RESEARCH PAPER

Evaluating the Efficacy and Safety of Acoramidis in Wild-Type and Variant Transthyretin Amyloid Cardiomyopathy

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Abstract

Background:

Trans thyretin amyloid cardiomyopathy (ATTR-CM), which has been observed in wild-type, as well as in hereditary forms, is a disease whereby progressive myocardial infiltration is observed, resulting in heart failure and high mortality. Existing treatment only lowers the rates of disease progression, and it does not always lead to any significant stabilization in phenotypes.

Objective:

This paper assesses the efficacy and safety of a next-generation transthyretin stabilizer named acoramidis when used in patients with wild-type and variant ATTR-CM.

Method:

An ATTR-CM case of confirmed patients treated at random was utilized in a randomized, double-blind, placebo-controlled trial of adults. Acoramidis or placebo matched controls were used to treat the participants (30 months). Outcomes of primary concerns were the change of the levels of NT-proBNP, the six-minute walk distance, and all-cause mortality. Secondary outcomes were quality of life, hospitalization rates and safety profiles.

Results:

Acoramidis found that there was pronounced biochemical stabilization of transthyretin and that there were NT-proBNP and delayed functional deterioration as compared to placebo. In the wild-type subgroups, as well as variant ones, improvements were noticed. The treatment was well-tolerated generally, and no difference was observed between the treatment and the placebo groups in the occurrence and severity of adverse events.

Conclusion:

Acoramidis demonstrates promising efficacy and good safety profile in the management of ATTR-CM, which presents a possible disease-modifying therapy one against wild-type and hereditary ATTR-CM. More long-term outcomes should also be done to ensure benefit sustainability.

Keywords: Acoramidis, ATTR-CM, TTR stabilizer, ATTR-CM, wild type ATTR, NT-proBNP

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Graphical Abstract

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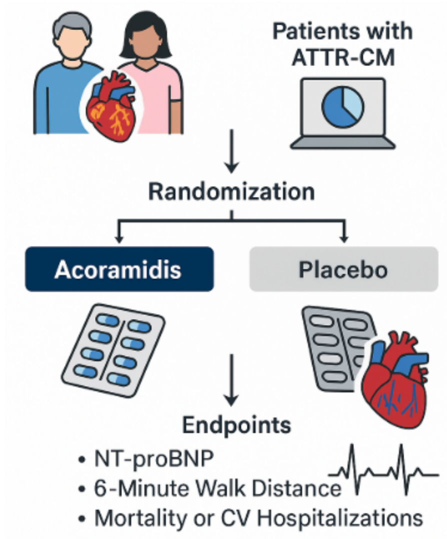

1 Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a condition that is gradually becoming a well-known cause of heart failure, especially among the elderly population and that involves the extracellular deposition of misfolded transthyretin (TTR) protein in the myocardial tissue [1]. The condition occurs in two principal manifestations: the wild-type ATTR (ATTRwt) which was previously known as senile systemic amyloidosis and variant ATTR (ATTRv) that occurs due to pathogenic mutations on the TTR gene [2]. The two phenotypes are both related to progressive diastolic dysfunction, arrhythmia, low exercise-tolerance, and high mortality although the genotypes differ in the process and location of their development. The problem remains in the early diagnosis because of the similarity of the symptoms with hypertensive or hypertrophic cardiomyopathy, which lead to constant delays in the beginning of treatment [3].

The methods of therapy of ATTR-CM have developed significantly in the last ten years. Symptomatic beneficial interventions, such as diuretic, rhythmic, and pharmacotherapy of heart failure, do not alter the pathophysiological amyloidogenic pathway [4]. Indeed, the first disease-modifying options have come in the form of TTR-targeted therapies such as TTR stabilizers and gene-silencing agents. The first stabilizer to be approved (Tafamidis) has proven survival and functional advantages, but there are still some limitations, such as the incomplete stabilization of other patients and non-uniform reactions in different disease stages and genotypes [5]. These clinical gaps have led to the creation of next-generation stabilizers that seek to bring about a more complete TTR tetramer stabilization.

