Efficacy and safety of onasemnogene abeparvovec in children with spinal muscular atrophy type 1: real-world evidence from 6 infusion centres in the United Kingdom

Vasantha Gowda,[a,*] Mark Atherton,[b] Archana Murugan,[c] Laurent Servais,[f,g] Jennie Sheehan,[a] Emma Standing,[a] Adnan Manzur,[e] Mariacristina Scoto,[e] Giovanni Baranello,[e,p] Pinki Munot,[e] Gary McCullagh,[d] Tracey Willis,[h] Sandya Tirupathi,[i] Iain Horrocks,[j] Anil Dhawan,[k] Michael Eyre,[l] Maria Vanegas,[a] Miguel A. Fernandez-Garcia,[a] Amy Wolfe,[a] Laura Pinches,[a] Marjorie Illingworth,[m] Marion Main,[e] Lianne Abbott,[e] Hayley Smith,[c] Emily Milton,[c] Sarah D'Urso,[b] Kayal Vijayakumar,[n] Silvia Sanchez Marco,[o] Sinead Warner,[d] Emily Reading,[d] Isobel Douglas,[i] Francesco Muntoni,[e,p,s] Min Ong,[b,s] Anirban Majumdar,[c,s] Imelda Hughes,[d,s] Heinz Jungbluth,[a,q,r,s] and Elizabeth Wraige[a,s]

[a]Children's Neurosciences, Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom
[b]Sheffield Children's NHS Foundation Trust, Sheffield, United Kingdom
[c]Department of Paediatric Neurology, University Hospital Bristol, Bristol, United Kingdom
[d]Royal Manchester Children's Hospital, Manchester, United Kingdom
[e]Dubowitz Neuromuscular Centre, Great Ormond Street Hospital, London, United Kingdom
[f]MDUK Oxford Neuromuscular Centre and NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, United Kingdom
[g]Division of Child Neurology, Centre de Référence des Maladies Neuromusculaires, Department of Pediatrics, University Hospital Liège and University of Liège, Avenue de l'Hôpital 1 4000 Liège, Belgium
[h]Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust, Oswestry, United Kingdom
[i]Royal Belfast Hospital for Sick Children, Belfast, United Kingdom
[j]Royal Hospital for Children, Glasgow, United Kingdom
[k]Paediatric Liver, GI and Nutrition Centre and MowatLabs, King's College Hospital, London, United Kingdom
[l]School of Biomedical Engineering and Imaging Sciences, King's College London, London, United Kingdom
[m]University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom
[n]Chelsea and Westminster Hospital, London, United Kingdom
[o]Paediatric Neurology Department, University Hospital of Wales, Cardiff, United Kingdom
[p]NIHR Great Ormond Street Hospital Biomedical Research Centre and Great Ormond Street Hospital NHS Foundation Trust, London, United Kingdom
[q]Randall Centre for Cell and Molecular Biophysics, Faculty of Life Sciences and Medicine (FoLSM), London, King's College London, London, United Kingdom
[r]King's College London, London, United Kingdom

Summary

Background Real-world data on the efficacy and safety of onasemnogene abeparvovec (OA) in spinal muscular atrophy (SMA) are needed, especially to overcome uncertainties around its use in older and heavier children. This study evaluated the efficacy and safety of OA in patients with SMA type 1 in the UK, including patients ≥2 years old and weighing ≥13.5 kg.

Methods This observational cohort study used data from patients with genetically confirmed SMA type 1 treated with OA between May 2021 and January 2023, at 6 infusion centres in the United Kingdom. Functional outcomes were assessed using age-appropriate functional scales. Safety analyses included review of liver function, platelet count, cardiac assessments, and steroid requirements.

Findings Ninety-nine patients (45 SMA therapy-naïve) were treated with OA (median age at infusion: 10 [range, 0.6–89] months; median weight: 7.86 [range, 3.2–20.2] kg; duration of follow-up: 3–22 months). After OA infusion, mean ± SD change in CHOP-INTEND score was 11.0 ± 10.3 with increased score in 66/78 patients (84.6%); patients aged <6 months had a 13.9 points higher gain in CHOP-INTEND score than patients ≥2 years (95% CI, 6.8–21.0; $P < 0.001$). Asymptomatic thrombocytopenia (71/99 patients; 71.7%), asymptomatic troponin-I elevation (30/89 patients; 33.7%) and transaminitis (87/99 patients; 87.9%) were reported. No thrombotic microangiopathy was

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*Corresponding author. Children's Neurosciences, Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, F02 – Becket House Lambeth Palace Road, London SE1 7EU, United Kingdom.
E-mail address: Vasantha.Gowda@gstt.nhs.uk (V. Gowda).
[s]Senior authors.

observed. Median steroid treatment duration was 97 (range, 28–548) days with dose doubled in 35/99 patients (35.4%). There were 22.5-fold increased odds of having a transaminase peak >100 U/L (95% CI, 2.3–223.7; $P = 0.008$) and 21.2-fold increased odds of steroid doubling, as per treatment protocol (95% CI, 2.2–209.2; $P = 0.009$) in patients weighing ≥13.5 kg versus <8.5 kg. Weight at infusion was positively correlated with steroid treatment duration ($r = 0.43$; $P < 0.001$). Worsening transaminitis, despite doubling of oral prednisolone, led to treatment with intravenous methylprednisolone in 5 children. Steroid-sparing immunosuppressants were used in 5 children to enable steroid weaning. Two deaths apparently unrelated to OA were reported.

Interpretation OA led to functional improvements and was well tolerated with no persistent clinical complications, including in older and heavier patients.

