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Pediatric SMA patients with complex spinal anatomy: Implementation and evaluation of a decision-tree algorithm for administration of nusinersen

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ABSTRACT

The approval of nusinersen for the treatment of spinal muscular atrophy (SMA) has significantly changed the natural history of the disease. Nevertheless, scoliosis secondary to axial muscle weakness occurs at some point in most of patients with SMA and a conventional posterior interlaminar approach for intrathecal administration of nusinersen can be particularly challenging to perform in patients with severe scoliosis and/or previous spine fusion surgeries. We developed a protocol for the administration of nusinersen in pediatric patients, which includes a decision-tree algorithm that categorizes patients according to the estimated technical difficulty for the intrathecal administration. Complex spine patients were defined as those with a Cobb angle greater than 50° and/or a history of spinal surgery, while the rest of patients were considered non-complex. Nusinersen was successfully administered through a conventional non-CT-guided lumbar puncture in all 14 non-complex spine patients (110 out of 110 procedures; 100%). The feasibility of the intrathecal injection in the 15 complex spine patients was assessed by 3D CT. Administration was considered unfeasible in 7 out of these 15 patients according to imaging. In the 8 complex spine patients in whom the administration was considered feasible, conventional non-CT-guided lumbar punctures were successful only in 19 out of 53 procedures (36%). The remaining 34 procedures (64%) were guided by CT scan, all successful. Our work demonstrates that a cut-off point of 50° in Cobb angle and history of spinal surgery can reliably be used to anticipate the need for CT guidance in nusinersen administration.

Abbreviations: SMA, spinal muscular atrophy; SMN1, survival motor neuron 1; AEMPS, Spanish Agency of Medicines and Health Products; HFMSE, Hammersmith Functional Motor Scale-Expanded; CSF, Cerebrospinal Fluid; MDCT, multi-detector computed tomography; HINE, Hammersmith Infant Neurological Examination; RULM, Revised Upper Limb Module; CTDIvol, CT Dose Index Volume; SSDE, Size Specific Dose Estimate; DLP, dose length product.

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1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disorder caused by homozygous deletions or loss-of-function mutations in the gene encoding survival motor neuron 1 (*SMN1*). This condition is characterized by the degeneration of alpha motor neurons, resulting in progressive muscular atrophy and weakness [1–3]. SMA incidence is approximately 1 in 10,000 live births, representing the most common genetic cause of childhood mortality [4,5]. It is classified in several major phenotypes, based on age at onset and maximal motor capacity achieved [6–8].

Antisense oligonucleotide nusinersen was approved for treatment of SMA by the United States Food and Drug Administration in 2016 and the European Medicine Agency in 2017. Nusinersen has significantly changed the natural history of this devastating disease, since it has proven to be effective in prolonging survival and improving motor and respiratory function in patients with SMA compared with placebo groups [9–12]. The new treatments available challenge us in keeping updated guidelines and to define the best risk/benefit profile for a wide clinical spectrum in SMA patients. Nusinersen modifies the splicing of the mRNA of the *SMN2* gene, thereby increasing the amount of functional SMN protein produced, thus compensating the genetic defect in the *SMN1* gene [13,14]. Antisense oligonucleotides cannot cross the blood-brain barrier and, therefore, intrathecal administration is required.

Scoliosis secondary to axial muscle weakness occurs at some point in most patients with SMA [15], and the conventional posterior interlaminar approach for intrathecal administration of nusinersen can be particularly challenging to perform in patients with severe scoliosis and/or previous spine fusion surgeries. In some of these patients needle placement into the spinal canal is therefore guided using imaging techniques. Among them, computerized tomography has been favored over fluoroscopy-assisted techniques due to its better performance in patients with complex spinal anatomy and in the presence of spine fusion instrumentation [16]. Similarly, CT scanning is preferred over ultrasound techniques and other non-ionizing radiation techniques given the poorer image quality of the latter when targeting deeper anatomical structures [16]. The extremely small but non-negligible malignancy risk associated to the CT scan ionizing radiation, the enhanced radio-sensitivity observed in children and young adults [17], as well as the long-term nusinersen therapy involving recurrent intrathecal administration strongly advocate for the application of the ALARA-principle [18], which entails the reduction of the radiation dose to the patient to a level as low as reasonably achievable.

To the best of our knowledge, there is no prospective study analyzing the feasibility and safety of the administration of nusinersen in cohorts of SMA patients with complex spinal anatomy. More common are retrospective studies analyzing the success of the procedure, mostly in adult patients [16,19–21]. These studies did not record the number of SMA patients considered unfeasible or how this decision was made. There are no validated algorithms for deciding which patients are treatable, based on objective, technical criteria. Such an algorithm would facilitate safe and cost-effective decision-making.

We analyze the feasibility and safety of a decision-tree algorithm for intrathecal administration of nusinersen in a large cohort of pediatric patients with SMA treated in a single center. Data regarding the rate of success, adverse effects and complications and radiation dose were included.

2. Material and methods

In this prospective study, we aimed to assess the feasibility and safety of our protocol for administration of nusinersen, based on a decision-tree algorithm. We included all SMA patients treated at Sant Joan de Déu children's hospital. The Spanish eligibility criteria for being treated with nusinersen are defined in the *Protocol for the treatment of patients with spinal muscular atrophy 5q with Spinraza®* and *Therapeutic Positioning Report for Nusinersen in SMA* of the Spanish Agency of Medicines and Health Products (AEMPS, in its Spanish acronym) [22]. All of the non-permanently-ventilated patients with SMA types 1b and 1c, 2 and 3 met these eligibility criteria, except the few patients with Hammersmith Functional Motor Scale-Expanded (HFMSE) higher than 54/64. Therefore, the main limiting factor was the technical feasibility of administering nusinersen to these patients intrathecally. Data were collected between March 2018, the date on which the first patient was treated with nusinersen in our center, and February 2020. Patients were informed in detail about the results of pivotal studies, as well as the risk associated with the procedure and the option of sedation.

