three, lithium salts. The comparative interventions included placebo, azoles, calcipotriol, a non-steroidal anti-inflammatory compound, and zinc, as well as different anti-inflammatory treatments compared against each other. Our outcomes of interest were total clearance of symptoms, erythema, scaling or pruritus scores, and adverse effects. The risk of bias in studies was most frequently classified as unclear, due to unclear reporting of methods. Steroid treatment resulted in total clearance more often than placebo in short-term trials (four weeks or less) (relative risk (RR) 3.76, 95% confidence interval (CI) 1.22 to 11.56, three RCTs, 313 participants) and in one long-term trial (lasting 12 weeks). Steroids were also more effective in reducing erythema, scaling, and pruritus. Adverse effects were similar in both groups.

There may be no difference between steroids and calcineurin inhibitors in total clearance in the short-term (RR 1.08, 95% 0.88 to 1.32, two RCTs, 60 participants, low-quality evidence). Steroids and calcineurin inhibitors were found comparable in all other assessed efficacy outcomes as well (five RCTs, 237 participants). Adverse events were less common in the steroid group compared with the calcineurin group in the short-term (RR 0.22, 95% CI 0.05 to 0.89, two RCTs, 60 participants).

There were comparable rates of total clearance in the steroid and azole groups (RR 1.11, 95% CI 0.94 to 1.32, eight RCTs, 464 participants, moderate-quality evidence) as well as of adverse effects in the short-term, but less erythema or scaling with steroids.

Authors found mild (class I and II) and strong (class III and IV) steroids comparable in the assessed outcomes, including adverse events. The only exception was total clearance in long-term use, which occurred more often with a mild steroid (RR 0.79, 95% CI 0.63 to 0.98, one RCT, 117 participants, low-quality evidence).

In one study, calcineurin inhibitor was more effective than placebo in reducing erythema and scaling, but there were similar rates in total clearance or adverse events for short-term treatment. In another study, calcineurin inhibitor was comparable with azole when erythema, scaling, or adverse effects were measured for longer-term treatment.

Lithium was more effective than placebo with regard to total clearance (RR 8.59, 95% CI 2.08 to 35.52, one RCT, 129 participants) with a comparable safety profile. Compared with azole, lithium resulted in total clearance more often (RR 1.79, 95% CI 1.10 to 2.90 in short-term treatment, one RCT, 288 participants, low-quality evidence).

It was concluded that topical steroids are an effective treatment for seborrhoeic dermatitis of the face and scalp in adolescents and adults, with no differences between mild and strong steroids in

the short-term. There is some evidence of the benefit of topical calcineurin inhibitor or lithium salt treatment. Treatment with azoles seems as effective as steroids concerning short-term total clearance, but in other outcomes, strong steroids were more effective. Calcineurin inhibitor and azole treatment appeared comparable. Lithium salts were more effective than azoles in producing total clearance. Steroids are similarly effective to calcineurin inhibitors but with less adverse effects. Most of the included studies were small and short, lasting four weeks or less. Future trials should be appropriately blinded; include more than 200 to 300 participants; and compare steroids to calcineurin inhibitors or lithium salts, and calcineurin inhibitors to azoles or lithium salts. The follow-up time should be at least one year, and quality of life should be addressed. There is also a need for the development of well-validated outcome measures (Kastarinen, et al 2014).

A systematic review was aimed to answer the following clinical questions: What are the effects of topical treatments for seborrhoeic dermatitis of the scalp in adults? What are the effects of topical treatments for seborrhoeic dermatitis of the face and body in adults? We searched: Medline, Embase, The Cochrane Library and other important databases up to February 2006 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). Authors included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). Manríquez and Uribe, 2007, found nine systematic reviews, RCTs, or observational studies that met our inclusion criteria. Authors performed a GRADE evaluation of the quality of evidence for interventions. In this systematic review authors present information relating to the effectiveness and safety of the following interventions: bifonazole, emollients, ketoconazole, lithium succinate, selenium sulphide, tar shampoo, terbinafine, and topical steroids (betamethasone valerate, clobetasol propionate, clobetasone butyrate, hydrocortisone, mometasone furate). Compared with placebo Ketoconazole shampoo is more effective than placebo at improving scalp symptoms such as scaling, itching, redness, and dandruff at 4 weeks in people with seborrhoeic dermatitis of the scalp. Authors found five RCTs ranging in size from 20 to 246 participants. All found improvements in symptoms with ketoconazole 2% shampoo after 4 weeks compared with placebo. Four of the five RCTs reported that there were no adverse effects of treatment. The fifth RCT reported one instance of scalp tenderness that was probably related to ketoconazole treatment (Manríquez and Uribe, 2007).

