Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value

Background and Scope

Hereditary transthyretin amyloidosis (hATTR) is a condition caused by deposits of transthyretin (TTR), a protein that is present in all human serum. Genetic mutations can increase the likelihood of TTR misfolding into an insoluble beta-pleated sheet, which deposits in body tissues. hATTR produces a spectrum of clinical manifestations ranging from pure polyneuropathy to selective heart involvement, and affects at least 10,000 people worldwide[1,2]. Due to under-diagnosis, the true number is likely greater. There are three major forms of transthyretin amyloidosis, which are distinguished by their symptoms and the body systems they affect: 1) hereditary ATTR (hATTR) amyloidosis, formerly known as familial amyloid polyneuropathy (FAP); 2) familial amyloid cardiomyopathy (characterized by arrhythmias, an enlarged heart [cardiomegaly], or orthostatic hypertension; and occasionally mild peripheral neuropathy); and 3) leptomeningeal amyloidosis (primarily affects the central nervous system, e.g. stroke, seizures, dementia).[3]

This review focuses on hATTR as the neurologic symptoms are among the most disabling, and promising new treatments are on the horizon. hATTR amyloidosis is a rare, progressive, and fatal hereditary disorder. Deposition of TTR-derived amyloid fibrils produces severe, disabling sensorimotor disturbances (loss of sensation, pain, muscle weakness and loss of ambulation) and varying degrees of autonomic, cardiovascular, gastrointestinal, renal, leptomeningeal and bowel or bladder dysfunction.[4] If untreated, death occurs approximately 10 years after onset of hATTR amyloidosis. The age at onset varies from the second to ninth decade of life, with a median survival of 5 –15 years. Researchers have estimated mean health care costs of 125,645€ ($154,819) per untreated patient.[5]

While there is no treatment available that reverses damage caused by amyloid deposits, there are treatments that may prevent or delay progression.[6] The liver produces almost all of the body's TTR. Therefore, liver transplantation, which removes the abnormal TTR, is one potential treatment. Limitations of this approach include transplant availability, disease progression following transplant, and substantial morbidity and mortality associated with transplant itself.

Diflunisal, a generic nonsteroidal anti-inflammatory drug (NSAID) which stabilizes transthyretin tetramers, is currently considered first-line treatment. Use of diflunisal to treat hATTR is off-label. In a randomized trial of 130 patients with symptomatic hATTR, diflunisal significantly reduced

progression of neurologic impairment at two years and preserved quality of life compared to placebo.[7]

Tafamidis, a TTR stabilizer administered orally once daily, is the only medicine approved to delay disease progression in hATTR, and is approved in the European Union and several South American and Asian countries.[8-10] However, the US FDA did not approve its use during a filing in 2012, due to limited efficacy data.[11] In addition, there are two investigational agents currently under FDA review for hATTR: patisiran (Alnylam Pharmaceuticals) and inotersen (Ionis Pharmaceuticals). Patisiran is an RNA interference therapeutic.[12,13] An IV infusion, patisiran suppresses the production of both mutant and nonmutant forms of TTR. Inotersen is an antisense oligonucleotide (ASO) that complements exactly the messenger RNA (mRNA) that encodes for TTR. A once weekly subcutaneous injection, inotersen binds the mRNA leading to degradation of TTR by RNAase. In Phase III clinical trials, both agents improved measures of neuropathy impairment, the primary study outcome. Secondary endpoints included body mass index (BMI) and albumin levels (a measure of nutritional status), as the product of serum albumin concentration and BMI correlates with survival in hATTR.[14] Measures of cardiac function were among exploratory outcomes in the trials.

As the first agents targeting the underlying pathophysiology of hATTR, clinical interest in the use of patisiran and inotersen is likely to be high. However, there may be uncertainties related to the translation of surrogate outcomes to longer-term clinical benefit, the durability of such benefit, potential harms of treatment, and the costs associated with the use of these medications. All stakeholders will therefore benefit from a comprehensive review of the comparative clinical effectiveness, safety, and economic impact of patisiran and inotersen relative to standard care for hATTR.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients and their families, patient advocacy groups, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. Patients, patient advocates and researchers have conveyed that hATTR is a devastating illness that profoundly impacts all aspects of quality of life. Patients with hATTR are frustrated by loss of independence, the impact on family life (caring for older family members and worrying about children), and their inability to work. Patients also voice concern that there are currently no treatments approved in the US specifically for hATTR. Current off-label treatments are of limited efficacy, and patients often have difficulty travelling to a small number of Amyloid Centers of Excellence at academic medical centers in the US to receive treatment. A final scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders

throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Report Aim

This project will evaluate the health and economic outcomes of patisiran and inotersen for hATTR. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms - including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs - are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the finalized scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Analytic Framework

The general analytic framework for assessment of therapies for hATTR is depicted in Figure 1.1.