Our decision-tree algorithm for nusinersen administration was developed in February 2018 and it is shown in Fig. 1. We used Cobb angle and history of spinal surgery to categorize the patients into two groups. Each group therefore was characterized by a different estimated technical difficulty for the administration of nusinersen. We defined as “non-complex spine patients” those with a Cobb angle less than 50° and no history of spinal surgery. We defined as “complex spine patients” those with a Cobb angle greater than 50° and/or a history of spinal surgery. A cut-off point of 50° was used because it is the Cobb angle from which it is recommended to consider surgical intervention in SMA patients [23] and, indeed, 50° was found to be the median preoperative Cobb angle in some cohorts of SMA patients who underwent surgery [15]. A conventional intrathecal injection was planned in the non-complex spine patients, whereas a 3D CT study was conducted in the complex patients to assess the feasibility of administration. In the complex spine patients in whom an accessible interspinal route was detected through the 3D CT scan, an intrathecal injection was planned in the radiology facilities. A neuroradiologist assisted by a Philips Brilliance iCT 256-slice scanner equipment (Philips Healthcare, Cleveland, OH, USA) guided the puncture. The administration of nusinersen was not attempted in those complex spine patients in whom no interspinal access was observed after a careful review of the 3D CT study.

In accordance with the recommended dosing schedule, nusinersen was administered on days 0, 14, 28, and 60, followed by maintenance doses every 4 months. In all the procedures, patients were positioned in lateral decubitus and the puncture site was located between L3/L4, L4/L5, and L5/S1. According to manufacturer instructions, 12 mg of nusinersen in 5 ml carrier solution were administered intrathecally for 1–3 min, after 5 ml of cerebrospinal fluid (CSF) had been removed. A Quincke needle (22 gauge) was used by a pediatric neurologist or an anesthetist. Conventional lumbar punctures in non-complex spine patients were performed in the procedure rooms whereas for complex spine patients nusinersen was administered in the radiology facilities. In the latter, a maximum of two unguided intrathecal administration attempts were performed by a pediatric neurologist with the patient already under anesthesia on the CT bed. In case of failure in these unguided attempts, an image-guided lumbar puncture was performed assisted by a multi-detector computed tomography (MDCT) scanner following a low-dose imaging protocol. This protocol was specifically established for the intrathecal administration of nusinersen, strictly observing the radioprotection measures. Tailored low dose CT acquisitions were sequentially performed until CSF was obtained. Two different acquisition protocols were designed depending on whether the patients had undergone spinal surgery history or not. Image reconstructions were performed using the iterative model reconstruction technique (Philips Healthcare, Best, The Netherlands). All