<u>Active comparator-controlled studies</u>

In a randomized double-blind trial, selenium sulfide 2.5% was tested against ketoconazole 2% and placebo in 246 patients with moderate to severe dandruff. Both ketoconazole and selenium sulfide shampoos were effective, but ketoconazole was better tolerated. Ketoconazole shampoo 2% is superior to 1% and can be used once-weekly as maintenance therapy for scalp seborrheic dermatitis. Zinc pyrithione 1% shampoo in comparison with ketoconazole 2% shampoo has produced inferior results, whereas selenium sulphide exhibited similar efficacy (Stefanaki and Katsambas, 2010).

Squire RA and Goode K conducted clinical study to compare the therapeutic efficacy of a shampoo containing 1.5% ciclopirox olamine and 3% salicylic acid (CPO/SA) with Nizoral

(2.0% ketoconazole shampoo) in 154 subjects with dandruff - 70 of whom also had seborrheic dermatitis of the scalp. The shampoos were used three times per week for 4 weeks, with 2-week washout and follow-up periods. Clinical and self-assessments were made throughout treatment and after follow-up (day 43). Within and between-treatment assessments of signs and symptoms were analysed. In the two groups, seborrheic dermatitis and dandruff improved significantly throughout treatment, with lower clinical and self-assessment scores at both the end of treatment (day 29) and follow-up (day 43). Only the subjects treated with CPO/SA shampoo showed a significant reduction in the itching of seborrheic dermatitis at these times. The study demonstrated that both CPO/SA and Ketoconazole 2 % shampoo (Nizoral) were safe and effective in the treatment of dandruff and seborrheic dermatitis (Squire and Goode, 2002).

In another study, 120 volunteers, who suffered from dandruff, were recruited into the study in 3 groups. The first group used Cepigene shampoo, the second group used Ketoconazole shampoo and the third group used vehicle. The samples were also cultured for fungi detection. For isolating the fungi and evaluating the rate of dandruff and seborrheic dermatitis, the subjects were sampled from their scalp in zero day of the study. Trypan blue assay was used to study the antifungal effects of cepigen and ketoconasole. There was a remarkable decrease in the scaling and itching of scalp after a weeklong treatment with Cepigene and Ketoconazole shampoo. Both products had delivered a reduction in ASF scores in comparison with those of controls. Trypane blue assay showed a dose-dependent decrease in the M. furfur and M. globosa viability following exposure to cepigen and ketoconazole. This study supports the efficacy in treating dandruff and seborrheic dermatitis with Cepigene shampoo enriched in appropriate chemical and herbal compounds (Ashtiani et al 2013).

Danby, et al conducted randomized, double-blind, placebo-controlled trial aimed to evaluate the safety and effectiveness of ketoconazole 2% shampoo versus selenium sulphide 2.5% shampoo and placebo shampoo in patients with moderate to severe dandruff. Features that had been assessed included adherent and loose dandruff scores, presence or absence of irritation, itching, yeast cells, and global improvement rating by the investigator. A total of 246 patients had been included. Mean total adherent dandruff score declined throughout the treatment period with both ketoconazole 2% and selenium sulphide 2.5% shampoos significantly better than placebo at all visits. Ketoconazole was statistically superior to selenium sulphide at day 8 only ($p = 0.0026$). Both medicated shampoos were significantly better than placebo for reducing irritation and itching. Of the nine adverse experiences reported during the treatment phase, all involved patients had been treated with selenium sulphide 2.5% shampoo. It was concluded that both ketoconazole 2% shampoo and selenium sulphide 2.5% shampoo are effective in the treatment of moderate to severe dandruff; however, ketoconazole 2% shampoo appears to be better tolerated (Danby, et al 1993).

