JOURNAL CLUB

What's hot that the other lot got

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NINTEDANIB IN SYSTEMIC SCLEROSIS-ASSOCIATED INTERSTITIAL LUNG DISEASE (ILD)

ILD is a common complication of systemic sclerosis, conveying a considerable impact on morbidity and mortality. Nintedanib is approved for clinical use in idiopathic pulmonary fibrosis (IPF), where it has been shown to significantly reduce forced vital capacity (FVC) decline. The Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS) trial (NEJM 2019;380:2518) used a randomised, double-blind placebo-controlled trial design to assess the impact of nintedanib on the annual rate of decline of FVC in patients with systemic sclerosis-associated ILD . The trial randomised 580 patients with scleroderma and ILD on high-resolution CT, to either placebo or nintedanib treatment. The nintedanib-treated group demonstrated a significantly reduced rate of decline of FVC of −52.4 mL/year compared with −93.3 mL/year in the placebo group (Δ41 mL/year, 95%CI 3 to 79 mL/year, p=0.04). However, there was no benefit observed in patient-reported outcomes, the St. George's Respiratory Questionnaire (SGRQ) or modified Rodnan skin scores. Reports of diarrhoea were higher in the nintedanib group (75.7%vs 31.6%), and although the adverse events profiles were similar discontinuation rates were higher in the nintedanib group (16%v 9%). The SENSCIS trial presents encouraging evidence to support the impact of nintedanib on lung function in systemic sclerosis-associated ILD, but the lack of change in patient-relevant outcomes should be noted.

RECOMBINANT HUMAN PENTRAXCIN 2 PROTEIN, A NOVEL THERAPEUTIC TARGET IN IPF?

The approval of nintedanib and pirfenidone represented a pivotal moment for IPF therapeutics but there remains a need for agents that stop disease progression and improve patient-relevant outcomes. A recent phase II double-blind randomised controlled trial assessing PRM-151, a recombinant human pentraxin 2 protein, showed a reduced decline in the percentage of predicted FVC and stabilisation of 6 min walking test (6MWT) distances in patients with IPF (NCT02550873). Following this, Raghu and colleagues (Lancet Respir Med. 2019;7:657) completed an open-label extension study, recruiting 111/116 patients from the previous trial, to assess the long-term safety and explore the efficacy of PRM-151 over 76 weeks. Although adverse events were common (occurred in 103/111 patients), most were minor and not treatment related. The most commonly reported adverse events were consistent with long-term sequelae of IPF and respiratory complications (infections, cough and dyspnoea). Patients who crossed over from placebo in the original trial to PRM-151 displayed a significant difference in the rate of decline in the percentage of predicted FVC, from a −8.7% change per year in weeks 0–28 to −0.9% per year from weeks 28 to 52(p<0.0001). The rate of change of the 6MWT distance also improved from −54.9 m/year to −3.5 m/year (p=0.02). A persistent treatment effect was seen in the patients who continued PRM-151, with a decline in percentage of predicted FVC of −3.6% per year and a 6MWT distance of −10.5 m/year at week 52. These results provide further evidence that a therapeutic agent leading to changes in patient-relevant outcomes in IPF may have been identified and data from a large phase III trial of PRM-151 will be much awaited.

AMBULATORY OXYGEN IMPROVES THE HEALTH-RELATED QUALITY OF LIFE (HRQL) OF PATIENTS WITH FIBROTIC ILD

Exertional breathlessness and associated oxygen desaturation are commonly experienced by patients with ILD and significantly impact health-related quality of life (HRQL). There are limited data for the use of supplemental ambulatory oxygen in patients with ILD. To address this, Visca and colleagues (Lancet Respir Med 2018;6:759) performed the first randomised controlled open-label crossover trial examining the effect of ambulatory oxygen on HRQL in patients with moderate to severe ILD and exertional hypoxia. The study randomised 84 patients to either ambulatory oxygen or no oxygen for 2 weeks with a further 2 week crossover. Following 2 weeks of ambulatory oxygen therapy, patients had statistically significant improvement in HRQL measures, including King's Brief Interstitial Lung Disease Questionnaire (K-BILD; mean difference 3.7 points, 95%CI 1.8 to 5.6, p<0.0001). Despite the improvement in K-BILD score, there was no evidence of improvement in physical activity or psychological symptoms with one in three patients discontinuing oxygen therapy after the trial. While the AmbOx study delivers promising evidence to support the use of ambulatory oxygen in improving patient HRQL, there remains unanswered questions on long-term clinical benefit.

NO BENEFIT FROM ADDITION OF SILDENAFIL TO NINTEDANIB THERAPY IN IPF

The Sildenafil Trial of Exercise Performance in IPF (STEP-IPF) demonstrated that sildenafil had no impact on 6 min walking distance in patients with severely impaired gas exchange (DLCO<35%). However, there were small changes in DLCO, dyspnoea, SGRQ scores and oxygenation at rest, especially in patients with right ventricular systolic dysfunction. The INSTAGE study was designed to clarify the potential benefit of sildenafil in patients with IPF and severe impairment in gas exchange using a randomised double-blind parallel-group trial comparing combination therapy of nintedanib plus sildenafil or placebo in 274 patients with IPF over 24 weeks (NEJM 2018;379:1722). They found no associated benefit for their primary outcome: a change from baseline in the SGRQ total score at week 12. A wide range of secondary outcomes were analysed with a possible benefit noted only in the composite outcome of absolute decline in FVC or death over the study period. Clearly, this needs to be interpreted in the context of multiplicity in testing and a negative primary outcome but as this study was powered from data in a monotherapy study, the use of combination therapy with a proven antifibrotic agent may have led to it being underpowered.

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