Phase 1 Trials of PNPLA3 siRNA in I148M Homozygous Patients with MAFLD

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To the Editor:

The development and progression of metabolic dysfunction–associated fatty liver disease (MAFLD) has a strong genetic component, the most robust of which is a single-nucleotide polymorphism (SNP) rs738409 (I148M) in the gene encoding patatin-like phospholipase domain–containing 3 (*PNPLA3*). Homozygosity for the *PNPLA3* risk allele is associated not only with liver fat accumulation but also with susceptibility to steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma.

JNJ-75220795 (also known as ARO-PNPLA3) is a hepatocyte-targeted *N*-acetylgalactosamine (GalNac)–conjugated small interfering RNA (siRNA) against *PNPLA3* that is under development as a precision medicine for the treatment of metabolic dysfunction–associated steatohepatitis associated with the I148M variant. In preclinical studies, JNJ-75220795 was shown to selectively target *PNPLA3* messenger RNA (mRNA) (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org) and to produce a profound (70% decrease from the baseline value) and sustained (≥1 month after the administration of a single dose) decrease in *PNPLA3* mRNA expression in the hepatocytes of nonhuman primates (Fig. S2). The safety, pharmacokinetics, and pharmacodynamics of JNJ-75220795 were evaluated in two phase 1, double-blind, placebo-controlled trials involving homozygous and heterozygous carriers of the PNPLA3 I148M variant that were conducted in the United States (trial 1, a first-in-human trial) and in Japan (trial 2). The trial protocols are available at NEJM.org.

A total of 64 participants (31 homozygous and 24 heterozygous participants in trial 1 and 9 homozygous participants in trial 2) were randomly assigned to receive a single subcutaneous injection of JNJ-75220795 (45 participants) or placebo (19 participants) and were then followed for 24 weeks to monitor safety, side effects, and liver fat reduction, as measured by magnetic resonance imaging–derived proton density fat fraction. JNJ-75220795 was administered at escalating doses in trial 1 (10 to 400 mg) and at a single dose level (75 mg) in trial 2. In trial 1, 93% of the participants were Hispanic or Latino, which was expected given the high prevalence of the *PNPLA3* risk allele in the Hispanic population,[1] and most participants in both trials were overweight or obese and had liver steatosis (Tables S2 and S3). The pharmacokinetic measurements of JNJ-75220795 increased approximately proportionally with increasing doses and were compatible with efficient and rapid liver uptake (Table S5).

Among homozygous participants in trial 1, a single administration of JNJ-75220795 at a dose of 75 mg, 200 mg, or 400 mg led to apparent dose-dependent decreases in liver fat content of up to 46% at 12 weeks with the highest dose (Figure 1 and Tables S6 and S7). The decrease in liver fat content was already apparent at the first

postdose measurement (i.e., 6 weeks) and was sustained for at least 24 weeks after the dose was administered (Figure 1). The results at the 75-mg dose level were confirmed in trial 2. In trial 1, no effect on liver fat content was observed in the low-dose cohorts (10 mg and 25 mg) (Table S6) or in heterozygous participants at any of the doses studied (i.e., 75 mg, 200 mg, and 400 mg) (Fig. S4). JNJ-75220795 did not cause clinically meaningful changes or trends in any of the monitored safety measures, including adverse events, laboratory values, electrocardiographic findings, or physical examinations (Tables S8, S9, and S10 and Figs. S9, S10, and S11).

The results of two phase 1 trials suggest that a single dose of a GalNAc-conjugated PNPLA3 siRNA reduced liver fat content in humans homozygous for the PNPLA3 I148M variant. These findings provide proof-of-concept for JNJ-75220795 as a precision-medicine approach for PNPLA3 I148M homozygous patients. Future studies are needed to assess potential histologic and long-term therapeutic benefit in homozygous patients with MAFLD.

ΣΧΟΛΙΟ

Ως γνωστόν, στην αιτιοπαθογένεια της MASLD περιλαμβάνονται και οι γενετικές μεταλλαγές, που αναστέλλουν τον ενδοηπατικό μεταβολισμό των λιπιδίων, όπως οι μεταλλαγές του TM6SF2 και του MBOAT7 ή ο πολυμορφισμός I148M του γονιδίου που κωδικοποιεί την φωσφολιπάση PNPLA3 (patatin-like phospholipase domain–containing 3), που απετέλεσε και το αντικείμενο των δυο μελετών, που αναφέρονται στο συγκεκριμένο «Letter to the Editor”.

Η γονιδιακή θεραπεία με τη χρήση μικρών παρεμβαλλόμενων RNA (siRNAs), παρότι εκτός κλινικού πλαισίου στην παρούσα φάση όσον αφορά την MASLD, αποτελεί μία ελπιδοφόρα προσέγγιση σε διάφορα νοσήματα πάνω από δυο δεκαετίες μετά την ανακάλυψη του καταλυτικού μηχανισμού δράσης τους. Κλινικές εφαρμογές έχουν ήδη εγκριθεί για νοσήματα, όπως η οξεία ηπατική πορφυρία, η αμυλοείδωση οφειλόμενη στην τρανσθυρετίνη και η υπερχοληστερολαιμία.

Η δυνατότητα θεραπείας της ηπατικής στεάτωσης με τη χορήγηση ενέσιμων σκευασμάτων ανά μερικές εβδομάδες ή μήνες στην ομάδα των ομοζυγωτών ως προς το γονίδιο I148M είναι ιδιαίτερα ενδιαφέρουσα, παρά την πολύ πρώιμη φάση των μελετών.. Μένει να αποδειχθεί η υψηλή αποτελεσματικότητα, η μακροχρόνια διατήρηση των αποτελεσμάτων και η χαμηλή συχνότητα παρενεργειών σε μεγαλύτερες πολυκεντρικές μελέτες, που θα περιλαμβάνουν ασθενείς με διαφορετικά χαρακτηριστικά.