The clinical efficacy of antidandruff shampoos is correlated with both their anti-Malassezia and their squamolytic acctivities. The sebum flow nourishing the lipophilic yeasts is another actor on the scene fueling the skin disorder. Piérard-Franchimont and colleagues performed study in 120 men in order to quantify the effect of eight proprietary antidandruff shampoos on sebum flow dynamics. Evaluation was made using the Lipometer©. Two shampoos exhibited a significant

effect upon the sebum follicular reservoir, steadily increasing the sebum excretion rate in time. One other product induced a significant decrease in sebum output. Present data give insight into the distinct effects of shampoos on the follicular reservoir function in androgenic alopecia. The resulting sebum flow dynamics may be significantly increased or decreased by proprietary products (Piérard-Franchimont et al 1997).

The efficacy and safety of Ketoconazole 2% and zinc pyrithione 1% in shampoo formulations were compared for the alleviation of severe dandruff and seborrheic dermatitis. This open randomized, parallel-group trial began with a 2-week run-in phase during which subjects applied a neutral non-antidandruff shampoo. It was followed by a 4-week randomized treatment phase and a subsequent 4-week follow-up phase without treatment. Shampooing during the treatment period was carried out twice weekly for the Ketoconazole group and at least twice weekly for the zinc pyrithione group in accordance with the label instructions. A total of 343 subjects were recruited to enter the trial. Of the 331 eligible volunteers, 171 were randomized to Ketoconazole 2% and 160 to zinc pyrithione 1%. Clinical assessments were performed. Beneficial effects were evidenced for both medicated shampoos, but the effect was significantly better for Ketoconazole 2%, which achieved a 73% improvement in the total dandruff severity score compared with 67% for zinc pyrithione 1% at week 4 ($p < 0.02$). The recurrence rate of the disease was also significantly lower following Ketoconazole 2% treatment than following zinc pyrithione 1% treatment. As a consequence, the overall clearing of the skin condition at the end of treatment and follow-up phase was in favor of the
Ketoconazole 2% formulation ($p = 0.004$). Side effects were minimal. It is concluded that after a 4-week treatment, Ketoconazole 2% shampoo was significantly superior to zinc pyrithione 1% shampoo in the treatment of subjects with severe dandruff or seborrheic dermatitis of the scalp. It is our assumption that this difference is noticeable for the patient and as a consequence relevant. Both formulations were well tolerated (Piérard-Franchimont, et al. 2002).

Placebo-controlled studies

In adults with seborrhoeic dermatitis of the scalp, antifungal preparations containing ketoconazole improve symptoms compared with placebo. Ketoconazole shampoo is more effective than placebo at improving scalp symptoms such as scaling, itching, redness, and dandruff at 4 weeks in people with seborrhoeic dermatitis of the scalp (moderate quality evidence). Five randomized control trials (RCTs) ranging in size from 20 to 246 participants found improvements in symptoms with ketoconazole 2% shampoo after 4 weeks compared with placebo. Four of the five RCTs reported that there were no adverse effects of treatment.
The fifth RCT reported one instance of scalp tenderness that was probably related to ketoconazole treatment (Manríquez and Uribe, 2007).
In the only placebo-controlled trial of seborrhoea treatment, it was demonstrated a significantly higher cure rate in adults with seborrhoea and cultures positive for M. furfur who were treated for 4 weeks with a twice-weekly ketoconazole shampoo (Marconi and Powell, 1992).
Twenty subjects (16 male, 4 female, aged 25-65 years) with seborrhoeic dermatitis of the scalp were studied; authors make no distinction between dandruff and seborrhoeic dermatitis, regarding them as parts of a spectrum of the same disease. Some patients, therefore, had dry,

fiaky desquamation, while others had the more classical yellowish-red, greasy scaling with underlying erythema, generally regarded as seborrhoeic dermatitis. Eighteen of these subjects had similar lesions on other areas of the body. The subjects entered a double-blind, controlled randomized cross-over study lasting 12 weeks. They were randomly allocated to two groups. During the first 4 weeks, one group used ketoconazole 2",, shampoo daily, and the other used the shampoo base as a placebo daily. This was followed by a 4-week washout period in which Johnson's Baby Shampoo was used by all subjects. During the final 4-week period, the two groups were crossed over and each used the alternative medication. Responses were measured by clinicians using clinical gradings, and by the patients using a linear analogue scale. No adverse reactions to treatment were reported in any period of the study. All 20 subjects completed the study, and filled in all the visual analogue scores, but complete clinical grading data were only available for 19 subjects. Scaling and itching of the scalp improved significantly with ketoconazole and no response was seen with placebo. Topical ketoconazole appears to be an effective therapy for seborrhoeic dermatitis of the scalp, and more suitable for long-term treatment than the oral preparation (Carr, et al 1987).

