AP&T Alimentary Pharmacology and Therapeutics

Systematic review: interferon-free regimens for patients with HCV-related Child C cirrhosis

M. Guarino*, F. Morisco*, M. R. Valvano†, A. M. Ippolito†, M. Librandi‡, N. Andriulli§, M. Greco¶, A. Amoruso**, A. Iacobellis†, G. Niro†, N. Caporaso* & A. Andriulli†

*Gastroenterology Unit, Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy.
†Division of Gastroenterology, Casa Sollievo Sofferenza Hospital, IRCCS, San Giovanni Rotondo, Italy.
‡Pharmacia Librandi, Cirò Marina, Italy.
§Pharmacia Tor Millina, Rome, Italy.
¶Division of Internal Medicine and Clinical Immunology, San Martino Hospital, IRCCS, Genova, Italy.
**Division of Emergency Medicine, San Carlo Hospital, Potenza, Italy.

Correspondence to:
Dr A. Andriulli, Division of Gastroenterology, "Casa Sollievo Sofferenza" Hospital, IRCCS, Viale Cappuccini 1, 71013 San Giovanni Rotondo, Italy
email: a.andriulli@operapadrepio.it

Publication data
Submitted 1 December 2016
First decision 21 January 2017
Resubmitted 21 January 2017
Resubmitted 7 February 2017
Accepted 7 February 2017
EV Pub Online 6 March 2017

The Handling Editor for this article was Professor Geoffrey Dusheiko, and this uncommissioned review was accepted for publication after full peer-review.

SUMMARY

Background
It is unclear whether the efficacy and long-term outcome of treating patients with hepatitis C virus (HCV)-positive cirrhosis with the new protease inhibitors will extend to those with Child C cirrhosis.

Aim
To assess the effectiveness of the interferon-free regimens in Child C cirrhotic patients with HCV infection.

Methods
A systematic Medline search was conducted to retrieve studies describing the treatment of Child C patients with direct-acting agents. Citations from identified studies were cross-referenced and abstracts from European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Disease (AASLD) meetings were checked. Extracted data were evaluated using a meta-analysis to calculate a weighted response rate.

Results
Seven full-text records and two conference abstracts were retained for analysis from the 649 records identified. Data from an Italian real-life trial were also interrogated. Information on treatment outcome was available for 228 of the 240 Child C patients evaluated in the 10 trials. Overall, the weighted mean sustained virological response (SVR12) was 74.9% (95% CI: 65.6–82.4%). Neither duration of treatment (24 or 12 weeks), nor addition of ribavirin influenced these rates. The weighted SVR12 was 65.4% (95% CI: 46.8–80.2) after sofosbuvir/simeprevir, 76.0% (95% CI: 54.4–89.3%) after sofosbuvir/daclatasvir and 83.0% (95% CI: 73.4–89.6) after sofosbuvir/ledipasvir. Some studies did not provide information on the rate of post-treatment relapse or functional improvement. However, in those studies that did provide such data, a relapse was documented in 12.1% of patients and an improvement of ≥2 points on the model for end-stage liver disease (MELD) score in 61.1% of patients.

Conclusion
The improvement in MELD scores strongly suggests HCV-positive patients with Child C cirrhosis should be treated with these agents.

Aliment Pharmacol Ther 2017; **45**: 1193–1200

doi:10.1111/apt.14017

INTRODUCTION

Cirrhosis encompasses a spectrum of clinical entities ranging from early (compensated) to more severe (decompensated) cirrhosis and terminal end-stage liver disease. Compensated cirrhosis is also heterogeneous with more severe forms observed when oesophageal varices, a reflection of portal hypertension, become evident.[1] Patients with hepatitis C virus(HCV)-related cirrhosis are at risk of developing life-threatening complications, such as decompensated liver disease and hepatocellular carcinoma (HCC), or may face an orthotopic liver transplant or death in cases with unmanageable, terminal disease.[2, 3] Antiviral treatment has the potential to improve long-term outcomes for patients with cirrhosis, and viral clearance is associated with histological improvement, a decreased risk of HCC, and a reduced incidence of decompensation and of liver- and non liver-related mortality.[4, 5]

