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Title: No one size fits all - shortening duration of therapy with direct acting antivirals for Hepatitis C genotype 1 infection

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Abbreviations: HCV, Hepatitis C; IFN, Interferon; DAA, Direct-acting antivirals; SVR, Sustained virologic response; FDA, Food and Drug Administration; IDSA, Infectious Diseases Society of America; AASLD, American Association for the Study of Liver Diseases; NICE, National Institute of Clinical Excellence; EOT, End of treatment; RVR, Rapid virologic response; RAS, Resistance associated substitutions; MEMS, Medication Events Monitoring System.

Abstract

The advent of shorter duration, highly effective and well tolerated interferon-free therapy now provides an opportunity for virtually all HCV infected individuals to be cured. However, there continues to be a need to simplify and shorten treatment duration. Shortening therapy to 8 weeks with sofosbuvir and ledipasvir can be considered in treatment patients with HCV genotype 1 infection and low baseline viral load. A number of other 8 week dual and triple therapy direct acting antiviral (DAA) regimens are in advanced clinical development. Several small studies have further demonstrated the feasibility of 6 weeks of sofosbuvir therapy in combination with an NS5A inhibitor and a protease inhibitor for HCV genotype 1. Four

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weeks of therapy with various combinations of the currently available DAAs appears to be sub-optimal with poor response rates observed in phase 2 trials. Response guided therapy is another promising tool that may allow for shorter therapy but require further research. Shortening therapy and retreating relapsers may be a viable cost-saving measure, but requires further cost-benefit analysis and more data on the impact of resistance on re-treatment options.

Keywords: HCV, Treatment, DAA, Shortening therapy

Introduction

Hepatitis C virus (HCV) infection remains a major global public health problem. Despite the declining number of new infections in the developed world, the healthcare and societal burden of advanced liver disease related to HCV is expected to increase over the next decade [1]. Historically, treatment with Interferon (IFN) was poorly tolerated, and associated with long treatment durations between 24 and 48 weeks [2]. The advent of shorter duration, highly effective and well tolerated interferon-free therapy now provides an opportunity for virtually all HCV infected individuals to be cured [3-12]. There continues to be a need to simplify therapy, and shorten treatment duration while maintaining high cure rates to expand treatment access.

The rapidity of viral suppression seen with two or more direct-acting antivirals in combination has allowed for shorter duration of HCV therapy compared to interferon-containing regimens. Three interferon-free direct acting antiviral (DAA) regimens for the treatment of hepatitis C genotype 1 infection have been approved in the US and Europe since 2014. Sofosbuvir and ledipasvir is licensed for 12 weeks or 24 weeks. Additionally, this

regimen is optional for 8 weeks of therapy in non-cirrhotic treatment naïve patients with a low viral load. The triple therapy combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir is approved for 12 or 24 weeks. The fixed dose combination of grazoprevir and elbasvir is approved for 12 or 16 weeks. These approvals were supported by extensive and robust phase 3 clinical trial programs [3-12].

These clinical trial programs were designed with the goal of maximizing the SVR rates across the overall treated population. As a result, some patients received longer therapy than they may have required, and 12 weeks of therapy may represent over-treatment for a proportion of patients. Shortening therapy has several potential advantages. Shorter therapy will reduce the cost of treatment, allowing more patients to access therapy, especially in the current environment of pricing per pill.

We review the available data on the treatment of hepatitis C therapy genotype 1 mono-infection for less than 12 weeks, including efficacy, resistance, compliance and cost-effectiveness.

Eight Week DAA Therapies

Sofosbuvir-ledipasvir

The ION-3 trial compared the efficacy of sofosbuvir-ledipasvir $\pm$ ribavirin for 8 weeks, or sofosbuvir-ledipasvir for 12 weeks in non-cirrhotic, treatment naive genotype 1 patients [5]. SVR rates were numerically lower in patients treated for 8 weeks with or without ribavirin, compared to 12 weeks of therapy with sofosbuvir-ledipasvir. However, in a per protocol analysis, patients with a baseline HCV viral load $< 6 \times 10^6$ IU/ml were found to have similarly high SVR rates regardless of whether they received 8 or 12 weeks of therapy [13]

(Figure 1). According to the approval of the Food and Drug Administration (FDA) this regimen is optional for 8 weeks in this sub-group of patients based on these data. However, the IDSA/AASLD HCV treatment guidelines continue to advocate 12-weeks of therapy with sofosbuvir-ledipasvir.

