

# Stability of serial platelet and urine protein measurements in patients receiving nusinersen for spinal muscular atrophy

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## Abstract

**Introduction/Aims:** Patients undergoing nusinersen treatment for spinal muscular atrophy are subject to measurements of platelet count and urine protein before each injection due to concern for platelet depletion and renal dysfunction according to the prescribing information. These tests may be uncomfortable or inconvenient and may cause delays in treatment. However, it is still unclear whether these values have been significantly affected by nusinersen treatment. Our aim in this study was to determine whether these measurements ever reached critical values that necessitated withholding treatment at our center.

**Methods:** Records from 57 patients treated with nusinersen at our institution between 2017 and 2020 were retrospectively analyzed. Laboratory values for platelet count, random urine protein, and total urine protein:creatinine ratio were collected from all patients before each procedure.

**Results:** Mean patient age was 28.9 years (range, 2-76 years). Mean platelet count was  $307 \times 10^9/L$  (range,  $96-755 \times 10^9/L$ ; normal lab limits,  $150-450 \times 10^9/L$ ), mean random urine protein was 0.164 g/L (range, <0.05-0.73 g/L), and mean total urine protein:creatinine ratio was 0.885 g per gram creatinine (range, 0.12-9.71 g per gram creatinine). No laboratory values precluded continuing treatment for any patient.

**Discussion:** Although further study on a larger cohort is warranted for more definitive conclusions, it may not be necessary to measure platelet count and urine protein before each nusinersen treatment, particularly in the maintenance phase.

## KEYWORDS

creatinine, nusinersen, platelet, spinal muscular atrophy, urine protein

## 1 | INTRODUCTION

Nusinersen is an antisense oligonucleotide (ASO) drug that has been shown to improve both ventilator-free survival and motor function in various subtypes of spinal muscular atrophy (SMA).<sup>1-4</sup>

Platelet testing is indicated due to concern for thrombocytopenia, an established adverse effect of ASOs.<sup>5</sup> Thrombocytopenia has been

observed in clinical trials for ASOs other than nusinersen, and one clinical trial was stopped due to intracranial hemorrhage in two pediatric patients with existing brain tumors.<sup>6</sup> In a clinical trial of 82 patients receiving nusinersen for later onset SMA, 3 patients developed severe thrombocytopenia. Urine protein is measured to monitor for renal toxicity, another adverse effect that has been seen with sustained ASO therapy.<sup>7</sup> In clinical trials of nusinersen for infantile-onset and later onset

SMA, 58% of patients receiving nusinersen showed elevated urine protein compared with 34% of sham-controlled patients.

Based on these data, patients should always be tested for platelet count and urine protein concentration before each nusinersen injection in accordance with the prescribing information.<sup>8</sup> However, it is unclear how often these values have been affected in a way that has changed management. These lab measurements are often inconvenient, leading to increased appointment time, laboratory costs, and potential delays in treatment and procedure start times for patients. Collection of blood and urine samples increases discomfort of treatment in a vulnerable patient population. The objective of this study was to determine whether platelet and urine protein measurements at our center ever reached critical values necessitating changes to treatment, and whether these values demonstrated any meaningful trends for which monitoring could be beneficial.

## 2 | METHODS

Electronic health records from 57 patients treated with nusinersen at our institution between 2017 and 2020 were analyzed retrospectively. All laboratory values for platelet count, random urine protein (UPt), and total urine protein-to-creatinine ratio (UPt:Cr) were collected for all patients. Linear mixed-effect regression models were used to assess the effect of the number of days from first measurement on the laboratory values in adult and pediatric groups, while including a random intercept for patients to account for the within-patient correlation.  $P < 0.05$  was considered statistically significant. Individual cases of extremes or otherwise unusual values were investigated in the health records. This retrospective study was determined not to involve human research according to institutional review board guidelines of the University of Minnesota, and thus consent was not required.

## 3 | RESULTS

The mean age for all those included in the study was 30.5 years (range, 2-76 years). Twenty-nine patients were male and 28 were female. Mean platelet count was  $307 \times 10^9/L$  (range,  $96-755 \times 10^9/L$ ; normal laboratory range,  $150-450 \times 10^9/L$ ), mean UPt was 0.164 g/L (normal range,  $<0.05-0.73$  g/L), and mean UPt:Cr was

0.885 g per gram creatinine (normal range, undetectable to 9.71 g per gram creatinine). Means for specific age ranges were also calculated (Table 1). There was a significant effect of the number of days from first measurement on platelet count in adults, calculated as a  $2.1 \times 10^9/L$  increase in platelets per 100 days ( $P = .031$ ). There was no significant effect of the number of days from first measurement on adult UPt, pediatric serum platelet count, or pediatric UPt. All data points for these populations were plotted (Figure 1).

