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Nephrotoxicity of Antisense Oligonucleotide Therapies in Duchenne Muscular Dystrophy: a warning or a challenge?

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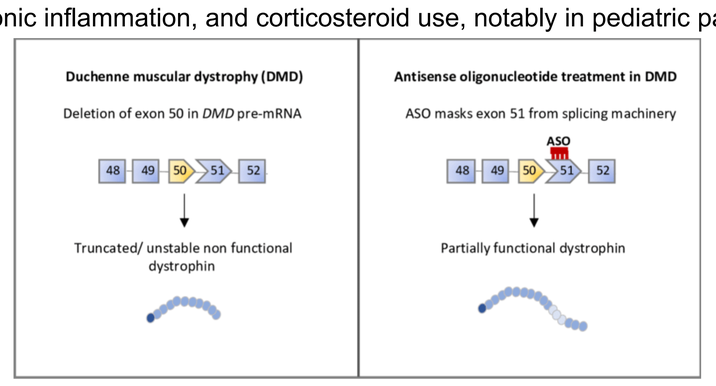
INTRODUCTION & OBJECTIVES OF THE STUDY

Duchenne Muscular Dystrophy (DMD) & treatments

- **DMD** is a severe X-linked **neuromuscular disorder** caused by dystrophin **gene mutations**.[1]
- **Antisense oligonucleotide (ASO) therapies** have emerged as mutation-specific treatments for DMD by promoting exon skipping to restore dystrophin expression.[2]
- However, concerns about **renal toxicity** — including proteinuria and electrolyte dysregulation — have been reported in preclinical and clinical studies.[3]
- DMD patients are particularly vulnerable due to long-term treatment exposure and underlying muscle degeneration, chronic inflammation, and corticosteroid use, notably in pediatric patients.[2]



Objectives

To review clinical trials involving ASO therapies used in DMD and to assess the frequency of nephrotoxic events (including proteinuria) reported across studies.

METHODS

Data sources and timeframe:

Systematic search of ClinicalTrials.gov and EU Clinical Trials Register up to March 2025.

Inclusion criteria:

Phase I–IV clinical trials assessing the safety or efficacy of approved or investigational ASOs in DMD :

Drug	Chemical Class	Mechanism
Eteplirsen	Phosphorodiamidate morpholino oligomer (PMO)	Morpholino neutral backbone, exon 51 skipping
Golodirsen	Phosphorodiamidate morpholino oligomer (PMO)	Exon 53 skipping, similar to eteplirsen
Viltolarsen	Phosphorodiamidate morpholino oligomer (PMO)	Exon 53 skipping, similar to eteplirsen
Casimersen	Phosphorodiamidate morpholino oligomer (PMO)	Exon 45 skipping, similar to eteplirsen
Drisapersen	2′-O-methyl phosphorothioate ASO	Exon 51 skipping, negatively charged backbone
Vesleteplirsen	Peptide-conjugated PMO	Exon 51 skipping, cell-penetrating peptide

Endpoints analyzed:

Frequency of renal adverse events (nephrotoxicity and proteinuria).
Comparison between treatment and placebo/control groups.

Data extraction:

Summary of renal events, trial phase and status, age range of participants and study duration per participant.

