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Effect of itraconazole on the quality of life in patients with moderate to severe seborrheic dermatitis: a randomized, placebo-controlled trial

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ABSTRACT

Background: Few studies have examined the effect of seborrheic dermatitis (SD) and/or its consequent therapy on a patient's quality of life. Itraconazole has been suggested as an effective therapy for severe SD but its impact on Quality of Life (QoL) in these patients has never been studied before.

Objective: The study aimed to verify the efficacy of the itraconazole on the quality of life in patients with moderate to severe SD.

Methods: A randomized, double-blind, placebo controlled trial was planned to describe the effect of SD per se on QoL and to determine the impact of oral itraconazole or placebo on QoL of SD patients. Sixty-eight patients with moderate to severe SD participated in the study to receive either itraconazole or placebo. Dermatology Life Quality Index was used to evaluate their quality of life before and after treatment. Itraconazole 200 mg/daily or placebo was prescribed for one week and then the first two days of every month for the following three months. Fifty-seven patients completed the study.

Results: Significant improvement was observed in QoL of both itraconazole and placebo groups, but itraconazole group showed significantly higher improvement as compared to placebo (p=0.001). QoL was impaired significantly with high disease severity (p=0.002) and facial involvement (p=0.017).

Conclusions: Itraconazole significantly improves the QoL in patients with moderate to severe SD.

Introduction

Seborrheic dermatitis (SD), a common skin disorder that typically presents as erythematous plaques or patches and can vary from mild dandruff to dense, diffuse, adherent scale affecting the areas where sebaceous glands are prominent, including the scalp, face and chest. Its precise etiology remains unknown, though it is associated with genetic, environmental, and general health factors. Other important pathogenic factor seems to be *Malassezia* colonization. Its role could be