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Keywords: Spinal muscular atrophy; SMA; Zolgensma; Onasemnogene abeparvovec; Motor neuron disorder; Gene therapy; Follow-up; Longitudinal; Safety; Efficacy; Real-world experience; United Kingdom

Research in context

Evidence before this study

We conducted a systematic literature search on Pubmed from January 1 2017 to April 30 2023 with the search terms (Spinal Muscular Atrophy [MeSH Terms]) AND ((onasemnogene abeparvovec) OR (Zolgensma) OR (gene therapy) OR (gene-replacement therapy)), with no language or type of publication restrictions. There was evidence for safety and efficacy of onasemnogene abeparvovec (OA) in a real-world setting, for children weighing less than 13.5 kg and younger than 2 years, but not for those weighing over 13.5 kg and aged above 2 years.

Added value of this study

Our study provides insights into the efficacy and safety outcomes in patients with spinal muscular atrophy type 1 treated with onasemnogene abeparvovec (OA) in a real-world setting in the UK, especially in patients 2 years or older and with a body weight of at least 13.5 kg.

Implications of all the available evidence

Our data indicate that in our treated cohort, OA was a safe treatment resulting in improved motor function in the majority. The dataset expands the scarce safety data available for patients over 2 years old or weighing at least 13.5 kg, in particular demonstrating that there is a linear correlation of weight with hepatotoxicity. These observations emphasize the importance of careful pretreatment counselling and post-treatment monitoring, and of a careful and personalized risk-benefit analysis as some in this group may show significant motor improvement with treatment. Moreover, while immunomodulation is necessary for gene therapy administration, careful consideration and monitoring are needed to balance the benefits with the known side-effects of prolonged steroid use; steroid-sparing agents may be considered in certain cases. Overall, OA appears to be effective in older and heavier children, but potential side-effects require close monitoring.

Introduction

Spinal muscular atrophy (SMA) is an autosomal-recessive disorder characterized by motor neuron degeneration and progressive skeletal muscle weakness[1] classified into 5 subtypes (types 0–4) dependent on the maximum motor milestone achieved. SMA type 1 has symptom onset during the first 6 months of life; unless permanently ventilated, survival beyond 2 years of age is unexpected.[1–3]

SMA is caused by pathogenic variants in the survival motor neuron (SMN) 1 gene (*SMN1*) on chromosome 5q13.2.[4] SMN protein is required for motor neuron development and viability.[5,6] *SMN1* pathogenic variants lead to deficiency of functional SMN protein, and subsequent death of lower motor neurons.[5] The SMN 2 gene (*SMN2*) is a homologous gene with variable copy numbers, producing only small amounts of functional SMN protein. The *SMN2* copy number is the major SMA disease modifier and correlates inversely with disease severity.[4]

There are 3 approved therapies for SMA, each increasing the production of functional SMN protein in motor neurons: the splicing modifiers nusinersen and risdiplam through their action on SMN2 gene and onasemnogene abeparvovec (OA) which uses a genetically modified adeno-associated virus type 9 (AAV9) vector for *SMN1* delivery.[7–9]

Two phase 3 trials (STR1VE-US and STR1VE-EU) demonstrated that *SMN1* replacement via OA improves survival and motor development in SMA type 1, with favorable benefit-risk profile for patients under 2 years.[10,11] Similar findings were reported from 2 long-term studies, demonstrating sustained OA efficacy

up to 7.5 years post-dosing with no new safety signals.[12,13] However, experience using OA in patients 2 years or older or heavier than 13.5 kg is limited.[14] Data from post-marketing use are emerging,[15–19] but more data are needed to better understand the safety and efficacy of OA in these subgroups.

In the UK, OA has been approved for treatment of patients with genetically confirmed 5q SMA type 1, or for infants up to 12 months old identified presymptomatically with up to 3 copies of *SMN2*.[20] Following its approval, the first UK patient was treated in May 2021. There are 6 infusion centres authorized to administer OA in the UK. In England, OA administration is managed via a centralized national multidisciplinary team (NMDT) comprised of members from each infusion centre, a representative from a non-infusion centre, and other health care professionals, including physiotherapists, clinical nurse specialists, pharmacists, who meet twice monthly. Infants 6 months or younger can be treated without prior discussion; for all others, referrals must be made to the NMDT for consideration of OA treatment. In the UK, patients are not funded for nusinersen or risdiplam after treatment with OA unless there is a demonstrable lack of sustained efficacy of OA. Patients on risdiplam were advised to stop risdiplam 1–2 days before the admission for OA dosing based on the known risdiplam half-life of approximately 50 h. For nusinersen-treated patients, a consensus was reached to allow a minimum gap of 1 month to avoid cumulative side effects and a maximum gap of <4 months between the last nusinersen dose and OA dosing, as the half-life of nusinersen is 19–25 weeks in the CSF.

Using real-world data from the 6 UK centres, we describe OA safety and efficacy in patients with SMA type 1, including patients ≥2 years old and weighing ≥13.5 kg.

Methods

Study design and participants

This was a multicentre, observational cohort study in pediatric patients with SMA type 1 treated between May 2021 and January 2023 with OA in accordance with the Zolgensma (onasemnogene abeparvovec) summary of product characteristics.[14] The follow-up cut off for these patients was May 2023. The patients received OA in one of the designated UK infusion centres (eMethods in Supplement 1). Standardized forms were used for safety data collection. Functional scores were tabulated from individual centres and collated separately. 4 patients included in this study received nusinersen through clinical trials after OA; all 4 were treatment naive and aged ≤6 months at the time of OA.

As all patient data were collected as part of standard clinical care in conjunction with national registry curated by SMAREACH, which has been approved by Research Ethics Committee, institutional review board approval was not deemed necessary. All procedures were performed in accordance with principles of the Declaration of Helsinki[21] and consistent with applicable regulatory requirements.

