Shortening the duration of therapy for chronic hepatitis C infection

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Combination direct-acting antiviral therapy of 8–24 weeks is highly effective for the treatment of chronic hepatitis C infection. However, shortening the treatment duration to less than 8 weeks could potentially reduce overall treatment costs and improve adherence. Here we explore the arguments for and against the development of short-duration regimens and existing data on treatment for 6 weeks or less among patients with chronic hepatitis C virus genotype 1 infection. Additionally, we identify potential predictors of response to short-course combination therapies with direct-acting antiviral drugs that might be explored in future clinical trials.

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The global prevalence of chronic hepatitis C virus (HCV) infection in 2015 was estimated at 1% of the world population (71 million individuals).[1] Of the 71 million individuals, only 15 million (21%) were diagnosed and only 439 000 (<1%) were treated.[1,2] An estimated 385 000 deaths in 2016 were attributed to HCV.[2] Infections are most commonly caused by HCV genotype 1, accounting for 31 million (44%) infected individuals.[1] Direct-acting antiviral (DAA) drugs, introduced in 2014, have substantially improved treatment effectiveness and safety compared with interferon-based treatment.[3] Under existing guidelines, most patients are prescribed 12 weeks of DAA therapy, a treatment duration that has shown high rates of sustained virological response (SVR) across various viral and host characteristics.[3] Shortening treatment duration could reduce overall treatment costs and adverse effects and potentially improve treatment adherence.

Existing guidelines do not encourage treatment for less than 12 weeks.[4–6] However, evidence increasingly suggests that many patients can achieve an SVR with only 8 weeks of therapy. In the ION-3 trial,[7] 202 (94%, 95% CI 90–97) of 215 patients with HCV genotype 1 infection, who were without cirrhosis and naive to treatment, had an SVR after receiving 8 weeks of ledipasvir and sofosbuvir, and many of those patients counted as treatment failures were actually lost to follow-up. Similar success has been observed with ledipasvir and sofosbuvir for 8 weeks in clinical practice, including an SVR in 271 (96%, 93–98) of 182 participants in the HCV-TARGET cohort[8] and in 622 (98%) of 634 patients in three clinical cohorts.[9] 8 weeks of treatment with some other regimens also appeared to be highly effective. In a trial[10] of patients with HCV genotype 1b, who did not have cirrhosis and were naive to treatment, 8 weeks of treatment with paritaprevir boosted with ritonavir, ombitasvir, and dasabuvir yielded an SVR in 162 (98%) of 166 participants. Similar results of high efficacy have been shown for 8 weeks of DAA therapy with new pangenotypic regimens. In the ENDURANCE-1 study,[11] 331 (99%) of 332 treatment-naive or treatment-experienced patients with HCV genotype 1 (including some patients coinfected with HIV), who were treated with glecaprevir and pibrentasvir for 8 weeks, had an SVR. In the POLARIS-2 trial,[12] treatment with sofosbuvir, velpatasvir, and voxilaprevir (formerly GS-9857) for 8 weeks resulted in an SVR in 476 (95%) of 501 patients with HCV genotype 1–6 who were with or without cirrhosis and naive to DAA therapy. Similarly, in the POLARIS-3 trial,[13] 106 (96%) of 110 patients with HCV genotype 3 and cirrhosis had an SVR. The C-CREST studies[14] of grazoprevir, ruzasvir, and uprifosbuvir for 8 weeks reported an SVR in 93% of patients with HCV genotype 1a and in 98% of patients with HCV genotype 1b. These high SVR rates among patients treated with licensed regimens suggest that it might be possible to treat a broad range of patients for only 8 weeks and that treatment for even shorter durations might be feasible for some groups of patients. Here we explore the arguments for and against the development of short-duration regimens and existing data about treatment of patients with HCV genotype 1 for 6 weeks or less. Moreover, we identify potential predictors of response to short-course combination therapies with DAA drugs that might be explored in future clinical trials.

