IADVL SIG Recalcitrant Dermatophytosis Position Statement on Super Bioavailable Itraconazole

Abstract

Itraconazole (ITZ) has been the mainstay of oral antifungal treatment for the current epidemic of recalcitrant dermatophytosis (RD) in India. Recently, a newer formulation of ITZ, super bioavailable itraconazole (SUBA-ITZ), is made available in the market by many pharmaceutical companies. It is important for dermatologists to understand the pharmacokinetic properties of SUBA-ITZ vis-a-vis conventional pellet formulation to use it effectively and safely. Indian Association of Dermatologists, Venereologists and Leprologists (IADVL) has established a special interest group for recalcitrant dermatophytosis (SIG-RD) to strengthen research, continuing medical education, and industry collaboration on the subject. This position statement on SUBA-ITZ by SIG-RD is an attempt to address current pieces of evidence and the position of this new formulation in the management of RD.

Keywords: *Dermatophytosis, position paper, SUBA itraconazole*

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Background

India has been witnessing an unprecedented scenario of treatment for recalcitrant dermatophytosis (RD) of the non-glabrous skin since 6–7 years.[1,2] This particular epidemic is marked by a mycological shift to, what is now accepted as a distinct species that originated in India and is now spreading worldwide, *Trichophyton indotineae*.[3-8] Clinically, it is marked by not just an increase in cases of dermatophytosis, but also unusually high number of cases of RD showing poor response to conventional antifungals such as terbinafine. Simultaneously, reports of increase in minimum inhibitory concentration (MIC) of terbinafine in fungal isolates and presence of genetic mutation in squalene epoxidase gene conferring this secondary resistance have been documented.[2,9-11] Dermatologists have addressed these challenges via shifting to itraconazole (ITZ) as the first-line drug and drug of choice for RD. Another approach deployed by some of the dermatologists was to extend the duration of treatment or to prescribe higher than the recommended doses of oral antifungals for the management. Discordance in laboratory interpretation of MIC and the clinical response observed by dermatologists is also not uncommon. ITZ is a weakly basic drug classified under the Biopharmaceutics Classification System (BCS) class II, characteristically having low solubility and high permeability. To overcome the dissolution problem of ITZ, pharmaceutical industries have been using pellet technology for drug delivery, wherein, ITZ admixed with polymer is coated on cellulose or sucrose pellets. This process of drug delivery with conventional itraconazole (C-ITZ) is affected by many factors such as pellet size, number, type of polymer used, its thickness of layering on the pellet, and the drug–polymer ratio.[12] There has been a sudden rise in the demand for C-ITZ in the last few years due to the explosion of cases of dermatophytosis, and the preference of most dermatologists for ITZ as the first-line drug in its management. This resulted into tremendous growth in generic manufacturing of C-ITZ with little consistency on vital parameters required for dissolution and bioavailability (BA) of drug.[13] To maximize the dissolution and absorption of C-ITZ, it can be taken with food or cola beverages. Concomitant administration of gastric acid-suppressing drugs such as proton pump inhibitors (PPIs) further reduces the BA of C-ITZ. Due to all of these factors,

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C-ITZ shows extreme interperson variability when it comes to BA. To overcome these issues, a novel formulation of ITZ has been developed, which uses the incorporation of the active drug in a pH-dependent polymeric matrix, hypromellose phthalate (HPMCP), which releases the active drug in the upper duodenum rather than the stomach. This formulation is labeled as super bioavailable itraconazole (SUBA-ITZ). Multiple companies in India have started generic manufacturing of this new formulation. On expected line, these branded generic SUBA-ITZ are being aggressively promoted among dermatologists for the management of dermatophytosis. Indian Association of Dermatologists, Venereologists and Leprologists (IADVL) has established a special interest group on recalcitrant dermatophytosis (SIG-RD) with an aim of promoting research, conducting continued medical education program, providing evidence-based publications, and improving liaison between the dermatologists and the pharmaceutical industries. With this background, SIG-RD deemed it necessary to produce position paper on SUBA-ITZ with an aim to disseminate the available scientific information on this formulation among dermatologists in India.

Two important terminologies will be frequently used in this article related to drug exposure: i) C_{max} which is defined as the highest concentration of drug in system before administration of next dose; and ii) Area under the curve (AUC), it represents the area under the plasma concentration curve where plasma concentration is plotted in relation to time.

