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Nexiguran Ziclumeran for ATTR Cardiomyopathy

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1. Abstract

Background: Transthyretin amyloid cardiomyopathy (ATTR-CM) is an under recognized cause of restrictive cardiomyopathy, resulting from the misfolding and extracellular deposition of transthyretin (TTR) protein in myocardial tissue. Both hereditary (hATTR) and wild-type (wtATTR) forms contribute to progressive heart failure and substantial morbidity, particularly in older adults.

Objective: This narrative review aims to critically evaluate Nexiguran Ziclumeran (NTLA-2001), a novel CRISPR-Cas9-based in vivo gene-editing therapy that targets the hepatic TTR gene. The focus is to elucidate its therapeutic mechanism, summarize key findings from early-phase trials, and discuss its potential role in transforming ATTR-CM management.

Methods: A targeted literature review was conducted across clinical trial registries, peer-reviewed journals, and expert consensus documents. The selection prioritized studies reporting on gene-editing strategies, NTLA-2001 pharmacodynamics, and clinical endpoints relevant to ATTR-CM.

Results: Phase 1 trials have demonstrated that a single intravenous dose of NTLA-2001 leads to sustained reductions in serum TTR levels up to 90% by 12 months with stabilization of cardiac biomarkers and improvements in functional capacity. The therapy was well-tolerated, with predominantly mild and transient adverse events.

Conclusion: Nexiguran Ziclumeran represents a paradigm shift toward potentially curative, single-dose therapies for ATTR-CM. While early data are promising, large-scale phase 3 trials are essential to confirm its long-term safety, efficacy, and integration into future clinical guidelines.

2. Introduction

2.1. ATTR cardiomyopathy: A concise summary

Transthyretin amyloid cardiomyopathy (ATTR-CM) is being recognized increasingly as a significant cause of heart failure, particularly among older adults, although it remains frequently overlooked [1]. It is categorized as part of systemic amyloidoses, a collection of disorders characterized by the buildup of insoluble amyloid fibrils in extracellular spaces, formed from misfolded precursor proteins [1]. While over 30 proteins capable of forming amyloid have been identified, cardiac issues predominantly arise from either transthyretin (TTR) or immunoglobulin light chains (AL) [1].

In ATTR-CM, transthyretin a tetrameric protein primarily synthesized in the liver, which normally transports thyroxine and retinol-binding proteins becomes pathologically unstable. It dissociates into monomers, which then misfold and aggregate into β-sheet-rich amyloid fibrils. These fibrils deposit in the cardiac muscle, gradually disrupting both the structural integrity and functionality of the heart [1].

This condition is further divided into two distinct categories

based on the TTR gene sequence: wild-type ATTR-CM (wtATTR-CM), which occurs without any genetic mutation, typically in elderly individuals, and hereditary or variant ATTR-CM (hATTR-CM), linked to pathogenic mutations in the TTR gene [2].

ATTR-CM can be deceptive in its clinical presentation, often showcasing symptoms that resemble those of more common types of heart failure [3]. Patients may exhibit symptoms such as breathlessness, fatigue, and swelling in the extremities [3]. However, because amyloid deposits have systemic effects, additional non-cardiac symptoms such as carpal tunnel syndrome and peripheral neuropathy can also emerge, making the diagnostic process more complex [3].

3. Global Impact of ATTR Cardiomyopathy and Health Implications

Once regarded as an uncommon condition, transthyretin amyloid cardiomyopathy (ATTR- CM) is now acknowledged as a significantly more prevalent cause of heart failure than previously thought [4-6]. With the advent of treatments specifically designed for the disease some already accessible and others undergoing clinical trials the approach to management is steadily changing. Nevertheless, the condition remains both misdiagnosed [7-8] and underdiagnosed [9], primarily due to a lack of awareness among healthcare professionals and the public [10-15].

Notably, over 70% of those surveyed believed that awareness of cardiac amyloidosis among clinicians is still limited. The repercussions of this lack of recognition are reflected in the high rate of misdiagnosis, estimated to be around 40-50% for cases of ATTR-CM [16-17]. Autopsy studies further illustrate the disease's often overlooked presence. In a study examining 56 random adult hearts from individuals aged over 75-years, cardiac amyloid deposits were observed in 43% of the cases, with half of those identified as ATTR [18].

The most extensive data available stems from a recent 14-year global investigation, involving 3,779 symptomatic patients and 1,830 asymptomatic carriers of harmful TTR mutations. Conducted across 84 research sites in 23 countries, this constitutes the largest dataset concerning ATTR amyloidosis [18].

Genetic ATTR disease displays a broad range in the age at which symptoms begin, extending from the second to the ninth decade of life. The p.Val50Met mutation (formerly Val30Met) is the most frequently identified TTR mutation worldwide [19]. This early-onset variant, primarily resulting in ATTR polyneuropathy or familial amyloidosis polyneuropathy, demonstrates significant regional clustering in Portugal, Sweden, and Japan [19]. Conversely, certain mutations more closely associated with ATTR-CM typically appear later in life. These include the late-onset variant of p.Val50Met, along with the p.Val142Ile mutation (previously V122I), which is more common in African-American, Western African, and Hispanic populations, with an estimated prevalence of 4% in the United States [20].

Additionally, other regional founder mutations have been recorded. For instance, the p. Ala117Ser variant is identified in China and Taiwan, while the p. Thr80Ala mutation often presenting as a mixed neuropathic and cardiomyopathic phenotype is predominantly observed in individuals of Irish descent [21-22]. These mutations are classified as regional founder mutations [23].

3.1. The clinical importance of ATTR

Transthyretin amyloid cardiomyopathy (ATTR-CM) is increasingly acknowledged as a significant but often misdiagnosed cause of heart failure among older adults [24].

The accumulation of improperly folded transthyretin (TTR) protein within the heart leads to a gradual stiffening of the myocardial tissue. This results in heart failure with preserved ejection fraction (HFpEF), in addition to arrhythmias and conduction issues. Its clinical significance arises not only from the substantial morbidity it causes but also from the diagnostic challenges it entails [24].