A randomized, double-blind, placebo-controlled study was performed in 20 patients with seborrheic dermatitis of the face, by using 2% ketoconazole shampoo and cream. Sixteen patients also had seborrheic dermatitis of the scalp and five had seborrheic dermatitis of the chest or back. Responses were measured by clinicians and patients independently, using a grading system and linear analogue scales, respectively. Face and scalp lesions, assessed by both patient and clinician, showed a significant improvement or complete clearance in the group treated with ketoconazole. The patients who had seborrheic dermatitis of the chest or back and were treated with ketoconazole also improved. There was no improvement with placebo. This study provides further evidence for the aetiological role of pityrosporon yeasts in seborrheic dermatitis and of the efficacy of topical ketoconazole in its treatment (Green, et al. 1987).

Ketoconazole 2% shampoo was effective not only in treating seborrheic dermatitis, but also in preventing relapse when used once weekly as prophylaxis. An 88% response rate was achieved among 575 ketoconazole-treated patients with moderate to severe seborrheic dermatitis. A 6-month prophylactic treatment phase comprised 312 of the responding patients, 102 of whom were randomized to once weekly treatment with placebo shampoo, 121 who used ketoconazole shampoo once weekly, and 100 who alternated ketoconazole and placebo once weekly. Relapse occurred in only 19% of the active treatment group, compared with 47% of the placebo group and 31% of the ketoconazole/placebo group (Peter and Richarz-Barthauer, 1995).

Non-controlled studies

Superficial mycotic infections such as seborrheic dermatitis, tinea pedis, tinea corporis, and onychomycosis are common in patients infected with human immunodeficiency virus (HIV). In communities where HIV infections are frequent, some of these clinical presentations serve as markers of the stage of HIV infection. The diagnosis of superficial fungal infection in HIV-positive patients may be difficult because of atypical clinical manifestations. Therefore, to ensure a correct diagnosis, skin scrapings should be collected for potassium hydroxide preparations and

cultures. Most forms of dermatophytosis in HIV-positive patients respond well to many topical antifungal agents, such as azoles, terbinafine, and ciclopirox olamine. If the disease is chronic and extensive, then ketoconazole, fluconazole, and itraconazole are each effective (Aly and Berger, 1996).

In the general population, the prevalence of seborrheic dermatitis varies between 3% and 5%, while in HIV positive patients there is an increased prevalence of seborrheic dermatitis ranging between 30% and 83%. Seborrheic dermatitis occurs early in the course of HIV disease and may be an initial clinical marker of HIV infection. Antimycotics remain a popular treatment for SD, in the form of shampoos or creams. Many double-blind studies have documented the efficacy of ketoconazole 2% in reducing flaking and *Malassezia* counts; furthermore, ketoconazole 2% shampoo has been shown to have a significant prophylactic effect when used once weekly. Nevertheless, low potency topical corticosteroids (e.g., hydrocortisone) and emollients have been used in the initial stages of treatment (Chatzikokkinou, et al., 2008).

Indication: Treatment of tinea (pityriasis) versicolor

Yeasts of the genus, Malassezia, formerly known as Pityrosporum, are lipophilic yeasts, which are a part of the normal skin flora (microbiome). Malassezia colonize the human skin after birth and must therefore, as commensals, be normally tolerated by the human immune system. The Malassezia yeasts also have a pathogenic potential where they can, under appropriate conditions, invade the stratum corneum and interact with the host immune system, both directly but also through chemical mediators. The species distribution on the skin and the pathogenetic potential of the yeast varies between different Malassezia related diseases such as head and neck dermatitis, seborrheic dermatitis, pityriasis versicolor, and Malassezia folliculitis. Skin diseases caused by Malassezia are usually treated with antifungal therapy and if there are associated inflammatory skin mechanisms this is often supplemented by anti-inflammatory therapy (Saunte, et al 2020). Many studies have been published after the taxonomic revision carried out in 1996 in which 7 species were recognized. Two new species have been recently described, one of which has been isolated from patients with atopic dermatitis (Gupta AK, et al 2004).

