Ozanimod

Approved indication: multiple sclerosis

Zeposia (Celgene)
230, 460 and 920 microgram capsules

The pathophysiology of multiple sclerosis is thought to involve the migration of lymphocytes into the central nervous system. This has led to drugs that alter the immune system being used in the management of patients with multiple sclerosis. In the 1990s interferons were used, followed by injectable monoclonal antibodies, such as alemtuzumab, in the 2000s. Later, oral drugs such as fingolimod were developed.

Like fingolimod, ozanimod is aimed at the sphingosine 1-phosphate (S1P) receptors on the surface of lymphocytes. By binding to these receptors ozanimod is thought to reduce the migration of lymphocytes into the central nervous system.

After absorption ozanimod is extensively metabolised. The parent molecule only accounts for about 6% of the drug activity in the circulation with the rest being accounted for by active metabolites. The multiple enzyme systems involved in the metabolism of ozanimod include cytochrome P450 (CYP) 3A4 and CYP2C8 and monoamine oxidase. There are many potential pharmacokinetic interactions and drugs such as rifampicin and monoamine oxidase inhibitors should be avoided. Ozanimod should not be used in patients with severe liver disease. As little ozanimod is excreted in the urine, it can be used in patients with renal impairment. The half-life of ozanimod is 21 hours, but it is several days for the main metabolites. The long half-life enables a once-daily dose.

The main double-blind clinical trials of ozanimod studied adults up to 55 years old with relapsing forms of multiple sclerosis (see Table).[1,2] These patients were randomised to receive oral ozanimod 0.5 mg or 1 mg daily, or weekly injections of interferon beta-1a. The primary outcome of the trials was the annualised rate of relapse. Brain lesions were evaluated by MRI and disability was assessed using the Expanded Disability Status Scale.[1,2]

In the SUNBEAM trial, 1346 patients were randomised and treated for an average of about 13.5 months. Approximately 93% of the patients completed the study. The annualised relapse rate was 0.24 with ozanimod 0.5 mg and 0.18 with ozanimod 1 mg. These rates were lower than the rate of 0.35 with interferon beta-1a. The number of new or enlarging lesions seen on MRI was also lower with ozanimod.[1]

The RADIANCE trial randomised 1320 patients and treated them for two years. Approximately 87% completed the study. The annualised relapse rate following treatment with interferon beta-1a was 0.28, compared with 0.22 for ozanimod 0.5 mg and 0.17 for ozanimod 1 mg. There were fewer new or enlarging lesions in the brains of the ozanimod group compared to the interferon group.[2]

Adverse events were common in the clinical trials. Approximately 3% of the patients taking ozanimod 1 mg stopped the drug because of these events.[1,2]

Treatment with ozanimod reduces the number of lymphocytes in the circulation. This increases the risk of infection. In the 24-month trial infections such as nasopharyngitis and urinary tract infection were more frequent with ozanimod than with interferon.[2] As herpes zoster was also more frequent, varicella zoster vaccine is recommended for non-immune patients at least one month before starting ozanimod. Live vaccines should not be used during treatment or for three months afterwards.

In addition to checking the patient's full blood count, liver function should be monitored. An increase in liver

Table **Efficacy of ozanimod in relapsing multiple sclerosis**

Trial	Patient allocation	Mean number of relapses in the year before treatment	Annualised relapse rate with treatment
			At 12 months
SUNBEAM[1]	448 interferon beta-1a	1.3	0.35
	451 ozanimod 0.5 mg	1.3	0.24
	447 ozanimod 1 mg	1.3	0.18
			At 24 months
RADIANCE[2]	443 interferon beta-1a	1.3	0.28
	443 ozanimod 0.5 mg	1.4	0.22
	434 ozanimod 1 mg	1.3	0.17

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Related article:
Siponimod for multiple sclerosis

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enzyme concentrations to five times the upper limit of normal was an indication to stop ozanimod in the clinical trials.

Drugs acting on the S1P receptor can cause bradycardia. An ECG is required before treatment and ozanimod is contraindicated if the patient has heart block or a recent history of cardiovascular events such as stroke or myocardial infarction. To reduce the risk of bradycardia the dose of ozanimod is titrated, to the recommended dose of 920 micrograms once daily, over eight days.

Some patients, such as those with diabetes, may be at increased risk of macular oedema while taking ozanimod. They should have ophthalmological examinations before and during treatment.

Animal studies found ozanimod was teratogenic. It should not be used in pregnancy, so women who could become pregnant should use effective contraception during treatment and for three months afterwards. Ozanimod should also not be used during lactation.

When efficacious treatments are available, it would probably not be ethical to compare ozanimod with a placebo, however interferon may not be the most appropriate comparator. While treatment with ozanimod had a larger effect on the rate of relapse, it did not have an advantage over interferon in the progression of disability.[2]

The more selective action of ozanimod on S1P receptors might give it a possible advantage over fingolimod. For example, a patient starting fingolimod requires cardiac monitoring for bradycardia over at least six hours. This is not required with ozanimod, but monitoring is also not needed with siponimod, another recently approved S1P receptor modulator.

Until there is more experience with the new oral drugs it will be uncertain if they have the same risk of rare, but serious, adverse reactions such as the cancers and progressive multifocal leukoencephalopathy seen with fingolimod.

T manufacturer provided the product information

REFERENCES

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2. Cohen JA, Comi G, Selmaj KW, Bar-Or A, Arnold DL, Steinman L, et al; RADIANCE Trial Investigators. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial. Lancet Neurol 2019;18:1021-33. https://doi.org/10.1016/s1474-4422(19)30238-8

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, and the European Medicines Agency.