Methodology

A review article was prepared based on the published literature on SUBA-ITZ. No systematic review was attempted because of the scarcity of the literature with respect to the use of SUBA-ITZ in dermatophytosis and all articles published in the English language in PubMed using the word "super bioavailable itraconazole" were retrieved. A two-step review process was adapted. Initially, the draft was prepared by the lead author and it was then validated by the second, third, and fourth authors. Then the draft was reviewed by all the SIG-RD members. Their feedback was collected and incorporated into the paper wherever necessary. The final statement was circulated among all members of SIG-RD, and the approval was obtained.

Literature review

Minimum inhibitory concentration of ITZ

Epidemiological cut off values (ECVs) or clinical breakpoints are not available at present for the predominant species causing the current epidemic of dermatophytosis in India. A study by Shaw *et al*.[14] investigated the MIC and upper limit of wild-type (UL-WT) distribution for *T. interdigitale* complex. They observed that the majority of isolates had MIC below UL-WT for ITZ (0.5 µg/ml). Available studies from India and abroad suggest that the prevalent species of the present epidemic of dermatophytosis in India exhibits low MIC for ITZ as yet.[15,16] There are no widespread reports of increase in MIC or any genetic mutation linked to reduce the susceptibility of *Trichophyton* genera of dermatophytes to ITZ.

Conventional ITZ drawbacks

BA of C-ITZ is known to be approximately 55% in capsule formulation due to poor dissolution of drug.[17] Owing to multiple factors that can affect the dispersion of drugs in C-ITZ, brand-to-brand variation in actual BA of ITZ is a possible phenomenon, although no robust studies comparing pharmacokinetic (PK) variables between various generic and original brands are available in India. C-ITZ shows considerable inter- and intrasubject variation in BA.[18] Acidic stomach environment is historically considered a prerequisite for good dispersion of C-ITZ.[19] This poses an additional challenge for dermatologists while treating patients who are on acid-suppressing drugs. In spite of these limitations of C-ITZ, reports of clinical failure with C-ITZ are not common in the present epidemic of dermatophytosis in India. Khurana *et al*.[20] have observed serum levels above 0.2 µg/ml to be associated with successful clinical outcomes. In addition to low MIC values for ITZ, one has to remember the favorable skin PK of ITZ, wherein the drug is concentrated 5 to 10 times higher in sebum compared to corresponding plasma levels.[21]

SUBA-ITZ Pharmacokinetics

SUBA-ITZ owing to its novel drug delivery technique provides a more controlled release of drug in upper duodenum, alleviating the need for acidic stomach environment. Under fed conditions, single dose of SUBA-ITZ (TOLSURA® 65 mg) provides 5% lower area under the concentration-time curve (AUC_{inf}) and 19% lower C_{max} as compared to C-ITZ (SPORANOX®100 mg).[22] Under repeat doses in fed condition scenario, which more realistically reflects clinical practice, SUBA-ITZ (65 mg 2 OD) gives 22% and 15% higher C_{max} and AUC, respectively, compared to SPORANOX (100 mg 2 OD) at 15 days.[23] In a most extensive population PK study, Abuhelwa *et al*.[24] observed that SUBA-ITZ had a relative bioavailability of 173% (95% CI: 156–190%) compared to C-ITZ (Sporanox®). Thus, 58 mg (95%CI: 52.6–

64 mg) dose of SUBA-ITZ would provide equivalent exposure to the marketed 100 mg C-ITZ formulation. Both 50 mg and 65 mg dose of SUBA-ITZ are expected to give "similar" exposure of ITZ compared to C-ITZ as regulatory approval are based on acceptable PK bridge worldwide including India. In Indian context, subsequent new drug (SND) division and various subject expert committees (SEC) of Central Drugs Standard Control Organization (CDSCO) have approved 50 mg, 65 mg, 100 mg, and 130 mg dosage forms of SUBA-ITZ detail of which is available in Table 1.[25-28] Notably, the formulator of 65 mg and 130 mg did not approach SEC dermatology for this approval. The biggest advantage of SUBA-ITZ established in all the recent studies is that there is lower intersubject variability in tune of 30 to 35% compared to C-ITZ.[11]

Effect of food and co-administration of acid-suppressing drugs

The effect of food on PK of ITZ has been studied very extensively in recent times. Historically, C-ITZ is considered to be absorbed better with food due to the requirement of acidic stomach PH. Recent studies counter this view. Recent study evaluating PK parameters of single-dose SUBA-ITZ and C-ITZ found that both formulations achieve lower C_{max} and AUC under fed conditions.[29] As the original product insert of C-ITZ mentioned that the drug is to be taken after meal, and manufacturer of SUBA-ITZ had established PK bridge based on repeat dose studies performed under fed conditions, prescribing information (PI) for SUBA-ITZ retains recommendation for administration under fed condition.

