Developing Therapies for Coccidioidomycosis: A Developer's Perspective

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NASEM Valley Fever Workshop

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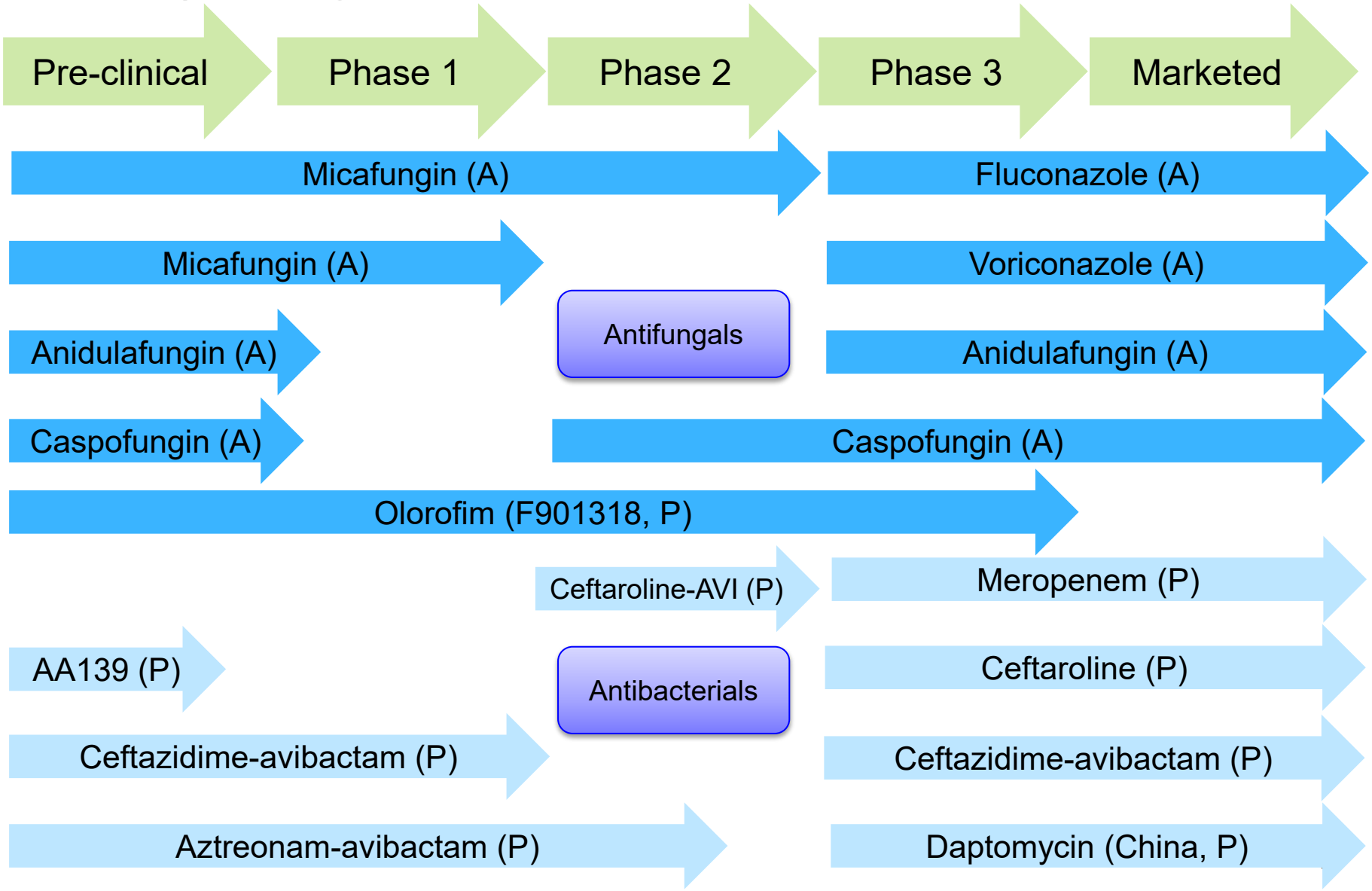
Please note these details!

Slides happily shared … drop me a note!