In two instances, platelet values were recorded at under  $100 \times 10^9/L$ , in two separate patients. One of these patients was an adult female in the sixth decade after four doses of nusinersen, who was hospitalized with urosepsis at the time of thrombocytopenia. The other patient was a 1-year-old child who had received onasemnogene aeparovvec gene therapy for SMA 8 days earlier. This patient's platelet count was within normal range (greater than  $150 \times 10^9/L$ ) on follow-up testing 4 days later. The highest recorded values for urine studies did not preclude continued treatment in the affected patients, and urine study results did not cause any patients to discontinue treatment.

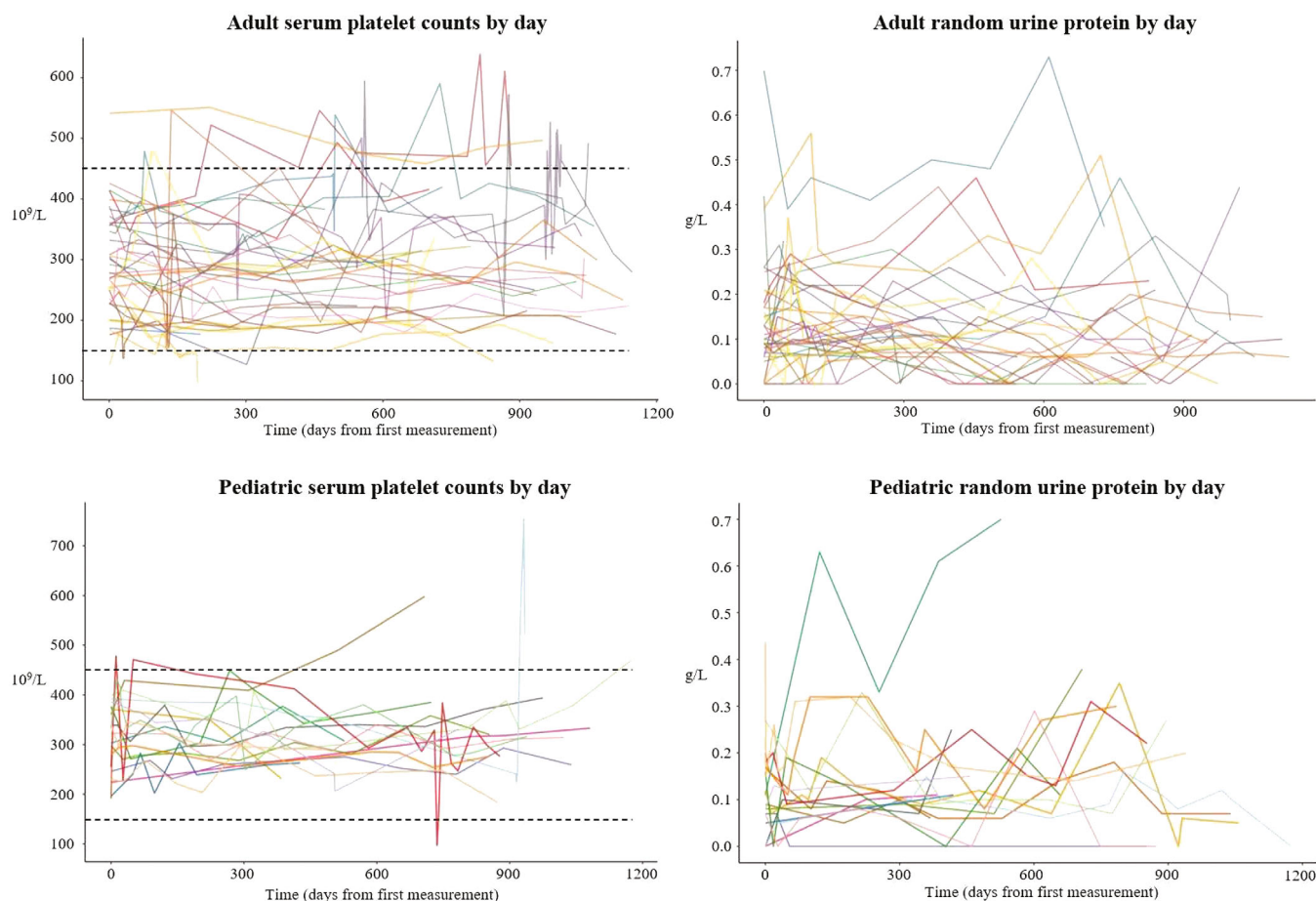
Baseline proteinuria, defined as UPt:Cr greater than 0.2 g/g creatinine on first recorded value, was found in 74% of adult patients (28 of 38) and 63% of pediatric patients (12 of 19). In the last recorded value for each patient, after receiving treatment, proteinuria was present in 76% of adult patients (29 of 38) and 74% of pediatric patients (14 of 19). Neither patient group had a statistically significant difference in presence of proteinuria when comparing the pre- and posttreatment values ( $P = .79$  in the adult group and  $P = .25$  in the pediatric group).

