Cost-effectiveness of obeticholic acid for the treatment of non-alcoholic steatohepatitis: An early economic evaluation

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ABSTRACT

BACKGROUND: Currently, there are no pharmacological options available for the treatment of non-alcoholic steatohepatitis (NASH). In the 18-month interim analysis of an ongoing randomized, placebo-controlled phase 3 trial (REGENERATE), early results demonstrated that obeticholic acid (OCA) 25 mg significantly improved fibrosis with no worsening of NASH among patients with NASH and fibrosis compared with placebo (PBO). This study aimed to assess the potential cost-effectiveness of OCA compared with PBO in NASH patients. METHODS: A state-transition model was developed to perform a cost-utility analysis comparing two treatment strategies, PBO and OCA 25 mg, from a Canadian public payer perspective. The model time horizon was lifetime with annual cycle lengths. Cost and utility parameters were discounted at 1.5% annually. The efficacy data were obtained from the REGENERATE trial, and costs and utilities were derived from other published literature. Probabilistic and deterministic sensitivity analyses were performed to test the robustness of the model. RESULTS: Treatment with OCA led to reductions of 3.58% in decompensated cirrhosis cases, 3.95% in hepatocellular carcinoma, 7.88% in liver transplant, and 6.01% in liver-related death. However, at an annual price of CAD $36,000, OCA failed to be cost-effective compared with PBO at an incremental cost-effectiveness ratio of $815,514 per quality-adjusted life year (QALY). An 88% reduction in drug price to an annual cost of $4,300 would make OCA cost-effective at a willingness-to-pay threshold of $50,000/QALY. CONCLUSIONS: OCA failed to be cost-effective compared with PBO, despite demonstrating clinical benefits due to a high drug cost. A significant price reduction would be needed to make the drug cost-effective.

KEYWORDS: cost-utility analysis; non-alcoholic steatohepatitis; obeticholic acid

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INTRODUCTION

Non-alcoholic steatohepatitis (NASH) is a form of fatty liver disease characterized by the presence of hepatic steatosis, inflammation, and hepatocyte injury (e.g., ballooning) with or without fibrosis (1). The presence of fibrosis in patients is the most important histological feature associated with long-term mortality and a worse prognosis, as increasing fibrosis can lead to cirrhosis. While patients may be asymptomatic and unaware of their liver condition, NASH can progress to more serious disease stages, such as decompensated cirrhosis (DC), liver failure, or hepatocellular carcinoma (HCC) (1,2).

With the increased availability of effective antiviral agents for hepatitis, non-alcoholic fatty liver disease (NAFLD) is becoming the most common cause of chronic liver disease in industrialized countries (3). In Canada, it is estimated that 20% and 4% of the population have NAFLD and NASH, respectively (4,5). Current guidelines on the management of NAFLD recommend non-pharmacological measures consisting of lifestyle modifications, such as diet and exercise to promote weight loss, which have been found to reduce hepatic steatosis and other markers of liver injury (3). However, some patients may be unable to maintain such behaviour long-term, leading to the potential need for pharmacological therapy. With vitamin E and pioglitazone already being recommended for the treatment of NASH by the American Association for the Study of Liver Diseases, obeticholic acid (OCA), a farnesoid X receptor agonist, is currently being investigated as a potential new treatment for NASH in a global phase 3 study (REGENERATE) (6,7).

The REGENERATE trial is a multicentre, randomized, double-blind, placebo-controlled study assessing the efficacy of OCA 10 mg and 25 mg compared with placebo (PBO) in adult patients with definite NASH, an NAFLD activity score of at least 4, and stage F2 or F3 fibrosis (6). The average age of the population was 55 years and mainly consisted of Caucasians (6). Patients were excluded if cirrhosis, other chronic liver diseases, elevated alcohol consumption, or confounding conditions were present (6). A full description of the cohort may be found in the REGENERATE study (6).

METHODS

Study design

A state-transition model comparing two treatment strategies, OCA 25 mg daily and placebo, was developed to perform an early cost-utility analysis in adult patients with definite NASH and fibrosis. OCA-associated model parameters were derived from the REGENERATE trial, while other parameters were obtained from published literature (6). The model time horizon was lifetime to capture the consequences of a chronic disease. The cycle length of the model was yearly to reflect the annual transitions in disease states as often demonstrated in epidemiological studies (1,2). The analyses were performed from a Canadian public payer perspective following the guidelines for economic evaluation set by the Canadian Agency for Drugs and Technologies in Health (CADTH) (9).

