Received: 16 April 2020 | Revised: 22 April 2020 | Accepted: 22 April 2020

DOI: 10.1002/mus.26903

ISSUES & OPINIONS

MUSCLE&NERVE WILEY

Spinal muscular atrophy care in the COVID-19 pandemic era

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has resulted in reorganization of healthcare settings affecting the delivery of clinical care to patients with spinal muscular atrophy (SMA). There is a concern that patients with SMA may be at increased risk of manifesting severe symptoms of COVID-19. Currently approved therapies for SMA improve survival and motor function; however, their delivery requires an increased exposure to the health system and a dedicated healthcare team. In this study, we discuss consensus recommendations pertaining to care of SMA patients during the pandemic. We highlight that SMA treatments should not be perceived as elective. Decisions regarding the delay of treatments should be made with consideration of the potential risks of COVID-19 exposure and the risk of that delay. We emphasize the importance of collaborative treatment decisions between the patient, family, and healthcare provider, considering any geographic- or institution-specific policies and precautions for COVID-19.

Abbreviations: CSF, cerebrospinal fluid; COVID-19, corona virus disease 2019; NBS, newborn screening; SMA, spinal muscular atrophy.

KEYWORDS
corona, epidemic, guidelines, pandemic, SMA, treatment

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a pandemic and public health emergency. The virus spreads efficiently and rapidly from person to person, and COVID-19 symptoms include fever, cough, fatigue, shortness of breath, sore throat, headache, diarrhea, and reduced taste sensation. Severe manifestations, including pneumonia, acute respiratory distress syndrome, and death are more common in older patients and those with medical co-morbidities.[1–3] Nevertheless, several unexpected deaths have been reported in previously healthy young adults and teenagers.[4,5] A recent US Centers for Disease Control and Prevention mortality and morbidity weekly report note that the majority of hospitalized children with COVID-19 in the United States for whom the information was available had one or more underlying medical conditions such as chronic lung disease, cardiovascular disease, and immunosuppression.[6] Management is supportive as there is no specific antiviral treatment currently available. Social distancing, the most important intervention to limit the spread of COVID-19,[6–8] has necessitated reorganization of healthcare practice. Though emergent and urgent care continue to be provided to patients in hospital and office settings, elective and nonurgent services are now being provided by telehealth or are being rescheduled.[9]

Currently available US Food and Drug Administration-approved therapies for spinal muscular atrophy (SMA), nusinersen and onasemnogene abeparvovec-xioi,[10–12] are life altering and are reshaping the natural history of the disease, resulting in improved survival and motor function. These treatments, however, are not a cure, and patients continue to live with substantial comorbidity, especially symptomatic infantile onset patients who may have pulmonary compromise and require daily supportive care.[13] Patients with SMA are at increased risk of respiratory infections in general, and may be at an increased risk of manifesting severe symptoms of COVID-19. Currently, there are no data on how the COVID-19 public health emergency and resultant healthcare restructuring have impacted the care of SMA patients. Both approved treatments require an increased exposure to the health system around their delivery. Peer-reviewed published literature pertaining to COVID-19 and SMA is lacking.

We assembled an expert panel of neuromuscular specialists to provide recommendations related to SMA care during this public health emergency. Expert leaders in SMA from across the United States and Europe were identified and invited to join the panel. The primary mode of communication was email for thorough point-by-point review to reach a consensus. There were no dissenting opinions with regard to the final recommendations. This report, therefore, reflects the consensus opinion of the authors.

First and foremost, patients with SMA and their families should follow national, and local guidelines as well as any additional recommendations for people at risk for serious illnesses from COVID-19.[14,15] Patients and families should also follow the guidelines pertaining to COVID-19 at the institutions where they receive their health care.

Surging COVID-19 rates are placing a tremendous burden on the healthcare system and healthcare providers, resulting in interruption of elective and/or nonemergent services and procedures. In some instances, this has interfered with planned treatments for SMA patients. SMA treatments are critical to the health and well-being of these patients and should not be perceived as elective or nonurgent. This is especially true for young children with infantile onset SMA.

