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Brachial plexus enhancement in acute flaccid myelitis: A novel radiographic finding

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doi: 10.1017/cjn.2019.159

Background: Acute flaccid myelitis (AFM) is a condition which causes acute paralysis in pediatric patients. Although awareness of AFM is increasing, the pathophysiology and full spectrum of clinical, biochemical, and radiographic features remain to be fully elucidated. **Methods:** We report a 5 year-old, previously healthy, male patient who presented with acute right upper extremity weakness following a two day history of fever, cough, and fatigue. The patient underwent extensive inflammatory and infectious workup in addition to MRI imaging of the brain, spinal cord, and bilateral brachial plexuses. **Results:** Infectious and inflammatory workup did not identify a causative agent. The patient was seen to have bilateral asymmetric (R>L) thickening and enhancement of the anterior horn cells of his cervical (C3-C7) spine, consistent with the spinal grey matter lesions previously described in patients with AFM. Enhancement of the corresponding anterior nerve rootlets and bilateral brachial plexuses was also seen. **Conclusions:** Patients with acute flaccid myelitis may demonstrate grey matter enhancement extending beyond the spinal cord to the peripheral nerves and plexuses, a radiographic finding which has not previously been published.

Neuromuscular Disease and EMG

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Time to treatment effect in Spinal Muscular Atrophy Type 1 (SMA1): an indirect comparison of treatments

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doi: 10.1017/cjn.2019.160

Background: SMA1 is a rapidly progressing disease resulting in death/permanent ventilation by 2 years. This study compared clinical trial data evaluating the relationship between treatment timing, time to treatment effect, and clinical outcomes in SMA1 patients **Methods:** A post-hoc indirect treatment comparison was conducted to measure time-to-effect differences in AVXS-101 (CL-101, NCT02122952, cohort 2) vs nusinersen (ENDEAR, NCT02193074) or risdiplam (FIREFISH, NCT02913482) using CHOP-INTEND scores. **Results:** Compared with nusinersen, AVXS-101 more rapidly increased mean CHOP-INTEND score from baseline (9.8- and 14.9-point increase at 1- and 2-months post-AVXS-101 vs ≤5-point increase at 2-months post-nusinersen). Greater survival benefits and lower rates of permanent ventilatory support were also observed in AVXS-101- vs nusinersen-treated patients. Compared with risdiplam treatment, AVXS-101 improved median CHOP-INTEND scores (14.0-point increase at 2-months post-AVXS-101 vs 5.5-point increase at ~2-months post-risdiplam). Treatment differences were maintained through 8-months with additional improvements at all time-points. **Conclusions:** Although patients in these 3 cohorts are not entirely matched (e.g. age, disease severity), useful comparisons can still be made. Based on CHOP-INTEND scores, the treatment effect of AVXS-101 appears to be more rapid vs nusinersen or risdiplam. These findings suggest that timely restoration of SMN protein may be essential for maximizing outcomes in SMA1 patients.

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The value of AVXS-101 gene-replacement therapy for Spinal Muscular Atrophy Type 1 (SMA1)

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doi: 10.1017/cjn.2019.161

Background: SMA1, a rapidly progressing disease, results in muscle weakness, respiratory failure, hospitalization, and early death. This study highlights the value of onasemnogene abeparvovec (AVXS-101) gene-replacement therapy for SMA1. **Methods:** Twelve SMA1 patients received a one-time intravenous proposed therapeutic dose of AVXS-101 (CL-101; NCT02122952). Event-free survival (no death/permanent ventilation), pulmonary/nutritional interventions, swallow function, hospitalization rates, CHOP-INTEND, motor milestones, and safety were assessed (2-year follow-up). **Results:** By study end, all 12 patients survived event-free; 7 did not require non-invasive ventilation; 11 had stable/improved swallowing function (6 exclusively fed by mouth); 11 spoke. On average, patients experienced 1.4 (SD=0.41, range=0–4.8) respiratory hospitalizations/year. The mean proportion of time hospitalized was 4.4% (range=0–18.3%); mean unadjusted rate of hospitalization/year was 2.1 (range=0–7.6), with a mean hospital stay of 6.7 (range=3–12.1) days. CHOP-INTEND increased by 9.8 (SD=3.9) and 15.4 (SD=6.4) points at 1- and 3-months post-treatment. At long-term follow-up, 11 patients sat unassisted, 4 stood with assistance, and 2 walked. Adverse events included elevated serum aminotransferase levels, which were attenuated by prednisolone. **Conclusions:** AVXS-101 in CL-101 resulted in dramatic survival and motor function improvements. The reduced healthcare utilization in treated infants could decrease cost and alleviate patient, caregiver, and societal burden.

