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SPECIAL REPORT

Dutch guidance for the treatment of chronic hepatitis C virus infection in a new therapeutic era

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ABSTRACT

Background: A new era for the treatment of chronic hepatitis C is about to transpire. With the introduction of the first-generation protease inhibitors the efficacy of hepatitis C treatment improved significantly. Since then, the therapeutic agenda has moved further forward with the recent approval of sofosbuvir and the expected approval of agents such as simeprevir and daclatasvir. This paper, developed parallel to the approval of sofosbuvir, is to serve as a guidance for the therapeutic management of chronic hepatitis C.

Methods: We performed a formal search through PubMed, Web of Science and ClinicalTrials.gov to identify all clinical trials that have been conducted with EMA-approved new agents in hepatitis C; for this version (April 2014) we focused on sofosbuvir. For each disease category, the evidence was reviewed and recommendations are based on GRADE.

Results: We identified 11 clinical trials with sofosbuvir and for each disease category recommendations for treatment are made. Not all disease categories were studied extensively and therefore in some cases we were unable to provide recommendations.

Conclusion: The recent approval of sofosbuvir will most likely change the therapeutic landscape of chronic hepatitis

C. The use of sofosbuvir-containing regimens can shorten the duration of therapy, increase efficacy and result in less side effects, compared with standard of care. The efficacy relative to standard of care needs to be weighed against the increased costs of sofosbuvir. With future approval of the other direct-acting antivirals, the outcome of hepatitis C treatment will likely improve further and this guidance will be updated.

KEYWORDS

Direct-acting antivirals, guidance, hepatitis C, sofosbuvir

INTRODUCTION

The recent approval of sofosbuvir (NS5B polymerase inhibitor) and the expected approval of other direct-acting antivirals (DAAs) such as simeprevir (protease inhibitor) and daclatasvir (NS5A inhibitor) will change the therapeutic arena for chronic hepatitis C.[1] Until 2012 the treatment of chronic hepatitis C consisted of pegylated interferon with ribavirin (PR) for 24 to 48 weeks.[2] As of April 2012 two first-generation protease inhibitors, telaprevir and boceprevir, were approved for reimbursement in the Netherlands for patients infected with hepatitis C virus (HCV) genotype 1.[3] These agents improved efficacy[3] but their safety profile was poor, especially in cirrhotic patients.[4-6]

In the Netherlands, the estimated hepatitis C seroprevalence is 0.1-0.4%, and the highest prevalence is seen in first-generation migrants from HCV-endemic countries.[7-9] Approximately 50% of Dutch patients are infected with genotype 1, 30% with genotype 3, 10% with genotype 2 and 10% with genotype 4.[10]

Sofosbuvir can be regarded as a game changer;[1] it is an orally administered nucleotide polymerase inhibitor, has pangenotypic activity *in vivo*, a high barrier to resistance and an acceptable safety profile.[11] Approval of other drugs in different classes of DAAs may be expected, first of all simeprevir (during revision approved) and daclatasvir. Additional drugs belonging to the protease inhibitor class (asunaprevir, ABT -450/r), the NS5A class (ledipasvir, ombitasvir) and the non-nucleoside polymerase inhibitor class (dasabuvir) are in later stages of clinical development.[1]

This paper may serve as a current guidance for the therapeutic management of chronic hepatitis C. This update of the earlier guidance[3] is necessary given the wealth of new information that has become available since. As a static version will become outdated, we encourage to review the most current version on the websites of the Netherlands Association of Hepato-gastroenterologists (NVMDL) or the Netherlands Association of Internal Medicine (NIV).[12]

METHODS

We performed a formal search through the databases PubMed, Web of Science and ClinicalTrials.gov to identify all relevant clinical trials performed with sofosbuvir, peginterferon and/or ribavirin for this version (April 2014). In addition we searched for future therapies and for the product characteristics provided by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Opinions, letters, narrative reviews, pre-clinical studies and articles in another language than English, Dutch or German were excluded. The search string is attached in *supplementary file 1*. We limited the search for patients with HCV mono-infection. For each disease category (treatment-naive, treatment-experienced and cirrhotic patients) the evidence was reviewed by the first and second author. The treatment-experienced category consists of patients with a prior relapse, prior partial response or prior null response. Sustained virological response (SVR) is defined as an HCV RNA below the lower limit of quantification at 12 weeks after the end of treatment. We listed the results of all individual trials in tables according to disease category. The level of evidence was formulated based on the GRADE method with the quality of evidence and a strength of recommendation (*supplementary file 2*).[13] The recommendations in this paper went through a formal approval process and were vetted by individual experts and all members of the NVMDL and representatives of the NIV.