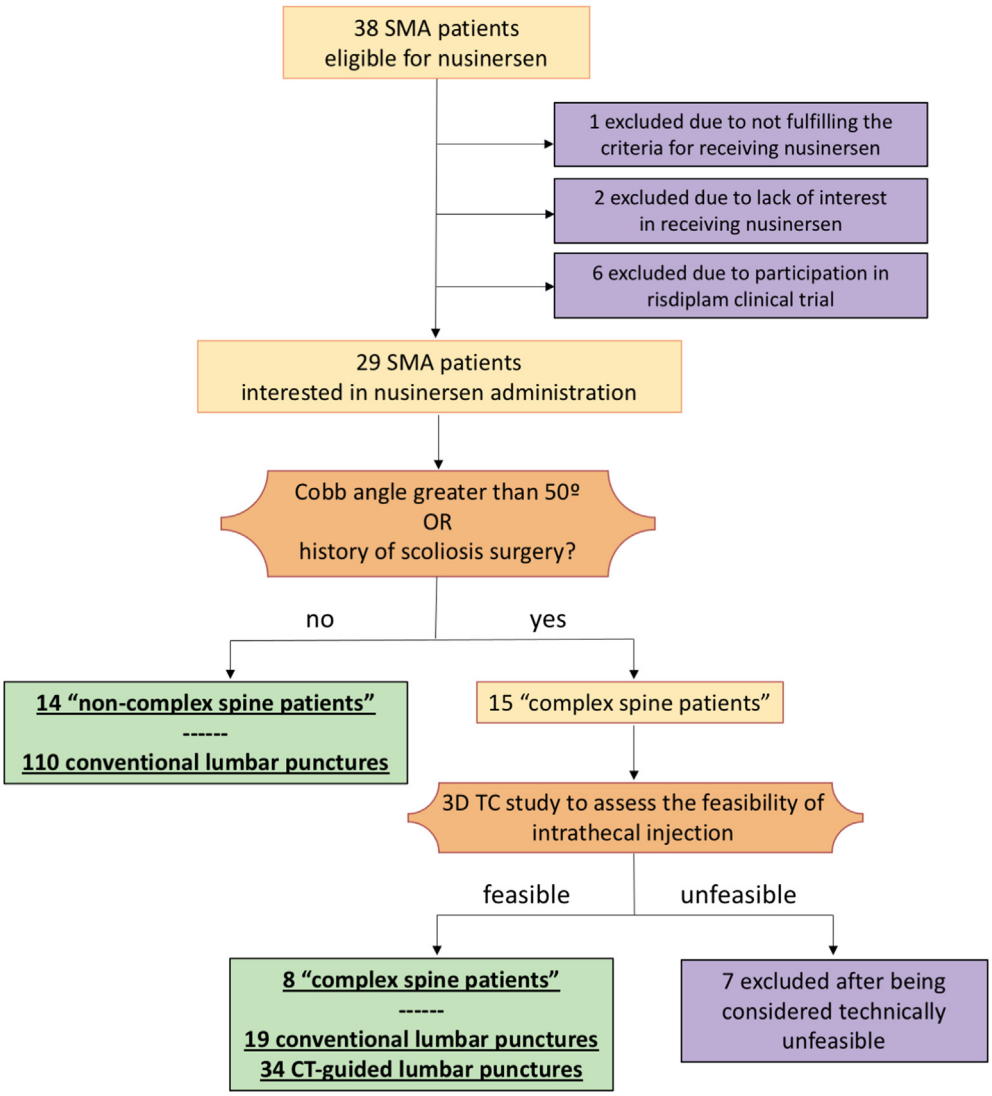

Fig. 1. Proposed decision-tree algorithm for administration of nusinersen.

the patients remained in supine position under observation during at least 2 h after the injection. They were discharged once a comprehensive physical exam had been performed and oral tolerance checked. We extracted data related to the anesthetic procedure such as type of sedation, method of induction and maintenance of anesthesia, duration, patient's position, puncture site as well as radiation dose, complications and side effects.

Demographic and clinical data, including age, sex, subtype of SMA, ASA classification, and motor function, were collected. According to SMA type a baseline motor assessment was performed following the guidelines and recommendation of the AEMPS, using the Hammersmith Infant Neurological Examination (HINE) and the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorder scale (CHOP INTEND) in SMA type 1, the HFMSE, Revised Upper Limb Module (RULM) in SMA type 2 and non-ambulant SMA type 3 and HFMSE, RULM and 6-Minute Walk Test in ambulant SMA type 3.

We recorded data related to the adverse events associated with the first five nusinersen administrations in each patient through a questionnaire designed by our team that was addressed to the parents. Special attention was paid to collecting information on headache, pain in the puncture area, fever, post-puncture syndrome, vomiting, muscle pain and/or myalgia. Post-puncture syndrome was defined, according to the criteria of the International Headache Society [24], as an orthostatic headache occurring within five days of a lumbar puncture, caused by low CSF pressure or CSF leakage, and usually accompanied by neck pain, tinnitus, changes in hearing, photophobia and/or nausea (the complete definition is available as supplementary material). Patients who had post-puncture syndrome were also included among cases who had headache, vomiting, or other side effects in case they had. Data collection was carried out following the guidelines of the Clinical Ethics Committee of Hospital Sant Joan de Déu.

Data were subsequently analyzed using SPSS 23.0 (IBM Corp.; Armonk NY). Categorical variables are described by means of frequency and percentages, and relations between them were tested using Chi-Square, Fisher and Gamma Ordinal tests. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Patient categorization

