Trichophyton indotineae and itraconazole failures: Is it really happening and what can we do about it?

The upsurge in dermatophytic infection cases resistant to terbinafine in recent years has been attributed to the emergence of the *Trichophyton indotineae* species, with a high rate of *SQLE* mutations, and has posed serious therapeutic challenges.[1] With the lowered efficacy of terbinafine, itraconazole has largely replaced as a first-line antifungal. The former remains useful, albeit at a higher dose of 250 mg twice daily.

The emerging concerns are the prolonged duration of treatment required with itraconazole and the purported failure to achieve a cure. Apparent "failure" has been attributed to the short durations of treatment. Multiple studies documenting low cure rates with itraconazole while using short duration add to the purported "increasing failure rate."[2] A recent randomised controlled trial (RCT) found that the mean itraconazole treatment duration required was 7.7 weeks for 100 mg/day, 7.2 weeks for 200 mg/day, and 5.2weeks for 400 mg/day, with no significant difference in treatment duration between 100mg/day and 200mg/day.[3] Notably, the cure rate at 8 weeks was 47.5% with 100 mg/day, 66.7% with 200 mg/day, and 86% with 400 mg/day, while the figures at 4 weeks were 19.6%, 17.4%, and 50%, respectively, with the three doses. Thus, as a starting point, it is ideal to wait for at least 6-8 weeks before considering itraconazole failure and shifting to alternative antifungals. It is imperative to make the patient aware of likely response times and treatment durations prior to initiating itraconazole so that the patients have reasonable expectations. About 50% clearance of lesions takes about 2.3 weeks with both 100 mg and 200 mg doses of itraconazole per day, while 90% clearance is expected in 4 weeks with both doses.[3]

Another important cause of "failure" is poor compliance, as it is difficult to ensure prolonged courses of an oral drug. A good practice is to prescribe for 14 days and ask the patient to revert with the empty strips to verify compliance and quality. Even though the use of -Super-Bioavailable (SUBA) itraconazole has offset some of the bioavailability concerns, it is better to consistently prescribe a single brand. We don't feel that conventional itraconazole and SUBA-itraconazole have profoundly different results. Moreover, in India, there is an issue of LASA (look-alike, sound-alike) drugs where the same brand name and even strengths exist in both the conventional and SUBA variants. Also, the needless marketing of 50, 65, 100, and 130 mg SUBA serves little purpose as they exceed the required dose, moreover the SUBA preparation has never been formally approved for dermatophytosis anywhere in the world, including India.

With a high overall cure rate of 92% in the clinical trial setting, the "failure" of itraconazole is an overrated phenomenon. However, in the small proportion wherein an actual clinical failure has occurred, there may be a possibility of mutations of the *ERG11* gene and efflux pumps. Notably, minimum inhibitory concentration (MIC) cut-off values (MIC >0.5µg/mL or >0.25µg/mL) for determining itraconazole resistance are an inaccurate measure in the absence of mutational studies or an assessment of the possible overexpression of target genes. Remember that azole exposure can lead to resistance, which may be specific to certain drugs in this class. Under azole pressure, there is an up-regulation of Erg11B transcripts combined with a downregulation of Erg1, suggesting a protective role for Erg11B with persistent upregulation of MFS1.[4]

The addition of fluconazole or voriconazole has been shown to induce enhanced expression of Erg11A, MDR3, and, to a lesser extent, Erg11B and Erg1 genes.[5] This explains the futility of giving these drugs in cases of failure of itraconazole. A more likely cause of itraconazole failures is the overexpression of efflux pumps of which of the varied families, the predominant is ATP Binding Cassette (ABC) superfamily, which includes three members-multidrug resistance (MDR), MDR- associated protein (MRP), and pleiotropic drug resistance (PDR) families. Existing data shows upregulation of transporters, including MDR1/2, MFS, MDR4, MDR5, and PDR1 in dermatophytes under azole pressure. *TinMDR3* overexpression and *MDR1* and *MFS* gene mutations have been observed in *T.indotineae*

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strains with low susceptibility to azoles. This has been noted in a study, where multiple genes of azole resistance and efflux pumps were overexpressed in clinical failures to both terbinafine and itraconazole and could be consequent to drug pressure.[6]

The use of agents like voriconazole and posaconazole lacks scientific basis, as these drugs are bound to fail in the case of documented *ERG11b* overexpression. Similarly, high MIC levels of fluconazole and griseofulvin have been observed against *T.indotineae* and thus are not recommended. Although ketoconazole has been shown to have a cure rate of 61%-67%, it should be used as a reserve drug, owing to its hepatotoxic potential. A better way to treat itraconazole failures would be to combine topical drugs with itraconazole based on synergy testing. A study from India noted that even in the presence of *SQLE* (Erg1) mutations, itraconazole was found to be synergistic with terbinafine, luliconazole, ketoconazole, and propylene glycol.[7] Thus, existing drugs could be combined judiciously in topical form without the need for expensive and "esoteric" azole drugs, which are best reserved for fatal systemic infections.

The myriad resistance mechanisms to azoles suggests that novel drugs, including efflux pump inhibitors, inhibitors of kinases, and heat shock protein inhibitors, could be researched for clinical use. Repurposed drugs include bisphosphonates, statins, calcineurin inhibitors, calcium channel blockers, and natural plant products. Plant products include an array of agents (oridonin, pyrogallol, pyrvinium pamoate, geraniol, vanillin, asiatic acid, curcumin, etc) with the promise of negligible toxicity but have not transcended beyond *in vitro* data. While there is data on the immunology of the host immune response, it doesn't seem to be markedly different to the prevalent species as compared to *T. rubrum* and isn't likely to be a cause for recalcitrance.

While true itraconazole failures are yet uncommon, any new drug introduced for dermatophytoses should be preceded by *in vitro* MIC data (cut-off values based on wild-type distribution of MIC),[8] minimum fungicidal concentration assessment, checkerboard studies, serum, and skin level pharmacokinetic assays as well as time-kill studies to determine synergism, indifference or antagonism. There is thus a need to decry the mere "renaming" of species, which serves little purpose except to clog PubMed with repetitive discoveries of the species across regions.[9] Also, possibly the species status of *T. indotineae* is hampered by insufficient genetic divergence from *T. mentagrophytes* and is an example of needless splitting of the complex and taxonomic inflation. An emergent need is to desist from prescribing voriconazole and posaconazole and focus on resistance mechanisms beyond Erg1 and Erg11 gene mutations and look at ways to surmount or prevent efflux pumps overexpression so that azoles as a class continue to be effective in the present epidemic of recalcitrant dermatophytoses.

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