RESULTS

We formulated recommendations on the basis of the available evidence and information from the label of sofosbuvir. The recommendations are given for each disease category. When no recommendation is given, treatment can be deferred or we refer to the earlier guideline.[3] First, all currently approved agents and expected agents are listed, followed by recommended treatment options for the different HCV genotypes once sofosbuvir is approved. Recommendations are valid for all patients with an indication for treatment as stipulated by the earlier guideline.[3]

List of currently approved drugs for treatment of chronic HCV infection:

- Peginterferon: polyethylene glycol attached to interferon-α
  - Peginterferon α -2a: 180 μg/week

  - Peginterferon α -2b: 1.5 μg/kg/week
- Ribavirin: nucleoside analogue, weight-based dose (< 75 kg 1000 mg/day and ≥ 75 kg 1200 mg/day, divided over two doses)
- Protease inhibitors (-previr):
  - Simeprevir (during revision approved, will be included in updated version)
  - Telaprevir: 2250 mg/day, divided over two or three doses
  - Boceprevir: 2400 mg/day, divided over three doses
- Nucleotide polymerase inhibitor (-buvir):
  - Sofosbuvir: 400 mg/day, in one dose
    No data in patients with renal impairment are available (eGFR < 30 ml/min/m^2)

List of HCV drugs in development:
This list is not exhaustive and can be expanded; we aimed to include drugs that are in phase III development.[1]

- Protease inhibitors (-previr):
  - Asunaprevir
  - Faldaprevir
  - ABT-450/r (ritonavir-boosted)
  - MK-5172
- NS5A inhibitors (-asvir):
  - Daclatasvir
  - Ledipasvir
  - Ombitasvir (ABT-267)
  - MK-8742
- Non-nucleoside polymerase inhibitors (-buvir):
  - Dasabuvir (ABT-333)

Watchful waiting
Watchful waiting is a preferred strategy in patients who do not have an urgent indication for treatment based on the earlier guideline,[3] in patients where no recommendation is given or when the quality of evidence is low and the strength of recommendation is weak (Level: C2). There are several arguments in favour of this strategy: (A) not all patient groups are represented in clinical trials, therefore the evidence for recommendations is weak in certain disease categories, (B) with the introduction of sofosbuvir we still need pegylated interferon and ribavirin in many patients and (C) improved efficacy and reduced toxicity is expected from interferon-free combinations of DAAs likely to be approved in the near future.[1]

Recommendations by HCV genotype, disease stage and treatment history

Genotype 1 treatment-naive patients

Recommendation: Sofosbuvir, peginterferon and weight-based ribavirin for 12 weeks (Level: B1)

Several trials have been performed in genotype 1 treatment-naive patients (*figure 1*). The recommended therapy was studied in two trials: NEUTRINO and ATOMIC. The NEUTRINO trial was a single-group open-label trial that achieved 89% SVR.[14] Patients without cirrhosis obtained 90% SVR in the ATOMIC trial. There was no additional benefit (i.e. no difference in SVR) for extension of treatment to 24 weeks or by extension with sofosbuvir monotherapy or sofosbuvir and ribavirin (n = 264).[15] The dose of sofosbuvir was determined on the basis of the PROTON study where 200 and 400 mg of sofosbuvir were compared. Here, the SVR rate was irrespective of the dose of sofosbuvir; however, three patients in the 200 mg group had a viral breakthrough, hence the selection of 400 mg.[16] Only one trial was of high quality,[16] the other trials were open-label trials of a low to moderate quality.[13]

Genotype 1 treatment-experienced patients

Recommendation: No recommendation based on data

The ELECTRON trial was the only trial that included treatment-experienced genotype 1 patients; these patients received sofosbuvir with ribavirin (12 weeks), only one of ten patients achieved SVR.[17] The label recommends consideration of treatment with sofosbuvir, peginterferon and ribavirin for 12 weeks or extension to 24 weeks,[18] but in our opinion more data are needed.

Genotype 1 cirrhotic patients

Recommendation: Watchful waiting (Level: C1)

Two clinical trials included patients with cirrhosis; the NEUTRINO trial reached 80% SVR with sofosbuvir on top of PR[14] and three of six cirrhotic patients with unfavourable characteristics achieved SVR with sofosbuvir and ribavirin in a single-centre trial.[19] The quality of evidence for sofosbuvir is low, the toxicity of the previous standard of care in cirrhotic patients is high[4] and future agents (e.g. simeprevir) are promising, hence watchful waiting is recommended.

Future perspective

For genotype 1 patients, multiple trials are currently underway; promising agents are simeprevir, asunaprevir, ABT-450/r (protease inhibitors), daclatasvir, ledipasvir, ombitasvir (NS5A inhibitors) and dasabuvir (non-nucleoside polymerase inhibitor). All oral treatment is expected to become possible in the near future for both treatment-naive and treatment-experienced patients.

Simeprevir and sofosbuvir with or without ribavirin were studied in the COSMOS trial in two cohorts, in prior null responders with F0-2 fibrosis (cohort 1) and in treatment naive or prior null responders with F3-4 fibrosis (cohort 2). High SVR rates were seen in cohort 1 (91-100%)[20] and cohort 2 (94-96%).[21,22] Therefore the combined treatment of simeprevir and sofosbuvir can be a reasonable option for these categories of patients in the near future. Simeprevir with PR has been studied in the ASPIRE, PILLAR and PROMISE studies and high SVR rates of 70-85% are seen