We assessed the feasibility of the intrathecal administration of

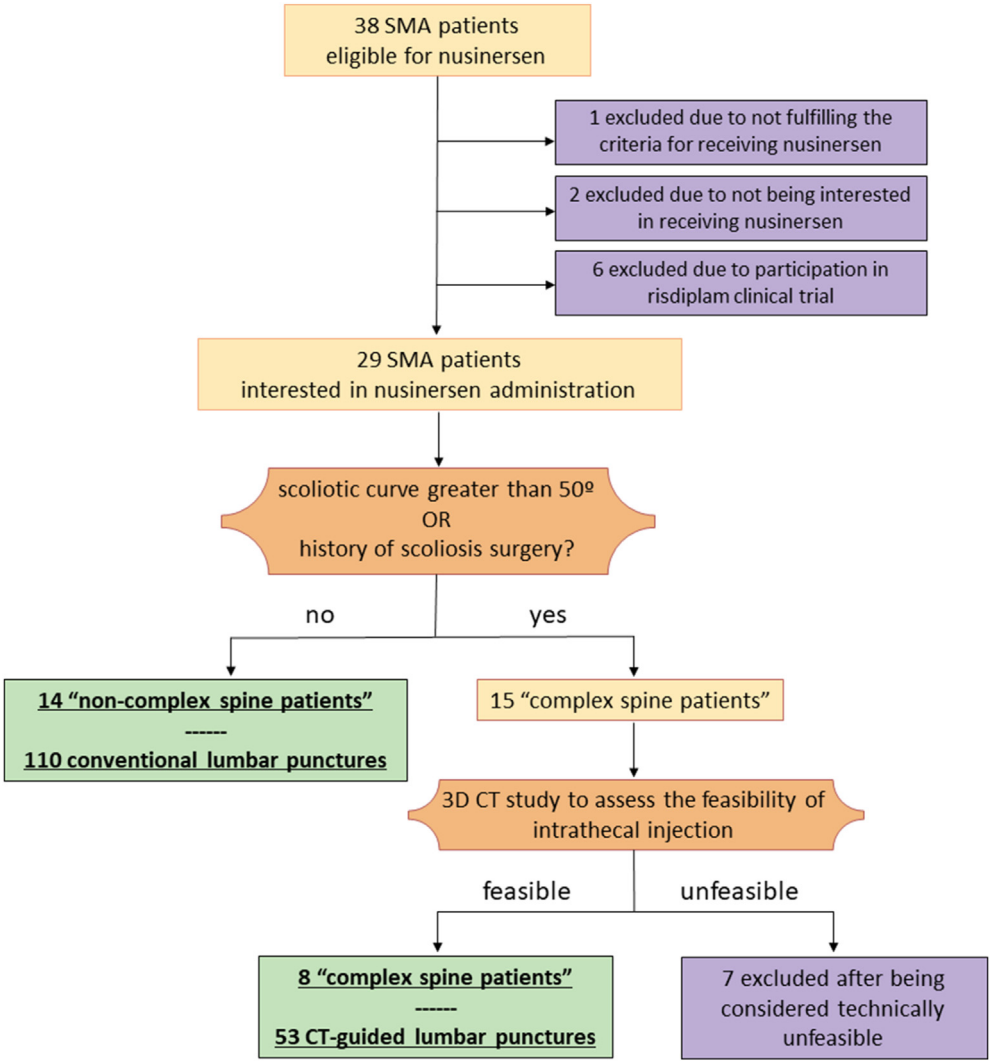

Fig. 2. Patients who fulfilled the entry criteria of the Spanish Agency of Medicines and Health Products (AEMPS) for receiving nusinersen. All of them were included in this study. Number of procedures in complex and non-complex spine patients.

nusinersen in 38 patients. Thirty-seven of them fulfilled the AEMPS inclusion criteria for receiving nusinersen (Fig. 2). The feasibility of the intrathecal injection was not assessed by 3D CT in 8 out of 37 patients. The reasons for exclusion of these 8 patients are listed in Fig. 2. The remaining 29 patients were categorized according to the proposed criteria of our algorithm resulting in a classification of 14 non-complex spine patients and 15 complex spine patients. Of the 15 complex spine patients, the administration of nusinersen was considered feasible in 8 (53%) after the 3D CT study was reviewed. It was considered unfeasible in 7 patients due to the complete fusion of their lumbar spines (Fig. 3). All these 7 patients had a spondylodesis that had been performed, on average, 6.4 years earlier (SD 3.7; range: 1–11).

3.2. Demography and motor functional assessment

Intrathecal nusinersen administration was performed in 22 patients (12 males, 10 females) with a mean age at first lumbar puncture of 9.2 years (range: 6 months –16.6 years). Two patients had SMA type 1, 16 patients had SMA type 2, and 4 patients had SMA type 3. Only 2 out of 22 patients were able to walk at the time of the first lumbar puncture. The detailed clinical baseline data from the 22 patients are shown in Table 1.

In the 7 complex spine patients that we excluded because the procedure was considered unfeasible, the mean age was 16 (SD:1.8). They had undergone previous extensive posterior spinal fusion operations and had a lower mean score for HFMSE (0) and RULM (8.3; SD:2.56) motor functional scales compared to the 8 complex spine patients (mean age: 10.5; SD: 3.08) for whom we determined that intrathecal delivery was feasible: HFMSE=3.6 (SD:3.9) and RULM=15.7 (SD:5.9).

3.3. Lumbar puncture procedure

A total of 163 lumbar puncture procedures were performed, all successful: 110 lumbar punctures in 14 non-complex spine patients and 53 in 8 complex spine patients (Fig. 2). Nusinersen was administered through a conventional non-CT-guided lumbar puncture in all 14 non-complex spine patients (110 out of 110 procedures; 100%).and in 36% of procedures performed in complex patients (19/53). The remaining 34 procedures in complex patients (64%) were guided by CT scan, all successful (Fig. 4). A mean of 7.4 injections per patient were administered, with all patients receiving at least the induction loading doses (the first four

