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The Role of S1P Receptor Agonists in MS: Strategies for Disease Management

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Dr. Weinstock-Guttman:
I'm Bianca Weinstock-Guttman, Professor of Neurology at the Jacobs School of Medicine and Biomedical Sciences. And we'll talk today about The Role of S1P Receptor Agonists in MS: Strategies for Disease Management.

S1P receptors have been proposed as a therapeutic target for various diseases due to their involvement in regulation of lymphocyte trafficking, brain and cardiac function, vascular permeability, vascular and bronchial tone.

S1P receptor modulators were first developed to prevent rejection by immune system following renal transplantation, but FDA approved today are only for multiple sclerosis and ulcerative colitis. The primary mechanism of action of S1P receptor modulators in MS is through binding S1P receptor subtype 1 on lymphocytes resulting in internalization of the receptor and loss of responsiveness to the S1P gradient that drives lymphocyte egress from lymph nodes. The reduction in circulating lymphocytes presumably limits inflammatory cell migration into the CNS. The S1P receptor 5 may benefit oligodendrocyte survival. Four S1P receptor modulators, fingolimod, siponimod, ozanimod, and ponesimod have regulatory approval for MS.

S1P modulators have complex actions on receptors, in some cases acting both as agonists with functional antagonism, and as traditional agonists in other cases. Subsequently developed S1P receptor modulators are more specific, with the goal of preserving effectiveness while mitigating some of the adverse effects, cardiac and vascular. They improve pharmacodynamics and subtype specificity for S1P receptor 1 and 5 may also contribute to improved bioavailability and potentially greater CNS effects compared with fingolimod. Fingolimod is a prodrug that requires phosphorylation, has broad receptor affinity, S1P receptor 1, 3, 4, and 5. Ozanimod and siponimod are selector moderators of S1P receptor 1 and 5. And ponesimod is specific for S1P receptor 1. All S1P receptor modulators are thought to have a similar effect on lymphocytes, although their different half lifetime is important when considering adherence and discontinuation therapy.

Phase 3 clinical trials had been completed for fingolimod, ozanimod, and ponesimod evaluating the efficacy in relapsing remitting MS. All studies found a significant reduction in the primary outcome of annual relapse rate over 12 to 24 months, compared with placebo, interferon beta-1a, or teriflunomide. There was also significant benefit on MRI markers, including gad-enhancing, and on T2 lesions, well as measures of tissue damage, as T2-hyperintense and T1-hypointense lesions, brain volume loss, and cortical matter, and thalamic volume loss.

There were variable changes in worsening of disability as measured by EDSS and MSFC, showing significant benefit in one fingolimod trial than siponimod when compared with placebo, but not reaching significance in the other studies that were evaluated against active comparators, interferon beta and teriflunomide.

All S1P modulators are today approved for clinically isolated syndrome, relapsing remitting, and secondary progressive; however, only

siponimod has so far demonstrated efficacy in active SPMS contrasting with the absence of clinical effects with fingolimod in primary progressive MS.

The important consideration in the use of S1P receptor moderators in MS is the slowing of heart rate and AV conduction with initial – initiation of a therapy. On initiation of therapy, fingolimod acts as an agonist activating S1P receptor leading to the transient bradycardia, delayed atrioventricular conduction, and prolongation of the QT interval. With continued administration, there is downregulation of S1P receptor and resolution of the cardiac effects. Therefore, for fingolimod there is a first dose effect required, also called FDO, first dose observation, for at least 6 hours for all patients starting this therapy and they're monitored with pulse and blood pressure hourly, ECG before dosing and at the end of the observation period. However, the benefit of dose up-titration as on ozanimod and siponimod over the first several days of treatment attenuates the need for initial cardiac effects, and no second- or third-degree AV block was reported in the phase 3 trials, eliminating the requirement for FDO in the absence of a cardiac history.

Additional side effects are considered to be related to vasoconstriction as increased blood pressure, macular edema, and pulmonary dysfunction. Many of the adverse effects observed with fingolimod were thought to be related to broader engagement of the S1P receptor which led to the development of the more selective S1P modulators. Infections were reported in all phase 3 clinical trials, including upper respiratory tract infection or urinary tract infections. One death occurred in the phase 3 trial with fingolimod due to disseminated varicella infection, leading to the recommendation to check varicella zoster antibodies before initiation. There are also rare cases of progressive multifocal leukoencephalopathy due to reactivation of JC virus and cryptococcal meningitis. There is also an increased risk for skin malignancy, especially basal cell carcinoma.

So, the recommendation for S1P use, there are contraindications in the prescribing of S1P modulators, including primary history of several cardiovascular conditions, that's MI, TIA, stroke in the last 6 months, unstable angina, as well as sick sinus syndrome, QT interval more than 500, and cardiac arrhythmia as well as severe sleep apnea or MAO use.

With siponimod, the majority of patients can initiate therapy without the need for monitoring, whereas FDO is recommended only for patients with sinus bradycardia. With ozanimod, no monitoring at treatment initiation is required, but cardiologist consultation is suggested for patients with conduction abnormalities.

Differential pharmacokinetic response to siponimod in patients with CYP2C9 genotypes 1/3 or 2/3 require the genotyping of patients for siponimod and that's to be performed before treatment starts, as the genetic changes require a lower dosage of 1 mg, instead of 2 mg as for usual patients.

Strong CYP2C8 inhibitors, as gemfibrozil, are contraindicated and advised to avoid foods containing a large amount of tyramine, as aged cheese or pickled herring, while taking recommended doses of ozanimod.

So general baseline and monitoring, we need bloodwork at baseline and monitoring with CBC because of the risk of lymphopenia, and liver function, evaluation of varicella zoster antibody. If negative, vaccination required before initiating therapy. Ophthalmology evaluation, including OCT, as related to risk for macular edema, at baseline and anytime there's change in vision. And dermatology yearly evaluation for the risk of cutaneous malignancy, as basal cell carcinoma, squamous cell, or melanoma.

Thank you very much for listening.

Announcer:
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