Selective Agonists of Thyroid Hormone Receptor Beta for the Treatment of NASH

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Nonalcoholic fatty liver disease (NAFLD) is a common condition associated with cirrhosis and hepatocellular carcinoma, affecting approximately 70% of people with obesity or type 2 diabetes.[1] In the absence of approved pharmacotherapies, current guidelines[1-3] recommend reversing nonalcoholic steatohepatitis (NASH) by targeting obesity or type 2 diabetes, either with weight loss from lifestyle intervention and the use of glucagon-like peptide-1 (GLP-1) receptor agonists or with the treatment of type 2 diabetes with an insulin sensitizer such as pioglitazone.[1-3] Thyroid hormone modulates hepatic glucose and lipid metabolism.[1] Hypothyroidism is associated with steatosis, although its role in steatohepatitis is difficult to separate from that of insulin resistance, obesity, and type 2 diabetes.[4-6] Thyroid hormone receptor beta (THR-β) agonists reverse steatosis by many mechanisms, including improving hepatic conversion of T4 to T3 and enhancing mitochondrial function.[5,6] Selective agonists of THR-β, such as resmetirom, activate the major thyroid hormone receptor isoform in the liver (THR-β, also predominant in the kidneys, pituitary gland, and brain) while believed to avoid thyroid hormone receptor alpha (THR-α)–related side effects in the heart and bones.

In this issue of the *Journal*, Harrison et al.[7] report the week 52 results of the ongoing phase 3 MAESTRO-NASH trial, in which 966 adults with NASH and liver fibrosis were randomly assigned to receive once-daily resmetirom at a dose of 80 mg or 100 mg or placebo. Both doses of resmetirom were superior to placebo with respect to the two primary end points: NASH resolution with no worsening of fibrosis (in 25.9 to 29.9% of patients receiving resmetirom vs. 9.7% of those receiving placebo) and an improvement (reduction) in fibrosis by at least one stage with no worsening of the NAFLD activity score (in 24.2 to 25.9% of patients receiving resmetirom vs. 14.2% of those receiving placebo). Resmetirom also ameliorated atherogenic dyslipidemia. It had overall neutral effects on body weight, insulin resistance, glycemia, heart rate, and blood pressure. The drug had an acceptable adverse-event profile, with only nausea, vomiting, and diarrhea occurring more frequently with resmetirom than with placebo. No increase in endocrine adverse events was reported.

Among the patients with available data, resmetirom markedly increased sex hormone–binding globulin levels and increased levels of total estradiol and testosterone. Elevations in sex hormone–binding globulin levels indicate THR-β engagement and are associated with treatment response. Although free testosterone levels were unchanged (free estradiol levels were not reported), it is unclear whether long-term elevations in sex hormone–binding globulin levels may alter delivery of testosterone to target tissues and promote clinically significant gonadal axis changes, because the binding dynamics of testosterone to its binding proteins are complex and incompletely understood.[8] Proper clinical monitoring and accurate measurement of free hormone levels by the reference-standard equilibrium dialysis method would be recommended.[8] Treatment affected the pituitary–thyroid hormone axis, with prohormone free T4 levels decreasing by approximately 17 to 21% and mean thyrotropin levels also decreasing. Although it was reassuring that mean plasma free T3 levels remained normal, further information on individual cases within the lower range of normal (or below normal) would be informative.

The long-term significance of the above hormonal changes, if any, is unclear. Theoretically, suppression of pituitary thyrotropin secretion by THR-β agonists could promote a hypothyroid state in tissues not targeted by the agent. Diagnosing mild hypothyroidism is difficult in terms of attributing symptoms to the thyroid dysfunction[9] and even more challenging when the thyrotropin level is normal or low with subnormal serum free T4 levels,[10] as with selective agonists of THR-β. Careful case finding during follow-up is needed, including endocrine-specific history taking, dedicated questionnaires, and reliable periodic free hormone measurements. With respect to bone metabolism, selective agonists of THR-β are considered to be safe overall because

bone loss is more closely related to long-term THR-α activation.[5,6] However, THR-β appears to also play an important role in bone metabolism.[11] In the subgroup of patients reported (23%), there was no shift in bone mineral density (BMD) T-score risk category. Data of value in the future would be vitamin D levels (vitamin D deficiency may develop in patients with persistent diarrhea), levels of biomarkers of bone turnover, and quantitative changes in BMD.