<u>Systematic review</u>

Choi, et al performed a systematic review of literature on topical ketoconazole (KTZ's) efficacy and adverse effects, as well as provide an overview on current insights regarding its mechanism of action and upcoming developments. A PubMed search was done to include randomized-controlled trials focusing on the use of topical KTZ on human subjects. Forty studies with 4566 patients were included in this review. Topical KTZ is clinically effective for the treatment of Malassezia-related conditions such as seborrheic dermatitis and pityriasis versicolor with a reported efficacy of 63-90% and 71-89%, respectively. At the end of this review, it was

discussed that topical KTZ demonstrates high clinical efficacy for Malassezia-related conditions. More efficacious alternatives are now available for Tinea and Candida. Although topical KTZ is safe, clinicians should be aware that allergic contact dermatitis may occur. Further studies should be completed to investigate the use of topical KTZ for hair loss and inflammatory dermatoses (Choi, et al 2019).

Active-controlled studies

Current guidelines for treating Tinea capitis recommend washing the hair with shampoos containing 2.5% selenium sulfide or 2% ketoconazole two to three times per week for a period of 4–8 weeks (Marais and Osuch, 2017).

Nagpal et al performed a comparative study in order to compare the relative efficacy and relapse rate of oral and topical ketoconazole therapy in patients with pityriasis versicolor.

Forty patients with pityriasis versicolor were enrolled for the study. Aftera detailed history and clinical examination, the diagnosis was confirmed byKOH examination and Wood's lampexamination. Patients who had received anysystemic or topical antimycotic therapy within a month of the start of thestudy or had associated dermatophyte infections or any seriousconcomitantillness were excluded from the study. Twenty patients were distributed randomly to each group and treated with ketoconazole 200 mg per day for 14 days (Group I) or 2% ketoconazole cream, once daily afterbathing, for 14days (Group II). They were followed-up one week and two weeksafter starting the treatment. Clinical assessment in terms of pruritus, scalingand erythema was made on a scale of 0-3 (3 -severe, 2 - moderate, 1 - mild,0 - absent). At the end of two weeks, clinical response was assessed globallywith the use of a broad scale of healed, mild residual disease, considerableresidual disease, unchanged and deteriorated. Patients with healed or mildresidual disease (i.e. response in the top two categories) were consideredas responders; in addition, they wereconsidered as cured if they had a negativeKOH smear.[2] These patients were examined, clinically and mycologically, at monthly follow-up visits for three months for any relapse. In the present study, the mycological and clinical cure rates were 90% in the oral ketoconazole treated patients (Group I) and 80% in topical ketoconazole treated patients (Group II). However, relapse was more common in the group treatedwith topical ketaconazole.

The results of this study suggest that the efficacy of oral ketoconazole is almost similar to that of topical ketoconazole in the treatment of pityriasis versicolor, although the relapse rate is higher with topical ketoconazole (Nagpal et al, 2003).

To prevent the transmission of spores, 2–4 times weekly use of 1% selenium sulphide, 1% or 2% zinc pyrithione, 2.5% povidone–iodine, and 2% ketoconazole shampoos have been shown to be effective (Kaul, et al 2017).

Comparative clinical trial investigated the effect of fluconazole alone or associated with topical ketoconazole in the treatment of pityriasis versicolor. Aim of the study was to compare the efficacy and the safety of two doses of fluconazole given 1 week apart alone or associated to ketoconazole shampoo. This study included all patients with pityriasis versicolor who attended in dermatology department of Habib Thameur Hospital, Tunis (over a 21-month period). During the considered period, patients were randomly assigned in two study groups: G1 receiving fluconazole two doses 300mg given 1 week apart with G2 taken an association of fluconazole

(two doses 300mg given 1 week apart) and ketoconazole shampoo the first day. Seventy-one patients were enrolled in our study: 35 in the fluconazole group and 36 in the fluconazole associated to ketoconazole shampoo comparator group. The mean age was 29.1 years [16-70 years]. Concerning the clinical form, 27% had macular lesions, 24% had plaques and 49% had mixed form. Lesions werehyperchromic52%; hypochromic 15% and erythematous 6%. As for main location, 67% had lesions on the neck; 66% on the trunk, 60% on the shoulders. At the end of the study, there was no significant difference in clinical presentation and in improvement rate of pityriasis versicolor between fluconazole and association of fluconazole and ketoconazole shampoo ((p=0.13 at day 14, p=0.57 at day 28 and p=0.2 at day56). In this study, authors have shown that the improvement rate of PV treated with two doses of 300 mg of fluconazole with one week interval was similar to those of an association of one application of ketoconazole shampoo and the same dose of fluconazole. No significant differences in safety and tolerability between the two drugs were observed (Badri, et al 2016).