Results from the PRACTICA study, which was carried out across various centers in Spain, highlight this problem. The study discovered newly diagnosed ATTR-CM in 16.8% of elderly patients suffering from HFpEF and increased thickness of the left ventricular wall many of whom had previously been mischaracterized or undiagnosed [24]. This underscores how often ATTR- CM may be missed in regular cardiology practice.

Additional support comes from the 2024 World Heart Federation (WHF) consensus report, which indicated that in 70% of countries, ATTR-CM is primarily diagnosed at tertiary care facilities [25]. Showing a lack of awareness and diagnostic resources at the primary care level.

The progression of ATTR-CM varies with the clinical stage. A 2022 multicenter study conducted in Japan established a validated three-stage model reliant on biomarkers troponin T, NT-proBNP, and eGFR. Median survival was categorized as 5.0-years for stage I, 3.6 years for stage II, and merely 2.0 years for stage III clearly indicating the aggressive nature of the disease once significant cardiac involvement has occurred [26].

Importantly, early treatment can significantly improve prognosis. In the long-term extension of the ATTR-ACT trial, patients who continued receiving tafamidis therapy saw a 41% relative decrease in all-cause mortality compared to those who were initially given a placebo and subsequently crossed over [27]. These results highlight the critical need for early diagnosis; not only to confirm the disease but also to maintain the opportunity for effective treatment.

Thus, the clinical importance of ATTR-CM is attributed to its high prevalence in certain populations, its progressive and potentially life-threatening nature, and the possibility for better outcomes with prompt recognition and intervention.

4. The Role of Transthyretin (TTR) in Disease Pathology

In hereditary transthyretin amyloidosis (hATTR), variations in the amino acid sequence of TTR decrease the protein's kinetic stability, making it more susceptible to misfolding and the formation of fibrils [15]. A commonly cited example is the Val30Met mutation, which frequently appears in clinical studies. In genetic analyses, this mutation is denoted as pV50M due to the inclusion of the signal peptide in the numbering system of amino acids [28].

On the other hand, wild-type ATTR (wtATTR) occurs in the

absence of mutations. The precise mechanism through which the transthyretin tetramer becomes destabilized in this variant remains unknown, although age-related changes at the molecular level are highly suspected to contribute [28].

Of the two natural ligands that bind to TTR, thyroid hormone associates with it at a rate of less than 5%, thereby having a negligible impact on aggregation. Conversely, holo-retinol-binding protein (holo-RBP) provides a stabilizing effect. Consequently, lower levels of holo-RBP may play a role in triggering or speeding up the disease in prone individuals [29].

The rate-limiting factor in amyloid formation is the dissociation of the stable TTR tetramer into its monomeric components, a process that may be facilitated by proteolytic cleavage. These monomeric units can partially lose their structure and break down into β-sheet-rich amyloid fibrils, along with other intermediate aggregate forms [30]. Besides disturbing tissue structure, these aggregates are thought to have direct proteotoxic effects, which further exacerbate the disease process [30].

5. Presenting CRISPR-Cas9 Gene Editing and Nexiguran Ziclumeran as Treatment Approaches

Gene editing has surfaced as a promising therapeutic method for transthyretin amyloid cardiomyopathy (ATTR-CM), seeking to target the illness at its genetic foundation [31]. The CRISPR-Cas9 system employs a guide RNA to direct the Cas9 nuclease to the TTR gene within hepatocytes-creating double-strand DNA breaks that impede gene expression. This gene-editing technique has shown effectiveness in reducing circulating transthyretin (TTR), a protein linked to amyloid formation [31]. Given the noted reductions in serum TTR levels, this strategy is expected to lessen amyloid build-up in various tissues, including the heart muscle [31]. NTLA-2001 represents a therapeutic gene-editing method utilizing CRISPR-Cas9 that functions in vivo. It includes lipid nanoparticles carrying Cas9 mRNA and a single-guide RNA aimed at the TTR gene, specifically designed to disrupt its expression and lower TTR production [31].

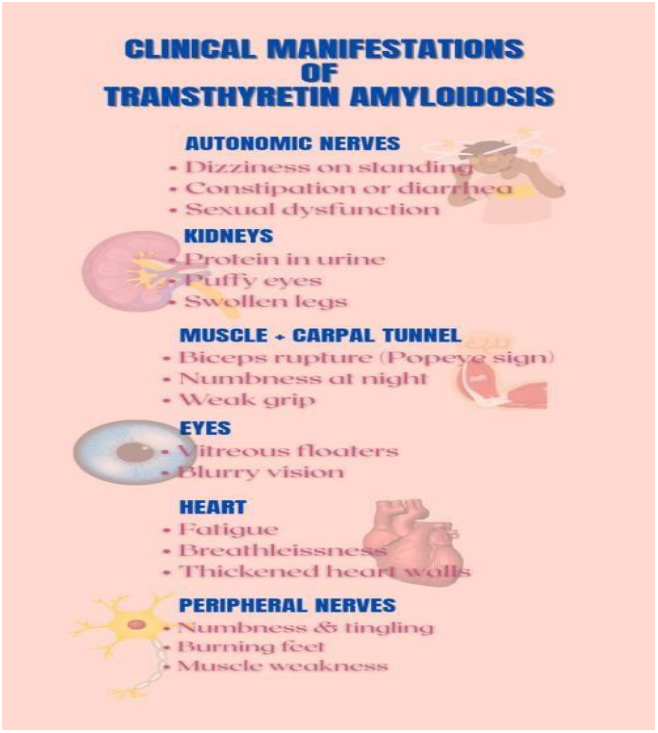
In a Phase 1 trial led by Gillmore and colleagues, a single intravenous injection of NTLA- 2001 resulted in an average decrease of 87% in serum TTR levels by day 28 in the 0.3 mg/kg group. There were no serious adverse reactions or dose-limiting toxicities reported [31].