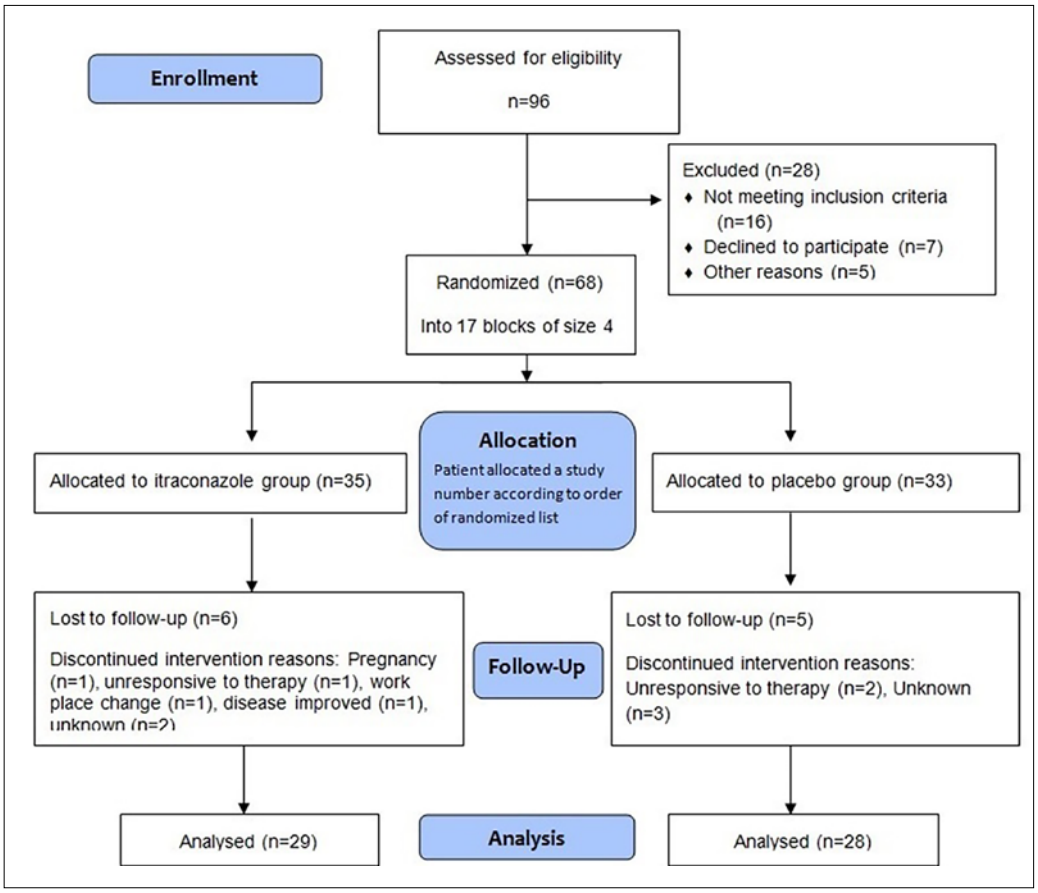

Figure 1. Flow diagram of the study. [Copyright: ©2016 Abbas et al.]

supported by the positive correlation between yeast density on the skin and the severity of SD and a high efficacy of antifungal agents in the treatment of this disorder [1,2,3].

While SD rarely causes serious complications, it almost always leads to marked aesthetic deterioration and psychological distress due to its chronic and relapsing nature. Despite high frequency of SD, surprisingly, only few studies have examined the effect of SD on Quality of Life (QoL) [4-6].

Although the topical treatment of SD with corticosteroids or antifungals is effective, there is a high risk of relapse and poor patient compliance [7], and therefore in some cases it is necessary to resort to systemic antifungals, especially in severe disease. Various oral antifungals have been used to control SD with variable success rates. Among them, itraconazole was the most frequently reported oral treatment particularly for severe SD [8], but therapeutic efficacy was evaluated only by clinical signs and symptoms in previous studies [7,9-11]. Assessing QoL can help in providing patients better service, by acknowledging their real needs and interfering with treatment decisions. Because QoL is a very important aspect in health and no study exists in the literature which assess the effect of treatment on QoL in SD patients, this randomized controlled trial was set up to determine the impact of oral itraconazole on QoL in patients with moderate to severe SD.

Methods

This was a randomized placebo controlled, double-blind trial carried out with patients attending the outpatient ward of the Dermatology Department at the Razi Hospital Tehran, between June 2012 and March 2014. Patients were informed clearly and understandably about the possible risks or benefits of the trial and informed consent was provided by each patient included in the study. The approval of the study was obtained by the local and university ethics committees and performed in accordance with the Helsinki Declaration of 1964, as revised in 2013.

The study design is summarized in Figure 1. Inclusion criteria were clinical diagnosis of SD made by a dermatologist, moderate to severe SD (Seborrheic Dermatitis Area Severity Index [SDASI] =4 plus: ≥3 anatomical sites involved and/or recurrent SD and/or disease unresponsive to conventional topical therapy) and age ≥18 years. Exclusion criteria included the following: any concomitant skin disease (e.g. acne, rosacea, contact dermatitis) or HIV+/AIDS, recent use of antiseborrheic treatment (2 weeks for topical and 4 weeks for systemic therapy), history of allergy to azoles, renal, liver or cardiac disease, patients using drugs interacting with itraconazole (e.g., cyclosporine, isoniazide, omeprazole, warfarin, statins), and pregnant/lactating women. Both itraconazole

