Researchers discover first treatment to improve survival in rare heart condition

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Tafamidis is the first treatment to improve survival and reduce hospitalisations in a rare heart condition called transthyretin amyloid cardiomyopathy, according to late breaking research presented today in a Hot Line Session at ESC Congress 2018 and published in the *New England Journal of Medicine*.

Professor Claudio Rapezzi, principal investigator, University of Bologna, Italy, said: "There are no medications specifically approved for the treatment of transthyretin amyloid cardiomyopathy. Tafamidis improved survival and quality of life, and reduced hospitalisations, indicating that it could be an effective therapy for these patients. A submission to the regulatory authorities for marketing approval is in process as a consequence of this study."

Transthyretin amyloid cardiomyopathy is a rare, progressive, fatal disease. The hereditary form is caused by mutations in the TTR gene and typically presents in 50-70 year-olds, while the acquired (wild-type) form presents in 60-80 year-olds. The disease is caused when the transport protein, transthyretin, becomes unstable and misfolds, leading to the formation of amyloid, which is deposited in the heart. This causes the heart muscle to become stiff and results in heart failure.

Patients have debilitating symptoms common to heart failure, such as shortness of breath, fatigue, orthostatic hypotension, and syncope, leading to frailty and poorer quality of life. Patients survive an average of three to five years after diagnosis. There are no approved drugs to improve survival, and therapy is limited to managing symptoms.

Tafamidis stabilises transthyretin, preventing misfolding and the formation of amyloid. Treatment with this therapy delays neurologic progression in transthyretin familial amyloid polyneuropathy, a similar condition in which amyloid is deposited in the nerves after transthyretin misfolding. The drug is approved for this condition in the EU.

The medicine has not been approved for the treatment of transthyretin amyloid cardiomyopathy, but has orphan drug designation from the European Medicines Agency (EMA) and Fast Track designation from the US Food and Drug Administration (FDA).

The ATTR-ACT tria assessed the efficacy and safety of tafamidis in patients with hereditary and acquired transthyretin amyloid cardiomyopathy. The trial enrolled 441 patients aged 18-90 years from 48 centres in 13 countries. Patients were randomised in a 2:1:2 ratio to tafamidis 80 mg, tafamidis 20 mg, or placebo—all taken orally, once a day, for 30 months.

The primary endpoint was the hierarchical combination of all-cause death and cardiovascular-related hospitalisations from baseline to 30 months. The two tafamidis groups were combined and compared with the placebo group. Secondary outcomes included the change from baseline to 30 months in exercise capacity (assessed with the six-minute walk test) and in health-related quality of life (assessed using the Kansas City Cardiomyopathy Questionnaire).

A total of 264 patients received the drug and 177 received placebo. Tafamidis significantly reduced death and cardiovascular-related hospitalisation compared to placebo (p=0.0006). During the 30-month follow-up, 78 (29.5%) patients receiving the medicine died compared to 76 (42.9%) receiving placebo—this included patients who underwent heart transplant or received a cardiac mechanical assist device as these were classified as death in the analysis. Rates of cardiovascular-related hospitalisations were 52.3% and 60.5% in the tafamidis and placebo groups, respectively.

The therapy also reduced the decline in six-minute walk distance and quality of life compared with placebo. The incidence of individual adverse events were similar or fewer with drug treatment.

Discontinuations of study drug due to treatment-related adverse events were less common with tafamidis than placebo.

Professor Rapezzi said: "ATTR-ACT is the largest randomised clinical trial in patients with transthyretin amyloid cardiomyopathy to date. The trial showed that tafamidis is superior to placebo in reducing the risk of death and cardiovascular-related hospitalisations. Tafamidis also reduced the decline in functional capacity and quality of life and had a favourable safety profile in these patients."

He concluded: "These findings provide strong evidence that tafamidis is an effective therapy for patients with transthyretin amyloid cardiomyopathy and can modify the natural history of this disease."

More information: "ATTR-ACT Trial - Efficacy and Safety of Tafamidis in Transthyretin Amyloid Cardiomyopathy" ESC Congress 2018

Mathew S. Maurer et al. Design and Rationale of the Phase 3 ATTR-ACT Clinical Trial (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial), *Circulation: Heart Failure* (2017). DOI: 10.1161/CIRCHEARTFAILURE.116.003815

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