RESULTS

Renal safety data within the clinical trials involving ASO therapies in DMD

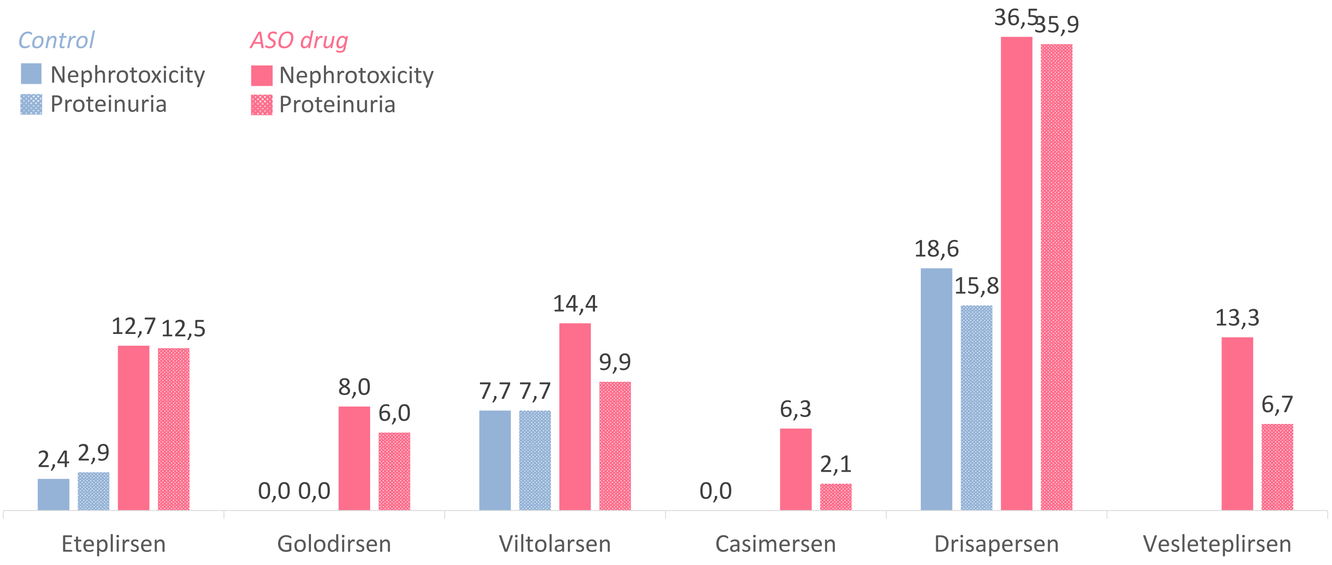
- **Total trials analyzed across 6 ASO molecules**:
  - 48 trials overall
  - **30 trials** with **available renal safety data**
- **Trial status**: 24 completed and 6 discontinued (mainly for safety or efficacy reasons).
- **Participants**: Predominantly male pediatric and adolescent patients.
- **Study duration**: Ranged from 12 to 212 weeks; most trials included long-term follow-up.
  - Mean → 57 weeks
  - Median → 48 weeks
- **Study designs**: the majority were randomized placebo-controlled phases, a few included untreated-control arms.

Table 1 : Main characteristics of the 30 clinical trials analyzed

Drug	# Clinical Trials (Phase)	Study Status	Population (Age range)	Study Duration (weeks, range)	Key Study Designs / Notes
Eteplirsen	**9 trials** → 2 phase I-II → 6 phase II → 1 phase III	8 Completed 1 Discontinued	0,5–21 y.o.	4–212	IV administration
Golodirsen	**3 trials** → 1 phase I-II → 1 phase II → 1 phase III	2 Completed 1 Discontinued	6–23 y.o.	48–168	IV administration
Viltolarsen	**6 trials** → 1 phase I → 1 phase I-II → 3 phase II → 1 phase III	6 Completed	4–16 y.o.	12–192	IV administration
Casimersen	**3 trials** → 1 phase I → 1 phase II → 1 phase III	2 Completed 1 Discontinued	0,5–23 y.o.	48–144	IV administration
Drisapersen	**8 trials** → 1 phase I → 1 phase I-II → 3 phase II → 3 phase III	5 Completed 3 Discontinued	5–80 y.o.	17–188	Subcutaneous administration; phase III failed primary endpoint; Discontinued due to dose-limiting toxicity and safety concerns (skin, renal, hematologic)
Vesleteplirsen	**1 trial** → 1 phase I-II	1 Completed	≥4 y.o.	135	IV administration