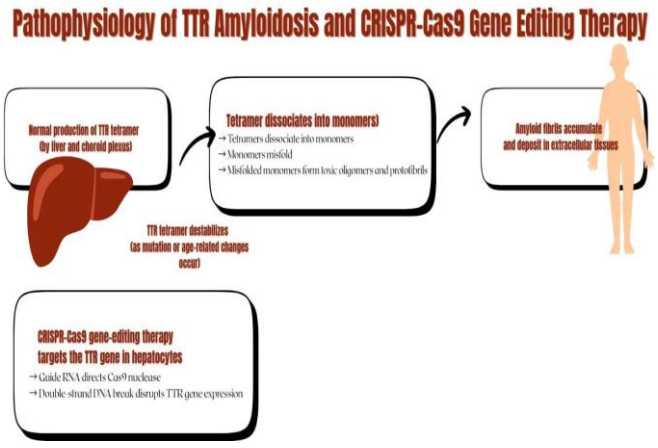
6. Objective

This narrative review is the first to thoroughly examine the use of Nexiguran and Ziclumeran in treating ATTR cardiomyopathy, as there has been no prior narrative review on this topic.

It intends to explore Nexiguran (Ziclumeran) as an innovative therapeutic approach for transthyretin amyloid cardiomyopathy (ATTR-CM), a progressive and life-threatening condition resulting from the misfolding of transthyretin and the deposition of amyloid in the heart. The main aim is to introduce Nexiguran in the context of emerging gene-silencing therapies and to emphasize its mechanism of action in reducing hepatic transthyretin production. Furthermore, this review aims to outline the current status of clinical development related to Nexiguran, focusing on its trial stages, reported results, and ongoing research efforts. Lastly, the review will investigate the expected influence of this therapy on the future treatment of ATTR-CM, especially regarding its potential to enhance or transform current treatment approaches.

7. Pathophysiology of ATTR-CM





8. How Misfolded TTR Proteins Result in Amyloid Deposition in the Heart

Transthyretin (TTR) typically exists in the bloodstream as a stable tetramer. In the case of hereditary transthyretin amyloidosis (hATTR), mutations in the TTR gene impair the stability of the tetramer, causing it to break into monomers. This destabilization of the tetramer is seen as the primary factor driving amyloid formation in hATTR. On the other hand, the reason for instability in wild-type ATTR (wtATTR) is not fully understood, although factors related to aging are believed to contribute [32].

After separating from the original tetramer, TTR monomers experience structural misfolding and start to self-assemble into soluble oligomers. These oligomers slowly aggregate to form protofibrils, which then develop into β-sheet-enriched amyloid fibrils that accumulate in cardiac tissue [33].

These fibrils build up in the myocardial interstitium, leading to thickening of the ventricular walls, reduced compliance, and diastolic dysfunction-characteristics typical of restrictive cardiomyopathy [34-36].

9. Progression from Amyloid Accumulation to Cardiomyopathy (ATTR-CM)

The transition from amyloid buildup to clear-cut cardiomyopathy (ATTR-CM) involves a series of structural and functional changes within the heart.

9. 1. Amyloid deposits in the extracellular space

Misfolded transthyretin proteins organize into amyloid fibrils that accumulate in the myocardial interstitium. This leads to the thickening and rigidity of the ventricular walls, ultimately resulting in a restrictive cardiac physiology pattern [37-39].

9. 2. Impaired diastolic function

As amyloid buildup progresses, it disrupts the relaxation and filling of the ventricles. Clinically, this manifests as heart failure with preserved ejection fraction (HFpEF), which is often the first functional indication of cardiac involvement [38,39].

9. 3. Systolic dysfunction

Although the left ventricular ejection fraction (LVEF) usually remains normal in the initial stages, systolic dysfunction becomes more pronounced as the disease progresses. In the later stages, a reduction in LVEF may be noted, indicating a decline in myocardial contractile reserve [40-41].

10. Importance of Targeting TTR Production in ATTR-CM

Lowering transthyretin (TTR) production has emerged as a key treatment objective in the management of ATTR cardiomyopathy, as both mutated and normal forms of TTR play a role in the formation of amyloid fibrils and their subsequent accumulation in the heart [42].

The liver is the main location for TTR production and is the primary contributor to circulating TTR, whereas the choroid plexus only produces a small amount [43].

Since the extent of amyloid deposits is linked to the levels of circulating TTR, decreasing its production minimizes the available substrate for fibril development, which in turn aids in slowing disease progression [44]. Gene silencing treatments such as patisiran are now approved for use in clinical settings. These therapies have shown to stabilize cardiac structure and function during clinical trials. In particular, they help to preserve exercise capacity, lower NT-proBNP levels, and maintain global longitudinal strain over prolonged treatment durations [45]. However, these treatments necessitate repeated dosing to maintain their benefits [46].

On the other hand, CRISPR-Cas9 in vivo gene editing, highlighted by NTLA-2001, presents an intriguing alternative. In early-phase trials, a single intravenous injection of NTLA-2001 led to an average 87% reduction in serum TTR levels by day 28. These reductions persisted for at least four to six months [47]. Although this indicates the potential for a one-time treatment option, the enduring effects and clinical significance of this method are still being explored [47].

11. CRISPR-Cas9

11.1. Overview

CRISPR-Cas9 opens a new chapter in genetic biotechnology by introducing precise gene editing in human cells. It targets the genomic loci and induces double strand breaks in the DNA by sRNA molecules [48]. Two main pathways are then followed to repair the DNA namely the Non homologous end joining (NHEJ) and Homology directed repair (HDR) [49].

Both present their own unique features; NHEJ is more prone to genetic mutations while HDR focuses on exact changes required in the gene via donor templates [50]. Recently, the introduction of base and prime editors now allows induction of specific changes in single base without even causing a break in the DNA [48].These advances allow a more optimal approach; when more precise genetic editing is required HDR is preferred while when spatiotemporal control is required Cas9 variants may be used [51,52].