The UK National Institute for Clinical Excellence (NICE) issued recommendations for the use of sofosbuvir-ledipasvir for treating chronic hepatitis C in early 2015 [14]. In contrast to the IDSA/AASLD, NICE recommended that all non-cirrhotic treatment naïve genotype 1 patients receive 8 weeks of therapy based on cost-effectiveness analyses, regardless of baseline viral load for patients receiving therapy in the UK National Health Service.

The 6-million IU/ml HCV RNA cut-off for prescribing 8 weeks of therapy was based on an uncontrolled *post hoc* analysis of the ION-3 trial; the findings of which did not approach statistical significance. The study was also not sufficiently powered to detect a statistically significant difference in relapse rates based on viral load cut-off levels between the 8-week and 12-week treatment arms [15]. Despite the controversy surrounding this viral load cut-off, early data from real-world registry studies appear to support the FDA 8-week label recommendation and 6-million IU/ml HCV RNA cut-off. The efficacy of 8-week label approved sofosbuvir-ledipasvir therapy for genotype 1 treatment naïve, non-cirrhotic patients was assessed in a large cohort treated in the TRIO network in the United States [16]. Virologic outcomes were compared to a group who received 12 weeks of therapy. SVR_{12} was achieved in 855/895 (95.5%) of patients in the entire cohort. Intent to treat SVR_{12} was 95.2% in patients in the label-approved 8-week group, and 95.5% in those treated for 12 weeks.

Data on the efficacy of this regimen for durations shorter than 8 weeks is limited. A phase 2 trial investigated the efficacy of 6 weeks of sofosbuvir-ledipasvir with ribavirin in genotype 1, treatment naïve non-cirrhotics [17]. SVR_{12} was achieved in 17/25 (68%) of patients. Mean HCV RNA was ~3.1 million IU/ml. Based on this small cohort, 6 weeks of therapy with sofosbuvir-ledipasvir with ribavirin does not appear to an optimal treatment duration for treatment naïve genotype 1 patients.

Sofosbuvir and Simeprevir

The OPTIMIST phase-3 trial was conducted to assess the efficacy of sofosbuvir and simeprevir for 8 or 12 weeks in DAA-treatment naïve patients without cirrhosis [18]. Intent to treat SVR_{12} in the 8 week arm was 83% (128/155), compared to 97% in the 12 week arm. In patients treated for 8 weeks, a relationship between baseline HCV RNA and achieving SVR was observed. Of the 48 patients with HCV RNA < 4 million IU/ml treated for 8 weeks, 46 (96%) had a sustained virologic response. The presence of the Q80K polymorphism in genotype 1a patients was associated with a lower SVR rate (73%) in the 8 week treatment arm; consistent with the reduced efficacy of simeprevir in the presence of this substitution.

Sofosbuvir and Velpatasvir + GS-9857

The combination of sofosbuvir and velpatasvir (100mg daily) for 8 weeks produced an SVR in 26/29 (90%) of treatment naïve patients without cirrhosis [19]. The addition of a protease inhibitor (GS-9857) to this regimen was associated with an SVR in 100% of interferon treatment experienced patients with cirrhosis. A phase 3 trial is investigating the efficacy of this regimen for 8 weeks in a larger group of patients [20].

ABT-493 and ABT-530

ABT-493 (300mg) is a pangenotypic NS3/4A protease inhibitor in development, in combination with ABT-530 (120mg), a pangenotypic NS5A inhibitor. The SURVEYOR-1 phase 2 trial assessed the efficacy of this regimen administered for 8 weeks in DAA treatment naïve patients without cirrhosis [21]. Intention to treat SVR_{12} was achieved in 33/34 (97%) of patients. No virologic failures or relapses were observed.