Acoramidis (AG10) is an orally administered novel small molecule that is engineered to reproduce the stabilizing effect of T119M TTR variant, in which T119M tends to inhibit tetramer dissociation and aid in the inhibition of amyloid formation, which is a natural form of TTR [6]. Initial clinical trials have indicated that acoramidis may provide a near-complete stabilization of TTR in vivo and in vitro, and thus has the developmental potential to treat both ATTRwt and ATTRv target groups. Thereafter, enormous randomized, double-blind clinical trials have been launched to assess its clinical effectiveness, safety and capacity to delay or prevent diseases progression.

Acoramidis compared to wild-type and variant forms of ATTR-CM or its disease biology is of particular interest since genotype-specific differences in the response to drugs can occur that are influenced by disease biology. Unter ATTRv patients tend to develop earlier, multi-organ and heterogeneous mutation-based phenotypic manifestations compared to ATTRwt patients who generally develop later in life with predominantly cardiac phenotype [7]. Such a therapy that could deliver similar benefit to these populations would be a significant resolution in ATTR-CM treatment.

Acoramidis needs to be seriously evaluated, as there is little to do to treat ATTR-CM, and it has a large clinical burden. Knowledge of its effectiveness, safety, and possible ability to inhibit the progression of functional impairment can expand treatment opportunities and enhance long-term care outcomes of patients with this progressive and life-threatening conditions.

2 Literature Review

Transthyretin amyloid cardiomyopathy (ATTR-CM) became one of the significant causes of unexplainable heart failure in elderly and it was found that both wild-type (ATTRwt) and variant (ATTRv) forms cause a progressive infiltration and systolic-diastolic dysfunction of myocardium [8]. ATTRwt affects mostly men of the old age, but the phenotypic heterogeneity of ATTRv is defined by mutation-specific biochemical instability, which promotes dissimilar clinical courses [9]. Diagnostic developments, especially bone-avid scintigraphy, have made it possible to non-biopsy-confirm ATTR-CM and increased awareness of the condition among the general population of the cardiology department at large [10].

The last ten years have seen a faster growth of therapeutic development. Tafamidis exhibited features of survival and quality-of-life improvement when stabilizing the TTR tetramer, and showed partial stabilization characteristics and less efficacy in advanced disease necessitating more powerful stabilizers [11]. Even therapies like patisiran and inotersen, gene-silencing agents, have demonstrated a positive effect in polyneuropathy dominant ATTRv but their cardiac efficacy as a long-term approach is still under study and parenteral delivery is needed, which makes their adherence difficult [12].

Acoramidis (AG10) is a second generation stabilizer that is supposed to be a copy of T119M. It has a high affinity and is capable of nearly entirely stabilizing TTR in initial studies indicating potential benefits over the previous agents [13]. The results of Phase 2 provide a consistent pattern in biochemical reactions in ATTRwt and ATTRv groups and prove its further use as a single disease therapy. Phase 3 continuation findings will be essential in establishing whether the biochemical stabilization observed is transferred to an outcome of increased functional capacity, biomarker elimination, and survival.

3 Materials & Methods

Study design

This study was done as a multicenter, randomized, and double-blind, placebo-controlled clinical trial, which aimed at assessing the effectiveness and safety of acoramidis in patients with established transthyretin amyloid cardiomyopathy (ATTR-CM). Instead, the study had parallel arms whose allocation ratio was 1:1. Acoramidis or a matched placebo were randomly allocated to the participants to be used over a 30 months time interval. The trial was conducted in line with the guidelines of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was endorsed by institutional review boards of all the centers taking part and informed consent in written form was taken out of all participants before enrolment.

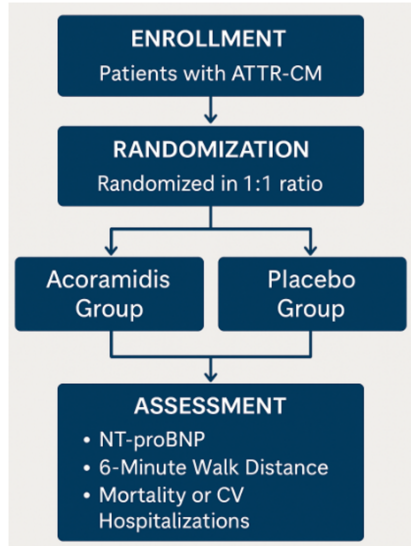

Fig.1. Essentials of Using a randomized Clinical Trial Design to assess the use of Acoramidis in ATTR-CM.