Treatment protocol details, summarized in the following sections, have been published previously.[22]

Pre-infusion screening

In all patients, confirmation of AAV9 antibody titers less than 1:50 was required. Anthropometric and vital sign measurements were recorded. To identify any contraindications to treatment, liver function tests (aspartate aminotransferase [AST], alanine transaminase [ALT], serum bilirubin, gamma-glutamyl transferase), full blood count, coagulation tests and cardiac assessment including troponin I measurement, electrocardiogram and, variably, an echocardiogram were performed 1 week prior to planned infusion.

Infusion process

Oral prednisolone (1 mg/kg/day) was commenced 24 h prior to OA infusion. Patients received OA via IV infusion (1.1×10^{14} vector genome/kg of body weight) over 1 hour as an inpatient and typically were observed for at least 48 h post-infusion.

Post-infusion monitoring and assessment

Prednisolone was continued at 1 mg/kg/day for at least 30 days, then tapered over 28 days if the liver enzymes were below twofold upper limits of normal (ULNs; defined for each centre in eTable 1 in Supplement 1). Patients had blood tests at least weekly in the first month and fortnightly thereafter.

In the case of transaminase levels exceeding twofold the ULNs, prednisolone dosage was doubled to 2 mg/kg/day and/or the tapering period was prolonged. If the transaminitis worsened, IV methylprednisolone and/or steroid-sparing agents were administered according to physician discretion, in discussion with hepatologists.

Functional outcomes were assessed using age-appropriate standardized scales: the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), Revised Hammersmith Scale (RHS), and Hammersmith Infant Neurological Examination (HINE) scores. Scores in the 2 weeks before and the highest score achieved during follow-up after gene therapy were reviewed.

Data analysis

Patients were stratified by age at infusion (<6 months, 6–12 months, 1–2 years, ≥2 years), weight at infusion (<8.5, 8.5–13.5, ≥13.5 kg) and pretreatment status (received nusinersen and/or risdiplam [pretreated cohort] versus treatment-naive). CHOP-INTEND score changes after OA were described using mean ± SD. The timepoints of CHOP-INTEND assessment after OA varied among patients and the highest-attained score

	Participants (n = 99)
Age at infusion, median (range), months	10 (0.6–89)
Age distribution, n	
<6 months	33
6–12 months	28
1–2 years	17
≥2 years	21
Weight at infusion, median (range), kg	7.86 (3.2–20.2)
Weight distribution, n	
<8.5 kg	61
8.5–13.5 kg	31
≥13.5 kg	7
Treatment received prior to OA, n	
Nusinersen	48
Risdiplam	5
Other[a]	1
None	45
***SMN2* copies, n**	
×2	62
×3	9
Liver enzyme elevations post OA infusion	
≥1 peak of >100 U/L, n (%)	
ALT (n = 99)	46 (46.5)
AST (n = 99)	67 (68.4)
ALT and AST (n = 99)	43 (43.4)
≥1 peak of >400 U/L, n (%)	
ALT (n = 99)	17 (17.2)
AST (n = 99)	12 (12.2)
ALT and AST (n = 99)	11 (11.1)
Steroid dose doubled post OA infusion, n/N (%)	
Full cohort	35/99 (35.4)
Subgroups stratified by weight	
<8.5 kg	11/61 (18.0)
8.5–13.5 kg	18/31 (58.1)
≥13.5 kg	6/7 (85.7)
Subgroups stratified by age	
<6 months	4/33 (12.1)
6–12 months[b]	11/27 (40.7)
1–2 years	6/17 (35.3)
≥2 years	14/21 (66.7)
Duration of steroid use post OA infusion[c,d]	
Mean ± SD, days	123.4 ± 90.7
Median (range), days	97 (28–548)
<90 days, n/N (%)	36/93 (38.7)
90–180 days, n/N (%)	46/93 (49.5)
180–365 days, n/N (%)	9/93 (9.7)
>365 days, n/N (%)	2/93 (2.2)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; OA, onasemnogene abeparvovec; *SMN2*, survival motor neuron 2. This table shows baseline characteristics of 99 patients who were dosed with OA. At infusion, median age and median weight were 10 months and 7.9 kg, respectively, with 54 patients receiving treatment prior to OA therapy. Post OA infusion, one or more peaks of ALT, AST, and both ALT and AST >100 U/L were reported in 47%, 68%, and 44% patients, respectively, and >400 U/L were reported in 17%, 12%, and 11% patients, respectively. Oral prednisolone dose was doubled in 35% patients from a starting dose of 1 mg/kg/day. Overall mean duration of steroid use was 119 days. [a]Received both nusinersen and risdiplam. [b]Data not available for 1 patient. [c]Data available for 93 of the 99 patients. [d]Variable recording of end of steroid use may introduce some uncertainty.

Table 1: **Baseline characteristics, liver enzyme elevations, and steroid use data for patients treated with OA.**

was used. Linear regression was used to evaluate change in CHOP-INTEND score (post-OA score minus pre-OA score) with independent variables: age at infusion (stratified as above, with <6 months as the reference category) and pretreatment status. This model was validated with a supplementary model in which pre-OA CHOP-INTEND score was also included as an additional covariate. Weight at infusion was not considered relevant for motor outcome and hence was not included in the CHOP-INTEND score models. Logistic regression was used to evaluate the binary outcomes of liver enzyme derangement of >twice the upper limit of normal (defined as patients with both ALT and AST peaks >100 U/L) and steroid dose doubling (patients requiring prednisolone dose doubling as per the post-infusion protocol) with independent variables: age at infusion (stratified as above, with <6 months as the reference category), weight at infusion (stratified as above, with <8.5 kg as the reference category), and pretreatment status; owing to multicollinearity of age and weight, the one with least statistical significance was omitted from the final model to improve stability and interpretability. Odds ratios were derived from the model coefficients. Serum biochemistry parameters and steroid treatment duration were log-transformed to evaluate univariate relationships with weight at infusion, tested with Pearson correlation (unless the variable contained zero values, in which case Spearman correlation was calculated on the raw values). The relationship between log-transformed steroid duration and age at infusion was also tested with Pearson correlation. Log-linear regression was used to calculate the expected change in biochemical parameters and steroid duration per 5 kg increase in weight at infusion and the expected change in steroid duration per 1-year increase in age at infusion (calculated only for variables with Pearson correlations significant at $P < 0.05$). Differences in steroid duration between patients <13.5 kg versus ≥13.5 kg and between those pretreated versus treatment-naive were tested with the Mann–Whitney U test. Analyses were conducted using Python 3.10 with SciPy v1.10.0 and statsmodels v0.13.5.

