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Onychomycosis an overview for management: Combined Itraconazole and Acitretin

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Abstract

Background: Onychomycosis is a chronic fungal infection of the nail, characterized by nail discoloration, subungual hyperkeratosis, and onycholysis. The involved pathogens are dermatophytes, yeasts (Candida), and non-dermatophyte molds.Dermatophytes such as Trichophyton rubrum and Trichophyton mentagrophytes are the most common agents of onychomycosis, with higher prevalence of the infection in toenails than in fingernails. Candida albicans affects almost exclusively the fingernails, and accounts for 10% of toenail onychomycosis.

Itraconazole is a broad-spectrum antifungal drug which is active against a range of fungal species, including yeasts, dermatophytes and some non-dermatophyte molds, is a more convenient antifungal drug for different types of onychomycosis. Itraconazole is licensed at a dose of 200 mg daily for 12 weeks continuously or intermittently as pulse therapy at a dose of 400 mg daily for 1 week per month for 2-3 pulses in fingernail infections and 3-4 pulses for toenail disease.Although itraconazole pulse therapy has proven to be an effective and acceptable onychomycosis therapies, the complete cure rate remains unsatisfactory, indicating that 3-4 cycles of pulse therapy for toenail onychomycosis might be inadequate for severe cases of onychomycosis. Thus, the development of a more effective and suitable therapeutic regimen to improve the complete cure rate is necessary.

Keywords:Onychomycosis, Itraconazole and Acitretin.

1.Introduction:

Onychomycosis, (Greek word Onyx = nail + Mykes = parasite), is fungal nail infection caused by dermatophytes, nondermatophytes, and yeast, and is the most common nail disorder seen in clinical practice **(1).**

It is an important problem because it may cause local pain, paresthesias, difficulties performing activities of daily life, and impair social interactions. Typically, it manifests as discoloration of the nail, nail plate thickening, and onycholysis. It is the most common nail pathology and accounts for about 90% of toenail infections worldwide **(2).**

1.1 Epidemiology of onychomycosis:

Onychomycosis is the most common nail disease with a worldwide prevalence of 5.5%. In the United States, Trichophyton rubrum (T. rubrum) was initially thought to be a culture contaminant, but since

the advent of international travel to Asia, T. rubrum has become the dominant causative organism in the United States. At least half of abnormal toenails are mycotic. The prevalence in the United States is estimated to be 2% to 14%, and the incidence is increasing. Onychomycosis is less common in children and more common in older individuals **(3).**

1.2 Pathogenic organisms:

In most cases, this infection is caused by anthropophilic dermatophytes (60%-70%), in particular by T rubrum (50%), followed by T. mentagrophytes var. interdigitale (20%), with remaining infections caused by E. floccosum, Microsporum spp., T. violaceum, and T. verrucosum. The non-dermatophyte molds (NDMs) are responsible for approximately 20% of fungal nail infections and the most common organisms are Scopulariopsisbrevicaulis, Aspergillus spp., Acremonium, Fusarium spp., Alternaria alternate, and Neoscytalidium. They can be involved in onychomycosis as primary pathogens or as contaminant agents and secondary pathogens (**5).**

Yeasts (10%-20%), like Candida albicans and Candida parapsilosis, represent the third cause of nail fungal infection. Onychomycosis caused by ≥2 fungal organisms are being increasingly identified with molecular biology, and bacterial-fungal infections are relatively common **(6)**

While fungi were previously believed to be planktonic (in suspension, free-floating, and acting independently), recent evidence supports the formation of biofilms. Biofilms are sessile microbial communities that attach to biological surfaces, such as the nail plate, via an extracellular matrix that encases them **(Figure 1).** It is believed that biofilms play an important role in resistance to antifungal drugs, increased virulence, and immune evasion. Dermatophytes, including T. rubrum and T. mentagrophytes, NDMs including Aspergillus fumigatus and Fusarium spp., and yeasts such as Candida albicans, all form biofilms in vitro **(7)**