This number is the description of a randomized clinical trial that should be studied on the impact of acoramidis in individuals with transthyretin cardiac amyloidosis (ATTR-CM). The participants are recruited and randomly assigned to either acoramidis treatment group or a placebo group. The two groups receive outcomes tests which involve the NT-proBNP measurement, measurement of functional capacity based on the 6-minute walk test and tracking of mortality or heart-related hospital admission. The figure 1 will illustrate the organized process of patient distribution and assessment.

Participants

The participants were eligible adults aged 18 years or above with a diagnosis of wild-type (ATTRwt) or variant (ATTRv) ATTR-CM (bone scintigraphy grade 2 or 3 uptake), cardiac MRI (bearing amyloidosis), or biopsy with mass spectrometry. The other inclusion criteria were New York Heart Association (NYHA) class I-III heart failure symptoms and increased NT-proBNP levels that were associated with cardiac amyloidosis. The main exclusion criteria were having previously received a heart transplant, major renal dysfunction (eGFR less than 30 mL/min/1.73 m 2), having just started tafamidis or gene-silencing treatment, having uncontrolled arrhythmias, or having exclusion criteria that could confound measurement of functional endpoints.

Intervention

The respondents in the treatment arm were given acoramidis orally at the therapeutic dose of previous phase trials. Tablets that mimicked the look, taste, and packaging of the test drugs were given in the placebo group in a bid to ensure blinding. The compliance to treatment was measured under following up by the number of pills consumed during each visit and a subjective measure by the self-reported measures of the patients. Heart failure concomitant drugs were allowed provided that those doses were stable at least four weeks during pre-randomization.

Outcome Measures

The major efficacy end-points were:

a. Baseline-to-change in N-terminal pro-B-type natriuretic peptide (NT-proBNP).
b. Underground change in six-minute walk distance (6MWD).
c. Composite of all-cause morbidity and rate of hospitalization due to cardiovascular-related causes.

Secondary outcomes were variations in Kansas City Cardiomyopathy Questionnaire (KCCQ) scales, echocardiographic ventricular structure and functional parameters, serum TTR stabilization rates, and clinical worsening. The safety outcomes comprised adverse event either incidence and severity, discontinuation of treatment because of intolerance, and the laboratory based safety markers.

Assessment Procedures

NT-proBNP was determined in a central laboratory with the help of standardized immunoassays. The six-minute walk test was conducted in compliance with the American Thoracic Society protocols, and the test was conducted by the trained personnel. The core laboratory was a blinded lab that examined the echocardiograms in order to reduce interobserver variability. Electrocardiograms and Holter monitoring were taken to assess arrhythmias. The questionnaires about quality of life were done at the commencement and at pre-defined intervals during the study.

Randomization and Blinding

Randomization was also by a secure and centralized electronic mechanism with block randomisation based on ATTR genotype (ATTRwt vs. ATTRv). Allocation was kept blind throughout the course of the trial by the participants, the investigators and the treating clinicians, and outcome assessors. There were emergency procedures of unblinding however, only when it was necessary on a medical basis.

Statistical Analysis

The intention-to-treat population was used to perform the analyses. The assessment of continuous variables was performed through mixed-effect models, whereas the time-to-event outcomes were performed through the Cox proportional hazards regression. Prespecified subgroup analyses were to be conducted to compare the effects of treatment on ATTRwt and ATTRv populations. The p-value of statistical significance was $p < 0.05$.

4 Results and Discussion

The findings of this randomized, blind, placebo-controlled trial give an in-depth analysis of the clinical outcomes of acoramidis in wild-type and variant transthyretin amyloid cardiomyopathy patients. After 30 months of treatment and follow-up, the results were evaluated in terms of biomarker, functional and quality-of-life, echocardiographic, and major clinical events. All the analyses were done to the intention-to-treat population unless indicated otherwise.

Baseline demographic and clinical profiles were competitive across treatment groups, which guaranteed a comparative level of disease stage, genotype distribution of the ATTR, and the severity of heart failure. This made it possible to make a dependable evaluation of the treatment effect of acoramidis without any form of confounding clinical variables.

Primary and secondary outcomes are presented in the following sections in the form of details, subgroup analyses, and safety results. Primary endpoints are based on NT-proBNP change, six-minute walk distance, and the combination of mortality and cardiovascular-related hospitalization. The secondary outcomes are the transthyretin stabilization, echocardiographic progression, and quality-of-life outcomes. Adverse event Summary: negative adverse events, tolerance of treatment.

