INPLASY

INPLASY2024100059

doi: 10.37766/inplasy2024.10.0059

Received: 14 October 2024

Published: 14 October 2024

Corresponding author:
Oguz Kagan Sahin

oguzkagansahin26@gmail.com

Author Affiliation:
Edremit State Hospital.

RNAi-Based Therapies for Hereditary Transthyretin Amyloidosis: A Meta-Analysis of Randomized Clinical Trials

Sahin, OK; Lajczak, P; Koppanatham, A; Campos, LR; Teixeira Carneiro, PH; Silva, Y; Cruccioli, M.

ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2024100059

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 October 2024 and was last updated on 14 October 2024.

INTRODUCTION

Review question / Objective P-patients with hereditary transthyretin-mediated amyloidosis [Hereditary Transthyretin Amyloidosis with Polyneuropathy (hATTR-PN) ; I-RNA-i drugs; C- any other care; O- mNIS+7 Score, Norfolk QOL-DN Score, Score on the Rasch-built Overall Disability Scale,Modified BMI,serum Transtransthyretin level reduction from baseline, serious TEA-Es; T- any follow-up time; T-Randomized Clinical Trials.

Rationale The rationale for this study stems from the growing recognition of RNA interference (RNAi) as a novel therapeutic strategy for hereditary transthyretin amyloidosis (hATTR), a severe genetic disorder that leads to progressive organ damage due to the accumulation of misfolded transthyretin (TTR) proteins. Despite the promising results of RNAi therapies in selectively silencing the mutant TTR gene, there remains variability in patient response, especially concerning different TTR mutations and the long-term safety of these treatments. Given the scarcity of conclusive evidence across trials, this meta-analysis aims to systematically assess the safety and efficacy of RNAi-based therapies in hATTR, providing a comprehensive overview of clinical outcomes and highlighting the need for further research to optimize treatment strategies.

Condition being studied Hereditary transthyretin amyloidosis (hATTR) is a rare, progressive, and life-threatening genetic disorder caused by mutations in the TTR gene, which lead to the misfolding and deposition of transthyretin proteins as amyloid fibrils in tissues and organs. These deposits primarily affect the peripheral nerves, heart, and gastrointestinal system, resulting in a wide range of symptoms, including neuropathy, cardiomyopathy, and autonomic dysfunction. hATTR is inherited in an autosomal dominant pattern, and its clinical manifestations vary widely depending on the specific mutation, making it a challenging condition to treat. Without effective intervention,

hATTR can lead to significant morbidity and early mortality, underscoring the need for advanced therapeutic approaches such as RNA interference (RNAi) to target the underlying genetic cause of the disease.

METHODS

Search strategy PubMed, EMBASE, and Cochrane Central databases will be searched. Due to study not being finished yet, the full search strategy will be provided in our published article. The search strategy incorporates the following terms with the use appropriate boolean operators: "hereditary transthyretin-mediated amyloidosis", "hereditary amyloidosis", "hattr", "amyloidosis", "si-rna", "rna-i", "rna interference", "small interfering rna", "small interfering ribonucleic acid", "patisiran", "vutrisiran", "inotersen", "eplontersen".

Participant or population The participants addressed in this review will be patients diagnosed with hereditary transthyretin amyloidosis (hATTR), a genetic disorder caused by mutations in the transthyretin (TTR) gene. These participants will include individuals who have undergone treatment with RNA interference (RNAi) therapies, such as patisiran, vutrisiran, inotersen, or eplontersen. The review will focus on randomized clinical trials that involve adult patients of any gender or ethnicity who have confirmed hATTR, regardless of the specific TTR mutation or the disease stage (neurological or cardiomyopathic). The aim is to evaluate the safety and efficacy of RNAi-based treatments in this diverse group of patients, with no exclusions based on comorbidities or previous treatments, ensuring a broad understanding of treatment outcomes across various patient populations.

Intervention The interventions evaluated in this review will be RNA interference (RNAi)-based therapies specifically designed to target and reduce the production of mutant transthyretin (TTR) protein in patients with hereditary transthyretin amyloidosis (hATTR). These therapies include:

Patisiran: A small interfering RNA (siRNA) drug that targets the liver production of mutant and wild-type TTR protein.
Vutrisiran: Another siRNA drug with similar mechanisms to patisiran but with an extended dosing schedule and different chemical modifications.
Inotersen: An antisense oligonucleotide (ASO) that binds to the TTR mRNA to reduce the production of TTR protein in the liver.
Eplontersen: A newer ASO designed to reduce both mutant and wild-type TTR production, similar to inotersen but with improved chemical stability and administration. by pooling the results, the review will evaluate their efficacy in slowing disease progression, improving neurological and/or cardiomyopathic symptoms, and their safety profiles based on adverse events, treatment discontinuations, and other side effects.

Comparator No comparator interventions planned in the analysis, since it will be a single arm meta analysis by pooling of the results.

Study designs to be included Randomized controlled trials, randomized uncontrolled trials.

Eligibility criteria
inclusion criteria:
1. randomized studies
2.patients with hATTR
3.The study Includes an arm in which RNA-i in monotherapy is administered

exclusion criteria:
1.Cohort studies, case series, case reports
2.Studies involving participants with secondary amyloidosis or non-hereditary forms of amyloidosis will not be included.
3.Animal or In Vitro Studies
4.Studies that do not provide sufficient data on primary efficacy and safety outcomes will be excluded from the analysis.

Information sources PubMed, EMBASE, Cochrane, ClinicalTrials.gov.

Main outcome(s) mNIS+7 Score, Norfolk QOL-DN Score, Score on the Rasch-built Overall Disability Scale,Modified BMI,serum Transtransthyretin level reduction from baseline, serious TEA-Es.

Data management Rayyan will be used for screening. R will be used for statistics.

Quality assessment / Risk of bias analysis ROBINS-I will be used for risk of bias assessment.

Strategy of data synthesis Data from randomized clinical trials will be extracted and analyzed using a random-effects model to assess the efficacy and safety of RNAi therapies in hereditary transthyretin amyloidosis (hATTR). Baseline characteristics of the studies and primary outcomes, such as neurological function and quality of life, adverse events will be evaluated. Heterogeneity will be assessed using the I^2 statistic, with subgroup and sensitivity analyses performed where necessary.

Risk of bias will be evaluated using the ROBINS-I tool. Results will be synthesized both quantitatively and narratively.

Subgroup analysis Subgroup analyses will be done based on the individual RNA-i drug that was used in that study arm.

Sensitivity analysis Leave one out analysis will be utilized.

Country(ies) involved Turkey, Brazil, Poland, India.

Keywords RNAi therapy; hereditary transthyretin amyloidosis (hATTR); safety; efficacy; systematic review; meta-analysis.

Contributions of each author

Author 1 - Luana Miyahira Makita.
Email: makitaluana@gmail.com
Author 2 - Paweł Łajczak.
Email: pawel.lajczak03@gmail.com
Author 3 - Aishwarya Koppanatham.
Email: aishwaryakoppanatham@gmail.com
Author 4 - Letícia Rocha Campos.
Email: ichbinleticiarochacampos@gmail.com
Author 5 - Pedro Henrique Teixeira Carneiro.
Email: pedroht2003@gmail.com
Author 6 - Yasmin Silva.
Email: picancoy@gmail.com
Author 7 - Murilo Cruccioli.
Email: murilocruccioli@gmail.com