WHAT’S NEW IN NAIL THERAPEUTICS?

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CONFLICT OF INTEREST

- RESEARCH GRANTS - TO UNIVERSITY
  - Dusa, Valeant, Viamet
  - Amgen, Abbvie, Boehringer Ingelheim, Celgene, Lilly, Merck, Novartis, Pfizer

- CONSULTANT - HONORARIUM
  - Anacor, Celgene, Lilly, Pfizer, Valeant
Objectives:

- What’s new in the diagnosis of Onychomycosis?
- New treatments for onychomycosis
- Know when to Xray the digit
HALF OF ABNORMAL NAILS -ONYCHOMYCOSES
THE OTHER HALF DO NOT!
Diagnosis of Onychomycosis

- **LABORATORY DIAGNOSIS**
  - PAS
  - KOH, fungal culture

- **CLINICAL DIAGNOSIS**
  - Clinical signs of onychomycosis
Diagnosis of Onychomycosis

- Presence or absence of fungal elements
  - KOH/ calcofluor
  - PAS stain

- Fungal identification
  - Fungal culture
  - PCR analysis

PCR may be available soon
PAS STAIN POSITIVE FOR SEPTATE HYPHAE
IF PAS POSITIVE FOR HYPHAE, DIAGNOSIS IS CONFIRMED

YEAST CELLS AND SPORES DO NOT COUNT!
Empiric treatment with terbinafine for patients with clinically suspected onychomycosis is more cost effective than confirmatory testing with minimal effect on safety.

However, with more expensive treatments, laboratory testing should be done.

No laboratory diagnostic tests
Mikailov A et al JAMA Derm 2015 online Dec 23
**CURRENT TREATMENT OF ONYCHOMYCOsis**

<table>
<thead>
<tr>
<th>ORAL DRUGS</th>
<th>TOPICAL DRUGS</th>
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<tbody>
<tr>
<td>Terbinafine</td>
<td>10% efinaconazole solution</td>
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<tr>
<td>Itraconazole</td>
<td>5% tavaborole solution</td>
</tr>
<tr>
<td>Fluconazole*</td>
<td>8% ciclopirox lacquer</td>
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<tr>
<th>ORAL NEW DEVELOPMENTS</th>
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<tr>
<td>VT-1161</td>
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*not FDA approved*
Onychomycosis: Terbinafine

Toenail / Fingernail

3 MONTHS DAILY FOR TOENAILS, AND 6 WEEKS FINGERNAILS

JAAD 1997;37:740-45 Drake et al

38% cure rate for 3 months
Terbinafine Pulse Dosing*

- Zais and Rebell published 250 mg daily for one week for every other OR Third month until nail is healthy
  - Arch Dermatol 2004;140 (6):691-695

- Other dosing regimens: 500 mg daily for one week repeated monthly for 3 months or “pulses”
  - JAAD 2005;53 (4): 578-584

ALCOHOL ANALOGY

*Off label
Onychomycosis: Itraconazole

Month 1
- Week 1: 400 mg/d
- Week 2-4: 400 mg/d

Month 2
- Week 1: 400 mg/d
- Week 2-4: 400 mg/d

Month 3
- Week 1: 400 mg/d
- Week 2-4: 400 mg/d

Month 4
- Week 1: 400 mg/d
- Week 2-4: 400 mg/d

OR

Month 1
- Week 1: 200 mg/d
- Week 2-4: 200 mg/d

Month 2
- Week 1: 200 mg/d
- Week 2-4: 200 mg/d

Month 3
- Week 1: 200 mg/d
- Week 2-4: 200 mg/d

Month 4
- Week 1: 200 mg/d
- Week 2-4: 200 mg/d

Toenail/Fingernail

14% COMPLETE CURE

*Pulse dosage not approved for toenails
When to use itraconazole?

