Antifungal Drugs for Coccidioidomycosis

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Background on Olorofim

• Olorofim
  • Is a novel mechanism candidate antifungal drug\(^1\)
    • It inhibits DHODH (pyrimidine biosynthesis pathway)
  • It shows broad microbiologic activity vs. mould fungi
    • Low MICs vs. *Aspergillus* spp., *Lomentospora prolificans*, *Scedosporium* spp., *Fusarium* spp., *Coccidioides* spp., and others
    • Fungicidal effects in vitro (*Aspergillus*) and in vivo (*Coccidioides*)\(^2,3\)
  • Dosed by mouth (30-mg tablet), it has FDA Breakthrough Therapy Designation based on
    • “preliminary clinical evidence indicating that it may ...
    • demonstrate substantial improvement over existing therapies ...
    • on one or more clinically significant endpoints.”
  • Now in an open-label Phase 2 study (NCT03583164) of mould IFD\(^4\) in patients with limited treatment options

\(^1\) Oliver JD et al. (2016). "F901318 represents a novel class of antifungal drug that inhibits dihydroorotate dehydrogenase." PNAS USA 113: 12809-14.
\(^4\) IFD = Invasive Fungal Disease
How to design a Cocci RCT?

• Day 42 All-Cause Mortality is OK for acute pulmonary IA\(^1\)
  • But it is a blunt tool that gets entangled with underlying disease\(^2\)
  • It doesn’t work at all for infections that progress inexorably but slowly

• EORTC-MSG defined an Overall response endpoint\(^3\)
  • Overall is built from clinical, radiological, & mycological responses
  • Overall Success logically requires improvement on all 3 sub-elements
  • Failure is likewise obvious

• But, the category of Stable is defined as a Failure
  • A patient with a Clinical Response but with < 25% radiologic improvement is scored as Failure-Stable

• This works well for pulmonary IFD, especially IA
  • It works poorly for disseminated coccidioidomycosis
  • Symptoms improve months before radiologic and mycologic response

• Alternative measures are needed; a PRO\(^4\) is proposed

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1. IA = Invasive Aspergillosis
4. PRO: Patient-Reported Outcome based on disease symptoms
Lengthy therapy is required for disseminated coccidioidomycosis

• Ongoing Phase 2 study of proven IFD$^{1,2}$
  • As of 22 Jul 2020, 7 patients enrolled with symptomatic coccidioidomycosis (lung, CNS, bone, skin) despite significant prior therapy with existing agents
  • Dosing durations: 10, 42, 79, 274, 310, 379, and 434 days

• Clinical improvement noted within 1-4 weeks – major improvement in activities of daily living and functional mobility

• Radiologic and mycologic (serologic) findings improve only very slowly

• A case is instructive…

1. Probable IA per EORTC-MSG 2008/2019 is also permitted.
2. F2G, Limited, data on file: Duration of dosing from the ongoing Phase 2 study (clinicaltrials.gov: NCT03583164) as of 13 July 2020.
Case of coccidioidomycosis

- Oct 2018: Pulmonary & CNS cocci: 45-year-old man with diabetes
- Mild CNS disease but multiple admissions for respiratory symptoms
  - Progressive dyspnea, weakness, fatigue, fever; Supplemental oxygen required
  - Fluconazole → voriconazole → posaconazole+AmBisome → posaconazole+micafungin
- 16 May 2019: Enrolled on study, Olorofim + posaconazole begun
- Improved steadily. By 8 Aug 2019 (Day 85):
  - Cough & malaise improved; other symptoms resolved
  - No longer needed supplemental O₂ or a cane to walk
  - Can do all activities of daily living
  - Cocci CF down to 1:32 from baseline of 1:64
  - EORTC Clinical Response: Success-Partial
  - EORTC Overall Response: Failure-Stable
- 17 Jan 2020 (Day 247): Continues to improve
  - Cocci CF titer down to 1:16
- 2 Jul 2020 (Day 414): Continues to feel well
  - Cocci CF titer stable at 1:16

2020-08-05 F2G comments at FDA Valley Fever workshop

Harvey 2020 ECCMID, Abstract #3203: Successful use of the novel antifungal olorofim in the treatment of disseminated coccidioidomycosis
If not EORTC-MSG, then what?

• Exploratory use of the EQ-5D-5L Health Index¹
  • A 5-level health index in 5 dimensions
  • 5D: Mobility, Self-Care, Activity, Pain, Anxiety-Depression
  • 5L: Scored 1-5: 1 = None vs. 5 = Severe limitations/issues
  • Extensively validated, available in 130 languages
  • Can convert to a Health Status Index; can inform QALY estimates

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<tr>
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<td>Unable</td>
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<td>Extreme</td>
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</table>

On the EQ-5D-5L scale, the patient improved steadily²
• Baseline: 43433
• Day 43: 33333
• Day 85: 11221

1. https://euroqol.org/
2. For this patient, scores were estimated retrospectively. In later patients, data have been collected prospectively and show similar patterns
Design conclusions

• EORTC-MSG defined a global response endpoint\(^1\)
  • Despite evident clinical improvement, patients are scored as Failure-Stable due to lags in radiology and serology\(^2\)

• Further, disseminated coccidioidomycosis is diverse
  • Brain, bone, lung, and other sites are all possible
  • Infections at these sites have different symptoms

• Our preliminary data show benefits in terms of simple activities of daily living using EQ-5D-5L
  • A PRO\(^3\) appears useful. EQ-5D-5L? NIH PROMIS?
  • Cocci-specific elements may not be needed given (i) the varied disease syndromes and (ii) the preliminary data

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3. PRO: Patient-Reported Outcome based on disease symptoms; NIH PROMIS: [https://www.healthmeasures.net/explore-measurement-systems/promis](https://www.healthmeasures.net/explore-measurement-systems/promis)