Agenda

- Scope and Disclosures
  - A focus on new drugs; I am the CMO of F2G
- Key Regulatory Principles
  - Required background: 5 Aug 2020 FDA workshop
- Preclinical Issues: Getting ready for human studies
  - Manufacturing, Safety, Dose Selection
- Trial Design: Populations, Endpoints
  - Many hard choices here – no easy answers
- Summary

At heart, I'm an ID doc who wants new antibacterials and antifungals. My comments come from this experience:



Rex JH - Drug Development History, (A)cademia & (P)harma

Scope, Disclosures

- My focus today is on **new** therapies for coccidioidomycosis
  - Current drugs with clinical activity are limited to two classes (azoles, amphotericin)
  - These agents require lengthy courses of therapy and are not uniformly curative
  - I think progress in treating cocci will require new therapies
  - *(Prevention would be better!)* Vaccines are covered in other talks
  - I am also (at times) going to broaden the discussion to cover Invasive Fungal Infections (IFIs) in general as I think this is useful
- I work at F2G, a company that has novel antifungal in development (F901318, olorofim)
  - I won't discuss olorofim today
  - But I will briefly mention work that we are doing on a PRO tool for coccidioidomycosis

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5 Aug 2020 FDA Public Workshop on Developing for Valley Fever

- Required reading
  - Online materials:
    - https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/coccidioidomycosis-valley-fever-considerations-development-antifungal-drugs-08052020-08052020
  - Published workshop summary
    - O'Shaughnessy E et al. FDA Public Workshop Summary-Coccidioidomycosis (Valley Fever): Considerations for Development of Antifungal Drugs. Clin Inf Dis 2022;74:2061-6
- Let's look at a few slides from FDA's presentation

Drugs for Treatment of Coccidioidomycosis

- FDA-approved: Ketoconazole, Amphotericin B deoxycholate
- Standard of care (not FDA-approved): Fluconazole, itraconazole
- Other (not FDA-approved): Voriconazole, posaconazole, etc.
- Investigational drugs in human studies/animal models e.g., VT-1598, NikkomycinZ, Olorofim, APX-001 (*see weblinks in references slide)*
- No approved new drug application (NDA) in > 20 years

Key takeaways

- *What comparator? Modern SOC agents are not approved for cocci and approved agents are non-starters as modern therapy*
- *FDA has flexibility to permit use of modern SOC (see III.B in FDA guidance on "Expedited Programs for Serious Conditions"*

Slide is from the FDA presentation given by O'Shaughnessy, Joshi, and Bala (https://www.fda.gov/media/141113/download)

Regulatory Pathways

- Traditional approval
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- Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD)
  - For drugs that are intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs
    - Examples: Pretomanid and Arikayce (liposomal amikacin inhalation suspension) were approved under the LPAD pathway

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Key takeaways

- *All pathways require "substantial evidence of efficacy based on adequate and well-controlled clinical investigations"*

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Key takeaways

- *All these pathways require "substantial evidence of efficacy based on adequate and well-controlled clinical investigations"*
- *Let's expand a bit on endpoints*

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Endpoints

- Quiz: Pick the valid endpoints for drug approval
  - All-cause mortality
  - Improvement of signs/symptoms of pneumonia
  - Drop in HIV viral load
  - Conversion of blood cultures to negative in endocarditis
  - Fall in serum cocci comp fix titer from 1:16 to 1:2

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  - Improvement of signs/symptoms of pneumonia[a]
  - Drop in HIV viral load[b]
  - Conversion of blood cultures to negative in endocarditis
  - Fall in serum cocci comp fix titer from 1:16 to 1:2
- Key: An endpoint[1] must either be a reliable and reproducible measure of how a patient "feels, functions, or survives" *OR* it must be a surrogate marker for how a patient *will* "feel, function, or survive"[2]
  a. These are **classic clinical** endpoints. ACM is easy to measure; symptom-based endpoints require careful consideration and should have obvious clinical relevance
  b. This is a well-defined **surrogate** endpoint and was used for many years as the basis for accelerated approval in the US.[3,4]

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2. The IOM's 2010 biomarker report (https://www.ncbi.nlm.nih.gov/books/NBK220297/) is a good read as is FDA's 2018 draft biomarker guidance (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/biomarker-qualification-evidentiary-framework).
3. The 2015 FDA guidance on approval of HIV products contains a fascinating history of how viral load went from surrogate (for Accelerated) to surrogate (for changes after 24 weeks) to being so well validated that it now accepted for standard approval. Go here to read it: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-immunodeficiency-virus-1-infection-developing-antiretroviral-drugs-treatment
4. Other uses of surrogate endpoints have been seen with bedaquiline for MDR TB (time to sputum culture conversion) and inhaled amikacin for refractory MAC (again, sputum culture conversion).

