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Dermatology

Comparative Evaluation of Therapeutic Efficacy of Terbinafine Double Dose (Standard), Versus Terbinafine Double Duration (Standard), Versus Combination of Terbinafine and Isotretinoin in Recalcitrant/ Recurrent Tinea Corporis/ Cruris

Dr. Sudeep[1*], Dr. B.K. Brar[2], Dr. Neerja Jindal[3], Dr. Jaskirat Kaur[4]
[1]Post Graduate Student, Department of Dermatology, Venereology and Leprology, Guru Gobind Singh Medical College and Hospital, Faridkot – 151203, Punjab, India
[2]Professor & Head, Department of Sermatology, Venereology and Leprology Guru Gobind Singh Medical College and Hospital, Faridkot – 151203, Punjab, India
[3]Professor & Head, Department of Microbiology, Guru Gobind Singh Medical College and Hospital, Faridkot – 151203, Punjab, India
[4]Post Graduate Student, Department of Dermatology, Venereology and Leprology, Guru Gobind Singh Medical College and Hospital, Faridkot – 151203, Punjab, India

Original Research Article

***Corresponding author**
Dr. Sudeep

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Abstract: Fungal infections are quite common in tropical and subtropical region. Many treatment modalities are available to treat superficial fungal infections, but with increasing number of recurrent/recalcitrant cases of tinea emerging these days, and lack of standard updated guidelines of treatment, new and effective therapy is needed to manage these cases. So this study is an attempt to find some effective therapy to manage these cases by conducting a comparative study to see the effect of double dose terbinafine, terbinafine used for double duration, and combination of terbinafine and isotretinoin in these recurrent/recalcitrant cases. A total of 90 patients with recurrent/recalcitrant tinea corporis/cruris were included. They were randomly divided into 3 equal groups of 30 patients each. In this study, comparison has been done between therapeutic efficacy and safety of oral Terbinafine 250 mg once daily for 6 weeks (double duration), vs oral Terbinafine 250 mg twice daily for 3 weeks (double dose), vs oral Terbinafine 250 mg once daily for 3 weeks plus oral isotretinoin 20 mg once daily for 6 weeks duration(combination of terbinafine and isotretinoin), in recalcitrant/ recurrent tinea corporis/ cruris. Follow-up was done at every 2 weekly intervals for a total duration of 12 weeks. When compared, highly significant results (P value=.000) were obtained when terbinafine was given for longer duration (6 weeks), whereas rates of relapse and incomplete response were more when terbinafine was given for shorter duration (3 weeks), either alone as given in Group B, or in combination with isotretinoin as given in Group C. Side effects in all the three groups were mild (nausea, chelitis, xerosis), and no patient required discontinuation of therapy.

Keywords: recalcitrant, recurrent, tinea, terbinafine, efficacy, safety.

INTRODUCTION

Superficial mycosis is a major skin disease affecting more than 20–25% of world population [1]. Dermatophytes are related fungi [2,3] capable of causing skin infection of the type known as ringworm or dermatophytosis. The ringworm species belong to three asexual genera: *Microsporum*, *Trichophyton*, and *Epidermophyton*, which attack the keratinized tissue and cause a wide spectrum of clinical manifestations [4,5], of which the most predominant type of infection is tinea corporis/cruris. Comparison of studies done on superficial fungal infections have revealed an increasing trend of dermatophytosis [6,7].The standard treatment recommendations which we have been following from the Western and Indian literature are no longer valid or even realistic[8,9]. While environmental factors, erratic use of topical and oral antifungal agents, increased prevalence of *Trichophyton mentagrophytes* infections causing inflammatory lesions and probably a growing resistance to antifungal agents may play an important role, one of the most formidable enemies that we have encountered in the recent times is the irrational fixed drug combination creams containing a steroid, antifungal, and antibacterial with three to five molecules in the product [10-12]. Although many studies done across

India have found *Trichophyton rubrum*, to be the most common organism, the prevalence is much less compared to the past. In all these studies, *Trichophyton mentagrophytes* has emerged as the co-21dominant pathogen with an increased prevalence in comparison to what was seen in the past [13,14].

