NeurologyAdvisor

How I Treat My Patients With Siponimod for Secondary Progressive Multiple Sclerosis

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I am Asaff Harel, MD. I work at the Multiple Sclerosis Center at Lenox Hill Hospital, as well as at the Cushing Neuroscience Institute, taking care of patients with multiple sclerosis (MS) and related conditions. I'm here to discuss siponimod, a newly approved medication for MS. I will be going through the indications for use and instructions on how to get started with the medication, as well as which patients might be appropriate for this kind of medication.

Siponimod is a novel S1P receptor modulator, similar to fingolimod, but it is highly selective for the S1P1 and S1P5 receptors; that means that it potentially has fewer side effects compared with fingolimod and potentially has different effects, as well. Siponimod is a once-daily pill, as is fingolimod. Siponimod acts on these S1P receptors, both on lymphocytes, which leads to lymphocyte sequestration with lymph tissue, but it also crosses the blood-brain barrier a little bit more readily than fingolimod does. Therefore, it may have some central effects on neurons in the central nervous system, astrocytes, microglia, and on oligodendrocytes, and so it could also provide a neuroprotective effect.

Siponimod was studied in a phase 2 study looking at people with relapsing remitting MS and in a phase 3 study looking specifically at people with secondary progressive MS. Siponimod actually had the first successful trial for people with secondary progressive MS. The primary end point in the study was looking at confirmed disability at 3 months. People on siponimod did statistically significantly better than people getting placebo, and people on siponimod had a reduction in confirmed disability by approximately 20%. Siponimod had substantial effects on lowering lesion accrual over time, and it also had effects on reducing brain atrophy.

As we have seen with some other studies, such as the study looking at ocrelizumab, siponimod also had more of an effect on people with inflammatory activity. So, people who recently had relapses or new lesion formation on magnetic resonance imaging (MRI) tended to do better with siponimod compared with people who were "inactive." Based on the data that showed siponimod had a statistically significant effect on disability worsening in people with secondary progressive MS who had recent disease activity – meaning relapses and new lesions – the US Food and Drug Administration (FDA) has approved it for what we call active secondary progressive MS. These are people with inflammatory activity. The FDA actually chose not to approve it for people with inactive secondary progressive MS.

As I mentioned before, siponimod is a once-a-day pill. It does not require a first-dose observation for cardiac effects, like fingolimod used to, because it is a more selective S1P receptor modulator. However, in order to decrease the risk of cardiac effects like bradycardia and heart block, titration of the medication is required. That titration takes 4 or 5 days depending on the patient's genotype.

Metabolism of sulfonamide is affected by the cytochrome P450 pathway, and patients do need to be genotyped prior to starting siponimod.

Most patient will fall into the category of needing to be on a 2-mg dose. A small proportion of patients will need a lower dose, and their genotype will help to determine that. As I mentioned before, a first-dose observation is not necessary. However, what I would recommend, what the manufacturer recommends, and what the FDA recommends is that people should still undergo electrocardiography to make sure there are no cardiac comorbidities. They should also have an eye examination to look for any evidence of macular edema. If there are people who ideally would benefit from this medication but they do have cardiac comorbidities – and a lot of the people with secondary progressive MS are older so they tend to have those cardiac comorbidities – at that point, the FDA does recommend that patients undergo a first-dose observation. In some cases, what I would recommend is to get a cardiologist involved.

So interestingly, in addition to having an effect on reducing disability worsening over time in people with secondary progressive MS, there are also some data that show that people who were on siponimod actually improved with regard to cognition, and people on placebo did not.

As I mentioned before, the FDA has approve siponimod for active secondary progressive MS, who are those with SPMS that have had relapses recently or at least disease activity on MRI recently. They have also proved that for relapsing remitting MS and for clinically isolated syndrome, even though they didn't have a phase 3 study with that population, it is based on class effect from fingolimod and also based on the phase 2 study.

Assuming that insurance is not an issue and that step edits may not be an issue, I think it is reasonable to offer siponimod as opposed to fingolimod in people with relapsing MS, with relapsing remitting MS, and with clinically isolated syndrome, but in actual practice, step edits do get in the way.

I think this medication is certainly indicated and would be of benefit in people with secondary progressive MS who have shown either new lesion accrual or who have had relapses over the last couple of years. What is a little bit more controversial and is as of right now unclear in my mind is whether anybody who is “stable” on an older medication – such as the “platform” injectable medications, for example – would benefit from a transition to siponimod.

There are some data out there to suggest that people who we consider “stable” in the clinic – those people who have not had relapses or disease activity on MRI and have not had worsening on Expanded Disability Status Scale (EDSS) score – may still have worsening of their disease and a substantial proportion of them for example may have cognitive worsening or worsening of brain atrophy. Therefore, it is possible that these people who have been “stable” on “platform” medications such as older injectable medications may benefit from a switch to another disease-modifying therapy. Further research is needed to really determine whether a switch from any of these “platform” agents would be helpful.

Given that siponimod is metabolized through the cytochrome P450 system, special care is necessary to evaluate for other comorbidities and other medications that may interact with the

system, such as cytochrome P450 inducers or inhibitors that may affect the amount of drug that is in the bloodstream. So as with fingolimod, there is a risk of cardiac effects, although those are upfront and generally mild, and there is potential risk of infection. However, with fingolimod, postmarketing data showed that there is a risk of progressive multifocal leukoencephalopathy (PML). There were no cases of PML in the EXPAND study, but that does remain a potential risk and vigilance is indicated. As with fingolimod, there is also a risk of macular edema with siponimod. It remains a small risk and ophthalmologic examination prior to starting the medication and then several months after starting the medication is certainly indicated, as well.