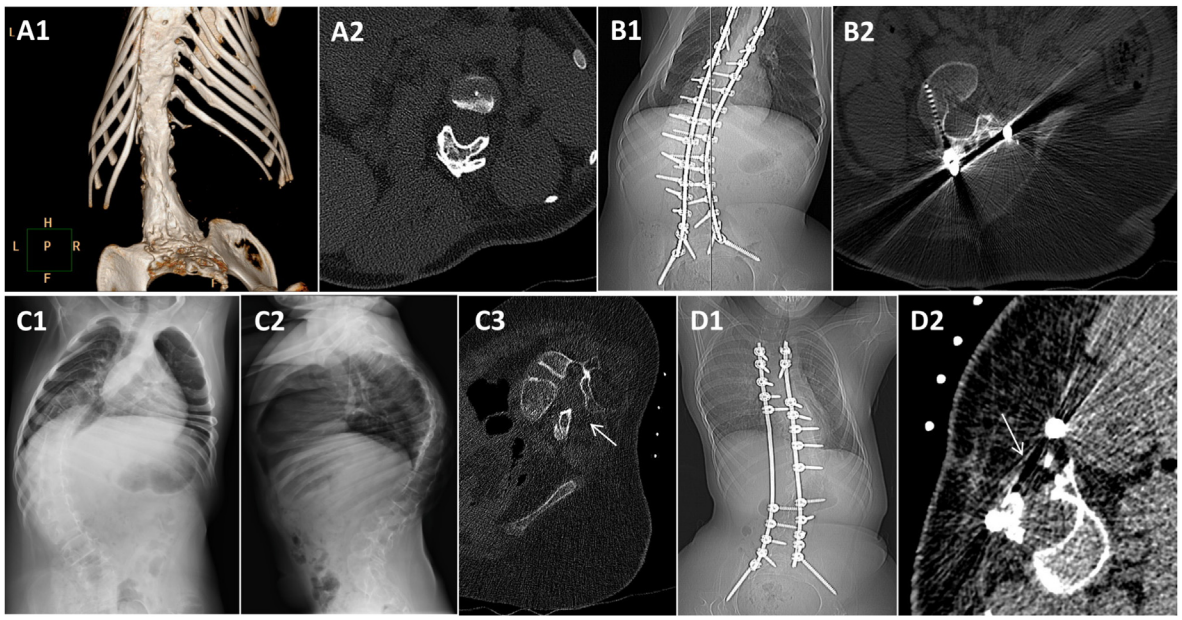

Fig. 3. Images from 4 complex spine patients. The administration of nusinersen was considered unfeasible in 2 of them (A and B) and feasible in the other 2 (C and D). A1 and A2: 3D-CT and axial CT show osseous fusion in a 17-year patient with SMA type 2. B1 and B2: Frontal spine radiograph and axial CT demonstrate posterior spinal osseous fusion extending to the sacrum of a 13-year-old patient with SMA2. C1 and C2: Spine radiographs show severe scoliosis and rotated vertebral bodies in a 12-year-old patient with SMA 2. Interspinous access was feasible when guided by CT (arrow in C3). d1: Spine radiograph of a 15-year-old patient with SMA 2 with implanted spondylodesis. Interspinous access was possible guided by CT (arrow in D2) in spite of the presence of a metal artifact.

Table 1
Patient demographics at baseline. SMA: spinal muscular atrophy. NIV: non-invasive ventilation. ASA: American Society of Anesthesiologists.

	SMA type 1	SMA type 2	SMA type 3	Total
Number of patients	2	16	4	22
Mean age at first injection (years)	3 (0.5–5.6)	8.9 (1.5–15.9)	13.5 (7.1–16.6)	9.2 (0.5–16.6)
Male:Female	1:1	9:7	2:2	12:10
Clinical data				
Ambulatory	0	0	2 (50%)	2 (9%)
Nocturnal NIV	2 (100%)	10 (62%)	0 (0%)	12 (55%)
Gastrostomy/jejunostomy	2 (100%)	2 (12%)	0 (0%)	4 (18%)
Scoliosis	1 (50%)	10 (62%)	1 (25%)	12 (55%)
Spinal surgery history	0 (0%)	3 (19%)	0 (0%)	3 (14%)
Complex spine cases	0 (0%)	8 (50%)	0 (0%)	8 (36%)
ASA III	2 (100%)	16 (100%)	4 (100%)	22 (100%)
Functional scales at baseline	CHOP: 29.5 (±6.4)	HFMSE: 8 (±7.9) RULM: 16.5 (±6.2)	HFMSE: 35.7 (±9.9) RULM: 31.5 (±6.4)	

injections). Spinal surgery was performed in one of the patients with severe scoliosis (Cobb angle: 116°) between the fourth and fifth administration of nusinersen.

Two different acquisition protocols were designed depending on the spinal surgery history the mean CT Dose Index Volume (CTDIvol) for the 32 cm dosimetry phantom was 2.32 mGy (SD 2.2; range: 0.7–7.9). Mean CTDIvol in patients without spondylodesis was 1.57 mGy (SD 0.66; range: 0.7–3.1) and mean CTDIvol in patients with spondylodesis was 3.45 mGy (SD 2.73; range: 0.9–7.9). The Size Specific Dose Estimate (SSDE) was 2.59 mGy (SD 1.11; range 1,20-4.93) in patients without spondylodesis and 4.95 mGy (SD 3.78; range 1,23-10.82) in patients with spondylodesis; after conversion factors were applied taking into account the patient sizes [25]. Median radiation dose in CT-guided punctures, indicated as dose length product (DLP), was 13.4 mGy*cm (range: 3.3–74.6). The mean number of acquisitions obtained per procedure was 2.8 ± 2.5 (range 1–15 acquisitions including initial scout), with a median of 3 acquisitions per procedure. The median estimated radiation dose per whole session (total DLP) comprising scout, helical, and sequential scanning was 32.7 mGy•cm (range: 6.1–248.8). No significant differences in the median effective radiation dose were observed based on the sequential position of a given administration for each patient.

Related to anesthetic technique, sevoflurane was the inhalational anesthetic used in all the patients classified as ASA III. It was used for induction in all 22 patients and for maintenance in 21 of them. Intravenous propofol was used for maintenance in the oldest patient. Parents were present during induction of anesthesia in all 163 procedures. Mean induction and maintenance of anesthesia time was significantly different in conventional and CT-guided procedures: 15.2 min (SD: 5.3; range: 6–38) and 49.2 min (SD: 19.7; range: 21–74), respectively ($p < 0.001$). An oral-nasal mask was applied in 131 procedures and laryngeal mask in 32, corresponding to 5 patients. No intraprocedural anesthetic complications occurred, including cardiovascular instability, major neurological events, respiratory failure or death. None of the patients required ventilatory support after the procedure.

