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Highlights

- Although direct-acting antivirals (DAAs) containing non-structural protein 5A (NS5A) inhibitors administered over eight to 12 weeks are effective in ~95% of patients with hepatitis C virus (HCV), the licensed duration of therapy may be unnecessary or less effective for selected patients. Patients with resistance to NS5A inhibitors have lower cure rates over eight weeks and would benefit more from standard 12 weeks treatment. Conversely, non-resistant patients generally do not require 12 weeks treatment; eight weeks treatment produces comparable cure rates. Testing for resistance to NS5A inhibitors at baseline and optimising treatment duration accordingly is one method that could be used to improve patient outcomes. However, the potential benefits of resistance testing must be considered in the context of the added cost of the resistance test.

- This is the first study to consider the cost-effectiveness of baseline testing in genotype 1 non-cirrhotic treatment-naïve patients. Furthermore, it is the first to consider it in the context of shortened eight weeks treatment duration, which has been shown to be cost-effective versus standard 12 weeks treatment for many commonly used DAAs.

- Baseline testing has low probability of being the most cost-effective treatment strategy if first- and second-line drug prices per 12-week course are high (£>20k). However, if drug costs are low (<£20k), baseline testing generally has the highest probability of being the most cost-effective strategy; it also has the highest probability of being most cost-effective if the cost of first-line treatment is low (<£20k) and second-line treatment is high (>£22k).

1

Abstract

Objectives: Direct-acting antivirals containing non-structural protein 5A (NS5A) inhibitors administered over 8-12 weeks are effective in ~95% of patients with hepatitis C virus. However, patients resistant to NS5A inhibitors have lower cure rates over eight weeks (<85%); for these patients, 12 weeks treatment produces cure rates above 95%. We evaluated the lifetime cost-effectiveness of testing for NS5A resistance at baseline and optimising treatment duration accordingly in genotype 1 non-cirrhotic treatment-naïve patients, from the perspective of the UK National Health Service.

Methods: A decision-analytic model compared: (1) standard 12 weeks treatment (no testing); (2) shortened eight weeks treatment (no testing); (3) baseline testing with 12/eight weeks treatment for those with/without NS5A polymorphisms. Patients that failed first-line therapy were retreated for 12 weeks. Model inputs derived from published studies. Costs, quality-adjusted life years (QALYs), and probability of cost-effectiveness were calculated.

Results: Baseline testing had an incremental net monetary benefit (INMB) of £11,838 versus standard 12 weeks (no testing) and low probability (31%) of being most cost-effective, assuming £30,000 willingness to pay. Shortened eight weeks (no testing) had an INMB of £12,294 and highest probability (69%) of being most cost-effective. Scenario analyses showed baseline testing generally had the highest INMB and probability of being most cost-effective if first- and second-line drug prices were low (<£20k).

Conclusions: Optimising treatment duration based on NS5A polymorphisms for genotype 1 non-cirrhotic treatment-naive patients in the UK is not cost-effective if drug costs are high; the strategy is generally most cost-effective when drug prices are low (<20k).

Key words: cost-effectiveness; hepatitis C virus; baseline testing

Introduction

The burden and prevalence of hepatitis C virus (HCV) worldwide remains high with more than 70 million people, or 1% of the world's population, currently living with the chronic infection [1]. The World Health Organisation (WHO) recently committed to reducing the number of new HCV cases and deaths worldwide by 2030 [2]. Efforts to reduce the burden of HCV have been invigorated by the advent of direct-acting antivirals (DAAs), which produce high cure rates (~95%) over relatively short courses of treatment (8-12 weeks) and offer good side effect profiles [3]. However, there is emerging evidence that, for selected patients, treatment over the licensed duration of therapy can be unnecessary or less effective. DAA regimens containing non-structural protein 5A (NS5A) inhibitor can be less effective in patients with NS5A polymorphisms, or resistance-associated substitutions (RASs). One widely used combination therapy, ledipasvir/sofosbuvir (LDV/SOF), for example, produces high and relatively comparable cure rates, or sustained virological response (SVR, effective cure), over standard 12 weeks treatment duration (96.3%) [4] as shortened eight weeks treatment duration (94.6%) in genotype 1 (GT1) non-cirrhotic treatment-naïve (TN) patients [5]. However, in NS5A inhibitor-resistant patients, significantly lower SVR has been observed over eight weeks treatment duration (82.8%) than 12 weeks treatment duration (95.7%) [5]. Outcomes for this group could be considerably improved if patients' resistance profile was determined at baseline using single gene sequencing, or resistance testing, and treatment duration was optimised accordingly.

Despite the clinical benefits resistance testing can provide, it is not widely used. In some circumstances resistance testing is recommended routinely when optimising treatment for an individual patient. One combination therapy, elbasvir/grazoprevir (ELB/GZR), recommends resistance testing to guide duration of therapy [6]. In patients with NS5A polymorphisms, 16 weeks treatment duration is recommended, while standard 12 weeks treatment duration is recommended for patients without the RASs. The cost-effectiveness of resistance testing has also been documented in the literature [7, 8]. Westerhout and colleagues [8] considered the cost-effectiveness of testing for NS5A polymorphisms at baseline in GT1 treatment-experienced (TE) patients with severe or compensated cirrhosis in Italy. Patients were treated for 12 weeks if they had severe cirrhosis and NS5A polymorphisms at baseline and 24 weeks if they had compensated cirrhosis and NS5A polymorphisms at baseline. The authors found baseline testing was cost-effective versus no testing (with non-stratified treatment durations of 12 or 24 weeks for patients with severe or compensated cirrhosis, respectively) [8]. In the US, Elbasha and colleagues [7] considered the cost-effectiveness of baseline testing in GT1a TN and TE patients.

However, the authors treated patients for 12 weeks if no NS5A RASs were present at baseline and 16 weeks otherwise. The authors similarly found the results favoured baseline testing versus no testing in non-cirrhotic TN patients [7]. No study has yet considered the cost-effectiveness of baseline testing in the context of shorter treatment durations, which have been shown to be highly effective [5, 9] and cost-effective [10] in GT1 non-cirrhotic TN patients.

