Nucleic acid polymers: much-needed hope for hepatitis D?

In the *Lancet Gastroenterology & Hepatology*, Michel Bazinet and colleagues[1] describe the results of a phase 2 clinical trial on the safety and efficacy of combined treatment with the nucleic acid polymer REP 2139 and pegylated interferon alfa-2a for treatment of patients with chronic hepatitis B virus (HBV) and hepatitis D virus (HDV) co-infection.

Chronic hepatitis D is considered the most severe and most difficult form of chronic viral hepatitis to treat. Despite affecting an estimated 15–20 million people worldwide, often in impoverished settings, the allocation of resources for the treatment of chronic hepatitis D is low compared with other chronic infections of similar prevalence.[2] At present, pegylated interferon alfa-2a is the only approved therapy for chronic hepatitis D, for which only a minority of patients are eligible because of the known safety issues of the drug.[3] Moreover, response rates are poor and late relapses are common, highlighting the urgent need for new therapeutic strategies.[4]

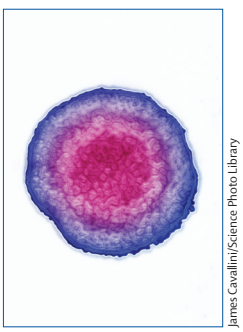
Nucleic acid polymers have shown antiviral activity against HBV, both in experimental models and in a proof-of-concept clinical trial.[5] The proposed mechanism of action involves both the inhibition of viral entry and, most importantly, the blockade of hepatitis B virus surface antigen (HBsAg) release and secretion of subviral particles, enabling restoration of the host immune response against the virus.[5] Because HDV is a defective virus that also depends on HBsAg for its assembly and is hypothesised to use the subviral particle secretion pathway for its egress,[6] these molecules are very attractive candidates to target HDV.

In this proof-of-principle trial by Bazinet and colleagues,[1] 12 patients, all without cirrhosis, received REP 2139, first as monotherapy for 15 weeks and then combined with pegylated interferon alfa-2a for another 15 weeks, followed by a 33 week course of pegylated interferon alfa-2a monotherapy. Substantial declines in both HBsAg concentrations and HDV RNA were observed by the end of REP 2139 monotherapy, which remained stable in most patients for 1 year after treatment withdrawal. The regimen also appeared to be relatively safe, despite the induction of pronounced alanine aminotransferase flares in some patients, which might limit the applicability of the treatment for patients with cirrhosis. Although these results appear promising, a more thorough evaluation of these molecules is warranted to validate their use.

First, the results of this uncontrolled study must be confirmed by a randomised controlled trial that includes at least a pegylated interferon alfa-2a monotherapy arm. Indeed, although all patients were reported to have had HDV infection for more than 1 year before treatment and the decline of HDV RNA and HBsAg concentrations was faster than that expected during the natural course of disease, data on IgM antibodies against hepatitis B core antigen were not provided. Thus, the possibility that some enrolled patients had a protracted acute HDV infection that spontaneously cleared cannot be excluded.

Second, the possibility of late relapses must be carefully ruled out, not only because they are common in patients with chronic hepatitis D infection who receive pegylated interferon alfa-2a,[4] but also because in the authors' previous study[7] on the efficacy of REP 2139 in patients with chronic HBV infection, relapses occurred as late as 123 weeks after treatment withdrawal, supporting the possibility of a transient, incomplete viral clearance. Long-term follow-up will also allow the risk of complications associated with the intrahepatic accumulation of viral products to be investigated.

Beyond the clinical implications, this study raises interesting questions about the effects of nucleic acid polymers on the life cycle of HDV. In most patients a steep decline in serum HDV RNA was observed before the introduction of pegylated interferon alfa-2a, which is consistent with the proposed inhibition of HBsAg assembly and egress by nucleic acid polymers, although this mechanism of action remains to be investigated in the context of HDV infection. More importantly, in some patients, the HDV RNA decrease occurred irrespective of HBsAg decline, and preceded the increase in alanine aminotransferase concentration that occurred after the introduction of pegylated interferon alfa-2a, which indicates that substantial lysis of infected cells is an unlikely explanation. Furthermore, direct inhibition of HDV replication by nucleic acid polymers has been excluded in vitro,[8] and the induction of the intracellular innate immune response has been ruled out in primary hepatocytes.[9] In view of the likely accumulation of HDV viral components inside hepatocytes, indirect antiviral effects might be considered—eg, inhibition of viral



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Published **Online**
September 27, 2017
http://dx.doi.org/10.1016/S2468-1253(17)30292-3

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replication induced by the large isoform of the HDV antigen.[10] Studies that investigate intrahepatic viral markers are required to clarify the mechanism by which serum HDV RNA is decreased. The results of Bazinet and colleagues' study indicate that some degree of control of HBsAg secretion is necessary to maintain a virological response after treatment withdrawal because HDV rebound occurred only in patients in whom HBsAg loss was not achieved.

Although the results of the study by Bazinet and colleagues must be interpreted with caution, they indicate that nucleic acid polymers might represent a promising new therapy that provides effective, long-lasting, and safe control of chronic hepatitis D infection.

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We declare no competing interests.

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The stomach and obesity: the missing link, at last?

Published **Online** September 25, 2017 http://dx.doi.org/10.1016/S2468-1253(17)30291-1

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Obesity is an apparently unstoppable epidemic in industrialised countries, caused caused by chronic positive energy balance (ie, caloric intake greater than energy expenditure). Prevention of, and therapy for, obesity remain major challenges.

Caloric intake is a vital function, regulated by common sensations such as appetite (desire to ingest food), satiation (sensation of fullness that induces meal termination), and satiety (sensation of fullness that persists postprandially). These sensations are controlled by signals arising in the brain (brain–gut axis) and by gastrointestinal digestive functions that feedback to the brain via neuroendocrine pathways (gut–brain axis).[1] Among the numerous neuroendocrine substances involved in the gut–brain axis, incretins (including peptide YY, oxyntomodulin, and GLP-1) are known to act both centrally by exerting vagally mediated inhibitory effects on the cephalic phase of digestion and peripherally by delaying gastric emptying.[2] Bariatric endoscopy[3] and bariatric surgery[4] are designed to decrease intragastric volumes and delay gastric emptying, decrease the intestinal absorbent surface, or both, but they have limitations and side-effects, and alternative medical treatments are being developed.[5] Both short-acting and long-acting GLP-1 receptor agonists are approved for the treatment of obesity,[5] but their mechanisms of action have not been elucidated.

In *The Lancet Gastroenterology & Hepatology*, Houssam Halawi and colleagues[6] report the results of an elegantly conducted and analysed placebo-controlled pilot study designed to investigate potential mechanisms of action of once-daily, subcutaneous injections of increasing doses of the long-acting GLP-1 receptor agonist liraglutide on gastric functions in individuals with obesity. Despite the small number of patients enrolled, liraglutide induced weight loss, delayed gastric emptying, and decreased maximum tolerated volume of liquid nutrient drink (ie, increased satiation) relative to placebo after both 5 weeks and 16 weeks. Gastric emptying times ($T_{1/2}$) correlated with the degree of weight loss both at 5 weeks and 16 weeks. Nausea was reported by more than 60% of participants in the liraglutide group, compared with less than 20% in the placebo group, but this should probably be regarded as a component of the therapeutic