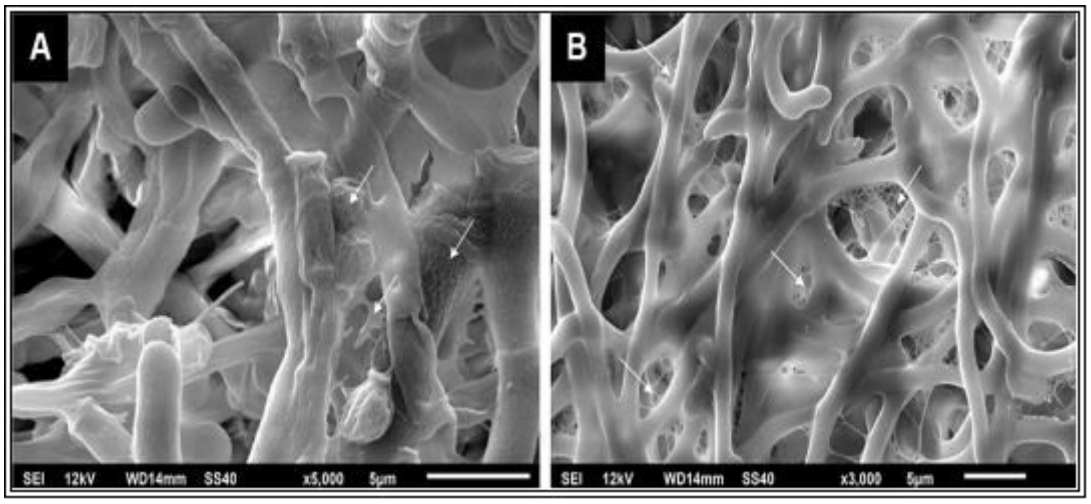

Fig. (1): Scanning electron microscopy of mature fungal biofilms formed in 24-well plates. White arrows denote extracellular matrix covering and connecting the hyphae. A: Trichophyton rubrum ATCC 28189. B: Trichophyton mentagrophytes ATCC 11481 **(1)**

2. diagnosis

diagnosis of onychomycosis is commonly confirmed by clinical examination side by side with regular laboratory diagnostic techniques such as direct microscopy (Figure 2) and fungal culture

(Table 1), which are considered the golden standards of diagnosis **(7).**

Table (1): Diagnosis of onychomycosis caused by dermatophytes (8).

Clinical diagnosis	Confirmatory laboratory specimens analysis
1- Primary criteria for diagnosis: **White/yellow or orange/ brown patches or streaks.**	**Positive microscopic evidence**
2- Secondary criteria for diagnosis: ❖ **Onycholysis** ❖ **Subungual hyperkeratosis/ debris** ❖ **Nail-plate thickening**	**Positive culture of dermatophyte**

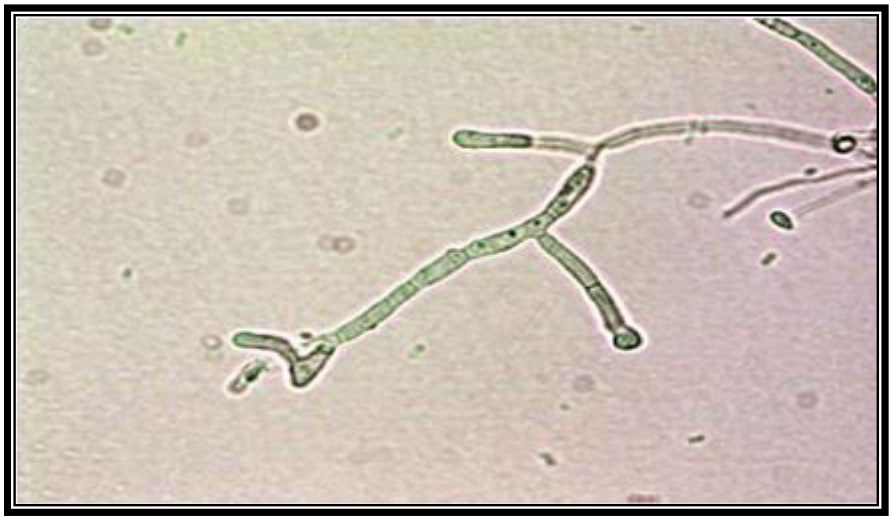

Fig. (2): Septate hyphae visible after nail digestion with potassium hydroxide solution. Potassium hydroxide preparation unstained; original magnification x400 **(9).**