Cohort

The study cohort was assumed to be identical to those reported in the REGENERATE trial. Notably, the cohort consisted of adults (≥18 years old) with definite NASH, NAFLD activity score of at least 4, and stage F2 or F3 fibrosis (6). The average age of the population was 55 years and mainly consisted of Caucasians (6). Patients were excluded if cirrhosis, other chronic liver diseases, elevated alcohol consumption, or confounding conditions were present (6). A full description of the cohort may be found in the REGENERATE study (6).

Treatment strategies

Two treatment strategies were explored in this study: OCA 25 mg and placebo (PBO). In the OCA arm, all patients were assumed to receive 25 mg daily. In the PBO arm, it was assumed that all patients were not treated with pharmacological interventions.

Decision model

A state-transition model was implemented using TreeAge Pro Healthcare 2020 decision analysis software (10). Eleven health states were implemented to reflect the natural history of NASH: stage F0–F1–F2–F3–F4 fibrosis, DC, HCC, liver transplant (LT), approval from regulatory bodies following the completion of the study, our study aimed to conduct an early economic evaluation of OCA 25 mg for the treatment of NASH in patients with fibrosis.
post-liver transplant (PLT), liver-related death (LRD), and non-liver death (Figure 1). All patients were assumed to be in the F2 or F3 state at the start of the model to reflect the study population of the REGENERATE trial (6).

**Model inputs**

**Efficacy**

All treatment-related probabilities were obtained from the REGENERATE study (6), while NASH-specific transition probabilities between health states were obtained from other published literature (Table 1). Probabilities for all-cause mortality were age-specific and obtained from Statistics Canada (11). To reflect NAFLD being a risk factor for chronic kidney disease, type 2 diabetes, and cardiovascular diseases, the model accounted for increased risk of non-liver-related deaths. Based on a recent meta-analysis of mortality rates in NAFLD patients, the model assumed the all-cause mortality rate in NASH patients would be 1.5 times higher than the average Canadian population (12).

**Costs**

CADTH reported the manufacturer’s submitted price for the approved indication of primary biliary cholangitis for both 5 mg and 10 mg tablets to be CAD $98.63 per tablet (13). As the drug cost does not appear to be dose-dependent and the indication-specific drug price for NASH is unavailable, we assumed in our model an average daily drug cost for once daily OCA 25 mg to also be $98.63, resulting in an annual price of $36,000. Costs associated with end-stage liver diseases, such as DC and HCC, were estimated from a hepatitis C study as NASH-specific data are unavailable (Table 1) (14). While NASH-specific end-stage liver disease costs in the United States and Europe have previously been reported and widely cited in the literature, it is important to note that these costs were also derived from hepatitis C studies (15). All currencies are represented in Canadian dollars (CAD$) unless otherwise specified.

**Utilities**

Due to the unavailability of literature on health utilities in NASH patients, utility parameters for non-cirrhotic NASH cases were derived from a type 2 diabetes study (16). Similarly, utility parameters related to end-stage liver diseases were informed from a hepatitis C study as, regardless of the initial diagnosis, the utility for end-stage liver diseases would be expected to be similar (Table 1) (17).

**Modelling assumptions**

In alignment with the REGENERATE trial, we assumed that only patients with NASH and fibrosis were treated with either OCA or PBO (6). Once patients progressed to F4 or improved to F0–F1 fibrosis, patients were taken off the treatment. As in the trial, patients with NASH stages F0 or F4 were excluded, and patients with stage F1 were not included in the REGENERATE 18-month interim analysis, although they are included in the
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Table 1: Key model input parameters

