UMASS MEDICAL SCHOOL Commonwealth Medicine

First Wave of Novel Drugs for NASH Does Not Live Up to Expectations, Clinical Pharmacy Service's Pipeline Monitoring Team Finds

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Overview

Nonalcoholic steatohepatitis (NASH) is an advanced form of nonalcoholic fatty liver disease (NAFLD) that is estimated to affect 5 - 21 million people in the United States. The condition is associated with cardiometabolic syndrome and can progress to liver cirrhosis, liver failure, and liver cancer. It is the second leading indication for liver transplants in the United States.

Although NASH is quite common and may be deadly, most patients are undiagnosed due to the asymptomatic nature of the condition, the need for a liver biopsy to confirm the diagnosis, and a lack of FDA-approved treatment options. To date, pharmacological options for NASH have been limited to off-label use of pioglitazone and vitamin E for biopsy-proven NASH only.

In 2016, NASH was widely discussed in the managed care community when one promising NASH treatment, obeticholic acid, was FDA-approved under the brand name Ocaliva® for another, less common liver disease known as primary biliary cholangitis. Limited efficacy and safety data for NASH and a high list price of $69,350 per year raised concerns among payers about potential off-label use.

What does the data show?

Treatment with obeticholic acid showed mixed results in the phase III REGENERATE study in which only the highest dose improved fibrosis while failing to achieve NASH resolution at 18 months. Similarly, in a phase III RESOLVE-IT study, elafibranor did not meet the primary endpoint of NASH resolution at week 72. Another investigational agent, selonsertib, also failed to meet the primary efficacy endpoint of fibrosis improvement at week 48 in STELLAR-3 and STELLAR-4 studies.

In June 2020, the FDA issued a Complete Response Letter regarding the New Drug Application for obeticholic acid to treat fibrosis due to NASH, noting that the drug's predicted benefit does not outweigh potential risks. In July 2020, the manufacturer of elafibranor terminated the Phase III RESOLVE-IT study as the results were unlikely to provide sufficient support for drug approval.

What value does obeticholic acid offer to payers for NASH?

A 2016 cost-effectiveness analysis of obeticholic acid for NASH based on data from a phase II study conducted by the Institute for Clinical and Economic Review found that a discount of more than 90 percent from the annual list price would be required to achieve a cost-effectiveness ratio of $150,000/quality adjusted life year.

Using disease prevalence data and predicted cost information for reference therapies from other disease states, the Commonwealth Medicine Clinical Pharmacy Services team produced an annualized budget impact forecast of $0.18 to $0.32 per member per year for a health plan with 100,000 members (Table 1).

Table 1. Annualized Budget Impact (100,000 Member Plan)

Drug Name	Key Assumptions	Projected No. of Members	Annual Cost/ Member	Estimated PMPY*
Obeticholic acid	• Disease prevalence: ~4% in the U.S. • Diagnosed: ~5% • Low drug update	4	$10,000 to $18,000	$0.18 to $0.32

**Adjusted for potentially suboptimal adherence to treatment for an asymptomatic condition*

Dispelling the hype around the first wave of NASH drugs

Although novel therapies hold the promise of halting the progression of liver fibrosis and preventing NASH complications, to date, the data has been mixed, and many questions remain. What is the long-term safety of these drugs, and what is their impact on mortality and liver-related complications? Who are the ideal candidates for treatment, and can they be identified using noninvasive diagnostic tools? Will patients remain adherent to potentially life-long therapy for an asymptomatic condition?

Despite unfavorable study results highlighted above, the NASH pipeline is rich. With the prevalence of NASH forecast to increase by 63 percent over the next decade and the potential for high drug costs, NASH drugs will represent a challenge for payers once the FDA approves them. If cenicriviroc and resmetirom continue to progress in development, they may become the first drugs approved for NASH in 2021 or 2022. Combination therapy is also being actively studied, which may increase drug costs.

Although they were much-hyped, the first wave of novel NASH drugs did not live up to expectations. The result highlights the need for continued monitoring and comprehensive assessment of clinical trial and cost-effectiveness data to ensure future NASH therapies offer value to payers. Possible drug management strategies that should be considered by payers include prior authorization requirements to confirm the diagnosis, promote adherence to the labeled drug indications, and ensure specialist consultation, as well as a refill reminder outreach.

How can we help you stay on top of the latest developments in the drug pipeline?

As part of our comprehensive drug pipeline monitoring and budget impact forecasting program, the Clinical Pharmacy Services team closely follows NASH drugs and many others currently in development.

To learn more about pipeline intelligence and budget impact forecasting services offered by Clinical Pharmacy Services, contact Bonnie Greenwood, PharmD, BCPS, Director, Clinical Programs.

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