ANTIFUNGAL THERAPY: NEW DEVELOPMENTS

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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, Sun, Valeant

OBJECTIVES

• Review NEW DEVELOPMENTS in the treatment of select cutaneous fungal infections
  - Malassezia:
    - Pityriasis (tinea) versicolor, Malassezia folliculitis, seb derm
    - Candidiasis
  - Update on treatment of onychomycosis including older oral antifungal drugs and newer topical agents
  - What to do with laboratory monitoring?

ANTIFUNGAL THERAPEUTICS 101

• Azole Family
  - Ketoconazole
  - Fluconazole
  - Itraconazole
  - Voriconazole (VT-1161)
• Allylamine family
  - terbinafine
• Griseofulvin

• Azole Family
  - Activity against yeasts, Candida, dermatophytes and non dermatophytes
• Allylamines and Griseofulvin
  - Anti-dermatophyte

Pityriasis Versicolor

MALASEZIA SPP.
Pityriasis (tinea) Versicolor

- Fluconazole 200 mg daily for 5-7 days
- Flu 300 mg once weekly for 2 weeks (98% cure rate)
- Itraconazole 200 mg daily for 5 days (100% cure rate)
- Oral terbinafine and griseofulvin are not effective
- Topical ketoconazole 2% shampoo and cream daily for 2 weeks
- Ketoconazole has best MICs for Malassezia

KETOCONAZOLE TABLETS

- July 2013 FDA withdrew indications for ketoconazole tablets
- Drug is still available, but no longer indicated for cutaneous fungal infections
- Does not effect ketoconazole cream or shampoo
- Substitute with another azole antifungal drug

KETOCONAZOLE TABLETS

- European Medicines Agency (CHMP) suspended usage of drug due to the conclusion that risk of liver injury is greater than benefit of antifungal treatment. July 2013
- Triggered by French authorities suspending the drug after a 2 year review

DO NOT ORDER

What about OTC treatment?

Aloe vera
Coconut oil
Oregano oil
Tea tree oil
Yogurt
Garlic
Home Remedies

Growth of Malassezia furfur on Sabouraud's dextrose medium in various oils

<table>
<thead>
<tr>
<th>Fatty Substance</th>
<th>Growth of M. furfur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butter</td>
<td>++++</td>
</tr>
<tr>
<td>Corn oil</td>
<td>+++</td>
</tr>
<tr>
<td>Olive oil</td>
<td>+++</td>
</tr>
<tr>
<td>Coconut oil</td>
<td>+++</td>
</tr>
<tr>
<td>Caster oil</td>
<td>++</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>++</td>
</tr>
<tr>
<td>Without oil</td>
<td>+</td>
</tr>
</tbody>
</table>

Key: ++++ = excellent growth  +++ = good growth  ++ = fair growth  + = poor growth


Growth of Malassezia is Enhanced With Certain Oils

Malassezia Folliculitis

PITYROSPORUM FOLLICULITIS

- Differential diagnosis of acne
- Acneiform pruritic monomorphic pustules on upper back and chest, occasionally face
- Diagnosis confirmed by skin biopsy showing organism in yeast state below level of epidermis

Malassezia Folliculitis

- Itraconazole 200 mg daily for 2 weeks - is lipophilic
- Fluconazole 200 mg daily for 2 weeks - not lipophilic
- Avoid oils to skin
Seborrheic Dermatitis

- Ketoconazole shampoo and cream

Avoid oils to face and scalp

Cutaneous Candidiasis

Fluconazole 200 mg for 5 to 7 days

Chronic paronychia—often caused by Candida

Acute paronychia caused by bacteria

Candida Paronychia

- Fluconazole 200 mg daily for 5 days then once weekly for 8 weeks (or until clear)
- Topical antifungal cream
  - Ciclopirox, ketoconazole or other azole cream
- Avoid cuticle manipulation to prevent recurrence

Avoid ketoconazole tablets

New developments in onychomycosis therapy
DISTAL LATERAL SUBUNGUAL ONYCHOMYCOSIS
FUNGUS IS UNDERNEATH THE NAIL PLATE AND NAIL PLATE IS NORMAL
DERMATOPHYTOSIS OF THE NAIL BED

CURRENT TREATMENT OF ONYCHOMYCOSIS

ORAL DRUGS
• Terbinafine
• Itraconazole
• Fluconazole*

TOPICAL DRUGS
• 10% efinaconazole solution
• 5% tavaborole solution
• 8% ciclopirox lacquer

*not FDA approved

ORAL NEW DEVELOPMENTS
VT-1161

TOPICAL ANTI FUNGALS

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

EFINACONAZOLE

• Triazole antifungal
  - New molecule
• Broad spectrum antifungal with activity against yeasts, molds and dermatophytes

Mycologic Cure (Week 52)

Study P3-01
Study P3-02

Mycologic cure mimics clinical experience
Mycologic Cure Rates (Pooled Data)

Source: package insert terbinafine and itraconazole

Proportion of Subjects

Cure likely higher if longer treatment duration

Elewski et al. JAAD Epub 2012.