Figure 1. *Trials in HCV genotype 1 patients*

Trial	Regime (weeks) 0 4 8 12 24 // 48	n	SVR	SVR (95% CI) 0 50 100	QoE
Genotype 1, treatment naive					
PROTON	SOF(200)+PR / PR / PR	48	90%		A
	SOF(400)+PR / PR / PR	47	91%		A
	placebo + PR / PR	26	58%		A
NEUTRINO	SOF+PR	292	89%		C
ELECTRON	SOF(+RBV)	25	84%		C
ATOMIC	SOF+PR	52	90%		B
	SOF+PR	109	93%		B
	SOF+PR / SOF(+RBV)	155	91%		B
Osinusi et al.[ʃ]	SOF+RBV(wb)	10	90%		C
	SOF+RBV(wb)	25	68%		C
	SOF+RBV(600)	25	48%		C
Genotype 1, treatment experienced					
ELECTRON	SOF+RBV	10	10%		C
Genotype 1, cirrhosis					
NEUTRINO	SOF+PR	54 †	80%		C
Osinusi et al.*[ʃ]	SOF+RBV(wb)	6 †	50%		C
	SOF+RBV(600)	7 †	29%		C

PR = pegylated interferon with ribavirin; QoE = Quality of Evidence (A: high, B: moderate, C: low); RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virological response; wb: weight-based; *calculated 95% CI, [ʃ]first cohort early-moderate fibrosis; second and third cohort unfavourable characteristics. In cirrhotics: †treatment naive.

in cirrhotic patients with prior relapse or prior partial response.[23-25] Clinical trials with simeprevir have shown that a Q80K mutation in genotype 1a patients significantly reduces the efficacy of the treatment.[26]

Sofosbuvir plus daclatasvir with or without ribavirin for 12 or 24 weeks was studied in the AI444040 study, 126 treatment-naive genotype 1 patients achieved 98% SVR. Furthermore 41 patients who failed therapy with telaprevir or boceprevir had 98% SVR with 24 weeks of sofosbuvir and daclatasvir with or without ribavirin. Cirrhotic patients were excluded.[27] Currently a compassionate use program of sofosbuvir and daclatasvir with or without ribavirin for Child-Pugh C patients is available.

The combination of an NS5B polymerase inhibitor and an NS5A inhibitor is also being studied in the LONESTAR, ION-1, ION-2 and ION-3 studies. The LONESTAR is a single-centre open-label study in genotype 1 treatment-naive patients and patients with virological failure on protease inhibitors. An SVR of 95-100% (n = 100) with different regimens (i.e. sofosbuvir/ledipasvir with or without ribavirin, 8 or 12 weeks) was reached.[28] In the ION-1 and ION-2 trials, SVR was reached in 94-98% of the patients with 12 weeks of sofosbuvir/ledipasvir with or without ribavirin.[29,30] In the ION-3 trial treatment-naive non-cirrhotic patients achieved 94% SVR with 8 weeks of sofosbuvir/ledipasvir.[31] Phase 2a trials have been performed with daclatasvir and asunaprevir in combination with PR or the non-nucleoside polymerase inhibitor BMS-791325 in prior null responders and treatment-naive patients for 12-24 weeks. High SVR rates, 92-100%, were achieved.[32-34] Three

studies (n = 571, n = 297 and n = 473) evaluated multiple regimens with ABT-450/r, dasabuvir and ombitasvir with or without ribavirin in different combinations and durations. High SVR rates (83-97%) were seen in treatment-naive and treatment-experienced non-cirrhotic patients.[35-37] The TURQUOISE-II trial studied the same regimen (with ribavirin) in compensated cirrhotic patients for 12 (n = 208) and 24 (n = 172) weeks. SVR was achieved in 92% and 96% of the patients, respectively.[38]

Genotype 2 treatment-naive patients

Recommendation: Sofosbuvir and weight-based ribavirin for 12 weeks (Level: A1)

Patients with an HCV genotype 2 infection have an SVR rate of 74-83% with PR for 24 weeks.[3,39,40] Multiple trials with sofosbuvir have been performed in treatment-naive genotype 2 patients (*figure 2*). Two trials of high quality and one of low quality studied the recommended interferon-free regimen (POSITRON, FISSION and VALENCE) with consistent good results. The POSITRON trial included patients for whom interferon was not an option and reached 93% SVR irrespective of cirrhosis.[11] In the FISSION trial SVR was reached in 97% of patients, while in patients treated with peginterferon and ribavirin (800 mg) for 24 weeks SVR was achieved in 78%.[14] The results of the VALENCE trial are similar to FISSION and POSITRON for the recommended regimen.[41,42] Addition of peginterferon showed no improved SVR rates.[16,17] In conclusion, sofosbuvir with ribavirin for 12 weeks in genotype 2 patients was effective in high-quality trials with implications for clinical practice because of an interferon-free regimen with a shorter treatment duration than the previous standard of care.[3]

Genotype 2 treatment-experienced patients

Recommendation: Sofosbuvir and weight-based ribavirin for 12 weeks (Level: B1)

In the FUSION trial, genotype 2 patients were treated with either 12 or 16 weeks of sofosbuvir and ribavirin. Patients in the 12-week arm received four weeks of placebo, they reached 86% SVR and in the 16-week arm this was 94%. For non-cirrhotic patients the FUSION trial failed to demonstrate additional value of extending the treatment to 16 weeks, hence the recommendation of 12 weeks.[11] The POSITRON included 17 patients with unacceptable side effects in prior treatment and they achieved an SVR of 78% with sofosbuvir and ribavirin.[11] The results of the VALENCE trial demonstrated a 90% SVR with the recommended regimen.[18,42] In another trial there was no additional value of peginterferon.[43] Again this treatment has significant implications for clinical practice because of the high SVR rates without interferon and shorter treatment duration. The trials were of high[11] and low quality[41,43] with consistent results.

