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Inside this issue: Idiopathic Pulmonary Fibrosis trials and Sarcoidosis

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I. Idiopathic Pulmonary Fibrosis trials

Treatment of Idiopathic Pulmonary Fibrosis with Ambrisentan

Authors: Raghu G, *et al.*

Reference: Ann Intern Med, 2013; 158: 641–9.

URL: *http://annals.org/article.aspx?articleid=1684850*

Comments: This study investigated the efficacy and safety of ambrisentan, an endothelin A receptor selective antagonist for the treatment of idiopathic pulmonary fibrosis (IPF), in a randomized, double-blind, placebo-controlled trial (i.e., the ARTEMIS-IPF trial).

Patients with IPF and minimal or no honeycombing on high-resolution computed tomography (HRCT) were enrolled. The study was terminated in the early stages because there was significantly more disease progression and respiratory hospitalization in the ambrisentan-treated group. Although the vasoconstriction along advancement of IPF might be compensation effect for maintaining oxygenation, the precise mechanisms for the poorer outcomes in the ambrisentan group remain unclear. Based on these results, ambrisentan is contraindicated for IPF or IPF-related pulmonary hypertension (PH) in many countries around the world. Presently, there is no evidence to support the use of endothelin antagonists for IPF and related PH.

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

Authors: Richeldi L, *et al.*

Reference: N Engl J Med, 2014; 370: 2071–82.

URL: *http://www.nejm.org/doi/full/10.1056/NEJMoa1402584*

Comments: Nintedanib, a triple kinase inhibitor, showed marginal significance in slowing the progression of IPF in a phase 2 study. To confirm the efficacy of the drug, two phase 3 trials (INPULSIS-1 and INPULSIS-2) were conducted, enrolling 1066 patients with IPF. The primary endpoint was the rate of decline in forced vital capacity (FVC) at 52 weeks. Major secondary endpoints included time to the first acute exacerbation and change in the St. George's Respiratory Questionnaire (SGRQ). In both trials, nintedanib (150 mg twice daily) significantly reduced the decline in FVC at 52 weeks. In INPULSIS-2, nintedanib significantly prolonged the time to the first acute exacerbation and improved the SGRQ score; however, there was no significant effect on these endpoints in INPULSIS-1. The most common adverse event was diarrhea; however, less than 5% of the patients required discontinuation of the treatment. Based on these trials, nintedanib was approved by the Food and Drug Administration (FDA) for the treatment of IPF in the United States. The availability of pirfenidone and nintedanib, with their different functions, is a major advancement in the treatment of IPF. Further investigation in IPF is expected to evaluate the efficacy of each drug, alone or in combination, for the treatment of acute exacerbations, PH, and reducing the incidence of lung cancer.

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Authors: King TE, *et al.*
Reference: N Engl J Med, 2014; 370: 2083–92.
URL: *http://www.nejm.org/doi/full/10.1056/NEJMoa1402582*
Comments: In previous phase 3 trials on the efficacy of pirfenidone in IPF, two out of three trials have shown the efficacy of pirfenidone in reducing the decline of vital capacity in IPF. However, the effect of pirfenidone on the survival in IPF remained unclear. In this phase 3 trial (the ASCEND trial), 555 patients with IPF [including severe cases with a diffusing capacity of the lungs for carbon monoxide (%DLCO) of 30%–35%] were enrolled to investigate the effect of pirfenidone on the FVC change over 52 weeks. Pirfenidone significantly reduced the decline in FVC. Pooled analysis with the CAPACITY-1 and CAPACITY-2 phase 3 trials (n = 1247) showed that pirfenidone significantly reduced all-cause and IPF-related death. Based on these results, the FDA approved pirfenidone for the treatment of IPF. This study enrolled patients with relatively more severe disease compared with the previous phase 3 Japanese and CAPACITY trials. In these trials, the efficacy of pirfenidone was not shown for acute exacerbations. However, to evaluate its efficacy on survival and acute exacerbation rates, it will be necessary to enroll patients with severe disease and high frequencies of acute exacerbations.

Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis

Authors: The Idiopathic Pulmonary Fibrosis Clinical Research Network

Reference: N Engl J Med, 2014; 370: 2093–101.

URL: *http://www.nejm.org/doi/full/10.1056/NEJMoa1401739*
Comments: In a randomized controlled trial conducted in 2005, N-acetylcysteine (NAC) was shown to improve pulmonary function when added to prednisone (PSL) and azathioprine (AZP) in patients with IPF. In this study, 341 patients with mild-to-moderate IPF were enrolled and randomly assigned to placebo, NAC alone, or triple therapy with PSL, AZP, and NAC. The aim was to confirm the efficacy of NAC in IPF. The three-drug regimen was stopped due to excess deaths, serious adverse events, and hospitalizations. After modifying the study protocol, 105 patients were added and the study was continued in patients receiving either placebo or NAC alone. However, NAC alone was not associated with any significant effect on FVC change over 60 weeks (primary endpoint), rate of death, or rate of acute exacerbations. This study not only showed that the efficacy of NAC was unclear but also that combination treatment with corticosteroids may be harmful. This interpretation is included in updated ATS/ERS/JRS/ALST treatment guideline for IPF. However, the efficacy of NAC in patients with severe IPF or other forms of interstitial lung disease (ILD) remains unclear. The use of NAC alone or in combination with corticosteroids is common practice in many countries. Practitioners should therefore carefully decide whether to change or continue treatment based on individual benefit and risk balance to the treatment and accuracy of diagnoses. The efficacy of inhaled NAC is also under evaluation, mainly in Japan. Further investigation is clearly necessary regarding the effects of NAC both alone and in combination with other drugs in IPF.

Safety and Pharmacokinetics of Nintedanib and Pirfenidone in Idiopathic Pulmonary Fibrosis

Authors: Ogura T, et al.

Reference: Eur Respir J 2015; 45: 1382–92.

URL: http://erj.ersjournals.com/content/45/5/1382.long

Comments: This randomized, double-blind, phase 2 trial was performed to evaluate the safety, tolerability, and pharmacokinetics of nintedanib alone or in combination with pirfenidone. The study enrolled 50 Japanese patients with IPF and assigned them to either placebo or one of three cohorts that received different nintedanib doses (50 mg, 100 mg, or 150 mg: all twice daily). All patients were on stable doses of pirfenidone and continued their usual treatment. The most common adverse event was gastrointestinal disorder, with more reports of nausea and vomiting for combination therapy than for nintedanib alone. Pharmacokinetic assessment revealed that the plasma concentration of nintedanib tended to be lower when added to pirfenidone, while nintedanib had no effect on the plasma concentration of pirfenidone. This study showed that nintedanib at doses up to 150 mg twice daily had acceptable safety and tolerability when given alone or in combination with pirfenidone to Japanese patients with IPF. The long-term safety and efficacy of combination nintedanib and pirfenidone therapy should be evaluated in future studies..

II. Sarcoidosis

An Integrated Clinicoradiological Staging System for Pulmonary Sarcoidosis: A Case-Cohort Study.

Authors: Walsh SL, *et al.*

Reference: Lancet Respir Med. 2014; 2: 123–30.

URL: http://www.sciencedirect.com/science/article/pii/S2213260013702765

Comments: Previous studies have related several clinical factors with poor prognosis in pulmonary sarcoidosis, including decreased FVC and the presence of pulmonary hypertension (PH). However, no comprehensive prognostic index has been established. In this study, 251 patients with pulmonary sarcoidosis were followed in a referral center and evaluated for pulmonary function and chest HRCT indices to establish an optimal staging algorithm for prognosis. The algorithm included the composite physiologic index (threshold = 40 units), the ratio of the main pulmonary diameter to the ascending aorta diameter (threshold = 1), and the extent of pulmonary fibrosis (threshold = 20%) on chest HRCT. The utility of the algorithm for estimating survival was confirmed in a validation cohort (n = 252). This simple and clinically useful staging algorithm reflects the severity of both pulmonary fibrosis and PH. However, decisions to treat pulmonary fibrosis or PH also rely on case-by-case assessments of symptoms and exercise capacity. Further information is necessary to evaluate whether this algorithm could be used to select lung transplant candidates.

