A Phase IIa Trial Study to Assess Safety and Efficacy of Interferon Gamma in the Treatment of Severe Pulmonary or Nonmeningeal Disseminated Coccidioidomycosis

Alexis V. Stephens[1], Terrie S Ahn[1], Timothy J. Thauland[2], Chantana Bun[2], Royce Johnson[3], Arash Heidari[3,] Manish J Butte[1,2], Maria I Garcia-Lloret[1]

David Geffen School of Medicine

[1]Division of Immunology, Allergy, and Rheumatology, Department of Pediatrics, University of California Los Angeles, Los Angeles, CA, 90095, USA
[2]Department of Microbiology, Immunology, and Molecular Genetics, University of California Los Angeles, Los Angeles, CA, 90095, USA
[3]Valley Fever Institute, Kern Medical Center, Bakersfield, CA

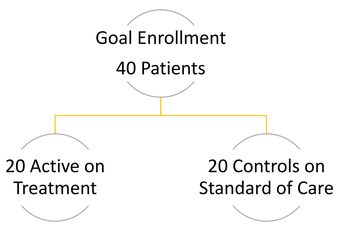
Valley Fever Institute at Kern Medical

Introduction:

About one percent of patients with coccidioidomycosis will go on to develop disseminated disease (DCM)involving extrapulmonary sites such as the bone, skin and central nervous system. Treatment with antifungals, while relatively effective in controlling disease in many patients, does not result in a permanent cure. Lifelong disability in DCM is not unusual and current therapies cannot avert death from overwhelming infection in a substantial proportion of patients.
Subjects with monogenic defects along the IL-12/gamma interferon pathway are especially susceptible to DCM, indicating that type 1 immunity is critical in host defense against coccidioides infection. Treatment of DCM with systemic IFN-γ has been attempted in a few cases and shown promise(1-3). Here, we present the rationale and preliminary data of an upcoming investigator initiated clinical trial which will address the safety and efficacy of Interferon gamma (Actimmune®) as adjunctive treatment in DCM

Methods:

A phase 2A clinical trial will explore whether IFN-γ administered three times weekly in combination with standard antifungal therapies improves clinical outcomes in severe pulmonary and/or non-meningeal disseminated coccidioidomycosis as compared to standard therapy alone. Assessments of efficacy will include reduction in complement fixation titer, C-reactive protein, and Th1/Th2 responses. Exploratory objectives will further understand the impact of type-2 immunity on the disease course of severe coccidioidomycosis and the effect of IFN-γ therapy on the same.



Rationale:

Impaired Type 1 responses in a patient with DCM.

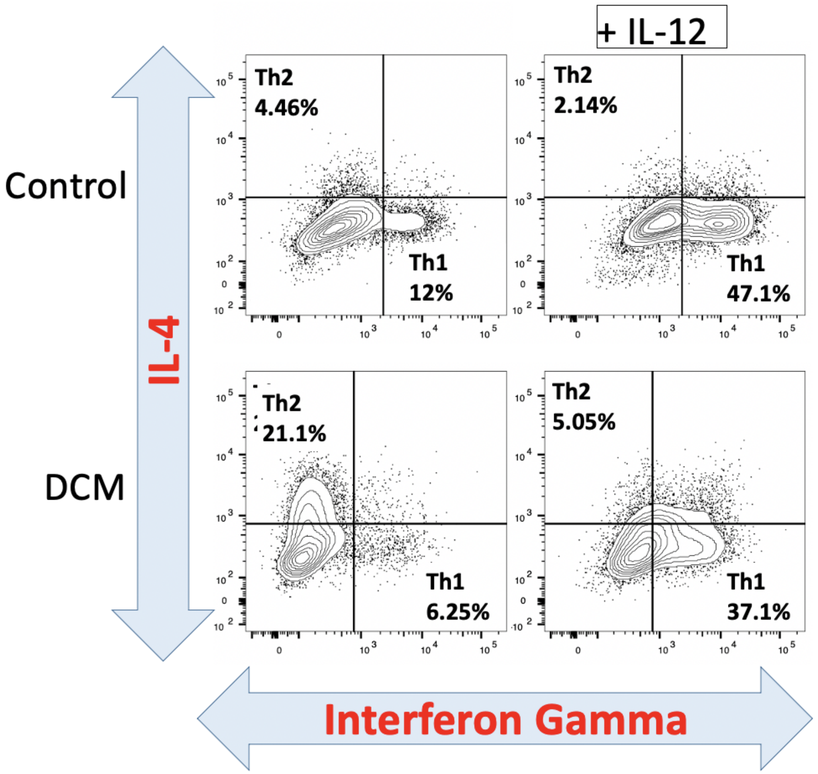


Figure 1. In vitro stimulation with IL-12 promotes Type 1 immunity in a healthy control and, to a lesser extent, in a patient with DCM . Note the associated downregulation of Type-2 Immunity.

Expected Outcomes:

We hope to identify biomarkers that identify those patients who would benefit the most from this treatment. We expect to see an increase in the proportion of Th1 cells after treatment with IFN-γ, further supporting the idea that restoration of the balance between types 1 and 2 immunity is associated with improved outcomes. We also hope to analyze genetic data to identify patients susceptible to disseminated coccidioidomycosis.

- Measure efficacy and safety of treatment
- Establish genetic and immunological signatures
- Evaluate the immunological responses that underlie success and failure in treatment
- Establish whether there is underlying genetic susceptibility

Acknowledgements:

Investigator initiated trial supported by Horizon Therapeutics.

References:

1. Duplessis CA, Tilley D, Bavaro M, Hale B, Holland SM. Two cases illustrating successful adjunctive interferon-γ immunotherapy in refractory disseminated coccidioidomycosis. J Infect 2011;63:223-228.
2. Kuberski TT, Servi RJ, Rubin PJ. Successful treatment of a critically ill patient with disseminated coccidioidomycosis, using adjunctive interferon-gamma. Clin Infect Dis 2004;38:910-912.
3. Tsai MS, Thauland TJ, Fitzwater S, Bun C, Garcia-Lloret MI, Krogstad P, Butte MJ. Refractory disseminated coccidioidomycosis disease successfully treated with IFN-gamma and dupilumab. N Engl J Med 2020; 382:2337-2343.