| Parameter                                                   | Point estimate | Lower limit | Upper limit | Source                      |
|-------------------------------------------------------------|----------------|-------------|-------------|-----------------------------|
| **Health state transition probabilities**                   |                |             |             |                             |
| Natural 1-stage fibrosis progression                        | 0.090          | 0.060       | 0.120       | Younossi et al (1)          |
| F4 to DC                                                    | 0.0371         | 0.026       | 0.0503      | Sanyal et al (22)           |
|                                                            |                |             |             | Bhala et al (23)            |
| F4 to HCC*                                                  | 0.026          | 0.020       | 0.033       | Ascha et al (24)            |
| DC to HCC*                                                  | 0.026          | 0.020       | 0.033       | Ascha et al (24)            |
| DC to LT*                                                   | 0.023          | 0.017       | 0.029       | CEPAC (20)                  |
| DC to LRD                                                   | 0.20           | 0.16        | 0.24        | Sanyal et al (22)           |
| HCC to LT*                                                  | 0.040          | 0.030       | 0.050       | Lang et al (25)             |
| HCC to LRD (year 1)                                        | 0.61           | 0.371       | 0.664       | Younossi et al (26)         |
|                                                            |                |             |             | Ries et al (27)             |
| HCC to LRD (subsequent years)                               | 0.162          | 0.1103      | 0.2306      | Younossi et al (26)         |
|                                                            |                |             |             | Ries et al (27)             |
| LT to LRD*                                                  | 0.160          | 0.120       | 0.200       | Charlton et al (28)         |
| PLT to LRD*                                                 | 0.071          | 0.053       | 0.088       | Charlton et al (28)         |
| HR of NAFLD versus non-NAFLD                                | 1.50           | 1.31        | 1.73        | Liu et al (12)              |
| **Treatment-related probabilities**                         |                |             |             |                             |
| OCA 1-stage fibrosis improvement*                           | 0.142          | 0.107       | 0.178       | Younossi et al (6)          |
| OCA 2-stage fibrosis improvement*                           | 0.063          | 0.047       | 0.079       | Younossi et al (6)          |
| Pruritus due to OCA*                                        | 0.289          | 0.216       | 0.361       | Younossi et al (6)          |
| Discontinue OCA due to pruritus*                            | 0.081          | 0.060       | 0.101       | Younossi et al (6)          |
| PBO 1-stage fibrosis improvement*                           | 0.076          | 0.057       | 0.095       | Younossi et al (6)          |
| PBO 2-stage fibrosis improvement*                           | 0.032          | 0.024       | 0.040       | Younossi et al (6)          |
| Pruritus due to PBO*                                        | 0.117          | 0.088       | 0.147       | Younossi et al (6)          |
| **Costs (CAD$)**                                            |                |             |             |                             |
| OCA*†                                                       | 36,000         | 27,000      | 45,000      | CADTH (13)                  |
| Treatment of pruritus*‡                                      | 480.60         | 360.45      | 600.75      | CADTH (13)                  |
| F4*†                                                       | 17,844         | 13,383      | 22,305      | Wong et al (14)             |
| DC*†                                                       | 43,908         | 32,931      | 54,885      | Wong et al (14)             |
| HCC*†                                                      | 50,856         | 38,142      | 65,570      | Wong et al (14)             |
| LT*†                                                       | 54,468         | 40,851      | 68,085      | Wong et al (14)             |
| PLT*†                                                      | 19,400         | 14,550      | 24,250      | Wong et al (14)             |
| **Utilities**                                               |                |             |             |                             |
| NASH non-cirrhosis (F0–F1–F2–F3)                            | 0.80           | 0.62        | 0.98        | Zhang et al (16)            |
| F4                                                          | 0.76           | 0.72        | 0.80        | Hsu et al (17)              |
| DC                                                          | 0.65           | 0.61        | 0.69        | McLernon et al (29)         |
| HCC                                                         | 0.69           | 0.65        | 0.73        | Hsu et al (17)              |
| PLT                                                         | 0.75           | 0.70        | 0.79        | Hsu et al (17)              |
| Disutility associated with pruritus                         | −0.0304        | −0.0380     | −0.0228     | Sullivan et al (30)         |

* Range is ±25%
† Annual cost
‡ One-time cost

F0 = Stage 0 fibrosis; F1 = Stage 1 fibrosis; F2 = Stage 2 fibrosis; F3 = Stage 3 fibrosis; F4 = Stage 4 fibrosis
DC = Decompensated cirrhosis; HCC = Hepatocellular carcinoma; LT = Liver transplant; CEPAC = Comparative Effectiveness Public Advisory Council; LRD = Liver-related death; PLT = Post liver transplant; HR = Hazard ratio; NAFLD = Non-alcoholic fatty liver disease; OCA = Obeticholic acid; PBO = Placebo; CADTH = Canadian Agency for Drugs and Technologies in Health; NASH = Non-alcoholic steatohepatitis
ongoing trial (6). Furthermore, DC and HCC were assumed to occur only at stage F4 fibrosis.