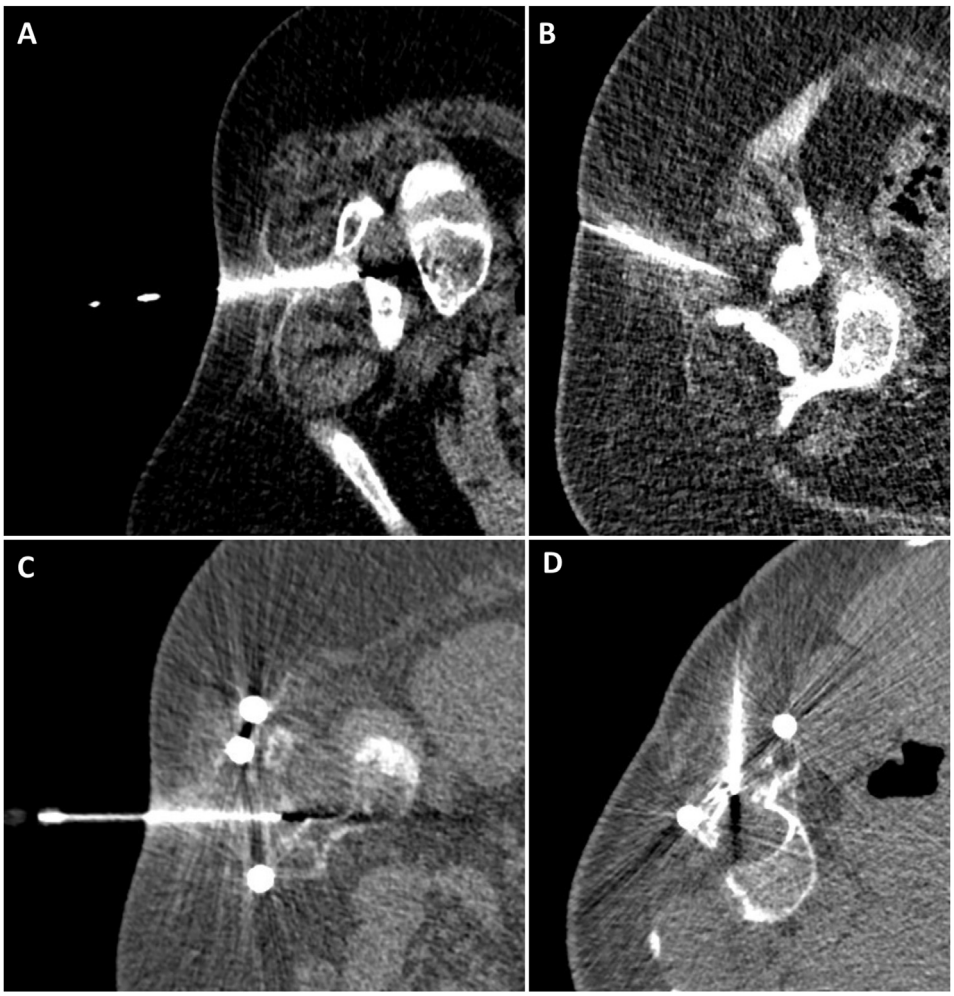

Fig. 4. Axial images from CT demonstrate percutaneous interspinal needle access for the intrathecal administration of the nusinersen in complex spine patients with severe scoliosis (A and B), including some with spinal surgery history (C and D). Note that the iterative model reconstruction technique provides low image quality, but it is sufficient for puncture guidance.

3.4. Adverse events related to procedure

Intrathecal administration of nusinersen seemed generally safe and well tolerated. Adverse events related to the first five lumbar punctures were observed in 38 of 109 (35%) procedures. Significant differences were observed depending on the sequential position of a given administration for each patient: the highest frequency of adverse events was observed after the first intrathecal injection with a subsequent steady decrease in the following administrations ($p = 0.002$) (Fig. 5). A particularly higher proportion of headache and vomiting/nausea were observed associated with the first and second procedures compared to the subsequent administrations (headache: 27% vs 12%; vomiting: 14% vs 2%). The most frequent adverse events were headache (18%), pain at the puncture site (15%), and back pain (7%) (Table 2). All of them were considered mild and were resolved with oral paracetamol. A Sprotte pencil point needle with a smaller diameter (24G) was used in a patient who presented post-lumbar puncture syndrome in the two first procedures. A standard 22G Quincke needle was used in the rest of the patients' procedures with good clinical response. Fever in the first 24 h after the nusinersen administration was reported in 4 cases. Symptoms associated with upper respiratory infection or pharyngotonsillitis appeared after a few days in 3 of these patients. One patient was admitted within 72 h after the procedure requiring intravenous antibiotic therapy. He was discharged with a fever of unknown origin/unconfirmed sepsis diagnosis. Finally, it is remarkable that the patient who undergone spinal surgery between the fourth and the fifth nusinersen administration had a CSF fistula and surgical wound infection secondary to surgery. CSF fluid leaked was observed after the fifth lumbar puncture. It was resolved applying local pressure. CSF leakage was detected again after two of the subsequent procedures and nusinersen discontinuation has been recently decided taking into account the risk-benefit relation.

Approximately equivalent incidence of adverse events per procedure were observed in the non-complex and complex spinal patients (34% vs 36%; $p = 0.87$) (Table 2). The overall incidence of adverse events was also similar in the conventional and the CT-guided lumbar punctures (33% vs 43%; $p = 0.33$). A similar incidence of adverse events was detected in all age groups. Side effects were significantly less common in patients with SMA type 1 (0%) than in patients with SMA type 2 and 3 (41%; 30%) ($p = 0.02$). No clear differences in side effects were found between patients with SMA 2 and SMA 3, although headache was more frequently observed after administration in patients with SMA 2 (23% vs 10%; $p = 0.17$).

