Value Assessment of Emerging Treatments for Nonalcoholic Steatohepatitis: Lessons From Institute for Clinical and Economic Review Evaluations

EE104

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Aims

ICER conducted 3 economic evaluations over the past decade for OCA and resmetirom for NASH (now known as MASH after a recent nomenclature change[1]) with mild to significant fibrosis (F1-F3) in the US.[2-4]

Our objective was to review the CE modeling approaches, data sources, and assumptions across ICER evaluations and identify implications and recommendations for future CE analyses in NASH.

Background

- NAFLD is the most common chronic liver condition worldwide; its progressive form, NASH, is characterized by steatosis, inflammation, hepatocyte injury (ballooning), and fibrosis. NASH affects roughly 1 in 20 adults in the US and 1 in 7 patients with diabetes.[5]
- Disease progression can include liver cirrhosis and cancer, where liver transplant is the only therapy option. A diagnosis of NASH is also associated with an increased risk of CV events, the leading cause of death for patients with NASH.[6]
- Treatments for precirrhotic NASH submitted for regulatory approval in the US in recent years include OCA (Ocaliva, Intercept Pharmaceuticals, Inc.), which was denied approval in 2023,[7] and resmetirom (Rezdiffra, Madrigal Pharmaceuticals, Inc.), which became the first approved treatment for NASH in March 2024.[8]

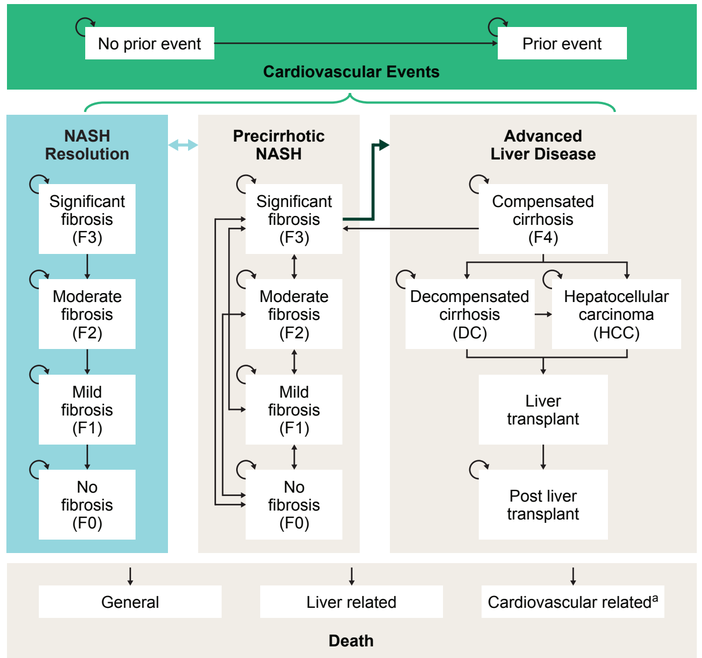
Methods

- We reviewed the CE analyses from the final evidence reports for the 2016 and 2020 ICER evaluations of OCA[2,3] and the 2023 ICER evaluation of OCA and resmetirom.[4]
- We extracted details on the following elements from each evaluation:
  - **Model structure:** Details included modeled health states and transitions.
  - **Natural history sources:** Model inputs included transition probabilities for improvement and worsening of fibrosis in precirrhotic health states, progression to advanced liver disease, CV event risk, and liver-specific mortality. We noted whether sources for inputs were NASH specific or for other chronic liver diseases such as hepatitis C.
  - **Efficacy endpoints:** We recorded whether efficacy focused on resolution of NASH, improvement of fibrosis, worsening of fibrosis, or a combination of these.
  - **Treatment discontinuation and stopping rules:** Details included which health states were indicated for treatment and whether patients in more advanced health states were permitted to continue treatment.
  - **Cost and utility sources:** We noted whether sources for health state–specific direct medical costs and utilities were NASH-specific or for other chronic liver diseases such as hepatitis C.
  - **CE results:** Results included discounted LYs, QALYs, treatment years, nondrug costs, and total costs; incremental cost per QALY gained; and threshold VBP estimates.

Results

- The model structures in all 3 evaluations used similar Markov-based frameworks with health states defined by fibrosis stages and cirrhosis complications (Figure 1).
  - NASH resolution health states were included in 2016 only, and CV events were included in 2020 and 2023.
- Natural history sources were similar across evaluations. Overall, more NASH-specific sources were used in the 2020 and 2023 evaluations than in the 2016 evaluation.
  - In all 3 evaluations, transition probabilities for precirrhotic health states were derived from a systematic review and meta-analysis of paired-biopsy studies that included patients with NAFLD and NASH.[9]
  - Many transition probabilities between advanced liver disease health states (i.e., F4, DC, and HCC), liver transplant, and death were derived from non-NASH (e.g., hepatitis C) studies in 2016. In 2020 and 2023, all sources were from NASH- or NAFLD-specific studies.
  - In 2016, overall survival of patients with NASH was calibrated to a NASH cohort followed for 16 years[10] to account for higher CV risk in patients with NASH than the general population. In 2020 and 2023, patients with a prior CV event were assumed to be at an increased risk for recurrent CV events and death.
- Efficacy endpoints shifted from NASH resolution without worsening of fibrosis in 2016 to improvement and worsening of fibrosis in 2020 and 2023.
  - Efficacy was applied as differences relative to natural history transition probabilities in all 3 evaluations. In 2023, an unadjusted indirect comparison was used for resmetirom using the placebo arm from the OCA phase 3 clinical trial as an anchor.
  - In 2020 and 2023, cycle-specific CV risk was adjusted using a relative risk per change in low-density lipoprotein cholesterol from baseline in the OCA-treated cohort.
- Treatment discontinuation and stopping rules varied significantly.
  - In 2016, there was no annual discontinuation rate, and treatment continued until F4. In 2020, there was no annual discontinuation rate, and treatment continued until DC or HCC. In 2023, there was 17% discontinuation per year,[11,12] and treatment continued until F4.
- Cost and utility sources evolved over time as NASH-specific estimates became available.
  - In 2016, health state–specific costs and utilities were obtained from hepatitis C studies. In 2020 and 2023, health state–specific costs and utilities were obtained from NASH- or NAFLD-specific studies.
- When comparing OCA with SOC (in common across analyses), incremental CE ratios decreased (from $2,748,300 to $568,000 per QALY gained) and threshold VBP estimates increased (from $5,100 to $38,200 per year) across the successive evaluations (Table 1).
  - The largest driver of the changes in CE estimates across evaluations was different estimates of time on treatment due to changes in discontinuation and stopping rules.
  - In one-way sensitivity analyses, CE estimates were sensitive to proportion of patients with NASH resolution for SOC and OCA (2016), SOC transition probabilities for fibrosis improvement and worsening (2020 and 2023), utilities for precirrhotic health states and F4 (2020 and 2023), and annual discontinuation rates (2020 and 2023).

