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Keywords:	Respiratory, Neuromuscular, Neurodisability, Costing

Healthcare Utilisation in Children with SMA Type 1 Treated with Nusinersen: a single centre retrospective audit

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Healthcare Utilisation in Children with SMA Type 1 Treated with Nusinersen

Abstract:

Background: Nusinersen has been used to treat spinal muscular atrophy type 1 (SMA1) in the UK since 2017. While initial trials showed neuromuscular benefit from treating SMA1, there is little information on the respiratory effects of nusinersen. We aimed to look at the respiratory care, hospital utilisation and associated costs in newly treated SMA1.

Methods: We reviewed the medical records of all children within the West Midlands with SMA1 treated with nusinersen at Royal Stoke University Hospital. Baseline demographics and hospital admission data were collected including: the reason for admission, total hospital days, HDU days, PICU days, days intubated, discharge diagnosis, doses of nusinersen and treatment complications.

Results: Eleven children (six girls) received nusinersen between May 2017 and April 2019. Their median (range) age was 29 (7–97) months. The median (range) number of nusinersen doses per child was 6 (4-8). All children were receiving long-term ventilatory support; this was non-invasive BiPAP in nine and tracheostomy ventilation in two. The total number of hospital days since diagnosis was 1101 with a median (range) of 118 (7-235) days per child. This included general paediatric ward days 0 (0-63), HDU 79 (7-173) days and PICU 13 (0-109) days per child. This equated to a median (range) of 20 (2 - 72) % of their life in hospital. The estimated cost of this care was £2.2M.

Conclusion: Patients with SMA1 treated with nusinersen spend a considerable proportion of their early life in hospital. Parents should be counselled accordingly. This healthcare utilisation has a significant cost implication.

Background

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterised by progressive muscular atrophy and weakness.(1) It has an incidence of 1 in 11,000 live births.(2) There are various subgroups of SMA classified clinically, with SMA type 1 (SMA1) accounting for approximately 60% of cases, and carrying the worst prognosis.(3) Until recently, SMA1 was the commonest genetic disease resulting in death in infancy.(4) Affected children usually present with symptoms before six months of age and historically died from respiratory failure by the age of two years.(5)

SMA1 is caused by the homozygous deletion or mutation of the survival motor neuron 1 (*SMN1*) gene. This results in reduced expression of the SMN protein, which is essential for the survival of motor neurones in the spinal cord and brain stem.(6) Inadequate expression of SMN protein causes degeneration of the motor neurone which in turn causes the associated muscles to atrophy. Humans have a variable number of copies of a second gene, *SMN2* which also encodes for SMN protein.(6) However, *SMN2* is a poor back-up gene and therefore leads to a truncated form of the protein, mostly degraded and a small amount, approximately 10%, of functional full length protein, as a result of aberrant RNA splicing. Approximately 80% of infants with SMA1 have only 1 or 2 copies of *SMN2* and are therefore unable to produce enough functional SMN protein to support normal muscle development.

Nusinersen is an antisense oligonucleotide which works by binding to the *SMN2* mRNA and in order to be effective it must be delivered into the cerebrospinal fluid. This binding modifies splicing of the *SMN2* gene to promote increased production of functional SMN protein.(7) Treatment with nusinersen has the potential to transform prognosis for these children offering hope of treatment for the first time. The drug has been used in the UK since early 2017. The drug costs £450,000 in the first year and £225,000 per annum subsequently and for patients beginning this from before November 2018, the manufacturer provided this free through an Expanded Access Programme.(8) NHSE provides an administration cost, but not the other aspects of care for these patients. While randomised controlled trials showed nusinersen improved motor function and development,(7) it is unclear whether the respiratory consequences produce similar benefits and thus the demands of treatment for families and health economies is yet to be established.

Royal Stoke University Hospital (RSUH) is a regional centre for nusinersen admistration and in March 2019 had the second largest cohort of patients in the UK. Before agreeing to act as a regional centre for nusinersen delivery, we carefully considered the potential effects on children, their families and

other healthcare services. However, data were lacking making counselling of families and planning of service provision difficult. We have carefully monitored healthcare utilisation of SMA1 children treated with nusinersen. The aim of this article is to report the data on service utilisation for these children to assist families and healthcare professionals.

Methods

Patients treated with intrathecal nusinersen at RSUH were identified from a local database. The paper notes and electronic clinical records were reviewed to collect relevant data from RSUH and the child's referring hospital. This included baseline demographics, age at diagnosis, details of ventilatory support, feeding support, number of nusinersen doses, complications following administration and details of all hospital admissions. Hospital admission data included: duration of admission, number of HDU days, PICU days and intubated days. Nusinersen usually necessitated admission for one night for the first dose only.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures. The results of this study will be disseminated to patient groups such as SMA UK and MD UK.

Approval and ethical considerations

The HRA decision tool (http://www.hra-decisiontools.org.uk/research) confirmed this project was audit not research and so ethical approval was not sought. The audit was approved by the departmental governance lead.

Results

We identified eleven children (six girls) who received nusinersen through the Expanded Access Program at RSUH between May 2017 April 2019. Parents of a 12th child declined nusinersen and the child died at 3 months of age. The median (range) number of nusinersen doses was 6 (4-8). Nine children received non-invasive BiPAP and two children were ventilated via tracheostomy. Two patients (including one on tracheostomy ventilation) have died suddenly at home from presumed mucous plugs, while one other patient had a cardiorespiratory arrest and has suffered hypoxic brain injury.

