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Original Research Article

A Pilot Randomized Controlled Trial on the Efficacy and Safety of Increased Dose and Duration of Oral Itraconazole Therapy in Chronic and Recurrent Tinea Corporis et/or Cruris at a Tertiary Care Hospital in Eastern India

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Conflict of interest: Nil

Abstract

Introduction: Oral antifungals are being used increasingly for chronic recurrent dermatophytosis treatment but still there is paucity of an evidence based effective drug and dosage regimen for the same. This pilot study was done to evaluate the efficacy of oral itraconazole with higher dose and duration in chronic, recurrent tinea corporis and cruris.

Material & Methods: A total of 120 patients divided into three groups were compared in this randomized controlled trial. Itraconazole 200mg twice daily was received by group A (for 4weeks), group B (for 8weeks) & group C (for 12 weeks). Both diagnosis and treatment efficacy was confirmed by microscopic examination of 10% potassium hydroxide (KOH) mount &Saboraud's dextrose agar (SDA) culture of skin scrapings. Liver function tests (LFT) were done before drug trial & every 4 weeks.

Results: At the end of follow up, the mycological cure (KOH negative & culture negative) was 75 % (group C) followed by 60% (group B) & 12.5% (group A) (P =0.000). Number of relapse cases were 4, 14 and 34 in group C, B and A respectively. There was no significant difference in the mean values of LFT parameters among the three groups. The rise of LFT parameters were more than 2 times in 3 cases (group B) and 1 case (group C). Treatment tolerability were good (more than 70%) in all groups.

Conclusion: Group C showed highest clinical and mycological cure rate, lowest relapse rate with good treatment tolerability and safety profiles.

Keywords: Dermatophytosis, Itraconazole, Chronic, Recurrent, Relapse

Introduction

The most common superficial fungal infection in humans is dermatophytosis (20%-25% population). [1] Dermatophytes infections are very common in India due to its climate and recently there are changes in the disease presentations, severity, treatment response, and relapse rate. [2,3] A clinico-mycological study conducted by Mahajan S *et al* showed that itraconazole is the most effective oral antifungal agent among all other oral antifungals. [4] Itraconazole has shown good results in the treatment of naive dermatophytosis at doses of 100 mg once a day for 2 weeks and with 200 mg once a day for 7 days. [5] Because of frequent recurrence at short intervals (less than six weeks), and in chronic cases (more than six months), some physicians have used it in doses of 200 mg once a day for prolonged durations. [6-8]

Patients with chronic and recurrent dermatophytosis are posing treatment challenges and there are no specific consensus guidelines for the management of these clinically resistant cases. Dermatologists are using a combination of oral antifungals, higher doses of oral antifungals, longer duration of treatment on a hit & trial basis to contain this menace. [9] We hypothesized that increased dose & duration of oral itraconazole might improve the efficacy and reduce the relapse rate of chronic recurrent tinea corporis et/or cruris without compromising safety.

Material and methods

Study design

A hospital based, three arm, phase II pilot randomized controlled trial (RCT) is planned in accordance with the declaration of Helsinki protocols. All participants were selected based on their eligibility criteria after getting their informed consent to participate in the above study. Ethical clearance before the treatment trial was obtained from the institutional ethical committee (KIIT/KIMS/IEC/168/2019).

Sample size

Screening for eligible male and female patients numbering 133 were done for enrollment and 39 subjects were expected to complete the study in each arm, considering 12% drop out rate.

