THOUGHT LEADERSHIP SERIES

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Despite numerous setbacks in developing effective treatments for metabolic dysfunction-associated steatohepatitis (MASH), recent breakthroughs hold promise in potentially altering the disease course and improving patient outcomes. This condition is correlated with the rising rates of cardiovascular disease. However, despite affecting millions of Canadians, there are no approved treatments.

Revising Terminology in the Face of an Evolving Landscape: MASH replaces NASH

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) were terms used to describe the presence of fat inside the liver, while excluding excessive alcohol consumption as the cause. The old terminology no longer reflected the growing research that identified the role of metabolic dysfunction as the significant driver to disease development. Therefore, multinational liver societies have changed the language from "non-alcoholic" to "metabolic dysfunction-associated".

Furthermore, the previous nomenclature has been found to be stigmatizing, due to the use of the word "fatty" to describe the disease. The associated stigma could hinder disease awareness and education among patients and healthcare professionals, as well as dissuade patients from seeking healthcare services.[1] Replacing that term with "steatotic", meaning fat accumulation in the liver, reflects the evolving understanding of this condition. These changes allow for a less biased approach which will improve diagnosis and treatment. NAFLD is now formally called metabolic dysfunction-associated steatotic liver disease (MASLD), while NASH is now MASH.[2]

Rising Tide of MASH

MASLD is a spectrum of progressive liver disorder. MASLD ranges from mild liver steatosis to more severe forms, including liver inflammation and fibrosis (found in MASH), cirrhosis (scarring of the liver), and eventually to end-stage liver dysfunction.

MASLD is one of the leading causes of liver disease worldwide, with a global prevalence estimated at 30%.[3] Among the patients with MASLD, about 5% are estimated to have progressed to MASH.[4] In Canada, there were close to 2 million estimated cases of MASH in 2019, which was expected to increase by 35% in 2030.[5] It is alarming that the number of patients at severe stages of MASH is expected to increase by 65%, from 349,000 cases to 578,000 cases between 2019 and 2030.[6]

Patients with metabolic disorders are at greater risk of developing MASLD. This condition affects more than 90% of patients with severe obesity, and approximately 70% of patients with type 2 diabetes (T2DM).[7] MASH carries a substantial risk of mortality not only from liver-related causes, but also from cardiovascular disease (CVD),

which is the predominant cause of mortality in these patients. Patients with MASH are 2.5 times more likely to develop fatal or non-fatal cardiovascular-related events such as heart attack or stroke.[8] The associated risk between CVD and MASH could further represent the growing evidence between the interrelationship observed in *cardiodiabesity* and other metabolic disease complications, as seen in individuals with impaired fat metabolism and increased insulin resistance.

Uphill Battle in Drug Development

The MASH therapeutic space has seen decades of failed treatments due to the complexity of the disease. Despite this, there is ongoing pipeline activity. Over 400 drugs are in preclinical and clinical stages of development. Among these, close to 20% are in Phase II and Phase III trials. There is a high unmet need for a MASH-focused treatment as there are still no approved medications in Canada.

The three key components that have been identified in disease development are metabolic dysfunction, inflammation, and fibrosis. Ideally, a potential MASH drug should be able to address these three components, and should have an acceptable long-term safety profile for chronic treatment.[9]

The most common off-label drugs prescribed are vitamin E and pioglitazone. Their long-term use is often limited by minimal data for vitamin E, and long-term safety concerns for pioglitazone which has long been associated with weight gain, heart failure, and fractures for its use in type 2 diabetes treatment.

Several other treatments have failed due to the reasons aforementioned. Initially approved for primary biliary cholangitis, obeticholic acid (OCALIVA®) was one of the two drug candidates in the race for market approval last year. Unfortunately, OCALIVA® was rejected by the FDA in June 2023, as it was determined that the drug's risk-benefit profile was not favourable. The decision was based on the drug failing to meet its primary endpoint. The drug was also found to be associated with side effects such as severe itching, abnormal blood lipid and sugar levels, and gallstone development. Other investigational drugs across different therapeutic classes showed promise in early clinical trials but ultimately failed to demonstrate efficacy in the later stages.

Innovations on the Horizon for MASH Treatment

The drug candidate that made it to the finish line is resmetirom. The FDA has approved resmetirom (REZDIFFRA®) as the first MASH treatment in March 2024. Resmetirom is an oral thyroid hormone receptor-beta (THRβ) agonist thought to enhance the liver's ability to metabolize fat. Its late-phase clinical trial is ongoing, but early results demonstrate that resmetirom therapy was associated with MASH resolution with no worsening of fibrosis in about 25% to 30% of patients. Unlike obeticholic acid, resmetirom had a reliable safety profile.[10]

There still remains a need to develop better treatments, given that only up to 30% of patients benefited from resmetirom. Industry analysts are predicting that manufacturers may establish partnerships to develop combination therapies that

target the multiple stages of MASH progression to increase their chances of market approval. Combination therapies for MASH treatment may result in a higher cost and thus create a larger financial impact for private payers when these therapies enter the Canadian market. Currently, the estimated annual cost of resmetirom is close to US$60,000, with its full approval dependent on the final results of the study. There is no submission under review for resmetirom by Health Canada at this time.