Duration and location of admissions

In 24 months, the 11 children had spent a total of 1101 days in hospital. The median (range) per child was 84 (7-235) days. This included a total of 91 general paediatric ward days, 762 HDU days and 248 PICU days. The median (range) per child was 0 (0-63) ward days, 79 (7-173) HDU days and 13 (0-109)

PICU days. Three children were responsible for all admissions to the general paediatric ward which occurred at their local hospital. Three children had not been admitted to PICU. Of the eight children that had, six had been intubated for a total of 38 days The median (range) proportion of life spent in hospital was 20% (2% - 72%). This was very variable with four children spending ≤10%, four 10-35% and three >35%.

Reason for admission

The median age (range) for initiation of nusinersen was 35 (2 – 372) weeks. Since initiation of nusinersen the eleven children had a total of 107 hospital admissions with a median (range) per child of 11 (1-25). The commonest reason for admission was lower respiratory tract infection (n=42), followed by elective administration of intrathecal nusinersen (n=38). There were seven admissions for gastrointestinal issues, six for an elective sleep study, five for aspiration pneumonia, four for increased secretions or airway issues and three for optimisation of ventilatory support.

Trends in admissions

Children in our cohort had the greatest requirement for hospital admission in the first 6 months following nusinersen initiation (see Figure 1). Much of this effect is driven by a tendency for children to have a long first admission (see Figure 2). Subsequent admissions tend to be shorter. The total number of hospital days for the children's first admission was 426 days with a median (range) of 20 (1 -235) days per child.

Cost implications and impact on local services

A total of 762 HDU days and 248 PICU days were required by the 11 children in our cohort over two years. This equates to 2.8 days in HDU and 0.93 days in PICU per child each month. RSUH has six HDU (four acute HDU beds and two long term ventilation) and eight PICU beds. The children therefore occupied 17% of the total HDU capacity and 4.2% of the PICU capacity over the study period. Based on current estimates of £1626 per day for a HDU bed and £1785 to £3784 for a PICU bed (depending on the level of care), the additional cost of these HDU/PICU days is £2.2M.(9) This is separate to the cost of the nusinersen and its administration.

Prior to the introduction of nusinersen, patients with SMA1 were generally not admitted for in-patient care, as they were managed within the community and local children's hospices.

Discussion

This is the first study which accurately reports the healthcare utilisation of a cohort of children treated with nusinersen. This information is vital for those planning healthcare services. In the first two years after diagnosis, these children spend one fifth of their early life in hospital. This places a significant burden on parents and families and they should be counselled accordingly. There is a considerable impact on hospital services, particularly on high dependency and PICU. This involves a substantial extra resource, in addition to the direct cost of the nusinersen. Reassuringly, the number of hospital days has reduced as the child gets older.

In addition to the costs associated with in-patient care, these children frequently require care packages which incur additional community costs. These costs are likely to continue throughout the child's life. NHSE has decided to fund nusinersen and so the numbers of SMA1 patients surviving and treated with nusinersen will increase, along with the demand on critical care and community services. Currently there is no ring-fenced funding for the health needs of SMA1 patients receiving nusinersen and this is something that must be explored to provide optimal care for these patient without affecting that of other children requiring critical care services.

We acknowledge the limitations of this study. It includes only eleven patients treated at one centre, although this is the second largest in the UK. The retrospective nature of the study may have introduced bias and we did not adjust for potential confounding factors such as socioeconomic status and co-morbidities. Estimates of the financial burden have concentrated on in-patient rather than community costs and will therefore be an underestimate.

There is a fall in the number of days spent in hospital. This may be explained by: i) a true improvement in the respiratory muscle strength of these children over time, or ii) a gradual improvement in the medical care provided, or iii) an improved ability of these families to cope with their medical conditions at home and in their own community or iv) deaths within our cohort. Whilst an important consideration, mortality alone seems unlikely to be the sole driver of this effect as only two children within the cohort have died at 12 and 16 months respectively.

It may be a function of all of these and we hope that the first three factors will continue to operate.

Conclusion

While the improved prognosis and life expectancy associated with nusinersen treatment is exciting for children with SMA1 and their families, we remain unsure that the respiratory benefits are as great as that shown for the neurological improvement in the preliminary trials. This study has highlighted that such children will spend a significant amount of their life in hospital, particularly in the first months after diagnosis. This places a significant burden on families and on the NHS in general. The

long term outcome for these children is still unknown but the trend for a reduction in hospital days as the child gets older may be reassuring. Further prospective studies with larger patient numbers are required to more accurately quantify the health care utilisation by these children and the associated financial burden.

What is already known on this topic:

Nusinersen improves prognosis and life expectancy in children with SMA 1.

Infants are now surviving with immense dependency on healthcare services.

NICE has just agreed to fund this new treatment (May 2019).

What this study adds:

Children with SMA1 who receive Nusinersen have significant ongoing medical costs in addition to the cost of the drugs received.

On average this currently is more than £100,000 per patient per year in the first two years of follow up.

Associated healthcare costs reduce as time progresses and are less in the second year of life.

