Antifungal Drugs for Coccidioidomycosis

John H. Rex, MD

Chief Medical Officer, F2G Limited

5 Aug 2020 FDA Workshop

The Rare Fungal Disease Company

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.
2. du Pre, S., et al. (2018). "Effect of the Novel Antifungal Drug F901318 (Olorofim) on Growth and Viability of Aspergillus fumigatus." AAC 62(8): e00231-18.
3. Wiederhold, N. P., et al. (2018). "The Orotomide Olorofim Is Efficacious in an Experimental Model of Central Nervous System Coccidioidomycosis." AAC 62(9): e00999-18.
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

1. IA = Invasive Aspergillosis
2. Wingard, J. R., et al. (2008). "Changes in causes of death over time after treatment for invasive aspergillosis." Cancer 112(10): 2309-2312.
3. Segal BH et al. (2008). "Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses study group and European Organization for Research and Treatment of Cancer consensus criteria." Clin Infect Dis 47(5): 674-683.
4. PRO: Patient-Reported Outcome based on disease symptoms

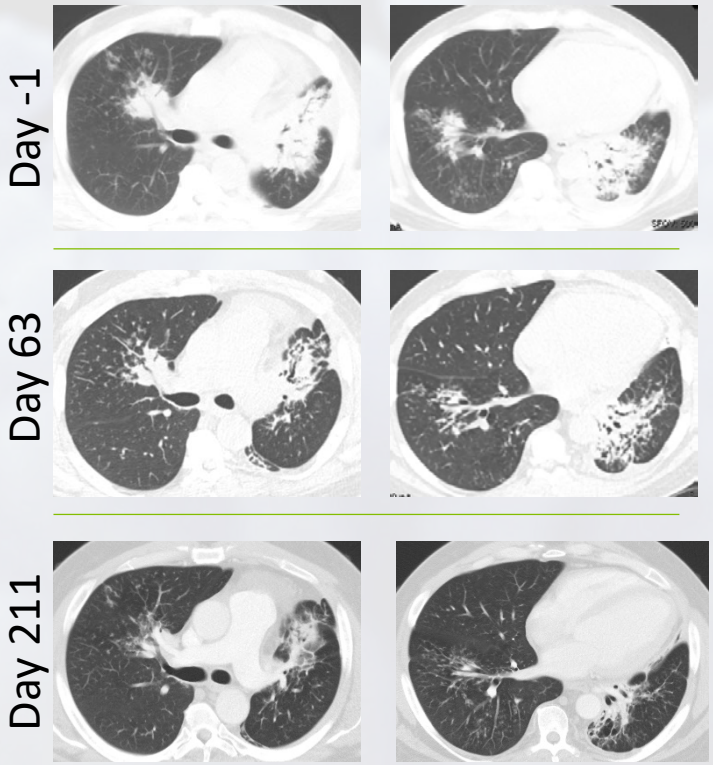
Lengthy therapy is required for disseminated coccidioidomycosis

- 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 O_2 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



Harvey 2020 ECCMID, Abstact #3203: - Successful use of the novel antifungal olorofim in the treatment of disseminated coccidoiodomycosis

If not EORTC-MSG, then what?

- Exploratory use of the EQ-5D-5L Health Index[1]
  - 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

Baseline

EQ-5D	Mobility	Self-Care	Activity	Pain	Anxiety
1	None	None	None	None	None
2	Slight	Slight	Slight	Slight	Slight
3	Moderate	Moderate	Moderate	Moderate	Moderate
4	Severe	Severe	Severe	Severe	Severe
5	Unable	Unable	Unable	Extreme	Extreme

Day 43

EQ-5D	Mobility	Self-Care	Activity	Pain	Anxiety
1	None	None	None	None	None
2	Slight	Slight	Slight	Slight	Slight
3	Moderate	Moderate	Moderate	Moderate	Moderate
4	Severe	Severe	Severe	Severe	Severe
5	Unable	Unable	Unable	Extreme	Extreme

Day 85

EQ-5D	Mobility	Self-Care	Activity	Pain	Anxiety
1	None	None	None	None	None
2	Slight	Slight	Slight	Slight	Slight
3	Moderate	Moderate	Moderate	Moderate	Moderate
4	Severe	Severe	Severe	Severe	Severe
5	Unable	Unable	Unable	Extreme	Extreme

On the EQ-5D-5L scale, the patient improved steadily[2]

- 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

1. Segal BH et al. (2008). "Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses study group and European Organization for Research and Treatment of Cancer consensus criteria." Clin Infect Dis 47(5): 674-683.
2. Galgiani, J. N., et al. (2020). "Treatment for Early, Uncomplicated Coccidioidomycosis: What Is Success?" Clin Infect Dis 70(9): 2008-2012.
3. PRO: Patient-Reported Outcome based on disease symptoms; NIH PROMIS: https://www.healthmeasures.net/explore-measurement-systems/promis