NEW DRUGS

Siponimod

Approved indication: multiple sclerosis

Mayzent (Novartis)
0.25 mg and 2 mg film-coated tablets

Most patients with multiple sclerosis have relapses and remissions, however some will eventually develop a progressive form of the disease. While there are several options available for relapsing-remitting disease, there are no effective drugs for secondary progressive multiple sclerosis.

Almost a decade ago, fingolimod was approved for use in patients with relapsing forms of multiple sclerosis to reduce the frequency of relapses and delay the progression of disability. Like fingolimod, siponimod binds to sphingosine-1-phosphate (S1P) receptors, but to a different range of receptor types ($S1P_1$ and $S1P_5$). These receptors are found on T lymphocytes and blocking them reduces the entry of T cells into the central nervous system. This reduces the inflammation which contributes to the progression of multiple sclerosis.

The daily dose is well absorbed irrespective of food. This metabolism is highly susceptible to inter-individual differences in cytochrome P450 (CYP) activity. CYP2C9 is the main enzyme involved, followed by CYP3A4. Pharmacokinetic interactions are therefore possible with inducers (such as carbamazepine) and inhibitors (such as fluconazole) of these enzymes. Siponimod has a half-life of 30 hours and most of the dose is excreted as metabolites in the faeces. No dose adjustments have been recommended for patients with liver or kidney disease. In pregnancy, animal studies show that siponimod can harm the fetus.

A phase II dose-ranging trial studied siponimod in 297 patients with relapsing-remitting multiple sclerosis. This found that siponimod reduced the number of lesions seen on MRI scans. For example, after three months of treatment with siponimod 2 mg daily there was a relative reduction of 70% compared to placebo. That dose reduced the annualised rate of relapse to 0.2 compared to 0.58 with placebo.[1]

The 2 mg dose was used in the main phase III trial in secondary progressive multiple sclerosis. This trial recruited patients with moderate–advanced disability. Approximately 60% of the patients were women. One group of 1100 patients took siponimod while 546 were randomised to placebo. The primary outcome of this trial was the progression of disability. This was assessed using the Expanded Disability Status Scale (a higher score indicates increasing disability). At the start of the study the mean score on the 10-point scale was 5.4. This increased (by 0.5 or 1.0 points depending on the patient's baseline score) in 32% of the placebo group and 26% of the siponimod group. MRI showed a smaller increase in the volume of lesions seen in patients taking siponimod. Their brain volumes also reduced at a lower rate than in the placebo group. The annualised relapse rates were 0.07 with siponimod and 0.16 with placebo.[2]

The median time patients participated in the phase III trial was 21 months. Adverse events resulted in 8% of the siponimod group and 5% of the placebo group stopping treatment. There were four deaths in each group. Adverse events that were more frequent with siponimod included abnormal liver function, hypertension, peripheral oedema, macular oedema, bradyarrhythmia and convulsions.[2]

The mechanism of action of siponimod results in fewer peripheral lymphocytes. This can increase the risk of infection and this hazard may persist for up to a month after treatment stops. In the phase III trial, the overall incidence of infections (49%) was not different from placebo, but herpes viral infections, including shingles, were more frequent with siponimod.[2] Patients without antibodies should be given varicella vaccine before starting siponimod. Live vaccines should be avoided.

The bradyarrhythmia associated with siponimod is seen at the start of treatment. An ECG is needed before treatment begins and the dose of siponimod must be titrated over several days. It should not be used in patients with conduction problems such as second degree (Mobitz type II) heart block.

An ophthalmological examination is recommended before treatment. In view of the risk of macular oedema, further examination is needed if there is a change in vision.

Siponimod is also contraindicated in patients with particular CYP2C9 genotypes. Genetic testing is therefore required before treatment.

At this stage there is limited evidence about the effectiveness of siponimod in preventing disability in secondary progressive multiple sclerosis. What impact will outcomes such as a 0.15% difference in decreased brain volume have on long-term disability? While there was a statistical advantage in changes on the EDSS score, there was no clear benefit in mobility. The time taken for patients to walk 25 feet (7.6 m) increased by at least 20% in 40% of the siponimod group and 41% of the placebo group. There was also no statistically significant difference on the Multiple Sclerosis Walking Scale. Subgroup analysis of the patients in the phase III trial suggests siponimod has less effect in older people, those with a long history of multiple sclerosis and those with higher levels of disability.[2]

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Aust Prescr 2021;44:69–70
https://doi.org/10.18773/austprescr.2021.014

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NEW DRUGS

REFERENCES

1. Selmaj K, Li DKB, Hartung H-P, Hemmer B, Kappos L, Freedman MS, et al. Siponimod for patients with relapsing-remitting multiple sclerosis (BOLD): an adaptive, dose-ranging, randomised, phase 2 study. Lancet Neurol 2013;12:756-67. https://doi.org/10.1016/s1474-4422(13)70102-9
2. Kappos L, Bar-Or A, Cree BAC, Fox RJ, Giovannoni G, Gold R, et al; EXPAND Clinical Investigators. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet 2018;391:1263-73. https://doi.org/10.1016/s0140-6736(18)30475-6

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.