Tinea corporis responds well to topical antifungal agents from the imidazole (clotrimazole, econazole, ketoconazole) and allylamine (terbinafine, tolnaftate) groups, where it is administered once or twice per day for one to three weeks. Treatment is continued for at least one week after clinical resolution has been achieved (Marais and Osuch, 2017).
Forty patients suffering from pityriasis versicolor were treated with either 2% ketoconazole shampoo (20 patients) or 2.5% selenium sulphide shampoo (20 patients), once a week for three weeks. On global assessment after one month of start of therapy, 19 (95%) out of 20 patients treated with ketoconazole shampoo were cured while one case had mild residual disease. In selenium sulphide shampoo group, 17 (85%) out of 20 patients were cured, one had mild residual disease and two had considerable residual disease. No significant difference was observed in the response rates in the two groups. Relapse occurred in one patient of ketoconazole group and two patients of selenium sulphide group during the follow-up period of three months (Aggarwal, et al 2003).
Topical treatments can be effective, including econazole cream, ketoconazole cream or shampoo, or selenium sulfide lotion or shampoo. Econazole and ketoconazole creams may be used every day for 2 weeks. Ketoconazole shampoo may be used every day (lather, rinse, and repeat) for 3 days; selenium sulfide can be used every day (left on the skin for 10 to 15 minutes and then rinsed off) for 10 to 14 days, then one night per month to prevent recurrence. Recurrences may occur less frequently if treated orally for a short time: itraconazole, 200 mg every day for 5 to 7 days; fluconazole, 400 mg single dose; or ketoconazole 200 mg every day for 5 to 10 days. Oral terbinafine is ineffective in treatment of tinea versicolor, although a spray preparation (used topically) seems to be effective (Straten Vander, et al., 2003).

Placebo-controlled studies

Controlled clinical study was performed in order to evaluate the efficacy and safety of a single application (1 day) versus three daily applications (3 days) of ketoconazole 2% shampoo versus placebo shampoo in the treatment of mycologically confirmed tinea versicolor. Three hundred twelve patients were included in the primary analyses for this 31-day study. Global evaluation

scores were measured on days 10 and 31 with a 5-point scale (1 = healed to 5 = worsening), and a cellophane tape test was done at baseline and days 3, 10, and 31. Efficacy was assessed by clinical response, defined as both a global evaluation score of 1 (healed) and a negative cellophane tape test on day 31. Signs and symptoms of tinea versicolor (scaling, itching, erythema, hypopigmentation, hyperpigmentation) also were evaluated at baseline, day 10, and day 31 with a 4-point scale (0 = absent to 3 = severe). Both regimens of ketoconazole shampoo were significantly ($P < .001$) more effective than placebo for rate of clinical response, global evaluation scores, and mycologic outcomes (cellophane tape test). The clinical response rates at day 31 were 73%, 69%, and 5% for the 3-day ketoconazole, 1-day ketoconazole, and placebo groups, respectively. The difference in the efficacy of the two ketoconazole treatment regimens was not statistically significant. There were no significant differences between any of the treatment groups in the number of patients who experienced adverse events. No serious adverse events occurred and no patient withdrew from the trial prematurely because of an adverse event. At the end of the study, it was concluded that Ketoconazole 2% shampoo, used as a single application or daily for 3 days, is safe and highly effective in the treatment of tinea versicolor (Lange, et al. 1998).

Non-controlled studies

Main recommendations in most cases of pityriasis versicolor and seborrheic dermatitis include topical treatment which has been shown to be sufficient. As first choice, treatment should be based on topical antifungal medication. A short course of topical corticosteroid or topical calcineurin inhibitors has an anti-inflammatory effect in seborrheic dermatitis. Systemic antifungal therapy may be indicated for widespread lesions or lesions refractory to topical treatment. Maintenance therapy is often necessary to prevent relapses. In the treatment of Malassezia folliculitis systemic antifungal treatment is probably more effective than topical treatment but a combination may be favourable (Hald, et al., 2015). The aim of one study was to evaluate the efficacy of ketoconazole 2% shampoo in the treatment of pityriasis versicolor, for which thirty patients were included. The shampoo was applied daily for 3 days and found to be very effective in clearing the signs and symptoms of the disease. There were no serious adverse effects (Rathi, 2003).