Genotype 2 cirrhotic patients

Recommendation: Sofosbuvir and weight-based ribavirin for 12 weeks (Level: B1)

There are four trials that evaluated sofosbuvir and ribavirin for 12 weeks in cirrhotic genotype 2 patients, mainly treatment-naive patients were studied. The FISSION demonstrated an SVR of 83% (n = 12), treatment with peginterferon and ribavirin (800 mg) for 24 weeks led to 62% SVR (n = 13).[14,18] The POSITRON trial showed an SVR of 94%. In treatment-experienced patients with cirrhosis an extension of duration of treatment from 12 to 16 weeks led to an improvement in SVR from 60% (n = 10) to 78% (n = 9) in the FUSION trial.[11] The VALENCE trial shows 82% SVR in 11 cirrhotic patients with sofosbuvir and ribavirin (12 weeks).[18,44] All trials included only a small number of patients, but implications for clinical practice are high as treatment is warranted and toxicity is expected to be less than with standard of care.

Future perspective

For genotype 2 patients the regimen of sofosbuvir with ribavirin leads to high SVR rates. Also, the AI444040 trial studied 26 treatment-naive genotype 2 patients; 24 (92%) achieved SVR with different regimens consisting of sofosbuvir and daclatasvir with or without ribavirin for 24 weeks. Cirrhotic patients were excluded.[27]

Genotype 3 treatment-naive patients

Recommendation:

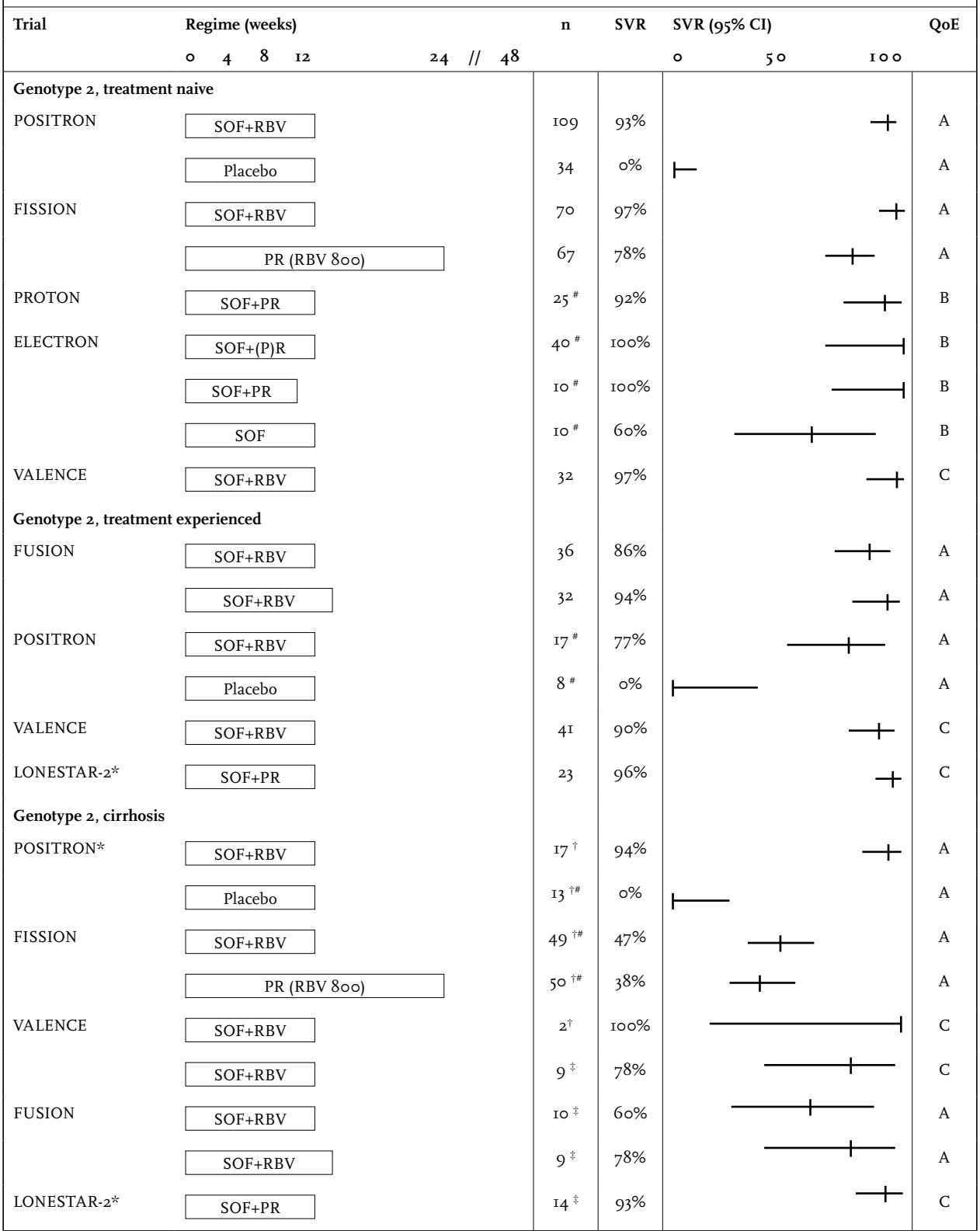
- *Watchful waiting*
- *Peginterferon and ribavirin (800 mg) for 24 weeks*
- *Sofosbuvir and weight-based ribavirin for 24 weeks*
- *Sofosbuvir, peginterferon and weight-based ribavirin for 12 weeks*