Efinaconazole 10% Solution:

Complete Cure at Week 52

“FAILURES” AT STUDY COMPLETION: CURES LIKELY IF STUDY DURATION WAS LONGER

Tavaborole Study Design

• Similar to efinaconazole - applied once daily for 48 weeks in mild to moderate disease
• Differences in studies:
  - No upper age limit in tavaborole study
  - Nails were 20-60% involved in tavaborole vs. 20-50% in efinaconazole

BORON IS FOUND IN FOODS: FRUITS, VEGETABLES AND NUTS
Tavaborole 5% Solution: Outcome Measures at 52 Weeks


*p<0.001

Baseline Day 180 Day 240 Day 300

2.4mm 10.5mm 7.1mm 8.7mm

Baseline Day 180 Day 240 Day 360

3.7mm 14.1mm 8.2mm 8.0mm

Tavaborole Solution: Some Cures are Incorrectly Reported

Before Treatment (KOH+, Culture+)

Week 52 (KOH-, Culture-)

Week 52 (KOH+, Culture+)

Complete Cure

ORAL ANTI FUNGAL THERAPY FOR ONYCHOMYCOSIS

### Onychomycosis: Terbinafine

- **Month 1**: 250 mg/d
- **Month 2**: 250 mg/d
- **Month 3**: 250 mg/d
- **Month 4**: 250 mg/d

**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 THERAPY**

### Onychomycosis: Itraconazole

- **Month 1**: 400 mg/d
- **Month 2**: 400 mg/d
- **Month 3**: 400 mg/d
- **Month 4**: 200 mg/d

**OR**

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

**Toenail/Fingernail**: 14% COMPLETE CURE

*Pulse dosage not approved for toenails*

### Onychomycosis: Fluconazole

- **Month 1**: 48% complete cure 450 mg/week
- **Month 2**: 46% complete cure 300 mg/week
- **Month 3**: 37% complete cure 150 mg/week

**NOT FDA APPROVED FOR THIS INDICATION**

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

### Fluconazole

- **Once weekly dosing**
- Parallels the slow nail growth - manages patient expectations

**NOT ALL PATIENTS CURED WITH CURRENT SYSTEMIC AGENTS**
**PHASE 3 CLINICAL STUDIES**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Complete Cure</th>
<th>Mycologic Cure</th>
</tr>
</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>

*Data Per Package label*

**NOT ALL PATIENTS ARE CURED**

**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

**VT-1161 IS 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

**BASELINE AND 6 MONTHS: IMPROVED**

**BASELINE AND 6 MONTHS LATER: CURED**
Onychomycosis: Fill in the Gaps

- VT-1161 has activity against dermatophytes, Candida and molds and is more potent than itraconazole.
- Intermittent dosing similar to fluconazole.
- Phase 3 study coming soon.
- Likely to offer a viable option to patients with onychomycosis, particularly those who failed or did not respond to oral terbinafine.

What About Diagnosis? Is There a Gap?

- Empiric treatment with terbinafine for patients with suspected onychomycosis is more cost effective than confirmatory testing with minimal effect on safety.
- Confirmatory testing before efinaconazole will reduce costs across a range of disease prevalence.

TREAT EMPIRICALLY WITH ORAL TERBINAFINE

Mikailov A et al JAMA Derm 2015 online Dec 23

Laboratory Monitoring

- Hepatic risk for Terbinafine: 1:50K to 120K
- Trend away from routine monitoring
  - Isotretinoin
  - Spironolactone
  - Terbinafine

Mikailov A et al JAMA Derm 2015 Jander MK JAMA Derm 2015 online Dec 23

Laboratory Monitoring

- Baseline hepatic panel and CBC for terbinafine, itraconazole and fluconazole: is this needed?
  - Trend is away from routine monitoring
  - Liver injury is very rare
  - Most common cause of drug induced hepatitis is trimethoprim-sulfamethoxazole
  - Pulse dosing likely safer - alcohol analogy

Kanzler MK JAMA Derm 2015 online Dec 23

KEY POINTS

- Oral ketoconazole should not be used at all!
- Avoid topical oils in patient with Malassezia
- Topical efinaconazole and tavaborole are effective.
- VT-1161 is an oral tetrazole antifungal with excellent potential in onychomycosis.
- Empiric oral terbinafine is cost effective.
- Side effects can occur so choose your treatment with care.

THE END