Adjusting treatment duration based on the presence of NS5A polymorphisms carries the potential to increase the rate of successful outcomes in patients through increased cure rates, thereby limiting the incidence of liver-related morbidity and mortality and associated health care costs. However, baseline testing introduces additional costs that must be considered in the context of its potential benefit. In this paper, we investigated the lifetime cost-effectiveness of testing for resistance to NS5A inhibitor-containing regimens at baseline in GT1 non-cirrhotic TN patients in the UK, with treatment duration optimised to 12 weeks in NS5A-resistant patients and eight weeks otherwise. We compared baseline testing against standard 12 weeks treatment duration for all patients, which is the generally recommended treatment duration. An additional strategy of shortened eight weeks treatment duration for all patients was also considered as the strategy is sometimes recommended, particularly for newer regimens [11], and may offer cost advantages beyond baseline testing that need to be considered.

Methods

We adapted a previously validated decision tree and Markov model [10] to assess the cost-effectiveness of baseline testing for NS5A polymorphisms from the perspective of the UK National Health Service (NHS). We assumed monthly cycles in the decision tree to simulate treatment outcomes in the first year, and annual cycles in the Markov model to simulate the natural disease history of HCV. We adopted a lifetime time horizon, projecting outcomes over 60 years, and discounted future costs and benefits at 3.5% per annum, in line with UK guidance [12].

Patient population

We modelled outcomes for HCV GT1 (subtypes 1a and 1b combined) non-cirrhotic TN patients in the UK. We considered outcomes for patients with mild (F0-F1) and moderate (F2-F3) liver fibrosis, as informed by UK data [13] (Table 1). Patients were aged 40 and 70% were male at model entry [13].

Treatment strategies

We compared the following strategies:

- *NoTest12wks*: 'standard 12 weeks treatment duration (with no testing)'

- *NoTest8wks*: 'shortened eight weeks treatment duration (with no testing)'

- *Test12/8wks*: 'baseline testing' with 12 weeks treatment duration if NS5A resistant, eight weeks otherwise

For the purposes of this analysis, we assumed *NoTest12wks* as the reference strategy as this is the standard recommended treatment duration in the UK. Under each strategy, we assumed that patients that failed first-line treatment were retreated for 12 weeks, as per recent UK guidelines [14, 15].

We assumed LDV/SOF as first-line therapy as it may be recommended for use over eight to 12 weeks in GT1 non-cirrhotic TN patients, so there's considerable evidence available on the effectiveness of the regimen in the studied population over the different treatment durations. LDV/SOF is an NS5A inhibitor-containing regimen that is administered daily using a fixed-dose tablet; each tablet contains 90mg LDV (NS5A inhibitor) and 400mg SOF (polymerase inhibitor) [4]. We assumed sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) as second-line therapy (i.e., retreatment regimen) as it is the currently recommended treatment regimen in patients that previously failed first-line therapy in the UK [14]. SOF/VEL/VOX is also an NS5A inhibitor-containing regimen that is administered once daily using a fixed-dose tablet; each tablet contains 400mg SOF, 100mg VEL (NS5A inhibitor), and 100mg VOX (protease inhibitor) [16].

Model structure

We used a decision tree and Markov model (Appendix 1) to assess treatment and lifetime outcomes, respectively. Patients were treated for either 12 or eight weeks, depending on the strategy, and assessed 12 weeks post end-of-treatment for an effective cure (SVR12). SVR12 was defined as having HCV ribonucleic acid (RNA) less than 25 IU per millilitre. A 12-week salvage regimen was administered at 24 weeks during the decision tree if patients failed first-line therapy.

A Markov model was used to reflect long-term outcomes beyond the decision tree. All patients entered the model based on their response to treatment (SVR or fail) and initial liver fibrosis (mild or moderate). HCV-cleared patients could become re-infected at any point during the model, while HCV-infected patients could progress to more advanced stages of liver disease, including compensated cirrhosis, decompensated cirrhosis,

and hepatocellular carcinoma. Patients in these advanced health states were at risk of requiring a liver transplant. The model captured the varying risk of liver-related mortality in these advanced health states, with additional health states included in the hepatocellular carcinoma and liver transplant health states to reflect the initial and subsequent risk of mortality. The model also captured the risk of all-cause mortality.

Model assumptions

During treatment, we assumed patients could not progress to more advanced stages of liver disease. Patients that failed first-line treatment were retreated at 24 weeks during the decision tree. There are no guidelines on when a salvage treatment should be administered, and it is unclear whether the timing of retreatment impacts patients' chance of viral eradication. In our model, we assumed the timing did not affect retreatment success. Although HCV-cleared patients could become reinfected, to be conservative we assumed these patients were not treated again and progressed through the model. We applied drug costs on a per-tablet basis (estimated monthly), rather than a per-treatment success/failure basis.

Parameter inputs

Model inputs are presented in Table 1 and described below.

Treatment-related inputs

The primary source of evidence on NS5A prevalence and first-line treatment efficacy was derived from Sarrazin and colleagues [5], who recently synthesised evidence from phase 2 and 3 clinical trials in Europe and the US. The authors reported outcomes for 2,144 patients who had been treated over 12 or eight weeks using LDV/SOF. At baseline, 11.5% of GT1 non-cirrhotic TN patients had at least one RAS that conferred more than 100-fold resistance to NS5A inhibitor using a 1% cut-off value for deep sequencing (Table 1). The RASs included Q30H, Q30G, Q30R, L31I, L31M, L31V, P32L, M28A, M28G, Q30E, Q30K, H58D, Y93C, Y93H, Y93N, and Y93S in GT1a and P58D, A92K, and Y93Hin GT1b. Overall, 94.6% of patients (including both those with and without NS5A polymorphisms) achieved SVR12 over eight weeks. Patients with NS5A resistance at baseline had similar SVR12 over 12 weeks at 95.7% than patients without the RAS treated for eight weeks at 96.4%. We used these prevalence and efficacy data and assumed beta distributions for *NoTest8wks* and *Test12/8wks*, with uncertainty around these estimates given in Table 1. In the UK, SVR12 in patients treated for standard 12 weeks treatment duration using the same regimen is 96.3% [4]. We used this efficacy source and assumed a beta distribution for *NoTest12wks*, with uncertainty in this parameter described in Table 1 also.

