Overview of Clinical Trials for Coccidioidomycosis Drug Development

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A very brief review of Clinical / Immunological Aspects of Cocci

1. Comment of clinical complexity of coccidioidal disease and response to treatment
2. Brief review of Immune status in Coccidioidomycosis
    1. Transfer Factor Treatment
3. Brief Review of early drug treatment trials

Immune defect in Cocci patients

- Delayed Type Hypersensitivity (skin testing)
  - When impaired mortality higher
- Cell Mediated Immunity (T cell function)
  - impaired in severe pulmonary and disseminated disease
- Immune reaction similar to concept proposed by Ward Bullock in Leprosy
- Transfer Factor described by Sherwood Lawrence in 1955
  - Set of proteins <5000 Daltons
  - Transfer DTH & CMI

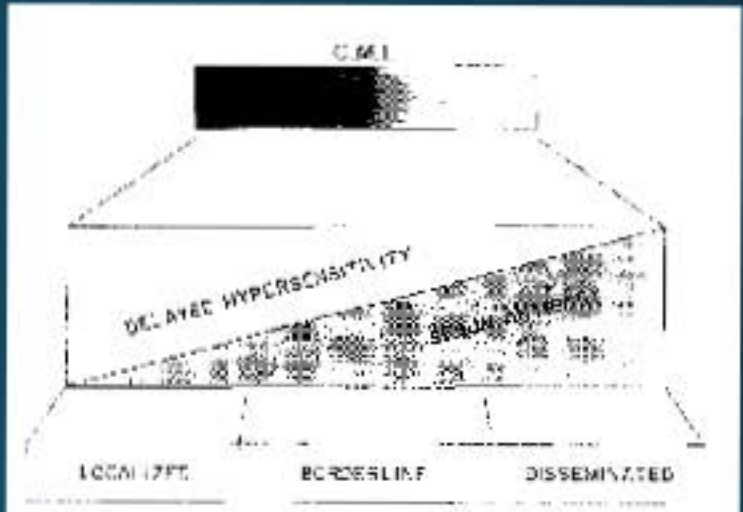

Fig. 1. The immunologic spectrum of chronic intracellular infectious diseases. CMI = cell-mediated immunity. Reproduced with permission from Bullock, W. E.: Anergy and Infection, in Stollerman, G. H.: *Advances in Internal Medicine*, vol. 21, Year Book Medical Publishers, Inc., Chicago, 1976.

Development of Immunologic and Clinical Staging for Immunotherapy

Antonino Catanzaro, M.D.
for the
Coccidioidomycosis Cooperative Treatment Group

- Together we treated 49 patients
  - All were failing on amphotericin
  - Transfer Factor added to ongoing treatment with amphotericin
    - 30 had a favorable response
    - 12 improvement dramatic and clearly associated with administration of TF
    - 19 failed to respond
      - 4 actually deteriorated

- Each patient served as his own control
- Linear studies

- No Control Group !

CLINICAL AND IMMUNOLOGIC RESULTS

OF TRANSFER FACTOR THERAPY IN COCCIDIOIDOMYCOSIS[1]

Presented by Antonino Catanzaro, M.D. and Lynn Spitler, M.D.
For the Coccidioidomycosis Cooperative Treatment Group (CCTG)[2]

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Research Corporation
Pulmonary SCOR USPHS HL 14169-05
General Clinical Research Center
GCRC/PHSRR00827-01

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San Diego: Dr. Antonino Catanzaro
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San Diego Naval Regional Medical Center:
Dr. Victor Iacovoni
Dr. Richard Schillaci
Stanford: Dr. David Stevens
Dr. Stanley Deresinski
Bakersfield: Dr. Hans Einstein

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University of Texas at San Antonio: Dr. David Drutz
Dr. Richard Crayhill
Dr. Daniel Tosi
San Antonio State Chest Hospital: Dr. Rebecca Cox
Dr. Joseph Vivas
Wilford Hall USAF Medical Center: Dr. Charles Coltman
Dr. Charles Ellenbogen
Dr. Ken McAlester
Dr. Jay Bearden
Brooks Army Medical Center: Dr. Theodore McNitt
Dr. Russell Steele