A sustained virological response with a positive impact on outcome in patients with HCV-related cirrhosis has been documented following therapy with peg-interferon and ribavirin.[6, 7] Initial and fragmentary information concerning a similar favourable effect following treatment with the new direct acting antivirals has been also reported.[8–10] However, previous data have been derived from the evaluation of patients with early cirrhosis, that is those in classes A and B of the Child classification. It remains unclear whether the therapeutic benefits will extend to patients treated for more advanced disease (Child C patients). Child C patients have been traditionally denied therapy with peg-interferon and ribavirin due to concerns about the safety of these regimens in patients with extreme derangements of liver function. A similar attitude is evident in studies evaluating the benefits of therapy with the new antiviral drugs, with Child C patients under-represented both in registrative clinical trials and real-worlds settings, although in most need of viral eradication. The low number of Child C patients treated so far with the new antivirals in the studies has precluded a definitive conclusion about the benefits and harms of treating this particular subgroup of patients.

In order to highlight the value of therapy for patients with Child C cirrhosis in most need of a reduction in the liver impairment caused by HCV infection, this systematic review seeks to assess the effectiveness of the interferon-free regimens in clinical practice in these patients, quantitatively synthesise available evidence where possible and estimate a weighed response following treatment with the new products.

METHODS

Literature search and selection of primary studies

The strategy for building the evidence base for the treatment of patients with cirrhosis and HCV infection consisted of two steps. First, an electronic, systematic review of the available evidence in the literature, conducted in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[11] was undertaken to identify all studies. Second, proceedings of the 2015 and 2016 Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), and of the 2016 Annual Conference of the European Association for the Study of the Liver (EASL) were hand searched. The systematic literature review was performed via a Medline search using the following index terms: cirrhosis AND HCV infection AND sofosbuvir (260 items identified), OR simeprevir (125 records retrieved), OR daclatasvir (101 articles), OR ledipasvir (93 items), OR ombitasvir/paritaprevir and dasabuvir (52 records). The final search was conducted on October 2016. Eighteen relevant abstracts were retrieved by reading the proceeding of the three scientific conferences.

Figure 1 presents the PRISMA flow diagram for the selection of studies. A total of 649 studies were identified. Studies were excluded if they were in languages other than English, did not separately report outcome data for patients with Child A, B or C cirrhosis, or referred to transplanted patients. Duplicate publications, narrative reviews and editorials were also excluded.

Data extraction and management

All information was extracted using a standardised data abstraction form. Data retrieved included: study characteristics (whether clinical trials or interventional studies); main infecting HCV genotypes; treatment history (naïve or treatment experienced); schedules of the direct acting antiviral agents administered, including dose and duration; concomitant use of ribavirin; efficacy of therapy as ascertained by a sustained virological response at 12 weeks following treatment (SVR12); change in the model for end-stage liver disease (MELD) score at 12 weeks after treatment; and safety outcomes for the longest reported treatment and follow-up period. Only data specifically referring to Child C patients were extracted from the included studies by a single author and checked by a second independent reviewer. Any disagreements were resolved through discussion.

Data synthesis

The primary efficacy outcome was SVR12 (undetectable HCV-RNA levels 12 weeks after the end of therapy).

