and quality. EMS services should aim to provide the best quality of CPR possible. High-quality manual CPR requires EMS commitment to training and quality review. Mechanical CPR requires the same commitment to training and attention to deployment practices. Mechanical CPR is also more costly than manual CPR. EMS systems worldwide routinely transport patients with cardiac arrest to hospital with ongoing manual CPR of doubtful quality.[12] Safety concerns for unrestrained crew using manual CPR in a moving ambulance are real. Mechanical CPR allows crews to be safely belted up and is a logical choice from the safety perspective.[13]

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MEHO is principal investigator of an industry-funded study involving a mechanical CPR device; has received grants from Laerdal Medical, grants and personal fees from Zoll Medical Corporation, and non-financial support from Bard Medical and Zoll Medical Corporation; and has a patent method of predicting patient survival licensed to Zoll Medical Corporation, and a patent system and method of determining a risk score for triage pending. VA is principal investigator in an industry-funded study on use of a mechanical CPR device in the out-of-hospital situation; has received non-financial support from Physio-Control Inc; and is a member of the Medical Advisory Board of Falck Foundation.

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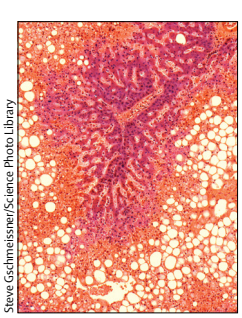
Starting the battle to control non-alcoholic steatohepatitis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Published Online
November 7, 2014
http://dx.doi.org/10.1016/S0140-6736(14)62010-9

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Non-alcoholic steatohepatitis occurs when hepatic fat, inflammation, and liver-cell injury develop in insulin-resistant individuals. Reports from US transplant registries show that non-alcoholic steatohepatitis is the third leading cause of end-stage liver disease,[1] and the second most common cause of primary liver cancer in patients listed for liver transplantation.[2] Yet no pharmacological therapy for non-alcoholic steatohepatitis is approved.

In *The Lancet*, Brent Neuschwander-Tetri and colleagues[3] report on the effects of obeticholic acid, a synthetic farnesoid X receptor agonist, in patients with non-alcoholic steatohepatitis, in a placebo-controlled, randomised trial (FLINT). Patients were treated for 72 weeks and the primary endpoint was improvement in histology, as measured by a two-point reduction in a composite activity histological score without worsening of fibrosis. The therapeutic phase of the trial was stopped early partly because a preplanned interim analysis showed that more patients on obeticholic acid (50 [45%] of 110) than on placebo (23 [21%] of 109) reached the primary endpoint (relative risk 1·9, 95% CI 1·3–2·8). Unexpectedly, for a trial not powered to detect fibrotic changes, the authors also reported an improvement in fibrosis: 36 (35%) of 102 obeticholic acid-treated patients regressed by one stage or more versus 19 (19%) of 98 placebo-treated patients. Neither pioglitazone, a peroxisome proliferator-activated receptor-γ agonist, nor vitamin E significantly improved fibrosis after 2 years of treatment, despite similar reductions in non-alcoholic fatty liver disease (NAFLD) activity score.[4]

Biologically, this effect is plausible since obeticholic acid had antifibrotic properties in some rodent models of liver fibrosis,[5] although interspecies differences could account for conflicting findings.[6]

Although the antifibrotic effects reported in FLINT are encouraging, the findings should be interpreted with caution. A one-stage reduction might not be equally relevant across the five-stage spectrum of fibrosis in human non-alcoholic steatohepatitis. Since bridging fibrosis (but not earlier stages) increases liver-related morbidity and mortality in most chronic liver diseases, including non-alcoholic steatohepatitis,[7] a more relevant endpoint would be the proportion of patients crossing this threshold in both directions. By this token, 14 (41%) of 34 patients in the obeticholic acid group no longer had bridging fibrosis versus eight (28%) of 29 in the placebo group (p=0·30). Conversely, progression to bridging fibrosis still occurred in the obeticholic acid group (ten patients from early or mild fibrosis to bridging), whereas two patients developed cirrhosis (as compared with 12 and five patients, respectively, in the placebo group). Enthusiasm for the overall fibrosis changes is understandable, as it provides proof-of-principle for a potential antifibrotic effect in human beings. Ancillary studies should be done using more sensitive measurements of fibrosis and studying the effect of the drug on fibrogenic markers. But we will ultimately need large and well-designed future trials.

