SPACE trial. A phase II, monocenter, double-blind, placebo-controlled, cross-over trial to assess efficacy of pyridostigmine in patients with spinal muscular atrophy types 2, 3 and 4

Background

Studies in SMA animal models and patients have shown abnormalities in anatomy and function of the neuromuscular junction (NMJ). NMJ dysfunction could contribute to weakness and fatigability in SMA patients. We hypothesized that pyridostigmine, an acetylcholinesterase inhibitor, could improve NMJ function. We conducted a monocenter, placebo-controlled, double-blind cross-over trial with pyridostigmine and placebo to investigate the effect and efficacy of pyridostigmine on muscle strength and fatigability in SMA. Primary outcome measures were: safety, a change in the MFM and repeated Nine-Hole Peg Test (r9HPT) before and after treatment. Secondary outcome measures included recently developed shuttle tests for fatigability, muscle strength, EMG and several patient reported outcome measures.

Results

In total, 37 unique patients were randomized and the final efficacy population consisted of 35 patients. Overall pyridostigmine was well tolerated. Adverse events happened in both treatment periods, although more in the pyridostigmine period, and were mostly acceptable and self-limiting. There were no serious adverse events that were thought to be connected to the study medication.

We found a significant decrease in the risk of dropout during the 20-minute shuttle endurance tests of 68.9% (HR 0.39, CI 0.19 to 0.79, p = 0.009) under pyridostigmine. A similar trend was seen in the MFM, which was on average, 41.1 (95% CI 40.0 to 42.3) under placebo and 42.1 (95% CI 40.9 to 43.2) under pyridostigmine, resulting in a mean difference of 0.97 points (95% CI -0.34 to 2.28, p-value = 0.14). There was, however, a significant interaction between treatment and period (p-value = 0.026). The mean difference between placebo and pyridostigmine during the first period was 0.85 points (95% CI -1.31 to 3.01, p-value = 0.43). A comparable trend was observed in the repeated nine-hole PEG test favoring pyridostigmine, with a slowing in the rate of increase in time needed over trials of -0.68s (95% CI -1.47 to 0.12, p-value = 0.09) or 44.7%. There was no evidence for a carry-over effect (p-value = 0.33).

Conclusions

We demonstrate that pyridostigmine reduces fatigability in patients with spinal muscular atrophy, as is shown by the decreased dropout during the endurance tests. We observed trends in the same direction in the primary endpoints. Adverse events happened in both treatment periods and were overall acceptable and self-limiting. There were no serious adverse events that were thought to be connected to the study medication. Pyridostigmine is a promising, low cost, (add-on) therapy for SMA, even for older patients with longer disease duration. The use of pyridostigmine can improve quality of life by reducing complaints of fatigability.

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