## 4 | DISCUSSION

In our patient population, treatment with nusinersen did not lead to changes in management for any patients due to measurement of platelet counts or renal function, and it did not lead to any complications such as missed or delayed doses of nusinersen, unexplained bleeding events, or renal intervention. It is unclear why a small positive effect was seen on platelet count in adults. Regardless, this work is consistent with recent studies showing mean platelet count does not decrease with therapy, and that instances of relative thrombocytopenia in patients receiving nusinersen have been transient.<sup>9,10</sup>

**TABLE 1** Summary data for serum platelets and urine protein values for each age group

Age range, years	n	Mean serum platelets, $\times 10^9/L$ (range)	Mean urine random protein, g/L (range)	Mean total urine protein: creatinine ratio (range)
0-9	6	318 (97-478)	0.13 (undetectable to 0.44)	0.87 (0.23-2.00)
10-19	16	319 (183-755)	0.15 (undetectable to 0.70)	0.88 (0.12-9.71)
20-29	6	244 (137-415)	0.09 (undetectable to 0.30)	0.89 (0.26-1.78)
30-39	16	345 (127-639)	0.16 (undetectable to 0.73)	1.00 (0.21-5.86)
40-49	5	306 (162-591)	0.11 (undetectable to 0.46)	1.00 (0.32-2.65)
50-59	5	226 (96-489)	0.17 (undetectable to 0.56)	0.68 (0.13-2.00)
60-76	3	270 (150-546)	0.08 (undetectable to 0.21)	0.26 (0.13-0.39)



**FIGURE 1** Lab values in patients receiving nusinersen for spinal muscular atrophy. All values are shown from the first recorded lab values for patients receiving nusinersen treatment to the most recent values recorded for all patients. The pediatric group consists of patients less than 18 years old, and the adult group consists of patients of 18 years and older. Each series represents a specific patient, with a line connecting the data points for a given patient. All series begin at day 0, with subsequent data points plotted with the number of days from this first measurement on the x axis. For platelet counts, the normal lab minimum and maximum are shown with horizontal dashed lines. The pediatric patient whose protein appeared to be trending upward at the end of the measurement period later stabilized at approximately 0.4 to 0.5 g/L

In adult and pediatric patients, the degree of proteinuria did not increase with nusinersen treatment, supporting previous work that suggests nusinersen for SMA does not cause structural or glomerular damage that was seen in treatment of other diseases with other ASOs.<sup>5</sup> Because adverse effects are variable based on specific backbone chemistry of the drug, broad statements of renal toxicity cannot be made purely based on the ASO drug class, or even for a generation of ASOs. In addition, most of these patients had significant proteinuria before starting treatment, with rates of qualitative proteinuria that did not change significantly with treatment. In an integrated study of clinical trials, Darras et al reported positive urine dipstick (a semiquantitative measurement roughly indicating at least 0.3 g/L proteinuria) in 19% of sham-treated infants and 15% of sham-treated patients with later onset SMA, with respective rates of 11% and 17% of patients with positive urine dipstick in treatment groups.<sup>11</sup> Comparing the prevalence of proteinuria in sham-treated infants (34%)<sup>6</sup> with our pediatric (63%) and adult (74%) patients before treatment, there is a suggestion that proteinuria develops with age due to the nature of SMA itself rather than

due to nusinersen treatment. Furthermore, there is considerable fluctuation in the degree of proteinuria over time for a given patient, which may relate to hydration status.

Even if monitoring of platelet and urine protein values is not forgone entirely, measurements before every dose may not be necessary. Although it has not been specifically quantified in this patient group, serum and urine testing causes discomfort, increased numbers of health-care visits, and delayed times to procedure. The lowest platelet values in clinical trials for nusinersen occurred at day 28 of the study.<sup>8</sup> This finding suggests monitoring in the early stages of treatment, during the first 2 months of loading doses, may be more important than continued monitoring in the maintenance phase of treatment in patients with stable laboratory studies. In addition, if a life-threatening thrombocytopenia or glomerulonephritis were to result from an adverse reaction to nusinersen in the maintenance phase, it would be better to detect it well before the next scheduled dose 4 months later. Our findings challenge the usefulness of these studies for rare, patient-specific adverse effects.

As a retrospective chart review, this study was limited to the data points for laboratory values in the electronic health record. Similarly, the study did not include a control group of patients with SMA who did not receive nusinersen treatment. This study is also limited to a single tertiary care institution and may not be generalizable to all patients receiving nusinersen for SMA. Some factors, such as cost of laboratory testing, time delay in treatment due to laboratory testing, and patient discomfort, were not measured. If measured in the future, these factors would help to quantify the benefits of decreased laboratory testing for this patient population.

## 5 | CONCLUSIONS

Treatment with nusinersen did not appear to negatively affect platelet counts or kidney function as measured by urine protein studies in this group of patients receiving treatment for SMA. Although further studies on a larger cohort are needed to inform more definitive recommendations on reducing the frequency of these measurements, it may not be necessary to measure platelet count and urine protein before every nusinersen treatment, particularly in the maintenance phase. Reduced monitoring of these laboratory values would improve time efficiency and patient comfort while decreasing costs.

## DISCLOSURE STATEMENT

D.R.N. consulted for Biogen, the maker of nusinersen. The remaining authors have no conflicts of interest to disclose.

## ETHICAL PUBLICATION STATEMENT

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

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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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