The high cost of DAA-based treatment remains a major barrier to accessibility and has fuelled the debate about the fairness and affordability of prices.[15,16] Similar to developments that facilitated the widespread treatment of HIV/AIDS, the large-scale manufacture of generic combinations of DAA drugs for treatment of HCV might eventually result in minimum target prices of US$100–250 for treatment durations of 12 weeks. However, the reduced cost associated with generic drugs is unlikely to apply until patent protection lapses in 15 years.[17] Until then, cost reduction might be feasible through shortened treatment durations, especially in countries such as the USA where pricing is per pill rather than per treatment course. The lack of transparency in prices set by pharmaceutical companies restricts accurate cost comparisons. In the USA, the wholesale acquisition cost of ledipasvir and sofosbuvir is $1125 per pill, and a course of ledipasvir and sofosbuvir is reduced from $94 500 to $63 000 when treatment is reduced from 12 weeks to 8 weeks.[18] However, shortening of regimens will not necessarily affect prices in countries that pay by treatment course rather than per pill, such as Australia, Canada, France, Spain, and Italy.

Shortened treatment durations could result in reduced overall costs; however, shortening of treatment should not be done at the expense of reducing overall efficacy.[19] The potential harms of short-duration therapy include increased relapse rates, development of viral resistance, and loss to follow-up. Regarding relapse, data from several clinical trials have indicated that there is a high likelihood of successful retreatment. In the SYNERGY trial,[20] patients who failed 4–6 weeks of ledipasvir and sofosbuvir (plus one or two additional DAAs) and were retreated with 12 weeks of ledipasvir and sofosbuvir had an SVR of 91%. Any short-duration therapy should incorporate retreatment strategies for patients who do not achieve an SVR.[21] Retreatment has been effective in clinical trials but has not been validated in real-world clinical settings, and payers might refuse to cover retreatment costs, even though these costs might be lower overall. Theoretically, a patient who fails a 6 week course of DAA therapy and is successfully retreated with a 12 week course would still receive fewer weeks of therapy than if they had received the initial 24 weeks. This theoretical calculation for overall duration is based on a similar approach used by O'Brien and colleagues,[21] who included both patients who relapsed and responded to retreatment with 24 weeks of ledipasvir and sofosbuvir and those who achieved an SVR with the initial 8 weeks of treatment to calculate an overall SVR of about 99%. In that study,[21] a high proportion of patients achieved an SVR with a shorter treatment duration than the usual initial course of 12 weeks, resulting in fewer pills and reduced overall treatment costs. However, failure to achieve an SVR with short-duration therapy might lead to emergence of resistance-associated variants (RAVs). The effect of RAVs on the success of retreatment has not yet been established. Future studies are needed to understand the natural evolution of RAVs over time and to develop retreatment strategies for patients with RAVs at baseline. Widespread use of ultrashort DAA therapy will depend on the success of retreatment of those who have failed short-duration therapy.

Another rationale for short-duration therapy is based on the argument that treatment adherence decreases as dosing frequency increases—ie, patients are more compliant with a once daily pill than they are with regimens based on pills taken twice or three times a day.[22] Adherence also decreases as treatment duration increases. For example, in the SYNERGY trial,[23] patients who received DAA therapy for 6 weeks with one to three pills a day showed high adherence (>95%) compared with those who received one pill per day for 12 weeks, as determined by use of the medication event-monitoring system, pill counting, and patient reports. However, adherence to a 12 week regimen, as assessed by the medication event-monitoring system, significantly declined between weeks 0–4 and 8–12 (p=0·04).[23] Outside of the clinical trial setting, regimens that have a shorter duration and low pill burden, with few adverse effects, could improve patient adherence. It is important to note, however, that the effect of shorter-duration regimens on patient adherence has not been further studied in real-world settings. The high rates of SVR observed in real-world studies[7–9] suggests either that patients are as adherent in real-world settings as they are in clinical trials with 12 week therapies or that there is a wide margin for non-adherence, and perhaps even that patients are being overtreated. Further studies are needed to understand the interaction between adherence and duration and how this interaction affects the effectiveness of combination DAA therapy.