Various proposed mechanisms of resistance are alteration in drug target, alteration in sterol biosynthesis, reduction in the intracellular concentration of target enzyme, alteration of other enzymes in the same biosynthetic pathway as the target enzyme, and overexpression of the antifungal drug target.

There are many treatment modalities available to treat superficial fungal infections, which include topical and systemic therapies, but with increasing number of recurrent/recalcitrant cases of tinea emerging these days, new and effective therapy is needed to manage these recalcitrant / recurrent cases.

Discovered in 1983, terbinafine is a member of the allylamine class of antifungals. It abrogates the formation of ergosterol by inhibiting squalene epoxidase, the catalytic enzyme responsible for converting squalene to 2,3-oxidosqualene (an ergosterol precursor)[15,16].

Isotretinoin is a synthetic derivative of vitamin A. It has a low affinity for retinoic acid receptors (RAR) and retinoid X receptors (RXR), but may be converted intracellularly to metabolites that act as agonists of RAR and RXR nuclear receptors.

AIMS AND OBJECTIVES

Comparative evaluation of oral Terbinafine 250 mg OD for 6 weeks, vs oral Terbinafine 250 mg BD for 3 weeks, vs oral Terbinafine 250 mg OD for 3 weeks plus oral isotretinoin 20 mg OD for 6 weeks duration in recalcitrant/ recurrent tinea corporis/ cruris.

MATERIALS AND METHODS

This study was conducted in Department of dermatology, G.G.S. Medical College & Hospital, Faridkot. 90 patients with clinically diagnosed recurrent/recalcitrant tinea corporis/cruris, and confirmed with KOH mount, were selected from the OPD after taking their written informed consent, and permission from ethical committee. They were randomly divided into three equal groups of 30 patients each. A written informed consent was obtained from each patient. Group A patients received oral tablet terbinafine in a dose of 250 mg once daily for 6 weeks, Group B patients received terbinafine in a dose of 250 mg twice daily for 3 weeks, and Group C patients received terbinafine in a dose of 250 mg once daily for 3 weeks and isotretinoin 20 mg once daily for 6 weeks. Following observations were recorded:

- Demographic parameters
- Comparison of grades of improvement in all the three groups
- Adverse effects

Results were analyzed statistically after follow-up period of 12 weeks. Follow-up was done at every two weekly interval for a total duration of 12 weeks.

A brief history along with details of any previous treatment was documented. The relevant biochemical and microbiological investigations were done. The importance of regular follow-up was stressed upon to all the patients.

Inclusion criteria

- Patients having recurrent or recalcitrant tinea corporis/ cruris, confirmed with KOH exam. In our study, Recurrent cases were defined as patients who have completed standard antifungal therapy and were recovered completely, and then having clinical signs/symptoms again within 3 months of completing the therapy, and Recalcitrant cases were defined as patients who have completed the standard antifungal therapy and did not show any improvement.
- Patients of age group 15-60 years.
- Patients willing to come for regular follow up.
- Patients having body weight 40-70 kg.

Exclusion Criteria

- Patients of age less than 15 years or more than 60 years.
- Patients not willing to come for regular follow up.
- Patients with known hypersensitivity to terbinafine or isotretinoin.
- All pregnant and breastfeeding females.
- Patients with raised plasma lipids and cholesterols.
- Patients with hepatic and renal disease.

Clinical and photographic evaluation was done at every follow up visit, according to which, the patients were divided into grades according to the response to the treatment and improvement in the lesions:
Grade 0: No response
Grade 1: <25% response
Grade 2: 26-50% response
Grade 3: 51-75% response
Grade 4: 76-100% response

STATISTICAL ANALYSIS

The descriptive statistics were calculated in the form of frequencies for categorical variables, and means and standard deviation for continuous variables. The categorical variables were analyzed statistically using Pearson's Chi Square test or Fisher's exact test wherever applicable.

