308. Idiopathic pulmonary fibrosis

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Phase 2 trial of FG-3019, anti-CTGF monoclonal antibody, in idiopathic pulmonary fibrosis (IPF): Preliminary safety and efficacy results

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Introduction: Connective tissue growth factor (CTGF) is implicated in the pathogenesis of IPF and is a potential novel therapeutic target.
Objectives: To evaluate the safety, tolerability, and efficacy of FG-3019 in subjects with IPF.
Methods: Phase 2 prospective, open label study of FG-3019 (15 mg/kg IV every 3 weeks for 45 weeks) in subjects with well-defined IPF (duration ≤5 years, evidence of disease progression during the preceding year, FVC 45−85% predicted, DLCO ≥ 30% predicted, and 10−50% parenchymal fibrosis by HRCT). Treatment response was assessed by changes in extent of parenchymal disease (HRCT and FVC).
Results: 54 subjects (males 83%, mean age 67 years, median FVC % predicted 63.2%) were enrolled. Quantified HRCT scores of whole lung fibrosis (QLF) and all abnormal interstitial lung disease (QILD) at week 24 showed decreases from baseline greater than analytical variability (±2%) in 6 (24%) and 8 (32%) of 25 subjects, respectively. Changes in both QLF and QILD score were significantly correlated with changes in FVC % predicted (for QILD, r=-0.55, p=0.004). Mean decreases in FVC % predicted were less than in historical controls. Safety findings to date include 13 SAEs (none drug-related), 1 acute exacerbation, 9 respiratory-related hospitalizations, and 3 deaths (all related to IPF).
Conclusions: FG-3019, a novel anti-fibrotic agent, is well tolerated by subjects with IPF. No drug-related SAEs have been reported to date. Promising results of measurement of quantified lung fibrosis scores and FVC warrant pursuing the clinical trial with a higher dose of FG-3019 to further assess safety and efficacy in subjects with IPF.

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Analysis of lung function and survival in RECAP: An open-label extension study of pirfenidone (PFD) in patients with idiopathic pulmonary fibrosis (IPF)

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Introduction: RECAP is an open-label extension study evaluating long-term treatment with PFD in IPF patients who completed one of the CAPACITY (CAP) trials.
Objective: Further examine the effect of PFD on lung function and survival in patients with IPF.
Methods: PFD 2403 mg/d was administered orally in 3 equally divided doses. Forced vital capacity (FVC) was measured at baseline and Wks 12, 36, and 60. To facilitate comparison with CAP outcomes, analyses were based on patients newly-treated with PFD in RECAP who had baseline FVC and DLco values that met CAP entry criteria.
Results: A total of 178 patients were newly-treated with PFD in RECAP and had baseline values that met CAP entry criteria. The mean change from baseline to Wk 60 in %FVC in this group was –5.8%; mean change over the corresponding period in CAP was –7.0% in the PFD group (N=345) and –9.4% in the placebo group (N=347). The percentage of patients with an FVC decline ≥10% was 16.6% in RECAP, compared with 16.8% and 24.8%, respectively, in the PFD and placebo groups in CAP. Overall survival in newly-treated patients in RECAP was similar to that of PFD patients in CAP (Figure 1).

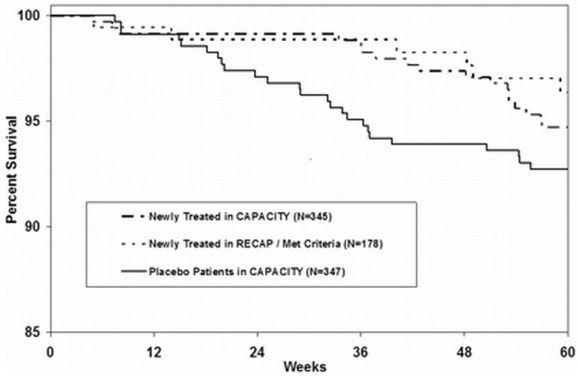

Figure 1. Kaplan-Meier estimates of overall survival.

