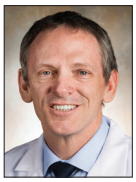
MASH IN FOCUS

Current Developments in the Management of Metabolic Dysfunction-Associated Steatohepatitis

Section Editor: Naim Alkhouri, MD

Insights Into Combination Therapy for Metabolic Dysfunction-Associated Steatohepatitis



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G&H What are the main reasons for using combination therapy for metabolic dysfunction-associated steatohepatitis?

MC Given the current landscape of efficacy across the different agents that have been studied in metabolic dysfunction-associated steatohepatitis (MASH), including the agent that was recently approved, the most important reason for using combination therapy is to improve efficacy. The agent that has been approved, resmetirom (Rezdiffra, Madrigal), appears to have fairly good tolerability and efficacy. However, efficacy is always something it is better to have more of. There are very few diseases in which therapeutic efficacy cannot be improved. Thus, efficacy is the primary motivation for combination therapy at this point.

Another reason to use combination therapy is to increase potency, which is slightly different from efficacy. Efficacy is the maximum effect (eg, in improvement in liver fibrosis) that a therapeutic agent can achieve, whereas potency, in essence, is the amount (eg, in milligrams) of agent required to produce that effect.

Additionally, combination therapy can be used to reduce side effects. For example, if one type of therapy induces dyslipidemia, it might be offset by a lipid-lowering agent used either in coformulation or coadministration.

G&H What considerations should be taken into account when choosing agents for potential combinations to treat MASH?

MC In general, the most important consideration is a different mechanism of action. It is preferable to have mechanisms of action that are complementary; an agent does not necessarily have to decrease or offset an adverse effect of the other agent it is being partnered with.

The MASH treatments currently being studied can be broadly divided into 3 types. One addresses delivery of harmful nutrients to the liver and consists of weight loss agents. These include glucagon-like peptide 1 (GLP-1) agonists, glucose-dependent insulinotropic polypeptide (GIP) agonists, and triple agonists with other mechanisms, for example, glucagon-like activity. Another type targets lipotoxicity with a direct- or indirect-acting lipotoxicity mechanism. This group includes thyroid hormone receptor-β (THR-β) agonists and fibroblast growth factor (FGF)19 and FGF21 agonists. Agents targeting lipotoxicity can also specifically target cholesterol-related inflammation. Reducing lipotoxicity can have pleiotropic or antifibrotic effects. Farnesoid X receptor (FXR) agonists were specific mediators of cholesterol toxicity, although the promise of this mechanism of action is fading. On the other hand, peroxisome proliferator-activated receptor (PPAR) agonists such as lanifibranor are showing promise. The third treatment type consists of direct antifibrotics. There has not been much success with pure antifibrotics such as simtuzumab (Gilead) to this point, but there is still hope for them in the future.

G&H How can the benefit of a combination be best predicted?

MC That is one of the most difficult questions in hepatology right now. Currently, the US Food and Drug Administration (FDA) only accepts histologic endpoints for late-phase clinical trials (ie, phase 3, possibly phase 2b). In phase 1 and phase 2a studies, and perhaps some phase 2b studies, noninvasive tests such as proton density fat

fraction (PDFF) can be used in conjunction with blood-based biomarkers such as transaminase levels depending on the mechanism of action of the drugs. For some purposes (eg, MASH resolution), PDFF is an outstanding biomarker of efficacy, but for others (eg, fibrosis response) it is much less consistently predictive. It is important to understand how a particular noninvasive test links with a specific mechanism of action. If a test is good and reliable, it can be used to plan for a phase 2b or phase 3 study. A host of noninvasive tests are available as well as histology, which involves fibrosis improvement by at least 1 stage and MASH resolution or improvement in Nonalcoholic Fatty Liver Disease Activity Score. Those endpoints have evolved over time. Artificial intelligence–based assessments or digital image assessment of histologic endpoints might improve power for earlier-phase clinical trials, but are not accepted as a way of assessing efficacy in phase 2b or phase 3 trials at this time.

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G&H What are the current regulatory requirements for approving combinations for MASH?

MC The FDA has put forward guidance that sponsors should develop evidence to support the rationale for a combination via in vivo or in vitro models relevant to the human disease. In other words, it first needs to be shown that the combination works, usually using a mouse model. There have been a number of very good animal models. For example, the model used by the Gubra platform was outstanding and reliably showed benefit if there is going to be any in humans.

Animal models should be able to show the likely efficacy of the combination as well as show that the components are effective individually. However, I do not know if the requirement for demonstration of individual efficacy will hold up because there were agents in hepatitis C virus and HIV, for example, that were not effective on their own, but were highly potent and efficacious in combination. I think there will be a move toward acceptance of the concept that agents may be efficacious in combination that are not efficacious individually in MASH.

G&H What other challenges are associated with developing combinations for MASH?

MC The FDA has said that each part should be tested as monotherapy, but also said it would be prepared to waive that requirement if a drug could not be administered alone or if there was a pharmacologic basis for drug B only working if given with drug A. This monotherapy efficacy requirement could be a potential roadblock.

