June 2014 Phoenix Pulmonary Journal Club: New Therapies for IPF and EBUS in Sarcoidosis

Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y, Kim DS, Kolb M, Nicholson AG, Noble PW, Selman M, Taniguchi H, Brun M, Le Maulf F, Girard M, Stowasser S, Schlenker-Herceg R, Disse B, Collard HR; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071-82. [CrossRef] [PubMed]

Nintedanib is a tyrosine kinase inhibitor that has been shown to decrease the decline of FVC in phase 2 trials of idiopathic pulmonary fibrosis (IPF). This study was a phase 3 trial in which 2 replicate trials comparing nintedanib 150 mg twice daily to placebo. The trials were randomized double blind placebo controlled performed over 205 sites in 24 countries. Inclusion criteria were an age > 40, FVC > 50% and DLCO 30-79%. Patients were excluded if on prednisone > 15 mg/day or any other treatment for IPF. Patients were followed for 52 weeks and underwent spirometry at weeks 2, 4, 6, 12, 36 and 52. The primary endpoint was decline in FVC and the secondary endpoint was exacerbations of IPF. The results of the 2 trials showed the treatment groups had a 1 year decline in FVC of 114.7 and 113.6 verses 239ml and 207ml in the placebo groups. There was a decrease in acute exacerbations in the Inpulsis 2 group while there was an increase in the time to 1st exacerbation in the Inpulsis 1 group. The most common side effect was diarrhea, which resulted in treatment cessation in 25 patients. The trial was well done and hit its primary endpoint. A near 50% preservation of FVC at 1 year is impressive and additional longitudinal studies are needed to see if the effects are sustained. A dose adjustment may be needed to help correct the effect of diarrhea and further studies looking at the effect of dose on FVC decline will also be needed.

King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, Lederer DJ, Nathan SD, Pereira CA, Sahn SA, Sussman R, Swigris JJ, Noble PW; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2083-92. [CrossRef] [PubMed]

Pirfenidone has been a promising agent in the fight against IPF. Prior studies showed conflicting results on the medications efficacy in preserving lung function, specifically forced vital capacity (FVC). This phase 3 clinical trial was performed over 127 sites within 9 countries. 555 patients with either biopsy proven or radiographically proven IPF were randomized to receive placebo (277 pts) or 2403 mg of pirfenidone (278 pts) daily for 52 weeks. Inclusion criteria were a diagnosis of IPF, FVC > 50%, DLCO > 30%, FEV1 > 80% and a 6 minute walk > 150 meters. The primary outcome was the change in FVC at week 52. Secondary outcomes were 6 minute walk distance, dyspnea, progression free

survival and death. The results showed that patients taking pirfenidone had 50% less decline in an FVC of > 10% and > 50% of patients had no loss of lung function. The pirfenidone group also had fewer patients with a loss of 50m or more in their 6 minute walk test. The medication was well tolerated with the main side effects being cough, nausea, headache and diarrhea.

It appears that pirfenidone will be the first drug approved specifically for the treatment of IPF. It has already been approved in Europe and it remains to be seen if the results seen in this trial are sustainable in more long term studies.

von Bartheld MB, Dekkers OM, Szlubowski A, Eberhardt R, Herth FJ, in 't Veen JC, de Jong YP, van der Heijden EH, Tournoy KG, Claussen M, van den Blink B, Shah PL, Zoumot Z, Clementsen P, Porsbjerg C, Mauad T, Bernardi FD, van Zwet EW, Rabe KF, Annema JT. Endosonography vs conventional bronchoscopy for the diagnosis of sarcoidosis: the GRANULOMA randomized clinical trial. JAMA. 2013;309(23):2457-64. [CrossRef] [PubMed]

Sarcoidosis is a granulomatous inflammatory condition with multisystem involvement. In 90% of cases the disease involves the lungs, mediastinal and hilar lymph nodes. Definitive diagnosis is obtained by histology obtained through either transbronchial needle aspiration of hilar or mediastinal lymph nodes, transbronchial parenchymal lung biopsy or cervical mediastinoscopy. Transbronchial lung biopsies have shown a sensitivity of 60% with risk of hemorrhage and pneumothorax in up to 6%. Endobronchial (EBUS) or endoscopic esophageal ultrasound (EUS) guided lymph node biopsy have been shown to increase sensitivity to 80% with less than a 1% risk of pneumothorax and hemorrhage. This study compared transbronchial lung biopsy and EUS/BUS in diagnosing sarcoidosis. The study was a randomized control trial done in 14 centers within 6 countries and included 304 patients. 149 patients underwent conventional bronchoscopic evaluation while 155 patients underwent EBUS/EUS evaluation. Bronchoscopic evaluation included bronchoalveolar lavage (BAL) CD4/CD8 ratios, at least 4 transbronchial lung biopsies and 4 endobronchial mucosal biopsy samples. Of note, fluoroscopy was only used in 39% of cases. In the endosonography group, EUS or EBUS was performed . The decision to perform an esophageal or endobronchial procedure was left to investigator. The results showed that EUS or EBUS identified granulomas in 74% of patients compared to 48% in the transbronchial group. It must be pointed out that the greatest yield was seen in with esophageal aspiration of subcarinal lymph nodes and that blind transbronchial needle aspiration of lymph nodes were not performed in the bronchoscopic group. The study had several limitations that deviates from standard practices. In our institution it is rare that a blind transbronchial needle biopsy of an accessible subcarinal node is not performed, in addition, fluoroscopy is routinely used in all parenchymal lung biopsies. Although the study did show that EBUS/EUS is superior to transbronchial lung biopsies and BAL, a study looking at blind transbronchial lymph node biopsies

versus EBUS/EUS would have been more valid. However after performing EBUS it will be hard to dispute that direct real time lymph node visualization in conjunction with on-site cytology is now the standard of care in the diagnosis of Sarcoid with lymph node involvement.

Manoj Mathew, MD FCCP MCCM