Section A -Research paper

Treatment of chronic, recurrent and recalcitrant dermatophytosis

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Abstract:

There has been an alarming rise in patients presenting with atypical recalcitrant types of dermatophytosis in the past few years, with frequent relapses shortly after finishing the treatment course. The emergence of widespread resistance to antifungals with increasing clinical failure rates warrants the search for a novel and antifungal strategy that brings about rapid clinical and mycological cure in cases of recalcitrant tinea.

Keywords: recurrent, recalcitrant dermatophytosis, management.

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Introduction:

There are unprecedented changes in the epidemiology, clinical features and treatment response of dermatophytic infections, with many patients presenting with chronic, recurrent, and recalcitrant dermatophytosis **(Dogra and Narang, 2017).**

Chronic dermatophytosis refers to "patients who have suffered from the disease for more than 6 months to 1 year duration, with or without recurrence, in spite of being treated". Recurrent dermatophytosis refers to "the re-occurrence of the dermatophyte infection within few weeks, after completion of systemic treatment in a proper dose and duration". The term "recalcitrant dermatophytosis" is used when there is no clinical cure in spite of treatment with systemic antifungal agents in an appropriate dose and duration **(Rengasamy et al., 2017 & Tyagi et al., 2020).**

There are cases with unusual manifestation of tinea which are termed as atypical tinea though it is not synonymous with tinea incognita. The term "tinea incognita" is generally used for steroid modified cases of dermatophytosis although subsequent reports have shown tinea incognita with tacrolimus and pimecrolimus as well. Atypical tinea can be seen in immunocompetent patients who are not using

any topical and systemic medicaments such as corticosteroids **(Zhan P et al., 2017).**

Treatment of recalcitrant dermatophytosis

𝒜) Combination of systemic antifungals of different mechanisms of actions

Patients with chronic/recurrent dermatophytosis are posing therapeutic challenges similar to those observed with chronic dermatoses like psoriasis, vitiligo, and pemphigus. There are no consensus guidelines for the management of these cases. Dermatologists are using a combination of oral antifungals, higher doses of antifungals, longer duration of treatment for the management of these recalcitrant tinea cases, but it is more of hit and trial rather than evidence-based approach **(Dogra and Uprety, 2016).**

Topical treatment with different topical antifungals have a limited role especially in adult population. Many antifungals are being used for complete cure, but success often is not being achieved. systemic medications like griseofulvin, ketoconazole and terbinafine are associated with low cure rates and a potential of side effects and adverse drug interactions. Itraconazole has higher cure rates and fewer adverse reactions **(Rahman, 2019).**

The incidence of tinea refractory to terbinafine treatment has been on the rise. Terbinafine acts by inhibiting the enzyme squalene epoxidase which is responsible for synthesis of ergosterol an essential component of fungal cell wall, Resistance to terbinafine has largely been attributed to point mutations in the squalene epoxidase target gene (*SQLE*). Identification of the point mutation can be achieved by DNA sequencing of the *SQLE* gene of the fungal isolate. Sub-therapeutic dosage, non-compliance to treatment, and drug abuse may also be contributory **(Singh et al., 2018 & Kakurai et al., 2020).**

Itraconazole is a triazole antimycotic agent with strong keratophilic and lipophilic properties. Similar to other azole antifungal agents, the mode of action of itraconazole involves inhibition of 14-α-demethylase, resulting in impaired sterol synthesis in fungal cell membrane. It is also increasingly being used as a first-line drug for tinea corporis and tinea cruris, but it is being given for longer periods **(Ardeshna et al., 2016 & Doncker et al., 2017).**

The most common regimen of itraconazole prescribed is 100 mg twice a day. Only 7% of dermatologists prescribe itraconazole 200 mg twice a day. About 39% of dermatologists prescribe systemic therapy for 4–6 weeks in localized infection, whereas in chronic cases, 21% prescribe up to 6–8 weeks, and 17% for more than 8 weeks **[Figure 1**]. In case of non-response to routine dose of systemic anti-fungals, about 72% of dermatologists up dose them.

