May 14, 2018

This letter is in response to a request for information about our experience using Spinraza to treat adults with Spinal Muscular Atrophy (SMA). The Stanford Neuromuscular Program began treating infants affected by SMA1 with Spinraza in 2013, and older children with SMA2 in 2015. We have now treated 80 people with Spinal Muscular Atrophy, including 40 adults. Our experience with adults on Spinraza can be organized into three basic realms:

1. Subjects in the early Ionis Pharmaceutical and Biogen trials (CS2) of older adolescents who are now young adults
2. Objective follow-up assessment of adults who have been treated with commercially available Spinraza for, currently, 2 years
3. Subjective responses of adult patients treated since early 2017 after Spinraza became commercially available.

Data on five patients treated in the adolescent Spinraza trial were reported at the Annual MDA patient conference in March, 2018. The ages ranged from 14.4 to 16 years when first treated, and 17.5 to 19.2 years when last assessed on treatment. Results from approximately 2.5 years of follow-up show:

- Hammersmith Functional Motor Scale, Expanded (HFMSE, n=5) ranged from change of 0 to +4 points, while natural history would on average be expected to decline by 1.0 to 2.5 points in that timeframe
- Revised Upper Limb Module (RULM, n=3) change of 0 points, while natural history would predict a decline of 1.0 to 2.5 points
- 6-minute walk test (6MWT, n=3) increased 32-150 feet, which differs from the natural history average response, which is to lose 25 to 50 meters in that period of observation

Regarding adults treated commercially with Spinraza at Stanford, we have treated a total of 40 patients, and as of April, 2018, have follow-up data for 32 patients (first evaluation after initiation of treatment is done at month 2 after completion of the loading sequence). Adults range in age from 18-65 years (mean 37 years), 17 being male and 13 female. Twenty-two were diagnosed as having SMA3, 8 with SMA2. Of these patients 22 were non-ambulatory and 8 remained ambulatory (able to walk at least 25m). Three of the patients had tracheostomies and required continuous ventilatory support. A total of 148 injections had been completed, 63 of which required Interventional Radiologic guidance, while 85 were completed by conventional lumbar puncture without radiologic guidance. There were few post-LP headaches, all of which were self-limited without need for blood patch. There were no other significant side effects or medical concerns from the procedure or the medication. Of the 21 patients with follow-up evaluation, results of different tests showed:

- Hammersmith Functional Motor Scale, Extended (HFMSE, n=4) showed a consistent slight average improvement with the natural history predicting a decline of ~1 points during this period
- 6-Minute Walk Test (6MWT, n=7) was very variable, but showed a slight decline in the first year, with the natural history predicting a more moderate decline of 10-20m during this period
- Revised Upper Limb Module (RULM, n=17) showed a mild consistent improvement, with natural history predicting a decline of 0.5-1.5 points during this period

- Forced Vital Capacity % Predicted (FVC %, n= 14) was very variable and on average showed a slight decline, with natural history predicting a more significant decline of 2-3% during the period of observation
- Maximum Inspiratory Pressure, cm H_20 (MIP, n=14) showed a consistent moderate improvement, with natural history for this measure being unavailable, but presumably showing at least a mild deterioration during this period
- Maximum Expiratory Pressure, cm H_20 (MEP, n=14) showed a consistent moderate improvement, with natural history for this measure being unavailable, but presumably deteriorating at least a few cm during this period

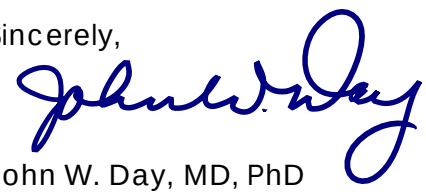
The subjective responses of patients receiving Spinraza are necessarily non-quantitative, but the accompanying testimonials are nonetheless impactful. Twenty-eight of thirty subjects reported subjective improvements; the other 2 subjects improved on objective measures, which they then acknowledged, but they were less inclined to subjectively report improvement. Several patients had noted subjective changes that directly affected their quality of life and independence, and (unlike most placebo effects) have persisted for 9 months or more, including:

- A 51yo woman who had previously lost the ability to feed herself or chew meat, after starting Spinraza noted she regained the ability to do both, improving her independence and quality of life
- A 45yo man noted that Spinraza improved his ability to climb stairs, and eliminated his need for a walking stick, allowing him to expand duties in an executive position rather than having to change employment
- A 40yo man could not be left unattended because he had no independent ability to regain a seated position if he fell forward while seated in his power wheelchair, risking suffocation. On Spinraza he regained the ability to bend over and sit back up completely by himself, increasing his independence and decreasing cost of care

We realize that these findings are preliminary, so we are continuing to collect data on the first 30 and additional adult patients we are treating. In addition, we are working to expand the available data on the natural history of SMA in adults who do not receive Spinraza.

Our data to date demonstrates that without treatment SMA causes continuously and gradually progressive motor disability in adults that affects all elements of motor function: bulbar and ventilatory function; truncal strength; appendicular strength. The early data we have collected on adults treated with Spinraza consistently demonstrates arrest of the natural deterioration and provides some evidence of mild to moderate improvement in some measures. Clearly, having the ability to stop the progression of SMA increases the motor function and extends lifespan, increasing each patient's independence and ability to participate in all aspects of life, and improving the many aspects of health related to motor function. I hope this information provides some useful information as you consider Spinraza use in patients of all ages.

Sincerely,



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