MULTIPLE SCLEROSIS

Fingolimod is an effective oral treatment for MS

Oral fingolimod, a sphingosine-1-phosphate (S1P) receptor modulator, is an effective treatment for relapsing–remitting multiple sclerosis (MS), according to two double-blind, randomized controlled trials published in *The New England Journal of Medicine*. The positive findings from the two studies are remarkably similar and give hope to patients with MS that an orally administered treatment for this condition could be available in the foreseeable future.

MS is a chronic disease affecting the CNS, characterized by an abnormal inflammatory response that results in demyelination of axons and neuronal damage, and which ultimately leads to severe physical and neurological disability in the majority of patients. Several treatments are available to treat the symptoms of this disease, but most are only moderately effective, and the more efficacious treatments are associated with rare but potentially severe adverse events. Moreover, "all of the approved medications are administered by injection, which negatively impacts on convenience, tolerability and compliance," notes Jeffrey Cohen of the Cleveland Clinic, the principal investigator of one of the new studies. "All of the available medications primarily target the abnormal inflammatory aspect of the disease and are not effective versus the degenerative components."

Fingolimod has good bioavailability when taken in an oral formulation. Functional antagonism of lymphocyte S1P receptors by the drug prevents lymphocytes from infiltrating into the CNS by preventing them leaving the lymph nodes in response to chemotactic cues. Furthermore, by interacting with S1P receptors on neurons and glia, fingolimod might have additional neuroprotective or restorative properties.

To determine whether oral fingolimod was an effective treatment for MS, Cohen and colleagues compared two daily doses (0.5 mg and 1.25 mg) with a weekly

30 μg dose of interferon β1a (IFN-β1a), an established treatment for MS that is delivered by intramuscular injection. The study end points were the annualized relapse rate and the number of new or enlarged lesions observed with MRI. Analysis of the 12 month study results revealed "both doses of fingolimod were superior to IFN-β1a in reducing relapses, reducing MRI lesion activity—new and enlarged T2 lesions, and gadolinium-enhancing lesions—and slowing brain atrophy progression," reports Cohen.

In the other study, Ludwig Kappos (University of Basel, Switzerland) and colleagues conducted a double-blind, randomized controlled study to compare the same doses of fingolimod with a placebo for the treatment of patients with relapsing–remitting MS. Again, the fingolimod treatment results were encouraging. Compared with placebo, both doses of fingolimod significantly reduced the annualized relapse rate and the risk of disability progression over the 2 year study period. Furthermore, as in the Cohen *et al*. study, both doses of fingolimod significantly reduced lesion activity and brain atrophy progression.

Another striking similarity between the two studies was that no significant difference in efficacy was evident between the two fingolimod doses. This finding is important because the higher dose of fingolimod seemed to be associated with infrequent but serious infections and cancers in the Cohen *et al*. study. "The rarity of these events makes it difficult to determine with certainty to what extent they were related to fingolimod" Cohen explains. "The results [of the Kappos *et al*. study] did not seem to support the suggestion of increased serious infections and cancer, which is reassuring. Nevertheless, infection and/or cancer would not be unexpected risks with potent immunological therapies."

Further research must be conducted before any direct effects that fingolimod might have on the CNS are fully understood. Cohen and Kappos agree that understanding whether fingolimod has neuroprotective and/or reparative properties, in addition to its effects on lymphocytes, will be important. "The balance between its advantages and potential risks will determine fingolimod's overall utility and whether it is appropriate as a first-line therapy for MS," concludes Cohen.

Nick Jones

Original articles Kappos, L. *et al*. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N. Engl. J. Med*. **362**, 387–401 (2010) | Cohen, J. A. *et al*. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N. Engl. J. Med*. **362**, 402–415 (2010)