Maryland
National Institutes of Health: Dr. Charles Kirkpatrick

Turning the tide on TF treatment of Cocci

- NIH declined to fund a trial of TF in the treatment of Cocci
- The Cocci Cooperative Treatment Group did a small unfunded trial
- We set up 3 groups
  - TF for Coccidioidin positive donors
  - TF for Coccidioidin negative donors
  - Normal Saline Negative control
- Unable to tell which group a patient was in by
  - Skin test results
  - In vitro lymphocyte transformation test
  - Clinical results

Azoles Treatment Trials

1. Ketoconazole for Treatment of Chronic Pulmonary Cocci
2. Ketoconazole for Treatment of Disseminated Cocci
3. Treatment of Cocci with Ketoconazole- An Evaluation Utilizing a New Scoring System
4. Fluconazole Penetration into CSF in Humans
5. Fluconazole in the Treatment of Persistent Cocci
7. Fluconazole Therapy for Cocci Meningitis
8. Fluconazole in the Treatment of Chronic Pulmonary and Nonmeningeal Disseminated Cocci
9. Comparison of Oral Fluconazole and Itraconazole for Progressive, Nonmeningeal Cocci
10. Safety, Tolerance and Efficacy of Posaconazole Therapy in Patients with Nonmeningeal Disseminated or Chronic Pulmonary Cocci
11. Posaconazole Therapy for Chronic Refractory Cocci

Ketoconazole for Treatment of Chronic Pulmonary Coccidioidomycosis

J. BURR ROSS, M.D.; BERNARD LEVINE, M.D.; ANTONINO CATANZARO, M.D.; HANS EINSTEIN, M.D.; RICHARD SCHILLACI, M.D.; and PAUL J. FRIEDMAN, M.D.; Phoenix, Arizona; and San Diego and Los Angeles, California

- 37 Patients with chronic pulmonary cocci minimum 12 months Ketoconazole 400 mg/day
  - 21 Patients with Chronic Infiltrative disease some with cavitation
  - 16 with chronic cavitary cocci
    - Clinical response
      - 9 improved
      - 3/9 converted sputum culture
      - 4 no change
      - 3 deteriorated
    - Radiographs
      - Improved in 2
      - No change in 12
      - Deteriorated in 2
  - Serology
    - Improved in most
- Patients will infiltrative disease did much better than those with chronic cavities

Annals of Internal Medicine. 1982;96:440-443.

Ketoconazole for Treatment of Disseminated Coccidioidomycosis

ANTONINO CATANZARO, M.D.; HANS EINSTEIN, M.D.; BERNARD LEVINE, M.D.; J. BURR ROSS, M.D.; RICHARD SCHILLACI, M.D.; JOSHUA FIERER, M.D.; PAUL J. FRIEDMAN, M.D.; San Diego and Los Angeles, California; and Phoenix, Arizona

35 patients with Disseminated Cocci treated with Ketoconazole 400 mg/day

		Improved on Rx
Synovitis	8	7
Osteomyelitis	8	3
Abscess or fistula	10	8
Skin	9	6

Follow up	Persistent lesion
Synovitis	1
Osteomyelitis	5
Abscess or fistula	5
Skin	3

Annals of Internal Medicine. 1982;96:436-440.

Treatment of Coccidioidomycosis with Ketoconazole: An Evaluation Utilizing a New Scoring System

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TABLE I Clinical Scoring System

Symptom	Score
Fever	1
Pain	1
Productive cough	1
Hemoptysis	1
Swelling	1
Pleural rub	1

TABLE II Chest Radiograph Scoring System

	Score
Size	
Less than 5 cm	1
Less than right upper lobe zone	2
More than above	3
Spread	
Unilateral	1
Bilateral	2
Miliary	3
Cavitation	1
Hilar adenopathy	1
Mediastinal adenopathy	2
Small effusion	1
Large effusion	2

TABLE III Serology Scoring System

Complement Fixation Serology	Point
1:4	0
1:8	1
1:16	2
1:32	3
1:64	4
1:128	5
1:256	6
Greater than 256	7