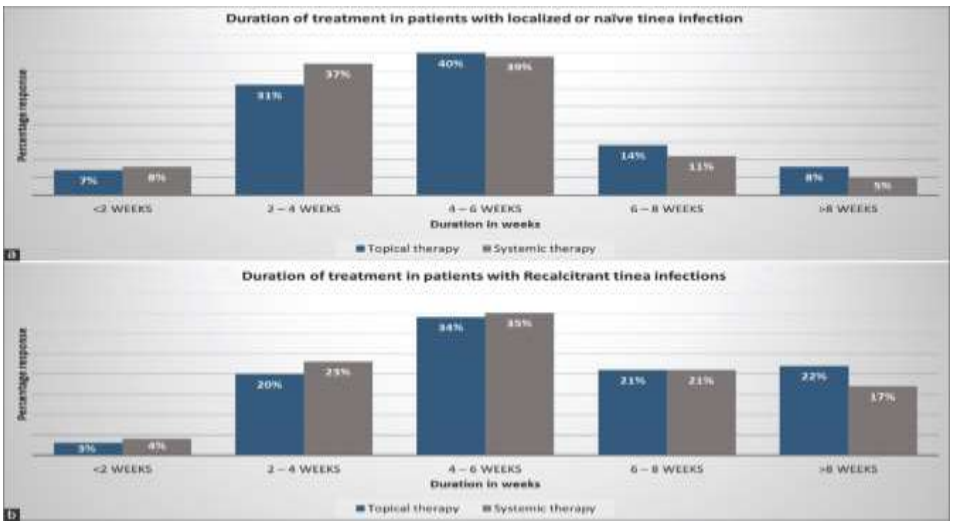


Fig (1): (a and b) Duration of treatment in different types of dermatophytosis.

A combination therapy of systemic antifungal drugs with different mechanism of action can enhance the cure rate and helps prevent drug resistance based on the concept of synergistic and additive effects of two or more drugs **(Russo et al., 2023).**

The practice of combination therapy has not been widely studied and published despite of being much practiced in many medical settings, recent study showed a comparatively better complete clinical cure rate with terbinafine and itraconazole (100%). This value was much higher compared to the study by Ramesh et al **(Ramesh et al., 2022)** that reported 48.3% complete cure and more comparable to the studies conducted by Singh et al., and Sharma P et al., that reported 79.2% and 90% clinical and mycological cure rate after three weeks and four weeks of combination therapy respectively **(Singh et al., 2020 and Sharma et al., 2020).**

ℬ) Combination of antifungals with oral retinoids (isotretinoin)

Retinoids act as modulators of epidermal growth and supervisor for differentiations, Although they act towards normalization in hyperprolifrative epithelia as in psoriasis, in normal epidermis they promote cell proliferation, therefore increased cell turnover in the epidermis may half the spread of ongoing infection by eliminating growth of dermatophyte when added to the standard antifungal treatment **(Seebacher et al., 2008).**

Dermatophytes work optimally at acidic pH and the skin being acidic gives an ideal ambient environment for the fungus. High transepidermal water loss and impaired barrier function of the skin are correlated with high skin PH. On being treated with retinoid therapy, the skin pH is raised, thereby possibly inhibiting the growth of dermatophytes. Retinoids are also known for their keratolytic effect. They reduce the corneocyte cohesiveness and also alter terminal differentiation of epidermis **(Ardeshna et al., 2016 & Rahman, 2019).**

Finally, retinoids stimulate humoral and cellular immunity, enhance antibody production and stimulate peripheral blood Th cells. Cell surface antigens of T cells and natural killer cells have been reported to increase after retinoid exposure *in vitro*. On the other hand, dermatophytes have mechanisms that allow them to evade the host response such as the immunosuppressive action of fungal mannans that causes reduction of inflammation and phagocytosis. Retinoids may counteract some of these immunosuppressive effects of the dermatophyte **(Giddey et al., 2007).**

Cheilitis is the most common adverse effect to isotretinoin followed by eczema, tiredness and mood changes. In lab investigations, an increase in the level of total cholesterol and serum triglycerides is observed. Side effects are mild and well tolerated. However, teratogenicity is a major concern; it is contraindicated in pregnancy (category X) and lactation. It is contraindicated in pregnancy and lactation **(Rademaker, 2010 & Brzezinski et al, 2017).**

C) New generations of antifungals

1-voriconazole:

There has been widespread resistance to various antifungal agents used in conventional dose with an increase in relapse rates. Studies show that fluconazole to be most resistant and voriconazole to be most sensitive drug for dermatophytes, so voriconazole could be a future alternative for treatment of chronic, recurrent, and recalcitrant dermatophytosis to achieve maximum results with fewer relapses **(Rahman, 2019 & Bhatia et al., 2019).**

Voriconazole is a synthetic second-generation triazole, structurally derived from fluconazole, which inhibits the cytochrome P450-dependent enzyme 14-α-sterol demethylase, thereby disrupting the cell membrane and halting fungal growth. It has a broad-spectrum activity against most clinically significant yeasts and moulds and is the first-line antifungal therapy for treatment of invasive aspergillosis **(Scott and Simpson, 2007).**

In recent study, voriconazole had shown complete clinical cure by (83.3), (70%) to combined itraconazole /isotretinoin therapy, and (53.3%) to itraconazole monotherapy in recalcitrant dermatophytosis **(Kattab et al., 2022).**