11.2. Specificity and efficacy

In the case of the TTR gene associated with transthyretin amyloidosis, CRISPR/Cas9 shows promising potential through various trials. A study conducted in mice reported over 97% reduction in the serum TTR for a minimum of 12 months after only single administration [53].

An introductory human trial involving 12 subjects reported significant reduction (90%) in serum levels of TTR in only 28 days [54]. High efficiency has been reported with polymer stabilized Cas9 nanoparticles used with modified templates [55]. However, it is to be noted that off-target effects remain a concern. Chemical inhibition of non-homologous end-joining pathways can modulate mutational outcomes and improve precise gene editing [56]. While CRISPR-Cas9 shows potential for treating transthyretin amyloidosis, there remain concerns regarding off-target effects, optimal treatment monitoring, and long-term safety [57-59].

12. Nexiguran Ziclumeran

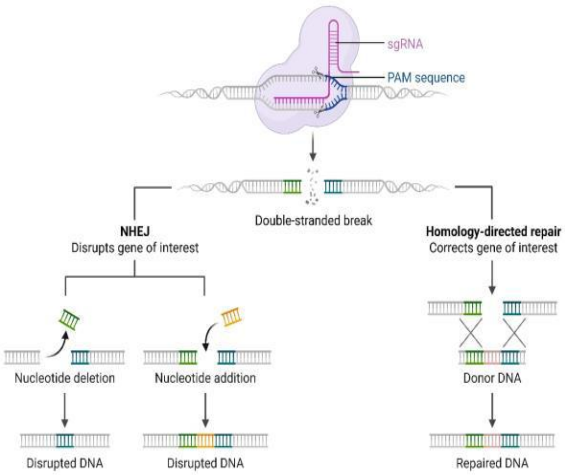
12.1. Overview

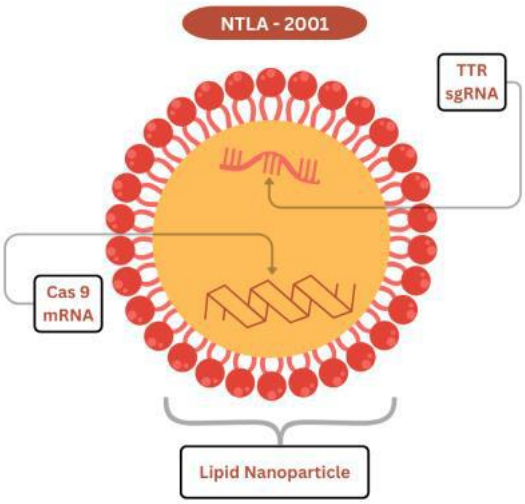
NEXIGURAN ZICLUMERAN (NTLA-2001) is an in vivo CRISPR-Cas9 gene-editing therapy targeting the transthyretin (TTR) gene for treating hereditary transthyretin amyloidosis (hATTR) [60]. It uses lipid nanoparticles in order to transport Cas9 encoding mRNA and sgRNA to hepatocytes, resulting in TTR gene knockout. In phase 1 trials, a single intravenous dose of NTLA- 2001 led to dose-dependent reductions in serum TTR levels, with mean reductions of 52% at 0.1 mg/kg and 87% at 0.3 mg/kg after 28 days [60]. Doses greater than these were reported to achieve 93% mean reduction in serum TTR levels [61]. The reduction in the serum TTR was sustained for at least 12 months [62]. Side effects reported were mainly mild adverse events while generally the therapy was well tolerated by most subjects [60-61]. hATTR therapy may be taking a new turn towards the single dose administration of Nexiguran Ziclumeran while the lifelong administration of gene silencing agents seems to be becoming a story of yesterday [63].

12.2. MOA

NTLA-2001 holds the ability to precisely target the TTR gene, which as discussed is the core cause of hATTR. It is composed of a single guided RNA (sgRNA) which plays the role of DNA sequence recognition and Cas9 enzyme which acts as an endonuclease causing double stranded break in the

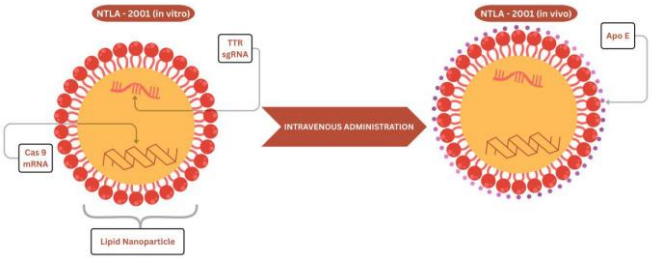
targeted region of the gene [64-65]. Now the DNA repair mechanisms come into play; mainly NHEJ is activated which repairs the double strand break by adding new nucleotides or removing some others due to high chance of a mutation the TTR gene may be rendered nonfunctional, secondarily HDR may also be activated which uses the homologous DNA sequence as a template to reproduce the same genome, however introducing a donor template allows us to modify the gene as per our discretion. This therapy essentially disrupts the production of TTR protein and has been found effective on both mutant and wild TTR protein. Multiple preclinical and many clinical assessments affirm the specificity of sgRNA, with no significant off target editing confirming the safety of the therapy [66].