January 24, 1983 The American Journal of Medicine

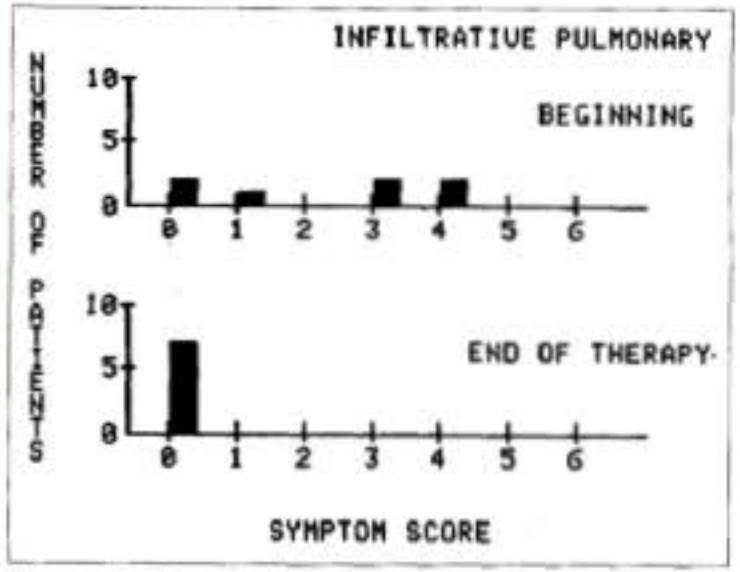

Figure 1. *Scores of seven patients with pulmonary coccidioidomycosis at the beginning and end of therapy.*

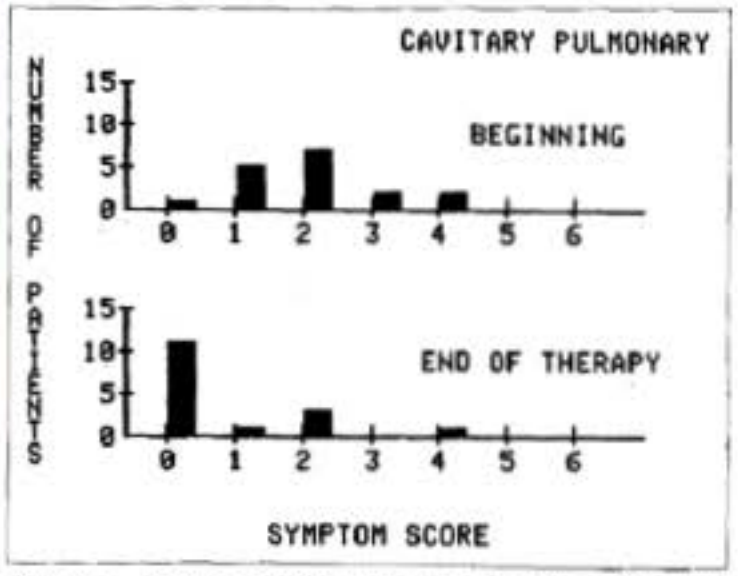

Figure 2. *Scores of 20 patients with chronic cavitary pulmonary coccidioidomycosis at the beginning and end of therapy.*

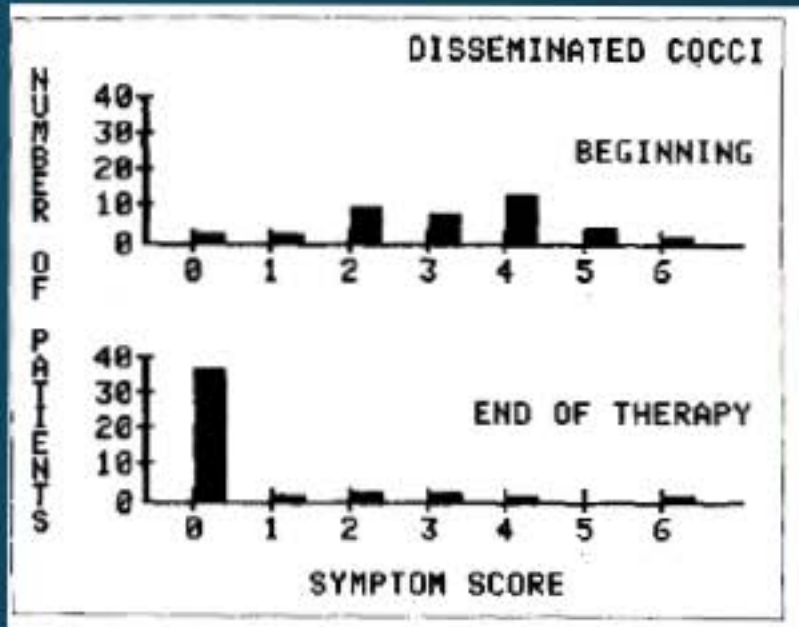

Figure 3. *Scores of 40 patients with disseminated coccidioidomycosis at the beginning and end of therapy.*