TABLE 1. Main characteristics of patients at baseline and at the end of study
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	Itraconazole	Placebo	*P* value
Patients enrolled	*n*=35	*n*=33	
Sex, *n* (%)			0.532
Male	23 (65.7%)	24 (72.7%)	
Female	12 (34.3%)	9 (27.3%)	
Education level, *n* (%)	19 (54.3%)	20 (60.6%)	0.652
Intermediate	14 (40.0%)	13 (39.4%)	
Bachelor	2 (5.71%)	0	
Master/PhD			
Age (years), *mean ±SD*	28.17 ±7.32	26.45±8.09	0.362
Duration of disease (years), *mean ±SD*	4.19±3.93	4.76±4.56	0.581
Number of relapses before treatment, *mean ±SD*	5.17±5.12	6.45±7.83	0.424
BMI(Kg/m2), *mean ±SD*	23.03±3.67	23.38±3.11	0.670
Quality of life (DLQI), *mean ±SD*	6.66±4.64	4.88±3.78	0.089
Patients who completed the study	*n*=29	*n*=28	
Quality of life (DLQI), *mean ±SD*			
Before	6.72±4.67	5.04±3.87	0.001
After[a]	1.79±1.63	3.57±3.27	
Severity of SD (SADSI), *mean ±SD*			
Baseline	9.78±4.41	10.47±3.71	0.023
At the end of study[a]	1.82±1.66	5.47±2.19	
Itching, *mean ±SD*			
Baseline	2.00±0.84	1.68±0.67	0.002
At the end of study[a]	0.52±0.63	1.07±0.53	
Burning sensation, *mean ±SD*			
Baseline	1.17±1.07	0.71±0.65	0.003
At the end of study[a]	0.17±0.46	0.43±0.50	
Side effects[b], *n* (%)	3 (10.3%)	5 (17.9%)	0.470

SDASI Seborrheic Dermatitis Area Severity Index, *DLQI* Dermatology Life Quality Index, *BMI* Body Mass Index, *SD* Seborrheic Dermatitis

[a] at the end of study=at the end of 16 weeks, [b] Nausea, abdominal pain, diarrhea

and placebo were in capsule form and identical in appearance and were delivered to patients by a third person recruited for this purpose. The study investigator and patients were blind to intervention, and that was maintained until patients completed their last follow up visit.

The QoL was assessed at the start and end of the study by a standard Dermatological Life Quality Index (DLQI) questionnaire (Persian version) filled by patients, which consisted of 10 questions each referring to the previous week. Each question was scored from 3 (very much) to 0 (not relevant or not at all). The maximum possible score was 30. A questionnaire including the patient's basic profile was filled in the first visit for assessing other secondary outcomes like effect of age, sex, education level, disease duration, number of relapses and body mass index (BMI) on QoL. SDASI was used to determine the disease severity. This scoring system was modified from Psoriasis Area Severity Index (PASI) and the Comert et al study [12] that had already been used in a previous study by Ghodsi et al [13].

The treatment was administered in two different phases. In the first phase (initial treatment), topical 1% hydrocortisone ointment once daily and 2% ketoconazole cream twice daily plus either oral itraconazole 200 mg/day or oral placebo was prescribed for one week. Patients were advised to apply topical therapy on the areas involved. Topical treatment was included in the study for ethical issues. In the second phase (one month after initial treatment), which was maintenance period, oral itraconazole 200 mg/day or oral placebo was given on the first two days of every month (400 mg/month) for three months. No other topical treatment, including therapeutic shampoos (except moisturizers) or oral medications, was allowed during this study period. During the second phase, in cases of relapse or flare of disease, patients of either group were allowed to use topical treatment (1% hydrocortisone ointment once daily and 2% ketoconazole cream twice daily) for a maximum of three days as a rescue regimen after informing the study investigator.

Statistical analysis was performed using IBM SPSS software. The difference in SDASI, symptom severity and DLQI scores before and after therapy was compared by using paired t-test. Comparisons of mean age, disease duration, number of relapses and BMI between itraconazole and placebo groups