Six Week DAA Therapies

Several phase 2 studies have examined the efficacy of a combination of 3 or 4 DAAs for the treatment of HCV genotype 1 infection in treatment naïve patients (Figure 2).

In the **FOURward** phase 2 study, treatment naïve genotype 1 patients were administered 4 DAAs in combination for 6 weeks - a protease inhibitor (asunaprevir), an NS5A inihibitor (daclatasvir), and a non-nucleoside (beclabuvir) and nucleoside (sofosbuvir) polymerase inhibitor. The majority of patients had Metavir F0-F2 fibrosis (86%) [22]. SVR_{12} was achieved in 8/14 (57%) of patients. SVR rates were generally higher in patients with lower baseline HCV RNA – the SVR rate in patients with baseline HCV RNA < 2 million IU/ml was 80%, although there were only 5 patients in this group.

The **C-SWIFT** study examined the efficacy of sofosbuvir in combination with grazoprevir and elbasvir for 6 weeks in treatment naïve non-cirrhotics [23]. Intention to treat SVR_{12} was achieved by 26/30 (87%) of patients. Mean baseline HCV RNA was ~ 3 million IU/ml. All patients that failed therapy experienced viral relapse by post-treatment week 4.

A phase 2A trial investigated 6 weeks of therapy with sofosbuvir-ledipasvir administered with (i) a protease inhibitor (GS-9451) or (ii) a non-nucleoside NS5B inhibitor (GS-9669). One quarter of patients had advanced (F3) fibrosis at baseline [24]. SVR_{12} (intention to treat) was achieved in 19/20 (95%) in both groups.

The combination of sofosbuvir with a novel NS5A inhibitor (velpatasvir), and a pangenotypic protease inhibitor (GS-9857) was also associated with high rates of SVR (93%) in treatment naïve non-cirrhotics with 6 weeks of therapy [20].

Four week DAA therapy

Five preliminary phase 2 studies have assessed the potential feasibility of four weeks of DAA for HCV genotype 1 infection (Figure 3). Treatment naïve patients without cirrhosis received therapy containing a sofosbuvir backbone with an NS5A inhibitor (ledipasvir, grazoprevir or daclatasvir), and a protease inhibitor (elbasvir, GS-9857, GS-9451) $\pm$ a non-polymerase NS5B inhibitor (GS-9799). SVR rates in all 5 studies were suboptimal (figure 3) – the highest SVR rate of 40% was achieved with 4 weeks of therapy with sofosbuvir, ledipasvir and GS-9451 [25].

Response guided therapy

Historically, on-treatment HCV viral kinetics served as a predictor of treatment outcome [27]. Additionally, response guided-therapy with interferon utilized day 28 HCV viral load level to inform duration of therapy [28]. On-treatment viral load also predicted treatment failure with the first generation protease inhibitors (boceprevir and telaprevir), providing the basis for stopping rules [29].

The rapid virologic decline observed with combination DAA therapy has called into question the utility of monitoring viral load during DAA therapy. In contrast to IFN-based therapy, early viral kinetics do not appear to predict treatment response with DAAs. However, there may be a role for on-treatment HCV RNA measurements to predict duration of DAA therapy needed to achieve SVR, potentially allowing for shortening therapy in some patients.

The SODAPI trial provided proof of concept for shortening therapy based on early virologic response with DAAs [30]. In this study, treatment naïve, non-cirrhotic Chinese patients with HCV genotype 1b were eligible for 3 weeks with sofosbuvir, an NS5A inhibitor (daclatasvir or ledipasvir), and a protease inhibitor (simeprevir or asunaprevir) if they achieved a rapid virologic response. Rapid virologic response was defined as a HCV RNA < 500 IU/ml by day 2 of therapy. Twenty-six patients were randomly assigned to receive sofosbuvir in combination with (a) ledipasvir and asunaprevir (n=12), (b) daclatasvir and simeprevir (n=6) or (c) daclatasvir and asunaprevir (n=8). Patients that did not achieve RVR by day 2 rolled over to a standard of care treatment arm (8-12 weeks of sofosbuvir and ledipasvir). RVR was achieved by 18/26 (69%) of patients. Baseline viral load was higher in patients without an RVR. End of treatment (EOT) response and SVR were achieved in 18/18 (100%) of patients with a rapid virologic response.