Bourliere and colleagues [17] provided evidence on the efficacy of retreatment using SOF/VEL/VOX over 12 weeks from two phase 3 clinical trials (POLARIS-1 and POLARIS-4). Overall, 97.3% of patients (142 of 146) achieved SVR12; this informed beta distributions on SVR12 in patients that failed either the *NoTest12wks* or *NoTest8wks* strategy. In patients with and without NS5A polymorphisms at baseline, 96.8% (120 of 124) and 97.7% (42 of 43) achieved SVR12, respectively; we used these data to inform beta distributions on SVR12 for *Test12/8wks* (Table 1).

We modelled the probability that treatment-related adverse events occur to reflect the potential impact of clinical events over different treatment durations. We used data from earlier work [10], which in turn was derived from Johnson and colleagues [18]. We estimated the probability of adverse events over 12 and eight weeks, respectively [10]. Although these events were observed for an alternative DAA, we assumed the probabilities were comparable as side effect profiles are generally good across DAAs and occur uniformly [19]. We applied the same probabilities for retreatment as first-line treatment. The events included anemia, rash, depression, grade 3 or 4 neutropenia, and grades 3 or 4 thrombocytopenia.

Epidemiological inputs

The natural disease history of HCV was modelled using the Markov model and annual transition probabilities, which are presented in Table 1. The parameter estimates were taken from published studies on the probability of reinfection (1% per annum) [18], fibrosis [20, 21] and non-fibrosis [22, 23] progression, liver-related mortality [20, 23, 24], and all-cause mortality, stratified by age and sex [25].

Costs

The model considered treatment-related and health state costs, from the perspective of the UK NHS (Table 1). Treatment-related costs included resistance test costs, drug costs, monitoring costs [4], and adverse event costs [18]. We assumed the cost of a resistance test (single gene sequencing) was £100 in the base case analysis. The cost of first-line treatment and retreatment was derived from the UK technology appraisals for LDV/SOF [4] and SOF/VEL/VOX [16], respectively. We assumed resistance test costs, drug costs, and monitoring costs were fixed in the model; these were not expected to vary in the UK. Health state costs derived from published studies in the UK [13, 26]. We valued costs at 2017/18 prices, expressed in Sterling (£), and inflated any outdated prices to current prices [27]. A gamma distribution was assumed for all non-fixed cost inputs.

Utilities and quality-adjusted life years

We used quality-adjusted life years (QALYs) as our measure of health benefit and calculated these using published utility estimates [21, 28]. Treatment-related utilities, which reflected the deterioration in quality of life due to adverse events, were derived from Chahal and colleagues [28] for first-line treatment (Table 1). We assumed the same utility penalties for retreatment as there were no published estimates available for the new salvage regimen (SOF/VEL/VOX) at the time of writing. Health state utilities were derived from Wright and colleagues [21]. We assumed HCV-cleared patients had a higher utility than HCV-infected patients by a score of 0.05, consistent with previous analyses [13, 18]. We set this utility as fixed in the model and assumed beta distributions for all other utility parameters (Table 1).

Cost-effectiveness analyses

Base case analysis

We compared the lifetime cost-effectiveness of *Test12/8wks* and *NoTest8wks* against *NoTest12wks* for GT1 non-cirrhotic TN patients in the UK. We calculated the expected lifetime costs and QALYs per 1,000 patients using probabilistic sensitivity analysis. We performed 10,000 Monte Carlo simulations, with point-estimates randomly sampled from predefined probability distributions, using Microsoft Excel software [29]. We report the expected net monetary benefit (NMB), and relative to *NoTest12wks*, we calculated the expected incremental net monetary benefit (INMB) and 95% credible intervals (CrIs) using willingness-to-pay thresholds of £20,000 and £30,000. The optimal strategy at a given willingness-to-pay threshold is the strategy with the highest expected INMB (or equivalently expected NMB). We explored uncertainty in the optimal strategy by reporting the probability that each strategy was the most cost-effective strategy in a cost-effectiveness acceptability curve (CEAC), and the probability that the optimal strategy was the most cost-effective in a cost-effectiveness acceptability frontier (CEAF), both plotted across a range of different willingness-to-pay thresholds. We also reported the number of liver-related events (i.e., decompensated cirrhosis, hepatocellular carcinoma, liver transplant) in each strategy and calculated the number of events avoided in the *NoTest8wks* and *Test12/8wks* strategies relative to *NoTest12wks*.

Sensitivity and scenario analyses

The prices paid for DAA regimens are not published. To take account of lower prices negotiated as part of large volume deals, we investigated a price reduction to the DAA regimens of 80%, which lowered the cost of first-line treatment (LDV/SOF) and retreatment (SOF/VEL/VOX) to £7,935 and £8,965 per patient over 12 weeks, respectively. We assumed this overall reduction to allow for differences in the cost of first- and second-line therapy, as SOF/VEL/VOX was expected to cost more than LDV/SOF.

Assuming the same 80% reduction in drug costs, we conducted a range of other sensitivity and scenario analyses. We undertook a one-way deterministic sensitivity analysis of *NoTest8wks* and *Test12/8wks* relative to *NoTest12wks*, respectively, to investigate how sensitive the results were to fluctuations in parameter values. Where we had limited data on parameters, such as the cost of first- and second-line treatment, we assessed uncertainty using +/-20%. We further investigated sensitivity to lower and higher resistance test costs (single gene sequencing), by varying the cost of the resistance test between £50 and £250. We investigated sensitivity to the SVR12 following first-line treatment in NS5A resistant patients treated for 12 weeks to determine the SVR12 threshold that would be required to ensure *Test12/8wks* is cost-effective. As there is no established evidence on the improvement in patients with mild/moderate liver fibrosis' quality of life following SVR, we assessed sensitivity to this assumption by removing the utility increase (of 0.05) and assuming the same utilities for HCV-cleared and -infected patients.