Conclusions: FVC and survival outcomes in IPF patients newly treated with PFD in RECAP were similar to those in PFD-treated patients in CAP. These data provide further evidence to support the use of PFD in patients with IPF.

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Combined pulmonary fibrosis and emphysema: A distinct entity?

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Introduction: Although combined pulmonary fibrosis and emphysema (CPFE) syndrome has been proposed as a distinct entity, it is controversial.

Objectives: To investigate whether the combined pulmonary fibrosis and emphysema has different prognosis and prognostic factors from pure idiopathic pulmonary fibrosis.
Methods: Clinical data and high resolution computed tomography images of 300 patients with idiopathic pulmonary fibrosis were retrospectively reviewed. The extent of emphysema and fibrosis were scored and the patients with moderate to severe emphysema (≥ grade 2) were categorized as combined disease group.
Results: Seventy five (25.0%) patients had combined disease and the survival period was not significantly different from isolated idiopathic pulmonary fibrosis (n=200, p=0.190). In both groups, survival period was significantly correlated with fibrosis score, but not with emphysema score. In isolated idiopathic pulmonary fibrosis group and also all patient group, forced vital capacity and fibrosis score were predictors for mortality on multivariate analysis. In combined disease group, pulmonary hypertension was more frequent and an independent prognostic factor. However, in both groups, diffusion capacity for carbon monoxide was a sole determinant of pulmonary hypertension, suggesting the combined effect of both fibrosis and emphysema on the development of pulmonary hypertension.
Conclusions: The combined pulmonary fibrosis and emphysema seems to be co-morbidity with similar survival period rather than a distinct disease entity.

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Extent of fibrosis by high-resolution computed tomography does not improve prediction of mortality in idiopathic pulmonary fibrosis when added to a simple clinical prediction model
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Background: We previously reported a simple clinical prediction model for mortality (the GAP model) in idiopathic pulmonary fibrosis (IPF): Gender, Age, and Physiology (forced vital capacity and diffusion capacity for carbon monoxide). Previous studies suggest extent of fibrosis on high-resolution computed tomography (HRCT fibrosis score) is an independent predictor of survival in IPF. We evaluated the additive predictive value of fibrosis score to the GAP model for IPF.
Methods: We included two of three cohorts used to develop the GAP model (n=354). All patients had HRCTs available within 1 year of baseline. Two radiologists independently calculated fibrosis scores. Interclass correlation (ICC) was used to assess reliability. Models were based on competing-risks regression for mortality, treating transplant as a competing risk. Predictive performance of the GAP model and GAP + fibrosis score (GAP-FS) model was compared by the C-index, net reclassification improvement (NRI), and clinical NRI (cNRI).
Results: ICC for fibrosis score was 74% indicating moderate inter-rater reliability. A higher fibrosis score was associated with shorter survival on unadjusted analysis ($p<0.001$) but not after adjustment for the GAP model (p=0.096). The C-index was identical (71.3 (95%CI 67.3-75.3)) for both the GAP and GAP-FS models. Adding fibrosis score to the GAP model did not show significant NRI or cNRI. Fibrosis score did not improve predictive performance in either sub-cohort.
Conclusion: When added to a simple clinical prediction model, extent of fibrosis by HRCT does not improve prediction of mortality in IPF.