Some clinical trials[24–33] have aimed to reduce treatment duration to less than 8 weeks (table). Overall, the proportion of patients with an SVR after 4 or 6 weeks of therapy was lower than that observed in large clinical trials of patients treated with 8 or 12 weeks of therapy. However, 6 weeks of sofosbuvir, velpatasvir, and voxilaprevir resulted in an SVR in 14 (93·3%, 95% CI 68·1–99·8) of 15 patients with HCV genotype 1 who were treatment-naive and did not have cirrhosis.[29] These clinical trials[24–33] of ultrashort-duration therapies had a small sample size of 6–31 patients each and only included patients with HCV genotype 1 infection. Larger studies with the new pangenotypic regimens are needed to determine whether 6 weeks of therapy might be suitable for selected subgroups of patients.[28]

	Duration (weeks)	Treatment-naive	Cirrhosis	Sustained virological response (n [%])
Sofosbuvir and odalasvir (PROXY)[32]	6	Yes	No	12 (100%)
Ledipasvir, sofosbuvir, GS-9669 (SYNERGY)[27]	6	Yes	No	19 (95%)
Ledipasvir, sofosbuvir, GS-9451 (SYNERGY)[27]	6	Yes	No	19 (95%)
Sofosbuvir, ledipasvir, ribavirin (ELECTRON)[31]	6	Yes	No	17 (68%)
Sofosbuvir, velpatasvir, voxilaprevir (formerly GS-9857; LEPTON)[29]	6	Yes	No	14 (93%)
Grazoprevir, elbasvir, sofosbuvir (C-SWIFT)[28]	6	Yes	No	26 (87%)
Daclatasvir, asunaprevir, beclabuvir, sofosbuvir (FOURward)[30]	6	Yes	No	8 (57%)
Sofosbuvir, velpatasvir, voxilaprevir (LEPTON)[29]	6	No	Yes	20 (67%)
Ledipasvir, sofosbuvir, GS-9451 (SYNERGY)[26]	6	No	Yes (48%)	20 (80%)
Grazoprevir, elbasvir, sofosbuvir (C-SWIFT)[28]	6	Yes	Yes	16 (80%)
Sofosbuvir, velpatasvir, voxilaprevir (LEPTON)[29]	6	Yes	Yes	13 (87%)
Ledipasvir, sofosbuvir, GS-9451 (SYNERGY)[26]	6	Yes	Yes (40%)	18 (72%)
Ledipasvir, sofosbuvir, GS-9451 (SYNERGY)[25]	4	Yes	No	10 (40%)
Ledipasvir, sofosbuvir, GS-9451, GS-9669 (SYNERGY)[25]	4	Yes	No	5 (20%)
Grazoprevir, elbasvir, sofosbuvir (C-SWIFT)[28]	4	Yes	No	10 (32%)
Sofosbuvir, velpatasvir, voxilaprevir (LEPTON)[29]	4	Yes	No	4 (27%)
Daclatasvir, asunaprevir, beclabuvir, sofosbuvir (FOURward)[30]	4	Yes	No	4 (29%)
Sofosbuvir, ledipasvir, asunaprevir (SODAPI)[33]	3	Yes (50%)	No	6 (100%)
Sofosbuvir, daclatasvir, simeprevir (SODAPI)[33]	3	Yes (67%)	No	6 (100%)
Sofosbuvir, daclatasvir, asunaprevir (SODAPI)[33]	3	Yes (83%)	No	6 (100%)

The SODAPI study was a clinical trial of response-guided therapy.