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Figure Legend

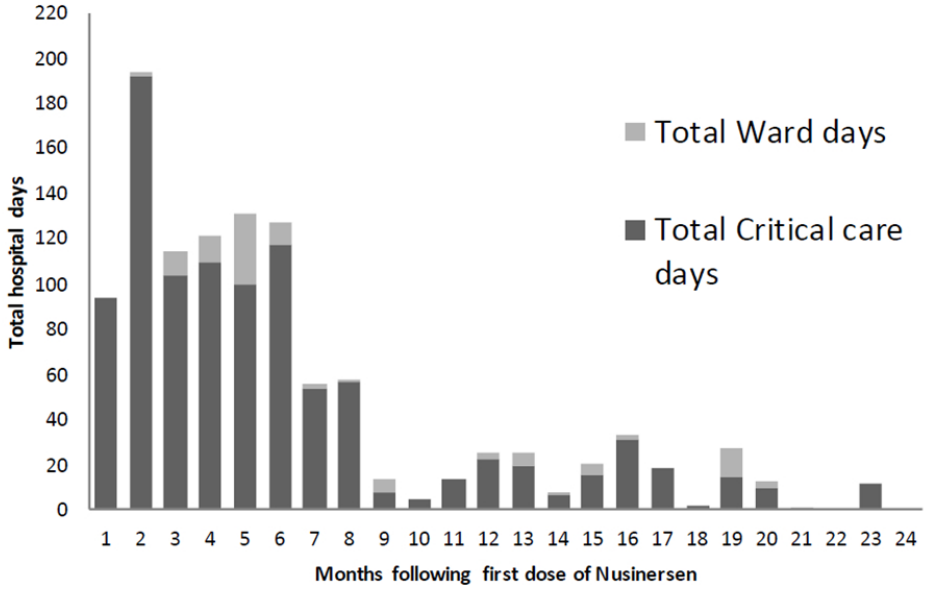
Figure 1: Total hospital days per month spent by children following commencement on nusinersen.

Figure 2: Median length of hospital stay per admission for all children.

Footnotes

Contributors: MS and JA originated the design of the study. IA collected the data and drafted the manuscript. FG and MS supervised the writing. IA, FG, WC, MS, JA, SC, TW and RK revised each draft for important intellectual content. All authors read and approved the final manuscript. MS had primary responsibility for the final content and is the guarantor. The corresponding author (MS) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Transparency: The manuscript's guarantor (MS) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.



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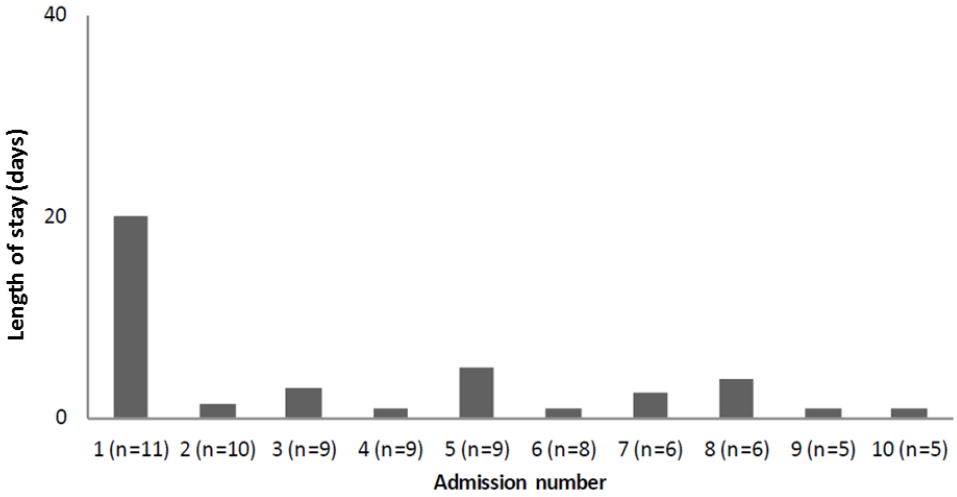

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Results: Eleven children (six girls) received nusinersen between May 2017 and April 2019. Their median (range) age was 29 (7–97) months. The median (range) number of nusinersen doses per child was 6 (4-8). All children were receiving long-term ventilatory support; this was non-invasive BiPAP in nine and tracheostomy ventilation in two. The total number of hospital days since diagnosis was 1101 with a median (range) of 118 (7-235) days per child. This included general paediatric ward days 0 (0-63), HDU 79 (7-173) days and PICU 13 (0-109) days per child. This equated to a median (range) of 20 (2 - 72) % of their life in hospital. The estimated cost of this care was £2.2M.

Conclusion: Patients with SMA1 treated with nusinersen spend a considerable proportion of their early life in hospital. Parents should be counselled accordingly. These data suggest that for every 10 children started on nusinersen an extra HDU bed is required. This has a significant cost implication.

Background

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterised by progressive muscular atrophy and weakness(1). It has an incidence of 1 in 11,000 live births(2). There are various subgroups of SMA classified clinically, with SMA type 1 (SMA1) accounting for approximately 60% of cases, and carrying the worst prognosis(3). Until recently, SMA1 was the commonest genetic disease resulting in death in infancy(4). Affected children usually present with symptoms before six months of age and historically died from respiratory failure by the age of two years(5).