Proteomic Profiling Reveals Autoimmune Targets in Sarcoidosis.

Authors: Häggmark A, *et al.*

Reference: Am J Respir Crit Care Med. 2015; 191:574–83.

URL:*http://www.atsjournals.org/doi/full/10.1164/rccm.201407-1341OC*

Comments: Although the cause of sarcoidosis remains unclear, the disease is considered to be driven by an abnormal immune response to extrinsic antigens (e.g., *Propionibacterium acnes* and mycobacterium species) with a background of genetic susceptibility. It is also suggested that some peptides such as vimentin might serve as autoantigens. In this study, immunoglobulin G (IgG) reactivity in the serum and bronchoalveolar lavage (BAL) fluid of patients with sarcoidosis was screened by antigen microarrays. These antigens were further verified by suspension-bead arrays. Four proteins were identified as potential autoimmune targets in sarcoidosis, including zinc finger protein 688, which is expressed on bronchial epithelial ciliated cells in normal lung tissue and maintained on the surface mucous membrane to keep it away from contaminants. This study also showed that antibody reactivity showed a high inter-individual variation. However, it remains difficult to conclude whether some cases of sarcoidosis are autoantibody mediated. Nevertheless, this study further illustrates the high heterogeneity in the pathogenesis of sarcoidosis.

Cardiac Positron Emission Tomography Enhances Prognostic Assessments of Patients with Suspected Cardiac Sarcoidosis.

Authors: Blankstein R, et al.

Reference: J Am Coll Cardiol. 2014; 63: 329–36.

URL: *http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3955730/*

Comments: This retrospective observational study investigated the prognostic value of cardiac positron emission tomography (PET) in patients with known or suspected cardiac sarcoidosis. They included 118 consecutive patients undergoing PET with 18F-fluorodeoxyglucose (FDG) and 82rubidium for the assessment of inflammation and perfusion defection, respectively, in cardiac sarcoidosis in a single hospital in the United States. PET findings were categorized into 1) normal, 2) either inflammation or perfusion defects, and 3) both inflammation and perfusion defects. Focal right ventricular (RV) FDG uptake was also assessed. The primary outcome was documented as sustained ventricular tachycardia (VT) or death from any cause. Over a median period of 1.5 years, 47 patients (40%) experienced VT or died. Multivariate analysis revealed that the combination of FDG uptake and a perfusion defect on PET was a significant predictor of death or VT (hazard ratio [HR] 2.87, P = 0.039) as well as left ventricular ejection fraction (HR 0.78, P = 0.04); however, neither the Japanese clinical criteria nor the presence of extracardiac FDG uptake was a significant predictor of death or VT. Additionally, focal RV FDG uptake was a significant risk factor for death or VT when entered into the multivariate model instead of FDG uptake and abnormal perfusion. Among patients with abnormal cardiac PET examinations, focal RV inflammation conferred a five-fold increased risk compared with normal RV FDG uptake and perfusion. Thus, PET scans can be surrogate markers for fatal cardiac sarcoidosis. In contrast to enhanced magnetic resonance imaging, PET can be performed in patients

with cardiac pacemakers or implanted cardioverter defibrillators. However, cardiac PET with FDG requires that patients consume a high-fat, low-carbohydrate diet and have sufficient rest to suppress normal myocardial glucose uptake, which could make it difficult to repeat in the outpatient setting. Nevertheless, this article suggests the possibility that PET exams can guide anti-inflammatory therapies in patients with cardiac sarcoidosis and improve outcomes. A prospective longitudinal study is needed to validate the responsiveness of cardiac PET findings to systemic therapies and its association with prognosis.