In a study by Dahari and colleagues [31], mathematical modelling was used to predict time to cure using on-treatment viral load testing with currently approved DAA regimens. The model was derived using intensive viral kinetic data from 58 patients treated for 12 weeks with sofosbuvir and ledipasvir or daclatasvir or simeprevir. Difficult to treat patients were well represented in the study, including 43% with advanced fibrosis (F3) and 57% with cirrhosis – genotype 1 was predominant (86%). Using the model, the mean predicted time to cure (i.e. <

1 viral copy in the entire extracellular body fluid) was 6.9 weeks [95% confidence interval; 6.1 – 7.7 weeks], with no difference between cirrhotics and non-cirrhotics. Pre-treatment viral load was not predictive of time to viral clearance. However, time to viral load < 15 IU/ml was highly associated with the time to cure. The modelling indicated that 92% of patients who had HCV < 15 IU/ml at day 14 would have reached the cure boundary with 6 weeks of therapy. The authors suggest that therapy could be shortened in more than 80% of patients in this study without affecting SVR rates.

Viral Resistance

The biggest concern with shortening therapy is the emergence of resistance-associated substitutions (RAS) in patients who relapse. This is particularly relevant to NS5A RAS, as they have been shown to persist for > 2 years after therapy, and impact on re-treatment success. In the ION-3 trial, 20/413 (4.6%) patients that received 8 weeks of sofosbuvir-ledipasvir ± ribavirin had virologic relapse post-therapy [5]. Of the 20 patients who had a relapse, 13 (65%) had NS5A RAS at the time of relapse.

A retreatment study examined the efficacy of 24 weeks of sofosbuvir-ledipasvir in patients who failed 8 weeks of therapy with sofosbuvir-ledipasvir [32]. Baseline NS5A RAS were present in 19/30 (63%). Of the 30 patients, 24 (80%) had a sustained virologic response – 13/19 (68%) and 11/11 (100%) of patients with and without NS5A RAS respectively. In contrast, 14/15 (93%) of treatment naïve patients that failed 12 weeks of sofosbuvir-ledipasvir ± ribavirin therapy in ION-1, -2, and -3 had NS5A RAS detectable at relapse. Retreatment efficacy with 24 weeks of sofosbuvir-ledipasvir was 46% in this group, although this cohort included a greater proportion of cirrhotics.

Patients that failed 4 or 6 weeks of therapy with sofosbuvir, daclatasvir, asunaprevir and beclabuvir in the **FOURward** study were offered retreatment. Only 50% had NS5A RAS after failure with 4 or 6 weeks of therapy [25]. Of the 15 patients that were retreated with 12 weeks of the same combination with ribavirin, 15 (100%) achieved SVR4/8.

Adherence

An added benefit of shortening therapy is the potential to improve adherence in populations with risk factors for poor or non-adherence. Adherence was measured in an urban cohort as part of the synergy study [33]. Psychiatric co-morbidity and recent drug/alcohol abuse were common in the study population. Adherence was assessed using MEMs caps and pill counts, and compared in patients randomized to receive 6 or 12 weeks of DAA combination therapy. Overall adherence was excellent in the study, although it was noted that increased pill burden and duration decreased adherence.

Discussion

The advent of highly effective DAA therapy for HCV has created a paradigm where virtually all treatment naïve patients can be cured of HCV once they receive 12 weeks of therapy. However, universal access to therapy is limited by a number of factors, including under-diagnosis, and drug costs. The commonly employed strategy to address costs at present is to limit access to the treatment (based on fibrosis stage). In the absence drug pricing reforms, shortening therapy without significantly compromising SVR rates would reduce the cost of therapy, allowing more patients to be treated within existing budgets. This is most feasible in treatment naïve patients without cirrhosis.