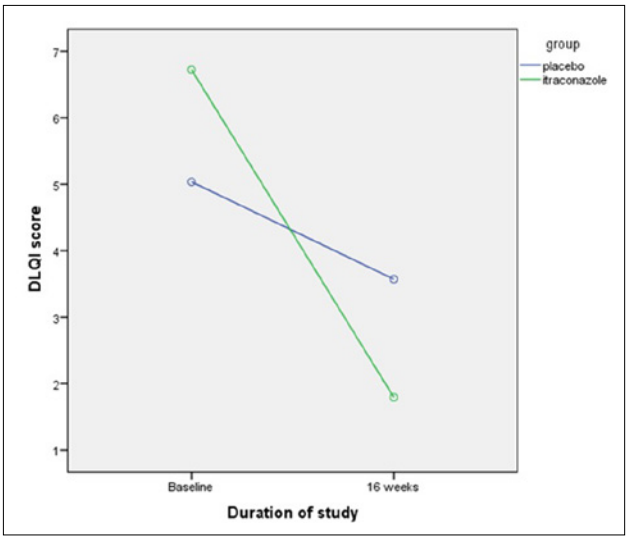

Figure 2. Comparison of DLQI before and after treatment in both groups. [Copyright: ©2016 Abbas et al.]

were performed using unpaired t-test. The Pearson correlation was used to assess the link between DLQI and other secondary parameters. P-value<0.05 was considered significant.

Results

Sixty-eight patients who met study criteria were randomly assigned to itraconazole and placebo groups. Eleven patients were lost to follow up. Consequently, 57 patients completed the study and were included in the analysis (Figure 1). The main characteristics of patients at baseline and at the end of study are summarized in Table 1. The mean DLQI score in our study was 5.88±4.30. Although DLQI scores decreased significantly in both groups (Table 1), patients taking itraconazole had greater reduction compared to placebo (p =0.001) (Figure 2). The most compromised elements of QoL were clinical symptoms, feelings (question 1, 2 of DLQI) and daily activities (question 3, 4) (Figure 3). QoL was not affected by age, sex, educational level, BMI, disease duration and number of relapses (p >0.05) but was impaired significantly with high disease severity (SDASI) (p =0.002) and presence of symptoms (itching and burning sensation) (p =0.001 each). Furthermore, DLQI was not significantly different between the two groups of itraconazole and placebo (p =0.089). The most common site involved in our study was the scalp, but the location with significant effect on quality of life was the face (including forehead, eyebrows, nasolabial folds and cheeks collectively compared with scalp and trunk) (p =0.017). One patient in the itraconazole group as opposed to four patients in the placebo group required rescue medication in the second phase of the study. Side effects like nausea, mild abdominal pain and diarrhea were reported by only three patients in itraconazole group.

Discussion

In our study, we showed that quality of life is significantly improved by systemic itraconazole in moderate to severe SD patients. One of the important findings of our study was that patients in the itraconazole group had experienced a 73.36% reduction in DLQI after four months' treatment, compared with 29.16% in the placebo group, and this effect of itraconazole on severe SD (mean DLQI before 6.72 and after 1.79) is comparable to systemic isotretinoin in acne patients (mean DLQI before=6.7, after=2.8) [14].