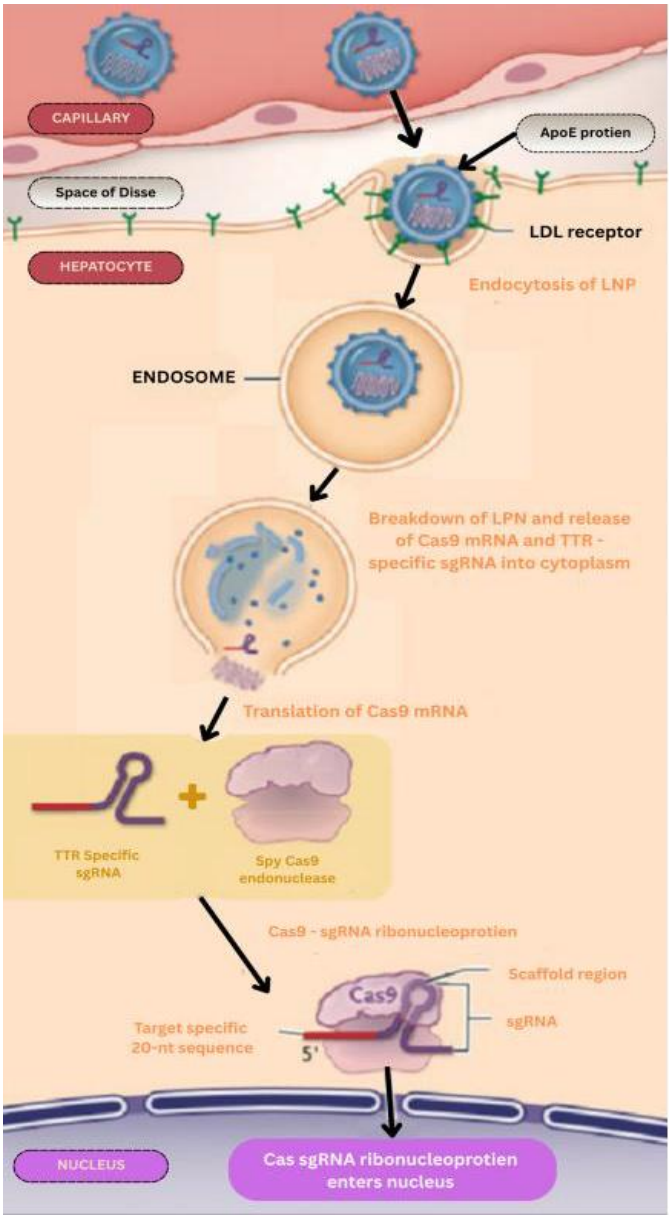
13. Mode of Delivery

Mode of delivery for NTLA 2001 or Nexiguran Ziclumeran is a lipid nanoparticle (LPN) system. This LNP formulation is crucial for efficient and targeted delivery to hepatocytes which are the primary site of TTR protein production .The LNPs are engineered with liver tropism, adsorbing apolipoprotein E (ApoE) from the bloodstream, which facilitates their uptake by hepatocytes through low-density lipoprotein receptor (LDL-R) mediated endocytosis [67].



LNPs then undergo endosomal escape, releasing the CRISPR components in the cell. Now Cas9 mRNA is translated to form active Cas9 protein. Note that the LNP system, in comparison to the viral vectors, is rapidly cleared from the body. Preclinical studies with a similar LNP demonstrated that biodegradable lipid components were cleared to undetectable levels within just three days post-administration, and Cas9 protein levels peaked approximately four hours after infusion, indicating a transient presence of the active enzyme [67-68].

NTLA-2001 is administered as a single, two-hour intravenous infusion. This rapid clearance minimizes prolonged systemic exposure, contributing to a favorable safety profile and broader patient applicability by avoiding issues like pre-existing immunity to viral vectors [67-68].



13.1. Pharmacodynamics and clinical efficacy

The Phase 1, open-label trial (NCT04601051), led by Fontana and colleagues, provided compelling evidence of Nexiguran Ziclumeran pharmacodynamic activity. A single intravenous infusion resulted in a remarkable mean reduction of 89% in serum levels of TTR levels recorded at 28 days post administration. This profound reduction was robustly sustained at 90% (95% CI, -93 to -87) at 12 months. Furthermore, this deep and sustained TTR suppression was maintained at 24 months in all 11 patients who completed the longer follow-up period [60,68].

It is to be noted that along with great reduction in TTR levels, changes in cardiac biomarkers have also been reported at 12 months post administration. These include markers like BNP, cardiac troponins, which is suggestive of destabilization of disease.

There is a median increase of 5 meters in functional capacity reported in a study using KCCQ scores indicating positive impact on quality of life, with 61% of patients reporting at least a 5-point increase. Additionally, 92% of patients showed either improvement or no change in their New York Heart Association (NYHA) functional class, suggesting stability or improvement in heart failure symptoms [68].

13.2. Advantages over traditional therapies

Nexiguran Ziclumeran offers several significant advantages over traditional ATTR-CM therapies, which include TTR stabilizers (for example: Acoramidis, tafamidis,) and TTR silencers (for example: Vutrisiran) . The most paramount advantage is its design as a single-dose, one-time treatment. This contrasts sharply with existing therapies that necessitate lifelong, continuous administration, which contributes significantly to patient burden and adherence challenges. The prospect of a single intervention providing a durable therapeutic effect represents a profound improvement in patient convenience and long-term disease management [66,68,69]. By permanently disrupting TTR production at its source, Nexiguran Ziclumeran offers the potential for more profound and sustained disease modification compared to therapies that merely slow progression. This provides arrest of pathological state and even reversal of the disease process hence providing a potential proper cure not merely the management of presenting symptoms. High specificity has also been established through assessments which further asserts the safety profile for this therapy [66].

14. Clinical Evidence of Nexiguran Ziclumeran in ATTR Cardiomyopathy

Single-Dose CRISPR-LNP Therapy: Preclinical Proof-of-Concept for ATTR [70]

Nexiguran Ziclumeran (NTLA-2001), developed by Intellia Therapeutics, represents a pioneering approach in treating hereditary transthyretin (ATTR) amyloidosis through in vivo CRISPR-Cas9 gene editing. Its preclinical evaluation was conducted in both murine and non-human primate models, using a delivery system based on biodegradable lipid nanoparticles (LNPs). These nanoparticles carried two essential components: A messenger RNA encoding the CRISPR- associated Cas9 enzyme, and a chemically stabilized single-guide RNA (sgRNA) specifically designed to target exon 1 of the transthyretin (TTR) gene. The proprietary chemical modifications of the sgRNA, including 2'-O-methyl nucleotides and phosphorothioate linkages, significantly enhanced its stability and editing efficiency compared to unmodified counterparts.