Shortening therapy to eight weeks with sofosbuvir-ledipasvir is supported by a strong evidence base. At present, it is also the only combination with optional treatment duration of less than 12 weeks. Pre-treatment factors to support prescribing this 8 week regimen include baseline viral load < 6 million IU/ml, the absence of cirrhosis and previous treatment. The 6-million IU/ml viral load cut-off from the ION-3 trial is controversial as it does not appear to be statistically justified. Outcomes from the TRIO network demonstrated comparably high SVR rates in patients meeting this criterion [7]. However, this data was not designed to specifically examine this cut-off, with only 8 patients in the TRIO network with a viral load of > 6 million IU/ml receiving 8 weeks of therapy. Outcome data from the National Health Service in the UK, where treatment is limited to 8 weeks for sofosbuvir-ledipasvir (regardless of baseline viral load) is awaited and will provide further evidence for the feasibility of shortening therapy in all non-cirrhotic patients.

Another promising 8 week regimen is the NS5A and protease inhibitor combination of ABT-493 and ABT-530, with 97% of patients achieving SVR in a phase 2 study [21]. The ENDURANCE-1 phase 3 trial is currently investigating the efficacy of this regimen for 8 or 12 weeks in treatment naïve patients without cirrhosis.

A combination of 2 DAAs from different classes for 8 weeks appears to be sufficient for a high proportion of patients. In contrast, shortening therapy $\leq$ 6 weeks requires a minimum of 3 DAAs in unselected patients. Sofosbuvir-ledipasvir with ribavirin for 6 weeks is associated with a lower SVR rate of 67% [17]. The replacement of ribavirin with a protease inhibitor (GS-9669 or GS-9451) was associated with an increased SVR of 95% [24]. However, these protease inhibitors are no longer in development.

The combination of sofosbuvir-velpatasvir and GS-9857 is currently in phase 3 development. In a phase 2 trial of 6 weeks with this regimen, the SVR rate was 93% [20]. However, only 8 week and 12 weeks of therapy are being investigated in the POLARIS phase 3 trials. Overall, data on 6 weeks of treatment is limited to small numbers of patients in phase 2 trials, and therefore it is difficult to recommend this duration without further investigation. This data is unlikely to be available in the short-term, with no phase 3 trials presently investigating therapy for less than 8 weeks.

The results of trials of 4 weeks of therapy for HCV genotype 1 have been poor. It is clear that treatment for 4 weeks with the currently available DAAs is not sufficient to achieve cure in the majority of patients. Response-guided therapy, where on-treatment viral response is used to select patients in whom therapy may be successfully shortened may have a role. While the results of the SODAPI trial are not likely to be generalizable given the highly selected nature of the patients enrolled (genotype 1b, Chinese, non-cirrhotic, treatment naïve), they do provide evidence to further investigate response guided therapy as a viable cost-saving strategy. The authors estimate that this strategy may be associated with drug cost-savings of between 12 to 44% compared to 8 weeks of therapy with sofosbuvir-ledipasvir in this patient group [30].

Treating hepatitis C genotype 1 for less than 12 weeks in unselected patients may result in a modest reduction in SVR. However, in the current model it may be more cost-effective to shorten duration and then treat relapsers. The development of viral resistance appears to be duration dependent. Patients who relapse with 4 or 8 weeks of therapy are less likely to develop NS5A RAS compared to those that fail 12 weeks of therapy [25, 33]. Re-treating the

small proportion of patients who relapse with 8-weeks of sofosbuvir-ledipasvir would result in considerably fewer treatment weeks than treating all patients for 12 weeks initially.

Shortening therapy may not be feasible in certain groups, including patients with cirrhosis, previous DAA treatment experience, and/or genotype 3 infection. Reducing treatment duration in cirrhotics is associated with a significant reduction in SVR, and a higher risk of developing RAS that may negatively impact re-treatment options [34].

Conclusion

In the current paradigm, there is a need to shorten treatment duration while maintaining high cure rates to expand treatment access. 8 weeks of therapy with sofosbuvir-ledipasvir for hepatitis C genotype 1 has been demonstrated to be highly effective in clinical trials and real-world cohorts. Shortening therapy and retreating relapsers may be a viable cost-saving measure, but requires further cost-benefit analysis. Response-guided therapy to shorten therapy to less than 8 weeks is a promising area for further research.

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There are no conflicts of interest in relation to this submitted work.