Topical treatment for Tinea capitis is only used as adjuvant therapy to systemic antifungals. Adjunctive topical therapies such as Selenium sulfide (Grade of recommendation B; strength of evidence II a) or ketoconazole (Grade of recommendation B; strength of evidence III) shampoos as well as fungicidal creams or lotions have been shown to decrease the carriage of viable spores responsible for the disease contagion and reinfection and may shorten the cure rate with oral antifungal. The topical fungicidal cream/ lotion should be applied to the lesions once daily for a week (Grade of recommendation C; strength of evidence IV). The shampoo should be applied to the scalp and hair for 5 minutes twice weekly for 2–4 weeks or three times weekly until the patient is clinically and mycologically cured (Grade of recommendation C; strength of evidence IV). The latter in conjunction with 1 week of topical fungicidal cream or lotion application is recommended by the authors. Clinical and mycologic examinations of the children should be conducted at regular intervals (2–4 weeks). The treatment may be stopped after the culture

becomes negative or when hair regrowth is clinically evident; consequently, the duration of treatment can be individualized according to the response (Kakourou, et al 2010).

A retrospective analysis was performed in order to evaluate the efficacy of prophylactic ketoconazole shampoo for tinea capitis in a high-risk paediatric population. Patients at high risk for tinea capitis received twice-weekly ketoconazole shampoo. The primary outcome of the study was a reduction in the number of documented tinea capitis infections between the 12-month preprotocol and 12-month postprotocol periods. A secondary outcome included the evaluation of predisposing risk factors for acquiring tinea infections. Ninety-seven patients, with a mean age of 8.06 years, were included. Most patients (78%) were African American. There were a total of 13 tinea capitis infections during the 12-month preprotocol period. During the 12-month postprotocol period, 41 infections were documented: 37 (90.2%) in the prophylaxis group and 4 (9.8%) in the nonprophylaxis group. The average numbers of per-patient infections in the postprotocol period were 0.79 and 0.08 in the prophylaxis and nonprophylaxis groups, respectively. Initiation of prophylaxis did not reduce tinea capitis infections (p=NS). Previous history of infection and a high level of care were significant predictors of infections ($p<0.05$). It was concluded that improved hygiene, adherence to prescribed treatment regimens, and prevention of recurrent environmental exposure to surviving fomites should be stressed in high-risk patients and supersede the need for an antifungal (ketoconazole shampoo) prophylaxis protocol (Bookstaver, et al 2011).

An open study

The purpose of one open study was to evaluate ketoconazole 2% shampoo as a monotherapy for the treatment of tinea capitis. A total of 16 black children, aged 3-6, all with proven tinea capitis caused by Trichophyton tonsurans, were treated daily for 8 weeks with 2% ketoconazole shampoo for a total of 56 treatments. Clinical and mycologic examinations were performed every 2 weeks and again at 4 weeks following treatment. The number of colonies were counted on each plate after each visit. Patients with positive cultures after 8 weeks were placed on oral griseofulvin; those with negative cultures were followed monthly by culture for an additional 12 months. Marked clinical improvement occurred in all patients within 2 weeks and absence of pruritus was noted by the patients as early as 2-6 days. After 8 weeks of shampoo, 14 of the 15 (93%) children were clinically healed. Mycologically, the cultures dropped from a confluent growth of T. tonsurans to less than 100 colonies within 2 weeks; fewer than 50 at week 4 and 20 colonies or fewer after week 6. At 8 weeks of treatment the number of colonies remained at 20 or fewer. Six of the 15 children (40%) had negative cultures after 2, 4, and 6 weeks. One child relapsed at the first 4-week follow-up visit. Five of 15 (33%) of the children remained culturally negative for 12 months post-treatment. It was concluded that Ketoconazole 2% shampoo alone reduces the number of viable arthroconidia in children with tinea capitis thus reducing the transmissibility and contagious nature of the disease. Unexpectedly, complete cure was obtained in 5/15 (33%) of the children. The children remained clinically and mycologically clear as long as one year after treatment (Greer, 2000).