

Reply: 3,4-Diaminopyridine in LEMS: concerns regarding presentation of previous studies

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We appreciate the letter from Dr. Oh, a leader in the treatment of Lambert-Eaton myasthenia (LEM).

DAPPER was a multicenter, monitored, randomized controlled trial of 3,4-diaminopyridine base (3,4-DAP) in LEM, using an objective primary outcome measure that assesses dysfunction characteristic of LEM.<sup>1</sup> All but one of the previous trials of 3,4-DAP in LEM were unmonitored single-center studies.<sup>2-5</sup> The 2016 study of 3,4-diaminopyridine phosphate used a composite outcome measure that included the quantitative myasthenia gravis QMG score and a subjective, patient-derived assessment.<sup>6</sup> Although the QMG of patients treated with 3,4-DAP showed marginally significant improvement in that study ( $p=0.045$ ), the mean difference in QMG was only 1.7 points, which is not considered clinically significant in myasthenia gravis (MG).<sup>7</sup> The clinical significance of change in QMG score has not been determined for LEM.

Use of the QMG is problematic in LEM, in which strength typically facilitates, and thus may improve during testing. Also, ocular and bulbar muscle functions, which are frequently normal in LEM, are major components of the QMG. In 2 previous trials of 3,4-DAP in LEM, the mean QMG improved 2.25 and 2.65 points, respectively, in patients receiving 3,4-DAP compared to those receiving placebo.<sup>3,4</sup> Meta-analysis of these studies showed a mean advantage of 2.44 QMG points of 3,4-DAP over placebo.<sup>8</sup> Because of the poor performance of the QMG in these previous studies, DAPPER used the Triple Timed-Up-and-Go (3TUG) test, an outcome measure that assesses typical LEM dysfunction.<sup>9</sup> To accommodate fatigue or facilitation,<sup>9</sup> the 3TUG involves 3 repetitions of the timed-up-and-go test, which has been validated in the elderly<sup>10,11</sup> and patients with Parkinson Disease.<sup>12,13</sup>

The highly significant 3TUG results ( $p < 0.0001$ ) of DAPPER were corroborated by highly significant improvement in patient self-assessment of weakness and by changes in compound muscle action potential amplitudes.

Studies are in progress to validate the 3TUG as a clinical measure in LEM.

Acronyms: 3,4-DAP – 3,4-diaminopyridine; 3TUG – triple timed up-and-go-test; DAPPER -- 3,4-DAP Product Efficacy Research; LEM – Lambert-Eaton myasthenia; MG – myasthenia gravis; QMG – quantitative myasthenia gravis score

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