Inside this issue: IPF trials and Sarcoidosis

I. About IPF trial design:

- Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. 2
- A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis 2

II. About endpoint of IPF trial

- Idiopathic Pulmonary Fibrosis: Clinically Meaningful Primary Endpoints in Phase 3 Clinical Trials 3
- Hot on the breath: Mortality as a primary end-point in IPF treatment trials: the best is the enemy of the good 4
- Idiopathic Pulmonary Fibrosis: Lung Function is a Clinically Meaningful Endpoint for Phase 3 Trials 4

III. About Sarcoidosis

- A Novel Sarcoidosis Risk Locus for Europeans on Chromosome 11q13.1 5
- Sarcoidosis-related Mortality in the United States from 1988 to 2007 5
- Inflammatory activity assessment by F18 FDG-PET/CT in persistent symptomatic sarcoidosis 6
- Development of a sarcoidosis murine lung granuloma model using Mycobacterium superoxide dismutase A peptide. 6
- Transforming growth factor-b gene polymorphisms in different phenotypes of sarcoidosis 7

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1. About IPF trial design

**Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis.**

**Authors:** Raghu G, *et al.*


**Comments:** In this double-blind, placebo-controlled trial, patients with idiopathic pulmonary fibrosis (IPF) with mild to moderate lung dysfunction were randomized to combination therapy with prednisone, azathioprine, and N-acetylcysteine (NAC), NAC only, or placebo in a 1:1 ratio to determine the safety and efficacy of these treatment regimens. Although the primary outcome was change in forced vital capacity during a 60 week treatment period, the study was halted after an interim analysis with approximately 50% of collected data demonstrated increased rate of death (10% vs. 1%, P=0.01) and hospitalization (30% vs. 0.09%) observed with the combination therapy group when compared with placebo. These were especially seen in the first 15 weeks of treatment. The hazard ratio for any cause of death from combination therapy was 9.26 when compared with placebo. The study concluded these findings provided evidence against combination therapy in patients with IPF. Although the study used prednisone of 0.5mg/kg which was the same as the IFIGENIA study, further examination of the study protocol suggests a rapid tapering schedule for the prednisone that coincides with events of acute exacerbation. Furthermore, the management of infections was not clearly delineated. Lastly, the trial seemed to be designed more for efficacy and not necessarily to investigate safety of the intervention arm. Therefore before concluding that combination therapy is harmful, perhaps there may be some room for further discussion as to ask what the risk/benefit ratio of combination therapy is in patients with IPF.

**A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis**

**Authors:** Noth I, *et al.*

**Reference:** Am J Respir Crit Care Med, 2012; 186: 88-95

**URL:** [http://ajrccm.atsjournals.org/content/186/1/88.long](http://ajrccm.atsjournals.org/content/186/1/88.long)

**Comments:** In this double-blind, placebo-controlled trial, patients with IPF were randomized to warfarin with target international normalized ratio of 2.0 to 3.0 or placebo in a 1:1 ratio. The primary outcome measure was the composite outcome of time to death, hospitalization (non-bleeding, non-elective), or 10% or greater decline of % forced vital capacity (FVC). The trial was halted by the data safety monitoring board after enrollment of 145 (warfarin n=72, placebo n = 73) of the 256 planned subjects due to low probability of benefit and an increase in all-cause mortality in the warfarin group compared with placebo (14/72 vs. 3/73, P=0.005). The adjusted HR was 4.85 (1.28 – 16.99). However, the incidence of death due to IPF and respira-
Tory failure with warfarin (9/72) vs. placebo (3/73) interestingly did not correlate with the % FVC decline of more than 10% in warfarin (4/72) vs. placebo (9/73). The cohort of IPF patients recruited for the study included patients with baseline DLCO < 35% and % FVC < 60% which may have contributed to the prognosis. The mean follow up period was 28 weeks. There are 2 points that were largely different from the Kubo trial that suggested potential benefit of warfarin as treatment for IPF patients. Firstly, low molecular heparin was used during acute exacerbation instead of warfarin alone. Secondly, the mean level for D-dimer was 2.1 µg/ml in the Kubo trial which was over twice the level when compared with 0.9 µg/ml in the ACE trial. There is no evidence that IPF is a disease that is mono-spectrum. Despite the common histopathology pattern it is understood that patients progress at varying rates from slow to rapid and thus also have various factors that determine prognosis. The trial attempts to elucidate the difference in an intervention under these assumptions, and thus there still exists a need to identify a group of IPF patients that may potentially benefit from warfarin as we balance the risk/benefit of the treatment. We should not hasten our conclusion as there remains some room still to identify the subgroup of patients who may benefit from treatment with anti-coagulant.