SMA1 is caused by the homozygous deletion or mutation of the survival motor neuron 1 (*SMN1*) gene. This results in reduced expression of the SMN protein, which is essential for the survival of motor neurones in the spinal cord and brain stem(6). Inadequate expression of SMN protein causes degeneration of the motor neurone which in turn causes the associated muscles to atrophy. Humans have a variable number of copies of a second gene, *SMN2* which also encodes for SMN protein(6). However, *SMN2* transcription in 80-90% of instances leads to production of a truncated, unstable form of the protein which is non-functional. Approximately 80% of infants with SMA1 have only 1 or 2 copies of *SMN2* and are therefore unable to produce enough functional SMN protein to support normal muscle development.

Nusinersen is an antisense oligonucleotide which works by binding to the *SMN2* mRNA and in order to be effective it must be delivered into the cerebrospinal fluid. This binding modifies splicing of the *SMN2* gene to promote increased production of functional SMN protein(7). Treatment with nusinersen has the potential to transform prognosis for these children offering hope of treatment for the first time. The drug has been used in the UK since early 2017. The drug costs £450,000 in the first year and £225,000 per annum subsequently. For patients beginning this before November 2018, the manufacturer provided it free through an Expanded Access Programme(8). NHSE provides an administration cost, but not the other aspects of care for these patients. While randomised controlled trials showed nusinersen improved motor function and development(7), it is unclear whether the respiratory consequences produce similar benefits and thus the demands of treatment for families and health economies is yet to be established.

Royal Stoke University Hospital (RSUH) is the regional centre for nusinersen administration in the West Midlands which has a population of approximately 6 million. In March 2019 RSUH had the second largest cohort of SMA1 patients in the UK. Before agreeing to act as a regional centre for nusinersen delivery, we carefully considered the potential effects on children, their families and other healthcare

services. However, data were lacking making counselling of families and planning of service provision difficult. We have carefully monitored healthcare utilisation of SMA1 children treated with nusinersen. The aim of this article is to report the data on service utilisation for these children to assist families and healthcare professionals.

Methods

Patients treated with intrathecal nusinersen at RSUH were identified from a local database. The paper notes and electronic clinical records were reviewed to collect relevant data from RSUH and the child's referring hospital. This included baseline demographics, age at diagnosis, details of ventilatory support, feeding support, number of nusinersen doses, complications following administration and details of all hospital admissions. Hospital admission data included: duration of admission, number of HDU days, PICU days and intubated days. Nusinersen usually necessitated admission for one night for the first dose only. All children received care in accordance to the published international guidelines for the care of children with SMA(9,10). Intrathecal nusinersen was administered by appropriately trained paediatricians in the PICU treatment room. In babies this was performed using local anaesthetic and in toddlers using low dose opiate analgesia and / or sedation. No child has required a general anaesthetic or interventional radiology.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures. The results of this study will be disseminated to patient groups such as SMA UK and MD UK.

Approval and ethical considerations

The HRA decision tool (http://www.hra-decisiontools.org.uk/research) confirmed this project was audit not research and so ethical approval was not sought. The audit was approved by the departmental governance lead.

Results

We identified eleven children (six girls) who received nusinersen through the Expanded Access Program at RSUH between May 2017 and April 2019. Parents of a 12th child declined nusinersen and the child died at 3 months of age. The median (range) number of nusinersen doses was 6 (4-8). Nine children received non-invasive BiPAP and two children were ventilated via tracheostomy (TIV). Six children had been commenced on ventilation prior to their first dose of nusinersen. Both patients receiving TIV had the tracheostomy inserted before nusinersen was commenced. Two patients (including one on tracheostomy ventilation) have died suddenly at home from presumed mucous

plugs at 12 and 16 months of age, while one other patient had a cardiorespiratory arrest and has suffered hypoxic brain injury.

Table 1: Characteristics of cohort

	Median	Range
Age at diagnosis (months)	16.6	9 – 53.2
Age of first dose nusinersen (months)	20.6	1– 217.2
Age at initiation of LTV 2 (months)	20.9	5.8- 92.5
Age at initiation of advanced care pathway (n= 4) (months)	54	18.1 – 179.4
Number of admissions per child*	11	1 – 25
Number of emergency admissions per child*	3	0 – 21
Number of elective admissions per child*	4	0 – 9
Hospital days per child*	84	7 – 235
General paediatric hospital days per child*	0	0 – 63
HDU days per child*	79	7 – 173
PICU days per child*	13	0 - 109

*Over 24 months.

Duration and location of admissions

In 24 months, the 11 children had spent a total of 1101 days in hospital. Details of the hospitalisation are summarised in Table 1.-Three children were responsible for all admissions to the general paediatric ward which occurred at their local hospital. During these admissions, the respiratory team at RSUH liaised closely with local providers to guide acute management and arranged transfer when necessary. Three children had not been admitted to PICU. Of the eight children that had, six had been intubated for a total of 38 days. The median (range) proportion of life spent in hospital was 20% (2% - 72%). This was variable with four children spending ≤10%, four 10-35% and three >35%.

Reason for admission

The median age (range) for initiation of nusinersen was 35 (2 – 372) weeks. Since initiation of nusinersen the eleven children had a total of 107 hospital admissions with a median (range) per child of 11 (1-25). The commonest reason for admission was lower respiratory tract infection (n=42), followed by elective administration of intrathecal nusinersen (n=38). There were seven admissions for gastrointestinal issues, six for an elective sleep study, five for aspiration pneumonia, four for increased secretions or airway issues and three for optimisation of ventilatory support. At each admission for nusinersen the patient and family were reviewed by the paediatric palliative care team who

administered intrathecal treatment and assessed palliative needs. Children also received physiotherapy whilst inpatients. The physiotherapy adjuncts used by patients are listed in table 2. Four children had advanced care pathways in place. Between hospital admissions all the children were reviewed regularly in the outpatient clinic by the Paediatric Respiratory Multidisciplinary Team.

