reduction, they are not considered as the first option for analgesic prescription for patients with low-back pain.

Both regular and as-needed use of paracetamol were analysed in PACE. Although participants were directed to take six regular tablets (containing paracetamol 665 mg or placebo) every day, equivalent to a daily dose of 3990 mg paracetamol, the median daily dose consumed by patients in the regular paracetamol group was 5·4 tablets (about 3500 mg) in the first week, falling to 4·3 tablets (about 2800 mg) in the second week. This finding could have decreased the contrast between the two strategies of drug intake and reduced the potential to record differences between regular and as-needed use of paracetamol in time to recovery. However, even in the first week the pain score did not differ between the two approaches, suggesting that regular and as-needed paracetamol regimens have much the same effect in this patient population.

Williams and colleagues are to be applauded for tackling this research question on a topic that has been without debate and evidence for such a long time. Other studies should now be done to investigate if the results in this study also apply to other populations. Furthermore, efforts to establish if prescription of simple analgesics has additional benefit to advice and reassurance of the favourable prognosis for acute low-back pain are very welcome.

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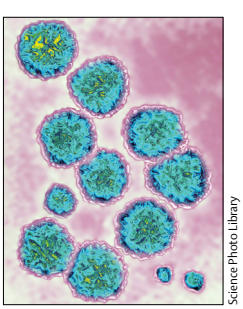
Hepatitis C beware—the end is nigh

Chronic infection with hepatitis C virus (HCV) is a global epidemic that affects more than 180 million individuals worldwide.[1] Because of low rates of treatment and an ageing population, the proportion of people infected with HCV in the USA who will develop established cirrhosis is projected to increase from 15% to over 45%.[2] This increase is expected to result in a trebling of the rates of HCV-related liver failure and hepatocellular carcinoma by 2030.[3] The benefits of current interferon-based therapies are limited by poor tolerability and efficacy.[4] The only means of reducing this future health burden, therefore, is through increased treatment with improved antiviral therapy. Direct-acting antiviral agents (DAAs) provide new opportunities for treatment of HCV and reduction in the need for interferon and ribavirin.

In large clinical trials the addition of a first-generation NS3/4A protease inhibitor, such as boceprevir or telaprevir, improved efficacy of pegylated interferon (peginterferon) and ribavirin in patients with chronic HCV genotype 1 infection, but reduced tolerability, increased pill burden (up to 18 tablets per day), and increased regimen complexity with substantial drug–drug interactions. The need for on-treatment monitoring was also increased. Real-world experience of protease-inhibitor-based triple therapy has shown poor tolerability and efficacy in patients with decompensated cirrhosis or portal hypertension.[5] Additionally, first-generation protease inhibitors have little or no antiviral effect against HCV genotypes 2–6, which comprise almost 40% of all infections worldwide.[6]

Patients with advanced liver disease, those unsuitable for interferon therapy, and those infected with HCV genotypes other than genotype 1 represent a large group of patients with unmet medical needs. The approach used in HIV treatment of combining antiretroviral drugs and agents with different mechanisms of action to increase efficacy and prevent resistance would seem the ideal strategy to remove the need for interferon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and improve tolerability of treatment. In a study of two combined DAAs to treat HCV infection, 24 weeks of the NS3/4A protease inhibitor asunaprevir plus an NS5A inhibitor, daclatasvir, without interferon or ribavirin, led to sustained virological response (SVR) in four of 11 patients.[7] Of note, all seven patients with virological failures were infected with HCV genotype 1a. In a Japanese study, the same regimen led to SVR in all of ten patients infected with HCV genotype 1b.[8] These observations shaped the phase 3 development of this DAA combination in patients infected with HCV genotype 1b.