Table: **Clinical trials of short-duration direct-acting antiviral regimens for patients with hepatitis C virus genotype 1 infection**

Although a reduction in treatment duration to less than 8 weeks was not possible with existing DAA drugs, clinical trials have identified potential predictors of an SVR with short-duration treatment. The SYNERGY trial[25] found that a lower viral load at baseline, young age, HCV genotype 1b infection, and absence of RAVs that confer more than 20 times resistance to therapy predict an improved response to short-duration therapy. Although on-treatment week 4 viral loads did not predict treatment outcome,[34] preliminary viral measurements—as early as the first or second week of therapy—might have some utility.[35] Additionally, modelling predicted that a more rapid second-phase viral decline would facilitate treatment durations of less than 8 weeks, although with a carefully selected regimen.[36] According to Perelson and Guedj,[36] nucleoside analogue inhibitors, although powerful DAA drugs associated with improved treatment responses, do not produce a rapid second-phase decline when used alone; the addition of protease inhibitors improves this crucial second phase of viral clearance. Similarly, O'Brien and colleagues[37] reported that a patient's sex and *IFNL4* rs12979860 genotype were associated with an SVR after 8 weeks of treatment with ledipasvir and sofosbuvir in the ION-3 study. In light of the results of ultrashort-duration DAA studies,[24–33] development of a predictive algorithm that provides an individualised estimate of an SVR for a given baseline viral load and host characteristics could streamline clinical decision making.

Lau and colleagues' response-guided therapy clinical trial[33] showed that patients treated with a regimen based on three DAA drugs (NS3/4 protease inhibitor and dual NS5A inhibitor–NS5B nucleotide analogue), who exhibit an ultrarapid viral response (defined as an HCV RNA concentration of <500 IU/mL by the second day of therapy), might be treated effectively in just 3 weeks. This small proof-of-concept trial,[33] which enrolled 18 Chinese patients with HCV genotype 1b infection and without cirrhosis, suggested that short-duration therapy could be highly effective in a select patient population and that the duration of treatment needed to achieve an SVR was shorter than previously recognised, at least for some patients. Although the generalisability of these results was restricted because of the selective patient population, patients who had an ultrarapid viral response by day 2 of therapy and received 3 weeks of DAA therapy had a significantly lower mean baseline concentration of HCV RNA than did those who did not achieve an ultrarapid viral response ($6 \cdot 0$ $\log_{10}$ IU/mL *vs* $7 \cdot 0$ $\log_{10}$ IU/mL; $p<0 \cdot 0001$).[33] These results suggest that the baseline concentration of HCV RNA should be used as part of a clinical algorithm to predict which individuals might respond favourably to short-duration therapy. The role of response-guided therapy has changed with the advent of highly effective DAA therapy.[38] However, individualising treatment duration with response-guided therapy might still be beneficial if we are able to validate the response-guided strategy for the objective of reducing treatment duration and identifying specific populations that might benefit from a shorter duration of DAA therapy.[38] Logistical barriers to doing viral testing early in the course of therapy exist, although it is by no means impossible. In fact, response-guided therapy was routine at the start of hepatitis C care when interferon-based methods were used. Reintroducing response-guided therapy to what has been, until now, relatively straightforward combination DAA-based therapy might increase the complexity of HCV therapy, which might discourage mid-level and non-specialist providers (ie, those not trained in hepatology or infectious diseases) from treating HCV. This obstacle is worth considering given the relative shortage of HCV providers compared with the global disease burden. However, providers can easily learn to make therapeutic adjustments with proper training.[39] Some health-care systems might choose to designate and train personnel in these types of treatment adjustments if such training could save on overall cost and improve treatment outcomes. In the future, larger clinical trials might allow for validation of the surrogate markers used in response-guided therapy, such as baseline HCV viral load, which might further simplify HCV treatment.

Just as existing treatment guidelines consider certain patient characteristics (eg, the presence of cirrhosis, treatment history) in recommendations regarding treatment durations of 8–24 weeks,[4] effective use of shorter durations of DAA treatment might require identification of the appropriate patient population. A simple, cost-effective clinical algorithm to predict which individuals are likely to respond favourably to short-duration therapy could provide a simpler management strategy to all types of providers and enhance a broad global uptake of DAA therapy. The clinical algorithm could be based on clinical characteristics, such as baseline HCV RNA concentrations, cirrhosis status, *IFNL4* genotype, absence of RAVs, sex, and concentrations of host cytokines. In countries where resources are scarce, testing at the individual level might not be feasible, but population data might suggest the most cost-effective treatment duration. For example, the rapid response to treatment in the study by Lau and colleagues[33] might reflect the predominance of HCV genotype 1b and the low frequency of unfavourable *IFNL4* alleles among Chinese patients. If specific populations respond well to shortened regimens, this would provide opportunities to more cost-effectively and more rapidly escalate HCV treatment in ethnically homogeneous areas (eg, China and Mongolia). Data from clinical trials and observational cohorts will be crucial to develop and refine clinical algorithms to streamline treatment management of patients by all types of providers.