(Level A2)

For genotype 3 patients, several options for treatment are available and the physician has to decide which strategy is currently better for the individual patient. Historically genotype 2 and genotype 3 patients achieve an SVR of 70-80% with peginterferon and ribavirin (800 mg) for 24 weeks.[3]

Different trials have been performed in genotype 3 patients; all trials with 12 weeks of sofosbuvir and ribavirin fail to show superiority in comparison with PR treatment (*figure 3*).[14] The addition of peginterferon or extension of treatment to 24 weeks showed improved results. In the ELECTRON trial, 25 patients received 12 weeks of sofosbuvir and ribavirin combined with peginterferon for 0, 4, 8 or 12 weeks: all patients achieved SVR.[17] The VALENCE trial obtained 94% SVR in 105 patients with sofosbuvir with ribavirin for 24 weeks.[18,42] Because of the above-mentioned results peginterferon with ribavirin (800 mg) for 24 weeks remains an option for therapy, ribavirin should be weight based in patients

Figure 2. *Trials in HCV genotype 2 patients*



PR = pegylated interferon with ribavirin; QoE = Quality of Evidence (A: high, B: moderate, C: low); RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virological response; *calculated 95% CI, # data of genotype 2 and 3 combined. In cirrhotics: † treatment naive, ‡ treatment experienced.

with baseline characteristics associated with a poor response.[3] Other options are watchful waiting, sofosbuvir with ribavirin for 24 weeks or sofosbuvir with PR for 12 weeks. The choice for one of the regimens is dependent on the individual patient, bearing in mind the higher costs of sofosbuvir.

Genotype 3 treatment-experienced patients

Recommendation: Watchful waiting

Alternative strategy: Sofosbuvir and weight-based ribavirin for 24 weeks OR sofosbuvir, peginterferon and weight-based ribavirin for 12 weeks (Level: B2)

Results of sofosbuvir for treatment-experienced genotype 3 patients are disappointing with high imprecision; only the VALENCE and LONESTAR-2 trials show acceptable results but are of low quality. The FUSION trial showed that extension of treatment by 4 weeks led to improvement of SVR.[11] Extension to 24 weeks was done in the VALENCE study and an SVR of 79% was achieved, while for the non-cirrhotic patients the SVR rate was 87%.[18,42] The LONESTAR-2 trial showed an SVR of 83% in 24 patients treated with sofosbuvir and PR for 12 weeks.[43] In the near future more effective combinations of DAAs are expected. Therefore, the general recommendation is watchful waiting. As an alternative strategy sofosbuvir with ribavirin for 24 weeks or sofosbuvir with PR for 12 weeks may be considered.

Genotype 3 cirrhotic patients

Recommendation: Watchful waiting

Alternative strategy: Sofosbuvir and weight-based ribavirin for 16 weeks OR sofosbuvir and weight-based ribavirin for 24 weeks (Level: B2)

Genotype 3 cirrhotic patients were treated with sofosbuvir in five trials with moderate SVR rates.

The FUSION trial showed an SVR of 19% with 12 weeks of sofosbuvir and ribavirin in treatment-experienced cirrhotic patients; extension of treatment to 16 weeks showed an SVR of 61%. The VALENCE trial studied 24 weeks of sofosbuvir and ribavirin in 60 cirrhotic patients, with 92% SVR in treatment-naive patients and 62% in treatment-experienced patients.[18]

Based on the above results with small numbers of patients, we advise watchful waiting as the recommended strategy since SVR rates are rather low, mainly in treatment-experienced patients and sofosbuvir is expensive. Alternative regimens are sofosbuvir and ribavirin for 16 weeks or 24 weeks.

Future perspective

Daclatasvir is one of the agents that are expected to be approved in the near future. The COMMAND GT 2/3 study included 151 genotype 2 and 3 patients and these patients received either 12 or 16 weeks of daclatasvir with PR or 24 weeks placebo with PR. SVR rates were 69% (12 weeks), 67% (16 weeks) and 59% (placebo). Treatment failure was mainly due to relapse in cirrhotic patients in the 12-week group.[45] The combination of sofosbuvir and daclatasvir with or without ribavirin for 24 weeks does hold promise for treatment-naive genotype 3 patients as SVR rates of 89% can be reached.[27] Treatment-naive genotype 3 patients received sofosbuvir/ledipasvir with or without ribavirin in the ELECTRON-2 trial (12 weeks). Dual therapy reached 64% SVR (n=25) while triple therapy reached 100% SVR (n=26).[46]

Genotype 4 treatment-naive patients

Recommendation: Sofosbuvir, peginterferon and weight-based ribavirin for 12 weeks. (Level: C1)

The recommended regimen is being studied in the NEUTRINO trial, 28 patients were treated with sofosbuvir and PR for 12 weeks and reached 96% SVR.[14] Extension of therapy to 24 weeks did not show an improved effect.[15] Egyptian patients (n = 28) received an interferon-free regimen for 12 or 24 weeks and achieved 79% and 100% SVR, respectively.[47] In general, data are scarce (*figure 4*) but in view of the high SVR rates sofosbuvir-based treatment is recommended.