Table 2. Physiotherapy adjuncts that SMA1 children required

Physiotherapy Adjunct	Number (percentage) of children requiring adjunct
Saline Nebulisers	8 (72%)
Suction	11 (100%)
Percussion	9 (82%)
Cough Assist machine	5 (45%)
High Frequency chest wall oscillation vest	1 (0.9%)

Trends in admissions

Children in our cohort had the greatest requirement for hospital admission in the first 6 months following nusinersen initiation (see Figure 1). Much of this effect is driven by a tendency for children to have a long first admission (see Figure 2). Subsequent admissions tend to be shorter. The total number of hospital days for the children's first admission was 426 days with a median (range) of 20 (1 -235) days per child.

Cost implications and impact on local services

A total of 762 HDU days and 248 PICU days were required by the 11 children in our cohort over two years. This equates to 2.8 days in HDU and 0.93 days in PICU per child each month. RSUH has six HDU (four acute HDU beds and two long term ventilation) and eight PICU beds. The children therefore occupied 17% of the total HDU capacity and 4.2% of the PICU capacity over the study period. Based on current estimates of £1626 per day for a HDU bed and £1785 to £3784 for a PICU bed (depending on the level of care), the additional cost of these HDU/PICU days is £2.2M(11). This is separate to the cost of the nusinersen and its administration.

In addition to the costs associated with in-patient care, these children frequently require care packages which incur additional community costs. These costs are likely to continue throughout the child's life. In this small cohort, we found families highly motivated to provide care for their children and no child experienced a prolonged hospital admission as a result of awaiting funding for the

provision of a care package. Four children had care packages implemented: one child had 16 hours of care a week and three of the children had over 85 hours care per week. These three children received care seven nights a week between nine to ten hours and three days a week between five to eight hours.

Discussion

This is the first study which accurately reports the in-patient healthcare utilisation of a cohort of children treated with nusinersen. This information is vital for those planning hospital healthcare services. In the first two years after diagnosis, these children spend, on average, one fifth of their early life in hospital although there is considerable inter-individual variation. This places a significant burden on parents and families and they should be counselled accordingly. There is a considerable impact on hospital services, particularly on high dependency and PICU. However, not all children required PICU admission and not all children admitted to PICU required endotracheal intubation. This involves a substantial extra resource, in addition to the direct cost of the nusinersen. Reassuringly, the number of hospital days has reduced as the child grows older. In our cohort, the 11 children required 762 HDU days over 24 months. This equates to the need for an additional HDU bed for every 10 children commenced on nusinersen.

NHSE has decided to fund nusinersen for the next five years so the numbers of SMA1 patients surviving and treated with nusinersen will increase, along with the demand on critical care and community services. Currently there is no ring-fenced funding for the health needs of SMA1 patients receiving nusinersen and this is something that must be explored to provide optimal care for these patients without affecting that of other children requiring critical care or general paediatric services. Only a small proportion of admissions was managed wholly at the children's local hospital where expertise in NIV is being slowly developed.

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Figure Legend

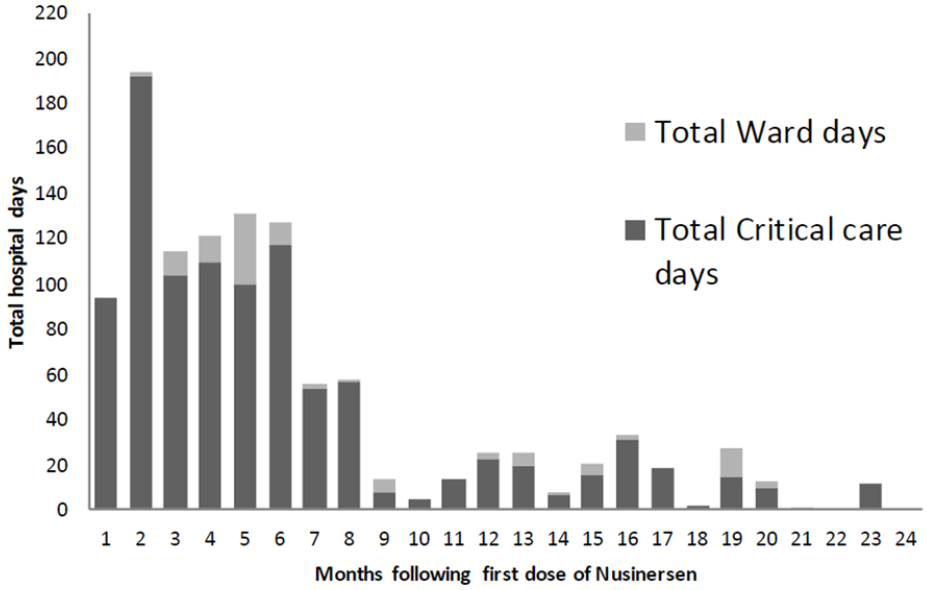
Figure 1: Total hospital days per month spent by children following commencement on nusinersen.

Figure 2: Median length of hospital stay per admission for all children.

