PR–Fampridine Improves Mobility in Patients With MS

Written by Maria Vinall

Prolonged release (PR)-fampridine treatment resulted in sustained and clinically meaningful improvement in walking ability and balance throughout a 6-month treatment period in individuals with multiple sclerosis (MS). The Exploratory Study to Assess the Effect of Fampridine (BIIB041) on Walking Ability and Balance in Participants With Multiple Sclerosis study [MOBILE; NCT01597297; Hupperts R et al. ACTRIMS/ECTRIMS 2014 (poster P922)] evaluated the effect of PR-fampridine on walking ability, dynamic and static balance, and subjective impressions of well-being. Raymond Hupperts, MD, Orbis Medical Center, Sittard-Geleen, the Netherlands, presented the findings in a poster session.

Maintaining mobility is among the greatest concerns for patients with MS [Sutliff MH. *Curr Med Res Opin.* 2010]. PR-fampridine was approved to improve walking in MS based on the results of 2 pivotal trials [Goodman AD et al. *Ann Neurol.* 2010; Goodman AD et al. *Lancet.* 2009] that demonstrated consistent improvements on the Timed 25-Foot Walk (T25FW). The T25FW, however, may not fully assess all of the domains that control walking ability, including balance [Nogueira LA et al. *Mult Scler Int.* 2013].

MOBILE was a randomized, double-blind, multicenter, placebo-controlled, exploratory 24-week phase 2 study conducted at 24 sites in 6 countries. Patients (n = 132) aged 18 to 70 years, with progressive and relapsing MS and an Expanded Disability Status Scale (EDSS) score of 4.0 to 7.0, were randomly assigned (1:1) to PR-fampridine 10 mg BID (n = 68) or placebo (n = 64) for 24 weeks. Outcome measures included walking ability assessment using the 12-item Multiple Sclerosis Walking Scale (MSWS-12) and Patient Global Impression of Change (PGIC); mobility and balance assessment using the Timed Up and Go (TUG) test and Berg Balance Scale (BBS); and subjective impression of well-being assessment using the Multiple Sclerosis Impact Scale (MSIS-29), physical subscale (PHYS), and EuroQoL-5 Dimension 5-level instrument (EQ-5D-5L). Safety and tolerability were assessed by monitoring adverse events (AEs).

Mean age of the patients was 49.8 years; 54% were women. The mean EDSS score was 5.7. Baseline to week 24 improvements in the MSWS-12, TUG test, BBS, and MSIS-29 PHYS were greater following treatment with PR-fampridine compared with placebo. Benefits declined by the week 26 visit following discontinuation of treatment at week 24.

More patients treated with PR-fampridine vs placebo reported improvement on the PGIC at the week 2 visit: 31 patients (46%) for PR-fampridine vs 16 (26%) for placebo. No apparent differences between treatment groups were observed in the EQ-5D-5L utility index. The cumulative percentage of patients with a mean improvement in the MSWS-12 score and TUG test was greater in the PR-fampridine-treated patients compared with the placebo group.

Safety findings were consistent with the known safety profile of PR-fampridine. The number of patients who discontinued (PR-fampridine, n = 13; placebo, n = 12) was similar. AEs were the main reason for discontinuation in both groups (PR-fampridine, n = 7; placebo, n = 5). No seizures were reported, and serious AEs were reported by fewer patients treated with PR-fampridine (2/68; 3%) compared with placebo (5/64; 8%). The common AEs were nasopharyngitis and urinary tract infection.

In this study, PR-fampridine improved a broad range of objective and patient-reported measures of walking ability. An ongoing phase 3 study will seek to confirm these findings.

Improvement in UI With OnabotulinumtoxinA Maintained Over 4 Years in Patients With MS

Written by Emma Hitt Nichols, PhD

A long-term extension trial demonstrated improvement in urinary incontinence (UI) as a result of neurogenic detrusor overactivity (NDO) caused by multiple sclerosis (MS). Philip J. Aliotta, MD, Western New York Urology Associates, Cheektowaga, New York, USA, presented data from A Long-term Follow-up Study of Botulinum Toxin Type A in Patients With Overactive Bladder as a Result of Spinal Injury or Multiple Sclerosis trial [NCT00876447; Aliotta PJ et al. ACTRIMS/ECTRIMS 2014; (poster P905)].

NDO can occur in patients with MS, which results in UI [de Sèze M et al. *Mult Scler.* 2007]. Two randomized trials demonstrated that intradetrusor onabotulinumtoxinA was effective and well tolerated for the treatment of NDO in patients with spinal cord injury or MS who did not achieve adequate relief with an anticholinergic agent [Ginsberg D et al. *J Urol.* 2012; Cruz F et al. *Eur Urol.* 2011]. According to Dr Aliotta, the purpose of this 3-year extension study was to evaluate the use of onabotulinumtoxinA for the treatment of UI as a result of

NDO in patients with MS over a long-term follow-up of up to 4 years.