Genotype 4 treatment-experienced patients

Recommendation: No recommendation based on data

There are no published data on sofosbuvir-based treatment available for treatment-experienced genotype 4 patients. The most recent data of the Egyptian study showed 59% SVR (n = 17) with 12 weeks of sofosbuvir and ribavirin and 87% SVR (n = 15) with 24 weeks of sofosbuvir and ribavirin.[47,48] The label recommends sofosbuvir and PR for 12 weeks, but more data are needed.

Genotype 4 cirrhotic patients

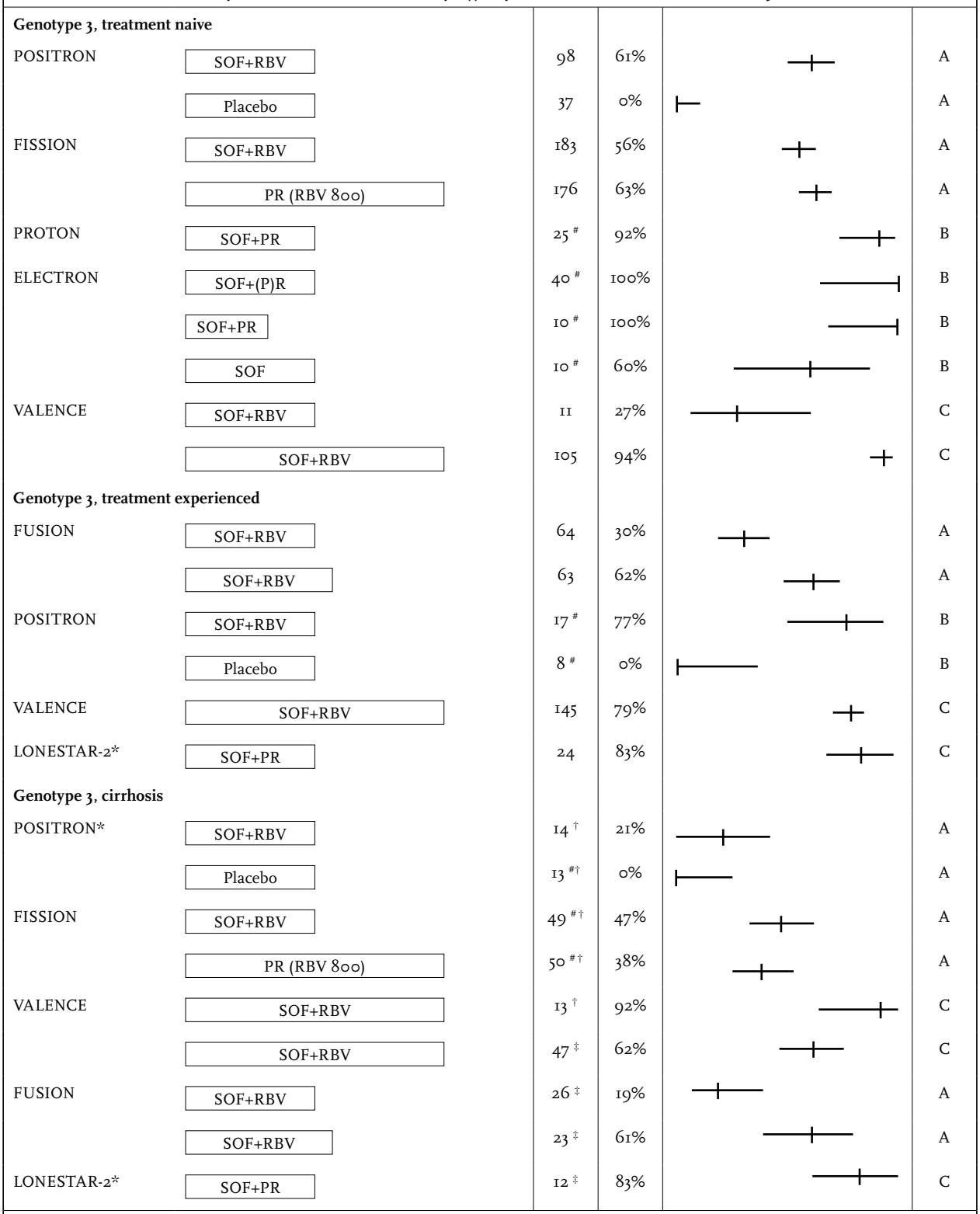
Recommendation: No recommendation based on data

Only a limited number of cirrhotic genotype 4 patients have been studied. The NEUTRINO trial included two cirrhotic genotype 4 patients of whom one achieved SVR with sofosbuvir and PR for 12 weeks.[14] In the Egyptian study treatment-naive cirrhotic patients achieved 33% (n = 3) and 100% (n = 3) SVR with 12 and 24 weeks of sofosbuvir and ribavirin. The SVR rates in treatment-experienced patients were 50% and 100% in both groups (n = 8).[47]

Future perspective

Simeprevir with PR (24 or 48 weeks) is studied in genotype 4 patients, overall 65% of the patients reached SVR with higher SVR rates in treatment-naive and relapse patients (83% and 86%).[49] Asunaprevir with PR has been studied in 18 genotype 4 patients for 24 weeks and 89% reached SVR, the control group consisted of seven patients of whom

Figure 3. *Trials in HCV genotype 3 patients*



PR = pegylated interferon with ribavirin; QoE = Quality of Evidence (A: high, B: moderate, C: low); RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virological response; *calculated 95% CI, # data of genotype 2 and 3 combined. In cirrhotics: † treatment naive, ‡ treatment experienced.