Collection of enough sample is important factor for microscopic examination and culture as too often, inadequate nail samples have led to failure of fungal diagnosis (either in quantity or quality) **(Figure 3, Table 2) (9).**

Table (2): Sites for sample collection **(10).**

DLSO	**Nail bed and underside (ventral side) of the nail plate from the advancing edge, most proximal to the cuticle.**
PSO	**Curette from deeper portion of nail plate and proximal nail bed as close to the lunula as possible after paring the superficial normal surface of the nail plate.**
SWO	**Surface scrapings/shavings from the friable areas of**

	leukonychia discarding the outmost surface and collecting the white debris underneath.
CO	**Material closest to the proximal and lateral nail edge.**
Endonyx &TDO	**Nail clipping.**

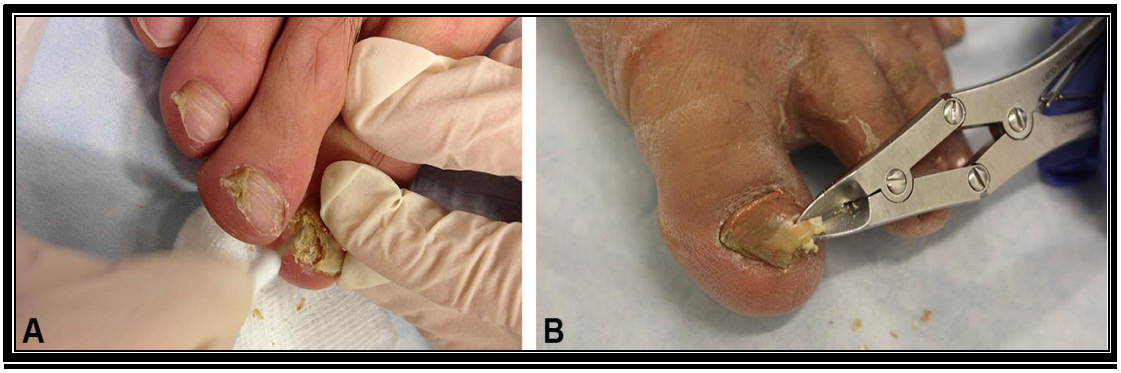

Fig. (3): Sample collection. A, For distal lateral subungual onychomycosis, a no. 1 curette is used to gently scrape the subungual debris after removal of the distal area of onycholysis. B, A double action nail clipper is used to sample a thickened nail plate **(1).**

2.1DermoscopicExamination:

Digital dermoscopy, also called onychoscopy, is an easy and quick procedure allowing differential diagnosis of onychomycosis from causes of nail dystrophies.

The peculiar features of DLSO, not seen on traumatic onycholysis and nail psoriasis, are

1. Proximal margin of the onycholytic area showing jagged edge, with sharp structures, directed to the proximal fold (the most common finding) **(Figure 4).**
2. Longitudinal striae of different colors in the onycholytic nail plate **(Figure 5).**

The overall appearance of the color of the affected nail plate in a matted variable discoloration (multi-color chromonychia) resembling the aurora borealis, which is a natural electrical phenomenon occurring in north and south poles **(Figure 6) (4&1)**

