A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

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Abstract

Background

Nonalcoholic steatohepatitis (NASH) is a progressive liver disease with no approved treatment. Resmetirom is an oral, liver-directed, thyroid hormone receptor beta–selective agonist in development for the treatment of NASH with liver fibrosis.

Methods

We are conducting an ongoing phase 3 trial involving adults with biopsy-confirmed NASH and a fibrosis stage of F1B, F2, or F3 (stages range from F0 [no fibrosis] to F4 [cirrhosis]). Patients were randomly assigned in a 1:1:1 ratio to receive once-daily resmetirom at a dose of 80 mg or 100 mg or placebo. The two primary end points at week 52 were NASH resolution (including a reduction in the nonalcoholic fatty liver disease [NAFLD] activity score by ≥2 points; scores range from 0 to 8, with higher scores indicating more severe disease) with no worsening of fibrosis, and an improvement (reduction) in fibrosis by at least one stage with no worsening of the NAFLD activity score.

Results

Overall, 966 patients formed the primary analysis population (322 in the 80-mg resmetirom group, 323 in the 100-mg resmetirom group, and 321 in the placebo group). NASH resolution with no worsening of fibrosis was achieved in 25.9% of the patients in the 80-mg resmetirom group and 29.9% of those in the 100-mg resmetirom group, as compared with 9.7% of those in the placebo group ($P<0.001$ for both comparisons with placebo). Fibrosis improvement by at least one stage with no worsening of the NAFLD activity score was achieved in 24.2% of the patients in the 80-mg resmetirom group and 25.9% of those in the 100-mg resmetirom group, as compared with 14.2% of those in the placebo group ($P<0.001$ for both comparisons with placebo). The change in low-density lipoprotein cholesterol levels from baseline to week 24 was −13.6% in the 80-mg resmetirom group and −16.3% in the 100-mg resmetirom group, as compared with 0.1% in the placebo group ($P<0.001$ for both comparisons with placebo). Diarrhea and nausea were more frequent with resmetirom than with placebo. The incidence of serious adverse events was similar across trial groups: 10.9% in the 80-mg resmetirom group, 12.7% in the 100-mg resmetirom group, and 11.5% in the placebo group.

Conclusions

Both the 80-mg dose and the 100-mg dose of resmetirom were superior to placebo with respect to NASH resolution and improvement in liver fibrosis by at least one stage. (Funded by Madrigal Pharmaceuticals; MAESTRO-NASH ClinicalTrials.gov number, NCT03900429.)

ΣΧΟΛΙΟ

Στην παρούσα μελέτη, η χρήση του Resmetirom, ενός εκλεκτικού αγωνιστή του THR-β, φάνηκε να συντελεί σε βελτίωση της στεατοηπατίτιδας και της ίνωσης σε στατιστικά σημαντικό ποσοστό των ασθενών, που χορηγήθηκε, σε σχέση με την ομάδα ελέγχου. Η μελέτη βρίσκεται ακόμα σε εξέλιξη, αλλά τα έως τώρα αποτελέσματα, στον ένα χρόνο θεραπείας, είναι υποσχόμενα. Δυνατό σημείο της μελέτης αποτελεί το γεγονός ότι η πλειοψηφία (>60%) των ενταχθέντων ασθενών είχε στάδιο ίνωσης F3 και μόνο περίπου 5% από τους συμμετέχοντες ήταν σταδίου F1B.
Η βελτίωση της φλεγμονής ή της ίνωσης αποτελεί το αρχικό κριτήριο με βάση τον οποίο θα αξιολογηθεί το φάρμακο, ωστόσο τα αποτελέσματα όσον αφορά στο κλινικό όφελος των ασθενών, συμπεριλαμβανομένης της εμφάνισης κίρρωσης, θα είναι διαθέσιμα με την ολοκλήρωση της μελέτης, στα 4,5 έτη παρακολούθησης των ασθενών.

ΕΜΜΑΝΟΥΗΛ ΚΟΥΛΛΙΑΣ

ΕΠΙΚΟΥΡΙΚΟΣ ΠΑΘΟΛΟΓΟΣ

Β’ ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ

ΓΝΑ ΙΠΠΟΚΡΑΤΕΙΟ