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Figure Legends

Figure 1 – Sustained virologic response (95% CI bars) with 8 or 12 weeks of treatment with sofosbuvir-ledipasvir in the ION-3 trial [5]

Figure 2 – Sustained virologic response (95% CI bars) with 6 weeks of therapy; SOF – sofosbuvir; DCV – daclatasvir; ASV – asunaprevir; BCV – beclabuvir; LDV – ledipasvir; RBV – ribavirin; GZR – grazoprevir; EBZ – elbasvir; VEL – velpatasvir

Figure 3 - Sustained virologic response (95% CI bars) with 4 weeks of therapy; SOF – sofosbuvir; LDV – ledipasvir; VEL – velpatasvir; DCV – daclatasvir; ASV – asunaprevir; BCV – beclabuvir; GZR – grazoprevir; EBZ – elbasvir [22-23, 25-26]

Figure 1

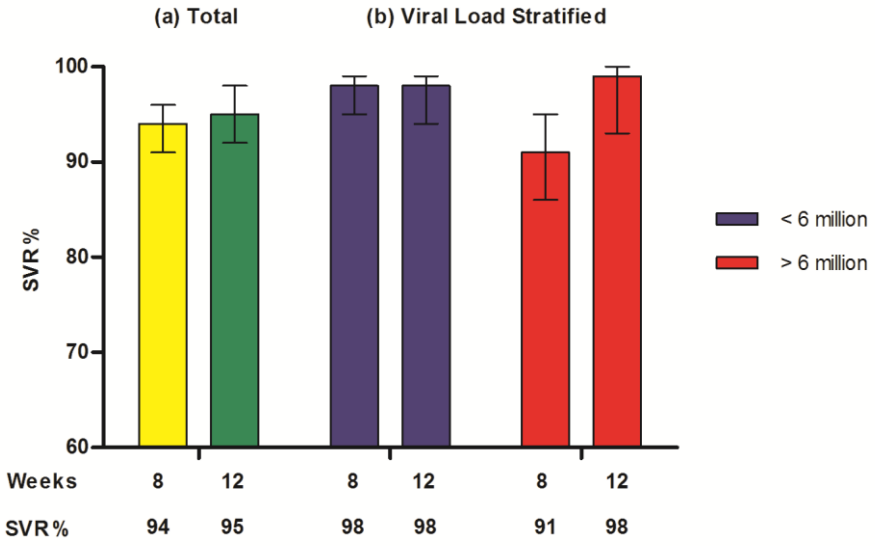

Figure 2

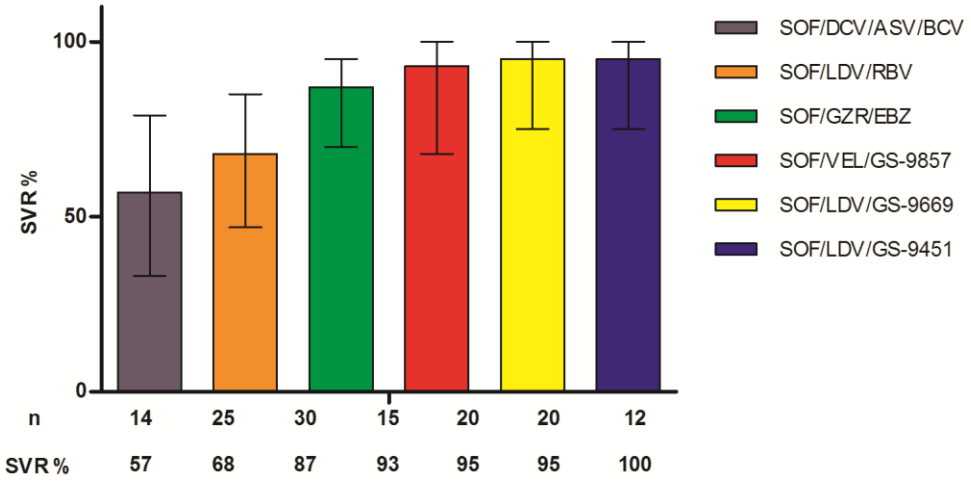

Figure 3