Nusinersen is given intrathecally with the recommended schedule of four loading doses in the first 2 months followed by maintenance doses every 4 months. The US package insert addresses missed nusinersen dosing, noting that if a loading dose is delayed or missed, administer it as soon as possible, with at least 14 days between doses, and continue dosing as prescribed. If a maintenance dose is delayed or missed, administer as soon as possible and continue dosing every 4 months.[10]

In response to a request for more information from Biogen around this issue, the company was able to share pharmacokinetic modeling data based on cerebrospinal fluid (CSF) and plasma samples from 370 patients who participated in the clinical development program (Biogen data on file; personal communication by means of email and telephone call). Higher nusinersen CSF exposure correlated with greater efficacy in motor outcome scales as well as greater decline in neurofilament levels. To maintain higher CSF exposure, the drug should be administered every 4 mo.[16–18] Based on the modeling in the maintenance phase, a one-time delay of 1 month results in approximately a 10% decrease in CSF exposure. If the patient continues with the original maintenance dosing schedule, the CSF steady state is restored. As an example, if a patient misses a dose at 4 months and instead receives it at 6 months, the subsequent dose of nusinersen would be given 2 months later as originally scheduled and the CSF steady state exposure is restored. If, instead, the original dosing timeline is altered, and the subsequent dose is given 4 months after the delayed dose, there is a prolonged delay to restore CSF steady state exposure. Every effort should be made to give a missed dose of nusinersen as soon as possible, and maintain the original dosing timeline to maximize the benefit of treatment.

Onasemnogene abeparvovec-xioi gene transfer is administered as a onetime intravenous infusion over 60 min followed by a few hours of observation in a controlled setting in the hospital, then several weeks of careful outpatient management and laboratory monitoring while immune-suppressed from corticosteroid treatment. Patients with SMA who receive onasemnogene abeparvovec-xioi require oral corticosteroids for at least 2 mo. Patients on corticosteroids should be advised not to discontinue these unless specifically discussed with, and approved by, their treating neurologist.

Corticosteroid-treated patients and their families should be extra-vigilant in practicing social distancing and other recommended precautionary measures. Gene transfer therapy also necessitates frequent laboratory monitoring for liver function abnormalities, elevated troponin, and thrombocytopenia. Adjustments to the standard monitoring schedule should be made only after discussion with the treating neurologist. Alternate options, such as home blood draws and telemedicine visits, if clinically appropriate should be considered to minimize exposures.

SMA treatments require a team of dedicated healthcare personnel and a secure setting, which might be challenging during a pandemic. We strongly recommend that healthcare providers work collaboratively to avoid treatment delays. Early and uninterrupted treatment, particularly for children with infantile onset SMA, leads to better outcomes.[16,18–20] We emphasize that treatment decisions should be individualized and made cohesively between the patient, family, and healthcare provider, taking into account any geographic- or institution-specific policies and precautions for COVID-19.

Insurance providers typically require standardized physical therapy assessments before and on a regular basis following or during treatment to document the impact of such treatment. We believe that these assessments should appropriately be deferred to minimize exposure of these fragile patients; partial functional assessments by means of telemedicine may be feasible in some care contexts. We recommend that coverage for nusinersen and onasemnogene abeparvovec-xioi should be provided without interruption even if formal clinical and physical therapy assessments are limited. Patients' neurologists may discuss these needs with third-party payers. The clinical urgency of ongoing physical, occupational, and speech therapies should be evaluated on a case-by-case basis and their suspension or continuation agreed upon between providers and their patients.

Newborn screening (NBS) programs have allowed presymptomatic identification and treatment of SMA patients, dramatically improving outcomes.[21] NBS for SMA is currently practiced or piloted in more than 30 states in the United States.[22] The full impact of the COVID-19 pandemic on the SMA NBS programs is unclear. However, this impact may include delay in implementing NBS programs in some states as healthcare resources are diverted; there may limited ability to arrange face to face patient evaluations and blood draws for testing while many medical practices severely limit in-person evaluations or transition to telehealth.[9] We continue to recommend urgent evaluation of infants with SMA identified by NBS with rapid initiation of treatment while following the regional and institutional policies pertaining to the public health emergency and maximizing the safety of patients and caregivers.

In summary, the COVID-19 pandemic presents tremendous challenges to the healthcare community, and disease-specific recommendations are rapidly evolving. We emphasize that: • SMA treatments should not be considered elective and should not be delayed or interrupted if at all possible. • It is important to resume the original schedule of nusinersen after a delayed dose. • Standardized physical therapy assessments to maintain insurance coverage for SMA treatments should be flexible.

We recommend strict adherence to established policies pertaining to the COVID-19 response and recommend that healthcare providers work closely with local and institutional authorities to ensure timely and uninterrupted care for patients with SMA taking into account the potential risks of COVID-19 exposure.

