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More players in the treatment of transthyretin amyloidosis? The HELIOS-B study

Elena Biagini [1,2]* **and Simone Longhi**[1,2]

[1]*Cardiology Unit, Cardiac Thoracic and Vascular Department, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna; and* [2]*European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart-ERN GUARD-Heart, Bologna, Italy*

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Transthyretin (TTR) amyloidosis is a progressive and fatal disease caused by the deposition of TTR amyloid fibrils in multiple organs and tissues. The HELIOS-B trial (a phase three, randomized, double-blind, placebo-controlled, multicenter study) tested the safety and efficacy of vutrisiran, a subcutaneous gene silencer, in patients with wild-type or inherited TTR cardiomyopathy. The two primary endpoints were a composite of all-cause mortality and recurrent cardiovascular (CV) events (CV hospitalizations and urgent heart failure visits) assessed in the overall population and the monotherapy group. Secondary endpoints included all-cause mortality up to 42 months and 30-month change in functional capacity, health status, and quality of life. A total of 655 patients were enrolled in the study (vutrisiran, $n = 326$; placebo, $n = 329$). The mean age was 77 years, and 40% received tafamidis at baseline. Treatment with vutrisiran resulted in a reduction in all-cause and CV mortality events, as well as preservation of functional capacity, quality of life, and health status in patients with TTR cardiomyopathy.

Transthyretin amyloidosis (ATTR) is a systemic, progressive, and fatal disease caused by misfolding of the transthyretin protein resulting in fibril infiltration into multiple organs and tissues, including the heart and peripheral nervous system.[1–3]

Transthyretin cardiomyopathy (ATTR-CM) can be caused by mutations in the transthyretin gene, either familial (hATTR) or wild-type (wt-ATTR), the latter being more common in older patients without evidence of pathogenic mutations.[3–7] Patients with ATTR-CM have debilitating symptoms and high morbidity and mortality, with a median survival of 2–6 years from diagnosis.[7,8]

To date, the only therapy that a cardiologist can prescribe for ATTR-CM is tafamidis. This transthyretin stabilizer inhibits the dissociation into monomers and thus the formation of new amyloid fibrils. As demonstrated in the ATTR-ACT study, tafamidis therapy slows the decline in functional capacity and quality of life and improves the prognosis after a period of 18 months in the case of mortality from any cause.[9]

Among the various molecules analysed for the aetiological treatment of ATTR-CM, there is vutrisiran.

Vutrisiran is a subcutaneously administered gene silencer that inhibits the hepatic synthesis of both hATTR and wt-ATTR transthyretin messenger RNA, resulting in rapid breakdown of the pathogenic protein before amyloid-causing monomers can form.[10–12] Vutrisiran is currently approved for the treatment of hATTR amyloidosis with polyneuropathy based on results from the phase three ‘HELIOS-A’ study, which demonstrated significant improvement in multiple disease-relevant endpoints in the vutrisiran arm vs. the placebo arm.[11,12] Results from an exploratory analysis of cardiac endpoints in the HELIOS-A study indicated a potential benefit of vutrisiran also in cardiac manifestations of the disease [N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, echocardiographic findings, and scintigraphic with technetium-99 m]; these results support the hypothesis

*Corresponding author. Email: elena.biagini73@gmail.com

that a reduction in the level of the amyloidogenic transthyretin protein may have a therapeutic benefit in patients with ATTR-CM.[13]

Starting from these assumptions, the 'HELIOS-B' study was designed. In this trial, the efficacy and safety of vutrisiran in patients affected by familial or wild-type ATTR-CM were analysed compared with placebo. The inclusion criteria included age between 18 and 85 years, diagnosis of ATTR-CA, and signs of cardiac involvement (interventricular septal thickness > 12 mm), a history of heart failure, NT-proBNP between 300 and 8500 ng/L, and ability to walk at least 150 m in the walk test.

In the study, patients were assigned in a 1:1 ratio to receive either vutrisiran (25 mg) or placebo subcutaneously every 12 weeks for up to 36 months. Randomization was stratified by tafamidis use at baseline, aetiologic type of transthyretin amyloidosis (hATTR vs. wt-ATTR), New York Heart Association (NYHA) functional class, and age (NYHA class I or II and age < 75 years vs. all others). Patients who were not receiving tafamidis at baseline could start receiving it after enrolment if deemed necessary by the study investigator. All patients were asked to take the recommended daily dose of vitamin A because of the potential disruption of vitamin A transport. At the end of the double-blind period (follow-up ranging from 33 to 36 months), patients were eligible to enrol in the open-label extension period of up to 24 months.