II. About endpoint of IPF trial

Idiopathic Pulmonary Fibrosis: Clinically Meaningful Primary Endpoints in Phase 3 Clinical Trials

Authors: Raghu G, et al.
Reference: Am J Respir Crit Care Med, 2012; 185: 1044-8
URL: http://ajrccm.atsjournals.org/content/185/10/1044.long
Comments: This publication discussed that clinically meaningful endpoints must be identified for IPF in Phase 3 clinical trials. The authors mention that 5% and 10% change in FVC and 30 meters for six-minute walk distance (6MWD) were not validated as surrogate endpoints in randomized controlled trials, instead most reliable meaningful endpoints might be all-cause mortality and all-cause non-elective hospitalization. Acute exacerbation of IPF may be a meaningful endpoint, however fatality in acute exacerbation may be ethnically different which may directly affect the survival rate. Furthermore, the authors suggest that surrogate endpoints should be in the causal pathway of IPF. However, if we believe in general that IPF is established by variable causal pathways, further investigation is needed to determine whether efficacy of tailored treatment patterns according to the potential causal pathways may exist.
**Hot on the breath: Mortality as a primary end-point in IPF treatment trials: the best is the enemy of the good**

**Authors:** Athol U Wells, *et al.*  
**Reference:** Thorax, 2012; 67: 938-40  
**URL:** [http://thorax.bmj.com/content/67/11/938.long](http://thorax.bmj.com/content/67/11/938.long)  
**Comments:** The authors discuss whether mortality should be a primary endpoint for trials in IPF from the theoretical and practical standpoint and how this may impact progress in treatment of IPF. Furthermore, the toxic effects related with treatment in clinical trials that attempts to examine efficacy is not validated. In a disease with heterogeneous mechanisms such as IPF, further elucidation of the how the treatment affected outcome and the reason as to why differences in mortality must be closely examined. As reported in the PANTHER trial, further examination as to why mortality increased in the combination treatment group is needed. These include the way the treatment were used and how to effectively counter possible side effects must be evaluated. As in the case of treatment of cancer which includes a comprehensive treatment strategies for bone marrow suppression and gastrointestinal toxicity as a result of treatment, similar comprehensive approach must be sought and examined with IPF treatments.

**Idiopathic Pulmonary Fibrosis: Lung Function is a Clinically Meaningful Endpoint for Phase 3 Trials**

**Authors:** du Bois R, *et al.*  
**Reference:** Am J Respir Crit Care Med, 2012; 186: 712-5  
**URL:** [http://ajrccm.atsjournals.org/cgi/pmidlookup?view=long&pmid=22798316](http://ajrccm.atsjournals.org/cgi/pmidlookup?view=long&pmid=22798316)  
**Comments:** This publication explores a counterpoint to the previously discussed publication by Raghu *et al.* in *AJRCCM* 185: 1044-8, 2012 that FVC is a robust and valid endpoint to serve as a clinical meaningful endpoint to patients and clinicians. If mortality is used as endpoints for clinical trials in patients with mild to moderate IPF, this will require a prolonged trial period to determine the conclusion which would be prohibitive for industries interested in this field to further treatment options. Investigators not only from the US but from around the globe as well as representatives from industry, patient advocates, and regulatory agencies perhaps should examine the standards for evaluating endpoints. We must take into account that IPF poses a unique challenge as an orphan disease with tremendous heterogeneity and unpredictable rates of progression. As the saying of “Rome was not built in a day”, treatment of IPF must be seen in a long-term and broader perspective. IPF is a heterogeneous disease and the attempt to come to a conclusion with large clinical trials may not necessarily bring us closer to the answer we need. We must learn from our experiences with past clinical trials with IFN-gamma, IFN-beta, ET-1 inhibitor, and PDE-5 inhibitor. The most pragmatic approach to advance treatment modalities in IPF would be to examine the most reliable surrogate marker of change of %FVC, FVC (change of %VC, VC) to document efficacy in clinical trials, which would allow novel treat-
ment modalities to be available for the public to further evaluate its efficacy. As many clinicians face many of their patients who succumb to the disease, an aggressive effort to identify responders to treatment modalities are in dire need. The examination of polypharmacologic regulation to effectively counter the multi-causal pathway of IPF may be superior to a single molecular inhibitor in treatment of IPF.