In *The Lancet*, Michael Manns and colleagues[9] report the final results of the HALLMARK-DUAL study. This large phase 3 study done in 116 sites across 18 different countries assessed 24 weeks of asunaprevir plus daclatasvir in 645 patients who had chronic infections with HCV genotype 1b. Patients were treatment naive, non-responders to peginterferon and ribavirin, or had medical contraindications or were intolerant to peginterferon or ribavirin. The inclusion criteria were intended to reflect real-world practice, and a third of patients had cirrhosis with platelet counts as low as 50×10^9/L. Efficacy was excellent across all three subgroups: SVR was achieved in 182 (90% [95% CI 85–94]) of 205 treatment-naive patients, 168 (82% [77–87]) of 205 non-responders, and 192 (82% [77–87]) of 235 patients with interferon contraindications or intolerance. Traditional baseline predictors of non-response to treatment, including *IL28B* genotype, presence of cirrhosis, treatment history, body-mass index, and ethnic origin, did not alter efficacy. The only baseline predictor for treatment failure was the presence of signature resistance-associated variants (RAVs) in NS5A or NS3 sequences, which were detected in 75 (13%) of 596 assessable samples (27 [5%] had RAVs at NS5A position L31, 48 [8%] at NS5A position Y93, and three [1%] at NS3 position D168). Virological failure occurred in 46 (61%) of 75 patients with, but in only 43 (8%) of 521 without, any of these three RAVs at baseline. This association suggests that testing for these RAVs should be done before asunaprevir plus daclatasvir are started and that this regimen should be avoided in affected patients. Of the 101 non-responders in the study, 75 had signature NS5A and NS3 RAVs identified at the time of virological failure, which conferred dual resistance to asunaprevir and daclatasvir. The post-treatment evolution of these RAVS will need to be determined but might limit the future treatment options with protease and NS5A inhibitors.

Serious adverse events (SAEs) were reported in only 39 (6%) patients and treatment-related discontinuation in ten (2%; mainly for increases of alanine aminotransferase concentrations in serum). Eight patients had transient grade 4 increases in alanine aminotransferase (to more than ten times the upper limit of normal). Increases in alanine aminotransferase were reported in previous studies of asunaprevir with or without interferon, but were all dose-related and quickly resolved after treatment was stopped.[10,11] Overall, the efficacy and safety of 24 weeks of asunaprevir plus daclatasvir represent huge improvements for patients infected with HCV genotype 1b compared with the standard 48 weeks of boceprevir-based or telaprevir-based triple therapy.

Also in *The Lancet*, Eric Lawitz and colleagues[12] provide further information on treatment without peginterferon and ribavirin. In the COSMOS study they assessed treatment with simeprevir, an NS3/4A protease inhibitor, and sofosbuvir, an NS5B nucleotide polymerase inhibitor. These two drugs have been approved for use in triple-therapy regimens that include peginterferon and ribavirin to treat chronic infection with HCV genotype 1. 167 patients with HCV genotypes 1a or 1b received 150 mg simeprevir and 400 mg sofosbuvir tablets once daily, with or without oral ribavirin, for 12 or 24 weeks. The study setting again aimed to reflect the real world, and patients were treatment naive or previous non-responders to peginterferon or ribavirin.

The primary endpoint in COSMOS was SVR 12 weeks after the end of treatment (SVR12), and was achieved in 154 (92%) of 167 patients overall. This endpoint was reached with 12 weeks of treatment without ribavirin in 26 (93%) of 28 patients, including those with compensated cirrhosis and previous non-response. Neither longer treatment duration (24 weeks) nor adding ribavirin improved SVR rates, although five of the six patients who relapsed were treated for only 12 weeks. Of note, five of these six had developed resistance-associated mutations to simeprevir (Arg155Lys, Asp168Glu, or Ile170Thr), but none showed resistance to sofosbuvir. Efficacy

was similar in patients with HCV genotypes 1a and 1b (SVR12 achieved in 119 [92%] of 130 and 35 [95%] of 37, respectively). Previous reports have shown reductions in the efficacy of simeprevir combined with peginterferon and ribavirin of almost 30% in patients with the Gln80Lys (Q80K) NS3 polymorphism at baseline.[13] With the combination of simeprevir and sofosbuvir used in COSMOS, however, the effect of this polymorphism was much reduced (SVR12 achieved in 51 [88%] of 58 with and 68 [94%] of 72 without). Larger studies of simeprevir and sofosbuvir are needed to investigate the true effect of this polymorphism, which is found in almost 50% of individuals infected with HCV genotype 1a in the USA.[14]

Treatment was safe and well tolerated with very few SAEs (four [2%]) or treatment-related discontinuations (four [2%]). With the primary endpoint being achieved after only 12 weeks of treatment, tolerability of this regimen was increased further.