Figure 1.1. Analytic Framework: Therapies for Hereditary ATTR (hATTR) amyloidosis
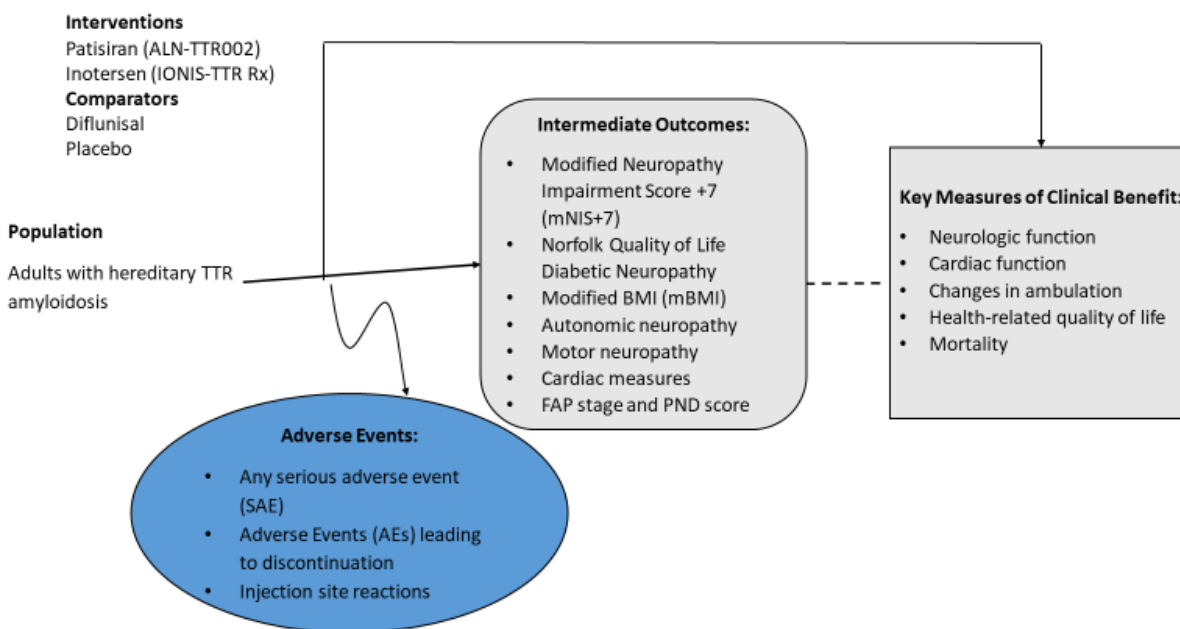
AE: adverse event, SAE: serious adverse event

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g. neuropathy impairment score), and those within the squared-off boxes are key measures of benefit (e.g., quality of life). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipse.

Populations

The population of focus for the review is adults with hereditary ATTR (hATTR) amyloidosis, formerly known as familial amyloid polyneuropathy (FAP).

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include. The full list of interventions is as follows:

- Patisiran

- Inotersen

Comparators

The comparator in clinical trials was placebo, reflecting best supportive care. Data permitting, we also intend to compare each of the agents to each other and to diflunisal.

Outcomes

The outcomes of interest are described in Table 1.1 below.

Table 1.1. Key Outcomes and Harms

Outcomes	Key Harms
Neuropathy (e.g., Modified Neuropathy Improvement Score)	Significant adverse events
BMI/albumin level	Adverse events leading to discontinuation
Living independently	Injection site reactions
Mobility	Thrombocytopenia (platelet count decrease) causing significant bleeding
Pain	
Ability to attend to activities of daily living	
Quality of life	
Cardiac function	
Mortality	

Timing

Evidence on intervention effectiveness will be derived from studies of at least one year's duration and evidence on harms from studies of at least three months' duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the United States.

Other Benefits and Contextual Considerations

Our reviews seek to provide information on other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in Table 1.2.

Table 1.2. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to "the comparator," there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic evaluation model to assess the cost-effectiveness of the treatments of interest (inotersen and patisiran) relative to conventional support therapy that has available clinical and economic evidence for the treatment of patients with hereditary ATTR (hATTR) amyloidosis, formerly known as familial amyloid polyneuropathy (FAP). A cohort of patients will transition between health states during predetermined cycles over a lifetime time horizon. The model will include one event, liver transplant, and 5 health states: (i) disease stage 1, where the patient does not require assistance with ambulation, (ii) disease stage 2, where the patient requires carer assistance or a walking aid, (iii) disease stage 3, where the patient is bed-bound, (iv) post-liver transplantation disease stage 1 and (v) death. The model will follow patients from treatment initiation until death, given available evidence. In addition, cost-effectiveness will be

estimated for shorter time horizons (e.g., five years) and if possible for patient subgroups reflecting heterogeneity within V30M populations.

Under ICER's modifications to the value assessment framework for treatments for ultra-rare diseases, we will consider dual "base cases," which will reflect the health system (i.e., a focus on direct medical care costs only) and societal perspectives. A societal perspective is included if appropriate data are available, and if it is anticipated that the impact of the treatment on patient and caregiver productivity, education, disability, and nursing home costs are substantial, and large relative to health care costs. If not assessed as a dual base case, a societal perspective will be considered in a scenario analysis.

Model inputs will be informed by existing clinical evidence and any published economic evaluations. Key model inputs will include clinical probabilities, overall survival, occurrence of adverse events, quality of life values, and health care costs. Treatment effectiveness will be estimated using published estimates and potentially meta-analysis of published evidence. Probabilities, costs, and other inputs may differ between treatments to reflect varying effectiveness between interventions; however, health state utility values will be consistent across interventions.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of life-years and quality-adjusted life years (QALYs) gained. Quality of life weights will be applied to each health state. The model will include direct medical costs, including but not limited to costs related to condition-related care and serious adverse events. Relevant pairwise comparisons will be made between treatments (when feasible), and results will be expressed in terms of the incremental cost per QALY gained, cost per life-year gained, and cost per intermediate outcome (e.g., neuropathy response) achieved.

In a separate analysis, we will explore the potential health system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment price and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating potential budget impact can be found at: http://icer-review.org/wp-content/uploads/2016/02/ICER-Value-Assessment-Proposed-Updates-Webinar-021317.pdf.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected by patisiran or inotersen, as these services will be captured in the economic model. Rather, we are seeking services used in the current management of transthyretin amyloidosis beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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