Study population

This study was conducted at the department of Dermatology, Venereology &Leprology outpatient department of Kalinga Institute of Medical Sciences, Bhubaneswar, India in the year 2019-20.Tinea patients who were partial responders to the conventional dose of oral itraconazole (100mg twice daily for 4wks) and suffering for more than six months(chronic) or showing frequent clinical recurrences (in less than six weeks) after taking standard fixed dosage regimens of oral itraconazole were included in this study.[6] Tinea corporis &/or tinea cruris patients diagnosed clinically & mycologically (KOH-10% & SDA Culture both positive) were selected only for they being the major share of tinea patient population. A treatment free interval of one-month duration was ensured for each patient's inclusion. Patients who were less than 18 years and more than 70 years of age, less than 40kg.body weight, patients with any immunocompromised medical status e.g. diabetes mellitus, HIV infection, immunosuppressive therapy or suffering from any other illness taking drugs like rifampicin, digoxin, phenytoin, anticoagulants, terfenadine, or having congestive cardiac failure, any liver disorders were excluded from this study. Defaulters in each group (group A-3(7%), group B-4(9%),

group C-6(13%) were not analyzed because of non-compliance of medications and not reporting because of personal reasons. No one on enquiry discontinued treatment due to drug adverse effects.

Case definition

Clinical diagnosis of tinea corporis et/or cruris were confirmed by the point of care test for the rapid detection of dermatophytosis i.e. microscopic examination of 10% KOH mount of skin scrapings. The fungus culture in saboraud dextrose agar (SDA) medium were done for additional confirmation of diagnosis.

Intervention

Eligible patients were allocated randomly by concealment (opaque envelope) to group A/ B/ C for treatment trial. Group A patients received oral itraconazole 200mg twice daily for 4weeks, group B patients received 200mg twice daily for 8weeks & group C patients received 200mg twice daily for 12 weeks' duration. The extended periods (8wks &12wks) of continuous therapy were administered to know, if any improved clinical cure rate & lesser relapse rate were achieved than the 4wks duration of therapy and with a good safety profile.

Each patient was assessed every 2 weeks for clinical improvements till the end of his/her duration of treatment and follow up period. A list of itraconazole capsule 200mg from reputed pharma companies with good bioavailability claims were offered to the patients to choose from. Oral antihistamines for 10 days were allowed to patients for initial relief from itching. White soft paraffin-based moisturizers were allowed to patients on an optional basis.

Safety assessment

Any adverse drug reaction (ADR) like skin rash, nausea, gastrointestinal upsets, abdominal pain, dizziness, headaches, leg edema, jaundice etc. were noted at each visit. Liver function test (LFT) measurements were done every 4 weeks to detect any abnormal rise in liver enzyme levels. Treatment tolerability assessment by investigator & patient were done by using a 4-point scale (Very Good/Good/Fair/Poor).

Treatment efficacy assessment

Clinical cure – Investigator's assessment of improvement in each of the clinical signs & symptoms (viz. pruritus, erythema, papulo-vesiculo-pustules, infiltrations, exudations, desquamations, post inflammatory pigmentations) were to be rated on a 4-point scale (absent-0, mild-1, moderate-2 or severe-3).

Taking into account all the signs and symptoms, treatment efficacy was measured by the investigator using a 4-point scale and declared as excellent, good, moderate and poor response if the total score was 0, 1-3, 4-8, >8 respectively. Clinical cure was assumed if investigator's rating was excellent or good. [5]

Mycological cure – KOH (10%) & SDA culture test were done at the beginning of treatment, end of treatment and end of follow up. Mycological cure was defined as both culture & KOH negative.

Disease relapse: Return of signs & symptoms of disease activity during the twelve weeks' follow-up period post treatment, with KOH & culture confirmation were recorded.

Statistical analysis

We reported the baseline characteristics as means and standard deviations or numbers and percentages. Descriptive analysis was performed including number (proportion) for categorical variables and mean±SD or median (IQR) were provided for continuous variables. Response of the three treatment regimens were compared using chi-square

test. Standard statistical software Stata 15.1 was used for all analysis.

Results

A total of 43 patients in group A, 44 patients in group B, and 46 patients in group C were randomized to trial medications, of whom 3 patients in group A, 4 patients in group B, 6 patients in group C were lost to evaluation during treatment and follow-up(fig.1).

Baseline demographic characteristics are presented in Table 1.

The mean age of patients showed no significant intergroup difference. Tinea corporis and cruris patients were noted to be 37.5% each, of the total number of patients (120). Tinea corporis et cruris patients were 25% of the total patient population. The major pathogens isolated at baseline were T mentagrophytes (58%), T rubrum (35%).

