Mepolizumab For The Treatment Of Patients With Eosinophilic Granulomatosis With Polyangiitis: A Phase Iii Randomized, Placebo-Controlled Trial

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Rationale: Eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss) is a systemic vasculitis associated with asthma, eosinophilia, sinusitis, pulmonary infiltrates, and neuropathy. In other hypereosinophilic syndromes and eosinophilic asthma, the anti-interleukin-5 monoclonal antibody mepolizumab has been shown to reduce blood eosinophil counts with concomitant clinical improvement.

Methods: We conducted a Phase III, randomized, placebo-controlled, double-blind, parallel-group, multi-center study (NCT02020889) in patients with EGPA and a history of relapsing or refractory disease on stable therapy with prednisolone/prednisone ≥7.5–≤50mg/day with or without additional immunosuppressive therapy for ≥4 weeks. Patients were randomized 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, based on an intent-to-treat analysis, were accrued duration of remission (Birmingham Vasculitis Activity Score [BVAS]=0, prednisolone/prednisone dose ≤4mg/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 intent-to-treat population included 136 randomized 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%, respectively, odds ratio: 16.74 [95% CI: 3.61,77.56]; p<0.001). Significant reductions in average daily glucocorticoid 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. (Funded by GSK [Study 115921] in collaboration with NIAID [U01 AI097073] and the Division of Intramural Research, NIAID, NIH).

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