RESULTS

Following observations were made-

Side effects in all the three groups were mild (nausea, chelitis, xerosis), and no patient required discontinuation of therapy.

Table-1: Follow up at 2 weeks

Grades of improvement	Group A N(%)	Group B N(%)	Group C N(%)
G0/1	6(20)	4(13.33)	4(13.33)
G2	15(50)	16(53.33)	17(56.67)
G3	9(30)	10(33.33)	9(30)
G4	0(0)	0(0)	0(0)

p value>=0.05 NS(.134)

Table-2: Follow up at 4 weeks

Grades of improvement	Group A N(%)	Group B N(%)	Group C N(%)
G0/1	3(10)	4(13.33)	4(13.33)
G2	2(6.67)	7(23.33)	9(30)
G3	15(50)	10(33.33)	10(33.33)
G4	10(33.33)	9(30)	7(23.33)

p value>=0.05 NS(.107)

Table-3: Follow up at 6 weeks

Grades of improvement	Group A N(%)	Group B N(%)	Group C N(%)
G0/1	3(10)	8(26.67)	12(40)
G2	1(3.33)	11(36.67)	11(36.67)
G3	4(13.33)	3(10)	2(6.67)
G4	22(73.33)	8(26.67)	5(16.67)

p value=0.000

Table-4: No. of treated, resistant and relapse cases within follow up period of 12 weeks

	Group A N(%)	Group B N(%)	Group C N(%)
Treated	20(66.67)	8(26.67)	5(16.67)
Resistant	3(10)	4(13.33)	4(13.33)
Relapse	7(23.33)	18(60)	21(70)

Table-5: Distribution of subjects according to side effects

	Group A N(%)	Group B N(%)	Group C N(%)
Positive	3(10)	2(6.67)	12(40)
Negative	27(90)	28(93.33)	18(60)