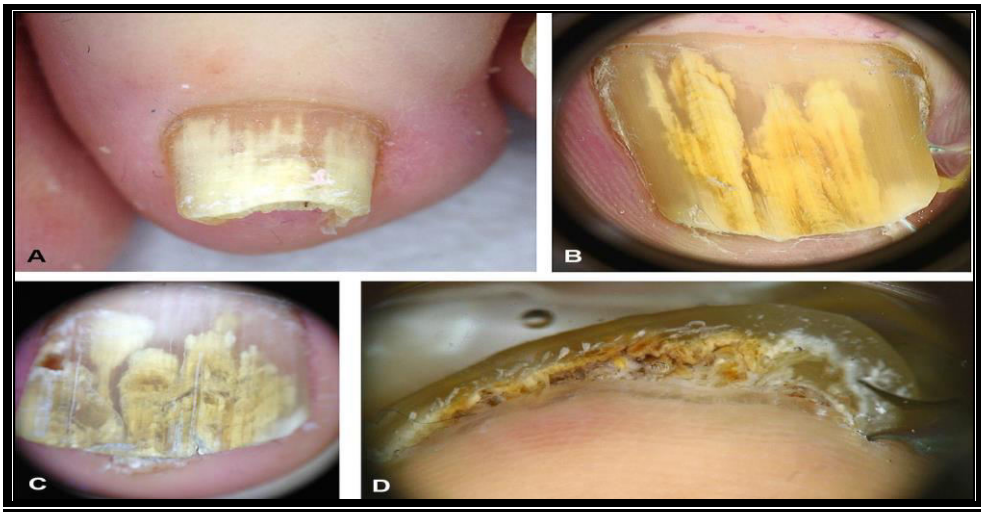

Fig. (4): Dermoscopy of onychomycosis. A: Fringed proximal margin of the onycholysis. B: Blurred yellow-orange-brown nail discoloration in longitudinal striae (the fading mimics Aurora Borealis). C: Distribution of the discoloration in longitudinal striae or round areas. D: Ruin-like appearance of the subungual scales that are white-yellow-orange in color **(1)**

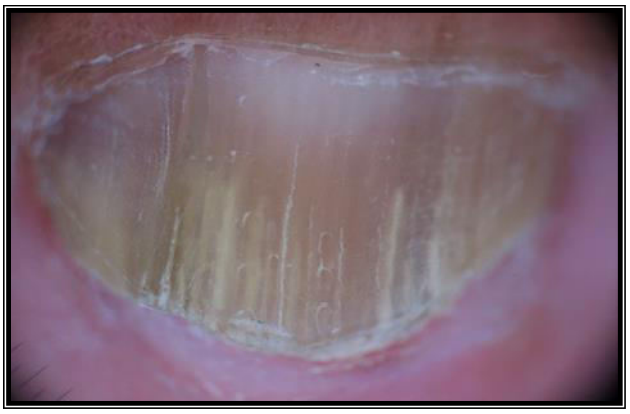

Fig. (5): Longitudinal striae of different colors in the onycholytic nail plate **(11)**

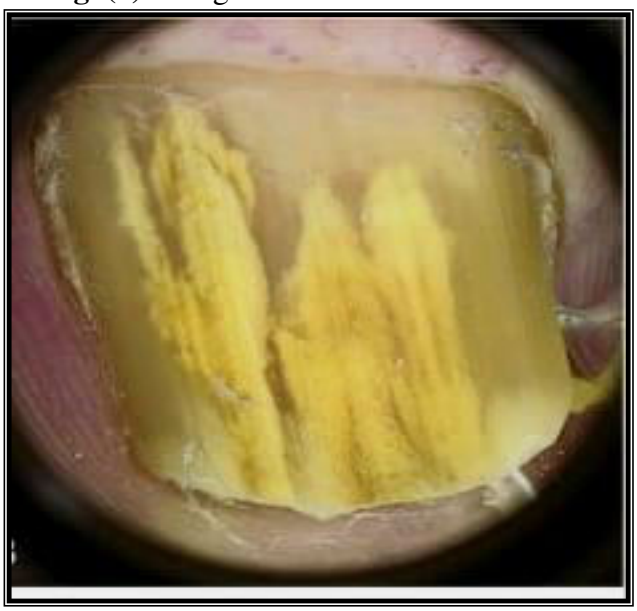

Fig. (6): a-Blurred yellow-orange-brown nail discoloration in longitudinal striae b-Aurora Borealis **(4).**

2.2 New tools in the diagnosis:

Some other interesting new tools in the diagnosis of onychomycosis are: dermatophyte test strip, fluorescence microscopy and Raman spectroscopy. The dermatophyte test strip is an immunochromatography test that uses a monoclonal antibody that reacts with Trichophyton species and gives a positive signal when in contact with one of these dermatophytes, after 15 min. It is a ready-to-use kit, very quick, easy to perform and not expensive. The test has a high sensitivity and negative predictive value, so it can be used to rule out onychomycosis in all doubtful cases **(12).**