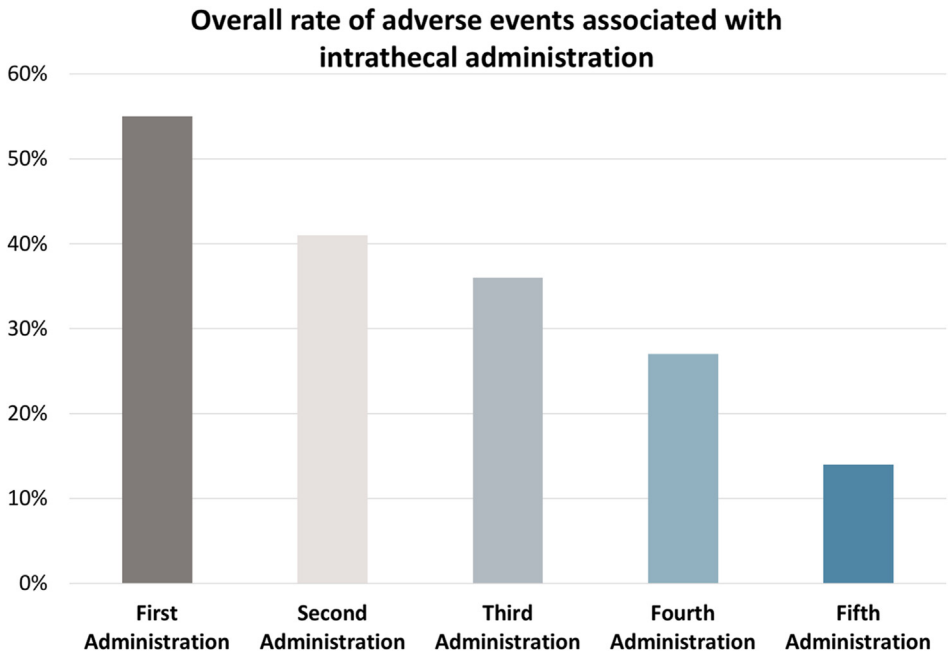

Fig. 5. Overall rate of events associated with intrathecal administrations. Significant differences were observed depending on the sequential position of a given administration for each patient: the highest frequency of adverse events was observed after the first intrathecal injection with a subsequent steady decrease in the following administrations.

Table 2
Summary of adverse events associated with the first 5 intrathecal injections in the 22 patients in whom nusinersen was periodically administrated. *Each one of these adverse events was also annotated in the case of those patients who had a post-lumbar puncture syndrome and presented any of these symptoms.

	Complex spinal patients	Non-complex spinal patients	Total
Adverse events	14/39 (36%)	24/70 (34%)	38/109 (34%)
Headache*	8/39 (21%)	12/70 (17%)	20/109 (18%)
Pain at the puncture site*	4/39 (10%)	12/70 (17%)	16/109 (15%)
Back pain*	1/39 (3%)	7/70 (10%)	8/109 (7%)
Vomiting/Nausea*	4/39 (10%)	3/70 (4%)	7/109 (6%)
Myalgia	2/39 (5%)	3/70 (4%)	5/109 (5%)
Fever	1/39 (3%)	3/70 (4%)	4/109 (4%)
Post–lumbar puncture syndrome	0/39 (0%)	4/70 (6%)	4/109 (4%)
Cerebrospinal fluid leakage	3/39 (8%)	0/70 (0%)	3/109 (0%)
Paresthesia	0/39 (0%)	0/70 (0%)	0/109 (0%)
Hypotension	0/39 (0%)	0/70 (0%)	0/109 (0%)
Dehydration	0/39 (0%)	0/70 (0%)	0/109 (0%)

4. Discussion

The approval of nusinersen for SMA patients has radically altered the landscape of SMA treatment. In the CHERISH clinical trial, children were not eligible for inclusion in the trial if they had evidence of spine curvature with a Cobb angle of >40° on radiography and all intrathecal nusinersen administrations were performed by conventional lumbar punctures [11]. However, in real-life conditions, virtually all SMA patients will develop further spinal deformities throughout their life [15,16,26,27] and intrathecal delivery may be very challenging in some of them. The need to develop protocols for administration, assessment of complications, safety and effectiveness is increasingly evident in this subgroup of patients with complex spinal anatomy after the FDA approval of risdiplam for the treatment of SMA in adults and children. Accurate data regarding the feasibility and adverse effects of nusinersen administration in complex spine patients is a prerequisite to decide which of the two drugs should be recommended. Previous reports have highlighted the difficulty of choosing the best approach to administer nusinersen in patients with severe scoliosis or previous spinal surgery in real world practice. A variety of approaches such as cervical puncture, intrathecal catheter, transforaminal access, translaminar drill, lumbar bone laminectomy and Ommaya device have been successfully used to achieve intrathecal access [28–37]. However, they have been performed only in a reduced number of patients and their use is not expected to be generalized to all patients due to their greater technical difficulty and/or increased risk of complications. The design, development and validation of easy-to-use nusinersen administration algorithms like the one presented here, which may be implementable in all kinds of centers, are expected to facilitate safe and cost-effective decision-making.

A multidisciplinary approach that involves neurologists, interventional radiologists and anesthesiologists is mandatory to accurately determine in which patients the intrathecal administration is feasible [38,39]. Here we show that the use of (i) Cobb angle and (ii) history of spinal surgery can reliably identify patients for whom a conventional lumbar puncture is appropriate to administrate nusinersen. As we have shown, a 3D CT study in patients with Cobb angle greater than 50° or a history of spinal surgery can determine in which patients the CT-guided administration of nusinersen is feasible and in which patients the oral risdiplam could be more convenient. This study, which includes a relatively large cohort of

pediatric SMA patients in whom a considerable number of procedures was performed, demonstrates that our protocol is safe and effective. We recognize that replicating it in other centers is essential for further validating this administration algorithm. It is important to notice that the present algorithm-decision tree is focused on minimizing the radiation exposure received by the patient, both by performing two puncture attempts before CT guidance needle placement, and also by applying dose-reduction protocols in order to achieve the minimal dose possible with the current CT equipment available.

