PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Healthcare Utilisation in Children with SMA Type 1 Treated with Nusinersen: a single centre retrospective review
AUTHORS	Ali, Imran; Gilchrist, Francis; Carroll, William; Alexander, John; Clayton, Sadie; Kulshrestha, Richa; Willis, Tracey; Samuels, Martin

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Hazel Evans Institution and Country: Southampton Children's Hospital Competing interests: None
REVIEW RETURNED	14-Sep-2019

GENERAL COMMENTS	This is an important topic and the impact (including health care utilisation) of the introduction of any new drug is important. The data is interesting. There are a number of areas that if addressed would enhance the generalisability of the paper. Abstract This is well written. Introduction 1. In general it is usual practice to place the reference number before any full-stop and I would suggest this is amended throughout the document 2. line 27 page 3 starting "However, SMN2 is a poor back-up " - this sentence doesn't read well and consideration should be given to rephrasing it 3. page 3 line 44 - use either "from" or "before" not both Methods These are described well Results 1. Page 4 line 45 "Program at RSUH between May 2017 April 2019" - please add dash between 2 dates 2. The original study included children commenced on nusinersen <7 months old - when describing the demographic is would be important to describe the age at which nusinersen was started for this population. It would be also be relevant to describe the number of children who were receiving ventilatory support prior to initiation of nusinersen 3. What was the reason for children requiring TIV - were they already receiving this prior to nusinersen or was it started as part of an admission once established on nusinersen - this is useful information as helps determine whether the drug has impacted on respiratory vulnerability or not.

	4. The outcomes in terms of death highlight the vulnerability of this cohort of children. Further description on whether these children had advanced care pathways would be helpful. The ages of the children who died are mentioned right at the end of the discussion - this should appear in the results section. What physiotherapy adjuncts were these children using. 5. Can you provide information on the frequency of respiratory follow-up - did this occur when the children attended for nusinersen or inbetween - what respiratory advice were families given - how much involvement was provided by the MDT/palliative care Duration and Location of Admissions a) what is the relative proportion of elective/emergency admissions - it would be good to expand the description of this in the reason for admission section b) were any admissions prolonged whilst awaiting provision of care packages c) were there any concerns that the placement of the child was inappropriate for the child's needs d) what was the indication for the child that spent 0 days on PICU as defined in your range. Please provide further details as to the indication for admission to PICU for the 2 children that were not intubated Trends in admission Can you describe the reasoning behind a longer first admission - does this relate to making the diagnosis, setting up respiratory provisions eg NIV/TIV, acute deterioration, application for care packages etc. Were the subsequent admissions shorter because parents were well educated to care for their child and everything was in place to do so. Cost Implications a) One way of explaining your data in terms of HDU usage is essentially for 10 patients with type 1 SMA being treated with nusinersen an additional level 2 bed is required. b) Given the cost of care packages it would be really beneficial to include data on the care package provision for these children and at least an estimation of these costs as this is additional cost to the NHS that would not have been necessarily long-term before the availability of this drug Discussion 1. The statement in the first sentence is not strictly accurate as all health care utilisation has not been explored. The statement should be limited to inpatient hospitalisations and should be rephrased to reflect this. 2. "these children spend one fifth of their early life in hospital". This statement needs to be amended and rephrased to reflect the variability of the population studied - many did not spend as much as this in hospital but some spent a greater proportion of time in hospital 3. It would be really helpful to provide information on the care package provision for these patients as this is an important health care cost which should be incorporated into this study Overall this is an important piece of work which will be of interest to a wide audience

REVIEWER	Reviewer name: Chiara Marini-Bettolo Institution and Country: The John Walton Muscular Dystrophy Research Centre, Newcastle University, The Newcastle upon Tyne NHS Trust. United Kingdom. Competing interests: I have no competing interests.
REVIEW RETURNED	21-Sep-2019

GENERAL COMMENTS	The authors address an important topic, which is very timely with novel treatments becoming available for SMA. This retrospective review is very helpful to assess the healthcare burden in SMA1 children receiving Nusinersen. Comments to the authors: 1. Authors don't mention Standards of care in the introduction or in the references. I think this would be helpful for completeness and understanding of complexity of care needs of this cohort of patients. 2. Authors mention that some of the admissions were at the children's local hospital. "Three children were responsible for all admissions to the general paediatric ward which occurred at their local hospital." I wonder whether this may have led to a different and less proactive approach in managing the patients if staff was less familiar with the condition. With this in mind it would be helpful to know what the catchment area of SMA1 patients attending RSUH for the administration of nusinersen is and this could have been a reason for increased hospital days. 3. Authors address the cost implications SMA1 related care in treated children taking into consideration days of hospital admission and type of admission. It would be helpful to understand what are the cost of Standard of care delivery and burden of care are in the absence of treatment to allow are fair comparison. In particular Authors state "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." However from the methodology it appears that this was not systematically reviewed and it is an approximate estimate. This would be an important comparison when quantifying the extra-added costs of SMA1 children treated with nusinersen. With this regards it would be important to reference a recent publications assessing the disease burden in Germany Orphanet J Rare Dis. 2016 May 4;11(1):58. 4. Page 6 lines19-20 should state that NHS England has funded nusinersen as part of a Managed Access Agreement for the next five years. 5. Authors do not describe the cohort of patients in detail which does not allow full interpretation and analysis of results. a. It would be interesting to correlate the days of hospital bed with disease severity and outcome measures (SMN2 copy numbers, functional ability, respiratory status or hrs of ventilation, age etc) b. There is no mention of patients having access to regular physiotherapy and cough assist or cough augmentation devices; hours of ventilation, respiratory management, swallowing, nutrition.