Confocal laser-scanning microscopy (CLSM) is an emerging diagnostic technique. The aspect of dermatophytes appears as a network of lengthy structures with high reflection and the typical shape of hyphae **(13).**

2.3 Comparison of techniques

Currently available diagnostic techniques include KOH with microscopy, fungal culture, histopathology, and PCR. One or more techniques can be used to diagnose onychomycosis, and the method chosen is dependent on patient characteristics, time to initiate therapy, sensitivity and specificity of the technique, and expertise of the clinician. The KOH examination is a rapid method for diagnosing onychomycosis, but it is highly expertise dependent**. (Table 3)** shows a comparison of diagnostic techniques **(1)**

Technique	Nail plate penetrance	Fungal viability	Identification of pathogen	Sensitivity (%)	Specificity (%)	Dependant on expertise of physician
KOH	No	No	No	67-93	38-78	Yes
Fungal culture	No	Yes	Yes	31-59	83-100	No
Histopathology with PAS	Yes	No	No	92	72	No
PCR	No	No	Yes	95	100	No

Table (3): Comparison of techniques used for diagnosis of onychomycosis (1).

2.3 Onychomycosis severity index:

The clinical features chosen for scoring in the Onychomycosis Severity Index (OSI) are the area of involvement, proximity of disease to the matrix, occurrence of dermatophytomas, and presence of severe subungual hyperkeratosis (>2 mm) **(14).**

The Onychomycosis Severity Index is calculated as follows: the score for area of involvement is multiplied by the score for the proximity of disease to the matrix, and 10 points are added for the presence of a dermatophytoma or subungual hyperkeratosis of greater than 2 mm. A cumulative score of 0 indicates cured; 1 through 5, mild onychomycosis; 6 through 15, moderate onychomycosis; and 16 through 35, severe onychomycosis **(15).**

3. Treatment:

3.1 Antifungal drugs:

- **Topical therapy**
- **Topical FDA-approved treatments:**

1-Ciclopirox

It has broad-spectrum coverage against dermatophytes, Candida spp., some NDMs, and Gram-positive and -negative bacteria. Ciclopirox 8% nail lacquer was approved by the FDA for the treatment of mild to moderate onychomycosis of fingernails and toenails without lunula involvement in immunocompetent patients caused by T. rubrum. Weekly clipping and monthly in-office debridement is recommended for better efficacy. For toenails, mycologic cure rates are 29% to 36% and complete cure rates are 5.5% to 8.5%. Adverse effects were localized and included burning, periungual erythema, and application site reactions **(16&1)**

1-Efinaconazole:

It is active against dermatophytes, NDMs, and Candida spp. both in vitro and in vivo. Efinaconazole 10% solution was approved by the FDA in June 2014 for the treatment of toenail onychomycosis caused by T. rubrum and T. mentagrophytes, with mycologic cure rates of 53.4% to 55.2% and complete cure rates of 15.2% to 17.8%. Adverse effects were limited to application site reactions and ingrown toenails **(17).**

3-Tavaborole:

It has broad-spectrum antifungal activity against dermatophytes, NDMs, and yeasts. Tavaborole 5% solution was approved by the FDA in July 2014 for the treatment of toenail onychomycosis caused by T. rubrum and T. mentagrophytes, Mycologic cure rates were 31.1% and 35.9% and complete cure rates were 6.5% and 9.1%. Adverse effects are local with the most common being, exfoliation, erythema, and dermatitis **(17&1).**

- **Systemic therapy (Oral antifungal agents):**
- **Terbinafine**
- **Terbinafine pulse dosing**
- **Booster therapy.**
- **Itraconazole**
- **Fluconazole**
- **New azoles**

3.2 Physical treatment:

Laser therapy:

It is a non-pharmacologic treatment thought to induce fungicidal activity through a photothermal effect on nail fungi using the principle of selective photothermolysis. The mechanism of action is not yet well understood, but one theory is that laser energy is preferentially absorbed by fungal mycelia in the affected tissue, resulting in a rapid elevation in temperature and fungal cell death **(18).**