Role of the funding source

In summary, the funder had no role in any aspect of the study other than awarding the grant for independent medical writing support to the authors. More specifically, Novartis Innovative Therapies AG had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Results

Patient demographics

The study included 99 patients with SMA type 1 treated with OA in the UK. At the point of OA infusion, median age was 10 (range, 0.6–89) months and median weight

7.86 (range, 3.2–20.2) kg (Table 1). Twenty-one patients were 2 years or older and 7 patients weighed at least 13.5 kg. Before treatment with OA, 54 patients had received prior therapy: 48, nusinersen; 5, risdiplam; and 1, both. Duration of follow-up varied from 3 to 22 months. One pre-symptomatic patient received OA on day-19 and another was on Nusinersen before receiving OA; the rest were symptomatic.

Functional scores

The follow-up duration for functional assessments was available for 90 patients and ranged from 3 to 22 months, with a mean of 8.9 months, median of 8 months and a mode of 3 months. Changes in functional scores (eTable 2 in Supplement 1) were calculated for patients who had both pre- and post-OA scores.

CHOP-INTEND

Pre- and post-OA scores were available for 78/99 patients (Fig. 1). The mean ± SD change in CHOP-INTEND score after OA was 11.0 ± 10.3, with increased score in 66/78 patients (84.6%). In the pre-treated cohort, pre- and post-OA scores were available for 41/54 patients; the mean ± SD change in score was 8.5 ± 9.1, increasing in 33/41 (80.5%). In the treatment-naive cohort, pre- and post-OA scores were available for 37/45 patients; the mean ± SD change in score was 13.7 ± 10.9, increasing in 33/37 (89.2%).

In a multivariable model evaluating the independent effects of age at infusion and pretreatment on change in CHOP-INTEND score after OA, patients younger than 6 months at infusion had an estimated 17.7-point gain in score (95% CI, 13.4–22.0), patients 6–12 months old had an estimated 11.9-point gain in score (95% CI, 8.4–15.4; −5.8-point difference relative to the younger than 6 months group, $P = 0.03$), patients 12–24 months old had an estimated 4.4-point gain in score (95% CI, −2.8 to 11.6; −13.3-point difference relative to the younger than 6 months group, $P < 0.001$) and patients 24 months or older had an estimated 3.8-point gain in score (95% CI, −3.6 to 11.2; −13.9-point difference relative to the younger than 6 months group, $P < 0.001$); there was no significant effect of pretreatment with nusinersen/risdiplam on change in CHOP-INTEND score after OA (eTable 3 in Supplement 1). In the model also including pre-OA CHOP-INTEND score as a covariate, the estimated gain in CHOP-INTEND score after OA was 3.6 points lower in the 6–12 months group ($P = 0.18$), 10.4 points lower in the 12–24 months group ($P = 0.002$) and 9.2 points lower in the >24 months group ($P = 0.02$) relative to patients younger than 6 months at infusion (eTable 4 in Supplement 1).

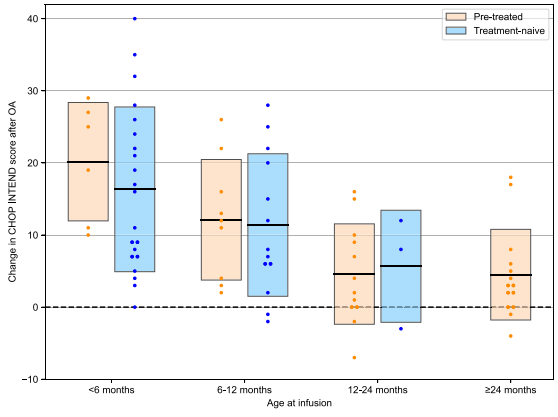

Fig. 1: Changes in CHOP INTEND scores from before to after OA therapy. Legend: Pre- and post-gene therapy CHOP INTEND scores were available for 78 patients: 41 pretreated with risdiplam, nusinersen, or both, and 37 treatment-naive. Plotted points show the difference between the pre- and highest attained post-OA scores for each patient, grouped according to age and pretreatment status. Box plots show the mean ± SD for each group. The majority of patients across all groups had an increase in CHOP INTEND score after OA therapy. CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; OA, onasemnogene abeparvovec.

Revised Hammersmith Scale and Hammersmith Infant Neurological Examination

Pre- and post-OA RHS and HINE scores were available for 10 and 47 patients, respectively. Three patients were assessed with RHS only, not CHOP-INTEND. There was a mean ± SD change of 1.0 ± 2.31 in RHS score post OA, with increased score in 5 patients. For HINE, a mean ± SD change in score of 4.19 ± 4.86 was reported post OA, with increased score in 37 patients.