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Recombinant thrombomodulin improves survival in acute exacerbation of idiopathic pulmonary fibrosis
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Background: Acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF) are episodes of acute respiratory worsening caused by unknown etiology with high short-term mortality. The presence of disordered coagulation and endothelial damage in AE-IPF have been reported. Recombinant human soluble thrombomodulin (rhTM) binds to thrombin to inactivate coagulation, and the thrombin-rhTM complex activates protein C to produce activated protein C. The purpose of this study is to examine the efficacy of rhTM for treating patients with AE-IPF.
Methods: Patients with AE-IPF in our hospital from 2006 to 2011 were enrolled. AE-IPF was defined using the revised Japanese criteria for AE-IPF (Eur Respir J. 2010;35:821-9.). All patients received corticosteroid pulse therapy and immunosuppressant (cyclosporine 3mg/kg/day, p.o). NPPV was the first line intervention. The initial 20 patients treated without rhTM (control group) and following 20 consecutive patients treated with rhTM (0.06 mg/kg/day) for six days (rhTM group) were compared. The predictors of 3-month survival (Cox proportional-hazards model) were evaluated.
Results: Baseline characteristics show age(mean:72.2), PaO_2/FiO_2(220), APACHE II(9.9), C-reactive protein(CRP) (7.1) mg/dl, KL-6(1485) U/ml. In univaliate analysis, respiratory rate, CRP, rhTM therapy were significant predictors for 3M survival. In multivaliate analysis, CRP (p=0.008,HR=1.133), rhTM therapy(p=0.015,HR=0.172) were significant predictor for 3M survival.
Conclusion: We found that rhTM therapy improves 3-month survival of AE-IPF in our case control study. The results observed here support further investigation of rhTM in randomized control trials.

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Significance of abnormal autoantibodies in patients presenting with IPF
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Introduction: A subset of patients with IPF present with abnormal auto-antibodies (AAs) without clinical features sufficient to diagnose connective tissue disease (CTD). CTD-associated ILD is generally associated with a better prognosis than IPF.
Aims: To study the prevalence and significance of abnormal AAs in IPF.
Methods: Consecutively presenting patients with suspected IPF between 1/1/02 and 31/12/10 were prospectively recruited to a database. All IPF diagnoses required exclusion of overt CTD and an HRCT appearance of UIP with ≥ 70% probability. Patients with HRCT scans with ≥ 95% probability of UIP, or a confirmatory surgical lung biopsy were defined as definite IPF. The remainder were defined as probable IPF. Abnormal AA profile was defined as the presence of at least one of: RhF ≥40, ANA ≥1/640 and/or positive specific ENA screen. Patients were followed-up until Dec 2011 (median [IQR] among survivors 45 [25-63] months). Of 233 patients recruited, 25 did not have AAs performed within 12 months of presentation and were excluded. Of the 208 patients reported, 95 had definite IPF.
Results: AAs were abnormal in 18% of patients. Definite v probable IPF, gender, age, smoking and baseline lung function were similar for normal and abnormal AA groups. Only 3 patients developed overt CTD and all had abnormal AAs. Median survival was lower in those with abnormal AAs (39 v 69 months; unadjusted HR 1.57 [0.97 to 2.53] p=0.07; adjusted for age, sex, baseline VC, smoking and definite/probable IPF, HR 1.69 [1.03 to 2.78] p=0.04).
Conclusions: Only 1% of all IPF patients developed overt CTD. Abnormal AA serology was associated with a poorer survival.

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Identification of the pathological pattern by transbronchial lung cryobiopsies in patients with fibrosing diffuse parenchymal lung disease
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Background: Specimens from transbronchial lung biopsies lack sufficient quality due to crush artifact and are generally too small to identify any pathological pattern for diagnosis of fibrosing diffuse parenchymal lung disease (DPLD). Flexible cryoprobes have been shown to be useful for obtaining more large biopsy samples of lung parenchyma bronchoscopically in patients with DPLD.
Objectives: The purpose of this prospective study was to identify the pathological pattern by transbronchial lung cryobiopsy (TLC) using flexible cryoprobe in patients with clinical and radiographic features compatible with fibrosing DPLD and/or chronic Idiopathic Interstitial Pneumonia (IIP)
Results: Biopsies obtained from 40 patients were evaluated. Adequate cryobiopsies specimens were available in 39 of 40 patients. The average size of cryobiopsies was 6.0 x 4.2 mm. Crush artifacts were not seen. In 34 cases (85%) TLC identified a pathological pattern and contained features to suggest a Usual Interstitial Pneumonia pattern (ie. at least 2 of three pathologic features of UIP present; ie. patchy interstitial fibrosis, fibroblast foci and/or honeycomb changes) in 21 cases; Non-specific Interstitial Pneumonia pattern in 8 cases; Organizing Pneumonia pattern in 2 cases; Desquamative Interstitial Pneumonia pattern in 1 case; Eosinophilic Pneumonia pattern in 1 case; bronchiolitis pattern in 1 case. In 6 cases (15%) a pathological pattern was not identified.
Conclusions: In this prospective study the use of the TLC may allow to identify a pathological pattern in patients with clinical and radiographic features compatible with fibrosing DPLD and/or chronic IIP.