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Burden of illness of spinal muscular atrophy (SMA): an update

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doi: 10.1017/cjn.2019.162

Background: In this retrospective claims analysis, real-world healthcare resource use (HRU) and costs among SMA type 1 (SMA1) patients were assessed. **Methods:** SMA1 patients were identified from Symphony Health's Integrated Dataverse® (09/01/2016–08/31/2018). The study period spanned from the index date (date of first SMA1 diagnosis after nusinersen approval [12/23/2016]) until death/end of available data. HRU and costs per-patient-per-year (PPPY; 2018USD) were described during the study period for all

patients and after treatment initiation for nusinersen-treated patients. **Results:** A total of 349 SMA1 patients (median age=1 year; 55.6% female) with median follow-up of 7.9 months were included. The proportion of patients receiving mechanical ventilation, nutritional support, and physical therapy/rehabilitation was 46.4%, 46.1%, and 22.6%. Patients had, on average, 59.4 days with medical visits/year (14.1 inpatient, 13.4 respiratory failure-related). The 45 nusinersen-treated patients had, on average, 56.6 days with medical visits/year (4.6 inpatient, 11.4 respiratory failure-related). Excluding nusinersen-related costs, mean healthcare costs PPPY were $137,627 (median: $43,167) for all patients and $92,618 ($29,425) for nusinersen-treated patients. Mean nusinersen-related costs were $191,909 ($144,487) per month for the first 3 months post-initiation and $36,882 ($16,132) per month thereafter. **Conclusions:** HRU and costs associated with SMA1 are substantial, even among patients treated with nusinersen.

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SUNFISH Part 1 results and Part 2 trial design in patients with type 2/3 spinal muscular atrophy (SMA) receiving risdiplam (RG7916)

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doi: 10.1017/cjn.2019.163

Background: SMA is characterized by reduced levels of survival of motor neuron (SMN) protein from deletions and/or mutations of the *SMN1* gene. While *SMN1* produces full-length SMN protein, a second gene, *SMN2*, produces low levels of functional SMN protein. Risdiplam (RG7916/RO7034067) is an investigational, orally administered, centrally and peripherally distributed small molecule that modulates pre-mRNA splicing of *SMN2* to increase SMN protein levels. **Methods:** SUNFISH (NCT02908685) is an ongoing multicenter, double-blind, placebo-controlled, operationally seamless study (randomized 2:1, risdiplam:placebo) in patients aged 2–25 years, with Type 2/3 SMA. Part 1 (n=51) assesses safety, tolerability, pharmacokinetics and pharmacodynamics of different risdiplam dose levels. Pivotal Part 2 (n=180) assesses safety and efficacy of the risdiplam dose level selected based on Part 1 results. **Results:** Part 1 results showed a sustained, >2-fold increase in median SMN protein versus baseline following 1 year of treatment. Adverse events were mostly mild, resolved despite ongoing treatment and reflected underlying disease. No drug-related safety findings have led to withdrawal (data-cut 06/17/18). SUNFISH Part 1 exploratory endpoint results and Part 2 study design will also be presented. **Conclusions:** To date, no drug-related safety findings have led to withdrawal. Risdiplam led to sustained increases in SMN protein levels.

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FIREFISH Part 1: 1-year results on motor function in infants with Type 1 spinal muscular atrophy (SMA) receiving risdiplam (RG7916)

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doi: 10.1017/cjn.2019.164

Background: SMA is characterized by reduced levels of survival of motor neuron (SMN) protein from deletions and/or mutations of the *SMN1* gene. While *SMN1* produces full-length SMN protein, a second gene, *SMN2*, produces low levels of functional SMN protein. Risdiplam (RG7916/RO7034067) is an investigational, orally administered, centrally and peripherally distributed small molecule that modulates pre-mRNA splicing of *SMN2* to increase SMN protein levels. **Methods:** FIREFISH (NCT02913482) is an ongoing, multicenter, open-label operationally seamless study of risdiplam in infants aged 1–7 months with Type 1 SMA and two *SMN2* gene copies. Exploratory Part 1 (n=21) assesses the safety, tolerability, pharmacokinetics and pharmacodynamics of different risdiplam dose levels. Confirmatory Part 2 (n=40) is assessing the safety and efficacy of risdiplam. **Results:** In a Part 1 interim analysis (data-cut 09/07/18), 93% (13/14) of babies had ≥4-point improvement in CHOP-INTEND total score from baseline at Day 245, with a median change of 16 points. The number of infants meeting HINE-2 motor milestones (baseline to Day 245) increased. To date (data-cut 09/07/18), no drug-related safety findings have led to patient withdrawal. No significant ophthalmological findings have been observed. **Conclusions:** In FIREFISH Part 1, risdiplam improved motor function in infants with Type 1 SMA.

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AVXS-101 gene-replacement therapy (GRT)) in presymptomatic spinal muscular atrophy (SMA): study update

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doi: 10.1017/cjn.2019.165

Background: SMA is a neurodegenerative disease caused by biallelic deletion/mutation of *SMN1*. Copies of a similar gene (*SMN2*) modify disease severity. In a phase 1 study, *SMN* GRT onasemnogene abeparvovec (AVXS-101) improved outcomes of symptomatic SMA patients with two *SMN2* copies (2x*SMN2*) dosed ≤6 months. Because motor neuron loss can be insidious and disease progression is rapid, early intervention is critical. This study evaluates AVXS-101 in presymptomatic SMA newborns. **Methods:** SPR1NT is a multicenter, open-label, phase 3 study enrolling ≥27 SMA patients with 2–3x*SMN2*. Asymptomatic infants ≤6 weeks receive a one-time intravenous AVXS-101 infusion ($1.1x10^{14}$ vg/kg). Safety and efficacy are