Footnotes

Contributors: MS and JA originated the design of the study. IA collected the data and drafted the manuscript. FG and MS supervised the writing. IA, FG, WC, MS, JA, SC, TW and RK revised each draft for important intellectual content. All authors read and approved the final manuscript. MS had primary responsibility for the final content and is the guarantor. The corresponding author (MS) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Transparency: The manuscript's guarantor (MS) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.



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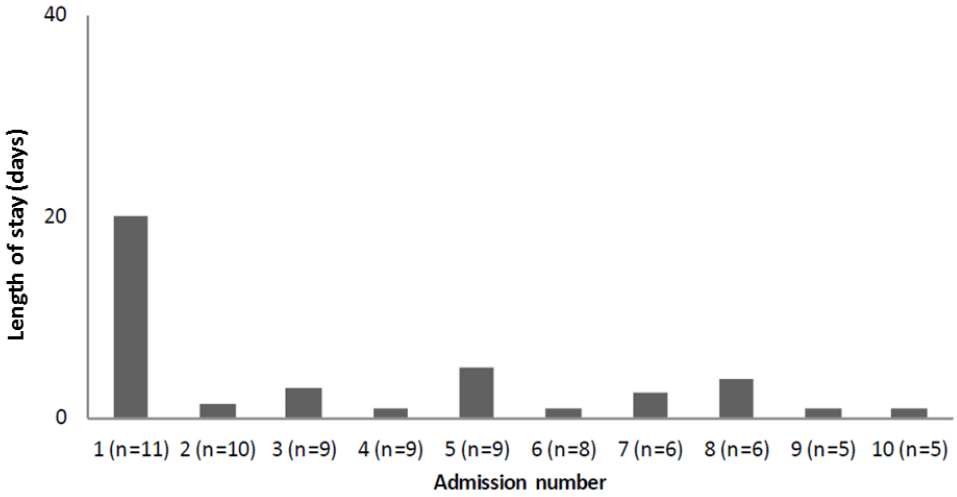

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Healthcare Utilisation in Children with SMA Type 1 Treated with Nusinersen: a single centre retrospective review

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Healthcare Utilisation in Children with SMA Type 1 Treated with Nusinersen: a single centre retrospective review

Abstract:

Background: Nusinersen has been used to treat spinal muscular atrophy type 1 (SMA1) in the UK since 2017. While initial trials showed neuromuscular benefit from treating SMA1, there is little information on the respiratory effects of nusinersen. We aimed to look at the respiratory care, hospital utilisation and associated costs in newly treated SMA1.

Methods: We reviewed the medical records of all children within the West Midlands with SMA1 treated with nusinersen at Royal Stoke University Hospital. Baseline demographics and hospital admission data were collected including: the reason for admission, total hospital days, HDU days, PICU days, days intubated, discharge diagnosis, doses of nusinersen and treatment complications.

Results: Eleven children (six girls) received nusinersen between May 2017 and April 2019. Their median (range) age was 29 (7–97) months. The median (range) number of nusinersen doses per child was 6 (4-8). All children were receiving long-term ventilatory support; this was non-invasive BiPAP in nine and tracheostomy ventilation in two. The total number of hospital days since diagnosis was 1101 with a median (range) of 118 (7-235) days per child. This included general paediatric ward days 0 (0-63), HDU 79 (7-173) days and PICU 13 (0-109) days per child. This equated to a median (range) of 20 (2 - 72) % of their life in hospital. The estimated cost of this care was £2.2M.

Conclusion: Patients with SMA1 treated with nusinersen spend a considerable proportion of their early life in hospital. Parents should be counselled accordingly. These data suggest that for every 10 children started on nusinersen an extra HDU bed is required. This has a significant cost implication.

Background

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterised by progressive muscular atrophy and weakness(1). It has an incidence of 1 in 11,000 live births(2). There are various subgroups of SMA classified clinically, with SMA type 1 (SMA1) accounting for approximately 60% of cases, and carrying the worst prognosis(3). Until recently, SMA1 was the commonest genetic disease resulting in death in infancy(4). Affected children usually present with symptoms before six months of age and historically died from respiratory failure by the age of two years(5).

SMA1 is caused by the homozygous deletion or mutation of the survival motor neuron 1 (*SMN1*) gene. This results in reduced expression of the SMN protein, which is essential for the survival of motor neurones in the spinal cord and brain stem(6). Inadequate expression of SMN protein causes degeneration of the motor neurone which in turn causes the associated muscles to atrophy. Humans have a variable number of copies of a second gene, *SMN2* which also encodes for SMN protein(6). However, *SMN2* transcription in 80-90% of instances leads to production of a truncated, unstable form of the protein which is non-functional. Approximately 80% of infants with SMA1 have only 1 or 2 copies of *SMN2* and are therefore unable to produce enough functional SMN protein to support normal muscle development.

Nusinersen is an antisense oligonucleotide which works by binding to the *SMN2* mRNA and in order to be effective it must be delivered into the cerebrospinal fluid. This binding modifies splicing of the *SMN2* gene to promote increased production of functional SMN protein(7). Treatment with nusinersen has the potential to transform prognosis for these children offering hope of treatment for the first time. The drug has been used in the UK since early 2017. The drug costs £450,000 in the first year and £225,000 per annum subsequently. For patients beginning this before November 2018, the manufacturer provided it free through an Expanded Access Programme(8). NHSE provides an administration cost, but not the other aspects of care for these patients. While randomised controlled trials showed nusinersen improved motor function and development(7), it is unclear whether the respiratory consequences produce similar benefits and thus the demands of treatment for families and health economies is yet to be established.