There are several drug candidates that target Peroxisome Proliferator-Activated Receptors (PPARs), Fibroblast Growth Factor 21 (FGF21), and GLP-1 receptor agonists (GLP1-RAs), which have been identified to be key regulators in liver metabolism, inflammation and fibrosis.

Table 1: MASH Pipeline Drugs

Drug Name	Route of Administration	Development Stage	Mechanism of Action	Significance of results
Resmetirom	Oral	FDA Approved since March 2024	THRβ agonist	• First-approved treatment for MASH • Resolution of symptoms and improvement in liver scarring
Lanifibranor	Oral	Phase III	Pan-PPAR activator	• First-in-class treatment • Improvement in MASH symptoms, but concerns over weight gain
Efruxifermin	Subcutaneous	Phase III	FGF21 analogue	• Improvement in liver scarring and may suggest reversal of liver cirrhosis
Pegozafermin	Subcutaneous	Phase III	FGF21 analogue	• Improvement in liver scarring and may suggest reversal of liver cirrhosis
Semaglutide	Subcutaneous	Phase III	GLP-1 agonist	• MASH is prevalent in patients with obesity and type 2 diabetes • Semaglutide is approved for diabetes (OZEMPIC®) and obesity management (WEGOVY®) • If successful, semaglutide could address all three interrelated diseases
Survodutide	Subcutaneous	Phase III	GLP-1/glucagon dual agonist	• Potential best-in-class treatment for MASH • Survodutide is also being investigated for the treatment of type 2 diabetes and obesity
Tirzepatide	Subcutaneous	Phase II	GLP-1/GIP dual agonist	• Tirzepatide is approved for diabetes (MOUNJARO®), though its obesity counterpart ZEPBOUND® is only approved in the United States • If successful, tirzepatide could follow the same path as semaglutide

Lanifibranor activates all three forms of PPARs and is undergoing phase III clinical trials. Previous results have deemed lanifibranor as safe and effective in MASH. However, due to its mechanism of action similar to pioglitazone, there have been growing concerns on weight gain (between 2.4 to 2.7 kg increase from baseline) which could have significant impact on the drug's success especially concerning patients with coexisting obesity.

Efruxifermin and pegozafermin are two leading FGF21 analogs in the MASH pipeline in their late phase trials. Both drug candidates have demonstrated MASH resolution and improvement in liver fibrosis in patients with moderate to severe disease. Early findings suggest that these drugs may reverse liver cirrhosis, which was previously thought to be an irreversible condition.

Lastly, GLP1-RAs are being investigated for the treatment of MASH, given their therapeutic efficacy in metabolic disorders such as in diabetes and obesity. There are ongoing phase III trials for semaglutide (OZEMPIC®/WEGOVY®) and survodutide, and a phase II trial for tirzepatide (MOUNJARO®/ZEPBOUND®). The latter two drugs are dual agonists, in which they activate glucagon receptors and glucose-dependent insulinotropic polypeptide (GIP) respectively, in addition to GLP-1 receptors. Semaglutide failed to meet their secondary endpoint in reducing liver fibrosis in their phase II trial, but this could change with longer treatment going into phase III. Lastly, survodutide has the potential to be a best-in-class treatment for MASH due to its top-line results, which demonstrated significant liver tissue healing and improvement in fibrosis.

Conclusion

MASH has been met by trial failures until the recent FDA approval of resmetirom. Following this success, many more investigational therapies are showing promise for the treatment of this complex disease. If approved, these therapies may revolutionize care as the prevalence of MASH is expected to increase. Private payers need to be aware of upcoming drugs, which address an unmet need, but also, the financial implications in the anticipated use of combination therapies for the management of MASH.

[1] American Association for the Study of Liver Diseases, Latin American Association for the Study of the Liver, European Association for the Study of the Liver. A call for unity: The path towards a more precise and patient-centric nomenclature for NAFLD. Hepatology (Baltimore, Md.) vol. 78,1 (2023): 3-5. doi:10.1097/HEP.0000000000000412

[2] Ibid.

[3] Younossi, Zobair M et al. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology (Baltimore, Md.) vol. 77,4 (2023): 1335-1347. doi:10.1097/HEP.0000000000000004

[4] Ibid.

[5] Swain, Mark G et al. Burden of nonalcoholic fatty liver disease in Canada, 2019-2030: a modelling study. CMAJ open vol. 8,2 E429-E436. 9 Jun. 2020, doi:10.9778/cmajo.20190212

[6] Ibid.

[7] Tilg, Herbert et al. NASH drug treatment development: challenges and lessons. The lancet. Gastroenterology & hepatology vol. 8,10 (2023): 943-954. doi:10.1016/S2468-1253(23)00159-0

[8] Mantovani, Alessandro et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. The lancet. Gastroenterology & hepatology vol. 6,11 (2021): 903-913. doi:10.1016/S2468-1253(21)00308-3

[9] Kingwell, Katie. NASH field celebrates 'hurrah moment' with a first FDA drug approval for the liver disease. Nature reviews. Drug discovery vol. 23,4 (2024): 235-237. doi:10.1038/d41573-024-00051-1

[10] Harrison, Stephen A et al. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. The New England journal of medicine vol. 390,6 (2024): 497-509. doi:10.1056/NEJMoa2309000