Finally, we conducted a two-way probabilistic sensitivity analysis on first-line treatment and retreatment drug prices to further explore the issue of drug costs and determine the most cost-effective strategy for a complete range of price combinations. Here, we considered differential percentage reductions in the cost of first- and second-line treatment.

Results

Base case findings

Compared to *NoTest12wks*, *Test12/8wks* generated lower expected lifetime costs due to reduced treatment costs in non-resistant patients, and higher expected QALY gains due to more favourable first- and second-line cure rates in non-resistant patients treated for eight weeks (Table 2). These patients were also exposed to the disutility of treatment for a shorter period of time versus *NoTest12wks*. However, *NoTest8wks* had the lowest

expected lifetime costs due to lower treatment costs overall and higher QALY gains versus *NoTest12wks* due to the shortened exposure to the side effects of treatment. At £20,000 willingness-to-pay, *NoTest8wks* had an INMB of £12,289 (95% CrI £10,439 to £14,100) and 74% probability of being the most cost-effective option; *Test12/8wks* had a lower INMB at £11,700 (95% CrI £10,439 to £13,334) and only 26% probability of being the most cost-effective strategy. At £30,000 willingness-to-pay, the probability that *Test12/8wks* was the most cost-effective strategy was marginally higher, at 31%. At both willingness-to-pay thresholds *NoTest8wks* was the optimal strategy with the highest expected INMB, and this finding was associated with a high level of certainty, as shown in the CEAC and CEAF (Appendix 3).

The number of liver-related events was relatively comparable across each strategy (Appendix 2). *Test12/8wks* had fewer cases of hepatocellular carcinoma, decompensated cirrhosis, and liver transplant than *NoTest12wks*, while *NoTest8wks* had slightly more; however, there was limited evidence to suggest the number of clinical events differed meaningfully across the strategies.

Sensitivity/scenario analyses findings

When drug prices were reduced by 80%, *Test12/8wks* became more cost-effective at £30,000 willingness-to-pay as the small improvement in QALY gains was cost-effective at the lower drug tariff and higher cost-effectiveness threshold (Table 2). *Test12/8wks* had an expected INMB of £2,782 (95% CrI £2,307 to £3,240) and 67% probability of being the most cost-effective strategy; *NoTest8wks* had an INMB of £2,671 (95% CrI £2,163 to £3,157) and 33% probability of being the most cost-effective strategy. At the lower cost-effectiveness threshold of £20,000, *NoTest8wks* had the highest probability of being most cost-effective (55%), although there was more uncertainty around the optimal strategy (see CEAC and CEAF in Appendix 3).

Figures 1 and 2 present the top ten varied parameters of the one-way sensitivity analysis of *NoTest8wks* and *NoTest12/8wks* versus *NoTest12wks*, respectively; the full complement of results is presented in Appendix 4. Both strategies remained cost-effective when parameters were held at their upper/lower bounds. The key drivers of cost-effectiveness were the cost and efficacy of first-line treatment. Lower first-line treatment costs reduced the expected INMB of both strategies relative to *NoTest12wks* due to reduced cost-savings overall. The INMB of *NoTest8wks* and *Test12/8wks* increased when SVR following first-line treatment was held at its upper value (97.2% and 98.5% (in non-resistant patients treated for eight weeks), respectively). The cost-effectiveness of

both strategies also increased when SVR in the *NoTest12wks* strategy was held at its lower value (93.3%). Few other inputs had an effect on the INMB of *NoTest8wks* and *NoTest12/8wks*.

Findings from the scenario analyses of (i) different resistance test costs and (ii) different first-line cure rates in patients with NS5A resistance are presented in Figure 3. The (a) probability of cost-effectiveness and (b) expected INMB are presented for each scenario at £30,000 willingness-to-pay. In each scenario, the probability of cost-effectiveness and expected INMB are presented on the vertical axis, with changes in the key parameter outlined on the horizontal axis. Results were somewhat sensitive to increases in the cost of the resistance test (i.e., single gene sequencing test). At resistance test costs above £220 (and assuming an 80% reduction in drug prices), *Test12/8wks* was no longer the most cost-effective strategy (base case cost was £100); at these costs, *NoTest8wks* had the highest probability (56%) of being most cost-effective. However, little difference in the expected INMB versus *NoTest12wks* was observed, with both strategies proving cost-effective. Results were sensitive to variations in the first-line cure rate in patients with NS5A resistance. At cure rates below 87.5% over 12 weeks, *Test12/8wks* was no longer the most cost-effective strategy (base case SVR12 was 95.7%), losing out to *NoTest8wks* which had lower overall lifetime costs. However, *Test12/8wks* remained more cost-effective than *NoTest12wks*, returning a positive expected INMB at all SVR rates below the base case.

The results remained generally unchanged when we assumed the same utilities for HCV-cleared as HCV-infected patients, as detailed din Appendix 5.

Finally, Figure 4 presents the results from the two-way probabilistic sensitivity analysis that compared differential percentage reductions in the cost of first-line treatment and retreatment. The percentage reduction in the cost of first-line treatment is presented on the y-axis, with the percentage reduction in the cost of retreatment depicted on the x-axis. The grid reports the probability that any strategy is the most cost-effective strategy for a given price combination (i.e., percentage reduction). When first-line treatment drug prices were low (<£20k), and retreatment drug costs were high (>£22k), the findings favoured *Test12/8wks*. Conversely, when retreatment drug costs were low (<£22k) and first-line treatment drug prices were high (>£20k), the results favoured *NoTest8wks*. When both first-line treatment and retreatment drug costs were below <£20k, the results largely favoured *Test12/8wks*, however, some uncertainty was observed. Increased percentage reductions in the cost of retreatment sometimes favoured *NoTest8wks* as the strategy had a greater number of patients requiring retreatment; hence, the strategy benefitted from reductions in the cost of the salvage regimen. For no given price combination was *NoTest12wks* cost-effective.