Costs and health outcomes were discounted at a rate of 1.5% annually, per the CADTH guidelines (9). A willingness-to-pay (WTP) threshold of $50,000 per quality-adjusted life year (QALY) was imposed to determine the cost-effectiveness as it is a commonly referenced threshold considered to be reasonable for funding in Canada (18).

**Analytic strategy**

In accordance with the CADTH guidelines, the cost and effectiveness values of the probabilistic sensitivity analysis (PSA) were used to calculate the incremental cost-effectiveness ratio (ICER) in the base-case analysis (9). The PSA was performed using a Monte Carlo simulation for 10,000 iterations to determine the probability of OCA being cost-effective compared with PBO at a WTP of $50,000 per QALY. A threshold analysis was also performed to assess at what price OCA would become cost-effective. A one-way sensitivity analysis was also performed to identify the impact of each model parameter on the overall outcome of the study.

The number of end-stage liver disease cases, such as DC, HCC, LT, and LRD, were also tracked in the treatment and placebo arms in order to compare the changes in health outcomes with OCA treatment.

**RESULTS**

**Base-case analysis**

OCA 25 mg daily was compared with PBO in the base-case analysis. In the OCA arm, a microsimulation of 10,000 iterations resulted in 1,643 cases of DC, 1,290 HCC, 269 LT, and 2,047 LRD, while the PBO arm resulted in 1,704 cases of DC, 1,343 HCC, 292 LT, and 2,178 LRD. These model-generated estimations resulted in reductions in cases of 3.58% in DC, 3.95% in HCC, 7.88% in LT, and 6.01% in LRD. These model-generated estimates resulted in reductions in cases of 3.58% in DC, 3.95% in HCC, 7.88% in LT, and 6.01% in LRD with OCA treatment (Table 2).

In terms of cost-effectiveness, OCA had a mean annual cost of $230,345 and a mean effectiveness of 14.79 QALYs compared with PBO, which had a mean cost of $116,173 and a mean effectiveness of 14.65 QALYs. With an incremental cost of $114,172 and incremental effectiveness of 0.14 QALY, the base-case analysis resulted in an ICER of $815,514 per QALY, indicating that OCA failed to be cost-effective at a WTP threshold of $50,000 per QALY (Table 3).

**Threshold analysis**

A threshold analysis found that an 88% reduction in the annual cost of OCA to $4,300, or $11.78 per dose, would be needed for the treatment to be cost-effective at a WTP threshold of $50,000 per QALY (Table 3). To be considered cost-effective at a WTP threshold of $100,000 per QALY, the annual cost of OCA would need to be reduced by 82% to $6,380, or $17.48 per dose.

**Sensitivity analysis**

The 10 most sensitive model parameters on the overall outcome of the study are illustrated as a tornado diagram in Figure 2. The utility value of non-cirrhosis NASH state and treatment effects of OCA and PBO on F1 and F2 improvement were the four most sensitive parameters. The one-way sensitivity analysis indicated that none of the parameters affected the conclusion of the base-case analysis that OCA failed to be cost-effective compared with PBO. The PSA indicated that the probability of OCA being cost-effective at WTP thresholds of $50,000 and $100,000 per QALY was 0%. The PSA results are illustrated as a scatterplot in Figure 3.

Similar results were seen when the analysis was performed by applying the cost of OCA in the United States. According to the Micromedex REDBOOK, the cost of OCA is US $276.39 per tablet for both 5 mg and 10 mg strengths (19), making the annual cost of OCA 25 mg CAD $129,129. At this price, the ICER becomes CAD $3,068,897 per QALY, again making OCA not cost-effective at any reasonable WTP threshold.

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**Table 2: Changes in health outcomes between treatment strategies**

| Strategy            | DC    | HCC   | LT    | LRD   |
|---------------------|-------|-------|-------|-------|
| Placebo             | 1,704 | 1,343 | 292   | 2,178 |
| Obeticholic acid    | 1,643 | 1,290 | 269   | 2,047 |
| % reduction         | 3.58% | 3.95% | 7.88% | 6.01% |

Ten thousand simulations were performed to assess the changes in liver-related health outcomes between treatment with OCA and PBO.