Various types of lasers have been investigated in the treatment of onychomycosis. The most extensively studied for this purpose is neodymium-doped yttrium aluminium garnet (Nd:YAG) laser. Onychomycosis has also been treated with fractional carbon dioxide lasers, diode lasers and

erbium:glass lasers **(19).**

Multiple treatments are typically performed with duration as long as 19 months, with limited efficacy. High cost, not covered under most insurance plans, is a matter of major concern. Pain associated with laser treatment is also an important concern. Based on the above issues, laser therapy cannot currently be recommended as a first-line treatment of onychomycosis **(20).**

- **Photodynamic therapy (PDT):**

The light within a defined narrow spectrum is used to excite a photosensitising agent applied directly to the target area and absorbed by the target organism, resulting in the formation of reactive oxygen species that selectively destroy infected tissue **(21).**
Reported side effects (mild pain, burning, erythema, oedema and blistering) were well tolerated and resolved within a few days **(22).**

- **Plasma therapy:**

Plasma therapy involves applying nonthermal plasma to the infected nail surface. Pulses of strong electric field are used to generate the plasma which ionizes surrounding air molecules to produce ozone, nitric oxide and hydroxyl radicals, which have antifungal properties. Nonthermal plasma has exhibited antifungal activity against T. rubrum in vitro **(23).**

3.3Combination Therapy:

Combining oral and/or topical drugs for onychomycosis, shows that combination therapy is sometimes (though not always) more effective than monotherapy. Most studies combined oral terbinafine or itraconazole with topical amorolfine 5%, ciclopirox 8% or terbinafine **(7).**

- **Prevention of recurrence:**

After treatment of onychomycosis, recurrences (ie, relapse [same infection after incomplete cure] or reinfection [same infection after complete cure]) occur at a rate of 20% to 25% **(4).**
In a retrospective chart review on patients with complete cure treated with oral terbinafine for toenail onychomycosis who then used a topical antifungal for prophylaxis, the recurrence rate was significantly lower in patients receiving prophylaxis. The ideal duration of prophylaxis is unknown, but may be required for life **(24).**

4. Itraconazole and Acitretin

4.1 Itraconazole:

Itraconazole is one of the most commonly used agents in clinical practice and is active against a range of fungal species, including yeasts, dermatophytes and some non-dermatophyte molds. Itraconazole is licensed at a dose of 200 mg daily for 12 weeks continuously or alternatively at a dose of 400 mg daily for 1 week per month. It is recommended that two of these monthly courses are given for fingernail infections and three courses for toenail disease **(25).**

Although itraconazole pulse therapy has proven to be more effective and acceptable than most of the other onychomycosis therapies, the complete cure rate remains unsatisfactory, indicating that three cycles of pulse therapy for toenail onychomycosis might be inadequate for severe cases of onychomycosis Thus, the development of a more effective and suitable therapeutic regimen to improve the complete cure rate is necessary **(26)**

Mechanism of action:

Itraconazole is a triazole agent, which functions as a broad spectrum antifungal drug. , it has been reported to inhibit the activity of cytochrome P450 (CYP) 3A4, resulting in impaired sterol synthesis in fungal cell membranes, therefore inhibiting fungal growth and eventually leading to cell death **(27).**

Itraconazole enters the nail rapidly and is perceptible in the nail as ahead of schedule as 7 days in the beginning of treatment and holds on in the nails for up to 6–9 months after treatment end **(28).**

Side effects:

The more common adverse effects are headache and gastrointestinal symptoms such as diarrhea, dyspepsia, abdominal pain, constipation, nausea, flatulence and dermatologic symptoms such as rash, pruritus, and urticaria **(29).**

Acute generalized exanthematouspustulosis is associated with both oral itraconazole and terbinafine and has been rarely reported in the literature. In most cases, there were nearly complete resolution of the pustular eruption within a few weeks following cessation of drugs and treatment with topical and systemic corticosteroids **(30**).