Additionally, when developing a drug that may or may not be effective, there is now a treatment benchmark with resmetirom, which received FDA subpart H approval for the treatment of MASH consistent with fibrosis stage 2 or 3. With an approved therapy, albeit a preliminary approval, it will likely be more difficult to enroll patients in a study than it used to be because the patients should be informed that there is an approved alternative available.

Also, many patients are currently taking agents that are not approved for MASH, but that appear to be effective for it, such as GLP-1 and GIP agonists like semaglutide and tirzepatide. Both have high-quality data for some aspects of therapy for MASH. Between the GLP-1 agonists, for which 20 million prescriptions were written last year, and the recent approval of resmetirom for reversing fibrosis in MASH, there have been significant headways. I have not seen data regarding their importance, and how difficult it is to enroll patients in studies of new MASH combinations, but our experience at The University of Chicago is that enrollment has become harder. In 2024, study enrollment was harder than in 2023, and I think it will be harder again in 2025.

G&H What findings have been reported thus far from trials of MASH combinations?

MC The ATLAS study, which was conducted by Gilead, examined cilofexor, a modestly effective FXR agonist, alone and in combination with semaglutide, firsocostat, and selonsertib. There were hints at a benefit with some of the combinations, but no definitive benefit was seen when combinations were compared with monotherapy, which was a little disappointing. Studies conducted by Terns also did not see meaningful improvement of efficacy when adding agents to FXR agonists. There is a focus now on non-FXR agonist–based combination therapies, for example, a GLP-1 agonist with a THR-β agonist or a GLP-1 agonist with a PPAR agonist such as lanifibranor or seladelpar (Livdelzi, Gilead). There are still combinations that have not been tested together.

G&H What might be the ideal combination for MASH treatment?

MC I think the ideal will likely be a THR-β agonist plus a weight-loss agent, such as resmetirom with semaglutide or tirzepatide. Not much weight loss might be needed, which may increase tolerability, adherence, and persistence. On the other hand, the combination might consist of, say, two oral agents with, for example, a THR-β agonist and a PPAR agonist such as seladelpar or lanifibranor. These would be inherently interesting studies, and I would like to see the combinations in animal models before going forward.

> … it is too early to say whether combination therapy will be the benchmark for all patients with MASH. I suspect not.

It is important to keep in mind that clinical trials use up a lot of patient resources. There are not that many ideal study participants, so it is necessary to be careful to utilize the resources we have in the most effective way possible. Therefore, we should make sure to do our best to perform the most effective clinical trials possible.

G&H Do you think combination therapy will likely be necessary for all patients with MASH?

MC I think drug development for hepatitis C will serve as an analogy. Both MASH and hepatitis C are liver diseases. In both, we are trying to avoid fibrosis. Some of the earlier direct-acting antiviral agents had decent efficacy, and there is good efficacy and tolerability with what we have right now with resmetirom. I think improved efficacy will come with combination therapy; it is just a question of when. However, it is too early to say whether combination therapy will be the benchmark for all patients with MASH. I suspect not.

G&H What are the most important next steps in research in this area?

MC There is a focus on identifying the best combinations, not just in theory but looking at them via in vivo models, and then identifying ways to achieve clinical success. For example, if a combination consists of a THR-β agonist with a GLP-1 agonist or an FGF21 agonist, then researchers may have to bring a component of the combination in-house or have the resources to develop a partnership. Companies and researchers should be open to partnerships to the extent practical so that they can move the field forward. Collaboration between independent companies can be challenging and did not occur much in hepatitis C drug development unless one company bought another. I am hoping that the MASH space will be different, where we will be able to see partnership in whatever form needed to be able to facilitate good combination studies.

MASH is already the most common reason for women to need a liver transplant and the second-most common reason for men, and by far, it is the most common reason for developing liver cancer. Database studies, including one of 16 million patients, have shown that only a small percentage of patients with MASH have been identified and assigned to an International Classification of Diseases (ICD)-10 code. Without screening for MASH, diagnosing it, and linking people to effective therapy, it will not be possible to bend the arc of this disease. I think combination therapy will be the future, but it is not inevitable. It takes an enormous amount of resources and forward thinking, and there are significant reasons combination therapy often does not happen. I am hoping that the hepatology community and pharmaceutical industry will make sure the right studies happen in the right way to bring together the best potential compounds for this disease.

Disclosures

Dr Charlton has done consulting for Bristol Myers Squibb, Sagimet, Novo Nordisk, Terns, Aligos, 89bio, Boston Pharmaceutical, Madrigal, NorthSea Therapeutics, and Gilead.

Suggested Reading

Alkhouri N, Herring R, Kabler H, et al. Safety and efficacy of combination therapy with semaglutide, cilofexor and firsocostat in patients with non-alcoholic steatohepatitis: a randomised, open-label phase II trial. *J Hepatol.* 2022;77(3):607-618.

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