DC = Decompensated cirrhosis; HCC = Hepatocellular carcinoma; LT = Liver transplant; LRD = Liver-related death
### Table 3: Base case and threshold cost-effectiveness analysis

| Strategy                      | Cost (CAD$) | Δ Cost   | QALY   | Δ QALY | ICER      |
|-------------------------------|-------------|----------|--------|--------|-----------|
| Annual OCA price: $36,000 (base case) |             |          |        |        |           |
| PBO                           | $116,173    | –        | 14.65  | –      | –         |
| OCA                           | $230,345    | $114,172 | 14.79  | 0.14   | $815,514/QALY |
| Annual OCA price: $4,300 (88% price reduction) |             |          |        |        |           |
| PBO                           | $116,173    | –        | 14.65  | –      | –         |
| OCA                           | $123,129    | $6,956   | 14.79  | 0.14   | $49,686/QALY |
| Annual OCA price: $6,380 (82% price reduction) |             |          |        |        |           |
| PBO                           | $116,173    | –        | 14.65  | –      | –         |
| OCA                           | $130,172    | $13,999  | 14.79  | 0.14   | $99,993/QALY |

A probabilistic sensitivity analysis of 10,000 iterations was performed for each scenario.

QALY = Quality-adjusted life year; ICER = Incremental cost-effectiveness ratio; OCA = Obeticholic acid; PBO = Placebo

**Figure 2:** Tornado diagram of 10 most sensitive model parameters on overall outcome of the study

NASH = Non-alcoholic steatohepatitis; Pr = Probability; OCA = Obeticholic acid; impr = Improvement; PBO = Placebo; prog = Progression; F4 = Stage 4 fibrosis; DCC = Decompensated cirrhosis; ICER = Incremental cost-effectiveness ratio; QALY = Quality-adjusted life year
DISCUSSION

We performed an early economic evaluation using a state-transition model that simulated the long-term outcomes of patients with NASH receiving OCA compared with PBO. Our analyses suggest that treatment with OCA 25 mg did improve patients’ health outcomes but at a significantly higher cost than PBO. At an ICER of $815,514 per QALY, OCA was not cost-effective at a WTP threshold of $50,000 per QALY.

It is important to consider the fact that the base-case analysis was performed using the cost of OCA for primary biliary cholangitis (PBC) in Canada due to the unavailability of the cost of the medication for OCA. Considering that PBC is a rare disease, it is reasonable to assume that the cost was listed at a much higher price than it would have been for a much more prevalent disease such as NASH. As such, it may be understood that, for NASH, OCA may be available at a more affordable price. The results of our threshold analysis to assess the price at which OCA will be cost-effective found that a reduction in annual cost from $36,000 to $4,300 and $6,380 will be needed to be cost-effective at WTP thresholds of $50,000 and $100,000 per QALY, respectively.

Our findings align with a 2020 report from the New England Comparative Effectiveness Public Advisory Council (CEPAC)—to our knowledge, the only other cost-effectiveness analysis of OCA for NASH, which also based the analysis on the REGENERATE trial and concluded the ICER to be US $1,756,000 per QALY (20). Like our model, the CEPAC model only included the 25 mg arm of the REGENERATE trial. While the CEPAC model was similar to our model overall, it did have a number of differences in design. Notably, our model assumed that complications such as DC, HCC, and LT could only develop in patients reaching stage F4 fibrosis, whereas the CEPAC model assumed that patients could transition to DC and HCC from stages F3 and F4 fibrosis (20). While such complications are possible from stage F3 fibrosis, we chose to simplify the model to only allow the transition from stage F4 as the probabilities of DC and HCC from stage F3 are so low (<1%). The CEPAC model also considered cardiovascular events, such as the risks of fatal and non-fatal myocardial infarction and stroke, using a combination of data from the REGENERATE trial, Framingham Heart Study risk calculators, American Heart Association statistics for heart disease and stroke, and risk ratio adjustments based on LDL-C level (20).

It is important to note that, while our model only considered OCA 25 mg and PBO, the ongoing REGENERATE trial includes an additional arm of OCA 10 mg. The decision to include only the OCA 25 mg arm in the model was based on the 18-month interim results, which showed that only the 25 mg arm met the primary end point of improvement in fibrosis with no worsening fibrosis (6). However, the effects of OCA from the interim analysis may be underestimated as improvement in fibrosis
is generally a slow process, thereby masking the long-term effects of OCA. Although not statistically significant, the OCA 10 mg arm did show improvement in fibrosis compared with the PBO arm (6).