Table 1: Details of regulatory approval for various dosage forms of SUBA-ITZ

Dosage of SUBA-ITZ	CDSCO committee	Recommendations
50 mg	Subsequent new drug (SND) division[25]	The firm presented the proposal along with the BE study report of itraconazole capsules 50 mg. After detailed deliberation, the committee recommended for grant of permission to manufacture and market itraconazole capsules 50 mg with the caution in the package insert as follows: "Caution: Itraconazole Capsules 50 mg has equivalent bioavailability with that of itraconazole capsules 100 mg. One capsule of Itraconazole Capsule 50 mg is therapeutically equivalent to one 100 mg capsule of conventional itraconazole capsules100 mg. The recommended dose of itraconazole Capsules 50 mg is therefore half the recommended dose for conventional itraconazole capsules 100 mg. Itraconazole Capsules 50 mg and conventional itraconazole Capsules 100 mg are not interchangeable".
100 mg	Subject expert committee (SEC) (Dermatology and Allergy)[27]	After detailed deliberation, the committee recommended for grant of permission for ITZ capsule 100 mg (Supra bioavailable) for the indication for already approved ITZ capsule 50 mg (Supra bioavailable) subject to conditions that firm should present package insert mentioning the effects of PPI, oral antacids, alcohol, other drugs interactions which may affect the bioavailability of the drug, etc., before the launch of the product in the market. The package insert should also include details of the results of the BE study conducted in the country
130 mg	SEC (Antimicrobial and Antiviral)[28]	After detailed deliberation, the committee recommended for grant of permission for manufacture and marketing of ITZ capsules 130 mg indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised adult patients: Blastomycosis, pulmonary and extrapulmonary Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant to amphotericin B therapy.
65 mg	SEC (Antimicrobial and Antiviral)[26]	After detailed deliberation, the committee recommended for grant of permission for manufacturing and marketing of ITZ capsule 65 mg for the indication which was already approved for ITZ capsules 130 mg.

SUBA-ITZ - Super bioavailable Itraconazole, CDSCO - Central Drugs Standard Control Organization, BE - Bioequivalence

Co-administration of acid-suppressing drugs particularly PPIs causes a 10-fold reduction in absorption of orally administered C-ITZ. Study on co-administration of SUBA-ITZ and omeprazole indicates that there was an increase in the systemic exposure of ITZ, in terms of both rate (C_{max} mean increase 31%) and extent (AUC_{inf} mean increase 22%).[30] This increase in both C_{max} and AUC_{inf} is outside the 80% to 125% no-effect boundary established by the United States Food and Drug Administration (USFDA), indicating that there is a significant drug–drug interaction between omeprazole and SUBA-ITZ. "Of particular concern, in terms of safety, is the increase in the C_{max} of ITZ. It is noteworthy that the magnitude of the increase in itraconazole C_{max} observed with co-administration of TOLSURA and omeprazole is with a single dose of TOLSURA, and it does not take into account, the known non-linear PK and potential plasma accumulation of itraconazole following dosing of TOLSURA to steady-state. Thus, the labeling recommendation for TOLSURA capsules include a cautionary statement regarding co-administration of omeprazole with TOLSURA."; mentions USFDA new drug application (NDA) multidisciplinary review report on TOLSURA©.[10]

Adverse event profile of SUBA-ITZ

With regard to the adverse event profile of SUBA-ITZ, as the parent drug and its metabolite remain the same as C-ITZ, innovator of SUBA-ITZ had not conducted additional safety studies. Safety bridge between the two formulations was established on the basis of the highest achievable plasma concentration of test formulation (C_{max}) not exceeding that of reference product in repeat dose in fed condition scenario. Prescribing information of SUBA-ITZ retains all warnings and adverse event profiles of C-ITZ. In view of this, clinician has to be as vigilant about the adverse events of SUBA-ITZ as in the case of C-ITZ, particularly in the wake of new information about the increased BA on fasting state and when co-administered with PPIs. Similarly, all drug-to-drug interactions of ITZ remain the same for C-ITZ and SUBA-ITZ. An additional new caution about co-administration of PPIs with SUBA-ITZ finds its mention in PI of SUBA-ITZ > as both the dosage forms of SUBA-ITZ do not achieve exact BE with 100 mg of C-ITZ, they are not interchangeable with other formulations of ITZ which is clearly mentioned in PI of SUBA-ITZ.