Following a single intravenous dose ranging from 0.3 to 3 mg/kg, the therapy demonstrated a profound reduction in serum TTR protein levels exceeding 97% in the highest dose group. In addition, next-generation sequencing confirmed approximately 70% allelic editing in liver cells, with the effect remaining durable for over a year. Importantly, there were no signs of liver toxicity, weight loss, or significant immune activation. Furthermore, both Cas9 mRNA and sgRNA were cleared from the plasma and liver within 72 hours, minimizing the risk of off-target activity. No unintended edits in coding DNA regions were detected through unbiased sequencing. The use of rapidly cleared LNPs (half-life of ~6 hours in the liver) allowed for safe, transient exposure, and repeat dosing studies suggested cumulative editing potential. Efficacy was also replicated in rat models, reinforcing the translational potential of NTLA-2001. Overall, this preclinical work laid a robust foundation for the successful initiation of human clinical trials, particularly for addressing the cardiac manifestations of ATTR amyloidosis through sustained suppression of pathogenic TTR protein production.

Phase 1 Trial in hATTR Polyneuropathy (NEJM 2021; Updated Nov 2024) [71]

In a phase 1, first-in-human, open-label, dose-escalation clinical trial, six patients aged approximately 46-64 years with hereditary transthyretin amyloidosis (hATTR) and polyneuropathy were enrolled to evaluate the safety and efficacy of NTLA-2001, a CRISPR-Cas9- based gene-editing therapeutic. The study employed a single intravenous infusion of NTLA-2001, with three patients receiving a dose of 0.1 mg per kilogram and three receiving 0.3 mg per kilogram. Serum transthyretin (TTR) levels were monitored as the primary pharmacodynamic endpoint. By day 28, the higher dose group exhibited an 87% reduction in serum TTR, which further increased to 91% at the 12-month follow-up. Durability of the treatment effect was confirmed, with sustained TTR knockdown observed at 24 months in an expanded cohort of 16 patients.

Clinical outcomes included a 4.5-point reduction in the neuropathy impairment score and a 54.7- point increase in modified body mass index (BMI), indicating significant improvements in both neuropathic symptoms and nutritional status. The treatment was well tolerated, with only mild infusion-related reactions reported and no treatment discontinuations due to adverse events. Based on these promising results, the study was expanded to include a total of 33 patients to further assess long-term safety, efficacy, and the potential for broader clinical application of NTLA-2001 in hATTR amyloidosis.

Phase 1 ATTR-CM Trial (NEJM 2024) [72]

A first-in-human, open-label phase 1 clinical trial (PMID: 39555828) was conducted to assess the safety, tolerability, and efficacy of a single intravenous dose of Nexiguran Ziclumeran (Nex-z), a CRISPR-Cas9-based in vivo gene-editing therapy, in patients with transthyretin amyloid cardiomyopathy (ATTR-CM). The trial enrolled 36 individuals, many with advanced disease; 50% were classified as NYHA class III, and 31% carried variant TTR mutations. The intervention produced a rapid and durable decline in serum transthyretin (TTR) levels. By day 28, TTR levels dropped by 89%, and this reduction deepened to 90%

in 12 months. Among 11 patients who completed two years of follow-up, TTR suppression was stably maintained, indicating long-term efficacy.

Cardiac biomarkers, including NT-proBNP and high-sensitivity troponin T, remained stable over 12 months. Functional assessment via the six-minute walk test showed a median improvement of 5 meters. Additionally, 92% of participants maintained or improved their NYHA class.

Patient- reported outcomes improved, with a median KCCQ score increase of 8 points; 61% achieved a clinically meaningful gain of at least 5 points. The therapy was generally well tolerated. Mild infusion-related symptoms (14%) resolved without intervention, and transient liver enzyme elevations (6%) normalized spontaneously. No treatment-related deaths or discontinuations occurred. Although 39% experienced serious adverse events, these were mainly attributed to disease progression.

These results support the potential of single-dose CRISPR-Cas9 therapy in modifying ATTR-CM and justify advancement to the phase 3 MAGNITUDE trial. Long-term monitoring is ongoing to evaluate delayed or rare outcomes.

Phase 3 MAGNITUDE trial (ATTR-CM, NCT06128629) [73]

The MAGNITUDE trial is an ongoing phase III, randomized, double-blind, placebo-controlled trial which evaluates the efficacy and safety of single intravenous dose of NTLA 2001, a CRISPR- Cas9 based gene-editing therapy, in ATTR-CM patients. The trial contains 765 participants (ages 18-90; both genders) randomized with 2:1, with confirmed ATTR-CM and stable hearty failure, excluding individuals with advanced heart failure (NYHA class IV) or those recently treated with RNA silencers. The key outcomes are the reduction of serum TTR levels and cardiac function improvement over a 24-months follow-up period, also the treatment related adverse effect. This study follows from prior Phase I trials, where NTLA-2001 reported 94% TTR knockdown with a favourable safety profile.

Phase 3 MAGNITUDE-2 trial (ATTRv-PN, NCT06672237) [74]

This is an ongoing Phase III, randomized, double blind, placebo -controlled trial which assesses the single dose of 55mg IV infusion of NTLA-2001 against placebo in approximately 50 patients (ages 18-85; both genders) with hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN). Participants are randomized 1:1 and individuals are excluded with non-TTR amyloidosis, diabetes-induced neuropathy, NYHA class III-IV heart failure, significant liver/kidney disease, HIV/HBV/HCV infection, prior TTR silencer therapy, or inability to take vitamin A supplementation. The primary endpoint includes serum TTR levels at 29 days and Modified Neuropathy Impairment Score +7 (mNIS+7) at 18 months. Quality of life, nutritional status and biomarker changes are the secondary outcomes.