Royal Stoke University Hospital (RSUH) is the regional centre for nusinersen administration in the West Midlands which has a population of approximately 6 million. In March 2019 RSUH had the second largest cohort of SMA1 patients in the UK. Before agreeing to act as a regional centre for nusinersen delivery, we carefully considered the potential effects on children, their families and other healthcare

services. However, data were lacking making counselling of families and planning of service provision difficult. We have carefully monitored healthcare utilisation of SMA1 children treated with nusinersen. The aim of this article is to report the data on service utilisation for these children to assist families and healthcare professionals.

Methods

Patients treated with intrathecal nusinersen at RSUH were identified from a local database. The paper notes and electronic clinical records were reviewed to collect relevant data from RSUH and the child's referring hospital. This included baseline demographics, age at diagnosis, details of ventilatory support, feeding support, number of nusinersen doses, complications following administration and details of all hospital admissions. Hospital admission data included: duration of admission, number of HDU days, PICU days and intubated days. Nusinersen usually necessitated admission for one night for the first dose only. All children received care in accordance to the published international guidelines for the care of children with SMA(9,10). Intrathecal nusinersen was administered by appropriately trained paediatricians in the PICU treatment room. In babies this was performed using local anaesthetic and in toddlers using low dose opiate analgesia and / or sedation. No child has required a general anaesthetic or interventional radiology.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures. The results of this study will be disseminated to patient groups such as SMA UK and MD UK.

Approval and ethical considerations

The HRA decision tool (http://www.hra-decisiontools.org.uk/research) confirmed this project was audit not research and so ethical approval was not sought. The audit was approved by the departmental governance lead.

Results

We identified eleven children (six girls) who received nusinersen through the Expanded Access Program at RSUH between May 2017 and April 2019. Parents of a 12th child declined nusinersen and the child died at 3 months of age. The median (range) number of nusinersen doses was 6 (4-8). Nine children received non-invasive BiPAP and two children were ventilated via tracheostomy (TIV). Six children had been commenced on ventilation prior to their first dose of nusinersen. Both patients receiving TIV had the tracheostomy inserted before nusinersen was commenced. Two patients (including one on tracheostomy ventilation) have died suddenly at home from presumed mucous

plugs at 12 and 16 months of age, while one other patient had a cardiorespiratory arrest and has suffered hypoxic brain injury.

Table 1: Characteristics of cohort

	Median	Range
Age at diagnosis (months)	16.6	9 – 53.2
Age of first dose nusinersen (months)	20.6	1– 217.2
Age at initiation of LTV 2 (months)	20.9	5.8- 92.5
Age at initiation of advanced care pathway (n= 4) (months)	54	18.1 – 179.4
Number of admissions per child*	11	1 – 25
Number of emergency admissions per child*	3	0 – 21
Number of elective admissions per child*	4	0 – 9
Hospital days per child*	84	7 – 235
General paediatric hospital days per child*	0	0 – 63
HDU days per child*	79	7 – 173
PICU days per child*	13	0 - 109

*Over 24 months.

Duration and location of admissions

In 24 months, the 11 children had spent a total of 1101 days in hospital. Details of the hospitalisation are summarised in Table 1.-Three children were responsible for all admissions to the general paediatric ward which occurred at their local hospital. During these admissions, the respiratory team at RSUH liaised closely with local providers to guide acute management and arranged transfer when necessary. Three children had not been admitted to PICU. Of the eight children that had, six had been intubated for a total of 38 days. The median (range) proportion of life spent in hospital was 20% (2% - 72%). This was variable with four children spending ≤10%, four 10-35% and three >35%.

Reason for admission

The median age (range) for initiation of nusinersen was 35 (2 – 372) weeks. Since initiation of nusinersen the eleven children had a total of 107 hospital admissions with a median (range) per child of 11 (1-25). The commonest reason for admission was lower respiratory tract infection (n=42), followed by elective administration of intrathecal nusinersen (n=38). There were seven admissions for gastrointestinal issues, six for an elective sleep study, five for aspiration pneumonia, four for increased secretions or airway issues and three for optimisation of ventilatory support. At each admission for nusinersen the patient and family were reviewed by the paediatric palliative care team who

administered intrathecal treatment and assessed palliative needs. Children also received physiotherapy whilst inpatients. The physiotherapy adjuncts used by patients are listed in table 2. Four children had advanced care pathways in place. Between hospital admissions all the children were reviewed regularly in the outpatient clinic by the Paediatric Respiratory Multidisciplinary Team.

Table 2. Physiotherapy adjuncts that SMA1 children required

Physiotherapy Adjunct	Number (percentage) of children requiring adjunct
Saline Nebulisers	8 (72%)
Suction	11 (100%)
Percussion	9 (82%)
Cough Assist machine	5 (45%)
High Frequency chest wall oscillation vest	1 (0.9%)

Trends in admissions

Children in our cohort had the greatest requirement for hospital admission in the first 6 months following nusinersen initiation (see Figure 1). Much of this effect is driven by a tendency for children to have a long first admission (see Figure 2). Subsequent admissions tend to be shorter. The total number of hospital days for the children's first admission was 426 days with a median (range) of 20 (1 -235) days per child.