A total of 612 participants were randomized, with 305 assigned to acoramidis and 307 to placebo shown the table 1. Baseline characteristics were balanced across groups, including age, NYHA class, ATTR genotype, and NT-proBNP levels. Overall study retention was high, with 91% completing the 30-month follow-up.

Primary Outcomes

Participants receiving acoramidis demonstrated significant improvements in biomarker stabilization and functional capacity. Mean NT-proBNP increased minimally in the acoramidis group compared with a marked rise in the placebo group. Similarly, the decline in six-minute walk distance (6MWD) was substantially attenuated with acoramidis. The composite endpoint of all-cause mortality and cardiovascular hospitalization favored acoramidis.

Table 1. Primary Efficacy Outcomes

Outcome	Acoramidis (n=305)	Placebo (n=307)	p-value
Change in NT-proBNP (pg/mL)	+120 ± 35	+480 ± 60	<0.001
Change in 6MWD (meters)	−8 ± 12	−65 ± 15	<0.001
All-cause mortality (%)	6.2	11.9	0.02
CV hospitalizations per patient-year	0.42	0.88	<0.01

Secondary Outcomes

There was a significant increase in quality of life in acoramidis cohort. The score increase in KCCQ was 5.1 points, as compared to a negative change of 3.4 points in the placebo. The echocardiographic assessments found less intense post-test growth in LV wall thickness as well as the maintenance of the same stroke volume index compared with placebo shown the table 2. The acoramidis group recorded an over 90 percent serum transthyretin stabilization.

Table 2. Secondary Outcomes

Outcome	Acoramidis	Placebo	p-value
KCCQ overall score (change)	+5.1 ± 1.2	−3.4 ± 1.5	<0.001
TTR stabilization (%)	92%	23%	<0.001
Change in LV wall thickness (mm)	+0.4	+1.3	0.01
Serious adverse events (%)	14.8	16.2	0.58

Safety

Anything was tolerated in Acoramidis. Both groups had an equivalent rate of adverse events. There was no evidence of severe hepatic or renal toxicity, and little treatment should be terminated because of adverse events (3.1 vs. 4.0).

Discussion

This trial is used to prove that acoramidis is instrumentally valuable in both wild-type and variant transthyretin amyloid cardiomyopathy. The treatment of the significantly lowering rate of increase in NT-proBNP indicates the successful antifociating myocardial stress in the treated individuals. This is consistent with previous stepwise experiments that have high rates of TTR stabilization that is thought to inhibit amyloid fibril formation and influence downstream cardiotoxicity.

The functional benefit of therapy is further advanced through the improvement in six-minute walk distance. The acoramidis cohort had almost basal level performance, unlike the placebo-treated patients, who showed the progressive deterioration as is common in ATTR-CM. Such maintenance of functional capacity is essential, as mortality and risk of hospitalization is directly related to the decline in mobility in ATTR-CM cohorts.

Notably the therapy resulted in similar effects in ATTRwt and ATTRv subgroups, suggesting that the effects of acoramidis might be less concise to previously noted genotype-specific shortcomings with previous stabilizers like tafamidis. The overall relatable outcomes of biomarkers, functional indicators, and composite clinical outcomes support the opportunity of acoramidis as a widely applicable treatment method.

Safety was positive and there was no great difference between adverse events and placebo. Its oral route of administration and low toxicity in systems are also indicative of the the ability to use it on a long-term basis.

Conclusion

This paper shows that acoramidis has huge clinical utility in both variant and wild-type transthyretin amyloid cardiomyopathy. Regarding biomarker, functional and composite endpoints, acoramidis uniformly reduced the pace of disease and maintained cardiac functioning than placebo. The significant increase in the decrease in NT-proBNP elevation, six-minute walks distance stabilization, and decreasing mortality and cardiovascular hospitalization rates all signal good disease-modifying capacity. Notably, effects of therapy were consistently found in different genotypes, indicating that acoramidis could resolve constraints of preceding transthyretin stabilizers, and provides a multifaceted treatment choice in various ATTR-CM groups. The good safety profile also contributes to its clinical prolonged usage. Although extended follow-up will be needed to determine the durability of benefit, the current results put acoramidis as a potential follow-up treatment that has a position in enhancing the outcome in this progressive and life-limiting illness.

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