A Statement on the Appropriate Administration of Tafamidis in Patients With Transthyretin Cardiac Amyloidosis

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Transthyretin cardiac amyloidosis is a progressive and life-threatening disease that is significantly underdiagnosed, and the actual number of patients with the disease is presently unknown. Accumulation of wild-type transthyretin-derived amyloid in the heart is a common finding in very elderly patients. Recent clinical trials demonstrated that tafamidis reduced all-cause death and the number of cardiovascular hospitalizations when compared with placebo. The Japanese Ministry of Health, Labour and Welfare approved tafamidis (Vyndaqel®, Pfizer Inc.) for the treatment of cardiomyopathy caused by both wild-type and mutated transthyretin-derived amyloidoses. This scientific statement on transthyretin-derived cardiac amyloidosis summarizes the conditions for reimbursement of the cost of tafamidis therapy, and the institutional and physician requirements for the introduction of tafamidis.

Key Words: Amyloid; ATTR cardiac amyloidosis; Japanese Circulation Society; Japanese Ministry of Health, Labour and Welfare (JMHLW); Tafamidis

Amyloidosis is a group of diseases in which amyloid fibrils deposit in the extracellular spaces of different organs, ultimately leading to progressive organ dysfunction. Amyloid fibrils are formed by an aggregation of misfolded proteins. The most common amyloid fibril proteins that can infiltrate the heart and lead to cardiac amyloidosis are immunoglobulin light-chain amyloid fibril protein (AL) and transthyretin (TTR) amyloid fibril protein (ATTR). Wild-type TTR-derived cardiac amyloidosis occurs mostly in older patients, in whom misfolded transthyretin proteins deposit in the heart.

TTR is a soluble human plasma protein that can be converted into amyloid by dissociation of the homotetramer into monomers. The drug tafamidis binds to the TTR tetramer and dramatically slows dissociation, thereby efficiently inhibiting aggregation. On March 26, 2019, the Japanese Ministry of Health, Labour and Welfare (JMHLW) approved tafamidis (Vyndaqel®, Pfizer) for the treatment of cardiomyopathy caused by both wild-type TTR (TTRwt) and variant TTR (TTRv)-derived amyloidoses. The approval was based on the Tafamidis Phase 3 Transthyretin Amyloid Cardiomyopathy Study, which was presented at the European Society of Cardiology 2018 Congress in Munich, Germany, and published in the New England Journal of Medicine. In that trial, 441 patients with ATTR amyloid cardiomyopathy (either hereditary ATTR [ATTRv] or ATTRwt) were randomized in a 2:1:2 ratio to 80 mg tafamidis meglumine (48.8 mg tafamidis), 20 mg tafamidis meglumine (12.2 mg tafamidis), or matching placebo and assessed for the

Received September 12, 2019; revised manuscript received October 6, 2019; accepted October 8, 2019; J-STAGE Advance Publication released online November 16, 2019
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primary outcome of all-cause death followed hierarchically by cardiovascular-related hospitalization. At 30 months, the patients randomized to tafamidis (both doses pooled) had a 13.4% absolute reduction in overall mortality and a 22% absolute reduction in yearly cardiovascular hospitalization at 30 months as compared with those who received placebo. No important safety concerns were observed in the tafamidis group. The benefits in overall survival and cardiovascular hospitalization were observed after 18 months, although symptoms appeared to improve by 6 months.

ATTR cardiac amyloidosis, once thought to be a rare disease, is being increasingly recognized through enhanced clinical awareness, improved diagnostic imaging, and the emergence of effective treatment strategies. It is often an unrecognized cause of diastolic heart failure in the elderly, although the actual number of patients with ATTR cardiac amyloidosis is presently unknown. A definitive diagnosis requires a tissue biopsy to identify amyloid deposits. In addition, whether the precursor protein of amyloid deposits in the tissue is TTR must be confirmed and excluded by cardiovascular-related hospitalization. At 30 months as compared with those who received placebo. No important safety concerns were observed in the tafamidis group. The benefits in overall survival and cardiovascular hospitalization were observed after 18 months, although symptoms appeared to improve by 6 months.

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In patients with New York Heart Association (NYHA) functional classification III, treatment may have a lower efficacy than in those with NYHA class I/II.

Treatment efficacy and safety in patients with NYHA class IV have not been established.

The necessity of tafamidis administration should be determined after fully understanding the mechanism of action of the drug and the relationship between the NYHA functional classification and the efficacy suggested in clinical trials, taking into account the patient’s condition.

It should be used in cases where the administration of tafamidis is considered appropriate, under the supervision of a physician who is familiar with the diagnosis and treatment of ATTR cardiac amyloidosis.

**JCS Institutional and Physician Standards for Tafamidis Treatment**

Early referral to a cardiovascular center of expertise is mandatory for timely treatment. To properly administer tafamidis under accurate diagnosis, the Japanese Circulation Society has set institutional and physician standards for introducing tafamidis to patients with ATTR cardiac amyloidosis and decided to conduct a post-marketing surveillance.

**I. Institutional Requirements**

As a general rule, only facilities that meet all of the following 6 requirements are permitted to start administration of tafamidis meglumine.

1. Cardiologist training facility certified by the Japanese Circulation Society.
2. Radiologist general training institute certified by the Japan Radiological Society.
3. Pathologist training facility certified by the Japan Society of Pathology.
4. Hematologist Training Facility certified by the Japanese Society of Hematology.
5. Neurologist educational facilities certified by the Japanese Society of Neurology.
6. Institution performs >15 cases of myocardial biopsy annually.

**II. Physician Requirements**

Physicians who fulfill the requirements (1) or (2) and commit to (3) are permitted to start administration of tafamidis meglumine.

1. Physicians who have used tafamidis meglumine for ATTRv amyloidosis before the approval date of indication expansion for ATTR cardiac amyloidosis.
2. Physicians who have identified at least 3 cases of ATTR cardiac amyloidosis by identifying the TTR precursor protein by immunohistological staining or mass spectrometry from a biopsy tissue sample obtained at their own institution or by asking another institution for identification.
3. Registration of all administration cases.

Continuous therapy for patients who have been introduced to the treatment can be prescribed at a cooperative hospital, considering the convenience of patients, but the facility and the physician that introduced tafamidis meglumine are responsible for maintaining follow-up of the clinical course.
Use of Tafamidis for ATTR Cardiac Amyloidosis

Disclosures
T.I., Y.S., Y.A., H.T. and K.F. received remuneration from Pfizer Inc.

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