POTENTIAL NEPHROCALCINOSIS RISK LINKED TO NUSINERSEN: INSIGHTS FROM FAERS-BASED SIGNAL DETECTION AND MOLECULAR DOCKING

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INTRODUCTION

Nusinersen is a trailblazing therapy for spinal muscular atrophy, which is an autosomal-recessive disorder characterized by degeneration of motor neurons in the spinal cord. The well-known neurologic adverse effects of nusinersen include arachnoiditis, aseptic meningitis, headache, hydrocephalus, meningitis, and reaction to post-lumbar puncture. Despite its therapeutic benefits, there are concerns regarding its safety profile, particularly in relation to rare adverse effects. This study leverages the FDA Adverse Event Reporting System (FAERS) to identify potential novel signals associated with nusinersen, focusing on nephrocalcinosis.

OBJECTIVE

- To detect and analyze adverse drug reactions (ADRs) related to nusinersen using the FAERS database.
- To perform a disproportionality analysis to identify significant signals of adverse effects.
- To explore the molecular interactions of nusinersen with proteins associated with identified adverse effects.

METHOD

Data Source:
The FAERS database was utilized to extract reports related to nusinersen from its FDA approval on December 23rd, 2016, to the present.

Analysis Techniques: Disproportionality analysis was conducted using the Open Vigil database.

- Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR) were calculated to assess the strength of the association between nusinersen and adverse effects.
- A positive signal was defined by PRR ≥ 2, ROR - 1.96SE > 2, chi-square > 4, and adverse events > 2

Bioinformatics Analysis:

- Bioinformatics databases like Gene Cards and the OMIM Gene Map were utilised to retrieve the genes. PubChem was utilised to identify the targets of nusinersen. InteractiVenn was used to identify the common gene targets of nusinersen and nephrocalcinosis. STITCH, STRING, Cytoscape, and Cytohubba were used to identify proteins and genes associated with nephrocalcinosis. Molecular docking was performed using Schrödinger software to explore the binding affinity of associated genes and proteins.

RESULTS

Data collected from FAERS

- A total of 6,685 reports related to nusinersen were identified in the FAERS database. Of these, 218 cases of nephrocalcinosis were reported and directly linked to nusinersen.

Disproportionality Analysis

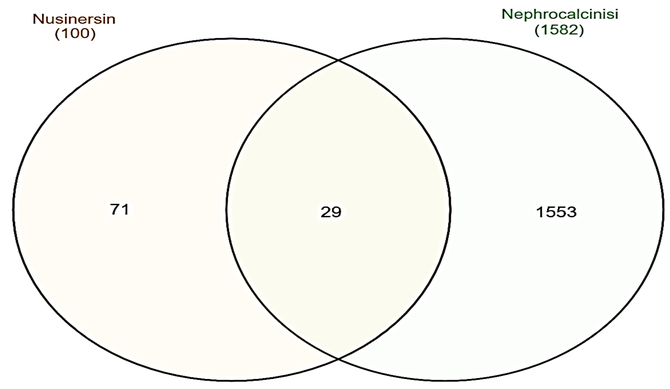
- The calculated PRR was 14.932 (95% CI: 5.588-39.9), and the ROR was 14.941 (95% CI: 5.588-39.954), indicating a strong association.
- The chi-squared value was 37.58, indicating a statistically significant difference between the observed and expected cases.

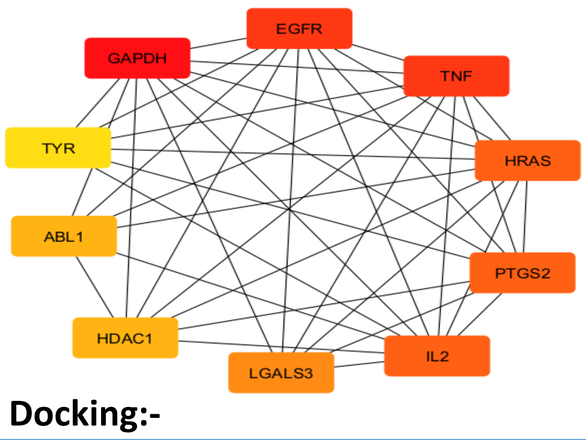
Gene and Pathway Analysis

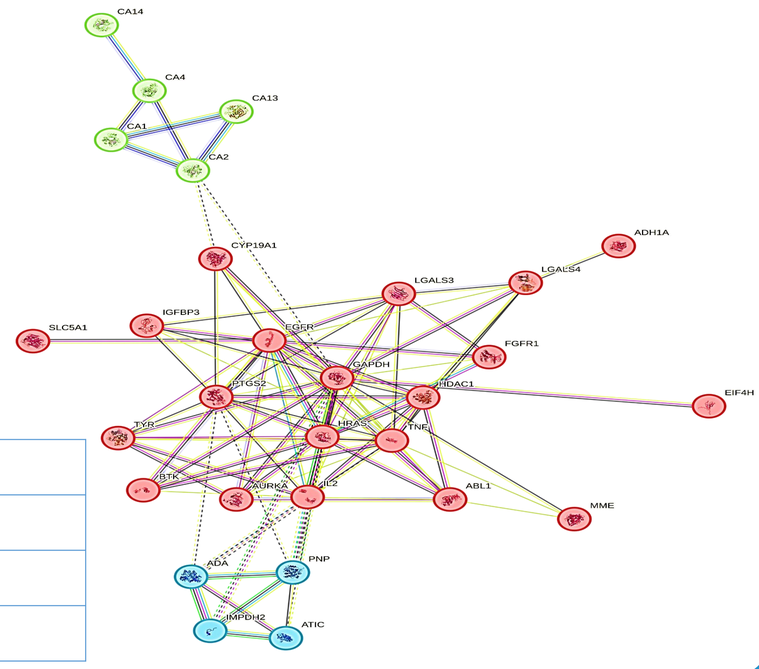
- Common gene targets identified include GAPDH, EGFR, and TNF, which are associated with nephrocalcinosis.

Case Count by Received Year

Category	Number of Cases
2025	184
2024	662
2023	716
2022	803
2021	933
2020	746
2019	962
Totals	**6,685**







Molecular Docking:-

Gene/Protein	Binding Affinity
GAPDH	-6.055
EGFR	-3.882
TNF	-7.602

CONCLUSIONS

- This pharmacovigilance study identified nephrocalcinosis as a potential adverse signal associated with nusinersen.
- The findings underscore the necessity for healthcare professionals to monitor patients closely for this potential risk.
- Further pharmacogenetic and epidemiological investigations are required to validate this signal and explore underlying mechanisms and risk factors.

REFERENCES

- FDA. SPINRAZA (nusinersen) injection, for intrathecal use - FDA Prescribing Information. U.S. Food and Drug Administration. December 23,
- U.S. Food and Drug Administration. FDA's Adverse Event Reporting System (FAERS). Updated August 10, 2024.
- Bioinformatics tools (InteractiVenn, STRING, Cytoscape, CytoHubba)

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