Safety of SUBA-ITZ in pregnancy, lactation and pediatric population is not being studied separately. All precautions in this regards for SUBA-ITZ remains same as for C-ITZ.

C-ITZ versus SUBA-ITZ in management of dermatophytosis

C-ITZ is approved for superficial dermatomycosis by USFDA and is being extensively used for the same in India. Presently, innovator SUBA-ITZ 50 mg (LOZANOC®) is approved by Australian Pharmaceutical Benefits Scheme (PBS) for use in various invasive fungal infections and superficial mycoses.[31] Innovator SUBA-ITZ 65 mg (TOLSURA®) is approved for the treatment of invasive fungal infections by USFDA. Indian manufacturers have obtained approval from the dermatology and non-dermatology SEC of CDSCO based on PK studies with C-ITZ. [Table 1]. As PK bridge with C-ITZ is established and the parent drugs remain same, SUBA-ITZ is expected to be used by clinicians for a variety of conditions currently treated with C-ITZ. This brings us to the most pertinent question, "Can SUBA-ITZ perform as good as or better than C-ITZ in the management of dermatophytosis?" Answer to this question can only be provided by an adequately powered multicentric randomized control trial. At present, we do not have the highest quality evidence for superiority or non-inferiority of SUBA-ITZ in the management of dermatophytosis. A study conducted by innovator, using SUBA-ITZ (LOZANOC 2 × 50 mg) for management of onychomycosis, showed that cure rates at the end of 24 weeks were comparable with C-ITZ (SPORANOX 2 × 100 mg).[32] Study by Mahajan *et al*. showed that 56% of patients on SUBA-ITZ (50 mg twice day) achieved complete clearance of lesions at 4 weeks compared to 34% on C-ITZ (100 mg twice day). Retrospective data analysis of patients treated with SUBA-ITZ by Ghate *et al*. also showed that only 51% of patients (mostly tinea cruris) achieved complete clearance by 4 weeks. Both these studies, however, were retrospective analyses. Shenoy *et al*.[33] studied SUBA-ITZ in comparison to C-ITZ in an open-label, single-center, randomized controlled trial. They observed that a significantly higher percentage of patients achieved complete cure in SUBA-ITZ arm (65.38% vs 33.33%) than C-ITZ arm by 4 weeks, although they did not observe any advantage in recurrence. Overall, SUBA-ITZ is expected to be efficacious in the management of dermatophytosis as the parent drug remains the same as C-ITZ, and no increase in MIC for ITZ is reported as of now. In a recent double-blind randomized controlled trial, Khurana *et al*.[32] compared cure rate and relapse rate in patient of dermatophytosis using 100 mg, 200 mg, and 400 mg C-ITZ and observed 82%, 93.2%, and 100% cure rate, respectively. They also did not observe any difference in relapse rate across the dosages regimes. During discussion on this article, all members of SIG-RD were unanimous that at present there are not enough scientific evidence to support poor BA of C-ITZ as cause of treatment failure or relapse. Furthermore, dose escalation of ITZ (both conventional and SUBA) for management of naïve or RD does not have robust scientific rationale at present. Across the world, approval of SUBA-ITZ is based on PK bridge with C-ITZ and not on head-to-head clinical studies in various indications. As this new formulation of ITZ is being marketed, more comparative clinical studies with C-ITZ and SUBA-ITZ may become available in due course. As discussed earlier, clinical failure defined as patient not achieving expected clearance of lesions and symptoms after appropriate duration of treatment, is not yet widely reported with C-ITZ