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Laboratory data are not used unless they can be tightly linked to disease state and progression. Yes, there is a general sense of a connection but the 1:1 character of HIV viral load is usually not present.

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Endpoints

- Endpoints should be well-defined and reliable
  - A clinical endpoint directly measures a therapeutic effect of a drug - an effect on how a patient feels (e.g., symptom relief), functions (e.g., improved mobility), or survives
  - A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure such as serology, that is likely to predict clinical benefit, but is not itself a measure of clinical benefit 21 CFR 314.126(b)(6)
- Clinical endpoints for Coccidioidomycosis
  - Will depend on spectrum of clinical presentations (localized vs. disseminated disease), characteristics of patient population
  - May include a patient reported outcome (PRO) measure
  - Cocci scoring system (CCS) has been used in published clinical trials
  - If a biomarker of disease is proposed, for example, a serological marker, *Coccidioides* DNA by PCR, it should be reasonably likely to predict clinical benefit

Key takeaways

- *"Well-defined and reliable" is a key phrase*

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Key takeaways

- *"Well-defined and reliable" is a key phrase*
- *No one symptom (or small group of symptoms) can capture the incredible diversity of the manifestations of cocci*
- *Composite endpoints are tricky … hard to weight the elements*

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Key takeaways

- *"Well-defined and reliable" is a key phrase*
- *No one symptom (or small group of symptoms) can capture the incredible diversity of the manifestations of cocci*
- *Biomarker must be "reasonably likely to predict clinical benefit"*

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Key takeaways

- *All these pathways require "substantial evidence of efficacy based on adequate and well-controlled clinical investigations"*
- *Let's expand a bit on endpoints*
- *Let's also look more closely at LPAD*

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LPAD: *Use this if possible!*

- Limited Population Antibacterial and Antifungal Drug
  - *LPAAAD!* Drug for **Serious or life-threatening** infection in a **limited population** with an **unmet need**
- Permits FDA to approve if there is
  - "a **positive benefit-risk** balance in the **limited population**, …
  - "… even though **insufficient data exist** to conclude that there is a favorable benefit-risk profile **in a broader population**.
  - "FDA will take into account the severity, rarity, or prevalence of the infection that the drug is intended to treat."
- This is not an easier pathway or way to fix a failed program
  - **As for any approval**, must provide **substantial evidence of effectiveness** and sufficient information to show safe use as labeled
  - But, it is a valuable support when seeking to develop for rare infections
- Drugs approved to date using LPAD
  - Inhaled amikacin for refractory *M. avium*; Pretomanid for XDR-TB

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The big question: **Is it a drug?**

- It's easy to kill bacteria and fungi
  - Steam, fire, and bleach are very effective
- **Selective killing is a subtle art**
  - Good checklist: AAC Instructions to Authors
    - https://journals.asm.org/journal/aac/scope
  - This 3-part newsletter series on halicin
    - https://amr.solutions/2020/02/21/chemicals-vs-drugs-the-end-of-bacitracin-the-buzz-around-halicin/
    - https://amr.solutions/2020/02/24/chemical-vs-drugs-part-2-how-do-you-discriminate-more-on-halicin/
    - https://amr.solutions/2020/02/25/chemicals-vs-drugs-part-3-xkcd-has-the-final-word/

- Let's take a brief tour of some key points
  - *Invisible from the outside, Pharma has a lot of important plumbing!*

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Can you make it? CMC[1]

- How does a molecule become a physical medicine (tablet, injectable, etc.) to give to a human?
- You must plan for
  - Early materials for preclinical studies
  - GMP (Good Manufacturing Practice) materials for human studies
  - Sufficient quantity at scale & on stability of the materials for Ph3 and registration
  - Avoid changes in formulation late in the game as this can lead to a need for more non-clinical studies / bridging studies
- **This is a science unto itself**
- Advice: Start early! Have a CMC guru on your team
  - Great CARB-X + GARDP workshop from 2017 on this:
  - Search for “amr.solutions 2017 bootcamp”

