Injectable siRNA Approved for Lowering Cholesterol

The FDA has approved an injectable small interfering ribonucleic acid (siRNA) therapy for lowering low-density lipoprotein (LDL-C) in certain adults. It is the first siRNA in its class and one of the first developed for a nonpharmacological indication.

Inclisiran, marketed as Leqvio, is injected subcutaneously twice a year after 2 initial injections administered 3 months apart. It is indicated for adults with atherosclerotic cardiovascular disease (ASCVD) including those who have had myocardial infarction or strokes or for adults with heterozygous familial hypercholesterolemia (HeFH), who still require LDL-C reduction despite maximally tolerated statin therapy.

Developed by Novartis with Alnylam Pharmaceuticals, inclisiran is 1 of a handful of siRNA therapies that have been approved since the first in 2018. siRNA therapies work by interfering with messenger RNA involved in the synthesis of specific proteins. Inclisiran reduces the production of proprotein convertase subtilisin/kexin type 9, an enzyme produced in the liver that increases the blood level of LDL-C by binding with hepatocyte receptors that would capture LDL-C rather than release it.

Inclisiran was found effective in 3 randomized, double-blind, placebo-controlled trials that enrolled 3457 adults with HeFH or clinical ASCVD. In 2 phase 3 studies of ASCVD involving 3178 patients, the inclisiran groups saw average LDL-C reductions of 51.3% and 45.8% at day 510 compared with increases of 1% and 4%, respectively, in the placebo groups. In the HeFH phase 3 study involving 482 patients, the inclisiran group had an average LDL-C decrease of nearly 40% compared with an increase of 8% in the placebo group.

Adverse events were similar in the treatment and placebo groups. Injection site reaction, joint stiffness, urinary tract infection, diarrhea, bronchitis, pain in extremity, and difficulty breathing were the most common. Clinical trials of inclisiran's effects on cardiovascular morbidity and mortality are currently underway.

Therapy Approved for All Types of Severe Asthma

The first treatment for severe asthma that isn't limited to a specific type of severe asthma, such as patients with high eosinophil levels or specific allergic or biomarker status, has received FDA approval. It is also the first asthma treatment targeting thymic stromal lymphopoeitin, a molecule involved in airway inflammation.

Tezepelumab-ekko, marketed as Tezpiro, is a biologic injected subcutaneously every 4 weeks as an add-on maintenance therapy for patients aged 12 years or older with severe asthma. Developed by AstraZeneca and Amgen, it was approved by the FDA under priority review, meaning it presented a significant improvement over available options in safety or efficacy or was effective in preventing serious conditions or in enhancing patient adherence. It is under regulatory review in the European Union, Japan, and several other countries, according to a company statement.

Tezepelumab-ekko's safety and effectiveness were demonstrated in a phase 2 trial involving 550 patients and in a phase 3 trial involving 1061 patients, all with severe asthma. Participants in the phase 2 study received 1 of 3 doses of tezepelumab-ekko, 70 mg every 4 weeks, 210 mg every 4 weeks, 280 mg every 2 weeks, or placebo. Those in the phase 3 study received 210-mg tezepelumab-ekko or placebo every 4 weeks for 52 weeks.

Participants receiving tezepelumab-ekko in both trials had significant reductions in the annualized rate of asthma attacks compared with placebo. In the phase 3 trial, the treated group's exacerbation rate was 0.93 events per patient-year, or less than half the 2.10 rate in the placebo group. Among patients with low eosinophil counts, the exacerbation rate for treated patients also was significantly lower than for those who received placebo. Fewer asthma attacks requiring emergency department visits and/or hospitalization occurred with tezepelumab-ekko treatment than with placebo.

Adverse events did not differ meaningfully between the 2 groups in the phase 3 trial. Adverse events associated with tezepelumab-ekko included nasopharyngitis and upper respiratory tract infection.

Draft Guidance on Remote Data Acquisition in Trials

The FDA has issued draft guidance for the use of digital health technologies (DHTs) for remote data acquisition in clinical investigations.

DHTs enable remote acquisition of data using computer platforms, electronic connectivity, software, and/or sensors. As such, they have the potential to greatly expand the scope and availability of clinical investigations by enabling capabilities such as 24-hour monitoring and geographically dispersed trials.

The guidance addresses issues including selection of DHTs for remote data collection, verifying and validating their accuracy and reliability, relating their findings to end points, ensuring their usability and acceptability by study participants, and identifying and managing their risks in clinical investigations including privacy risks. Although not binding on investigators, sponsors, or other interested parties, the guidance, when finalized, will reflect the FDA's current thinking on DHT use in clinical investigations for developing drugs, biologics, and devices.

The FDA is seeking comments on the draft guidance through March 22.

~ Howard D. Larkin

Note: Source references are available through embedded hyperlinks in the article text online.