The rationale for short-duration DAA regimens has both strengths and limitations. Limitations include the complexity of treatment management, increased relapse rates and viral resistance, retreatment of patients who

Search strategy and selection criteria

We did a review of abstracts presented in the hepatitis C virus treatment, therapeutics, new and existing agents, or clinical trials sessions of the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases conference (2014–16) with the key words "6 weeks", "4 weeks", or "short". We searched for the identified abstracts in the National Library of Medicine through PubMed to determine whether they had been published as an article. If a paper had been published, we cited the published article, otherwise we cited the conference abstract. We included randomised trials if they cited sustained virological response as a primary or secondary endpoint.

relapse, and loss to follow-up. Further clinical trials and observational studies are needed to address these limitations before moving forwards with the growing number of new pangenotypic DAA regimens. Additionally, post-treatment surveillance of these DAA regimens will be needed. Although these limitations exist, the rationale cannot be ignored, including lower overall costs as result of fewer pills during treatment and potential increased adherence. Development of a simple, cost-effective clinical algorithm is key to implementation of short-duration therapy in the real-world setting.

In conclusion, shortening HCV therapy in targeted populations seems possible and should be further explored. For the treatment of all patients with chronic hepatitis C, newer DAAs with increased potency and a longer half-life need to be developed. Factors that might predict an SVR with ultrashort-duration combination therapy with DAAs need to be explored further in large clinical trials. Coordinated global strategies to explore short-duration therapy for hepatitis C are warranted to escalate HCV care worldwide.

Contributors

BE, EMW, TRO, SK, and GL did the literature search and interpreted the data. BE and EMW wrote the first draft of the manuscript. All authors reviewed and had the opportunity to revise the report.

Declaration of interests

EMW reports research funding to her institution from Gilead Science. All other authors declare no competing interests.

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References

1 The Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol* 2017; **2:** 161–76.

2 Polaris Observatory. Hepatitis C. 2016. http://polarisobservatory.org/polaris/hepC.htm (accessed Jan 23, 2017).

3 Kohli A, Shaffer A, Sherman A, Kottilil S. Treatment of hepatitis C: a systematic review. *JAMA* 2014; **312:** 631–40.

4 AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology* 2015; **62:** 932–54.

5 European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2016. *J Hepatol* 2017; **66:** 153–94.

6 Omata M, Kanda T, Wei L, et al. APASL consensus statements and recommendation on treatment of hepatitis C. *Hepatol Int* 2016; **10:** 702–26.

7 Kowdley KV, Gordon SC, Reddy KR, et al, for the ION-3 Investigators. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med* 2014; **370:** 1879–88.

8 Terrault NA, Zeuzem S, Di Bisceglie AM, et al. Effectiveness of ledipasvir–sofosbuvir combination in patients with hepatitis C virus infection and factors associated with sustained virologic response. *Gastroenterology* 2016; **151:** 1131–40.

9 Kowdley KV, Sundaram V, Jeon CY, et al. Eight weeks of ledipasvir/sofosbuvir is effective for selected patients with genotype 1 hepatitis C virus infection. *Hepatology* 2016; published online Dec 27. DOI:10.1002/hep.29005.

10 Welzel TM, Asselah T, Dumas EO, et al. Ombitasvir, paritaprevir, and ritonavir plus dasabuvir for 8 weeks in previously untreated patients with hepatitis C virus genotype 1b infection without cirrhosis (GARNET): a single-arm, open-label, phase 3b trial. *Lancet Gastroenterol Hepatol* 2017; **2:** 494–500.