Box 1: IADVL SIG-RD Position Statement on Super Bioavailabe Itraconazole

1. Predominant fungal species causing current epidemic of dermatophytosis in India maintain low minimum inhibitory concentration for itraconazole (ITZ) yet, which means resistance to ITZ is not widespread as of now in India
2. Pharmacokinetics (PK) of ITZ in skin is favorable, in terms of higher levels of drug achieved in stratum corneum of non-glabrous skin and sebum compared to corresponding levels in plasma. This advantageous PK parameter is independent of the formulation used.
3. Conventional itraconazole (C-ITZ) preparation shows considerable intersubject variability in PK parameters related to drug exposure (C_{max} and AUC). This is historically considered a major drawback of C-ITZ, which makes response of C-ITZ variable from patient to patient.
4. Bioavailability of C-ITZ considerably varies when administered under fasting and fed conditions. This makes it necessary to administer C-ITZ after meal or with Cola beverages to optimize the absorption.
5. Super bioavailable itraconazole (SUBA-ITZ) utilizes novel drug delivery technology for controlled release of drugs in the upper duodenum bypassing requirement of acidic gastric pH, which makes absorption of SUBA-ITZ less dependent on stomach environment.
6. SUBA-ITZ demonstrates considerably lower intersubject variability in PK parameters related to drug exposure. This is a major advantage over C-ITZ, which is expected to give more consistent plasma levels and resultantly clinical outcomes.
7. Recent studies have shown that BA of ITZ under fed conditions is lower for both formulations compared to fasting conditions. Prescribing information (PI) for both formulations recommends administration under fed conditions which should be followed, as extensive safety data under fasting conditions is lacking at present. Dermatologists should advise administration of SUBA-ITZ under fed conditions as recommended in PI.
8. At present, 50 mg and 65 mg (and their corresponding double strength 100 and 130 mg) dosage forms of SUBA-ITZ are marketed in India. Single-dose and steady-state (repeat dose for 15 days) PK bridge for 50 mg and 65 mg forms are established by manufacturers with 100 mg C-ITZ. Both doses give "similar" drug exposure compared to 100 mg C-ITZ. Population PK study has predicted 58 mg of SUBA-ITZ to achieve equal exposure to 100 mg C-ITZ. As stated in PI for both dosages, none of them are interchangeable to C-ITZ formulation. This information should be taken into consideration while decision of shifting to SUBA-ITZ from C-ITZ in management of dermatophytosis is made.
9. The decision of a dermatologist to utilize either of the dosage form of SUBA-ITZ should be based on the understanding of exposure kinetics of individual product. As ITZ follows non-linear kinetics, repeat dose PK studies from manufacturers should be taken into consideration rather than single-dose PK.
10. Co-administration of C-ITZ with proton pump inhibitor (PPI) reduces its overall BA, which makes use of C-ITZ in patients who are on PPI difficult and clinical outcome less predictable.
11. Co-administration of SUBA-ITZ with PPI increases the overall exposure of ITZ (possibly beyond acceptable safe limit), which suggests possible drug-to-drug interaction. More so, this effect may become more profound in repeat dose setting. Dermatologist can co-administer SUBA-ITZ with PPI but has to be more vigilant for adverse events related to ITZ.
12. Adverse event profile of SUBA-ITZ has not been studied separately by manufacturers. As maximum achievable concentration (C_{max}) of SUBA-ITZ did not exceed that of C-ITZ at any point during studies conducted for regulatory approval, safety bridge was established on PK data. PI for SUBA-ITZ retains all the warning and adverse event information as that for C-ITZ. The dermatologist has to screen patients for all possible adverse events (AEs) of ITZ as performed with C-ITZ. Monitoring of AE should ideally be more stringent compared to C-ITZ as higher plasma levels are expected to be achieved at equivalent doses.
13. Drug interaction profile of SUBA-ITZ also remains the same as that for C-ITZ, with addition of caution for increase in ITZ exposure if co-administered with PPI.
14. As PK bridge for approval of SUBA-ITZ is established on acceptable exposure kinetics of C-ITZ and SUBA-ITZ, and not on exact bioequivalence (BE) of both the products, any dosage form of SUBA-ITZ is not interchangeable with C-ITZ.
15. As of now no robust clinical trials are available to establish the superiority of SUBA-ITZ over C-ITZ in terms of better cure rate or lower relapse rate in the management of dermatophytosis. Better PK parameters of SUBA-ITZ need not be automatically translated into a better cure rate or lesser relapse rate of dermatophytosis, and hence dermatologists must build upon their own experience in this regard till more data are available.

in India. Recurrence in sizable number of patients is a major therapeutic challenge for most of the dermatologists in India. Factors responsible for this are under investigation as of now. Various factors like inadequate BA of C-ITZ, poor concentration of drug at the site of action and dip in plasma concentration (due to different stomach environment during treatment duration) are actually giving opportunity to fungi to grow; at present, these are just theoretical possibilities as robust therapeutic drug monitoring studies are lacking from India. Box 1 shows position statement by IADVL SIG-RD on SUBA-ITZ.

Limitation of this position statement

This position statement is based on the opinions of members of IADVL SIG-RD only and does not necessarily represent the view of all experts in field. Unstructured literature review was done. Although all members of IADVL SIG-RD approved final draft of paper, no formal voting was done to find out the quantitative consensus.

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Conflicts of interest

There are no conflicts of interest.

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