Taken together, these results are encouraging to the field. Both NASH resolution and fibrosis improvement were more likely with resmetirom than with placebo. If conditional approval is given by the Food and Drug Administration, it may boost guideline recommendations to screen in primary care persons at high risk for NASH, especially to identify those with stage F2 or higher fibrosis (known as "at risk" NASH).[1-3] However, the trial also highlights the challenging nature of the disease. Although resmetirom treatment was successful, the placebo-subtracted effect of resmetirom was overall modest (16.4 to 20.7 percentage points for NASH resolution and 10.2 to 11.8 percentage points for fibrosis), which means that approximately 2 of 10 patients treated will have NASH resolution and approximately 1 of 10 patients treated will have fibrosis improvement. Thus, most patients will need combination therapy with agents for obesity and type 2 diabetes recommended in guidelines (GLP-1 receptor agonists or pioglitazone).[1-3] If resmetirom is approved to treat F2 to F3 (moderate to advanced)) fibrosis, it is speculated that it will be a costly medication. How would resmetirom be used among less expensive medications that are effective for NASH and recommended in current guidelines[1-3] for obesity or type 2 diabetes? In the United States, at least 11.6 million people have NASH, and this figure is expected to nearly double during the next 15 years.[12] The estimated prevalence of stage F2 or F3 fibrosis among patients with type 2 diabetes (a population with the highest risk of cirrhosis) is 12 to 15%,[13,14] which means 4 to 5 million potential candidates for treatment just in the United States. The large number of person needing treatment will open a debate about treatment access and about how to best monitor treatment response and when to discontinue resmetirom in patients who do not have a response in order to avoid futile long-term therapy.

The 52-week results of this ongoing clinical trial are a step forward that brings hope to a field in desperate need of new therapies. They also create new management dilemmas and renew a sense of urgency conveyed in current guidelines to screen in primary care and endocrine settings for patients who may benefit from available and future treatments.[1-3] Resmetirom appeared safe overall, although careful surveillance to detect early endocrine disease that is related to potential thyroid, gonadal, or bone disease appears warranted to avoid any potential risks from long-term treatment. Definitive answers await the long-term safety and efficacy results of this ongoing 54-month trial.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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Psoriasis — More Progress but More Questions

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Psoriasis is a chronic inflammatory disease that affects more than 60 million persons worldwide and is characterized by red, scaly plaques that itch, crack, and bleed. Any area of the skin can be affected, with the scalp, genitals, palms, and soles being especially burdensome. The disease course is varied; approximately 20% of patients have moderate-to-severe cutaneous involvement, and among those patients, inflammatory arthritis develops in approximately 30%. Advances in genetics, immunology, and epidemiology have redefined psoriasis — previously thought to be "just a skin disease" — as a systemic condition associated with obesity, diabetes, major cardiovascular events, and a life expectancy of 5 years less than that of persons without psoriasis.[1-3]

Although psoriasis is multisystemic, clinical trials have focused on the skin response. The most common physician-reported end point is the Psoriasis Area and Severity Index (PASI). This index accounts for the degree of red, scaly, and thick plaques and multiplies this factor by the area of affected skin, yielding scores that range from 0 to 72, with higher scores indicating greater extent or severity of psoriasis. Traditionally, a 75% reduction in the PASI score (i.e., PASI 75 response) has been chosen to be the primary end point. A 90% reduction in the PASI score (i.e., PASI 90 response) is similar to a result of clear or nearly clear skin, indicates a better clinical response than the PASI 75 response, and is increasingly the standard by which therapeutic agents for psoriasis are judged.

Over the past two decades, stunning progress has been made in the treatment of moderate-to-severe psoriasis. Most of these advances have been the development of monoclonal antibodies — large proteins that are administered parenterally. In the early 2000s, subcutaneous tumor necrosis factor α (TNF-α) inhibitors such as etanercept and adalimumab resulted in a PASI 90 response in 20 to 45% of patients.[4] Subsequently, ustekinumab (which targets interleukin-12 and interleukin-23) was associated with a PASI 90 response in 45% of patients.[4] In the 2010s, biologic agents targeting interleukin-17A (brodalumab, ixekizumab, and secukinumab) and interleukin-23 (guselkumab, risankizumab, and tildrakizumab) led to PASI 90 responses in 56 to 70% and in 36 to 75% of patients, respectively. More recently, bimekizumab, which targets interleukin-17A and interleukin-17F, was associated with a PASI 90 response in 86%.[5]

In this issue of the *Journal*, Bissonnette et al.[6] report the results of a phase 2 dose-finding trial of an orally administered interleukin-23–receptor antagonist peptide (JNJ-77242113) that blocks interleukin-23 signaling and the resulting interleukin-17 production. Advances in bioengineering have made it possible for complex proteins to penetrate gastrointestinal proteases, mucus, and cellular barriers, thereby enabling oral bioavailability; semaglutide is a notable example.[7]

JNJ-77242113 showed a dose–response relationship, with the highest dose (100 mg twice daily) resulting in a PASI 90 response in 60% of patients, which — if confirmed by larger studies — would be similar to the most effective injectable biologics.[4] Moreover, there was no evidence of a relationship between the JNJ-77242113 dose and the occurrence of side effects. However, two occurrences of infection (coronavirus disease 2019 and an infected cyst) and a suicide attempt were reported as serious adverse events; larger trials will be needed to determine whether such events are attributable to chance, psoriasis itself, or inhibition of interleukin-23 signaling. Furthermore, JNJ-77242113 needs to be taken on an empty stomach, and therefore, effectiveness may be lower in real-world settings. The response may also be di-