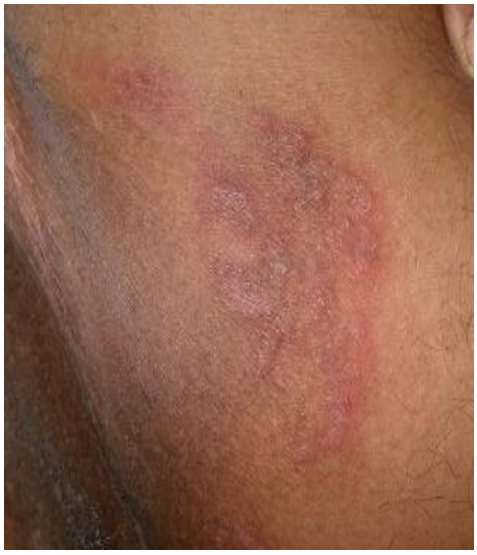

Fig-1: 0 Week- Before Treatment

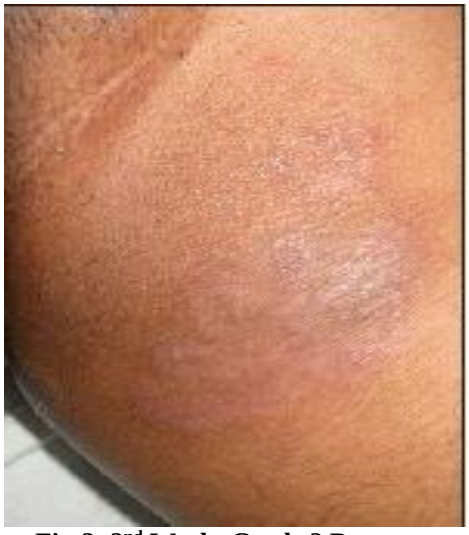

Fig-2: 2nd Week- Grade 2 Response

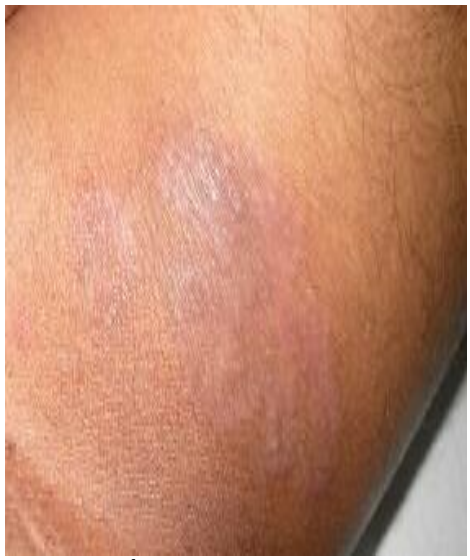

Fig-3: 4th Week- Grade 3 Response

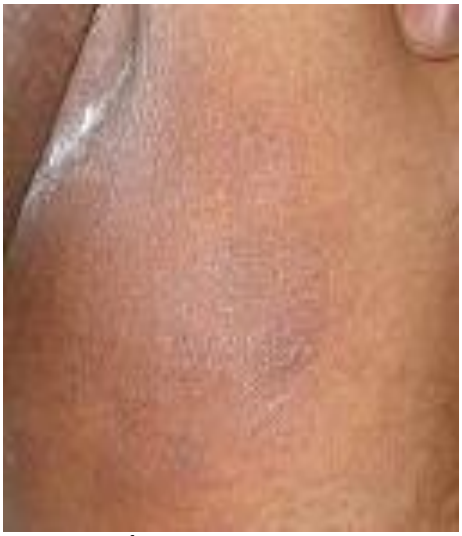

Fig-4: 6th week- Grade 4 Response

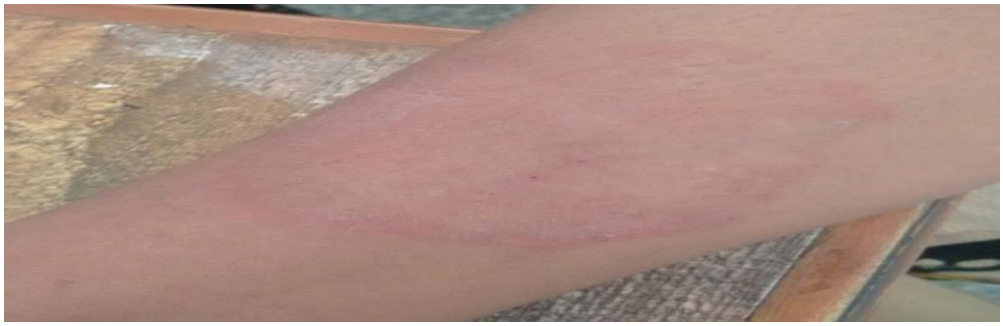

Fig-5: 0 week -before treatment

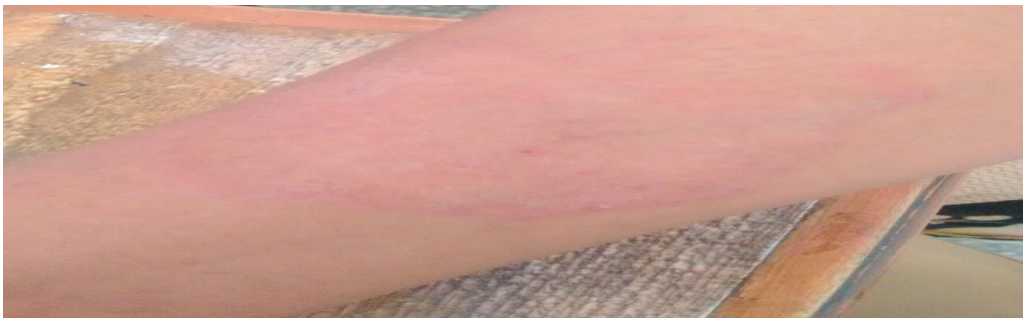

Fig-6: 2nd week-grade 2 response

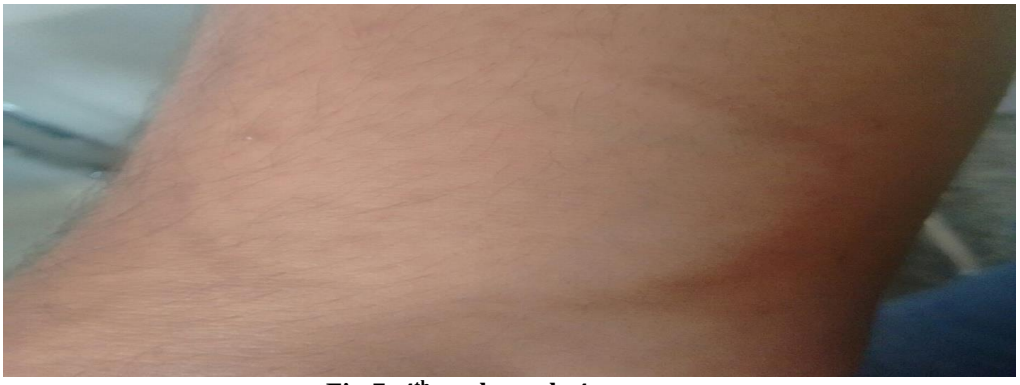

Fig-7: 4th week-grade 4 response

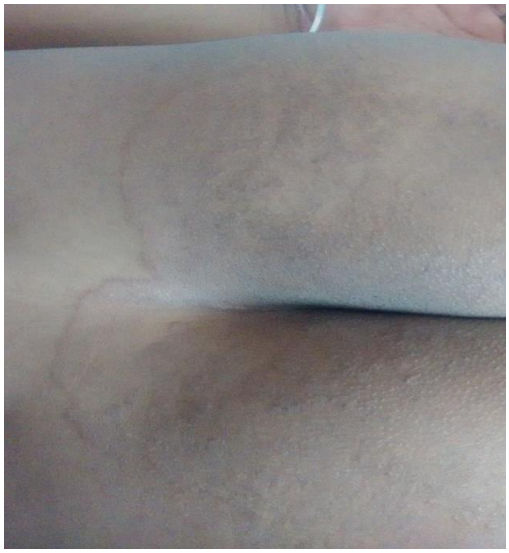

Fig-8: 0 Week- Before Treatment

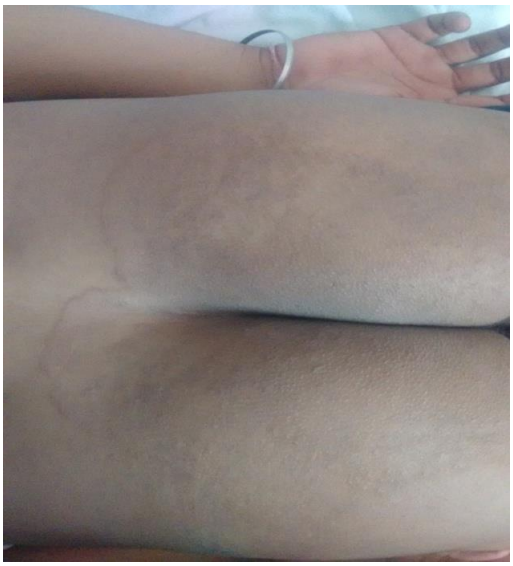

Fig-9: 2 Week- Grade 2 Response

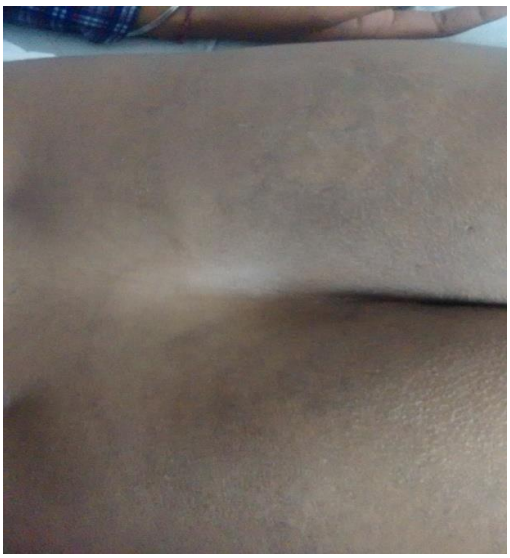

Fig-10: 4 Week- Grade 3 Response

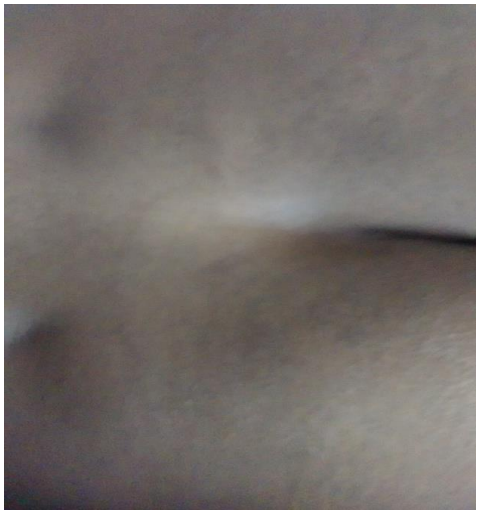

Fig-11: 6 Week- Grade 4 Response

RECALCITRANT TINEA

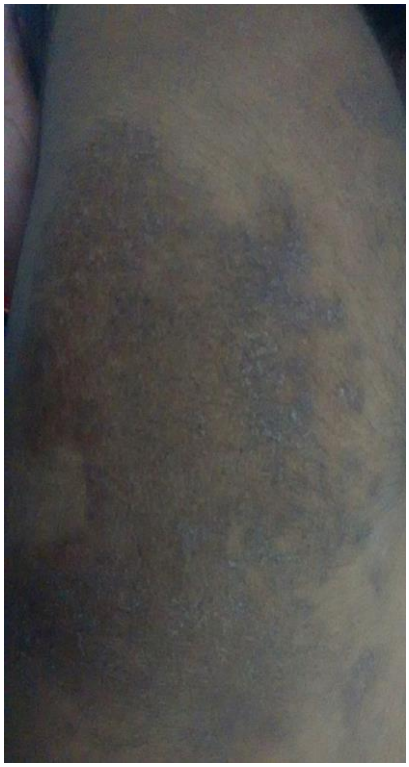

Fig-12: Before Treatment

Fig-13: After Treatment

DISCUSSION