	7. For completeness of data it would be helpful to know how and where the intrathecal procedure was carried out. Was this performed in theatre, day unit, ward, under local or general anaesthesia and what was the requirement of overnight admission for the 1st administration? 5. It would be helpful if results were presented in a table.

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1

1. Introduction

In general it is usual practice to place the reference number before any full-stop and I would suggest this is amended throughout the document

We have changed the referencing format to fit with the guidance of BMJ Paediatrics Open

2. line 27 page 3 starting "However, SMN2 is a poor back-up " - this sentence doesn't read well and consideration should be given to rephrasing it

We have altered the wording to: ‘However, SMN2 transcription in 80-90% of instances leads to production of a truncated, unstable form of the protein which is non-functional..’

3. page 3 line 44 - use either "from" or "before" not both

Removed from

Results

4. Page 4 line 45 "Program at RSUH between May 2017 April 2019" - please add dash between 2 dates

Edited to include ‘and’ between the dates

5. The original study included children commenced on nusinersen <7 months old - when describing the demographic is would be important to describe the age at which nusinersen was started for this population.

The median (range) age of starting nusinersen has now been included

6. It would be also be relevant to describe the number of children who were receiving ventilatory support prior to initiation of nusinersen

We have added this as suggested.

7. What was the reason for children requiring TIV [TRACH INVASIVE VENTILATION - were they already receiving this prior to nusinersen or was it started as part of an admission once established on nusinersen - this is useful information as helps determine whether the drug has impacted on respiratory vulnerability or not.

Both patients receiving TIV had the tracheostomy inserted before nusinersen was started. This is now clarified in the results section. We have now also included the mean (range) timing of onset of LTV compared to commencing nusinersen.

8. The outcomes in terms of death highlight the vulnerability of this cohort of children. Further description on whether these children had advanced care pathways would be helpful.

We had added this into Table 1.

9. The ages of the children who died are mentioned right at the end of the discussion - this should appear in the results section.

This has been moved as suggested.

10. What physiotherapy adjuncts were these children using.

We have included this in Table 2.

11. Can you provide information on the frequency of respiratory follow-up - did this occur when the children attended for nusinersen or inbetween - what respiratory advice were families given - how much involvement was provided by the MDT/palliative care

A section has been added to the 'Reason for Admission' section: explaining this

Duration and Location of Admissions

12. what is the relative proportion of elective/emergency admissions - it would be good to expand the description of this in the reason for admission section

We have now included the number of emergency admissions and elective admissions per child.

13. were any admissions prolonged whilst awaiting provision of care packages

Surprisingly this did not delay discharge in our cohort. We have added a sentence to the discussion to explain this.

14. were there any concerns that the placement of the child was inappropriate for the child's needs

An additional sentence has been added to the discussion section to highlight this potentially difficult area.

15. what was the indication for the child that spent 0 days on PICU as defined in your range.

One of the children did not require PICU as all their care needs were met on HDU. A sentence has been added to the Discussion to clarify this point.

16. Please provide further details as to the indication for admission to PICU for the 2 children that were not intubated

The children were admitted for observation post-procedure but did not require intubation. (they were already on NIV). A sentence has been added to the Discussion to clarify this point.

Trends in admission

17. Can you describe the reasoning behind a longer first admission - does this relate to making the diagnosis, setting up respiratory provisions eg NIV/TIV, acute deterioration, application for care packages etc. Were the subsequent admissions shorter because parents were well educated to care for their child and everything was in place to do so.

This is an important point and a sentence has been added to the discussion to explain factors contributing to the prolonged first admission.

Cost Implications

18. One way of explaining your data in terms of HDU usage is essentially for 10 patients with type 1 SMA being treated with nusinersen an additional level 2 bed is required.

This is a really powerful way to express the data. We have included this in the abstract and the discussion

19. Given the cost of care packages it would be really beneficial to include data on the care package provision for these children and at least an estimation of these costs as this is additional cost to the NHS that would not have been necessarily long-term before the availability of this drug

We have now included information on care packages and how many hours per week children received care.

Discussion

20. The statement in the first sentence is not strictly accurate as all health care utilisation has not been explored. The statement should be limited to inpatient hospitalisations and should be rephrased to reflect this.