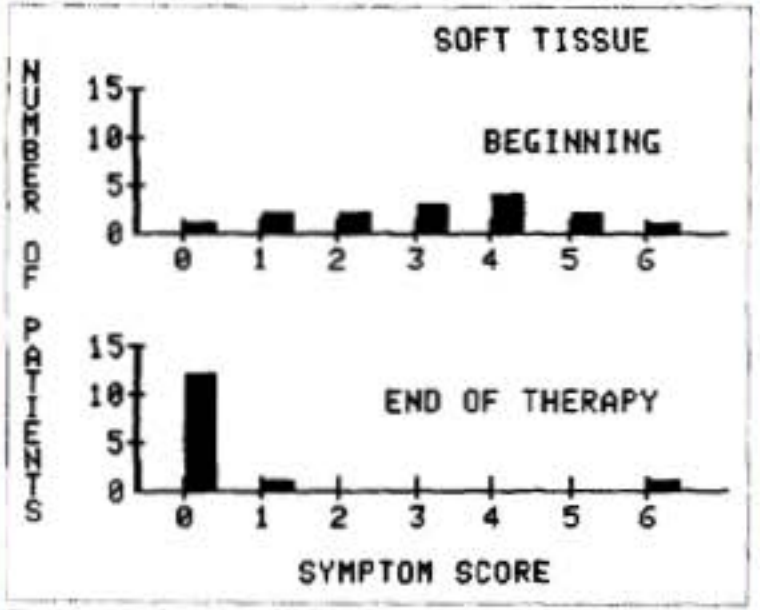

Figure 4. *Scores of 15 patients with disseminated coccidioidomycosis involving soft tissue at the beginning and end of therapy.*

Fluconazole in the Treatment of Persistent Coccidioidomycosis*

Antonino Catanzaro, M.D., F.C.C.P.; Joshua Fierer, M.D.; and Paul J. Friedman, M.D., F.C.C.P.

- 14 Patients with persistent cocci
  - Treated with fluconazole
    - 50 mg or 100 mg
    - 13 months
  - Results
    - 12 number responds
      - 1 relapsed after 7 months of treatment
      - 7 number reactivated
    - 2 failed to respond
    - 1 responded but died of an MI

Follow up

6 relapsed - 7 days – 13 months after Rx stopped

4 remained well 14 months after Rx stopped

Toxicity - none

(Chest 1990; 97:666-69)

Fluconazole Penetration into Cerebrospinal Fluid in Humans

George Foulds, PhD, Doreen R. Brennan, Charles Wajszczuk, MD, Antonino Catanzaro, MD, Dyal C. Garg, MD, William Knopf, MD, Michael Rinaldi, PhD, and Donald J. Weidler, MD, FCP

Fluconazole in CSF and Serum One Hour After IV Doses to Normal Male Volunteers

Dose		Concentration (mg/L)		Fluconazole Penetration
(mg/d)	Days	Serum	CSF	(CSF/Serum)
50	6	2.36	1.12	0.47
50	6	2.14	1.20	0.56
50	6	2.81	1.46	0.52
100	7	4.50	2.80	0.62
100	7	3.86	2.26	0.59
100	7	4.96	3.17	0.64

J Clin Pharmacol 1988;28:363–366

Fluconazole Therapy for Coccidioidal Meningitis

John N. Galgiani, MD; Antonino Catanzaro, MD; Gretchen A. Cloud, MS; Jean Higgs, RN; Barry A. Friedman, MD; Robert A. Larsen, MD; John R. Graybill, MD; and the NIAID-Mycoses Study Group