Voriconazole is generally well tolerated. The most common side effect is a reversible disturbance of vision (photopsia). Skin rashes are the second most common adverse effect. Elevations in hepatic enzyme levels occur with voriconazole therapy, as they do with other azoles. Other less commonly side effects include headache, nausea and vomiting, diarrhea, abdominal pain, and visual hallucinations. Voriconazole-induced photosensitivity reactions include erythematous eruptions of sun-exposed areas, such as facial erythema, chelitis, hyperpigmentation of the hands, exfoliative dermatitis, discoid lupus erythematosus, and pseudoporphyria. It should not be used with pregnancy unless the benefit clearly outweight the risk to the fetus (FDA category not assigned **(Saravolatz et al., 2003).**

2-Posaconazole:

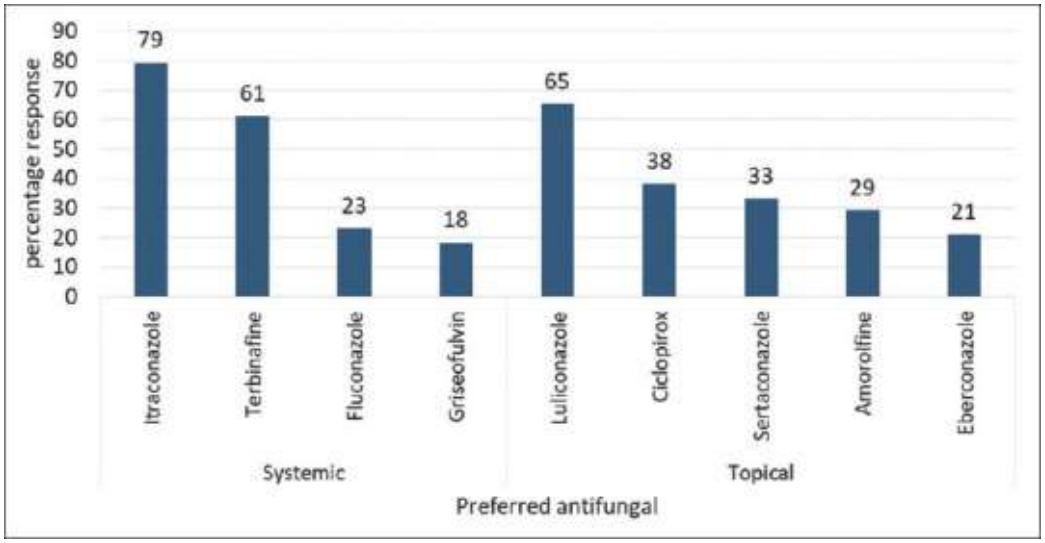
Posaconazole is a triazole antifungal agent, it exerts its antifungal activity through blockage of the cytochrome P-450 dependent enzyme, sterol 14α-demethylase, in fungi by binding to the heme cofactor located on the enzyme. This leads to the inhibition of the synthesis of ergosterol, a key component of the fungal cell membrane, and accumulation of methylated sterol precursors. This results in inhibition of fungal cell growth and ultimately, cell death **(Schiller et al., 2007).**

It is a drug derived from itraconzaole through the replacement of the chlorine substituents with flourine in the phenyl ring, as well as hydroxylation of the triazolone side chain. These modifications enhance the potency and spectrum of activity of the drug. Posaconazole can be either fungicial or fungistatic in action **(Theuretzbacher et al., 2010).**

It is indicated in prophylaxis of invasive aspergillus and candida infections in immunocompromised patients as hematopoietic stem cell transplant (HSCT), recipients with graft-versus-host disease (GVHD), or due to hematologic malignancies with prolonged neutropenia from chemotherapy **(Ullmann et al., 2006).**

3-luliconazole:

Luliconazole is the most commonly prescribed topical antifungal drug followed by ciclopirox olamine **[Figure 2].** All topical antifungals are prescribed for up to 4–6 weeks depending upon the severity of the disease. Additionally, both systemic and topical antifungal drugs are prescribed for additional 2 weeks for better clearance of lesions as reported by 82% and 89% of the respondents, respectively **(El-Gohary et al., 2014).**



Fig(2): Preferred antifungal in management of dermatophytosis.