Limitations
Some limitations exist in our model. First, we assumed that only patients with NASH in stage F2 or F3 fibrosis were treated. In our model, we tried to replicate the results from the REGENERATE trial, in which treatment was only indicated for patients with NASH and stage F1–F3 fibrosis. However, results on the treatment efficacy for patients in stage F1 fibrosis are yet to be released. As such, once patients progressed to F4 or improved to F0–F1, patients were taken off OCA in the model. Theoretically, patients would be able to re-initiate an intervention if they progressed back to stage F2–F3 fibrosis; however, in our model, we assumed that initiation of therapy only occurred at the beginning of the simulation.

Second, we assumed that patients could only progress to clinical outcomes such as DC or HCC once they reach stage F4 fibrosis even though the risk of developing clinical liver outcomes exists in any fibrosis stage (1). Due to these assumptions, our model may slightly underestimate the number of liver-related outcomes. However, while the development of HCC from non-cirrhotic NASH is possible, the annual risk is extremely low at less than 0.05%, making the impact minimal (15).

Third, our analysis only compared OCA to placebo despite current established or proposed treatment methods, such as lifestyle modifications, pioglitazone, or vitamin E (7). This was because OCA has not been studied in NASH patients except against placebo. This makes it difficult to fairly conduct an economic evaluation of OCA versus a comparator other than a placebo. An economic evaluation of OCA compared with pioglitazone or OCA in conjunction with lifestyle modifications may be warranted in the future when comparative data becomes available.

Last, with the availability of effective interventions for viral hepatitis, NAFLD will continue to become a more significant and prevalent form of liver disease. However, much remains unknown in the literature about NAFLD. A recent systematic review of 19 cost-effectiveness studies on NASH highlighted individual study limitations driven by a lack of NASH-specific data (21). A similar limitation was seen in our model in which data from other disease states, such as diabetes and chronic hepatitis C, were used as a proxy. More research is warranted to enhance the accuracy and reliability of future cost-effectiveness studies.

CONCLUSIONS
Our early economic evaluation showed that patients receiving OCA 25 mg had an increase in health outcomes compared with PBO but at a significantly higher cost. At an assumed cost of $36,000 per year, OCA was not cost-effective at a WTP threshold of $50,000 per QALY, and an 88% reduction in drug price would be necessary for OCA to be cost-effective.

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REFERENCES

1. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73–84. https://doi.org/10.1002/hep.28431. Medline:26707365

2. Perumpail BJ, Khan MA, Yoo ER, Cholankeril G, Kim D, Ahmed A. Clinical epidemiology and disease burden of nonalcoholic fatty liver disease. World J Gastroenterol. 2017;23(47):8263–76. https://doi.org/10.3748/wjg.v23.i47.8263. Medline:29307986

3. Leoni S, Tovoli F, Napoli L, Serio I, Ferri S, Bolondi L. Current guidelines for the management of non-alcoholic fatty liver disease: a systematic review with comparative analysis. World J Gastroenterol. 2018;24(30):3361–73. https://doi.org/10.3748/wjg.v24.i30.3361. Medline:30122876

4. Canadian Liver Foundation. Non-alcoholic steatohepatitis (NASH) [webpage on the Internet]. Markham, ON: Canadian Liver Foundation; 2020 [cited 2020 Feb 28]. https://www.liver.ca/patients-caregivers/liver-diseases/nash/.

5. Swain MG, Ramji A, Patel K, et al. Burden of nonalcoholic fatty liver disease in Canada, 2019-2030: a modelling study. CMAJ Open. 2020;8(2):E429-36. https://doi.org/10.9778/cmao.20190212. Medline:32518095

6. Younossi ZM, Loomba R, Rinella M, et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2019;394(10215):2184–96. https://doi.org/10.1016/S0140-6736(19)30341-7.

7. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328–57. https://doi.org/10.1002/hep.29367. Medline:28714183

8. Ratziu V, Sanyal AJ, Loomba R, et al. REGENERATE: design of a pivotal, randomised, phase 3 study evaluating the safety and efficacy of obeticholic acid in patients with fibrosis due to nonalcoholic steatohepatitis. Contemp Clin Trials. 2019;84:105803. https://doi.org/10.1016/j.cct.2019.06.017. Medline:31260793

9. Canadian Agency for Drugs and Technologies in Health (CADTH). Guidelines for the economic evaluation of health technologies: Canada - 4th edition [Internet]. Ottawa, ON: (CADTH); 2017 Dec 4 [cited 2021 Jul 26]. https://www.cadth.ca/node/101497.

10. TreeAge Software, LLC. TreeAge Pro Healthcare [Software]. Williamstown, MA: TreeAge Software, LLC; c2020 [accessed 2020 Jan 19]. https://www.treeage.com/product/treeage-pro-healthcare/.

11. Statistics Canada. Life tables, Canada, provinces and territories, 1980/1982 to 2016/2018. Catalogue no. 84-537-X - No. 002 [Internet]. Ottawa, ON: Statistics Canada; 2020 Jan 28 [cited 2020 Feb 1; accessed 2021 Jul 26]. Available from: https://publications.gc.ca/collections/collection_2020/statcan/84-537-x/84-537-x2019002-eng.pdf.

12. Liu Y, Zhong GC, Tan HY, Hao FB, Hu JJ. Nonalcoholic fatty liver disease and mortality from all causes, cardiovascular disease, and cancer: a meta-analysis. Sci Rep. 2019;9(1):11124. https://doi.org/10.1038/s41598-019-47687-3. Medline:31366982

13. Canadian Agency for Technologies and Drugs in Health (CADTH). Pharmacoeconomic review report obeticholic acid (Ocaliva). CADTH Common Drug Review. Ottawa, ON: CADTH; 2017 Aug. https://www.ncbi.nlm.nih.gov/books/NBK534952/.

14. Wong WWL, Haines A, Bremner K, et al. Health care costs associated with chronic hepatitis C virus infection: A real-world, population-based analysis in Ontario. CMAJ Open 2021;9:E167-E174. https://doi.org/10.9778/cmao.202000162.

15. Younossi ZM, Blissett D, Blissett R, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology. 2016;64(5):1577–86. https://doi.org/10.1002/hep.28785. Medline:27543837

16. Zhang P, Brown MB, Bilik D, Ackermann RT, Li R, Herman WH. Health utility scores for people with type 2 diabetes in U.S. managed
21. Johansen P, Howard D, Bishop R, Moreno SI, Buchholtz K. Systematic literature review and critical appraisal of health economic models used in cost-effectiveness analyses in non-alcoholic steatohepatitis: potential for improvements. Pharmacoeconomics. 2020;38(5):485–97. https://doi.org/10.1007/s40273-019-00881-7. Medline:31919793

22. Sanyal AJ, Banas C, Sargeant C, et al. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. Hepatology. 2006;43(4):682–9. https://doi.org/10.1002/hep.21103. Medline:16502396

23. Bhala N, Angulo P, van der Poorten D, et al. The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: an international collaborative study. Hepatology. 2011;54(4):1208–16. https://doi.org/10.1002/hep.24491. Medline:21688282

24. Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology. 2010;51(6):1972–8. https://doi.org/10.1002/hep.23527. Medline:20209604

25. Lang K, Danchenko N, Gondek K, Shah S, Thompson D. The burden of illness associated with hepatocellular carcinoma in the United States. J Hepatol. 2009;50(1):89–99. https://doi.org/10.1016/j.jhep.2008.07.029. Medline:18977551

26. Younossi ZM, Otgonsuren M, Henry L, et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. Hepatology. 2015;62(6):1723–30. https://doi.org/10.1002/hep.28123. Medline:26274335

27. Ries L, Young G, Keel G, Eisner M, Lin Y, Horner M. SEER survival monograph: Cancer survival among adults: U.S. SEER program, 1988-2001, patient and tumor characteristics. Bethesda, MD: National Cancer Institute; 2007.

28. Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for non-alcoholic steatohepatitis in the United States. Gastroenterology. 2011;141(4):1249–53. https://doi.org/10.1053/j.gastro.2011.06.061. Medline:21726509

29. McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. Med Decis Making. 2008;28(4):582–92. https://doi.org/10.1177/0272989X08315240. Medline:18424560

30. Sullivan PW, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. Med Decis Making. 2006;26(4):410–20. https://doi.org/10.1177/0272989X06290495. Medline:16855129