Conclusions

We investigated the cost-effectiveness of testing for resistance to NS5A inhibitor-containing regimens at baseline, with treatment duration optimised according to the presence of NS5A polymorphisms, in GT1 non-cirrhotic TN patients in the UK. The cost of treatment proved the key driver of cost-effectiveness in this study. Using cost-effectiveness thresholds of £20-30,000, we found baseline testing (*Test12/8wks*) has low probability (26-31%) of being cost-effective when the cost of first-line treatment and retreatment are high (~£40,000 and ~£44,000 per patient over 12 weeks, respectively). At these prices, shortened eight weeks treatment duration (*NoTest8wks*) has the highest probability (69-74%) of being most cost-effective. However, when drug prices are reduced by 80%, the results are reversed at the higher £30,000 cost-effectiveness threshold. In fact, we found baseline testing has the highest probability of being most cost-effective when first-line treatment drug prices are low (<£20,000) and retreatment drug prices are high (>£22,000). When both first-line treatment and retreatment drug prices are low (<£20,000), baseline testing largely remains the most cost-effective strategy; however, shortened eight weeks treatment is sometimes favoured as the strategy benefits more from increased price reductions in the cost of retreatment due to greater numbers requiring the salvage regimen. Although the cost of first-line treatment and retreatment remain unknown, we present the complete range of price combinations that could exist and report the combinations at which the proposed strategies have the highest probability of being most cost-effective, provided society is willing to pay £30,000 per QALY gained.

The results are somewhat sensitive to increases in the cost of the resistance test. Baseline testing is most cost-effective up to a threshold of £220 per resistance test (assuming an 80% reduction in drug prices). Single gene sequencing is expected to cost in the region of £50 to £150 in the UK, suggesting the strategy is cost-effective at the lower drug tariffs. The strategy is also sensitive to variations in SVR12 in patients with NS5A resistance treated over 12 weeks (assuming the same 80% reduction in drug prices). At cure rates below 87.5%, the strategy is no longer the most cost-effective option. However, DAAs rarely produce cure rates below 90% over 12 weeks treatment duration, suggesting this threshold is unlikely to be breached. Overall, we found standard 12 weeks treatment (*NoTest12wks*) is not cost-effective versus either baseline testing or shortened eight weeks treatment.

Discussion

Strengths and limitations

This is the first study to consider the cost-effectiveness of testing for resistance to NS5A inhibitor in the UK. Furthermore, it is the first study to consider it in the context of stratifying patients to shortened eight weeks treatment duration in the absence of NS5A polymorphisms. Previous analyses that considered baseline testing used longer treatment durations, with patients stratified to 12 weeks treatment duration in the absence of NS5A polymorphisms or 16 weeks treatment duration in the presence of NS5A polymorphisms, which is more costly and often of limited clinical benefit [8]. Elbasha and colleagues [7] also considered longer durations, however, the authors investigated the cost-effectiveness of baseline testing in patients whom generally require extended treatment durations due to severe liver fibrosis or compensated cirrhosis. In GT1 non-cirrhotic TN patients, eight weeks treatment duration is effective [5, 9] and cost-effective across a range of DAAs currently approved for use in the UK [10]. The shortened treatment duration is becoming more commonplace, with newer regimens now being administered over eight weeks [11]. However, our findings suggest that where significant price reductions are available the non-stratified treatment approach (*NoTest8wks*) is less favourable than the stratified/personalised treatment approach (*Test12/8wks*) considered here.

We used LDV/SOF as our first-line treatment regimen due to the availability of data on the effectiveness of the regimen over shortened eight weeks treatment duration and by NS5A resistance. Our findings may be generalisable to newer regimens, such as ELB/GZR and SOF/VEL, which carry similar costs and health utilities, if the cure rates produced by these regimens are comparable to LDV/SOF over the same treatment durations and by NS5A resistance. At present, these regimens are licensed for 12 weeks in the UK [6, 30], so there's limited evidence on the effectiveness of these regimens over the shortened treatment duration and by NS5A resistance. It is likely, however, that comparable cure rates may be achieved with the newer regimens, suggesting our findings are not limited to use of LDV/SOF, but other commonly used DAAs currently licensed for 12 weeks. Whether resistance testing is preferable to eight or 12 weeks treatment duration then largely depends on the price combination of first- and second-line DAA therapy, which we report in full in this analysis.

There are limitations associated with this work. Although we used rich data from Sarrazin and colleagues [5] on the prevalence of NS5A resistance among genotype 1 non-cirrhotic treatment-naïve patients, we acknowledge these data, which were derived from clinical trials in Europe and the US, may not reflect the prevalence of

NS5A resistance in the UK population. We combined information on subtypes GT1a and GT1b in our analysis and assumed the same outcomes (SVR) in patients with NS5A polymorphisms across the two subtypes. It is possible that outcomes differ between GT1a and GT1b. Sarrazin and colleagues [5] observed slightly higher SVR in GT1a than GT1b TN patients, however, the authors could discern no significant difference between the two subtypes. We grouped NS5A RASs (i.e., Q30H, Q30G, Q30R, etc.) in our analysis, as in Sarrazin and colleagues [5], but further stratification by RASs could be undertaken. However, such an analysis requires a detailed breakdown of SVR by each polymorphism, which has yet to be undertaken or made available, to the best of our knowledge. We explored the cost-effectiveness of testing for NS5A resistance, but other resistance variants exist (e.g., NS5B and NS3) and could be explored with further research. However, Sarrazin and colleagues [5] found no association between these variants and treatment outcomes. The Markov model assumed yearly cycles to reflect the known natural disease history of HCV. A limitation of using yearly cycles is the model could not capture the probability of two events occurring in the same year, such as progression to compensated cirrhosis and hepatocellular carcinoma. The probability of these events occurring, however, particularly hepatocellular carcinoma, is low in this population of non-cirrhotic patients, and few patients progress to compensated cirrhosis overall due to the highly efficacious nature of first- and second-line treatment. Shorter cycles could be adopted, but are unlikely to detect meaningful differences between the strategies, which had similarly low numbers of clinical events. The model assumed that patients that failed first-line therapy were quickly retreated and that there was no loss to follow-up. However, in practice, second-line therapy may be delayed, leading to a potential loss to follow-up, particularly in problematic populations, such as chaotic drug users or prison inmates serving short sentences. Future research should explore the potential cost-effectiveness of baseline testing in these specific populations.