11 Zeuzem S, Feld J, Wang S, et al. ENDURANCE-1: a phase 3 evaluation of the efficacy and safety of 8- versus 12-week treatment with glecaprevir/pibrentasvir (formerly ABT-493/ABT-530) in HCV genotype 1 infected patients with or without HIV-1 co-infection and without cirrhosis. AASLD. The Liver Meeting; Boston, MA; Nov 2016. http://www.natap.org/2016/AASLD/AASLD_32.htm (accessed Jan 20, 2017).

12 Jacobson IM, Gordon SC, Kowdley KV, et al. A randomized phase 3 trial of sofosbuvir/velpatasvir/voxilaprevir for 8 weeks compared to sofosbuvir/velpatasvir for 12 weeks in DAA-naïve genotype 1–6 HCV infected patients: the POLARIS-2 study. AASLD. The Liver Meeting; Boston, MA; Nov 2016. http://www.natap.org/2016/AASLD/AASLD_33.htm (accessed Jan 20, 2017).

13 Foster GR, Thompson A, Ruane PJ, et al. A randomized, phase 3 trial of sofosbuvir/velpatasvir/voxilaprevir for 8 weeks and sofosbuvir/velpatasvir for 12 weeks for patients with genotype 3 HCV infection and cirrhosis: the POLARIS-3 study. AASLD. The Liver Meeting; Boston, MA; Nov 2016. http://www.natap.org/2016/AASLD/AASLD_34.htm (accessed Jan 20, 2017).

14 Lawitz E, Buti M, Vierling JM, et al. Safety and efficacy of a fixed-dose combination regimen of grazoprevir, ruzasvir, and uprifosbuvir with and without ribavirin in patients with and without cirrhosis with chronic hepatitis C virus genotype 1, 2, or 3 infection (C-CREST-1 and C-CREST-2, part B): two randomised, phase 2, open-label trials. *Lancet Gastroenterol Hepatol* 2017; published online Aug 9. http://dx.doi.org/10.1016/S2468-1253(17)30163-2.

15 Chhatwal J, Kanwal F, Roberts MS, Dunn MA. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. *Ann Intern Med* 2015; **162:** 397–406.

16 Iyengar S, Tay-Teo K, Vogler S, et al. Prices, costs, and affordability of new medicines for hepatitis C in 30 countries: an economic analysis. *PLoS Med* 2016; **13:** e1002032.

17 Hill A, Khoo S, Fortunak J, Simmons B, Ford N. Minimum costs for producing hepatitis C direct-acting antivirals for use in large-scale treatment access programs in developing countries. *Clin Infect Dis* 2014; **58:** 928–36.

18 Rosenthal ES, Graham CS. Price and affordability of direct-acting antiviral regimens for hepatitis C virus in the United States. *Infect Agent Cancer* 2016; **11:** 24.

19 Younossi ZM. The price of shortening anti-hepatitis C virus therapy: is this truly cost saving? *Clin Liver Dis* 2015; **6:** 126–28.

20 Wilson EM, Kattakuzhy S, Sidharthan S, et al. Successful retreatment of chronic HCV genotype-1 infection with ledipasvir and sofosbuvir after initial short course therapy with direct-acting antiviral regimens. *Clin Infect Dis* 2016; **62:** 280–88.

21 O'Brien TR, Feld JJ, Kottilil S, Pfeiffer RM. No scientific basis to restrict 8 weeks of treatment with ledipasvir/sofosbuvir to patients with hepatitis C virus RNA <6 000 000 IU/mL. *Hepatology* 2016; **63:** 28–30.

22 Saini SD, Schoenfeld P, Kaulback K, Dubinsky MC. Effect of medication dosing frequency on adherence in chronic diseases. *Am J Manag Care* 2009; **15:** e22–33.

23 Petersen T, Townsend K, Gordon LA, et al. High adherence to all-oral directly acting antiviral HCV therapy among an inner-city patient population in a phase 2a study. *Hepatol Int* 2015; **10:** 310–19.