Bosentan for Sarcoidosis-Associated Pulmonary Hypertension: A Double-Blind Placebo Controlled Randomized Trial.

Authors: Baughman RP, et al.

Reference: Chest. 2014; 145: 810–7.

URL: http://journal.publications.chestnet.org/article.aspx?articleid=1763838

Comments: This was the first double-blind placebo-controlled trial to determine the effects of bosentan therapy in patients with sarcoidosis-associated PH (SAPH). Thirty-five patients with SAPH, but with neither left-sided heart failure nor pulmonary congestion, confirmed by right-sided heart catheterization (RHC) were enrolled. Participants completed 16 weeks of therapy; 23 were treated with maximum-dose bosentan at 125 mg bid and 12 received a placebo). The primary endpoint was the change in mean pulmonary artery (PA) pressure after 16 weeks. Bosentan therapy significantly reduced mean PA pressure (–4.0 ± 6.6 mmHg, P = 0.0105) and pulmonary vascular resistance (PVR) (–1.7 ± 2.75 Wood units, P = 0.004), whereas placebo did not. However, bosentan failed to improve the 6-min walk distance and patient-reported outcomes (e.g., Borg dyspnea scale, fatigue assessment scale, SF-36 and SGRQ scores). No patients experienced severe adverse effects, but two bosentan-treated patients required an increase in supplementary oxygen (>2 L) after 16 weeks of treatment. These results suggest that bosentan has hemodynamic benefits and is safe in patients with SAPH, but that it remains to be determined whether lowering mean PA pressure and PVR can improve survival. Indeed, improving RHC indices did not lead to better exercise tolerance or symptom control. As the authors mentioned in the article, SAPH is a multifactorial disease with several subtypes. Further studies are required to define the subtypes of SAPH for which bosentan provides the greatest benefit.

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration vs Conventional Transbronchial Needle Aspiration in the Diagnosis of Sarcoidosis.

Authors: Gupta D, et al.

Reference: Chest. 2014; 146: 547–56.

URL: http://journal.publications.chestnet.org/article.aspx?articleid=1819631

Comments: This was an open-label, randomized, controlled trial to explore the best bronchoscopic approach to obtain pathological conformation in patients with suspected sarcoidosis. They randomly assigned 130 patients with enlarged right paratracheal (station 4R) and subcarinal (station 7) lymph nodes to either conventional transbronchial needle aspiration (cTBNA, n = 68) or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA, n = 66). All patients also underwent endobronchial biopsy (EBB) and transbronchial lung biopsy (TBLB). TBNA specimens were obtained from lymph nodes at stations 4R and 7 in both groups. The primary endpoint was granuloma detection. Granulomas were detected similarly between the cTBNA group (cTBNA plus EBB and TBLB, 85.5%) and the EBUS-TBNA (EBUS-TBNA plus EBB and TBLB, 92.7%) (P = 0.34). EBUS-TBNA had a superior diagnostic yield (74.5%) compared with cTBNA (48.4%, P = 0.004) or EBB (36.3%, P < 0.0001), and was similar to that for TBLB (69.6%, P = 0.54). EBB and TBLB enhanced the diagnostic yield of cTBNA significantly, while the addition of TBLB, but not EBB, to EBUS-TBNA increased the detection of granulomas. These results indicate that the combination of EBUS-TBNA and TBLB is optimal for diagnosing sarcoidosis. When EBUS-TBNA is unavailable, cTBNA is a suitable alternative only when combined with both EBB and TBLB. Some clinicians prefer BAL combined with TBLB and/or EBB to evaluate suspected sarcoidosis, but BAL cannot provide pathological confirmation of granulomas. In the era of EBUS-TBNA, the role of BAL in the diagnostic approach for sarcoidosis should be reviewed.

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