- Onychomycosis caused by non dermatophyte fungi
- Dermatophytes resistant to or non responsive to terbinafine
- Patients on no other oral medications to avoid drug drug interactions
Onychomycosis: Fluconazole

- 48% complete cure 450 mg/week until clear
- 46% complete cure 300 mg/week until clear
- 37% complete cure 150 mg/week until clear

JAAD 1998; 38:S77-86 Scher R. et al

**NOT** FDA APPROVED FOR THIS INDICATION
Once weekly dosing
Parallels the slow nail
Growth- manages
Patient expectations
## PHASE 3 CLINICAL STUDIES

<table>
<thead>
<tr>
<th></th>
<th>COMPLETE CURE</th>
<th>MYCOLOGIC CURE</th>
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</thead>
<tbody>
<tr>
<td>Terbinafine</td>
<td>38%</td>
<td>70%</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>14%</td>
<td>54%</td>
</tr>
<tr>
<td>Meltrex itra</td>
<td>22%</td>
<td>44%</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>37-48%*</td>
<td>47%-62%*</td>
</tr>
</tbody>
</table>

**NOT ALL PATIENTS ARE CURED**

Data Per Package label*

** Fluconazole not FDA approved for onychomycosis

Complete cure= normal nail, myc cure
VT–1161: A CYP51 INHIBITOR

- Novel potent inhibitor of fungal lanosterol demethylase (CYP51) and binds more tightly to fungal CYP51 than human CYP51
- Less potential for drug interaction than azoles due to less inhibition of P450 enzymes
- Broad spectrum activity - dermatophytes, Candida and molds
VT-1161

- Next-generation oral antifungal
- Very high penetration into nail
- Favorable oral PK profile; once-weekly dosing
- Robust safety profile to date
- EXCELLENT results thus far in phase 2 onychomycosis study

Novel “Tetrazole” Metal Binding Group
BASELINE AND 6 MONTHS: IMPROVED

VT-1161 ORAL ANTIFUNGAL
BASELINE AND 6 MONTHS LATER: CURED

VT-1161 ORAL ANTIFUNGAL
TOPICAL ONYCHOMYCOSIS TREATMENT

- SOLUTIONS:
  - Efinaconazole 10%
  - Tavaborole 5%
- Non-lacquer alcohol based therapies can be delivered on, under and around the nail bed
Mycologic cure mimics clinical experience

Elewski et al. JAAD Epub 2012.
Mycologic Cure Rates (Pooled Data)

Source: package insert terbinafine and itraconazole
Tavaborole 5% Solution: Outcome Measures at 52 Weeks

- **Complete Cure**
- **Mycologic Cure**

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<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
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<tbody>
<tr>
<td>Tavaborole</td>
<td>6.5%</td>
<td>31.1%</td>
</tr>
<tr>
<td>Vehicle</td>
<td>0.5%</td>
<td>9.1%</td>
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When infection is present
  - To rule out osteomyelitis
When tumor is present
  - To rule out invasive disease
62 year old man with about 1 year history of a thick fingernail that has become increasingly painful over the last few months.

He is concerned because he cannot trim the nail.

All other finger and toenail are normal.

Otherwise good health.
Onychomatricoma
Keratoacanthoma
Amelonotic melanoma
Squamous cell carcinoma
Verruca
What would you do next?

- Biopsy
- Xray
- Culture
- Treat for onychomycosis
What would you do next?

- Biopsy
- Xray
- Culture
- Treat for onychomycosis
Prominent soft tissue tumor with erosion and deformity of the distal phalanx
Verrucous carcinoma
Verrucous carcinoma invading into bone
Status Post Amputation
May need to rule out osteomyelitis
OBTAIN X-RAYS IN DIGITS WITH CHRONIC INFECTION TO R/O OSTEOMYELITIS

BONE DIRECTLY BENEATH NAIL UNIT WITHOUT SUBCUTANEOUS TISSUE
MRSA PARONYCHIA IN TRANSPLANT RECIPIENT
When Xray is Required

- Chronic infections
- Pain, tenderness
- Diabetics
- Immunocompromised
- Fails to respond to treatments
- Associated cellulitis
Diagnosis of onychomycosis - clinical only for oral terbinafine

Oral fluconazole, itraconazole and terbinafine do not cure everyone

Antifungal solutions may be effective and preferred

VT-1161 is a new oral antifungal with excellent potential in onychomycosis

Xray nails that may have a suspected malignancy prior to biopsy and in those high risk patients with chronic infections