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Anti-androgen Treatment for Spinal and Bulbar Muscular Atrophy

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Spinal and bulbar muscular atrophy (SBMA), or Kennedy's disease, is a hereditary motor neuron disease caused by an expanded polyglutamine repeat in the androgen receptor.[1] The repeat expansion causes the mutant protein to be toxic to motor neurons, and evidence from animal models indicates that the toxicity is androgen dependent.[2–4] Male but not female mice develop the manifestations of the disease because they have greater levels of androgens (testosterone and dihydrotestosterone). In transgenic mice, female mice given exogenous androgens become weak, and male mice treated with anti-androgens do not.[5] This, of course, has important therapeutic implications. A controlled clinical trial is needed to answer the question whether the treatment that has been shown to be effective in mice is also effective in SBMA patients.

In this issue, Banno and colleagues[6] report a randomized, double-blind, placebo-controlled, 48-week, 50-subject, phase 2 study of the anti-androgen leuprorelin in patients with SBMA. The authors recognized the importance of a prespecified, clinically meaningful primary endpoint, with multiple secondary endpoints. Dr Banno and colleagues[6] chose the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) for the primary outcome measure, and included multiple secondary outcome measures: cricopharyngeal opening duration (CPOD) visualized by videofluorography; the frequency of 1C2-positive cells in scrotal skin biopsies; pulmonary function measures; serum enzyme levels; the sum of the ALSFRS-R speech, salivation, and swallowing subscores; nerve conduction studies; and measures of muscle strength. By including outcome measures that explore a variety of clinical manifestations, the authors increased the likelihood that the study would detect any clinical activity of the study drug.

Unfortunately, at the end of the double-blind, placebo-controlled, 48-week portion of the study, comparison of the two study arms (ie, leuprorelin vs placebo) for the primary endpoint (ALSFRS-R) showed no significant difference. In contrast, CPOD improved in subjects who received leuprorelin but deteriorated in subjects who received placebo ($p < 0.05$). Based on this evidence, the authors suggest that CPOD may be useful as a "practical biomarker to evaluate therapy efficacy for SBMA in short-term trials."[6] However, until there is additional experience that better establishes the characteristics (eg, reliability, sensitivity to change, resistance to bias, correlation with clinically meaningful endpoints) of

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CPOD as a surrogate outcome measure, clinical trialists should be hesitant to trust CPOD to test potential treatments in SBMA trials.

Banno and colleagues[6] also included a 96-week, open-label extension (OLEX) at the end of the double-blind portion of the trial. An OLEX is often useful as an incentive for recruitment, to provide long-term safety data, and rarely to provide long-term efficacy data. Forty-nine subjects participated in the OLEX; 34 subjects took leuprorelin in the OLEX, whereas 15 subjects received no treatment. These 15 subjects "declined to continue leuprorelin administration mostly due to economic reasons." As a result, the OLEX enrolled 49 subjects into 4 different groups. The authors present an analysis (see Fig 3B) that shows that the deterioration in the ALSFRS-R over the entire 144 weeks (48-week blinded period + 96 week OLEX) was directly proportional to the duration of leuprorelin exposure in each group. The difference between subjects who never received leuprorelin (Group D) and subjects who received leuprorelin for all 144 weeks (Group A) was statistically significant at p less than 0.001. This is in striking contrast with the "no significant difference" result during the 48-week blinded portion of the study.

However, there are problems with this analysis of the 144-week data. First, the four groups have different numbers of subjects and were not selected by randomization. Without randomization, there are likely to be important, but unknown, prognostic differences between the groups; these differences may produce a biased result.

Second, as seen in Figure 3A in Banno and colleagues'[6] article, through the double-blind 48 weeks, the placebo-treated Group D subjects were relatively stable. When blinded treatment was withdrawn, the Group D ALSFRS-R scores declined precipitously. This discrepancy between the behavior of Group D during the two periods of the study may be because of expectation bias. The administration of blinded placebo produced an expectation of benefit (ie, a placebo effect) that caused stabilization of the ALSFRS-R during the 48-week blinded period. In addition, and perhaps more worrisome, is the possibility that administering no treatment produced an expectation of deterioration that resulted in the exaggerated decline of the ALSFRS-R during the OLEX. This expectation of deterioration may have been particularly acute if the subjects were denied leuprorelin because of their economic status. Therefore, the study design, particularly the loss of blinding during the OLEX, may account, in part, for the group differences presented in Figure 3B.

Clearly, further study is needed: ideally, a multiyear, placebo-controlled trial with a clinically meaningful primary endpoint. Although Banno and colleagues'[6] study shows biological effects, it does not demonstrate clinical efficacy; thus, it does not yet support the use of leuprorelin in patients with SBMA. Whether antiandrogen treatment is safe and effective in SBMA is still to be determined. However, the authors are to be commended for completing this preliminary trial that could lead to a definitive answer.

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