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Clinical development of hepatitis C virus host-targeting agents

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Hepatitis C virus (HCV) is a leading cause of liver disease. Direct-acting antivirals have revolutionised management of patients with chronic hepatitis C by increasing viral cure rates while reducing treatment duration and side-effects.¹ However, some limitations remain including direct-acting antiviral failure and resistance in a subset of patients, difficult-to-treat genotypes in patients with cirrhosis, few treatment options for patients with advanced renal insufficiency, limited retreatment options for those who do not respond, and limited access to therapy because of high costs.² Next generation direct-acting antivirals and host-targeting agents are in development to further optimise antiviral regimens.^{2–4} MicroRNA-122 (miR-122), a small non-coding RNA highly expressed in hepatocytes, regulates lipid metabolism and acts as a tumour suppressor.⁵ This agent represents an interesting host target for antiretroviral therapy as HCV usurps miR-122 for its replication.⁵ The first proof-of-concept study⁶ has shown that the miR-122 inhibitor miravirsen efficiently reduced viral loads in patients chronically infected with HCV.

In *The Lancet*, Meike van der Ree and colleagues⁷ present results from a phase 1B study that assessed the miR-122 inhibitor RG-101 in 32 patients chronically infected with HCV genotypes 1, 3, or 4. RG-101 was highly efficient as it led to about a 4–5 log₁₀ reduction of viral load in all patients 4 weeks after subcutaneous administration as a single dose of 2 mg/kg or 4 mg/kg (the median viral load reduction from baseline was 4.42 log₁₀ IU/mL [IQR 3.23–5.00] in patients treated with 2 mg/kg RG-101 and 5.07 log₁₀ IU/mL [4.19–5.35] in those treated with 4 mg/kg RG-101). Although this decrease in viral load was transient in most patients (viral rebound at week 8 in six of 28 patients and between weeks 12 and 52 in 16 of 22 patients), undetectable HCV RNA levels were observed after 76 weeks in three patients, suggesting viral cure. Viral rebound between weeks 5 and 12 was associated with mutations and polymorphisms in miR-122 binding sites within the HCV genome (eight patients), suggesting viral resistance. No mutations were noted in six patients who had viral rebound at later timepoints, suggesting that lower RG-101 concentrations rather than viral resistance might have led to viral rebound in those patients. Overall, RG-101 was well tolerated. In line with the physiological targets of miR-122, RG-101 induced a prolonged but reversible decrease in total plasma cholesterol levels and a prolonged transient increase in serum alkaline phosphatase.

What are the differences between RG-101 and miravirsen? While both are miR-122 oligonucleotide inhibitors with similar mechanisms of action, RG-101 has a different chemistry than miravirsen by conjugation to an N-acetylgalactosamine structure enhancing its hepatocyte uptake and potency.^{6,7} Although the different study design and follow-up preclude definitive conclusions, the altered chemistry might have rendered RG-101 more efficient: although five patients who received five miravirsen injections at weekly intervals achieved transiently undetectable HCV RNA levels (weeks 5–14), all but one patient relapsed at week 18.⁶ In the patients exhibiting viral rebound after RG-101 administration, van der Ree and colleagues found two resistance associated mutations and three polymorphisms.⁷ No mutation was detected during the miravirsen trial,⁶ although subsequent reanalysis of patient samples identified one resistance-associated variant previously uncovered for RG-101.^{6–8}

How can miR-122 inhibitors address the limitations of present direct-acting antivirals? The most striking finding is that RG-101 was effective in a single-dose regimen. Although a long-term follow-up will be required to draw definitive conclusions, the absence of detectable viral RNA in three patients suggests the possibility of sustained virological response. More detailed mechanistic analyses comparing virus (eg, detailed kinetics) and host factors (eg, miRNA host biology) in patients with relapse and sustained response would further advance this approach—for example, by defining patients responding best to miR-122 inhibitors. Given that direct-acting antivirals and host-targeting agents can have synergistic antiviral activities,⁹ this approach holds promise to shorten direct-acting antiviral treatment duration, to improve the management of difficult-to-treat patients, and to prevent direct-acting antiviral failure. One drawback might be the parenteral mode of administration; however, a single dose regimen might be conveniently integrated into combination therapy. Because RG-101 targets an essential liver miRNA, a careful safety analysis will be required to assess RG-101's suitability in patients with advanced liver disease or kidney failure. Will there be long-term side-effects? How might RG-101 affect the residual hepatocellular carcinoma risk after cure in patients with advanced liver disease¹⁰ due to miR-122's tumour suppressor function? Additional clinical trials are clearly the next step to answer these questions and take this innovative approach to the next stage of its clinical development.

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