Primary treatment efficacy as mycological cure rate is shown in fig.2. Better mycological cure rate was observed between the end of treatment and end of follow up periods in group B and C.

Clinical cure rate is shown in fig. 3.

There was excellent to good improvement in the scores(0-3) of desquamation, erythema, pruritus etc. and highest seen in group C.

Tolerability of medications by the patients were rated more than 70% in all the treatment groups (fig. 4).

Tolerability ratings were significantly equivalent in both the investigator's and patient's groups. Adverse drug reaction events such as maculo-papular skin rashes reported in group A-two patients, group B – two patients and group C -three patients. Four pedal edema cases were also seen (group A - 1, group B - 1, group C - 2).

Disease relapse rate (fig.5) shows highest value (65.4%) for group A and lowest value (7.6%) for group C among the total no. relapsed cases (52) during the 12weeks of follow up periods.

Table 1: Baseline demographics and disease characteristics

Characteristics	Group A	Group B	Group C
Patient (n)	40	40	40
Male:Female (n)	27:13	20:20	23:17
Age (years)	30±7.12 (18-48)	31±7.03 (20-54)	31±8.00 (18-53)
Tinea Corporis	13	17	15
Tinea Cruris	14	14	17
Tinea Corp. et Cruris	13	9	8

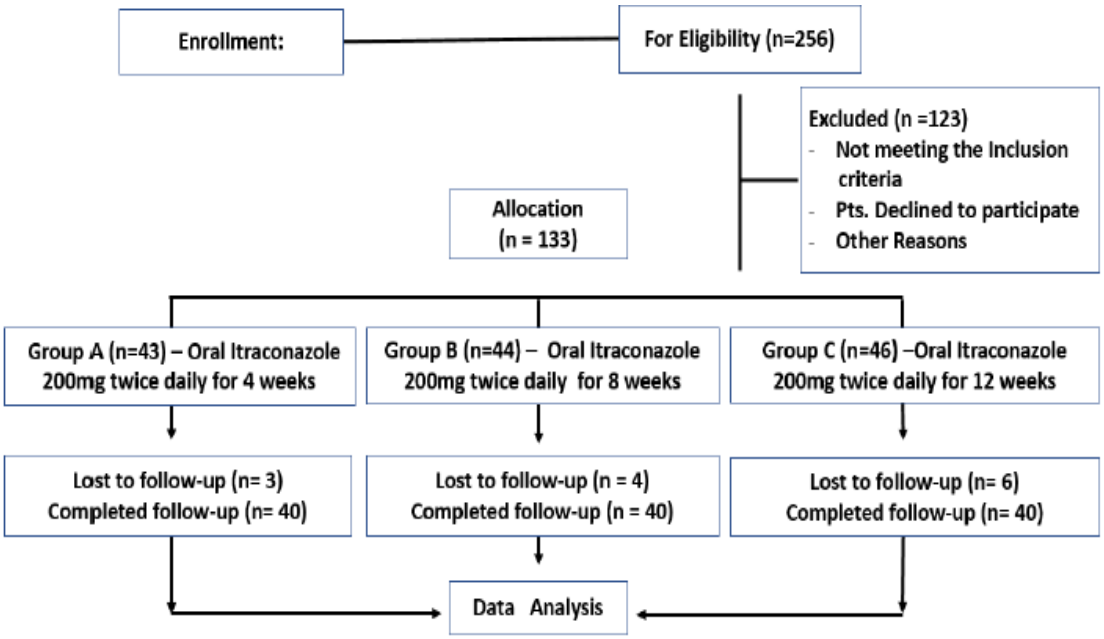

Figure 1: CONSORT study flow diagram, lost to follow up-Gr.A: Personal reasons (PR)-3, Adverse drug effects (AE)-0, Gr.B: PR-4, AE-0, Gr.C: PR-6