Post-infusion adverse events

One child who was well prior to OA infusion became unwell within 24 h of infusion with systemic inflammatory response syndrome, stabilizing after treatment with fluid bolus and antibiotics. Infection screen was negative. Post OA, 71/99 patients (71.7%) had asymptomatic thrombocytopenia (<150 × 10^9/L) typically in the first week following infusion and resolving spontaneously, usually by the second week. Seven patients had a platelet nadir below 50 × 10^9/L; comparing their age, weight at infusion, pretreatment status and immunomodulation, no common characteristics were noted (Table 2). There was no significant correlation between weight at infusion and platelet nadir (Fig. 2A) for the whole cohort. Thrombotic microangiopathy (TMA) was not observed.

Troponin-I data were available for 89/99 patients. Elevated levels (>35 ng/L) were reported in 30 patients (33.7%), typically within 2 weeks post-infusion, with levels above 100 ng/L in 7 (7.9%). There was an inverse correlation between weight at infusion and troponin-I peak ($r = -0.27$, $P = 0.006$; Fig. 2B). All patients with elevated troponin-I were asymptomatic with normal echocardiograms.

Post-OA infusion, 87/99 patients (87.9%) had AST or ALT levels above ULN. There were log-linear

Age in months	Weight in kilograms	Platelet values	Previously treated	Steroids doubled
4	6.2	45 × 10^9/L	None	No
5	6.16	50 × 10^9/L	None	No
10	6.79	27 × 10^9/L	None	No
10	9.16	39 × 10^9/L	Nusinersen	Yes
11	10.87	20 × 10^9/L	Nusinersen	Yes
20	7.7	24 × 10^9/L	Nusinersen	No
23	8.45	47 × 10^9/L	Nusinersen	Yes

Table 2: **Summary of patients with platelets nadir of ≤50 × 10^9/L post OA.**

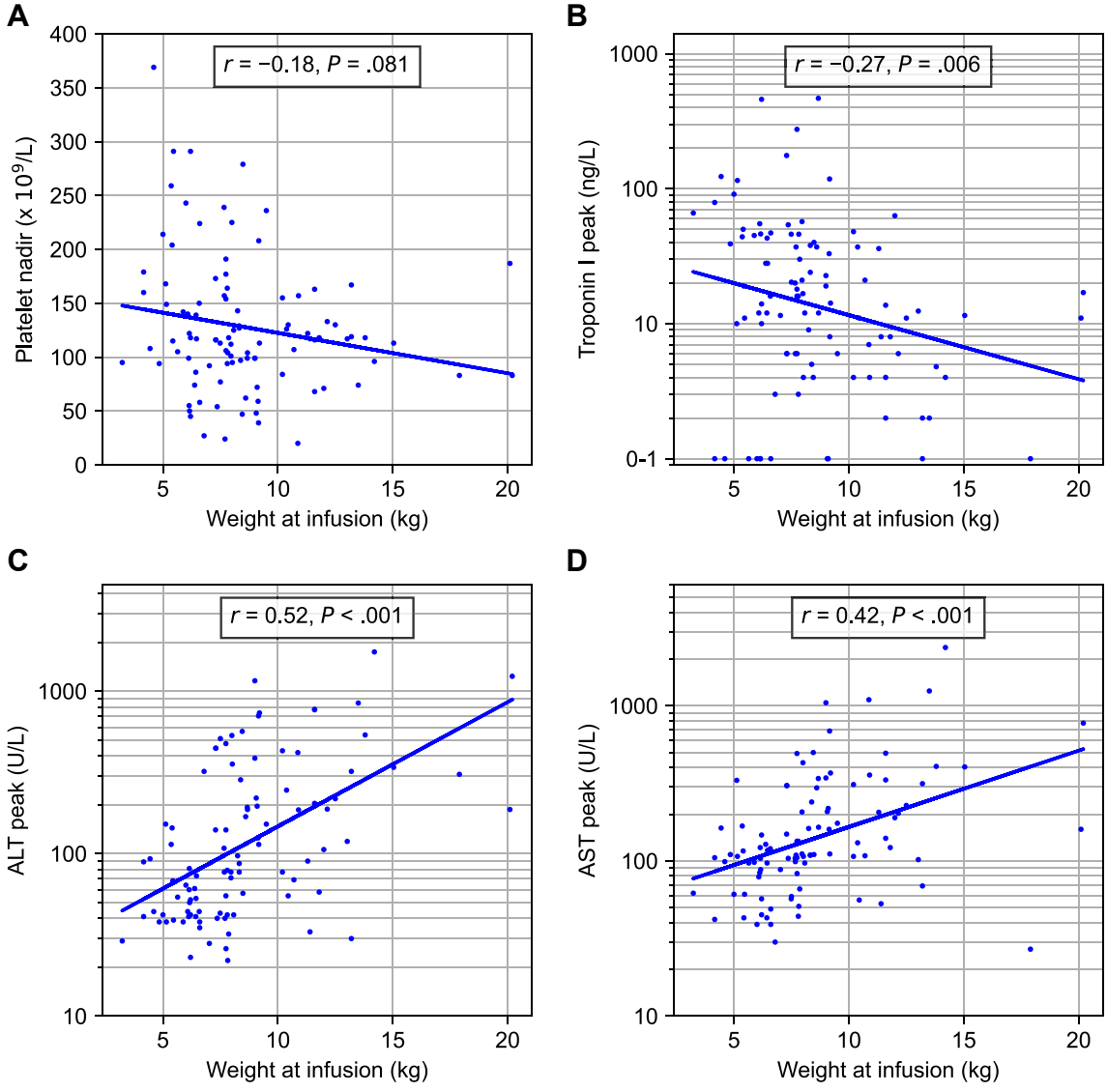

Fig. 2: Relationships between weight at infusion and blood parameters during post-infusion follow-up. Legend: Scatterplots showing relationships of weight at infusion with post-infusion platelet nadir (A), troponin I peak (B), ALT peak (C), and AST peak (D). Spearman's *r* was calculated for platelet nadir and troponin I peak. For ALT and AST peaks, Pearson's *r* was calculated on the log-transformed data. Troponin I zero values were replaced with ones prior to log transformation for visualization. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

