Prospects of siponimod in secondary progressive multiple sclerosis

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Marisa McGinley and Robert J. Fox

The characterization and treatment of progressive multiple sclerosis has been a challenging area of research. Despite many advances in treatments options for relapsing–remitting multiple sclerosis (RRMS), there are a paucity of treatment options for progressive MS, either primary progressive MS or secondary progressive MS. The pathophysiology of progressive MS is unknown, but likely includes the infiltrative inflammatory damage seen in relapsing MS, along with compartmentalized inflammation and neurodegeneration.[1,2]

EXPAND was a randomized double-blind phase III clinical trial comparing siponimod (n = 1099) with a matching placebo (n = 546) in patients with secondary progressive MS.[3] Siponimod is a selective modulator of the sphingosine-1-phosphate (S1P) receptors SIP1 and SIP5. Other S1P modulator therapies include fingolimod, which is approved for relapsing forms of MS, and ozanimod and ponesimod, which are under development for use in MS.[4] One mechanism of action of siponimod is the reduction of lymphocyte egress from lymphoid tissue, which prevents lymphocytes from circulating to the central nervous system. Other hypothesized mechanisms are prevention of synaptic neurodegeneration and promotion of remyelination due to its ability to cross the blood–brain barrier and potentially act directly within the brain.

In the EXPAND trial, 1646 patients with secondary progressive MS were randomly assigned to receive either siponimod or placebo. Enrolled patients were typical of those seen in clinical practice, with a mean age of 48 years and disease duration of 16–17 years. All trial participants continued the assigned treatment until a target number of participants had sustained progression of disability. As a result, participants had a variable exposure to treatment. A total of 81% of patients completed follow up, which ranged from 11 to 37 months (median 18 months).

The primary outcome was the 3-month confirmed disability progression (CDP), where siponimod demonstrated a relative risk reduction of 21% compared with placebo. A similar relative risk reduction was also seen for the 6-month CDP, where there was a 26% reduction. The rate of clinical relapses also was significantly lower in the siponimod group, as was the time to confirmed first relapse. Magnetic resonance imaging outcomes included a change in T2 lesion volume from baseline and brain volume, both of which were reduced in siponimod-treated patients compared with placebo. Additionally, siponimod patients had fewer gadolinium-enhancing lesions and new or enlarging T2 lesions. The only key secondary outcome that did not favor siponimod was time to 3-month confirmed worsening of at least 20% in the timed 25 foot walk (T25FW).

Exploratory subgroup analyses suggested that the treatment effect became less pronounced with increasing age, disability, baseline disease duration, and diminishing signs of disease. This finding is similar to what was seen with ocrelizumab in primary progressive MS, where greater benefit was seen in younger patients and those with gadolinium-enhancing lesions at baseline.[5]

These observations raise the question of whether the observed benefits of siponimod may be attributed to systemic anti-inflammatory properties, as this drug class is well known to have anti-inflammatory effects in MS. However, there are arguments for other mechanisms of action. Siponimod is known to cross the blood–brain barrier, which

Correspondence to:
Robert J. Fox
Cleveland Clinic, 9500 Euclid Avenue, U-10, Cleveland, OH 44120, USA.
foxr@ccf.org

Marisa McGinley
Cleveland Clinic, Cleveland, OH, USA

may allow it to affect not only systemic inflammation, but also the compartmentalized inflammation seen in progressive MS. Additionally, the deceleration of brain atrophy progression suggests that siponimod could slow down disease progression *via* routes beyond an anti-inflammatory effect. Finally, in a mouse model, siponimod was shown to modulate biological pathways involved in cell survival with subsequent attenuation of demyelination.[6] A study using another mouse model of brain inflammation reported that siponimod can prevent loss of GABAergic interneurons, which is thought to contribute to neurodegeneration.[7]

The most common safety events that occurred more frequently with siponimod use were lymphopenia, increased liver transaminase, bradycardia and bradyarrhythmia at treatment initiation, macular edema, hypertension, *Varicella zoster* reactivation, and convulsions. Most of these safety events have been reported with other medications in the same class.

In summary, in a large, placebo-controlled trial, siponimod was found to slow the sustained progression of disability in secondary progressive MS and had an acceptable safety profile. Further analysis of this dataset and additional research is needed to better understand whether the benefit was primarily driven by the anti-inflammatory effect that is well established by this class of therapies. Nonetheless, siponimod is a promising therapeutic option for secondary progressive MS.

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