43% reached SVR with PR for 48 weeks.[50] Furthermore daclatasvir was studied in 24 treatment-naive genotype 4 patients, 67% achieved SVR with 20 mg daclatasvir and 100% achieved SVR with 60 mg daclatasvir with PR for 24 weeks.[51] Daclatasvir with asunaprevir and BMS-791325 were studied in 12 patients, 11 achieved SVR and 1 patient is still in follow-up.[52] The PEARL-I study included 86 treatment-naive genotype 4 patients who received ABT-450/r plus ombitasvir with or without ribavirin (12 weeks), 91-100% SVR was achieved.[53] Patient numbers are limited but in view of the high SVR rates of future therapy, watchful waiting can be considered in genotype 4 patients until further data allow approval of newer DAAs.

Genotype 5, 6

Data from well-powered clinical comparative trials for genotype 5 and 6 patients are lacking. We think it is unlikely that such data will become available in the near future for the novel DAAs. Therefore we consider it acceptable to use treatment results for genotype 1 as a template for treatment of genotype 5 and 6.

Genotype 5, 6 treatment-naive patients

Recommendation:

- *Genotype 5: No recommendation based on data, consider genotype 1 treatment regimen as template (Level: C2)*

Figure 4. *Trials in HCV genotype 4, 5 and 6 patients*

Trial	Regime (weeks) 0 4 8 12 24 // 48	n	SVR	SVR (95% CI) 0 50 100	QoE
Genotype 4, treatment naive					
NEUTRINO*	SOF+PR	28	96%		C
ATOMIC	SOF+PR	11	82%		C
Ruane et al.*	SOF+RBV	14	79%		C
	SOF+RBV	14	100%		C
Genotype 4, treatment experienced					
Ruane et al.*	SOF+RBV	17	59%		C
	SOF+RBV	15	87%		C
Genotype 4, cirrhosis					
NEUTRINO*	SOF+PR	2 †	50%		C
Ruane et al. *	SOF+RBV	3 †	33%		C
	SOF+RBV	4 ‡	50%		C
	SOF+RBV	3 †	100%		C
	SOF+RBV	4 ‡	100%		C
Genotype 5 and 6, treatment naive					
NEUTRINO*	SOF+PR	7	100%		C
ATOMIC	SOF+PR	5	100%		C
Genotype 5 and 6, treatment experienced					
No available trials					

PR = pegylated interferon with ribavirin; QoE = Quality of Evidence (A: high, B: moderate, C: low); RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virological response; *calculated 95% CI, if 100% SVR then no CI could be calculated. In cirrhotics: † treatment naive, ‡ treatment experienced.

- *Genotype 6: sofosbuvir, peginterferon and weight-based ribavirin for 12 weeks (Level: C2)*

Only 12 treatment-naive patients with genotype 5 or 6 have been treated in two trials (NEUTRINO and ATOMIC). In the NEUTRINO trial six genotype 6 patients and one genotype 5 patient were treated with 12 weeks of sofosbuvir and PR and all patients achieved SVR.[14] In the ATOMIC trial only five patients with genotype 6 received sofosbuvir with PR for 24 weeks, all achieved SVR.[15] More data are needed, however, considering the high SVR rates a sofosbuvir-based treatment is recommended for genotype 6.

Genotype 5,6 treatment-experienced patients

Recommendation: No recommendation based on data, consider genotype 1 treatment regimen as template (Level: C2)

There are no data on sofosbuvir-based treatment available for treatment-experienced genotype 5 or 6 patients.

Genotype 5, 6 cirrhotic patients

Recommendation: No recommendation based on data, consider genotype 1 treatment regimen as template (Level: C2)

The NEUTRINO trial included 20% cirrhotic patients but it is unknown if cirrhotic genotype 5 or 6 patients were included.[14]

Drug-drug interactions

Many of the DAAs are substrates of CYP450 and the membrane transporter P-gp; they may both be the victim of drug interactions or cause these interactions with other agents.[54,55] Sofosbuvir has a relatively mild drug interaction profile as it is only a substrate of P-gp and does not interfere with CYP450 enzymes. It is necessary to check for interacting co-medications, including over the counter drugs (e.g. St. John's Wort), before starting DAA-based HCV treatment (http://www.hep-druginteractions.org).