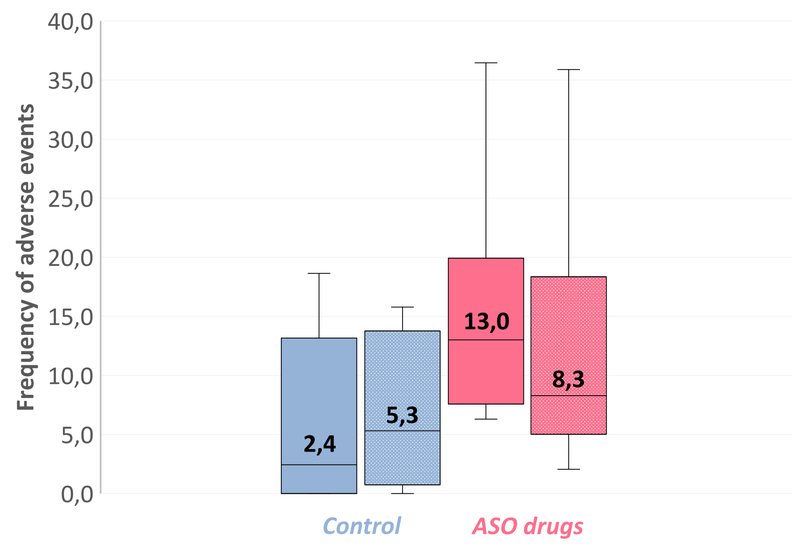
Incidence of renal adverse events in clinical trials involving ASO therapies in DMD

Figure 1 : Incidence of renal adverse events for each ASO drug compared to control



- The frequency of renal adverse events is heterogeneous across ASO drugs but seems higher than control.
- Proteinuria account for most of renal toxicity events

Figure 2 : Overall incidence of renal adverse events in ASO drugs compared to control



- Nephrotoxicity (mainly proteinuria) is more frequent in ASO-treated arms than control arms.

DISCUSSION

- The **incidence of renal toxicity** appears **higher in ASO-treated patients than in placebo groups**, particularly for earlier ASO (Drisapersen).
- **Proteinuria** → often **mild and transient** but can signal underlying renal dysfunction.
- Potential **driver mechanisms** include proximal tubular accumulation, endocytic uptake and lysosomal overload, leading to **inflammation**.
- **Inflammatory triggers** (e.g., post-vaccination, infection, steroid use) may **transiently modulate ASO pharmacokinetics** and **exacerbate renal stress**.
- These results highlight the need for dynamic pharmacovigilance and **renal biomarker monitoring** during ASO therapy.

CONCLUSION

- ✓ ASO therapies are a key precision medicine approach in DMD but require rigorous renal safety monitoring.
  - Most renal events are **mild and reversible**, yet their **frequency** requires systematic screening.
  - Recommended monitoring: proteinuria, serum creatinine, cystatin C, electrolytes, and urinary biomarkers.
- ✓ The challenge is to **balance** molecular efficacy with renal safety through **optimized dosing, schedule of administration** and **patient-specific risk** assessment.
- ✓ Future trials should aim to identify **predictive biomarkers of renal risk** and **standardize renal safety protocols** across DMD trials.

[1] *Duan D, et al. Duchenne muscular dystrophy. Nat Rev Dis Primers. 2021 Feb 18;7(1):13. doi: 10.1038/s41572-021-00248-3.*
[2] *Sabrina Haque U, et al. Comprehensive review of adverse reactions and toxicology in ASO-based therapies for Duchenne Muscular Dystrophy: From FDA-approved drugs to peptide-conjugated ASO. Curr Res Toxicol. 2024 Jun 18;7:100182. doi: 10.1016/j.crtox.2024.100182.*
[3] *Wu H, et al. Nephrotoxicity of marketed antisense oligonucleotide drugs. Curr Opin Toxicol. 2022 Dec;32:100373. doi: 10.1016/j.cotox.2022.100373.*