24 Nafisi S, Roy S, Gish R, Manch R, Kohli A. Defining the possibilities: is short duration treatment of chronic hepatitis C genotype 1 with sofosbuvir-containing regimens likely to be as effective as current regimens? *Expert Rev Anti Infect Ther* 2016; **14:** 41–56.

25 Kohli A, Kattakuzhy S, Sidharthan S, et al. Four-week direct-acting antiviral regimens in noncirrhotic patients with hepatitis C virus genotype 1 infection: an open-label, nonrandomized trial. *Ann Intern Med* 2015; **163:** 899–907.

26 Kattakuzhy S, Wilson E, Sidharthan S, et al. Moderate sustained virologic response rates with 6-week combination directly acting anti-hepatitis C virus therapy in patients with advanced liver disease. *Clin Infect Dis* 2016; **62:** 440–47.

27 Kohli A, Osinusi A, Sims Z, et al. Virological response after 6 week triple-drug regimens for hepatitis C: a proof-of-concept phase 2A cohort study. *Lancet* 2015; **385:** 1107–13.

28 Poordad F, Lawitz E, Gutierrez JA, et al. O006: C-swift: grazoprevir/elbasvir + sofosbuvir in cirrhotic and noncirrhotic, treatment-naive patients with hepatitis C virus genotype 1 infection, for durations of 4, 6 or 8 weeks and genotype 3 infection for durations of 8 or 12 weeks. *J Hepatol* 2015; **62:** S192–93.

29 Gane EJ, Schwabe C, Hyland RH, et al. Efficacy of the combination of sofosbuvir, velpatasvir, and the NS3/4A protease inhibitor GS-9857 in treatment-naïve or previously treated patients with hepatitis C virus genotype 1 or 3 infections. *Gastroenterology* 2016; **151:** 448–56.

30 Sulkowski MS, Flamm S, Kayali Z, et al. Short-duration treatment for chronic hepatitis C virus with daclatasvir, asunaprevir, beclabuvir and sofosbuvir (FOURward study). *Liver Int* 2016; published online Dec 10. DOI:10.1111/liv.13335.

31 Gane EJ, Stedman CA, Hyland RH, et al. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. *Gastroenterology* 2014; **146:** 736–43.

32 Gane E, Schwabe C, Mader M, et al. LP06: sustained virologic response after ACH-3102 and sofosbuvir treatment for 8 or 6 weeks: a phase 2 "proxy" study. *J Hepatol* 2015; **62:** S266.

33 Lau G, Benhamou Y, Chen G, et al. Efficacy and safety of 3-week response-guided triple direct-acting antiviral therapy for chronic hepatitis C infection: a phase 2, open-label, proof-of-concept study. *Lancet Gastroenterol Hepatol* 2016; **1:** 97–104.

34 Sidharthan S, Kohli A, Sims Z, et al. Utility of hepatitis C viral load monitoring on direct-acting antiviral therapy. *Clin Infect Dis* 2015; **60:** 1743–51.

35 Maasoumy B, Vermehren J, Welker MW, et al. Clinical value of on-treatment HCV RNA levels during different sofosbuvir-based antiviral regimens. *J Hepatol* 2016; **65:** 473–82.

36 Perelson AS, Guedj J. Modelling hepatitis C therapy—predicting effects of treatment. *Nat Rev Gastroenterol Hepatol* 2015; **12:** 437–45.

37 O'Brien TR, Lang Kuhs KA, Pfeiffer RM. Subgroup differences in response to 8 weeks of ledipasvir/sofosbuvir for chronic hepatitis C. *Open Forum Infect Dis* 2014; **1:** ofu110.

38 Maasoumy B, Vermehren J. Diagnostics in hepatitis C: the end of response-guided therapy? *J Hepatol* 2016; **65** (suppl 1)**:** S67–81.

39 Thornton K, Deming P, Manch RA, et al. Is response guided therapy dead? Low cure rates in patients with detectable hepatitis C virus at week 4 of treatment. *Hepatol Int* 2016; **10:** 624–31.