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Late stage of experimental pulmonary fibrosis is modulated by collagen V
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Background: The IPF is a disease with high morbi-mortality. Several experimental models of pulmonary fibrosis (PF) has been proposed, however, a later stage of

these models tend to go for the resolution of the fibrosis, but in different degrees of intensity depending on the strain. Thus these mechanisms in certain strains may participate in the progression of PF.

Aims: To study the immune-fibrotic pattern in different models of PF in the late stage (21d).

Methods: We used the models of Bleomycin-Balb/c (BLM), Paraquat-Balb/c, Bleomycin-C57BL/6 and BLM-IL17RA-KO-C57BL/6. We analyzed the amounts of total collagen (TC) and collagen V (Col5) through the morphometric evaluation by the picrosirius and IF. These data were validated by RT-PCR of Col5.

Results: The peribronchiolar TC by PPM did not differ between the treated groups, but the peripheral interstitial TC was higher in the C57BL/6, independent of the absence of IL-17RA. The protein expression of Col5 was higher in IL-17RA-KO (75,5±9% X 52,7±13%; p=0,01) and lower in BLM-Balb/c (69,8±3,4% X 53,3±14,3%; p<0,05). Likewise, the gene expression of Col5 was also higher in the IL17RA-KO (p<0.0485) and lower in the BLM-Balb/c (p<0.0037) (Figure 1).

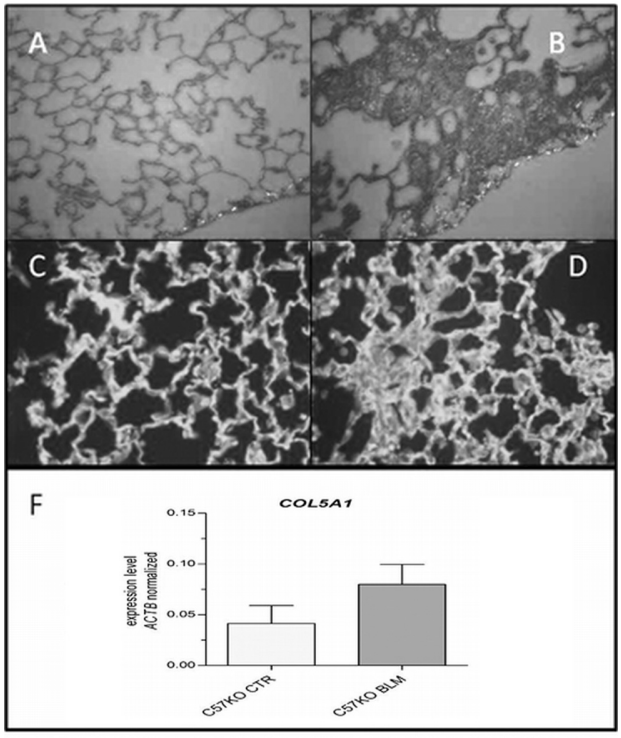

Figure 1 – Total Collagen by picrosirius (A and B) and Collagen V by IF (C and D) and RT-PCR (F). Note the increase of collagen in the BLM-IL-17-KO group (B, D and F) compared to control (A, C and F). 40xx

Conclusion: The perpetuation of PF in fibrosis-susceptible mice is related to expression of Col5 in a IL-17-independent manner and this suggests that Col5 is an important component responsible for the development of PF.