4-Echinocandins:

Echinocandins (caspofungin, anidulafungin and micafungin) are

lipopeptides derived from the fermentation of broths of various fungi, which have been synthetically modified. These compounds act by inhibiting the synthesis of cell wall β-1,3-glucan, Echinocandins have been approved for invasive aspergillosis and candidiasis, Echinocandins generally exhibit fungistatic and fungicidal activities against *Aspergillus* and *Candida* species, respectively. Echinocandins have also shown in vitro activity against dermatophytes but reports on clinical use are lacking however, the data on the antifungal efficacy of echinocandins to dermatophytes in vitro are limited **(Patterson et al., 2016).**

5-Amphotericin B:

AMB is a broad spectrum antifungal drug that has been used parenterally for many years. It remains the "gold standard" for treatment of disseminated invasive mycoses, It is fungicidal primarily because of its unique structure characterized by both hydrophilic (polyhydroxyl) and hydrophobic (polyene) faces on its long axis, AMB binds to ergosterol, forming pores that cause rapid leakage of monovalent ions (K+ Na+, H+, and Cl−) and subsequent fungal cell death **(Sosa et al.,2017).**

AMB was more effective than the other four drugs against T. rubrum and T. verrucosum. Against T. mentagrophytes and *E.floccosum*, AMB was found to be better than other drugs but was inferior to terbinafine and itraconazole. Aktas et al. compared five antifungal drugs against dermatophytes using the E-test method. They found that caspofungin and itraconazole were the most effective drugs and that AMB was consistently better than ketoconazole and fluconazole against all the dermatophytes **(Aktas et al., 2014).**

𝒟) Immunotherapy of chronic, recalcitrant dermatophytosis

Immunotherapy of chronic dermatophytosis can be by specific antigen containing both *T. rubrum* and *T.mentagrophytes,* and non specific antigen containg pure *candida albicans* suspended in saline with 0.5% phenol added and contained 5 x 10 spores/ml, *Trichophyton antigen* was prepared as above and contained 70 mg/ml (dry weight) of *T. rubrum* and *T. mentagrophytes* in equal parts (**Tager et al., 1973).**

Immunotherapy attempts were instituted with the same antigens used in the skin tests. A dose of 0.1 ml was injected intradermally as follows: during the first 2 months, twice weekly during the next 2 months, once weekly, and during the following 6 months, once fortnightly. A total course comprised 35 injections over a period of 10 months.

Immunotherapy is an exciting treatment option in patients with unresponsive or reccurent warts **(Silverberg et al., 2000).**

Although immunotherapy with repeated injections of *Candida* antigen appears to be effective in clearing superficial and nodular BCCs (**Kent et al., 2005).**

Homologous autoimplantation is a simple technique that works by inducing cell-mediated immune response against the antigens essential for the clearance of dermatophytes. It has already provoked a good clinical response in patients with verruca vulgaris in various clinical studies **(Shivakumar et al., 2009).**

ℰ) Novel theories in the future of treatment of recalcitrant dermatophytosis

1) Chemical peeling:

Patients suffering from active tinea infections with positive potassium hydroxide (KOH) were included, Pregnant females, children (younger than 18 years) and those with a negative KOH were excluded, Patients with extensive involvement (more than 20% body surface area) as well as those using topical or oral antifungals within the preceding 2 weeks were excluded. Itching was classified as per severity into three grades: mild itching - grade 1, moderate - grade 2, and severe - grade 3 **(Arif et al., 2015).**

Salicylic acid 30% was prepared by adding acetone to 30 g of salicylic acid powder to make it 100 mL giving a 30% w/v salicylic acid, Salicylic acid 30% application was done over the lesions (and 1 cm beyond the lesional border). The maximum quantity of salicylic acid used during a single treatment session was 10 mL (3 g of salicylic acid), While applying salicylic acid in the inguinal area, care was taken to protect the scrotum. In case of severe burning, ice pack application was done **(Taylor et al., 1975).**

The treatment was repeated every week (with a delay of up to 3 days considered acceptable) for 4 weeks. Thereafter, the patients were followed up weekly for four visits by the same set of investigators for all visits.

No systemic or topical antifungal drugs were co prescribed during the study period. KOH mounts were done at the baseline visit for confirming the diagnosis and repeated at the end of fifth visit (1 week after the last application) for the assessment of the response, and then every week till 4 weeks after the last application **(Bari et al., 2005).**

2) Photodynamic Therapy for the Treatment of Fungal Infections:

Photodynamic therapy (PDT) is effective against fungal infections and serves as an alternative treatment strategy. PDT was originally discovered in 1900 and was used for its anti-microbial action, however, this treatment is gradually being accepted as an anti-fungal treatment option since the 1980s **(Hamblin et al., 2016).**

The rapid onset of action, mild adverse effects, combinations with other therapies, and applicability in patients with contraindications to other drugs or in those with unresponsiveness to oral antifungal agents serve as advantages of PDT, Little to no risk of development of resistance and its repeatability are other advantages of this treatment **(Shen et al., 2020).**

Currently, PDT is widely used to treat many cutaneous fungal infections, such as onychomycosis, tinea capitis, pityriasis versicolor (PV), oral candidiasis, vulvovaginal candidiasis (VVC), chromoblastomycosis (CBM) and cutaneous sporotrichosis, among others, of which onychomycosis is the focus of most research. PDT is a potentially promising therapeutic alternative for treatment of cutaneous fungal infections **(Gupta et al., 2015).**

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