- 50 consecutive cases of cocci meningitis
  - 25 no previous treatment
  - 9 with HIV
- Treated with Fluconazole 400 mg/day
  - 37/47 (79%) responded
  - Most in within 4-8 months
  - Long time responses (20 months) 15/20
  - No withdrawal due to side effects

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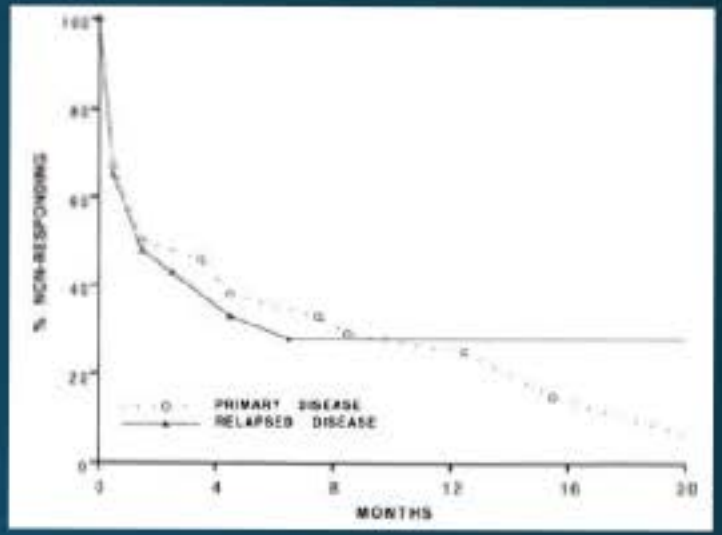

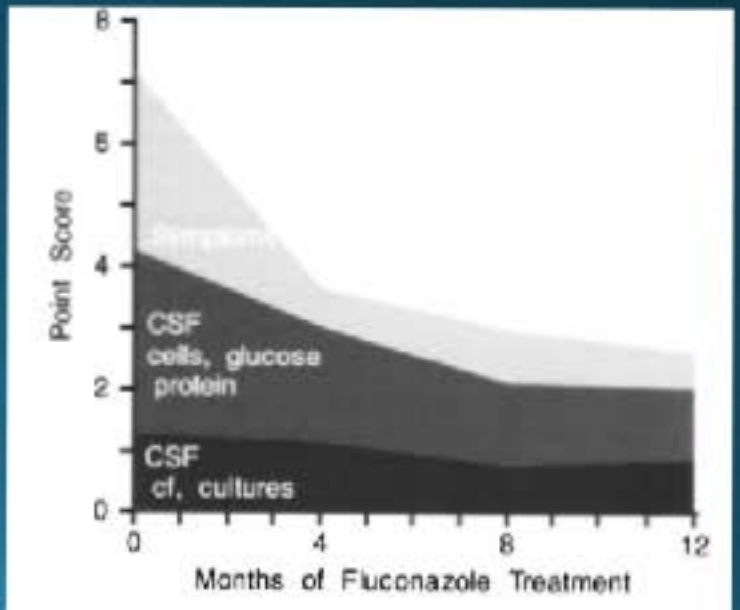

Fluconazole in the Treatment of Chronic Pulmonary and Nonmeningeal Disseminated Coccidioidomycosis

Antonino Catanzaro, MD, San Diego, California, John N. Galgiani, MD, Tucson, Arizona, Bernard E. Levine, MD, Phoenix, Arizona, Patricia K. Sharkey-Mathis, MD, San Antonio, Texas, Joshua Fierer, MD, San Diego, California, David A. Stevens, MD, San Jose, California, Stanley W. Chapman, MD, Jackson, Mississippi, Gretchen Cloud, MS, Birmingham, Alabama, and the NIAID Mycoses Study Group.