The study enrolled 655 patients with ATTR-CA. Baseline demographic and clinical characteristics of patients were similar between the two groups, except among patients in the monotherapy population where NT-proBNP and troponin I levels were higher in the vutrisiran group than in the placebo group. In the overall population, the mean age was 77 years and the majority of patients were men (93%), with wt-ATTR (88%) and NYHA functional class II (78%). Among the 76 patients with hATTR amyloidosis, there were 13 different pathogenic variants of transthyretin; 49 patients (64%) had the V122I variant. Demographic and clinical characteristics of patients in the monotherapy population at baseline did not differ from those of the overall population.

The primary endpoint was a composite of death from any cause and recurrent cardiovascular events (defined as hospital admissions for cardiovascular causes or urgent care visits for heart failure) in the overall population and the monotherapy population.

Secondary endpoints investigated all-cause mortality up to 42 months, change from baseline to 30 months in functional capacity [assessed by 6 m walk distance (6MWD)], and quality of life [assessed by the Kansas City Cardiomyopathy Questionnaire overall summary (KCCQ-OS)]. The monotherapy population was defined as patients not receiving tafamidis at baseline.

Treatment with vutrisiran showed a lower risk of death from any cause and recurrent cardiovascular events compared with placebo [hazard ratio (HR), 0.72; 95% confidence interval (CI), 0.56–0.93; $P = 0.01$]. It also documented a reduction in all-cause mortality and cardiovascular events of 33% in the subgroup not on tafamidis at baseline (HR, 0.67; 95% CI, 0.49–0.93; $P = 0.02$) and of 21% in the subgroup on tafamidis (HR, 0.79; 95% CI, 0.51–1.21). Survival curves show that the benefit of vutrisiran, in terms of the primary endpoint, was most evident after 6 months of therapy.

Treatment with vutrisiran resulted in a lower risk of death from any cause over 42 months compared with placebo (HR in the overall population, 0.65; 95% CI, 0.46–0.90; $P = 0.01$) with a separation of the survival curves after 18 months.

The prognostic benefit of vutrisiran was similar across all predefined subgroups. Treatment with vutrisiran was also associated with a smaller decline in 6MWD compared with placebo (mean difference, 26.5 m; 95% CI, 13.4–39.6; $P < 0.001$) and a smaller reduction in KCCQ-OS score (mean difference, 5.8 points; 95% CI, 2.4–9.2; $P < 0.001$).

In the overall population, the incidence of adverse events was similar in the two groups (99% in the vutrisiran group and 98% in the placebo group). Serious adverse events occurred in 201 patients (62%) in the vutrisiran group and 220 patients (67%) in the placebo group. Adverse events leading to discontinuation of vutrisiran or placebo occurred in 10 patients (3%) and 13 patients (4%), respectively.

The HELIOS-B study was designed to include a group of patient representative of the contemporary ATTR-CM population, and this is a further strength of the trial. In the last 10 years, the progress of imaging techniques and the greater knowledge of pathology have led to the diagnosis of ATTR-CM at an early stage of the pathological process, with a less severe clinical phenotype and a better prognosis.[14] This is confirmed by comparing the baseline characteristics of patients with ATTR-CM enrolled in phase three clinical trials in recent years. Patients in the HELIOS-B study generally had lower severity of the disease at enrolment (greater distance covered in the 6 min walk test, higher KCCQ-OS score, lower levels of NT-proBNP and troponin I, and NHYA functional class) compared with those enrolled in the ATTR-ACT study.[9] Despite a healthier patient population at baseline and substantial concomitant use of tafamidis and SGLT2 inhibitors (40% of patients were on tafamidis at baseline, 22% of patients in the monotherapy population initiated tafamidis during the study, and 33% of patients in the overall population initiated SGLT2 inhibitor therapy during the study), vutrisiran, compared with placebo, was associated with a HR of 0.65 for death from any cause up to 42 months in the overall population.

In patients with ATTR-CM, treatment with vutrisiran resulted in a lower risk of all-cause death and recurrent cardiovascular events. Vutrisiran also preserved functional capacity and quality of life and prevented the worsening of heart failure symptoms. These effects were consistent across all pre-specified subgroups, including patients receiving background tafamidis.

Overall, these data suggest that the rapid knockdown of transthyretin by vutrisiran reduces morbidity and mortality among patients with ATTR-CM.

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Data availability

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