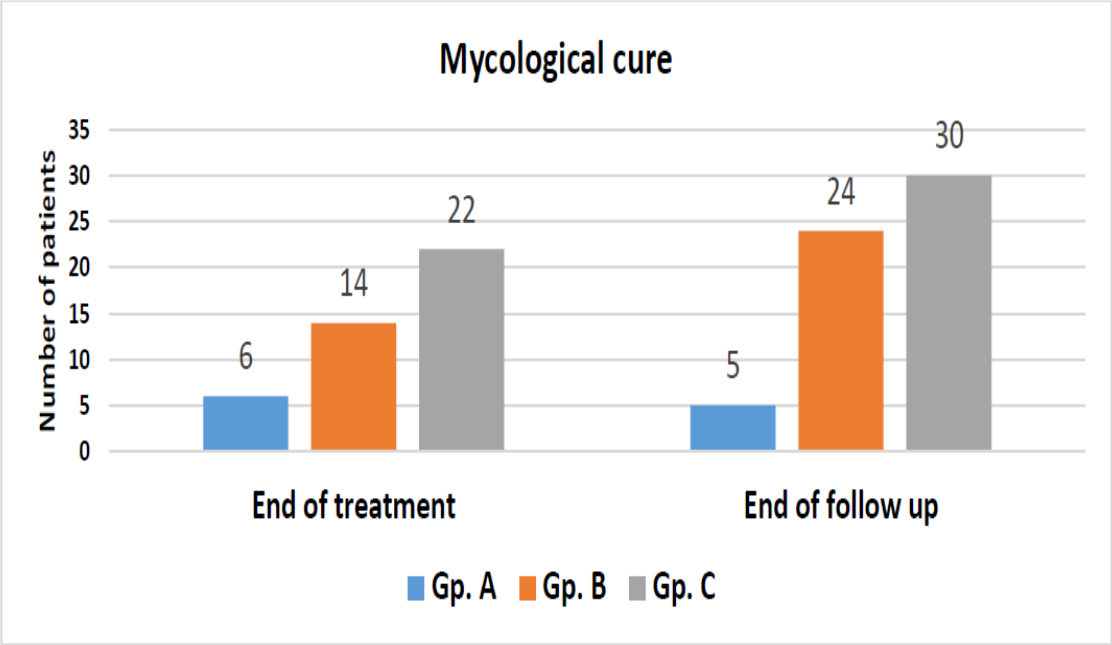

Figure 2: Mycological cure (primary efficacy). Mycological cure is defined as both KOH and SDA culture results negative.