III. About Sarcoidosis

A Novel Sarcoidosis Risk Locus for Europeans on Chromosome 11q13.1

Authors: Fischer A, et al.
Reference: Am J Respir Crit Care Med, 2012; 186: 877-885
URL: [http://ajrccm.atsjournals.org/content/186/9/877.long](http://ajrccm.atsjournals.org/content/186/9/877.long)
Comments: This study aimed to identify additional loci that may be at risk for sarcoidosis in acute and chronic forms in European cohorts. The study analyzed imputed data from a genome-wide association scan for these phenotypes. The authors found chromosome 11q13.1 as a novel locus influencing susceptibility to sarcoidosis with genome-wide significance with odds ratio of 0.67 to 0.77 in various European populations. This locus has previously been shown to be associated with Crohn’s disease and psoriasis. This study provides evidence for association of chromosome 11q13.1 with sarcoidosis and thus identified a further genetic risk locus shared by sarcoidosis, Crohn’s disease and psoriasis.

Sarcoidosis-related Mortality in the United States from 1988 to 2007

Authors: Swigris JJ, et al.
Reference: Am J Respir Crit Care Med, 2011; 183:1524-30
URL: [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3137141/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3137141/)
Comments: Mortality in sarcoidosis have not been examined over the past two decades. This study examined mortality rates and underlying causes of death among United States decedents with sarcoidosis from 1988–2007. Over this time, the age-adjusted, sarcoidosis-related mortality rate increased 50.5% in women and 30.1% in men. The greatest absolute increase in death rates was among non-Hispanic black females. Regardless of sex or race, mortality rates climbed most in decedents 55 years or older. The underlying cause of death in most patients with sarcoidosis was the disease itself. Among young sarcoidosis decedents, those with pulmonary fibrosis or a cardiac cause contributing to death were more likely to be black than white.
Inflammatory activity assessment by F18 FDG-PET/CT in persistent symptomatic sarcoidosis

Authors: Mostard RL, et al.
Comments: Inflammatory activity in patients with persistent disabling symptoms from sarcoidosis were examined with F18 FDG-PET/CT scan. In 73% of these patients, F18 FDG-PET/CT scan was positive with 80% of them showing evidence of inflammatory activity with serologic markers such as angiotensin converting enzyme, soluble interleukin-2 receptor, and neopterin. Furthermore, 80% of patients with stage IV disease had extrathoracic lesions. This study showed F18 FDG-PET/CT scan may be helpful in identifying inflammatory activity in sarcoidosis patients with persistent disabling symptoms in the absence of serological inflammatory activity and to detect extra-thoracic lesions.

Development of a sarcoidosis murine lung granuloma model using Mycobacterium superoxide dismutase A peptide.

Authors: Swaisgood CM, et al.
Reference: Am J Respir Cell Mol Biol, 2011; 44: 166-74
URL: [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3049230/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3049230/)
Comments: No animal model associated with sarcoidosis granuloma are available to date. Using a distinct superoxide dismutase A peptide (sodA) associated with sarcoidosis granuloma, authors developed a pulmonary model of sarcoidosis granulomatous inflammation. The use of microbial peptides distinct for sarcoidosis reveals a histologic and immunologic profile in the murine model that correlates well with those profiles noted in human sarcoidosis, providing the framework to investigate the molecular basis for the progression or resolution of sarcoidosis.

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Series Editors: Chi Chiu Leung, Christoph Lange and Ying Zhang

Transforming growth factor-b gene polymorphisms in different phenotypes of sarcoidosis

Authors: Pabst S, et al.
URL: http://erj.ersjournals.com/content/38/1/169.long

Comments: SNPs in TGF-β2 (rs1891467) and TGF-β3 (rs3917200) were investigated in 296 patients with sarcoidosis (acute/self remitting, n = 70 (including 62 patients with Löfgren's syndrome); chronic, n = 168; acute/chronic, n = 58) by real-time PCR. The authors found G-allele in rs1891467 in TGF-b2 was significantly associated with an acute/self remitting course of sarcoidosis compared to a chronic course. Furthermore, there was borderline significance between TGF-β3 (rs3917200) and lung fibrosis. The study suggests that carriers of the G-allele in TGF-β2 (rs1891467) may be protective in sarcoidosis.