Notably, a 100% of success rate was achieved and a serious adverse effect was observed in only one patient. Side effects were significantly less common in patients with SMA type 1 than in patients with SMA type 2 and 3. This is probably explained by the fact that SMA 1 patients were significantly younger than SMA 2 and SMA 3 patients and detecting adverse effects in younger patients is harder. Another factor to consider is that scoliosis was much milder in the youngest patients. Our results confirm that the CT-guided approach in pediatric complex spine patients is safe and effective, similarly to previous studies performed in adult patients [16,40]. The rate of adverse events was similar in the non-complex spine patients who received a conventional lumbar puncture and the complex spine patients in whom the lumbar puncture was guided by CT. Either way, the feasibility of lumbar punctures might be limited in patients with postoperative fistula or expansive lesions within the route of needle insertion [16,40]. The artifacts arising from previously implanted surgery material that may restrict the imaging is another potential barrier, but it did not limit the intrathecal administration of nusinersen in any patient of our cohort. The trend towards a lower adverse events occurrence with repeated administrations was somehow unexpected and we wonder if it could be related to a kind of adaptative capacity for intrathecal pressure fluctuations.

Radioprotection measures and low-dose protocols that follow the ALARA principle ("as low as reasonably achievable") are mandatory in CT-guided lumbar punctures [41]. Despite this, a certain amount of radiation exposure inevitably occurs. Median radiation dose in SMA patients with CT-assisted procedures had been reported to be considerably high (DLP = 85–120 mGy•cm) [16,40] until Cordts et al. obtained low radiation doses in adult SMA patients using a low-dose MDCT protocol with the iterative model reconstruction technology [42]. This protocol is quite similar to the one we have implemented in the CT-guided lumbar punctures performed in patients with complex spinal conditions. Radiation doses obtained in our study and that of Cordts et al. were roughly equal (Median DLP: 13.4 vs 10 mGy•cm. Median DLP per whole session: 32.7 vs 32.4) [42], demonstrating that the low-dose MDCT protocol is reproducible. In 2011, the Center for Radiation, Chemical and Environmental Hazards of the Health Protection Agency, in the United Kingdom published an estimation of the lifetime risk of radiation-induced cancer to the patients associated to several medical x-rays procedures [43]. The report estimated the risks associated to the lumbar spine CT scans, and thus accounted for the total malignancy risks associated to the irradiation of the same organs that were irradiated during the CT-guided lumbar puncture. Despite of the fact that adult organ-doses with no size-adjustment nor iterative model reconstruction techniques were used (mean DLP ranging from 510 to 560 mGy•cm) [44], once combined with age and sex specific risk coefficients, the estimated lifetime risks of radiation-induced cancer were extremely low. The level of risks typically ranged from about 65 in a million (10^{-6}) for a girl in the same age range (0–9 years) at the time of exposure than the mean age of our population having a CT scan of the lumbar spine, to over 70 in a million for a same age boy having the same procedure. It is, therefore, reasonable to assume than using doses that are, on average 16 times lower will result in even much reduced long-term risks associated to the CT radiation exposure.

Nonetheless, given the recurrence and long-term dosing schedule of nusinersen, we embrace the idea of informing and discussing with the legal guardians of the patient the risk-benefits of the CT-guided intrathecal administration of the treatment, as well as carry out a close dose monitoring for optimization of the procedure and follow-up on the potential risks.

The mean effective radiation dose for patients with spondylodesis, regardless of the SMA type, tended to be higher than that for patients without a spinal fusion. In contrast with previous studies [42,45], we did not find a decrease in the mean effective radiation dose for CT-guided injections during the course of the treatment.

This study has some limitations. First, it was conducted in a single medical center and it would be desirable to validate the proposed algorithm at other centers. Second, individual expertise in CT-guided intrathecal injections is variable, which may impact the success rate of nusinersen administration. Third, at the time this protocol was designed, risdiplam had not yet been approved and, therefore, this convenient oral alternative was not included in our algorithm. Forth, a cost-benefit analysis that took into account the clinical benefits and the costs arising from the use of interventional radiology techniques was not carried out. Further improvements in the algorithm may include the use of 3D CT study only for patients with a positive history of spinal surgery and/or using ultrasound to guide the first intrathecal injection attempt in complex spine patients. In addition, a transforaminal approach could be used in selected patients.

5. Conclusion

In summary, our data provide evidence for the feasibility and safety of this straightforward decision-tree algorithm for the intrathecal administration of nusinersen in pediatric SMA patients. It could guide the decision-making process for treating patients with severe scoliosis or spondylodesis in real-world practice. A cut-off point of 50° in Cobb angle and history of spinal surgery can reliably be used to anticipate the need for CT guidance in nusinersen administration.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. CO has received funding from AveXis as speaker in sponsored educational activities. DNdB has received funding from AveXis and Biogen as speaker in sponsored educational activities. AN has received funding as a speaker in sponsored symposium and educational activities or a member of advisory boards for SMA studies for AveXis, Biogen, Ionis Pharmaceuticals, Novartis, Roche Pharmaceuticals and Scholar Rock. AN is the principal investigator for ongoing Avexis, Ionis Pharmaceuticals/Biogen, Roche and Scholar Rock clinical trials. Research support from FundAME has been received.

Appendix A. Supplementary data

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