Summary box of recommendations for HCV monoinfected patients

Genotype	Patient group	Recommendation	Future perspective
1	Treatment naive	Sofosbuvir, peginterferon and ribavirin for 12 weeks	Daclatasvir, simeprevir, ledipasvir, asunaprevir, ABT-450/r, dasabuvir, ombitasvir
	Treatment experienced	No recommendation based on data	
	Cirrhotic	Watchful waiting	
2	Treatment naive	Sofosbuvir and ribavirin for 12 weeks	Daclatasvir
	Treatment experienced	Sofosbuvir and ribavirin for 12 weeks	
	Cirrhotic	Sofosbuvir and ribavirin for 12 weeks	
3	Treatment naive	Physician opinion to determine the strategy, options: • Watchful waiting • Peginterferon and ribavirin (800 mg) for 24 weeks • Sofosbuvir and ribavirin for 24 weeks • Sofosbuvir, peginterferon and ribavirin for 12 weeks	Daclatasvir, ledipasvir
	Treatment experienced	Watchful waiting Alternative strategy: • Sofosbuvir and ribavirin for 24 weeks OR • Sofosbuvir, peginterferon and ribavirin for 12 weeks	
	Cirrhotic	Watchful waiting Alternative strategy: • Sofosbuvir and ribavirin for 16 weeks OR • Sofosbuvir and ribavirin for 24 weeks	
4	Treatment naïve	Sofosbuvir, peginterferon and ribavirin for 12 weeks	Simeprevir, daclatasvir, asunaprevir, ABT-450/r, ombitasvir
	Treatment experienced	No recommendation based on data	
	Cirrhotic	No recommendation based on data	
5, 6	Treatment naive	Genotype 5: No recommendation based on data, consider genotype 1 treatment regimen as template Genotype 6: Sofosbuvir, peginterferon and ribavirin for 12 weeks	
	Treatment experienced	No recommendation based on data, consider genotype 1 treatment regimen as template	
	Cirrhotic	No recommendation based on data, consider genotype 1 treatment regimen as template	

DISCUSSION

The current guidance comes at a time when the landscape of HCV treatment is undergoing a rapid change. There are currently four comparable guidances, one was issued by the American Association for the Study of Liver Diseases (AASLD), one by European Association for the Study of the Liver (EASL) and the other two are guidances from Germany.[56-59] Our guidance differs from the AASLD and EASL guidances and we do not offer advice on the use of simeprevir and daclatasvir in this version. The main difference with the other guidances is that we offer the clinician the option to defer treatment in genotype 3 and some subgroups of patients. The reason is that, except for the VALENCE trial, the currently published evidence has not proved efficacy beyond standard of care. The proportion of cirrhotic patients in the various trials is disappointingly low and recommendations cannot be given for this category, with the exception of genotype 2. This contrasts with clinical practice where cirrhotic patients have the most urgent treatment indication.[3] For genotypes 5 and 6 the current evidence is poor. The AASLD, EASL and German guidances recommend sofosbuvir triple therapy for genotype 5 and 6. The consensus in the Hepatology Committee was that the evidence for sofosbuvir was acceptable for genotype 6 naive patients, while we recommend standard of care or considering the genotype 1 regimen as template for other disease categories in genotype 5 and 6. At odds with other guidances we do not recommend sofosbuvir-based treatment for genotype 1 and 4 treatment-experienced patients given the lack of evidence. This guidance only includes recommendations for HCV monoinfected patients. Sofosbuvir and other DAAs are also being studied in HIV/HCV patients; this will be updated in a new version of this guidance.

The rapid pace of development of drugs to treat HCV infection introduces not only great expectations but also uncertainty about the optimal timing to initiate therapy.[60] The key question here is which patients can benefit from the DAAs that are now available. Sofosbuvir is a first-generation polymerase inhibitor that is in the vanguard of a wave of drugs that have the potential to cure HCV. With the approval of the EMA, sofosbuvir will be released on the Dutch market soon. As medication is an important costdriver, the added efficacy of sofosbuvir relative to standard of care should be weighed carefully.[61] As the pipeline with new antiviral drugs is full and new releases can be expected in 2014 and 2015, this paper serves as a dynamic document and will be continually edited and updated.[12]

DISCLOSURES

Conflicts of interest

F.A.C. Berden: none

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Supplementary file 1. *Search*

An initial search was conducted on 25-Feb-2014 with the term: '2-((5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-ylmethoxy)phenoxyphosphorylamino) propionic acid isopropyl ester [Supplementary Concept]' as a MeSH term. Furthermore we included 'sofosbuvir OR GS-7977 OR PSI 7977 OR PSI7977 OR PSI-7977 OR Sovaldi' in our search. In total 98 articles were found in PubMed. All were scanned on title and abstract for inclusion. New results of the search were added until 8-Apr-14. For the future perspectives we searched the agents in phase III of clinical trials, including simeprevir (as MeSH combined with 'simeprevir OR TMC 435350 OR TMC435350 OR TMC-435350 OR Olysio OR TMC 435 OR TMC435 OR TMC-435', with the limit of clinical trials). We did the same for daclatasvir, ledipasvir, asunaprevir and the ABT formulations in PubMed. Clinicaltrials.gov was used to get more information about the unpublished trials. Prior to submission, the abstracts of the International Liver Congress 2014 (49th annual meeting of the European Association for the Study of the Liver) were scanned and relevant studies were included in the future perspectives of the different genotypes.

Supplementary file 2. *Evidence grading (adapted from the GRADE system)*

Level	Evidence quality	Strength of recommendation
A1	High	Strong
B1	Moderate	Strong
C1	Low	Strong
A2	High	Weak
B2	Moderate	Weak
C2	Low	Weak

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