[1]Chemistry, Manufacturing, & Controls

What dose? PK, ADME, and PD

- PK: Where does it go? What happens to it?
  - ADME: Absorption, Distribution, Metabolism, and Excretion
  - Does it go to the right body compartments?
  - How many doses/day? Is it oral?
    - ***For cocci, it really has to be oral (IV would be a nice-to-have)***
  - Does it have (is it likely to have) drug-drug interactions?
  - **You can't really know the answers in detail until P1**, but you can make guesses once you have some PK in some animal species
- PD (Pharmacodynamics): What concentration do you need?
  - Strong PK-PD is a key support for smaller programs
  - Deciding on a target exposure is a subtle art – see Hope 2016[1]
  - ***Animal models for cocci exist*** but require specialized facilities

1. Hope W, Drusano GL, Rex JH. Pharmacodynamics for antifungal drug development: an approach for acceleration, risk minimization and demonstration of causality. JAC 71:3008-19, 2016

Is it safe? Toxicology

- In addition to an array of in vitro safety assays[1], you need to study supratherapeutic exposures of new agent *and its metabolites* in 2 animal species
- Invasive fungal infections often require prolonged therapy: **your in vivo studies must span relevant periods[2]**
  - 0-90 days of exposure: day-for-day coverage in man
  - 180-270 days: enough for indefinite exposure
  - **Big implications for cocci** as long-term therapy (6 months or more) will almost certainly be needed: must plan for adequate drug supply and adequate time to get the studies done!
- Metabolites can be tricky. You can try to predict human metabolites but you don't *know* until Ph1
  - Sometimes you need additional studies

1. There are multiple non-clinical assays available that help you look for off-target effects
2. See ICH M3 (R2) … there tables on required durations in Sections 5.1 and 5.2. Carcinogenicity studies will also be needed, but these can usually be deferred to run in parallel with P3 or later

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Trial populations

- You've got a candidate compound
  - An oral formulation is available (and maybe also an IV formulation)
  - PK in Phase 1 gives exposures in your target range
  - Tox data at least to day 90 and safety looks acceptable
- Does the spectrum permit study of other fungi?
  - If so, this may be a far easier path!
  - If nothing else, perhaps you do P2 dose-finding with another fungus
- But, at some point you decide you want to do a controlled study in cocci
  - Let's start with the goal of an RCT
  - We need to consider a lot of questions: study population, comparator, duration, and endpoint

Possible RCT trial populations

- Primary uncomplicated pneumonia (PUP)
  - Con: Hard to diagnose (seromarkers develop slowly).
    - Con: Relative to other forms, this might make LPAD harder to use
  - Con: Presentation is entangled with CABP
    - FLEET[1] showed how hard it is to disentangle
  - Con: Safety, lack of DDIs[1] needed to enable enrollment
  - Pro: Superiority might be possible based on time to improvement: Observational data suggest that azoles have little effect[2,3]
  - Pro: Low medical risk if new agent fails to perform
- Chronic fibronodular/fibrocavitary (CFN-FC)
- Non-CNS complicated: Extrapulmonary and progressive pulmonary (EP-PP)
- CNS (meningeal, CM)

(1) Messina JA et al. Contemp Clin Trials Commun 2021;24:100851. (2) Blair JE et al. Emerg Infect Dis 2014;20(6):983-90. (3) Ampel NM et al. Clin Infect Dis 2009;48(2):172-8.

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  - Pro: Azoles seem to have some effect[1] but therapy needs to be ≥ 1 year and there is a 30% recurrence rate[2]
  - Pro: Superiority design (maybe): ↓duration, ↓recurrence
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  - Pro: Medium medical risk if the new agent doesn't perform
  - Con: Bone seems harder to treat[1] – study separately?
  - Pro/Con – Superiority design (time to response or cure)? Azoles have some effect[2] but responses take months and recurrence is a problem. This leaves room for improvement!
  - Pro: Has good potential for LPAD-based approval
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  - Pro: The most challenging form: If the new agent works, that's very impressive
  - Pro/Con – Superiority design? Fluconazole has some effect[1] but responses take months. It's not clear how you'd know to stop[2] There's real room to improve here!
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Endpoints (1 of 2): Classical ideas