Cost implications and impact on local services

A total of 762 HDU days and 248 PICU days were required by the 11 children in our cohort over two years. This equates to 2.8 days in HDU and 0.93 days in PICU per child each month. RSUH has six HDU (four acute HDU beds and two long term ventilation) and eight PICU beds. The children therefore occupied 17% of the total HDU capacity and 4.2% of the PICU capacity over the study period. Based on current estimates of £1626 per day for a HDU bed and £1785 to £3784 for a PICU bed (depending on the level of care), the additional cost of these HDU/PICU days is £2.2M(11). This is separate to the cost of the nusinersen and its administration.

In addition to the costs associated with in-patient care, these children frequently require care packages which incur additional community costs. These costs are likely to continue throughout the child's life. In this small cohort, we found families highly motivated to provide care for their children and no child experienced a prolonged hospital admission as a result of awaiting funding for the provision of a care package. Four children had care packages implemented: one child had 16 hours

of care a week and three of the children had over 85 hours care per week. These three children received care seven nights a week between nine to ten hours and three days a week between five to eight hours. One with a large care package had tracheostomy ventilation, but the parents of the other child with tracheostomy declined a care package.

Discussion

This is the first study which accurately reports the in-patient healthcare utilisation of a cohort of children treated with nusinersen. This information is vital for those planning hospital healthcare services. In the first two years after diagnosis, these children spend, on average, one fifth of their early life in hospital although there is considerable inter-individual variation. This places a significant burden on parents and families and they should be counselled accordingly. There is a considerable impact on hospital services, particularly on high dependency and PICU. However, not all children required PICU admission and not all children admitted to PICU required endotracheal intubation. This involves a substantial extra resource, in addition to the direct cost of the nusinersen. Reassuringly, the number of hospital days has reduced as the child grows older. In our cohort, the 11 children required 762 HDU days over 24 months. This equates to the need for an additional HDU bed for every 10 children commenced on nusinersen.

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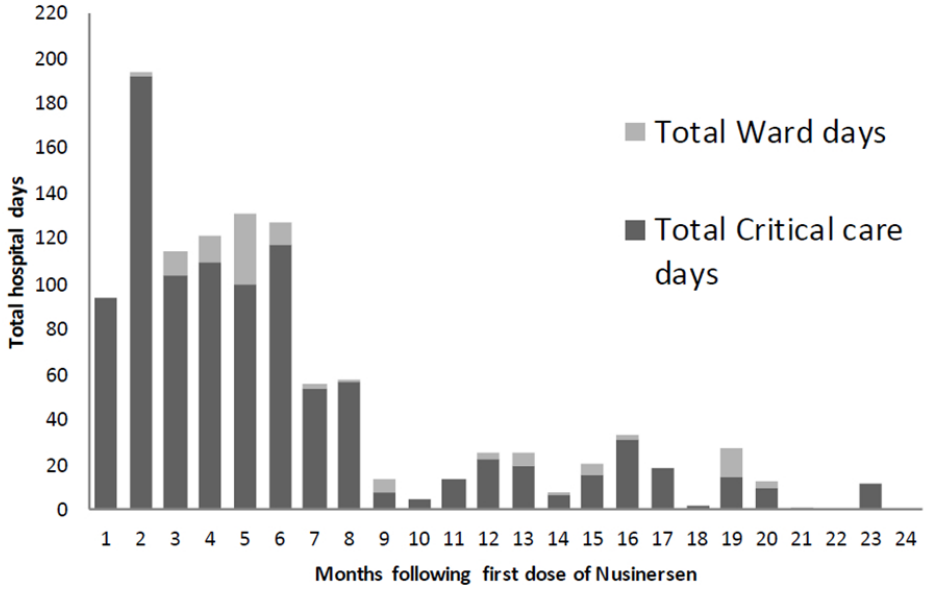

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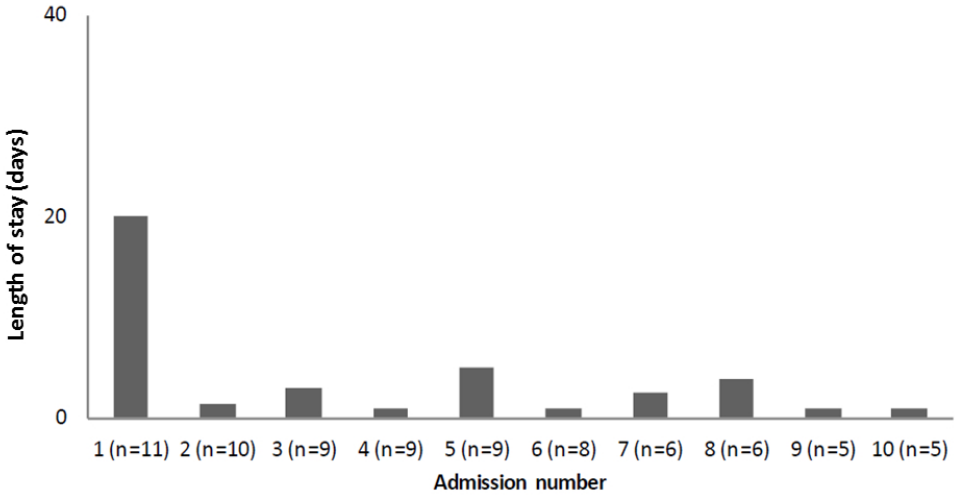

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