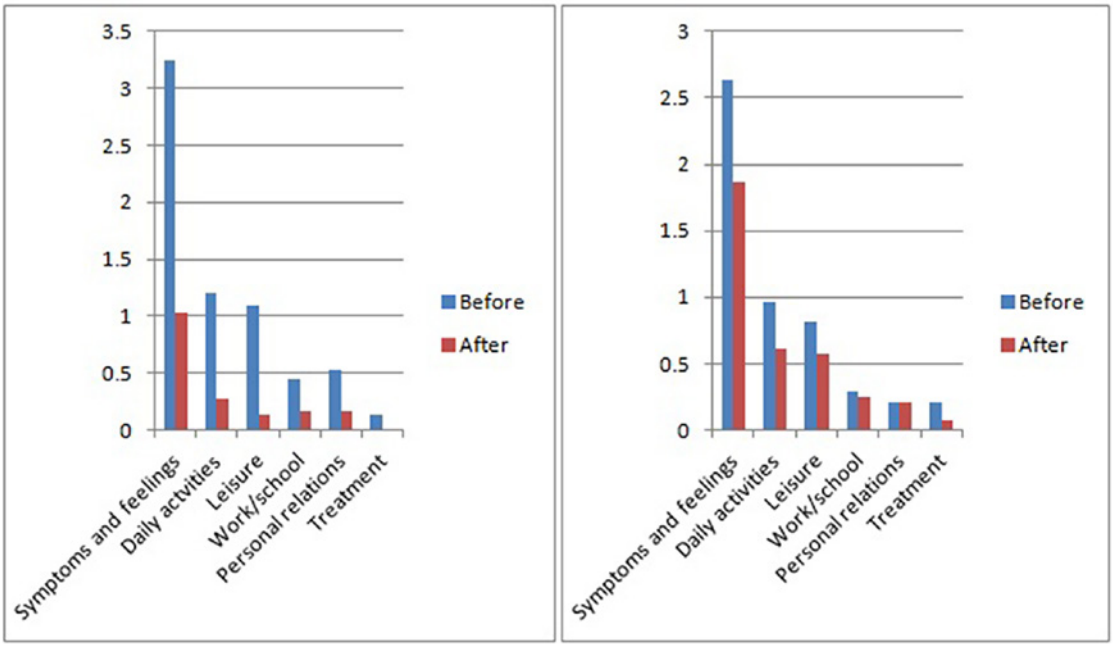

Figure 3. Categories of DLQI and comparison of mean score in both groups (left itraconazole, right placebo). [Copyright: ©2016 Abbas et al.]

The mean DLQI score in our study was similar to Harlow et al (mean DLQI: 5.9, n=20) [15] but lower than Szepietowski et al (mean 6.92±5.34) [4]. The difference could be explained by the different regional and social backgrounds and disease severity level in these studies. There is marked impairment of QoL in patients with more severe disease, with a greater effect observed in women and in young patients (age subgroup: 26-35 years) with higher educational level (master and PhD level), and this is almost parallel to previous studies [4-5]. Interestingly, in our study, disease duration and number of relapses had no effect on QoL. Here, adaptations of the patients to the nature of their disease and coping more efficiently with the disease and therapies over a certain period of time may have had effect. The most common site involved in our study was the scalp, but QoL impairment was higher significantly in facial disease. As the appearance plays important role in the society, a patient with a red and flaky face may feel more embarrassed.

The assessment of the impact on quality of life in patients with skin diseases is important for clinical management. It is essential to detect patients at a higher risk of experiencing a worse quality of life in order to treat him/her in a more integrated way. To our knowledge, this trial was the first using a randomized, placebo-controlled design that investigated the effect of itraconazole on the quality of life in moderate to severe SD patients.

Therapeutic efficacy of itraconazole has already been studied in many previous clinical trials [7, 9-11, 13]. Although study designs and measurement scales were different, the results regarding effect of itraconazole were almost similar in these studies, and this fact shows the marked efficacy of itraconazole in the treatment of severe SD.

Our study met with several limitations. First, no fungal culture was performed and therefore clinical outcome could not be correlated directly to *Malassezia* colonization. Second, the power of the study is limited by the monocentric design and small sample size of our study, therefore, a larger, multicentric study is warranted to evaluate the therapeutic effect of itraconazole or other newer therapies for SD patients. Third, the short period of follow up; a longer study period would have been beneficial. Fourth, it is well known that SD may worsen or improve due to many factors such as seasonal variation, host immunity, and host mood status; these factors might have changed the clinical condition in some patients. Fifth, although the effect of topical therapy declined mainly after two weeks, it might have affected partly over the final result of clinical picture and DLQI.

Conclusions

SD can significantly reduce QoL particularly in severe disease and facial involvement. Pulse therapy with itraconazole can dramatically improve quality of life and disease severity. Due to the complex interactions among diseases, the patients' QoL and therapeutics, physicians must couple subjective assessment of QoL with objective measurements for the proper management of severe SD.

Trial registration: IRCT2012091510842N1 (www.irct.ir)

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