correlations between weight at infusion and ALT peak (r = 0.52, P < 0.001; Fig. 2C) and AST peak (r = 0.42, P < 0.001; Fig. 2D): each 5-kg increase in weight was associated with a 2.4-fold higher ALT peak (95% CI, 1.8–3.2) and 1.8-fold higher AST peak (95% CI, 1.4–2.3). More pronounced transaminitis (ALT or AST >100 U/L) was observed in 70 patients (Table 1). 42 patients had both peaks >100 U/L; the odds of this occurring were increased 13.4-fold and 22.5-fold, respectively, in patients weighing 8.5–13.5 kg at infusion (95% CI, 4.4–40.3, P < 0.001) and those weighing at least 13.5 kg (95% CI, 2.3–223.7, P = 0.008), compared with those weighing less than 8.5 kg. There were no significant independent effects of pretreatment or age at infusion (eTable 5 in Supplement 1). Serial measurements of ALT and AST for each patient are shown in eFigure 1 in Supplement 1.

Two deaths were reported: one child died from a comorbid condition unrelated to SMA or treatment and the second was evaluated to have died from SMA complications, although postmortem examination was not undertaken.

Use of steroids

Oral prednisolone was doubled in 35/99 patients (35.4%; Table 1). ALT and/or AST levels typically improved within a week of doubling prednisolone. Compared with patients weighing less than 8.5 kg, patients weighing 8.5–13.5 kg at infusion had 5.4-fold increased odds (95% CI, 2.0–15.0, P = 0.001) and patients weighing at least 13.5 kg had 21.2-fold increased odds (95% CI, 2.2–209.2, P = 0.009) of steroid doubling; there were no significant independent effects of pretreatment or age at infusion (eTable 6 in Supplement 1).

The mean ± SD and median number of days that patients were on steroids were 123 ± 90.7 days and 97 (range, 28–548) days, respectively (Table 1). There was a log-linear correlation between weight at infusion and steroid duration (r = 0.43, P < 0.001; Fig. 3A): each 5-kg increase in weight was associated with 46.0% longer duration of steroid therapy (95% CI, 24.1%–71.7%). Median steroid duration in patients weighing less than 8.5 kg was 91.5 days, in patients weighing 8.5–13.5 kg was 109 days and in patients weighing at least 13.5 kg was 235 days. There was a log-linear correlation between age at infusion and steroid duration (r = 0.41, P < 0.001; Fig. 3B): each 1-year increase in age was associated with 13.8% longer duration of steroid therapy (95% CI, 7.2%–20.7%). Median steroid duration in pretreated patients was 96 days versus 98 days in treatment-naive patients (P = 0.43).

IV methylprednisolone was administered to 5 patients with worsening acute transaminitis despite being on prednisolone 2 mg/kg/day. Of these, 4 patients were commenced on steroid-sparing immunosuppressants (Table 2). One patient did not receive IV methylprednisolone but started Mycophenolate for treatment of chronic transaminitis. Liver biopsy was performed in 3 patients, showing mild fibrosis with no inflammation in one, a small, isolated focus of suspected lobular inflammation in the second and moderate-to-severe interface and lobular hepatitis in the third; the last patient developed coagulopathy and cholestasis and was managed with tacrolimus with good outcome. Patients

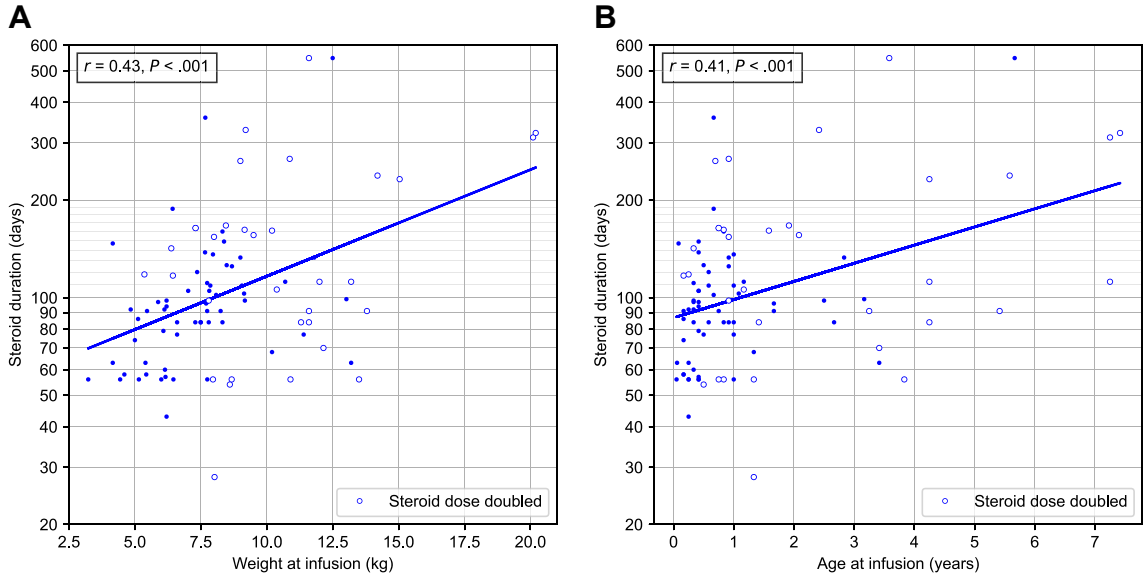

Fig. 3: Relationships between age and weight at infusion and post-infusion steroid course duration. Legend: Scatterplots showing relationships of weight (A) and age (B) at infusion with post-infusion steroid course duration. Pearson's *r* was calculated on the log-transformed data. Hollow points indicate patients who required doubling of the steroid dose.

were treated according to physician discretion in consultation with a hepatologist rather than according to a defined protocol, taking into consideration the liver function test results and trends, time duration from infusion, response to steroids, presence of intercurrent illness and degree of respiratory impairment. Following the addition of a steroid-sparing agent, a response was observed from within 2 weeks of achieving therapeutic doses, however this observation is difficult to generalize, as there were confounding factors in some patients, such as delay in achievement of therapeutic dose of the steroid sparing agents due to minor, steroid-sparing agent-related side effects.

