T- and B-Lymphocyte Modulation Associated With Teriflunomide Treatment in Patients With Relapsing-Remitting MS: Analysis of the Phase 3b Teri-DYNAMIC Study

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INTRODUCTION

Teriflunomide, a once-daily oral immunomodulator approved for the treatment of patients with RRMS, selectively and reversibly inhibits dihydroorotate dehydrogenase, a key intermediate enzyme in pyrimidine synthesis, in T and B lymphocytes. In a multiple sclerosis (MS) trial, there was no evidence of apparent changes to the bone marrow microenvironment; however, changes in lymphocyte subsets were observed and were consistent with previous studies in other patient populations with MS. The effects of teriflunomide on T-cell proliferation and cytokine production were assessed in a rat experimental autoimmune encephalomyelitis (EAE) model of MS and in a phase 3b trial of patients with RRMS. These results are consistent with the hypothesis that modulation of lymphocyte subsets and cytokine production may have a role in the efficacy of teriflunomide in MS.

METHODS

Study Design

- Teri-DYNAMIC (NCT01591284) is an exploratory, open-label, phase 2b clinical trial that included patients with RRMS, 18-65 years of age, meeting the McDonald 2010 criteria for RRMS.
- Patients were randomized to receive placebo (n=52), 7.5 mg, or 14 mg/day teriflunomide (n=51) for 48 weeks. Patients with a recent history of IFNB or GA treatment prior to the protocol-mandated washout period were not included.
- The safety, efficacy, and pharmacodynamics of teriflunomide were assessed in patients with RRMS.
- The per-protocol population comprised all patients with no major/critical pharmacodynamic-related adverse events.
- The contrast between effects on proliferation ex vivo vs in vitro supports a reversible effect of teriflunomide.

RESULTS

- The safety population (n=105) consisted of patients with RRMS with a median (min–max) baseline age of 47.6 (28–75) years and a median (min–max) baseline EDSS score of 2.5 (0–6.0).
- The per-protocol population comprised all patients with no major/critical pharmacodynamic-related adverse events.
- Treatment with teriflunomide in patients with RRMS reduced the absolute numbers and frequencies of total lymphocytes, CD8+ T cells, and CD19+ B cells, consistent with observations from the phase 3 teriflunomide trials, TEMSO, TOWER, and TOPIC.
- The per-protocol population comprised 38 patients who were randomized to receive placebo, 28 patients to receive 7.5 mg/day teriflunomide, and 29 patients to receive 14 mg/day teriflunomide.
- The relative size of the CD4+ population increased, while the CD8+ population decreased.
- The contrast between effects on proliferation ex vivo vs in vitro supports a reversible effect of teriflunomide.
- The results of the Teri-DYNAMIC trial further support the efficacy of teriflunomide as an immunomodulatory agent to treat patients with RRMS.

CONCLUSIONS

- The effects of teriflunomide on various immune cell types enhance our understanding of the teriflunomide unique mechanism of action, involving both activated T and B cells.
- Treatment was associated with reduced the absolute numbers and frequencies of total lymphocytes, CD8+ T cells, and CD19+ B cells, consistent with observations from the phase 3 teriflunomide trials, TEMSO, TOWER, and TOPIC. However, total lymphocyte counts remained within normal range throughout the study.

- Teriflunomide evoked a selective effect on different CD4+ T-cell subsets, possibly supporting a shift in T-cell populations from proinflammatory to regulatory, potentially anti-inflammatory, T cells.

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