Tralokinumab Reduced Acute Exacerbations in a Phase 2 Study of Severe Asthma

Written by Mary Mosley

Tralokinumab, a human immunoglobulin-G4 monoclonal antibody, potently and specifically neutralizes interleukin (IL)-13, a pleiotropic cytokine thought to be a central mediator of asthma [Mitchell J et al. *Curr Opin Investig Drugs* 2010]. Christopher E. Brightling, MBBS, University of Leicester, Leicester, United Kingdom, presented the overall results from A Phase 2b, Randomized, Double-Blind Study to Evaluate the Efficacy of Tralokinumab in Adults With Asthma [NCT01402986; Brightling CE et al. *Am J Crit Care Med* 2014]. In brief, the study showed that acute exacerbation rates (AERs) were reduced with the every-2-week (Q2W), but not the every-4-week (Q4W), tralokinumab dosing regimen compared with placebo and that tralokinumab was well tolerated and safe, with similar rates of adverse events in all groups.

Eligible patients at screening had severe asthma with forced expiratory volume in 1 second (FEV_1) reversibility of ≥12% and ≥200 mL within 3 years of screening and ≥2 exacerbations in the prior year. Following a 5-week run-in period, subjects with FEV_1 of 40% to 80% predicted or Asthma Control Questionnaire 6 (ACQ-6) scores ≥1.5 were randomly assigned to receive subcutaneous tralokinumab 300 mg every 2 weeks for 52 weeks (Q2W group; n=150) or every 4 weeks for 12 weeks and then every 4 weeks to Week 48 (Q4W group; n=151) or placebo (n=151). Subjects received fluticasone 500 µg and salmeterol 50 µg or equivalent and were continued on prestudy control medications. The primary end point was the AER over 52 weeks, with secondary end points of FEV_1, ACQ-6 scores, and safety.

The mean age of the study patients was 50 years, 65% were women, 56% were Caucasian, and 34% were Asian. The average baseline FEV_1 was 68.6%.

The primary efficacy endpoint of AER, defined as the use or increase in dose of systemic corticosteroids for ≥3 consecutive days for asthma symptoms, at 52 weeks was not significantly reduced in either tralokinumab dosing regimen (Q2W, 7%; 95% CI, –30% to 33% [p=0.67]; Q4W, –2%; 95% CI, –46% to 29% [p=0.91]) in the intention-to-treat analysis.

The secondary end point of percentage change in FEV_1 increased significantly in the Q2W group (7.10%; 95% CI, 2.35% to 11.84%; p=0.003) but not the Q4W group (1.57%; 95% CI, –3.22% to 6.35%; p=0.52). There were trends for improvements in measures of health status, measured by the ACQ-6 and Asthma Quality of Life Questionnaire (AQLQ) in the overall study.

Investigation of biomarkers in predefined subgroups revealed a trend toward a reduction in AER in patients with FEV_1 reversibility and elevated levels of periostin or dipeptidyl peptidase-4 (DPP-4) treated with Q2W tralokinumab compared with placebo. In the Q2W group, there were greater improvements in ACQ-6 and AQLQ scores in the patients with FEV_1 reversibility and high levels of periostin and DPP-4.

The frequency of treatment-emergent serious adverse events or adverse events was similar within the safety population (tralokinumab Q2W, 89.3%; tralokinumab Q4W, 84.8%; placebo, 84.8%).

Although there was not an overall reduction in AER in either tralokinumab dosing regimen compared with placebo, the trends toward improvements in AER in the predefined subgroup analysis in subjects with airway reversibility and high levels of periostin or DPP-4 are hypothesis generating and suggest populations that may benefit from IL-13 blockade in future studies.

Phase 3 Trial Confirms Benefits of Pirfenidone for IPF

Written by Brian Hoyle

The Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis trial [ASCEND; King TE et al. *N Engl J Med* 2014] was a Phase 3, multinational, double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis (IPF). The findings were presented by Talmadge E. King, Jr, MD, University of California, San Francisco, San Francisco, California, USA.

IPF is a chronic, progressive, and irreversible lung disease characterized by pulmonary scaring that ultimately leads to pulmonary dysfunction and death. The prognosis is poor, with a median survival time from diagnosis of 2 to 5 years. Two of 3 prior Phase 3 studies with pirfenidone demonstrated a reduction in lung deterioration and progression-free survival (PFS) [Taniguchi H et al. *Eur Respir J* 2010; Noble PW et al. *Lancet* 2011]. On the basis of the inconsistent Phase 3 data, it was recommended by US regulatory authorities that the ASCEND trial be undertaken.

In the ASCEND trial, 555 eligible patients with IPF (summarized in Table 1) were randomized 1:1 to receive oral pirfenidone (2403 mg/day; n=278) or placebo (n=277) for 52 weeks. Clinical follow-up included assessments at Day 1 and Weeks 13, 26, 39, and 52 on therapy as well as 28 days after the last dose of study drug. The primary end point was the change in forced