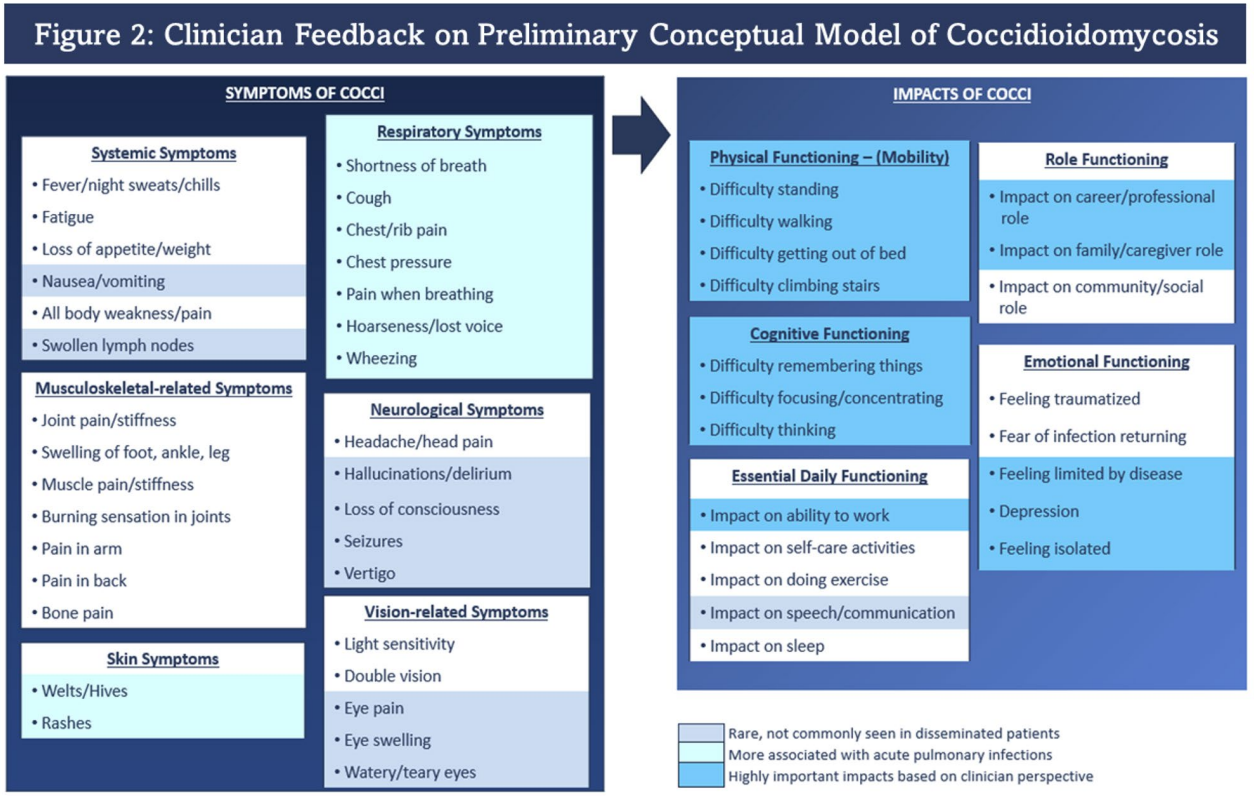
- EORTC-MSG[1] Score: Traditional endpoint design
  - Overall based on Clinical, Radiological, and Mycological response
    - Success requires improvement in all 3 sub-domains
  - Strength: Very simple, makes intuitive sense
  - Flaw: Slow serological/mycological clearance in cocci (months to years)[2] limits best Overall Score to Stable … which is a Failure
  - Fixes: Focus on Clinical Response
- Point-based ideas: Success defined in % point reduction
  - MSG Score (multiple iterations[3,4]): Points for symptoms, involved sites, +cultures, magnitude of seropositivity
  - FLEET Score[5]: Points for symptoms, fever, hypoxia
  - Flaw: Assumes points are additive … does obtunded (3 points) really equal CSF comp fix titer of 1:16 (3 points)?

(1) Segal BH et a. Clin Infect Dis 2008;47(5):674-83. (2) McHardy IH et al. J Clin Microbiol. 2018;56(12). (3) Catanzaro A et al. Am J Med 1983;74(1B):64-9. (4) Galgiani JN et al. Ann Intern Med 1993;119:28-35. (5) Messina JA et a. Contemp Clin Trials Commun. 2021;24:100851.

Endpoints (2 of 2): PRO[1] tool

amr.solutions

- No PRO exists for coccidioidomycosis[2]
- With an FDA grant, F2G are developing a PRO
- The goal is a PRO capturing relevant aspects of how a patient with cocci feels and functions



Excerpt from Harvey et al., "Developing a Patient-Reported Outcome (PRO) Instrument for Coccidioidomycosis: The Importance of Clinician Feedback". Abstract at MSGERC 2022 (7-9 Sep 2022, Albuquerque).