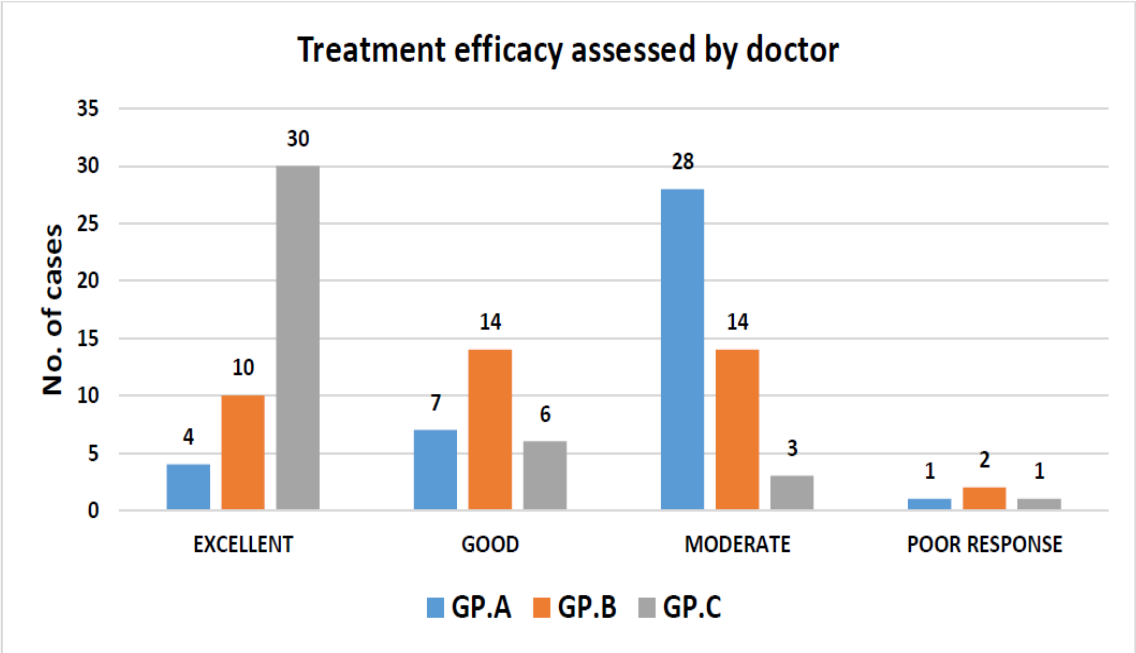

Figure 3: Treatment efficacy (clinical cure assessment by investigator). (Excellent -score-0, Good -score <4, Moderate -score 4-8, Poor -score >8)

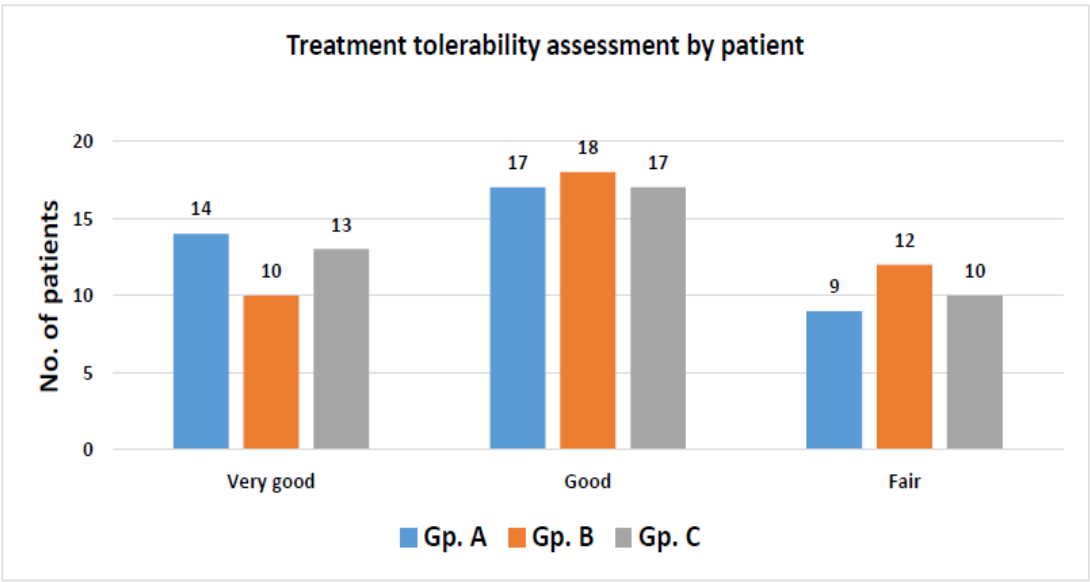

Figure 4: Treatment tolerability assessment by patient: (Very good -No adverse drug effects (AE), Good- improvement in AE within one week of onset, Fair- improvement in AE within two weeks two weeks of onset, Poor- persistence in AE beyond two weeks of onset)