In the 3-year extension study, 231 patients received ≥1 treatment of the same dose of onabotulinumtoxinA (200 U or 300 U) as that administered in the core trials; however, an amendment to the extension trial allowed a change in the treatment from 300 U to 200 U of onabotulinumtoxinA, if requested. Patients received treatment as needed over 4 years and the change in baseline UI episodes per day was evaluated, as were the incidence of adverse events (AEs) and the initiation of clean intermittent catheterization (CIC). At baseline, the mean number of UI episodes per day ranged from 4.6 to 4.8, and CIC was in use in 33% to 46% of patients.

Treatment with onabotulinumtoxinA resulted in a decrease in the number of UI episodes per day, and 45.2% to 61.9% of patients achieved complete continence at 6 weeks with the 200 U dose. The efficacy was similar in patients who switched from the 300 U to 200 U dose of onabotulinumtoxinA. The median duration of the anti-UI effect was 9.1 months for patients who received 200 U of onabotulinumtoxinA and 9.6 months for patients who received 300 U. After the first treatment cycle of onabotulinumtoxinA, de novo use of CIC was highest but declined after the second and third treatment cycles for both doses of the drug.

Common AEs included urinary tract infections and urinary retention. Retreatment with onabotulinumtoxinA did not increase the rate of AEs. Discontinuation of the study drug as a result of AEs or lack of efficacy occurred in 3% and 1.7% of patients, respectively.

In conclusion, Dr Aliotta stated that the results from this long-term extension trial indicate that the efficacy of onabotulinumtoxinA was maintained over 4 years, with no new safety signals.

Potential Genetic Locus Associated With MS Identified in African Americans

Written by Brian Hoyle

An analysis of genetic determinants of multiple sclerosis (MS) in African Americans has implicated the locus for non-sense-mediated mRNA decay factor 7 (*SMG7*), located on chromosome 1, as a potentially unique MS-associated site in this population. The results were reported by Noriko Isobe, MD, PhD, University of California at San Francisco, San Francisco, California, USA.

While the prevalence of MS in people of African origin was once thought to be relatively low, this may not be the case. In African Americans, not only is the prevalence of MS higher than anticipated, it appears to be on the rise [Langer-Gould A et al. *Neurology.* 2013; Wallin MT et al. *Brain.* 2012]. The MS that develops in African Americans has been described as more severe than that in Europeans [Cree BAC et al. *Neurology.* 2004], with *HLA-DRB1*15:01* and *HLA-DRB1*15:03* being especially associated with MS in African Americans [Isobe N et al. *Neurology.* 2013; Oksenberg et al. *Am J Hum Genet.* 2004].

The use of the ImmunoChip technology, in which different single nucleotide polymorphisms (SNPs) and small regions harboring genetic insertions or deletions are spaced out on a support that is used to probe entire genomes for the targets, has identified nearly 197 000 SNPs linked to a variety of diseases including type 1 diabetes, psoriasis, autoimmune thyroid disease, ankylosing spondylitis, ulcerative colitis, celiac disease, Crohn's disease, rheumatoid arthritis, MS, and others. Of these SNPs, 110 have been associated with MS in Europeans, with a further 48 identified as novel MS loci [IMSGC. *Nat Genet.* 2013].

The present study assessed whether the MS-associated loci identified in Europeans were also identified in African Americans, and if there were other, unique loci in this population. Chromosome samples from 843 African Americans with confirmed MS were examined along with samples from 1612 subjects without any symptoms of MS. Twenty one of 96 European MS loci were properly matched with the particular SNP, indicating the accuracy of the approach. A standard ImmunoChip analysis identified 110 MS-associated SNPs that were not present in Europeans. Of these, 8 were located in linkage disequilibrium regions ($r^2 > 0.5$) of the original MS-associated SNPs. Of the 8, 7 were determined to lie outside of known MS-associated SNPs ($P < .0001$). Finally, of the 7, *SMG7*, located on chromosome 1, was implicated as being associated with MS in African Americans.

The rs2702180 SNP involved with *SMG7* has been linked to the expression of *SMG7* in brain tissue and lymphoblastoid cells [Gibbs JR et al. *PLoS Genet.* 2010; Stranger BE et al. *Nat Genet.* 2007]. *SMG7* abuts *NCF2*, a gene that has been linked with systemic lupus erythematosus [Cunninghame Graham DS et al. *PLoS Genet.* 2011].

The researchers concluded that the *SMG7* locus located on chromosome 1 is a potential candidate site in African Americans with MS. Next, since the ImmunoChip focuses on SNPs and not functional variants, studies involving more samples and functional analyses are needed to conclusively assess this potential association.