TNF NEUTRALIZATION IN MS: RESULTS OF A RANDOMIZED, PLACEBO-CONTROLLED MULTICENTER STUDY

The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group

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Objective: A double-blind, placebo-controlled phase II study was conducted in 168 patients, most with relapsing-remitting MS, to evaluate whether lenercept would reduce new lesions on MRI. **Background:** Tumor necrosis factor (TNF) has been implicated in MS pathogenesis, has been identified in active MS lesions, is toxic to oligodendrocytes in vitro, and worsens the severity of experimental allergic encephalomyelitis (EAE) in animals. Lenercept, a recombinant TNF receptor p55 immunoglobulin fusion protein (sTNFR-IgG p55), protects against EAE. **Methods:** Patients received 10, 50, or 100 mg of lenercept or placebo IV every 4 weeks for up to 48 weeks. MRI scans and clinical evaluations were performed at screening, at baseline, and then every 4 weeks (immediately before dosing) through study week 24. **Results:** There were no significant differences between groups on any MRI study measure, but the number of lenercept-treated patients experiencing exacerbations was significantly increased compared with patients receiving placebo ($p = 0.007$) and their exacerbations occurred earlier ($p = 0.006$). Neurologic deficits tended to be more severe in the lenercept treatment groups, although this did not affect Expanded Disability Status Scale scores. Anti-lenercept antibodies were present in a substantial number of treated patients; serum lenercept trough concentrations were detectable in only a third. Adverse events that increased in frequency in treated patients included headache, nausea, abdominal pain, and hot flushes. **Conclusions:** Lenercept failed to be beneficial, but insight into the role of TNF in MS exacerbations was gained.

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Comment from Richard M. Ransohoff, MD, Associate Editor: This article reported another counterintuitive MS clinical trial result and heralded an era of enhanced appreciation of the complexity of MS pathogenesis.

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