Implications for practice

The clinical and practical benefits of stratifying patients to different treatment durations based on the presence of NS5A polymorphisms are clear. Patients' chances of viral eradication are increased, and for any patient failing first-line therapy, their future likelihood of viral eradication with retreatment is high, with success rates in excess of 96% observed, even in patients with NS5A resistance [17]. Treating the majority of patients over shortened eight weeks treatment duration provides an opportunity to not only address the burden of high treatment costs that arise with longer treatment durations, but to better deliver care to more patients quicker. This may be particularly relevant in health systems where the cost of HCV drugs remains a barrier to wider

access. Aside from cost, the main negative issue related to resistance testing is the time taken and degree of specialisation needed to receive and interpret results. In some settings, this may present an obstacle to increasing access to treatment, particularly in high burden/low income settings where infrastructure is limited. In the UK, testing for resistance to NS5A inhibitors at baseline is routinely recommended for patients receiving ELB/GZR so the infrastructure exists to expand this to all patients.

Testing for resistance to NS5A inhibitor-containing regimens in GT1 non-cirrhotic TN patients in the UK is cost-effective as drug prices fall to lower levels. The personalised approach to treatment offers significant clinical and practical benefits: patient's chances of viral eradication are maximised; fewer patients progress to more advanced stages of liver disease and more patients can be effectively treated quicker.

References

1. WHO: Global hepatitis report 2017. In. France: World Health Organisation; 2017.

2. WHO: Global health sector strategy on viral hepatitis 2016-2021. In. Geneva, Switzerland: World Health Organisation; 2016.

3. Falade-Nwulia O, Suarez-Cuervo C, Nelson DR, Fried MW, Segal JB, Sulkowski MS: Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review. *Ann Intern Med* 2017, 166(9):637-648.

4. NICE: Technology appraisal guidance [TA363]: Ledipasvir–sofosbuvir for treating chronic hepatitis C. In. London: National Institute for Health and Care Excellence; 2015.

5. Sarrazin C, Dvory-Sobol H, Svarovskaia ES, Doehle BP, Pang PS, Chuang SM *et al*: Prevalence of Resistance-Associated Substitutions in HCV NS5A, NS5B, or NS3 and Outcomes of Treatment With Ledipasvir and Sofosbuvir. *Gastroenterology* 2016, 151(3):501-512.e501.

6. NICE: Technology appraisal guidance [TA413]: Elbasvir–grazoprevir for treating chronic hepatitis C. In. London: National Institute for Health and Care Excellence; 2016.

7. Elbasha EH, Robertson MN, Nwankwo C: The cost-effectiveness of testing for NS5a resistance-associated polymorphisms at baseline in genotype 1a-infected (treatment-naive and treatment-experienced) subjects treated with all-oral elbasvir/grazoprevir regimens in the United States. *Aliment Pharmacol Ther* 2017, 45(3):455-467.

8. Westerhout KY, Bouwmeester W, Duchesne I, Pisini M, Piena MA, Damele F *et al*: Optimizing choice of oral interferon-free treatment for genotype 1 hepatitis C virus using testing for NS5A resistance: a cost-utility analysis from the perspective of the Italian National Health Service. *Clinicoecon Outcomes Res* 2017, 9:163-172.

9. Kowdley KV, Lawitz E, Poordad F, Cohen DE, Nelson DR, Zeuzem S *et al*: Phase 2b Trial of Interferon-free Therapy for Hepatitis C Virus Genotype 1. *New England Journal of Medicine* 2014, 370(3):222-232.

10. Fawsitt CG, Vickerman P, Cooke G, Welton NJ: A cost-effectiveness analysis of shortened direct-acting antiviral treatment in genotype 1 non-cirrhotic treatment-naïve patients with chronic hepatitis C virus. *Value in Health* 2019, 22(6):693-703.

11. NICE: Technology Appraisal Guidance [TA499]: Glecaprevir–pibrentasvir for treating chronic hepatitis C. In. London: National Institute for Health and Care Excellence; 2018.

12. NICE: Guide to the methods of technology appraisal 2013. In. London: National Institute for Health and Care Excellence; 2013.

13. Hartwell D, Jones J, Baxter L, Shepherd J: Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. *Health Technol Assess* 2011, 15(17):i-xii, 1-210.

14. NHS: National Clinical Guidelines for the treatment of HCV in adults. In. Scotland: National Health Service Scotland; 2018.

15. NHS: Specialised Commissioning Drugs Briefing: Spring 2018. In. London: National Health Service; 2018.

16. NICE: Technology Appraisal Guidance [TA507]: Sofosbuvir–velpatasvir–voxilaprevir for treating chronic hepatitis C. In. London: National Institute for Health and Care Excellence; 2018.

17. Bourliere M, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M *et al*: Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. *N Engl J Med* 2017, 376(22):2134-2146.

18. Johnson SJ, Parise H, Virabhak S, Filipovic I, Samp JC, Misurski D: Economic evaluation of ombitasvir/paritaprevir/ritonavir and dasabuvir for the treatment of chronic genotype 1 hepatitis c virus infection. *J Med Econ* 2016:1-12.

19. Solund C, Andersen ES, Mossner B, Laursen AL, Roge BT, Kjaer MS *et al*: Outcome and adverse events in patients with chronic hepatitis C treated with direct-acting antivirals: a clinical randomized study. *Eur J Gastroenterol Hepatol* 2018, 30(10):1177-1186.