15. Overall Summary

Nexiguran Ziclumeran (NTLA-2001) speaks to a groundbreaking headway within the treatment of transthyretin (ATTR) amyloidosis through a single-dose, in vivo CRISPR-Cas9 quality altering approach focusing on the TTR quality. Preclinical thinks about illustrated strong and significant concealment of serum TTR levels (>97%) maintained over 12 months in creature models, affirming tall viability, long-lasting affect, and a solid security profile.

Early-phase clinical trials encourage approved these discoveries in people, appearing quick and strong >90% knockdown of TTR protein levels. These trials included both genetic ATTR with polyneuropathy (hATTR-PN) and ATTR cardiomyopathy (ATTR-CM) cohorts. Clinically, patients shown advancements in neuropathy scores and stabilization or enhancement in cardiac work, recommending important malady alteration. Security information stay empowering, with mild-to-moderate antagonistic occasions reported-such as transitory rise in liver chemicals and mellow implantation reactions-with no trial discontinuations due to security concerns.

Right now, two essential Stage 3 studies MAGNITUDE and MAGNITUDE-2 are underway to evaluate the adequacy, security, and strength of NTLA-2001 in bigger and more different persistent populaces. On the off chance that fruitful, these trials may clear the way for administrative endorsement and build up NTLA-2001 as the primary possibly corrective, one-time treatment for ATTR amyloidosis.

Table 1: Summary of Clinical Trials for Nexiguran Ziclumeran (NTLA-2001) in ATTR Amyloidosis.

Trial Phase	Design	Participant(s)	Male % / Female %	Demographics	Key Efficacy Findings	Safety Findings	Fundings	Clinical Trials.gov ID
Preclinical(1)	LNP-CRISPR in mice and non-human primates	Animal models	N/A	Mice and non- human primates (varied doses: 0.1–3 mg/kg)	>97% TTR reduction (12 months), 70% liver editing	No hepatotoxicity, no off- target effects	Intellia Therapeutics	Not applicable
Phase 1 (hATTR-PN)(2)	Open-label, dose escalation + expansion	6 → 33 patients	N/A	Mean age: ~60s, hereditary ATTR polyneuropathy, various genotypes	91% TTR reduction at 12 months, NIS −4.5 points, mBMI ↑ 54.7	Mild infusion reactions, no SAEs	Intellia Therapeutics	NCT04601051
Phase 1 (ATTR-CM)(3)	Single-arm, open-label	36 patients	~78% / ~22%	Mean age: >65, 50% NYHA III, 31% variant ATTR- CM	90% TTR reduction, NT-proBNP stable, 6MWT +5m, KCCQ 8	Transient liver enzyme elevations (6%)	Intellia Therapeutics	NCT05248190

Phase 3 (MAGNITUDE)	RCT, double-blind, placebo-controlled	765 patients (2:1 randomization)	~75% / ~25% (expected)	ATTR- CM, older adults, global sites	Pending (Compo site CV endpoint in 2026)	Ongoing (completion 2028)	Intellia Therapeutics + Regeneron	NCT06128629
Phase 3 (MAGNITUDE- 2)	RCT, crossover	50 patients (1:1 randomization)	Not reported	hATTR -PN, expected middle-aged cohort	Pending (mNIS+ 7 at 18 months)	Ongoing (completion 2028)	Intellia Therapeutics	NCT06672237

16. Clinical Implications and Future Directions

ATTR cardiomyopathy (ATTR-CM) is a condition marked by the buildup of amyloid fibrils derived from unstable transthyretin (TTR) protein, primarily affecting the myocardium early detection of transthyretin cardiac amyloidosis (attr-cm) via non-invasive diagnostic methods is crucial since patient outcomes are significantly improved by starting recently developed disease- modifying treatments before there is severe cardiac dysfunction. In addition to typical heart failure treatments, current clinical guidelines from organizations such as the American Heart Association (AHA) and the European Society of Cardiology (ESC) recommend medications, including TTR stabilizers like tafamidis, for administration. However, these treatments do not provide a cure; rather, they primarily slow the progression of the disease [75].

The guidelines followed in the management of ATTR cardiomyopathy are as follows [76]:

1. Rule out AL amyloidosis with serum-free light chains and immunofixation.
2. Confirm ATTR-CM with technetium-labeled cardiac scintigraphy or biopsy.
3. Perform genetic testing to differentiate wild type (wtATTR) from hereditary (hATTR).
4. Start TTR stabilizers early: tafamidis (FDA-approved) or acoramidis (newer alternative).
5. Use diuretics cautiously for symptom relief; beta-blockers and RAAS inhibitors only if tolerated.
6. Avoid digoxin and nondihydropyridine calcium channel blockers.
7. In atrial fibrillation, anticoagulation regardless of CHA_2DS_2VASc score.
8. Amiodarone is the antiarrhythmic of choice.

A CRISPR-Cas9-based gene-editing treatment called Nexiguran Ziclumeran (NTLA-2001) is intended to target and deactivate the TTR gene in vivo specifically. Treatment with NTLA-2001 resulted in Phase 1 clinical research that was reported in the New England Journal of Medicine yielding more than 90% long-term drops in blood TTR levels, encouraging tolerance and efficacy. As a single-dose therapy, it may significantly reduce the burden associated with lifelong treatments. In patients with hereditary transthyretin amyloidosis, CRISPR-Cas9 gene editing can safely and effectively decrease the production of the defective transthyretin (TTR) protein, providing hope for a permanent cure [77]. For patients with hereditary or wild-type ATTR-CM, particularly those with mild to moderate functional impairments, NTLA-2001 may be positioned in future therapy guidelines as early intervention if verified in bigger studies like the MAGNITUDE 1 and MAGNITUDE 2 trials [78,79].