Dermatophytoses have always been among the commonest infective dermatoses in India. The infection is apparently much more resilient, having a tendency to recur more frequently and the overall number of patients presenting with chronic/recurrent/recalcitrant dermatophytosis is much more. In our study, Mean age of patients in Group A, B, C was 40.6 years, 38.23 years, 37.9 years with a standard deviation of 11.73, 11.9, and 13.08 years respectively.

There was slight male preponderance in our study, with a Male: Female ratio of 1.2:1. Family history was positive in 63.33% of the Group A patients, 66.77% of the Group B patients, and 63.33% of the Group C patients. Overall 27.77 of the patients were fungal culture positive (p value=0.946). Out of these 25 patients, 15(60%) were found positive for T. mentagrophytes, and 8(32%) were positive for T. rubrum, and 2(8%) were positive for T. violaceum.

In a study conducted by US Agarwal *et al*. Trichophyton mentagrophytes, grown in 91 (37.9%) cases was the most common isolate, and as also noted by Sahai and Mishra[17] On the other hand, a study conducted in 2008 in our geographical area(Jaipur) by Jain *et al*. [18] found that *Trichophyton rubrum* was the most common dermatophyte. So our results are comparable with some studies, and different geographical distribution of various species maybe the cause of different results on fungal culture, and varied response to standard antifungals. In our study, 6 patients found positive for T. rubrum, and 2 patients found positive for T. mentagrophytes didn't either respond to treatment, or showed mild improvement over same duration of therapy as compared with other patients.

On evaluation of patients 2 weeks after initiation of treatment, 30% patients in Group A, 33.33% patients in Group B, and 30% patients in Group C showed grade 3(50% or more improvement) response.(Table No.1) No patient in any group showed grade 4(75% or more improvement) improvement or complete response. Grade 0/1(no improvement to upto 25% improvement), and grade 2(25-50% improvement) responses were also comparable in all the three groups. These values were comparable but statistically speaking, significant improvement was not obtained at 2 weeks. P value was found to be insignificant.

