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Vasculitis clinical and pathogenic highlights

OP0130 MEPOLIZUMAB FOR THE TREATMENT OF PATIENTS WITH EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS: A PHASE III RANDOMISED, PLACEBO-CONTROLLED TRIAL

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Background: Mepolizumab reduces blood eosinophils with concomitant clinical improvement in some hypereosinophilic syndromes and eosinophilic asthma.

Objectives: To investigate the efficacy and safety of mepolizumab in patients with eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss).

Methods: We conducted a Phase III, randomised, placebo-controlled, double-blind, parallel group, multi-centre study (NCT02020889) in patients with EGPA and a history of relapsing or refractory disease on stable therapy with prednisolone/prednisone ≥ 7.5 – ≤ 50 mg/day with or without additional immunosuppressive therapy for ≥ 4 weeks. Patients were randomised 1:1 to receive mepolizumab 300mg or placebo subcutaneously, in addition to standard of care, every 4 weeks for 52 weeks. After Week 4, glucocorticoid dose could be tapered, per physician judgment, according to a suggested standard of care protocol. Co-primary endpoints (intent-to-treat [ITT] analysis) were accrued duration of remission (Birmingham Vasculitis Activity Score [BVAS]=0, prednisolone/prednisone dose ≤ 4 mg/day) over 52 weeks; and the proportion of patients in remission at both Weeks 36 and 48. Secondary endpoints included average glucocorticoid dose during Weeks 49–52 and time to first EGPA relapse. Safety was also assessed.

Results: The ITT population included 136 randomised patients (mepolizumab n=68, placebo n=68). Baseline characteristics were similar between groups. Duration of remission accrued over 52 weeks was significantly prolonged with mepolizumab vs placebo (odds ratio: 5.91 [95% confidence interval (CI): 2.68,13.03]; $p < 0.001$); a significantly higher proportion of patients were in remission at Weeks 36 and 48 (32% vs 3%, odds ratio: 16.74 [95% CI: 3.61,77.56]; $p < 0.001$). Significant reductions in average daily prednisolone/prednisone dose during Weeks 49–52 were seen with mepolizumab vs placebo (odds ratio: 0.20 [95% CI: 0.09,0.41]; $p < 0.001$). Median (range) prednisolone/prednisone dose during Weeks 49–52 was 5.0 (0.0–113.4)mg/day in the mepolizumab group and 10.0 (0.0–46.3)mg/day in the placebo group. Time to first EGPA relapse was significantly longer with mepolizumab vs placebo (hazard ratio: 0.32 [95% CI: 0.21,0.50]; $p < 0.001$). Rates of adverse events (AEs) and serious AEs were similar for mepolizumab and placebo.

Conclusions: Treatment with mepolizumab significantly increased the likelihood and duration of remission, while reducing glucocorticoid use, in patients with EGPA, with a safety profile consistent with previous studies in severe asthma and EGPA. This demonstrates consistent and meaningful clinical benefits of mepolizumab in patients with EGPA.

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OP0131 OPTIMAL DOSE OF TOCILIZUMAB FOR THE TREATMENT OF GIANT CELL ARTERITIS: EFFICACY, SAFETY, AND EXPOSURE-EFFICACY ANALYSIS FROM GIACTA

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Background: GiACTA, a randomized, double-blind, placebo-controlled trial, evaluated the efficacy and safety of tocilizumab (TCZ), an IL-6 receptor- α inhibitor, in patients with giant cell arteritis (GCA).^{1,2}

Objectives: Secondary analyses to evaluate the differential efficacy and safety of TCZ between patients with new-onset and relapsing GCA and to evaluate the TCZ exposure-efficacy relationship at week 52 of the trial.

Methods: Patients aged ≥ 50 years with active GCA were randomly assigned 1:1:2:1 to short-course prednisone (PBO+26), long-course prednisone (PBO+52) (26-week or 52-week prednisone taper + weekly subcutaneous [SC] placebo, respectively), weekly (TCZ-QW) or every-other-week (TCZ-Q2W) SC TCZ 162 mg + 26-week prednisone taper. Subgroup analysis was performed by disease-onset status (new-onset vs relapsing) to evaluate the proportions of patients in sustained remission at week 52 and time to flare. The impact of TCZ exposure, categorized into high, medium and low tertiles, on time to flare was evaluated across all patients in all treatment arms.

Results: Randomization included 251 patients, 119 (47%) with new-onset and 132 (53%) with relapsing GCA, distributed evenly across groups. Higher proportions of patients achieved sustained remission in the TCZ vs placebo groups regardless of disease onset (new-onset, relapsing-TCZ-QW: 59.6%, 52.8%; TCZ-Q2W: 57.7%, 47.8%; PBO+26: 21.7%, 7.4%; PBO+52: 21.7%, 14.3%, respectively). Patients with relapsing disease at baseline were in relapse-free remission longer and thus had lower risk for flare (hazard ratio) when treated with TCZ-QW than TCZ-Q2W. Hazard ratio (99% CI) for flare vs PBO+26 was 0.23 (0.09–0.61) for TCZ-QW and 0.42 (0.14–1.28) for TCZ-Q2W; vs PBO+52 it was 0.36 (0.13–1.00) for TCZ-QW and 0.67 (0.21–2.10) for TCZ-Q2W. TCZ exposure-efficacy analysis showed that most patients in the low exposure tertile had been treated with TCZ-Q2W (80%) whereas those with medium and high exposure primarily received TCZ-QW (84% and 98%, respectively). Kaplan-Meier analysis demonstrated that patients with higher exposure benefited from a longer time to flare (Figure). Adverse events (AEs) were similar across groups. Serious AEs were reported in 15.0% TCZ-QW, 14.3% TCZ-Q2W, 22.0% PBO+26 and 25.5% PBO+52 patients; rates were similar between new-onset and relapsing patients.

Figure. Time to first GCA flare after clinical remission by exposure (tertile of $C_{ss,8}$)

Patients on TCZ were categorized into 3 bins based on high/medium/low TCZ exposure (derived as average exposure from weeks 1–8, $C_{ss,8}$); patients in the 2 placebo groups were categorized in 2 independent bins.

Conclusions: The compelling treatment effect of TCZ in GCA patients as measured by sustained remission to 52 weeks was consistent regardless of disease-onset status. Duration of relapse-free remission until flare was longer in patients with higher TCZ exposure, most notably in relapsing patients treated with TCZ-QW.

References:

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