The current clinical status of these patients is outlined in Table 3.

Discussion

In this study, we describe data from 99 patients with SMA type 1 treated with OA, including 21 patients aged 2 years or older and 7 patients weighing at least 13.5 kg.

In contrast to untreated children with SMA type 1,[23–25] children treated with OA have consistently achieved CHOP-INTEND scores of at least 40 in both trial and real-world settings.[26–30] In this study, over 80% of patients showed an increase in CHOP-INTEND score after OA, indicating improvements in motor function, most notably in younger patients. Although the average improvement in CHOP-INTEND score after OA was less in older patients, a small number of patients aged 24 months or older did make significant gains. For example, one patient aged 29 months had a 17-point gain and one aged 25 months had an 18-point gain after OA. Pretreatment with nusinersen, risdiplam, or both before OA did not have a significant effect on CHOP-INTEND scores.

The side-effect profile of OA possibly results from the systemic inflammatory response to the AAV9 vector, as transgene immune reaction is not expected since SMA patients produce low levels of SMN protein from the SMN2 genes. Potential adverse effects include thrombocytopenia, TMA, elevated cardiac enzymes, and hepatotoxicity.[31,32]

Dorsal root ganglia inflammation was observed in nonhuman primates, but no clinical features suggestive of ganglionopathy were recorded in clinical studies, nor observed in our study.[31] Symptomatic acute liver failure has been observed despite immunosuppression, typically up to 2 months post infusion.[14] Two acute liver failure-related fatalities have been reported.[33] Thrombocytopenia and TMA mostly occur in the first 2 weeks after OA infusion, and ALT and/or AST elevations, after 1 week with a second peak often seen 1–2 months after OA infusion.[14,15,34]

The side-effect profile in our study is similar to previous reports[15,16,26,28–30,34,35]: Over two-thirds of patients had asymptomatic thrombocytopenia typically in the first week after OA, which resolved spontaneously usually by week two; elevated troponin-I, an indicator of cardiac toxicity, was reported in 34% but was not associated with any other clinically relevant cardiac signs and symptoms. TMA following OA, particularly seen in those who had recent infection, vaccination or prior treatment with nusinersen was not observed in our study.[26,31,36]

In this study, patients were on steroids for a median duration of 97 days, which is similar to the duration of completed steroid treatment in other studies.[15,26,37] Median steroid duration in patients weighing at least 13.5 kg was 235 days. While immunomodulation is necessary for gene therapy administration, careful consideration and monitoring are needed to balance the benefits with the known side-effects of prolonged steroid use; steroid-sparing agents may be considered in certain cases.

In our study, most patients with significant transaminitis responded to doubling of prednisolone. However, five patients with worsening transaminitis despite being on prednisolone 2 mg/kg/day were treated with IV methylprednisolone, similar to previous reports.[15,26,28] Liver biopsies may provide important information to help guide immediate treatment decisions, in particular identifying whether or not there is evidence for on-going inflammation; however, their invasive nature may limit utility.[38]

Ninety-eight of the 99 patients included in this analysis tolerated the infusion well. The 2 deaths reported in this study appeared to be unrelated to gene therapy.

In this study, heavier patients had more markedly elevated liver enzymes and consequently higher steroid requirements and treatment duration, similar to previous studies,[15,16,18,26,29,30,35,37,39] including a meta-analysis in which 71.7% of patients older than 8 months had elevated aminotransferases versus 28.5% of patients 8 months or younger.[19] Varying immune response to AAV9 may explain the variably raised transaminase levels; pretreatment with nusinersen or risdiplam were not a significant factor after controlling for differences in weight at infusion between the pretreated and treatment-naive cohorts. Higher rates of thrombocytopenia in patients weighing 8 kg or over have been reported previously[19,26]; however, no significant correlation between platelet nadir and weight at infusion was found in our study.

As OA dose is proportional to body weight, the total viral vector load is higher in heavier patients and thus the adverse event profile is likely to be more severe in this patient group. Furthermore, the more mature immune system of older infants may contribute to the increased likelihood of severe adverse events seen with increasing age.[40]

Apart from primary medical considerations, we have also found that the complexity of assessment and

Age group at OA infusion	Weight at OA infusion (kg)	IV methylprednisolone administered	Peak ALT U/L AST U/L GGT U/L Bilirubin umol/L	Steroid-sparing agent administered	Last known status[a]				Liver biopsy
					Steroid-sparing agent status	Steroid therapy	Liver function tests (AST, ALT, GGT, Bilurbin)	Clinical condition	
8–11 months	7–9	Yes	446 306 38 8	Tacrolimus	Off	Prednisolone–weaned and stopped	Normal Normal Normal Normal	Well	No
8–11 months	7–9	Yes	1160 1047 101 9	Mycophenolate	Off	Prednisolone–weaned and stopped	ALT normal AST 41 (ULN 34) Normal Normal	Well	Yes
8–11 months	7–9	Yes	534 430 150 6	No	NA	Prednisolone–weaned and stopped	Normal Normal Normal Normal	Well	No
5.5–7.5 years	14–21	Yes	1746 2377 571 21	Mycophenolate	Off	Prednisolone–weaned and stopped	ALT normal, AST 46 (ULN 34) Normal Normal	Well	No
5.5–7.5 years	14–21	Yes	1236 774 434 137	Tacrolimus	Off	On hydrocortisone	ALT 45 (ULN 35) AST 64 (ULN 50) Normal Normal	Well	Yes
2–4 years	11–13	No	775 495 109 12	Mycophenolate	Continues	Prednisolone–small steady dose	All normal; ALT/AST elevated with intercurrent illnesses	Well	Yes

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; IV, intravenous; NA, not applicable; OA, onasemnogene abeparvovec; ULN, upper limit of normal; U, units. This table summarizes information on the 6 patients who required IV methylprednisolone and/or steroid-sparing immunosuppressants (including their last known therapy), liver function, and clinical status. [a]End of October 2023.