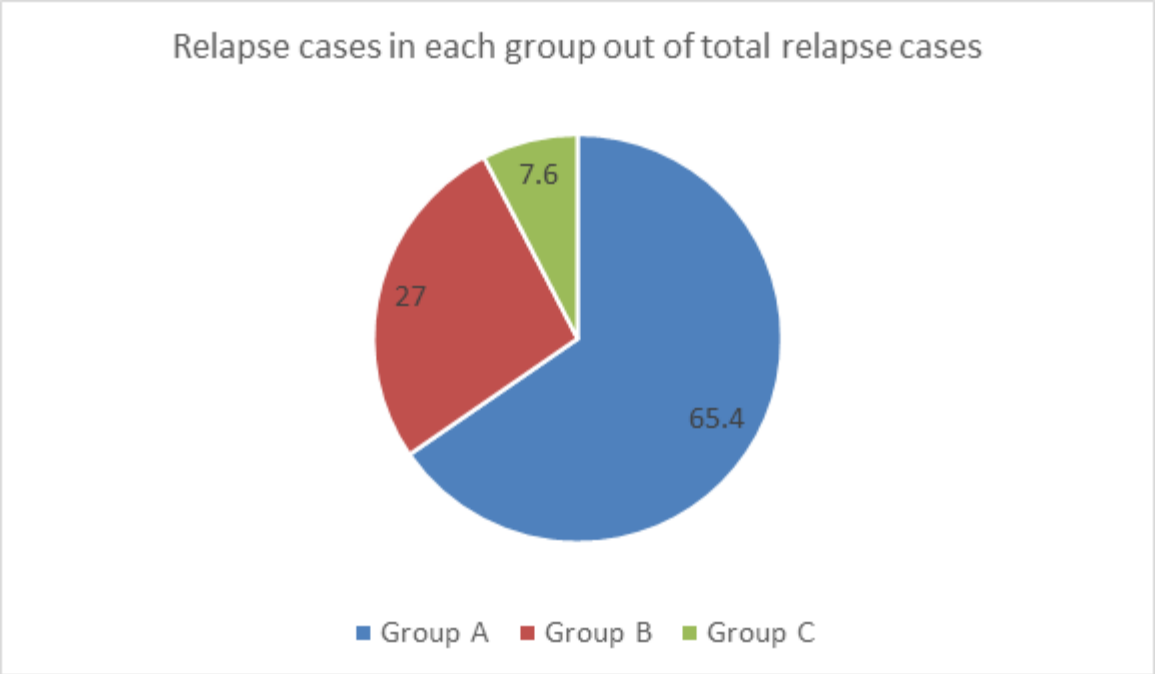

Figure 5: Relapse rate: Group C – 4 (7.6%), Group B – 14 (27%), Group A – 34 (65.4%) out of Total relapse cases 52 nos.

Discussion

There has been always a search for an orally active, broad-spectrum antifungal agent with a relatively short treatment period, low toxicity and good tolerability for the treatment of dermatophytosis. Itraconazole is an orally active triazole derivative with potent antifungal activity against a broad spectrum of human pathogenic fungi, including dermatophytes and is being used for the treatment of dermatophytosis since 1980. In the current scenario partially responding chronic and recurrent forms of dermatophytosis are rising with the emergence of multidrug resistant strains which is becoming a nightmare for many clinicians. [10]

Itraconazole has been safely used earlier at a dose of 400mg/day for 6-12 months in the treatment of deep fungal infections.[11] Indian association of dermatologists, venereologists and leprologists (IADVL) Task force against recalcitrant tinea (ITART) consensus on the management of glabrous tinea (INTACT) has pointed out the need for undertaking further study on oral itraconazole and other oral antifungal agents, as conventional oral antifungal regimens are proving ineffective and more research work needed to provide the required level of evidence. [12] Since there was scarcity of trials, so we conducted this pilot study to know the efficacy, safety and relapse rate of increased dose and duration of oral itraconazole in chronic recurrent tinea corporis and/or cruris.

Primary assessment of efficacy was performed by culture and KOH test. At the end of follow up in group C the KOH & SDA culture was negative in 75% cases followed by 60% cases in group B. KOH & culture test was negative in 12.5% cases in group A, thereby signifying failure of treatment (P value 0.000). A study by Gupta A *et al* on itraconazole pulse therapy had shown that efficacy of oral itraconazole therapy in toe nail candida onychomycosis clinical and

mycological cure 75%, only mycological cure 90.6% and also for finger nail candidial onychomycosis clinical and mycological cure was 91.7%. [13] Secondary assessment of efficacy, clinical cure (excellent & good score) was 90% in patients of group C followed by 60% in patients of group B and 27.5% in group A (P value= 0.000). There was a study conducted by Sharma P *et al* evaluating the efficacy of oral itraconazole continuous therapy for 3-6weeks ,which concludes that with 200 mg/day dose showing 50% result whereas combination with terbinafine showing 90% result in clinical and mycological cure.[14] In contrast to this study our study has shown that itraconazole alone in chronic recurrent tinea corporis et/or cruris with a higher dose and duration (200mg twice daily for 12 weeks) has a treatment efficacy of 90% clinical cure & 75% mycological cure.

