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TRIAL WATCH

Phase III promise for oral multiple sclerosis therapy

Novartis has released the first results from a Phase III trial of FTY720 (fingolimod), a novel oral therapy for multiple sclerosis (MS). They show that FTY720 reduced relapse rates compared with intramuscular injections of interferon-β1a, which is a current standard treatment.

This 1 year, double-blind, randomized study involved 1,292 patients with relapsing–remitting MS, who received either 0.5 mg or 1.25 mg FTY720 or interferon-β1a (Avonex; Biogen Idec). Participants receiving interferon-β1a had an annualized relapse rate of 0.33, whereas the corresponding rates for those receiving the low and high doses of FTY720 were 0.16 and 0.20, respectively. FTY720 was generally well tolerated, but two fatal cases of herpes infections were reported among patients receiving the 1.25 mg dose. Both cases involved confounding factors, although the possibility of involvement of FTY720 could not be ruled out, given its immunosuppressive effects.

Current disease-modifying therapies for MS, a chronic inflammatory disorder in which autoreactive T cells and macrophages cause demyelination of nerve cells in the central nervous system (CNS), also act by suppressing the immune system (*Nature Rev. Drug Disc.* 7, 909–925; 2008). However, finding the optimal balance between effective immunosuppression and the risk of adverse events is a particularly challenging task. As Ludwig Kappos, Chair of the Department of Neurology, University Hospital, Basel, Switzerland, points out: "Approved first-line drugs [for MS] have demonstrated modest efficacy in suppressing the inflammatory activity of the disease, reducing relapse frequency and severity, and in slowing down disease progression. Improved efficacy without additional risks would be highly appreciated."

FTY720 binds to the sphingosine-1-phosphate receptor, which is predominantly expressed on lymphocytes and regulates their migration from secondary lymphoid tissues to sites of injury or infection. FTY270 initially acts as an agonist, but promptly induces downregulation of receptor expression, therefore blocking the signal required for lymphocyte migration and preventing systemic trafficking of self-reactive T cells to the CNS (*Pharmacol. Ther.* 108, 308–319; 2005). A differential effect on particular subsets of T cells, or potential direct effects on oligodendrocyte and dendritic cell maturation, myelinogenesis and astroglia proliferation, might account for its therapeutic effectiveness and adverse-effect profile.

Importantly, compared with interferon-β products, which are administered by injection, the oral availability of FTY720 would "certainly increase acceptance and the necessary long-term compliance to treatment," says Kappos. "FTY720 is one of five orally administered drugs currently in Phase III testing," adds Howard Weiner, Professor of Neurology at Harvard Medical School, suggesting that we may be on the verge of a new era of oral treatments for MS.

Further analyses of the trial are expected to be reported later this year, and two Phase III placebo-controlled trials are also ongoing. Novartis is aiming to submit regulatory applications for FTY720 by the end of 2009.