However at 4 weeks of initiation of therapy there is significant improvement in Group A patients, with 50% of patients showing grade 3 improvements and 33.33% of patients showing grade 4 improvements. In Group B and C, 33.33% patients each showed grade 3 improvement, and 30% patients in Group B and 23.33% patients in Group C showed grade 4 improvement.(Table No.2) At 6 weeks of initiation of therapy, Grade 4 response is significantly better for Group A as compared to Group B and C. P value(0.000) is highly significant. 73.33% of patients of Group A showed grade 4 improvement, which was significantly higher than Group B and C. 26.67% of patients in Group B and 16.67% of patients in Group C showed grade 4 improvement.(Table No.3)

Isotretinoin is a synthetic derivative of vitamin A which is traditionally used in the treatment of severe, recalcitrant nodular acne and moderately severe acne/as well as gram-negative folliculitis, hidradenitis supportive, and severe rosacea as well as many other off-label uses. Various proposed mechanisms of action of isotretinoin in tinea are increased epidermal cell turnover, increase in skin pH, immunomodulatory effect.

Holly Bartell *et al*. described a case of acne vulgaris with tinea versicolor and prescribed 40 mg once daily isotretinoin. At 1 month followup, the tinea versicolor lesions were completely resolved, and remained clear throughout the isotretinoin therapy [19]. In another case report by Kenit P Ardeshna *et al*. oral isotretinoin (20 mg/day) and Iitraconazole (200 mg/day) along with topical sertaconazole was given for a period of 1 month. Following this treatment, the skin lesions resolved completely [20].

Relapse was seen in 23.33% of Group A patients, 60% of Group B patients, and 70% of Group C patients. 66.67% patients of Group A, 26.67% patients of Group B, 16.67% patients of Group C were completely treated. 10% patients in Group A, 13.33% patients each in Group B and C were resistant to therapy (Table No.4).

10% patients in Group A, 6.67% patients in Group B, and 40% patients in Group C had side effects.(Table No.5) Side effects in all the three groups were mild(nausea, chelitis, xerosis), and no patient required discontinuation of therapy. Cheilitis was quite common in patients taking isotretinoin, but none required discontinuation of therapy. Liver function test and fasting lipid profile were within normal limits in all the patients, before and after the treatment.

In our study there is persistence of disease in most of the patients in Group B and C after completion of 3 weeks terbinafine therapy. It is seen that the duration of therapy is perhaps more important than the doses higher than 250mg/day of oral terbinafine for better therapeutic effect.

CONCLUSION

When compared, highly significant results were obtained when terbinafine was given for longer duration (6 weeks), whereas rates of relapse and incomplete cure were more when terbinafine was given for shorter duration, as seen in Group B and C, where terbinafine was given for 3 weeks only, either alone as given in Group B, or in combination with isotretinoin as given in Group C. There was highly significant statistical difference with regard to overall response in all the three groups. Not much added advantage was seen with increasing the dose of terbinafine, by compromising total duration of therapy. Overall terbinafine is a safe drug, and infrequent mild gastrointestinal side-effects (like nausea) were seen. Cheilitis was quite common in patients receiving isotretinoin. In our study, we did not find any added advantage of isotretinoin in treatment or maintenance of remission in tinea patients, and broader spectrum studies need to be carried out to find its role in dermatophytes and other fungal infections. Duration of antifungal therapy was found to be more important than higher dosage in normal weight patients. There is an alarming increase in misuse of topical steroids, and over-the-counter drugs, leading to rise in recalcitrant/recurrent tinea infection. In such a scenario, there is need of evidence-based management guidelines that will account for the changes in epidemiology and pathogen etic behaviour of the fungi, if any. Also, drug

of choice and duration of therapy needs to be standardized, by comparing various newer antifungals, role of adjuvant measures.

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