Table 3: **Summary of patients requiring IV methylprednisolone and/or steroid-sparing immunosuppressants.**

treatment decisions benefits from a multidisciplinary collaborative approach to ensure optimum patient care. The NMDT setup in the UK includes neuromuscular specialists from infusion centres, representation from referring centres and an external expert, in addition to physiotherapists, clinical nurse specialists and pharmacists as well as local/national input from hepatologists and cardiologists as needed; this set-up allows for joint decision-making, sharing of experience, and streamlined patient care; it also facilitates equitable access to treatment.

Our study has some limitations including missing measurements for some patients, variable follow-up duration and timepoints of functional assessment post infusion. *P*-values were not corrected for multiple comparisons. For pretreated patients, it is not possible to say if improvements in motor function and side-effects were due to OA, previous therapy, or a combination of both owing to the limited duration of follow-up.

Conclusion

This is one of the largest studies of patients with SMA type 1 treated with OA. Our data indicate that in our treated cohort OA was a safe treatment resulting in improved motor function in the majority. The dataset expands the scarce safety data available for patients over 2 years old or weighing at least 13.5 kg, in particular demonstrating that there is a linear correlation of weight with hepatotoxicity. These observations emphasize the importance of careful pretreatment counselling and post-treatment monitoring, and of a careful and personalized risk-benefit analysis as some in this group may show significant motor improvement with treatment.

Contributors

Study conception: Vasantha Gowda, Elizabeth Wraige, Anirban Majumdar, Archana Murugan, Min Ong, Mark Atherton, Gary McCullagh, Imelda Hughes, Francesco Muntoni.

Data acquisition, analysis/interpretation: all authors.

Statistical analysis: Michael Eyre, Vasantha Gowda.

Data interpretation: all authors.

Writing the original manuscript: Vasantha Gowda.

Revising the work for important intellectual content: all authors.

All authors contributed to the article and approved the submitted version.

Data sharing statement

Data that underline the results reported in this article and the respective individual participant data will not be shared. Aggregate data and study protocol will be available on request after the publication of the study.

Declaration of interests

Vasantha Gowda has participated in scientific advisory boards, scientific symposia and teaching initiatives for Biogen, Roche, Novartis, Wave Life Sciences, PTC therapeutics and Pfizer, received honoraria from Neurology Academy, Roche, Novartis and has been involved as principal investigator with PTC therapeutics, Wave Life Sciences and Catabasis. Mark Atherton has received conference sponsorship from Novartis. Jennie Sheehan has participated in advisory boards for Roche, received conference sponsorships from Roche and Biogen and honoraria from Novartis. Mariacristina Scoto has been involved as principal investigator in clinical trials from Roche, Biogen and Novartis and has participated in Scientific Advisory boards and teaching initiatives for Roche, Novartis and Biogen. Giovanni Baranello has been involved as principal investigator of clinical trials sponsored by Roche, Novartis, Sarepta, Pfizer, NS Pharma, Reveragen, Scholar Rock, and has received speaker and/or consulting fees from Sarepta, PTC Therapeutics, Pfizer, Biogen, Novartis Gene Therapies, Inc. (AveXis), and Roche, and grants from Sarepta, Roche and Novartis Gene Therapies. Archana Murugan has received conference sponsorship from Roche. Anil Dhawan has participated in advisory boards for Novartis, BitBio, Aspect Bio, Astellas. Michael Eyre is supported by Action Medical Research and the British Paediatric Neurology Association. Laurent Servais reports participation in advisory boards and scientific symposia from Biogen, Roche, Novartis, Scholar Rock and BioHaven and grants from the aforementioned and Zentech, Perkin Almers. Francesco Muntoni reports participation in advisory boards and scientific symposia from Biogen, Roche and Novartis and funding from Biogen and Roche for the SMA REACH National database. Min Ong has participated in advisory boards for Biogen, Novartis, Roche & CSL Behring and has received conference sponsorship from Roche and speaker fees from Biogen, and honorarium from Neurology Academy. Imelda Hughes has received honoraria from Santhera, Roche, PTC Therapeutics, Sarepta, Biogen and Novartis, conference sponsorships from PTC Therapeutics, Novartis and Biogen. Heinz Jungbluth has participated in advisory board activities for Pfizer, Astellas, Audentes and Armgo. Elizabeth Wraige has undertaken consultancy work for Novartis. Maria Vanegas has received conference sponsorship from Novartis and meeting sponsorship from SMA Europe. Sandya Tirupathi has received conference sponsorships from Novartis and PTC. Marjorie Illingworth has received conference sponsorships from Roche and Biogen. Adnan Manzur received honorarium and meeting sponsorship from Pi Healthcare. Sarah D'Urso has received conference sponsorship from Biogen. Tracey Willis has received honorarium and conference sponsorship from Novartis. Sinead Warner has received conference sponsorship from Novartis and consultancy fees from Roche. No other disclosures were reported.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2023.100817.

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