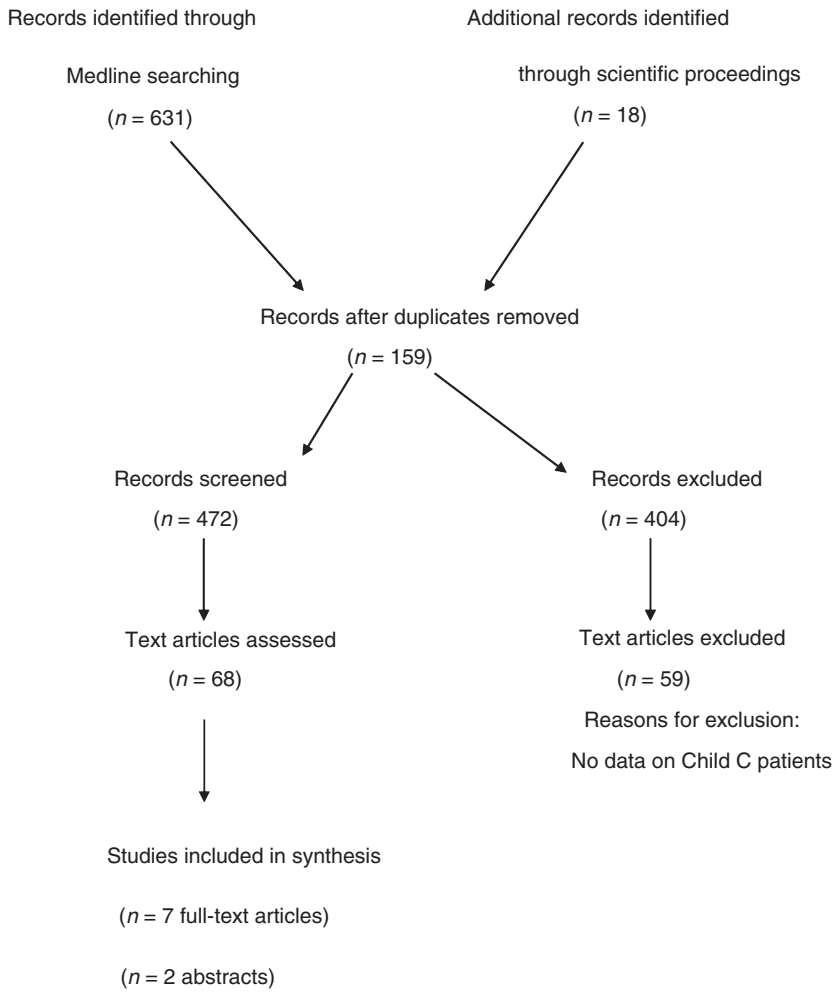

Figure 1 | PRISMA flow diagram showing the study selection process

Owing to the risk of overestimating a beneficial outcome in trials not designed specifically for patients with Child C cirrhosis undergoing antiviral therapy and including very few patients with Child C cirrhosis, separate analyses were performed for each treatment schedules, dose and duration, and for the concomitant use or not of ribavirin, whenever possible.

Statistical analyses

SVR12 rates were the measure of interest in this meta-analysis. Given the small number of patients and the very low or very high numbers in some studies, the 95% confidence intervals were calculated using the Wilson score interval.[12] Subgroup analyses were carried out to explore the impact on the SVR rate of treatment duration (24 or 12 weeks), the inclusion of ribavirin in the treatment schedule and the different new drugs regimens. We used random rather than fixed-effects models to estimate pooled proportions in order to account for the heterogeneity.[13] All analyses were performed using the Comprehensive Meta-analysis software (Version 2.2061, Biostat, Englewood, NJ, USA).

RESULTS

Figure 1 shows the PRISMA flow diagram of the literature selection process. Seven full-text records[14–20] and two conference abstracts[21, 22] were retained for analysis. Additional information for one selected trial[19] was retrieved from a follow-up study of the same cohort of patients.[23] Of the nine selected studies, three were clinical trials,[14, 15, 18] and five were real-life studies with a prospective[19, 20] or a retrospective design;[16, 17, 21] the design of the ninth investigation was not explained.[22] Data from an ongoing large, prospective Italian program evaluating treatment with the new antivirals in patients with chronic HCV infection were also interrogated,[24] and information for patients with Child C cirrhosis was extracted and pooled in the final analysis. The main characteristics of patients with cirrhosis evaluated in the 10 selected studies are shown in Table 1. The number of patients enrolled in the individual trials varied from 42

to 2037, and their median ages were generally <60 years. The majority of patients with cirrhosis were infected by HCV genotype 1, were in Child B class and presented with a mean MELD score of <15. About two-thirds of patients had failed a previous treatment course with peg-interferon and ribavirin.

Information on treatment outcome was available for 228 of the 240 Child C patients evaluated in the 10 trials. The SVR12 rates described in the individual studies are shown in Figure 2: the rates varied from low values of 50.0% and 56.3% reported in two studies[17, 18] to high values of 94.4% and 96.0% found in two other reports.[21, 24] Overall, the weighted mean SVR12 rate was 74.9% (95% CI: 65.6–82.4%) using a random effects model. Several sub-analyses were run to explore the potential impact of the different regimens administered in the selected studies; the individual results are given in Figures S1–S5 and the pooled estimates in Figure 3.