(1) PRO = Patient-Reported Outcome. (2) Multi-purpose PROs exist (EuroQol EQ-5D-5L, PROMIS) but exploratory work with these tools suggest that they did not appear to be sensitive/specific measures for coccidioidomycosis.

And we also have to solve for…

- Duration: When do you measure the endpoint?
  - At least with azoles, this is a very slow disease
  - Intervals of 4 months have been used in multiple studies
  - What about relapse? Would add years to trials
- Effect size with these endpoints at that duration
  - Whatever endpoint we choose, we need good estimates of effect size, preferably relative to placebo
  - This is a substantial research project!
- And for any given new drug
  - How do you develop Phase 2 dose-finding data to inform Phase 3?
  - What comparator in the RCT?
- Net: Initiating an RCT in cocci is very, very hard

Does it have to be an RCT?[1]

Reasons not to RCT

- We (genuinely) don't need to…
  - There are settings where treatment effects are unequivocal, and magnitude can be understood, without a concurrent control arm
    - Usually where the **effect without treatment is entirely and accurately predictable**, e.g., regression of tumors, reaching developmental milestones in spinal muscular atrophy, survival in ADA-SCID etc.
    - Where an external dataset exists against which **a comparison can be made that can be demonstrated to be reliable**
- We (genuinely) can't…
  - … ethics, operational aspects …
  - rarity … "underpowered" RCTs?
  - Many issues here
- We don't want to / can't afford to …
  - That's different…

1. Slide borrowed/adapted with thanks from Rob Hemmings based on a talk he gave during the 2021 Trends in Medical Mycology meeting

Single-arm trial (SAT) ideas[1]

- SATs when outcome without treatment is reliably predictable (baseline controls, ICH E10)
  - Tumors do not spontaneously regress
  - Endocarditis does not cure itself. **Ditto extrapulmonary cocci**
  - Superiority is shown relative to expected lack of response
- SATs with external controls
  - SAT compared with external controls with similar characteristics
  - Provides comparative context on the SAT data
- These approaches are mutually complementary
  - Both approaches are biased – must accept this – **but that doesn't mean the data are uninterpretable**
  - Unlikely to see 0% vs. 100%, but a large effect can be compelling in a setting with an obvious counterfactual (what would have happened otherwise)

1. Ideas borrowed with thanks from Rob Hemmings based on a talk he gave during the 2021 Trends in Medical Mycology meeting

Agenda

- Scope and Disclosures
  - A focus on new drugs; I am the CMO of F2G
- Key Regulatory Principles
  - Required background: 5 Aug 2020 FDA workshop
- Preclinical Issues: Getting ready for human studies
  - Manufacturing, Safety, Dose Selection
- Trial Design: Populations, Endpoints
  - Many hard choices here – no easy answers
- Summary

Key messages

- Developing a new drug for cocci is surprisingly hard
- Basic requirements are substantial
  - Must be oral (IV is nice-to-have)
  - Must have safety data for very long durations of dosing
  - Must have substantial drug supply to support both the animal safety studies and studies in man
- Clinical requirements are very substantial
  - There are no easy trial populations for an RCT
    - And this means that Phase 2 dose-finding studies are hard
  - There are no standard comparators
  - Available endpoint tools are limited as are performance data (effect size at best timepoints) with those tools

Big Picture: We need an updated consensus on what is adequate for IFI[1]

- "Regulatory hurdle" is not a great phrase
  - Try to avoid using it! **The desire for better data is universal!**
  - But when you hear "we need an RCT," think about (i) feasibility and (ii) what you can learn from / know about natural history of the infection
- There is no easy fix for the challenge of rare pathogens such as cocci
  - RCTs always study a limited subset of the patients of interest: *Only those who consent at your sites! Moving patients to a master site is hard!*
  - Superiority is sometimes proposed as it does permit small sample sizes (if the effect size is large) but this is not (usually) a fix – no one wants to be randomized to inappropriate therapy – we always want to try something
- **We (as a community) have to engage on this**
  - The relatively rare nature of fungal infections makes this particularly critical if we are to develop new antifungal therapies
  - The core question: What is enough data to establish benefit-risk for rare (orphan drug frequency) infections? How far can we stretch statistical boundaries ($p < 0.10$, for example)?

1. IFI = Invasive Fungal Infections; I am going to generalize here beyond cocci as I think the conversation requires a big picture.

Thank you!