Simeprevir and sofosbuvir have both been approved for use with peginterferon and ribavirin in the USA and Europe. The almost immediate acceptance in clinical practice of combined simeprevir and sofosbuvir without either peginterferon or ribavirin for use in patients intolerant or with contraindications to interferon is remarkable. Moreover, within 3 months of approval combined simeprevir and sofosbuvir had become the recommended first-line treatment for these interferon-ineligible patients.[15,16] In practice, ineligibility for interferon therapy could be applied to anyone who wants to avoid interferon and, therefore, could include most treatment-naive patients infected with HCV genotype 1. The introduction of these drugs in practice was based on only interim safety and efficacy data from the first 80 patients in one phase 2 study presented in 2013,[17] and large confirmatory phase 3 registration studies are still being done (NCT02114177 and NCT02114151). The enthusiasm for combined simeprevir and sofosbuvir is also remarkable because of the cost: 12 weeks of treatment costs around US$150 000.[18] Although the high SVR rate and short duration of treatment with combined simeprevir and sofosbuvir improves cost-effectiveness, the high cost of even short-term therapy will be prohibitive in most countries outside the USA.

HALLMARK-DUAL and COSMOS represent important steps towards the development of universally effective, entirely oral treatment for HCV. The findings of Manns and colleagues[9] remind us that virological failure remains an issue when two DAAs with low barriers to resistance are combined, even when this therapy is limited to the easier-to-treat genotype 1b population. The study by Lawitz and colleagues[12] shows the benefits of including a DAA with a high barrier to resistance to increase efficacy and reduce treatment duration.

Two other combination DAA regimens are approaching approval: ledipasvir and sofosbuvir for 8–12 weeks, and ABT-450, ombitasvir, and dasabuvir, with or without ribavirin.[19-23] These new regimens have certainly raised the bar for future DAA development to at least 95% SVR with less than 12 weeks of treatment. The development of a combination regimen of two pangenotypic drugs, GS-5816, a second-generation NS5A inhibitor, plus sofosbuvir, seems to place a pangenotypic regimen within grasp.[23] In the future such combination treatments might remove the need for testing for *IL28B* and HCV genotypes at baseline.

The minimum duration of treatment to cure HCV is not yet clear. Before the development of DAAs, viral kinetic modelling with interferon suggested that 24–48 weeks of therapy were necessary because of the slow second-phase decline, which represented immune clearance of infected hepatocytes.[24] This effect might be accelerated to only 12 weeks by combining two DAAs (protease and polymerase inhibitors).[25] The addition of an NS5A inhibitor could shorten this time further because of the inhibition of HCV assembly and release.[26] In the SYNERGY study,[27] only 6 weeks of triple DAA therapy (ledipasvir, sofosbuvir, and GS-9451, an NS3 protease inhibitor) led to SVR in all 20 non-cirrhotic patients infected with HCV genotype 1. Studies are also exploring whether only 4 weeks of triple or quadruple DAA therapy will be sufficient (NCT02133131 and NCT02175966).

In the future, very-short-duration, all-oral DAA regimens should improve treatment uptake and success, and reduce the health burden from liver-related complications.[28] When combined with targeted testing and treatment of populations who transmit infection (ie, treatment as prevention), these DAA regimens might eventually eliminate HCV infection. The only barrier to achieving this goal will be the ability to access these new therapies. In many developing countries where HCV is endemic, interferon-based therapy will

remain the first choice because of the high cost of DAAs and lack of reimbursement. As almost 75% of all patients with HCV infection reside in economically deprived regions of eastern Europe, Asia, and the Middle East, consideration should be given to discounting prices in these regions.[29] Eradication of HCV infection worldwide will only be achievable through universal access to HCV testing and new DAA regimens.

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