The main result of FLINT, nonetheless, is a clear improvement in all histological features of non-alcoholic steatohepatitis, including steatosis, inflammation, and liver-cell injury, together with a reduction in aminotransferases, a biochemical marker of hepatic damage. The histological improvement was measured through the reduction of the composite NAFLD activity score. While recognising the ability of the drug to improve liver injury in this setting, this raises the challenging and unsettled question of the best histological outcomes to be achieved in registration trials. The NAFLD activity score does not predict liver-related complications[7,8] and the prognostic value of an arbitrarily chosen two-point reduction is so far unproven. Conversely, steatohepatitis (*vs* steatosis without steatohepatitis) is associated with a significant increase in liver-related outcomes and a reduction in overall survival.[7,9] Hence, resolution of steatohepatitis, an endpoint achievable through short-term trials,[3] would be a stronger surrogate than a reduction in NAFLD activity score. In FLINT,[3] 22 (22%) of 102 patients in the obeticholic acid group had resolution of non-alcoholic steatohepatitis versus 13 (13%) of 98 patients in the placebo group (p=0·08). This difference provides reasonable optimism that a larger study could have met this endpoint. Although the best endpoint for definitive approval should ultimately be reduced progression to cirrhosis and its complications, this will require longer-term studies. Meanwhile, since fibrogenesis is driven by inflammation and liver-cell injury associated with steatohepatitis, resolution of non-alcoholic steatohepatitis is a prerequisite for long-standing fibrosis improvement.

Despite its merits, FLINT has some methodological limitations that could reduce statistical power. First, because there was no centralised pathological assessment of study eligibility, patients were included based on local pathological assessments. When analysed centrally at study end, a substantial proportion of patients did not have the full features of steatohepatitis at inclusion; this might have underestimated the efficacy of obeticholic acid. Second, obtaining end-of-treatment liver biopsies was stopped early, which resulted in fewer patients with complete datasets available for histological analyses than initially planned. Moreover, truncated trials could overestimate treatment benefits[10] and no statistical stopping rules eliminate this risk.

Any drug candidate for non-alcoholic steatohepatitis needs to have a very good tolerability and safety profile, as it targets a population of mostly asymptomatic patients with numerous metabolic and cardiovascular comorbidities. In FLINT, obeticholic acid increased LDL and slightly decreased HDL concentrations, with both effects diminishing after the initial weeks of therapy. The clinical significance of these findings is unclear. Future studies will need to assess whether other atherogenic lipoprotein subfractions or inflammatory endothelial markers are altered, whether this confers an increase in the overall cardiovascular risk, and if this can be mitigated by statin use. Animal models of atherosclerosis have shown that farnesoid X receptor reduces atherosclerosis,[11] an effect mediated through a decrease in vascular cholesterol load and inflammation.[12,13] The only tolerability issue with

obeticholic acid was pruritus, clearly more frequent and more intense in the obeticholic acid group, although just one patient was discontinued. Whether a lower dose might reduce the incidence of pruritus, while maintaining histological efficacy, needs to be tested.

Patients with non-alcoholic steatohepatitis for whom diet and lifestyle measures fail to work need pharmacological therapy. FLINT provides a clear indication of the efficacy of obeticholic acid in alleviating liver injury and should be followed by more in-depth assessment of efficacy and safety. But there is a substantial proportion of non-responders, which, together with the multiplicity of pathways that result in steatohepatitis and fibrosis progression, mandates testing of other pharmacological agents with strong preclinical rationale: dual peroxisome proliferator-activated receptor α/Δ (GFT505), C-C motif chemokine receptor type 2 (CCR2) and CCR5 antagonists (cenicriviroc), antifibrotic agents (simtuzumab), Takeda G-protein coupled receptor 5 (TGR5) agonists or dual TGR5–farnesoid X receptor agonists, or fatty acid–bile acid conjugates (aramchol). Most of these agents are already in advanced, phase 2b and phase 3, clinical trials. The drug pipeline is slowly building to address the clinical need in this silent but damaging liver disease.

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VR has received consulting fees from Abbott, AstraZeneca, Galmed, Genfit, Gilead, Intercept, Roche-Genentech, and Tobira.

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Progress with the global tobacco epidemic

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During the 20th century, tobacco smoking killed some 100 million people, most of them in high-income countries.[1] In the 21st century the corresponding figure is likely to be about 1 billion, most in low-income and middle-income countries.[1,2] Similar to the evolution of smoking within populations of high-income countries, the global smoking epidemic is now moving from the rich to the poor. Driven by the financial heft of transnational tobacco companies with a combined income higher than most individual countries,[3] built on a business model of peddling an addictive product to children and young people, and sustained by practices that prioritise corporate profit over health, the current global epidemic of smoking represents a triumph of corporate self-interest over human wellbeing.[4] It is also a challenge that national and international health systems remain ill-equipped to face.

The WHO Framework Convention on Tobacco Control (FCTC) is a global treaty, indeed the first ever global health treaty, designed to counter the smoking epidemic.[5] The FCTC aims to equip countries, poor