Figure 1. Model Structures Across ICER Evaluations



Note: Resolution health states (in blue) were included only in the 2016 evaluation. History of CV event health states (in green) were included only in the 2020 and 2023 evaluations. Health states in gray were included in all 3 analyses.

[a] CV-related death was accounted for in 2016 by a calibration parameter applied to general mortality. In 2020 and 2023, CV-related death was modeled explicitly.

Table 1. Characteristics, Settings, and Model Outcomes of ICER Evaluations

	2016 evaluation[2]		2020 evaluation[3]		2023 evaluation[4]		
Characteristics and settings							
Population at baseline	NASH F1 (39%), F2 (27%), or F3 (34%) Age = 49 years		NASH F2 (45%) or F3 (55%) Age = 55 years		NASH F2 (45%) or F3 (55%) Age = 55 years		
Comparators	OCA vs. SOC		OCA vs. SOC		OCA and resmetirom vs. SOC		
Treatment cost	OCA: $69,350/year		OCA: $80,340/year		OCA: $85,000/year Resmetirom: $19,000/year		
Treatment effect	138% increase (OCA vs. SOC) in NASH resolution without fibrosis worsening		65% increase (OCA vs. SOC) in fibrosis improvement 38% decrease (OCA vs. SOC) in fibrosis worsening		65% (OCA) and 52% (resmetirom) increase (vs. SOC) in fibrosis improvement 38% (OCA) and 57% (resmetirom) decrease (vs. SOC) in fibrosis worsening		
Treatment stopping	No discontinuation; treat until F4		No discontinuation; treat until DC or HCC		17% discontinuation/year (for both); treat until F4		
Model outcomes	**OCA**	**SOC**	**OCA**	**SOC**	**OCA**	**Resmetirom**	**SOC**
LYs (discounted)	NR	NR	14.22	13.62	14.88	15.05	14.56
QALYs (discounted)	11.02	10.91	9.92	9.43	10.47	10.66	10.05
Treatment years (discounted)	NR	–	~11.0 (derived)	–	~3.8 (derived)	~4.0 (derived)	–
Nondrug costs (discounted)	NR	$70,300	$230,000 (derived)	$367,000	$359,000 (derived)	$340,000 (derived)	$439,000
Total costs (discounted)	$371,000	$70,300	$1,094,000	$367,000	$676,000	$416,000	$439,000
Incremental $/QALY gained	$2,748,300	–	$1,482,000	–	$568,000	Dominant	–
VBP (at $150,000/QALY gained)	$5,100/year	–	$19,100/year	–	$38,200/year	$47,100/year	–

Conclusions

- Among the changes in modeling approaches, data sources, and assumptions across ICER evaluations in NASH, differences in treatment discontinuation and stopping rule assumptions appeared to have the greatest impact on economic value.
  - Future CE analyses of treatments for NASH should use clinically realistic discontinuation rates and stopping rules and include sensitivity analyses on these influential parameters.
  - Other notable changes between the 2016 and 2020 evaluations included the evolution of efficacy endpoints to focus on fibrosis changes and the addition of CV events.
  - Future CE analyses also should consider treatment effect on CV risk and other potential treatment benefits such as weight loss.
- Although more NASH-specific sources were used to inform model inputs by 2023, data gaps persist, including the following:
  - Studies that focus on the natural history of patients with NASH and advanced liver disease, in particular health state–specific fibrosis improvement and worsening transition probabilities and liver-related mortality for precirrhotic health states; transition probabilities associated with the DC health state; and health state–specific CV risks.
  - Studies that focus on the natural history of patients with NASH and common comorbidities (e.g., CV disease, diabetes, and obesity).
  - Health state–specific utilities, particularly for patients with NASH and advanced liver disease.

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Abbreviations

CE, cost-effectiveness; **CV**, cardiovascular **DC**, decompensated cirrhosis; **F1-F3**, mild to significant fibrosis; **F4**, compensated cirrhosis; **HCC**, hepatocellular carcinoma; **ICER**, Institute for Clinical and Economic Review; **LY**, life-year; **MASH**, metabolic-dysfunction associated steatohepatitis; **NAFLD**, nonalcoholic fatty liver disease; **NASH**, nonalcoholic steatohepatitis; **NR**, not reported; **OCA**, obeticholic acid; **QALY**, quality-adjusted life-year; **SOC**, standard of care; **US**, United States; **VBP**, value-based price.

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