Approximately 26% of diabetic patients have onychomycosis, and compared with nondiabetics, this patient population is at increased risk of secondary complications, including onychocryptosis, bacterial cellulitis, osteomyelitis, gangrene, or foot ulcers. Effective treatment that does not interact with oral hypoglycemic or cardiovascular agents, or worsen glycemic control, is therefore of high importance. Azole antifungal agents are not desirable under such a setting **(17).**

Contraindications:

Itraconazole is contraindicated in patients with congestive cardiac failure due to the increased risk of negative inotropic effects. Itraconazole may also prolong the QT interval, and therefore co-administration with other drugs that also increase the QT interval is contraindicated **(29).**

4.2 Acitretin

Mechanism of action in onychomycosis:

Successful installation of dermatophytes requires rapid germination of arthroconidia and penetration of hyphae into the stratum corneum. Failure to do so will result in elimination by the continuous desquamation of the epithelium **(31).**

Systemic retinoids like acitretin act as modulators of epidermal growth and supervisors of differentiation. Although they act toward normalization in hyperproliferative epithelia as in psoriasis. In normal epidermis, they promote cell proliferation. Therefore, increased cell turnover in the epidermis may cease the spread of ongoing infection by eliminating the growing dermatophyte **(32).**

Retinoids are also known to alter terminal differentiation towards a non-keratinizing, metaplastic and mucosa-like epithelium. The glycosylation pattern of normal skin treated with retinoic acid resembles that of mucosal epithelium with a reduction of tonofilaments, decreased corneocyte

cohesiveness, impaired function of the permeability barrier and increased transepidermal water loss, thus explaining the keratolytic effect of retinoids in hyperkeratotic disorders **(32).**

Dermatophytes de-repress non-specific proteolytic enzymes and keratinases which have optimum activity at acidic pH and are important virulence factors. Thus, growth is dependent on the pH of the skin which being acidic gives an ideal ambient environment for the fungus.
High transepidermal water loss values and impaired barrier function of the skin are correlated with high skin pH which being increased with retinoid therapy raises the skin pH, thereby possibly inhibiting dermatophyte growth **(32).**

Finally, retinoids are generally thought to stimulate humoral and cellular immunity. Retinoids can enhance antibody production, stimulating peripheral blood T helper 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 immuno-suppressive action of fungal mannans that causes reduction of inflammation and phagocytosis. Retinoids may counteract some of these immunosuppressive effects of the dermatophyte **(31)**

Side effects:

- **Mucocutaneous side effects:**

Hair loss, dry mouth with thrush, dry mucosa, palmoplantar peeling, dry skin with pruritus, epistaxis, facial dermatitis, dry eyes, conjunctivitis, and hair color change **(33).**

Systemic adverse effects:
Hyperlipidemia:
Hyperlipidemia is the most common systemic side effect of retinoids, which is often proportional to the dose and reverses 4-8 weeks after the discontinuation of the drug. The elevation of triglycerides is more pronounced and occurs in 50% of the patients taking acitretin **(34).**

Alopecia:
Alopecia and telogen effluvium due to the use of systemic retinoids have been reported. Hair loss is most frequently seen with acitretin. Hair loss is a dose-dependent effect and is reversible in 2 months after reducing the dose or discontinuing the treatment **(34).**

Teratogenicity:
For the first time, **Cohlan** (**1954**) reported teratogenicity due to high dose vitamin A. Today, the teratogenetic potential of retinoids is well documented; acitretin is classified by FDA in category X and are absolutely contraindicated during pregnancy and lactation **(34).**

Contraindications:
Absolute:
Pregnancy, lactating mothers, women of childbearing period who cannot gurantee adequate contraception during and up to 3 years **(35).**

Acitretin should not be used in the following medical problems:
Hyperlipidemia, pancreatitis, history of hypervitaminosis A and history of hypersensitivity to

etretinate, isotretinoin, tretinoin, or vitamin A **(35).**

Risk-benefit should be considered in the following medical problems:
Diabetes mellitus type 1 or 2, hepatic disease, renal disease, alcohol abuse and concomitant intake of hepatotoxic drugs **(35).**
The observation that onychomycosis is rare in children due to rapid nail growth, together with the proven fungistatic activity against both dermatophytes and C. albicans, and its reported immunomodulatory properties, drives us to think of the possible role of systemic retinoids, whether as monotherapy or as a candidate for novel combined antifungal strategies for onychomycosis. So, acitretin could potentially be a new therapeutic player in the field of onychomycosis.

5. Conflict of Interest: Noconflictofinterest.

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