Fingolimod Slows Brain Volume Loss Regardless of Inflammatory Activity


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INTRODUCTION AND PURPOSE

Fingolimod, a novel oral immunomodulatory agent, has been approved for relapsing-relapsing multiple sclerosis (MS).

In three pivotal studies, fingolimod 0.5 mg significantly reduced brain volume loss by 37% over 1 year compared with the approved therapy, interferon (IFN-β 1a subcutaneously [SC], TYSABRI®; TEVA/BI, 2007), 0.1 mg compared with placebo (PBO; DISCO).

Methods

Here, we report the results of a subgroup analysis from TRANSFORMS assessing reductions in brain volume loss over 12 months according to magnetic resonance imaging (MRI) inflammatory disease activity at baseline or during therapy with fingolimod (0.5 mg).

RESULTS

In this double-blind, phase 3 study of relapsing-remitting MS were randomized 1,131 to receive once-daily fingolimod 0.5 mg, fingolimod 1.25 mg, or weekly PBO (PBO; 75 mg IM q4w) for 12 months.

For the primary outcome, brain volume loss was calculated by a semi-automated, radiologist-based, 3D structural image analysis using, in a subset of patients, a 3T MRI scanner.

The annualized rate of new or worsened T2 lesions at 12 months was 0.60% in fingolimod 0.5 mg, 0.90% in fingolimod 1.25 mg, and 2.01% in PBO.

CONCLUSIONS

- Irrespective of treatment, brain volume loss proceeded at a faster rate in patients with inflammatory lesion activity at study entry than in those without.

This is consistent with results from previous studies indicating that ongoing inflammatory activity developing Gd+ lesions over 1 year are correlated with increased brain volume loss.1,2

Large discrepancy in MRI inflammatory activity at entry or during the study and fingolimod 0.5 mg sufficiently reduced the effects of both in the brain volume loss over 1 year compared with PBO 1.2 mg, with comparisons reaching significant in most subgroups for both fingolimod doses, despite the fact the study did not powered to detect treatment effects within subgroups.

In addition to potency, the mode of action of various MS treatments may account for differences in their effects on brain volume, reflecting the efficacy of anti-inflammatory (pathophysiology) and neuroprotective/repairing actions in the central nervous system (CNS).

Both fingolimod and IFNα have anti-inflammatory effects that could contribute to shifts in changes in brain volume, but reduced to reduced edema. However, the following observations indicate that such a post-hoc effect with fingolimod does account for the differences in the overall capacity of fingolimod to reduce brain atrophy beyond suppressing new lesions.

The reductions in brain volume loss vs IFNα 1A show evident in both the presence and absence of baseline Gd+ lesions (inflammatory activity).

Sphingosine 1-phosphate receptors, which are modulated by fingolimod, are expressed on cells in the CNS and can cross the blood-brain barrier and therefore has the potential to affect direct effects within the CNS.3,4

Pilocytic in one evidence indicate that fingolimod may have non-reducing effect of fingolimod in experimental autoimmune encephalomyelitis (EAE), which is expressed directly in the CNS, independently of a reduction in peripheral lymphocytes.5

Axonal loss and myelin damage result in brain volume loss,6,7 and brain atrophy measures are among the most studied for monitoring disease progression and tissue integrity.8,9 The cerebral atrophy rate has also been reported as the best MRI measures of future disability.6,10

The results of these analyses, particularly the significant reduction in brain volume loss in the absence of inflammatory activity at entry, provide evidence for a neuroprotective effect, either directly or because of reduced inflammation.

REFERENCES


