Journal club

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PROPHYLACTIC ANTIBIOTICS IN IDIOPATHIC PULMONARY FIBROSIS (IPF): BEST TO AVOID FOR NOW

Lung dysbiosis is associated with disease progression in IPF. While a recent trial failed to demonstrate improved outcomes with regular cotrimoxazole use, preliminary data suggest doxycycline may offer benefits. Martinez *et al* (*JAMA 2021;325:1841*) explored how antimicrobial use impacted emergency hospitalisation and mortality in an open-label randomised control trial. The trial was terminated early due to perceived futility with 513 adults with IPF randomised to receive standard care (n=259) or add-on antimicrobials (cotrimoxazole, n=128, or doxycycline, n=126). No significant difference in all-cause mortality or respiratory-associated emergency hospitalisation was observed between groups (HR 1.04, 95% CI: 0.71 to 1.53). While the antimicrobial group developed fewer infections (7; 3% vs 17; 7%), they reported a greater rate of serious adverse events (71; 28% vs 65; 25%). This might explain low adherence rates among the antimicrobial group (47.2% at 12 months), raising questions about the acceptability of long-term treatment. While the study does not support the routine addition of these antimicrobials to standard treatment, it did not analyse respiratory microbiomes directly, and there may be a patient subset for whom their effect on lung dysbiosis could bring benefit.

THE QUEST FOR A SIMPLE PROGNOSTIC BIOMARKER IN IPF: COULD MONOCYTE COUNT (MC) BE USED?

IPF has an unpredictable course, and there remains clinical need for low-cost prognostic biomarkers. Kreuter *et al* (*Am J Respir Crit Care Med 2021;204:74*) carried out a retrospective pooled analysis using data from four randomised controlled trials (pirfenidone and interferon-γ to placebo), exploring whether baseline MC could serve as a prognostic marker in patients with IPF. A total of 2067 patients with IPF were stratified by baseline MC into three cohorts, with cut-offs determined by post-hoc bivariate analysis. Compared with patients with MC<0.60 GI/L (n=1609), those with MC 0.60 to <0.95 GI/L (n=408) and MC≥0.95 GI/L (n=50) had higher rates of IPF progression at 1 year (HR 1.25, 95% CI: 1.04 to 1.50, p=0.016; and HR 1.80, 95% CI: 1.23 to 2.63, p=0.002, respectively), defined as ≥10% absolute decline in predicted forced vital capacity (FVC), ≥50 m decline in 6-minute walk distance (6MWD), or death. At 1 year, the MC 0.60 to <0.95 GI/L and MC≥0.95 GI/L cohorts had higher rates of all-cause hospitalisation and mortality. These findings were maintained following adjustment for age, sex, baseline percent predicted FVC and baseline 6MWD. Changes during the study period in MC from baseline were minimal. While the study has a number of limitations: low numbers in the MC≥0.95 GI/L cohort, higher rates of coronary artery disease among this group acting as a potential confounder, and lack of patients with severe IPF, the data are encouraging, suggesting further research into the prognostic value of MC is warranted.

TREATMENT OF IPF-ASSOCIATED PULMONARY HYPERTENSION (PHTN): STILL NO PROVEN BENEFIT

In advanced IPF, pHTN can have a significant impact on morbidity and mortality, and no therapies for patients with pHTN secondary to respiratory disease have been approved. Behr *et al* (*Lancet Resp Med 2020;9:85*) conducted a multicentre, double-blind, randomised placebo-controlled trial exploring the impact of regular sildenafil on disease progression. Patients with IPF, established on pirfenidone and at risk of developing pHTN, were randomised to receive either sildenafil (n=88) or placebo (n=89). There was no difference between groups in disease progression over 12 months, defined as decline from baseline in 6MWD, respiratory-related emergency hospitalisation or all-cause mortality. Between group difference in disease progression was 3.06% (95% CI: −11.30% to 17.97%, p=0.65). Comparing sildenafil to placebo, there was no difference in decline in 6MWD (HR 0.94, 95% CI: 0.62 to 1.41) or all-cause hospitalisation (HR 1.06, 95% CI: 0.70 to 1.62). Adherence was low, with only 37/89 in the placebo group and 51/88 in the sildenafil group completing the treatment period; this reflects the more severe baseline disease in the placebo group, as well as the long study duration compared with similar trials conducted previously. Safety profile was similar for both groups. While there may remain a specific subset of patients who may find benefit from sildenafil, this study suggests its use among patients with IPF at risk of pHTN remains limited.

MEASURING HEALTH-RELATED QUALITY OF LIFE (HRQL) IN PULMONARY FIBROSIS (PF): IT ONLY TAKES A MINUTE (OR 2)

The importance of accurate assessment of HRQL is increasingly acknowledged in both research and clinical medicine. There are, however, limited tools validated in specific groups such as PF. Scallon *et al (Eur Respir J 2021 DOI:* 10.1183/13993003.00917–2021*)* developed a novel tool to assess HRQL in PF, termed the 'R-scale', and assessed its validity in a prospective, single-centre study. Focus group sessions were used to generate a list of factors contributing to HRQL, with further semi-structured interviews used to establish five domains. These were assessed along a numerical rating scale, generating an overall score, with lower scores indicating higher HRQL. A total of 100 patients (age 71±8 years, 67% men, 91% Caucasian) completed the R-scale during a routine visit, alongside the Kings Brief Interstitial Lung Disease (K-BILD) and the EuroQol 5-Dimentional 5-Level (EQ-5D-5L) questionnaires in a random order alongside routine clinical assessments. The R-scale demonstrated good internal consistency, and had a moderate-to-strong negative correlation with K-BILD (r=−0.7, p<0.01) and EQ-5D-5L (r=−0.67, p<0.01). Correlation was weaker with physiological parameters, including 6MWD (r=−0.38), p<0.01) and FVC (r=−0.31, p<0.01). Of note, patients reported the K-BILD as the most representative of their quality of life and while it took double the time to complete, this was on average 2 as opposed to 1 min for the R-scale. Only 53 patients completed further visits, and the emergence of COVID-19 precluded collection of physiological data. While the R-scale showed correlation with validated tools, the single-centre and limited ethnic diversity of the study population does limit generalisability, and further refinement of the scale is required prior to ongoing validation studies.

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