20. Grieve R, Roberts J, Wright M, Sweeting M, DeAngelis D, Rosenberg W *et al*: Cost effectiveness of interferon alpha or peginterferon alpha with ribavirin for histologically mild chronic hepatitis C. *Gut* 2006, 55(9):1332-1338.

21. Wright M, Grieve R, Roberts J, Main J, Thomas HC: Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol Assess* 2006, 10(21):1-113, iii.

22. Cardoso AC, Moucari R, Figueiredo-Mendes C, Ripault MP, Giuily N, Castelnau C *et al*: Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *J Hepatol* 2010, 52(5):652-657.

23. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P *et al*: Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997, 112(2):463-472.

24. Bennett WG, Inoue Y, Beck JR, Wong JB, Pauker SG, Davis GL: Estimates of the cost-effective of a single course of interferon-alpha2b in patients with histologically mild chronic hepatitis C. *Ann Intern Med* 1997, 127.

25. National Life Tables, 2013-2015 [https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables]

26. Backx M, Lewszuk A, White JR, Cole J, Sreedharan A, van Sanden S *et al*: The cost of treatment failure: resource use and costs incurred by hepatitis C virus genotype 1-infected patients who do or do not achieve sustained virological response to therapy. *J Viral Hepat* 2014, 21(3):208-215.

27. Curtis L, Burns A: Unit Costs of Health and Social Care 2017. In. University of Kent, Canterbury: Personal Social Services Research Unit; 2017.

28. Chahal HS, Marseille EA, Tice JA, Pearson SD, Ollendorf DA, Fox RK *et al*: Cost-effectiveness of Early Treatment of Hepatitis C Virus Genotype 1 by Stage of Liver Fibrosis in a US Treatment-Naive Population. *JAMA Intern Med* 2016, 176(1):65-73.

29. Microsoft: Microsoft Excel (2016). In. Redmond, WA: Microsoft Corporation; 2016.

30. NICE: Technology Appraisal Guidance [TA507]: Sofosbuvir–velpatasvir for treating chronic hepatitis C. In.: National Institute for Health and Care Excellence; 2017.

Table 1 Summary of treatment, epidemiological, cost, and quality of life inputs for probabilistic sensitivity analyses

Variable	Base case	Distribution	Alpha[a]	Beta[a]	Source
Patient characteristics					
Initial distribution of liver fibrosis					
Mild (F0-F1)	51.1%	-	-	-	[13]
Moderate (F2-F3)	48.9%	-	-	-	[13]
Age	40	-	-	-	[13]
Male	70%	-	-	-	[13]
Efficacy (SVR12)					
First-line treatment – LDV/SOF					
NoTest12wks	0.963	Beta	208	8	[4]
NoTest8wks	0.946	Beta	209	12	[5]
Test12/8wks					
NS5A (12 weeks)	0.957	Beta	45	2	[5]
No NS5A (8 weeks)	0.964	Beta	185	7	[5]
Retreatment – SOF/VEL/VOX					
NoTest12wks//NoTest8wks	0.973	Beta	142	4	[17]
NS5A (Test12/8wks)	0.968	Beta	120	4	[17]
No NS5A (Test12/8wks)	0.977	Beta	42	1	[17]
Resistance prevalence					
NS5A	0.115	Beta	102	785	[5]
Annual transition probabilities					
Fibrosis progression					
Mild-to-moderate	0.025	Beta	38	1484	[20, 21]
Moderate-to-CC	0.037	Beta	27	699	[20, 21]
Non-fibrosis progression					
CC-to-DCC	0.039	Beta	15	359	[23]
CC-to-HCC	0.014	Beta	2	135	[22]
DCC-to-HCC	0.014	Beta	2	135	[22]
HCC-to-liver transplant	0.020	Beta	98	4801	[13]
DCC-to-liver transplant	0.020	Beta	98	4801	[20]
Liver-related mortality					
DCC-to-liver death	0.130	Beta	147	983	[23]
HCC-to-liver death (first year)	0.430	Beta	117	155	[23]
HCC-to-liver death (subsequent year)	0.430	Beta	117	155	[23]
Liver transplant-to-liver death (first year)	0.150	Beta	85	481	[20]
Liver transplant-to-liver death (subsequent year)	0.057	Beta	85	1407	[24]
Reinfection	0.010	Beta	4	391	[18]
Costs					
Resistance test costs					
Single gene sequencing	£100.00	Fixed	-	-	Assumption
Treatment-related costs					
LDV/SOF (monthly)	£13,225.20	Fixed	-	-	[4]
SOF/VEL/VOX (monthly)	£14,942.33	Fixed	-	-	[16]
Monitoring costs (monthly)	£162.34	Fixed	-	-	[4]
Health state costs					
SVR Mild (F0-F1)	£60.36	Gamma	34	2	[26]
SVR moderate (F2-F3)	£60.36	Gamma	34	2	[26]
Mild (F0-F1)	£166.50	Gamma	13	13	[13]
Moderate (F2-F3)	£612.50	Gamma	35	17	[26]

CC (F4)	£951.13	Gamma	17	54	[26]
DCC	£12,833.96	Gamma	15	849	[13]
HCC (first year)	£11,436.41	Gamma	13	894	[13]
HCC (subsequent year)	£11,436.41	Gamma	13	894	[13]
Liver transplant (first year)	£51,769.79	Gamma	15	3473	[13]
Liver transplant (subsequent year)	£1,949.08	Gamma	14	136	[13]
Adverse event costs					
Anaemia	£501.58	Gamma	10	48	[18]
Rash	£166.50	Gamma	16	10	[18]
Depression	£414.17	Gamma	16	26	[18]
Neutropenia	£980.26	Gamma	10	98	[18]
Thrombocytopenia	£875.16	Gamma	14	62	[18]
Utilities					
Treatment-related utilities (penalties)					
Mild (F0-F1) (monthly)	-0.002	Beta	72	39466	[28]
Moderate (F2-F3) (monthly)	-0.002	Beta	72	39466	[28]
Health state utilities					
SVR mild (F0-F1)	0.820	Fixed	-	-	[21]
SVR moderate (F2-F3)	0.710	Fixed	-	-	[21]
Mild (F0-F1)	0.770	Beta	141	42	[21]
Moderate (F2-F3)	0.660	Log-normal	-	-	[21]
CC (F4)	0.550	Log-normal	-	-	[21]
DCC	0.450	Beta	55	67	[21]
HCC (first year)	0.450	Beta	55	67	[21]
HCC (subsequent year)	0.450	Beta	55	67	[21]
Liver transplant (first year)	0.450	Beta	55	67	[13]
Liver transplant (subsequent year)	0.670	Beta	32	16	[21]