Infrastructure for long-term surveillance and the administration of genetic treatment would probably be needed for the clinical deployment of NTLA-2001. NYHA Class I-II patients verified by genetic screening may be excellent candidates. For safety and reliable delivery results, its utilization in specialist facilities with gene-editing capabilities would be crucial. In early-phase trials for transthyretin amyloid cardiomyopathy (ATTR-CM), Nexiguran Ziclumeran (NTLA- 2001), a first-in-human CRISPR-Cas9 gene-editing treatment, demonstrated encouraging outcomes. Clinical stability was noted in cardiac biomarkers (NT-proBNP, troponin T), functional capacity (6-minute walk test), and NYHA class after NTLA-2001, when administered as a single intravenous dosage, produced a sustained drop in serum transthyretin (TTR) levels of up to 90%. With modest infusion-related responses and temporary increases in liver enzymes, the therapy showed a good safety profile. Its usage is now limited to clinical studies even though it has not been authorized for ordinary use. It is anticipated that the current MAGNITUDE Phase III study will yield conclusive safety and effectiveness information [80].

A disease-modifying strategy for ATTR-CM is to target TTR production, which lessens the source of amyloid accumulation. The circulating TTR levels are significantly reduced by gene-silencing and editing medicines (e.g., patisiran, vutrisiran, NTLA-2001), which restrict hepatic TTR production in contrast to stabilizers that just stop TTR misfolding. When started early, this upstream intervention may be more successful in slowing or stopping the course of the illness.

17. Design Limitations: Narrative vs. Systematic Review

This review has fundamental biases because it takes a narrative approach rather than a methodical one. Because an organized framework like PRISMA does not constrain narrative evaluations, there is a greater chance of subjective interpretation and the deletion of important material. Narrative reviews often constitute lower reproducibility in terms of literature review [81].

18. Limited Clinical Evidence and Trial Phase

The key clinical evidence currently available, including data from the NTLA-2001 Phase 1 trial, remains maiden [82].

The things to be noted are as follows;

- The sample size in this study was small (n = 6 in the dose-escalation group).
- The follow-up period was short.
- Interim data from the MAGNITUDE 1 trial (ClinicalTrials.gov, NCT06128629) and MAGNITUDE 2 trial (ClinicalTrials.gov, NCT06672237) are still pending.

19. NO Comparison performed

There are currently no comparable studies comparing the effectiveness of NTLA 2001 to conventional treatments like patisiran or tafamidis. The clinical trials always need a comparison to prove a better option [83]. Otherwise, NTLA-2001 remains a promising but theoretical option.

20. Limited Population Diversity in Trials

ATTR-CM has two types of population: hereditary and wild type. The population studied in the early phase of NTLA-2001 was ATTR-CM Hereditary predominantly. Patients with ATTRv (hereditary) may respond differently to treatments than those with ATTRwt, creating a knowledge gap in treatment generalizability [84].

21. Affordability and Infrastructure Challenges

Gene editing technologies are quite expensive, limiting the population to undergo the trial. There is currently no information on NTLA-2001's cost-effectiveness, and its applicability in environments with restricted resources is still debatable. In low- and middle-income nations, the financial and technological needs of gene-editing treatments present a major obstacle [85].

22. Our recommendations

- Promote extensive, multicenter RCTs that include patients with ATTRv and ATTRwt.
- Promote head-to-head comparisons with tafamidis and patisiran.
- Make such model for NTLA-2001 that will be in the budget of all the patients.
- The sample size should be increased.
- The interim period should be extended.

23. Conclusion

The emergence of Nexiguran Ziclumeran (NTLA-2001) as a first-in-class, single-dose CRISPR-Cas9 gene-editing therapy represents a significant advancement in the therapeutic landscape for transthyretin amyloid cardiomyopathy (ATTR-CM). Clinical data from early-phase trials have demonstrated that this therapy leads to a rapid, robust, and sustained reduction in serum TTR levels up to 90% at 12 months after a single intravenous dose. Beyond biochemical improvement, patient-centered outcomes such as enhanced functional status, improved quality of life scores, and stabilization of cardiac biomarkers support its disease-modifying potential. Importantly, these therapeutic gains were achieved without the need for chronic dosing, contrasting sharply with current RNA-silencing or stabilizer therapies that require lifelong administration.

Nexiguran Ziclumeran's mechanism involves precise in vivo editing of the TTR gene in hepatocytes using lipid nanoparticle-mediated delivery of CRISPR components. The subsequent disruption of TTR protein synthesis directly targets the amyloidogenic driver of the disease. Unlike conventional agents like tafamidis and patisiran, which slow disease progression, this approach halts or even reverses pathology at the genetic level. Safety data from phase 1 studies are promising, with only mild and transient adverse events observed. The pharmacodynamic profile of this therapy suggests long-term efficacy, potentially offering a cure rather than management of symptoms.

These findings underscore the transformative role of gene editing in the management of hereditary disorders. CRISPR-Cas9 enables precise, durable modification of pathogenic genes, ushering in a new era of molecular therapeutics. In the context of ATTR-CM, a disease with significant diagnostic delays and limited curative options gene editing is not only scientifically innovative but also clinically necessary. NTLA-2001 stands as proof of concept that single-administration genome editing can provide durable benefits with minimal systemic exposure, circumventing challenges posed by viral vectors or repeated dosing regimens.

Despite this optimism, several critical gaps remain. Current evidence is largely derived from small, early-phase studies. Larger, randomized controlled trials such as the ongoing MAGNITUDE and MAGNITUDE-2 trials are essential to validate the safety, durability, and broad efficacy of NTLA-2001 in diverse populations, including both hereditary and wild-type ATTR-CM. Moreover, head- to-head comparisons with existing therapies like tafamidis or vutrisiran are needed to define its place in clinical guidelines. Concerns regarding affordability, infrastructure needs for gene-editing delivery, and long-term surveillance of potential off-target effects must also be addressed before widespread adoption.

In conclusion Nexiguran Ziclumeran has demonstrated the potential to redefine ATTR- CM therapy by offering a one-time, potentially curative intervention. Its success could pave the way for broader integration of gene editing into cardiology and rare disease therapeutics. However, robust clinical validation, health economics assessment, and equitable access strategies are imperative to fully harness its clinical promise.

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