We changed this sentence as suggested and this is acknowledged as a limitation of the study further into the discussion section.

21. "these children spend one fifth of their early life in hospital". This statement needs to be amended and rephrased to reflect the variability of the population studied - many did not spend as much as this in hospital but some spent a greater proportion of time in hospital

22. This has been clarified as suggested

3. It would be really helpful to provide information on the care package provision for these patients as this is an important health care cost which should be incorporated into this study SEE COST IMPLICATIONS B) ABOVE

Reviewer: 2

1. Authors don’t mention Standards of care in the introduction or in the references. I think this would be helpful for completeness and understanding of complexity of care needs of this cohort of patients.

Care for all children was in accordance with the Standards of Care which has now been clarified in the Methods and the appropriate references added

2. Authors mention that some of the admissions were at the children’s local hospital. “Three children were responsible for all admissions to the general paediatric ward which occurred at their local hospital.” I wonder whether this may have led to a different and less proactive approach in managing the patients if staff was less familiar with the condition.

Close liaison with the local teams ensured standards of care where appropriate and the child was transferred when necessary. This has been clarified in the results section.

3. With this in mind it would be helpful to know what the catchment area of SMA1 patients attending RSUH for the administration of nusinersen is and this could have been a reason for increased hospital days.

We have clarified the catchment population in the introduction

4. Authors address the cost implications SMA1 related care in treated children taking into consideration days of hospital admission and type of admission. It would be helpful to understand what are the cost of Standard of care delivery and burden of care are in the absence of treatment to allow are fair comparison. In particular Authors state “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.” However from the methodology it appears that this was not systematically reviewed

It is difficult to make healthcare comparison for children that previously had very limited life expectancy. We have added a comment to the limitations section of the discussion highlighting this difficulty

5. With this regards it would be important to reference a recent publications assessing the disease burden in Germany Orphanet J Rare Dis. 2016 May 4;11(1):58.

Many thanks for this reference we have added this to the discussion section.

6. Page 6 lines19-20 should state that NHS England has funded nusinersen as part of a Managed Access Agreement for the next five years.

This has been amended

7. Authors do not describe the cohort of patients in detail which does not allow full interpretation and analysis of results.

a. It would be interesting to correlate the days of hospital bed with disease severity and outcome measures (SMN2 copy numbers, functional ability, respiratory status or hrs of ventilation, age etc)

Given the small numbers of children in this cohort we have elected not to report a detailed phenotype and correlation to healthcare utilisation as any observed correlations may be spurious and open to misinterpretation. Instead, we have chosen to consider the cohort as a group as this allows funders, clinicians and those planning healthcare services to make better informed decisions. We have acknowledged this lack of granularity in the discussion section.

8. There is no mention of patients having access to regular physiotherapy and cough assist or cough augmentation devices; hours of ventilation, respiratory management, swallowing, nutrition.

We have added this data as suggested.

9. For completeness of data it would be helpful to know how and where the intrathecal procedure was carried out. Was this performed in theatre, day unit, ward, under local or general anaesthesia and what was the requirement of overnight admission for the 1st administration?

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. This has been clarified in the methods section

10. It would be helpful if results were presented in a table.

Thank you for this suggestion. We have added a table to summarise the key results of the paper and removed the relevant text.

We believe that we have fully responded to all the reviewers' comments making the article acceptable for publication.

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Hazel Evans Institution and Country: Southampton Children's Hospital Competing interests: None
REVIEW RETURNED	08-Oct-2019

GENERAL COMMENTS	Thank you for addressing all the comments. The paper is an excellent piece of work which will be of interest to a wide audience. I would like to make a single further comment. 1. For the children with the large care packages I am assuming that these are the children receiving TIV - it would be helpful to add a comment to reflect this on page 8 after line 4. It would also be of interest if actually it is the NIV patients that are requiring the large care packages!

REVIEWER	Reviewer name: Chiara Marini-Bettolo Institution and Country: The John Walton Muscular Dystrophy Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle University. Competing interests: None
REVIEW RETURNED	23-Oct-2019

GENERAL COMMENTS	The authors address a very timely and import topic on their experience and cost implications in delivering a new treatment, Nusinersen, available for patients with SMA type 1. All previous comments have been addressed and clarified some points of this review. Chiara Marini-Bettolo

REVIEWER	Reviewer name: Institution and Country: Competing interests:
REVIEW RETURNED	

GENERAL COMMENTS	

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Thank you for addressing all the comments. The paper is an excellent piece of work which will be of interest to a wide audience. I would like to make a single further comment.

1. For the children with the large care packages I am assuming that these are the children receiving TIV - it would be helpful to add a comment to reflect this on page 8 after line 4. It would also be of interest if actually it is the NIV patients that are requiring the large care packages!

We have inserted a line on this in the manuscript outlining the care packages received by patients receiving TIV.

We believe that we have fully responded to all the reviewers' comments making the article acceptable for publication.