[a] Parameters of a Beta distribution describing uncertainty in probability parameters

SVR12, sustained virological response at 12 weeks; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LDV/SOF; ledipasvir/sofosbuvir; SOF/VEL/VOX, sofosbuvir/ velpatasvir/voxilaprevir

NoTest12wks: 'standard 12 weeks treatment duration (with no testing)';
NoTest8wks: 'shortened eight weeks treatment duration (with no testing)';
Test12/8wks: 'baseline testing' with 12 weeks treatment duration if NS5A resistant, eight weeks otherwise

Table 2 Cost-effectiveness findings

			£20,000 WTP			£30,000 WTP		
	Costs	QALYs	e(NMB)[a]	e(INMB)[a]	p(CE)	e(NMB)[a]	e(INMB)[a]	p(CE)
	(95% CrI)	(95% CrI)		(95% CrI)			(95% CrI)	
Base case analysis								
NoTest12wks	£43,976	15.515	£266,319	-	0.00	£421,467	-	0.00
	(£42,150 to £46,470)	(15.011 to 16.167)	(£254,664 to £280,379)			(£404,872 to £442,028)		
NoTest8wks	£31,698	15.515	£278,608	£12,289	0.74	£433,761	£12,294	0.69
	(£29,744 to £34,227)	(15.01 to 16.167)	(£266905 to £292,679)	(£10,439 to £14,100)		(£417,198 to £454,346)	(£10,411 to £14,142)	
Test12/8wks	£32,552	15.529	£278,019	£11,700	0.26	£433,305	£11,838	0.31
	(£30,731 to £34,982)	(15.021 to 16.182)	(£266,301 to £292,130)	(£10,074 to £13,334)		(£416,594 to £453,941)	(£10,183 to £13,505)	
Sensitivity analysis (80% reduction in drug prices)								
NoTest12wks	£12,053	15.510	£298,150	-	0.00	£453,252	-	0.00
	(£10,591 to £14,268)	(15.008 to 16.165)	(£286,460 to £312,194)			(£436,581 to £473,817)		
NoTest8wks	£9,399	15.511	£300,815	£2,665	0.55	£455,923	£2,671	0.33
	(£7,946 to £11,612)	(15.009 to 16.166)	(£289,139 to £314,856)	(£2,194 to £3,116)		(£439,265 to £476,535)	(£2,163 to £3,157)	
Test12/8wks	£9,683	15.524	£300,795	£2,645	0.45	£456,034	£2,782	0.67
	(£8,242 to £11,851)	(15.018 to 16.181)	(£289,020 to £314,850)	(£2,224 to £3,064)		(£439,299 to £476,640)	(£2,307 to £3,240)	

[a] Versus 'NoTest12wks'

CrI, credible interval; e(INMB), expected incremental net monetary benefit; p(CE), probability most cost-effective; QALYs, quality-adjusted life years; WTP, willingness-to-pay

NoTest12wks: 'standard 12 weeks treatment duration (with no testing)';
NoTest8wks: 'shortened eight weeks treatment duration (with no testing)';
Test12/8wks: 'baseline testing' with 12 weeks treatment duration if NS5A resistant, eight weeks otherwise

Figure 1 One-way sensitivity analysis of *NoTest8wks* versus *NoTest12wks*

* Assumes 80% reduction in drug costs

NoTest12wks: 'standard 12 weeks treatment duration (with no testing)';
NoTest8wks: 'shortened eight weeks treatment duration (with no testing)';

Figure 2 One-way sensitivity analysis of *Test12/8*wks versus *NoTest12wks*

* Assumes 80% reduction in drug costs

NoTest12wks: 'standard 12 weeks treatment duration (with no testing)';
Test12/8wks: 'baseline testing' with 12 weeks treatment duration if NS5A resistant, eight weeks otherwise

Figure 3 Results on the (a) probability of cost-effectiveness and (b) expected incremental net monetary benefit versus 12 weeks (no testing) of various scenario analyses, at £30,000 willingness-to-pay:
(i) Different resistance test costs (assuming 80% reduction in drug costs)
(ii) Different first-line cure rates in patients with NS5A resistance (assuming 80% reduction in drug costs)

NoTest12wks: 'standard 12 weeks treatment duration (with no testing)';
NoTest8wks: 'shortened eight weeks treatment duration (with no testing)';
Test12/8wks: 'baseline testing' with 12 weeks treatment duration if NS5A resistant, eight weeks otherwise

Figure 4 Results on the probability of cost-effectiveness of differential percentage reductions in the cost of first-line treatment and retreatment, at £30,000 willingness-to-pay

NoTest12wks: 'standard 12 weeks treatment duration (with no testing)';
NoTest8wks: 'shortened eight weeks treatment duration (with no testing)';
Test12/8wks: 'baseline testing' with 12 weeks treatment duration if NS5A resistant, eight weeks otherwise

Supplementary material

Appendix 1 – Model structure

Appendix 2 – Number of clinical events (avoided)

Appendix 3 – Cost-effectiveness acceptability curves and cost-effectiveness acceptability frontier – base case and sensitivity analysis

Appendix 4 – Complete results of the one-way sensitivity analyses for *NoTest8wks* and *Test12/8wks* versus *NoTest12wks*

Appendix 5 – Sensitivity analysis with increment in utility following SVR excluded