AUTHOR DISCLOSURES

A.V. has served on advisory boards for Biogen, PTC therapeutics, and AveXis and serves as an associate editor for neuromuscular disorders at Medlink Neurology. A.V. serves as principal investigator and sub-investigator at Arkansas Children's Hospital for studies in DMD and SMA. A.M.C. serves on advisory boards for Sarepta, AveXis, Roche, and Acceleron. She serves on a DSMB (Catabasis) and serves as Sub-Investigator at Nationwide Children's Hospital for studies in DMD (Sarepta) and SMA (AveXis). R.S.F. has received personal compensation for activities with Ionis Pharmaceuticals, Biogen, AveXis, Capricor, Catabasis, Lilly, Roche, Novartis; and the SMA Foundation, SMA Europe and Cure SMA as a consultant or advisor. R.S.F. has received research support from Ionis Pharmaceuticals, Biogen, Lilly, Cytokinetics Sarepta, NIH, MDA, and Summit. K.A. serves as site principal investigator for AveXis RESTORE registry for SMA. K.D.M. serves as site principal investigator for AveXis RESTORE registry for SMA. K.D.M. receives research funding from NIH, CDC, Friedreich's ataxia research alliance, MDA. K.D.M. serves as site principal investigator for studies involving Sarepta, Retrotope, Reata, PTC, Italfarmaco, Santhera, Catabasis, CSL Behring, and BMS. E.C.S. has received research support and consulting fees from AveXis and Biogen. D.C. has served in advisory boards for AveXis, Biogen, PTC therapeutics, Genentech, and Sarepta. D.C. serves in medical advisory boards for Cure SMA, GBS-CIDP Foundation, and MGF. D.C. receives research funding from AveXis, Biogen, Fibrogen, PTC, Reveragen, and Sarepta. R.J.B. has received personal compensation for serving on the scientific advisory boards of Biogen and Sarepta. RJB has received research/grant support as principal investigator of studies from Acceleron, AveXis, Biogen, Capricor Catabasis, National Institutes of Health and National Institute of Neurological Disorders and Stroke, Pfizer, PTC, and Sarepta. J.A.P. has received compensation / research support from Biogen, AveXis, Genentech, Scholar Rock, Sarepta, and PTC. L.S. has received consulting fees from Roche, Biogen, AveXis, Cytokinetics, Audentes, Sarepta, Pfizer, Biphytis, PTC therapeutics, and Lupin. N.K. reports personal fees for participation in medical advisory boards for Audentes, AveXis, Biogen, Cytokinetics and Sarepta. MK has received support from Novartis and Biogen. V.K.R. has received support for consultation with Avexis, Biogen, Sarepta, and PTC therapeutics. J.F.B. reports consulting for Alexion, Audentes, AveXis, Biogen, Cytokinetics, Genentech, PTC Therapeutics, Sarepta, and WaVe and has received research funding as a site investigator from Alexion, AveXis, Biogen, CSL Behring, Cytokinetics, Fibrogen, Pfizer, PTC Therapeutics, Sarepta, Summit, and WaVe. E.M. has received funding as a member of advisory boards for SMA studies for AveXis, Biogen, Ionis Pharmaceuticals, Novartis, Scholar Rock and Roche. E.M. has served as principal investigator for Ionis Pharmaceuticals, Biogen, AveXis and Roche clinical trials. Has received funding from Famiglie

SMA Italy, Italian Telethon, Biogen, and SMA Europe E.C. has received personal compensation for serving on advisory boards and/or as a consultant for AveXis, Biogen, Medscape, Pfizer, PTC Therapeutics, Sarepta, Ra pharma, Wave, the Patient-Centered Outcomes Research Institute and Strong bridge Biopharma. E.C. has received personal compensation for serving on a speaker's bureau for Biogen. E.C. has received research and/or grant support from the Centers for Disease Control and Prevention, Cure SMA, Muscular Dystrophy Association, National Institutes of Health, Parent Project Muscular Dystrophy, PTC Therapeutics, Santhera, Sarepta Therapeutics, Orphazyme, and the US Food and Drug Administration. E.C. has received royalties from Oxford University Press and compensation from *Medlink* for editorial duties.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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How to cite this article: Veerapandiyan A, Connolly AM, Finkel RS, et al. Spinal muscular atrophy care in the COVID-19 pandemic era. *Muscle & Nerve*. 2020;1–4. https://doi.org/10.1002/mus.26903