- Fluconazole 200 mg/day
  mg-323 days+/- 230 days
- Evaluated every 4 months
  - using a predefined assessment of disease related abnormalities
  - MSG Cocci score
- Non responders moved up to 400 mg/day

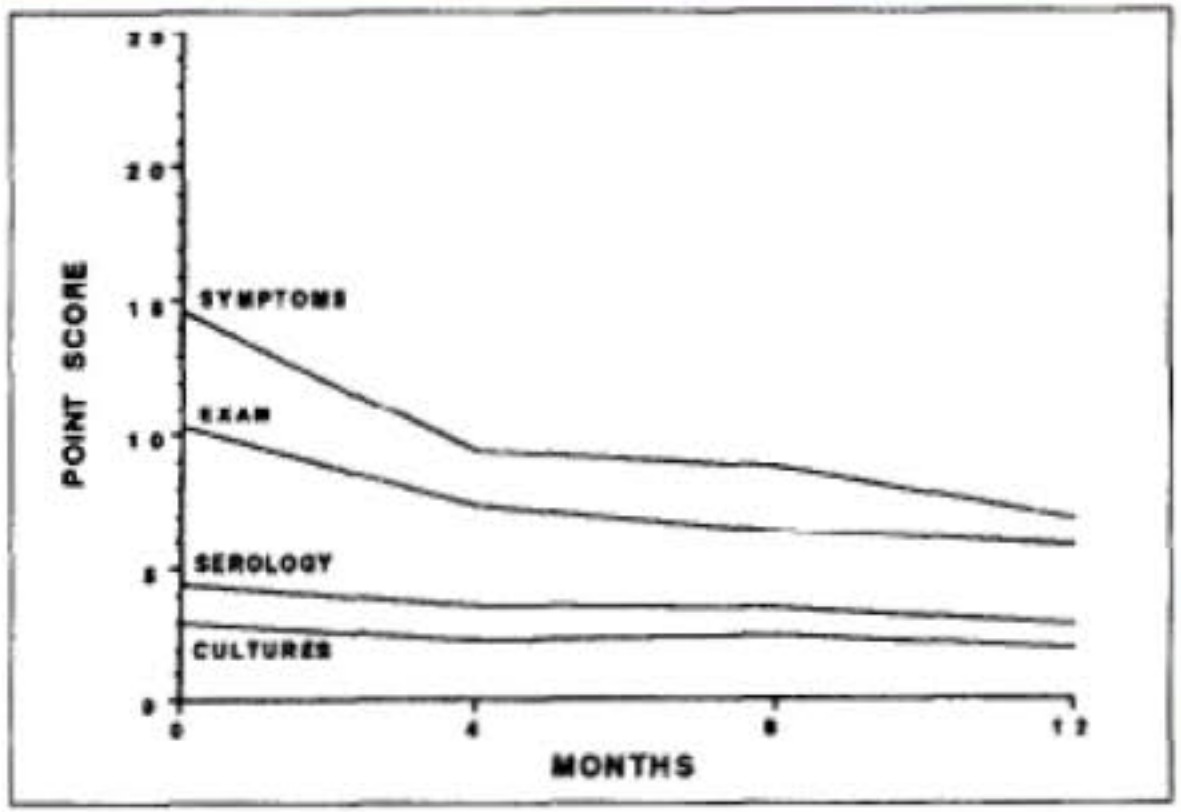

Figure 2. Changes of different score components with therapy.

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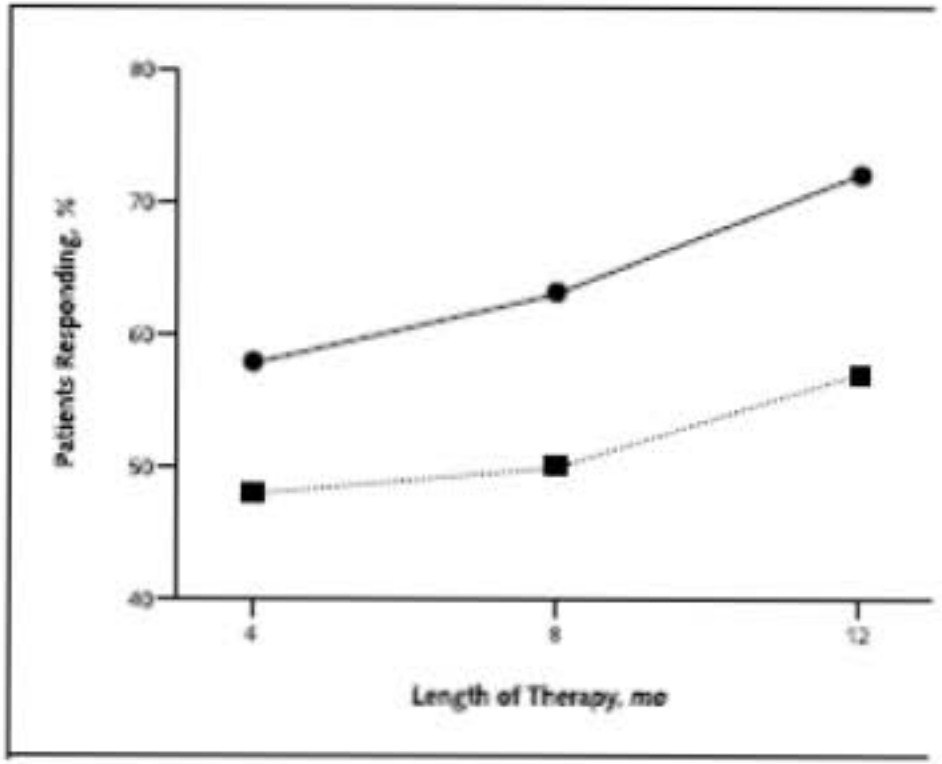
Comparison of Oral Fluconazole and Itraconazole for Progressive, Nonmeningeal Coccidioidomycosis

