Update on the Treatment of Onychomycosis

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Onychomycosis is not a single entity but has different sites and severity of involvement. The portal of entry of fungi determines the subtypes of onychomycosis: (1) Distal and lateral subungual onychomycosis, the most common type; (2) Superficial white onychomycosis; (3) Proximal subungual onychomycosis; (4) Endonyx onychomycosis, involving the nail plate only.

For effective treatment, the clinicians have to choose between three main possibilities: the new oral drugs, topical therapy and the removal of the nail plate. A combination of different modalities often provides the best option.

Some patients are unable or unwilling to take oral drugs. They perceive the infection as trivial to deserve systemic therapy. The use of potent systemic drugs may sometimes be limited by side effects, such as loss of taste, hepatic toxicity, or the possibility of drug interactions.

Suggested scheme for the treatment of onychomycosis

A stepped therapeutic approach to the treatment of onychomycosis is suggested. The risks of failure of treatment include the fungal involvement of the lunula portion, the lateral edge of the nail and the subungual area. Infection of the subungual area may lead to extensive onycholysis or dermatophytoma presenting as a hard subungual mass or as a distal to proximal yellow spike, both of which inhibit the penetration of the antifungals into the diseased areas.

The first line of therapy for mild or moderate fungal involvement which spares the proximal third of the nail plate is topical monotherapy with the nail lacquers that act as a transungual drug delivery system.

If monotherapy is ineffective after six months, a combination of treatments is indicated. However, when the proximal third of the nail is involved, double pronged therapy should be considered as a first step and amorolfine should be combined with systemic medication. This will, additionally, provide effective oral therapy against tinea pedis which often precedes onychomycosis.

When there is a risk of failure, because of interruption in the transport of the drug from the nail into the nail bed, immediate eradication of the pathogen is indicated. In this triple therapy, mechanical or chemical removal of the diseased nail (or portion of the nail) is combined with systemic therapy; the antifungal nail lacquer should be maintained on the remaining normal looking part of nail keratin, as some fungi may be left beneath its lateral margin.

New topical antifungal agent

Attempts to deliver active agents onto the nail include:

1. Improve the conventional topical treatments, using a modification of the vehicle pH (as in miconazole where a high concentration of the active agent is achieved by decreasing the formulation pH, thereby increasing drug solubility in the vehicle).
2. New formulations such as Faergeman's solution (lactic acid, urea, propylene glycol) or 28% tioconazole or 40% urea. The two former solutions have produced only moderate results and urea paste acts principally on the pathologic nail plate – nail bed attachment. Non surgical avulsion with an urea based preparation such as bifonazole-urea eradicates the pathogens. However, this antifungal chemotherapeutic keratinolysis has some drawbacks: it is cumbersome if several nails are involved, inefficient when the nail is affected beneath the proximal nail fold, and fungi may still be present under the margin of the remaining normal nail keratin adherent to the nail bed.

3. Development of a new vehicle in the form of a cosmetic nail lacquer. The polymer forms a film which reduces transungual water loss. The nail lacquer maintains the active agent in the polymer film reservoir on the nail surface from which the chemical diffuses evenly through the nail keratin to reach the nail bed. After evaporation of the solvent of the nail lacquer, the concentration of the diffusion molecule in the film increases, which in turn enhances penetration and diffusion.

Amorolfine belongs to a new family of antifungal drugs, the morpholines. Amorolfine inhibits the steps in the pathway of ergosterol biosynthesis which play an important role in regulating membrane fluidity. This leads to accumulation of abnormal sterols and inhibits fungal growth. Amorolfine possesses a broad antimycotic spectrum against fungi pathogenic to plants and humans. In addition, it shows a strong fungicidal activity which is dependant on both concentration and time. Amorolfine exerts a fungicidal action against yeast, dimorphic and dematiaceous fungi.

New systemic antifungal agents

The newer triazoles, fluconazole and itraconazole as well as the oral allylamine, terbinafine, differ from the traditional antifungal drugs either because of rapid penetration into the nail via the nail bed, and/or their ability to bind to the matrix tissue allowing drug retention in the nail plate after discontinuation of therapy. This produces continuous improvement compatible with a short duration of treatment and even intermittent therapy.

Itraconazole

Itraconazole has the broadest in vitro spectrum of the oral antifungal drugs. It is effective against dermatophytes, *Candida* and some moulds. Due to its characteristic pharmacokinetic profile, with a high affinity for nail keratin, the recommended schedule is 200 mg twice daily, for one week each month in an "à la carte" treatment regimen comprising two months for fingernail infections and three to four months for toenails. Although the nail will not be normal when therapy is discontinued, improvement continues, sometimes at a slower rate than during the treatment period, where an increase in linear nail growth is often observed.

Fluconazole

Fluconazole is active against *Candida*, and other yeasts as well as dermatophytes. It has been used widely in HIV-infected patients. The dosage of 150-300 mg administered once a week may be a useful intermittent regimen in patients taking multiple medications.

Terbinafine

Terbinafine is the only in vitro fungicidal oral antifungal with activity against the dermatophytes, some species of *Candida* and even some moulds. It is detectable in the nail plate in one to three weeks and persists for up to four months after therapy has been discontinued. A 12-24 weeks course of 250 mg terbinafine once a day is effective in toenail infection, while six weeks of therapy is sufficient for fingernail disease.

Long-term intermittent therapy

Finally, long-term intermittent therapy with topical antifungal agent should prevent the re-establishment of tinea pedis and limit the possibility of reinfection. Periodic use of transungual drug delivery systems, which are retained in nail keratin after active therapy is interrupted, appears to be a logical and safe method for preventing recurrences.

Learning points:

Subtypes of onychomycosis may require different or combination of topical, oral and chemical-surgical treatment.