The relapse rate was also observed in the three groups. During the 12 weeks of follow up after treatment stoppage only four cases (7.6%) out of total 52 relapsed cases belonged to group C as compared to 27% (group B) and 65.4% (group A) (P value= 0.01). Such a high incidence of relapse in group A is due to poor response to treatment.

In our study the safety of treatment was assessed by recording investigator's & patient's assessment of tolerability rating and by measuring the routine biochemical parameters in liver function test (LFT). Results of tolerability as assessed by investigator and patient were quite similar and there was not much of a difference, P value=0.622 for investigator's assessment and P=0.755 for patient's assessment among the three groups, showing that increased dose and duration has little effect on treatment tolerability profile. Majority of patients assessed their tolerability of treatment as very good and good (77% in group A, 71.6% in group B and 77% in group C). There was no significant difference in the mean value of LFT parameters among the three groups, measured at the end of 4, 8 and 12 weeks. The rise of LFT parameters were more than 2 times only in 3 cases of group B and 1 case of group C.

Previous studies have shown that the incidence of adverse drug reactions (ADR) to be 1.1 % and 2 % respectively. [15,16] In our study occurrence of ADRs in the form of maculopapular rashes were higher in incidence but mild in nature. Therapy was not discontinued because of the very mild nature of adverse drug reactions. Chang C *et al* in a meta-analysis study have shown that for itraconazole continuous therapy the risk of treatment discontinuation is 1.96 % with 100 mg/day and 4.21 % with 200mg/day and risk of asymptomatic rise in liver enzymes is less than 2%, risk of liver injury requiring termination of treatment is 0.11% with 100 mg/day of itraconazole.[17]

Gupta A *et al* in their study evaluating hepatic safety of itraconazole concluded that the incidence of higher grade abnormalities in LFT profile with continuous therapy is less than 2%. [18] In our study we also found that increased dose and duration of oral itraconazole did not significantly affect liver parameters.

Conclusion

The present pilot study on oral itraconazole monotherapy of 200mg twice daily for 4-, 8- and 12-weeks' durations in chronic and recurrent tinea corporis et/or cruris showed the highest clinical cure rate of 90% and mycological cure rate of 75% (KOH & SDA culture negative), relapse rate of 7.6% in group C(12wks.).

Treatment tolerability among the 3 groups (4/8/12 weeks) were good (77% / 71.6% / 77%), Adverse drug reactions (maculopapular rash/ pedal edema) were self-limiting without any treatment discontinuation. LFT profiles in all groups

showed minimal alterations of more than 2 times rise in liver enzymes.

A larger RCT for chronic, recurrent tinea patients treated with higher dose and duration of oral itraconazole needs to be undertaken to corroborate the results of the present pilot study which showed promising results.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Ethical approval

This study was approved by the Research Ethics Committee of the Institute. This study was conducted in accordance with the Declaration of Helsinki.

Clinical Trial Registration No. - CTRI/2019/12/022283

Clinical Trials Registry India (http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=38598)

Author's contribution

RD -Study Concept and Designing, definition of Intellectual contents, Literature search, Clinical Study, Data acquisition and analysis, Manuscript Editing and review.

KV-Data acquisition and analysis, Manuscript Preparation and editing. RT-Study Design, Literature search, Data analysis, Statistical analysis, Manuscript preparation, Editing and review.

LB-Clinical study, Literature search, Manuscript Editing and review. MS-Clinical study, Data acquisition, Manuscript Editing and review. HKK-Study concept and Designing, Data analysis, Manuscript editing and review.

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