A Randomized, Double-Blind Trial

John N. Galgiani, MD; Antonios Catanzaro, MD; Gretchen A. Cloud, MS; Royce H. Johnson, MD; Paul J. Williams, MD; Lawrence F. Mirels, MD; Earle Nevner, MD; Ian F. Fuia, MD; David A. Stevens, MD; P. Ray Shadley, MD; Vipul B. Singh, MD; Robert A. Larsen, MD; Kathy L. Delgado, LPN; Cynthia Flanigan, BS; and Michael G. Rinaldi, PhD, for the National Institute of Allergy and Infectious Diseases-Mycoses Study Group

- 198 patients enrolled
- Treatment
  - Oral Fluconazole 400 mg/day
  - Oral Itraconazole 200 mg twice a day
- Assessment using MSC Score
  - 4,8,12 months
- Results at 8 months
  - 47/94 (63%) responded to Fluconazole
  - 61/97 (63%) responded to Itraconazole
  - P=0.08
- Skeletal at 12 months
  - 57% responded to Fluconazole
  - 73% responded to Itraconazole
  - P=0.05

Figure 3. Patients responding after different mean durations of protocol therapy with fluconazole (*dotted line*) or itraconazole (*solid line*).



- Relapse Rate
  - 28% following Fluconazole
  - 18% following Itraconazole

Ann Intern Med. 2000;133:676-686.
For author affiliations, current addresses, and contributions, see end of text.

Safety, Tolerance, and Efficacy of Posaconazole Therapy in Patients with Nonmeningeal Disseminated or Chronic Pulmonary Coccidioidomycosis

Antonio Catanzaro,[1] Gretchen A. Cloud,[2] David A. Stevens,[3,4] Bernard E. Levine,[5] Paul L. Williams,[2] Royce H. Johnson,[3] Adilia Rinaldi,[6] Laurence F. Mirels,[7] Jon E. Lutz,[8] Melissa Holloway,[9] and John N. Galgiani[10]

- Safety, Tolerance, and Efficacy trial
  - Chronic Pulmonary or nonmenengial dissemination
    - Treatment 400 mg/day posaconazole for up to 6 months
    - Median treatment 173 days-stopped by pharmaceutical company
  - Results
    - 17/20 (85%) had a satisfactory response
      - 4 had cultures at onset and end of treatment all 4 converted to negative
      - 9 had a satisfactory response and followed off drug
        - 6/9 remained well off medication
        - 3/9 relapsed off medication
  - Side effects reported in 12/20
    - Dry mouth 5/20 (25%)
    - Headache 3/20 (15%)

Clinical Infectious Diseases 2007; 45:562–8

Summary

- Cocci is a complicated infectious disease
- Assessment of response must be multidimensional
- We have evaluated a series if increasingly effective antifungals
- Most are fungistatic and responses are often followed by relapses

Acknowledgments and Thank yous

- The Pioneers and those who participate in the Cocci Study Group
- The many many who share my interest and enthusiasm
  - All of my publications have been collaborations
- The Sponsors
  - NIH
  - CDC
  - Pharmaceutical Houses
- The patients who suffer this disease