The first sub-analysis considered the effect of the length of treatment: the weighted mean SVR12 rate was 82.3% (95% CI: 0.71–99.0) when treatment lasted for 24 weeks, and 70.9% (95% CI: 62.0–78.5) when treatment lasted for 12 weeks (Figure 3 and Figure S1); a trend toward a significant difference was seen ($P = 0.085$). The inclusion of ribavirin in the treatment schedules did not affect these rates (Figure 3 and Figure S2): the weighted mean value was 76.4% (95% CI: 64.7–85.1) when ribavirin was added to the new antivirals, and 79.9% (95% CI: 54.9–92.9) when was not ($P = 0.758$). Next, we analysed the interaction between treatment length and ribavirin administration. When treatment lasted for 24 weeks, the administration of ribavirin did not affect the SVR12 rates, which were 81.7% (95% CI; 63.1–89.9) and 95.4% (95% CI: 73.5–93.4%) when ribavirin was and was not administered respectively (Figure S3). When treatment lasted for 12 weeks, the weighted SVR12 rates were 73.6% (95% CI: 62.0–82.7) and 69.2% (95% CI: 47.3–83.7) respectively. No previous differences were statistically significant (Figure S3).

Sufficient data were available to evaluate the efficacies of three different schedules of direct acting antiviral agents, although no information was available on the efficacy of ombitasvir/paritaprevir and dasabuvir in patients with Child C cirrhosis (Figure S4). The regimen of sofosbuvir plus simeprevir given for 12 weeks was evaluated in four studies:[16, 17, 24, 30] in the 31 patients with Child C cirrhosis treated with this schedule, the weighted mean SVR12 rate was 65.4% (95% CI: 46.8–80.2). In four studies,[18, 21, 22, 24] 55 patients received sofosbuvir plus daclatasvir, the majority of them for 24 weeks: the corresponding weighted mean SVR12 rate was 76.0% (95% CI: 54.4–89.3%). In three studies,[14, 15, 24] sofosbuvir was administered in combination with ledipasvir to 101 patients: a weighted mean SVR12 rate of 83.0% (95% CI: 73.4–89.6) was observed. As this last treatment schedule was given for 12 or 24 weeks, we explored the impact of treatment length on SVR12 rate: weighted mean SVR12 rates were 82.3% (95% CI: 69.0–90.7) in patients treated for 24 weeks, and 83.5% (95% CI: 69.3–92.0) in those treated for 12 weeks.

The relapse rate after treatment was reported in four studies[14–16, 24] and the data are presented in Table 2: only 13 (12.1%) of the 197 patients with Child C

Table 1 | Characteristics of Child classes A–C cirrhotic patients, enrolled in the studies selected for the meta-analysis

			HCV genotype				Child classes			Mean	MELD >	Previous
	Total	Mean age (range)	1	2	3	4	A	B	C	MELD (range)	15 (%)	treatment (%)
Charlton, 2015	108	59 (53–62)	105	–	–	3	–	59	49	(10–25)	41	65
Manns, 2016	107	54 (47–63)	97	–	–	10	–	56	51	(10–25)	45	75
Shiffmann, 2015	120	60 (29–79)	120	–	–	–	81	25	14	N.A.	N.A.	61
Foster, 2016	409	54 (28–79)	200	–	–	172	71	297	41	12 (7–32)	N.A.	60
Modi, 2016	42	58 (32–69)	42	–	–	–		35	7	(6–25)	9,5	52
Poordad, 2016	60	58 (19–75)	45	5	6	4	12	32	16	13 (8.27)	30	60
Saxena, 2016	156	62 (58–65)	61	–	–	–	101	49	6	12 (10–14)	N.A.	55
Leroy, 2016	93	55	N.A.					85	8	13	N.A.	75
Petersen, 2016	147	56 (28–85)	108	–	39	–	–	127	20	N.A.	20	69
Ippolito, 2016	2037	65 (28–88)	1427	350	137	113*	1759	249	29	8 (5–25)	68	49

NA, not assessed.

* N = 10 mixed genotype.

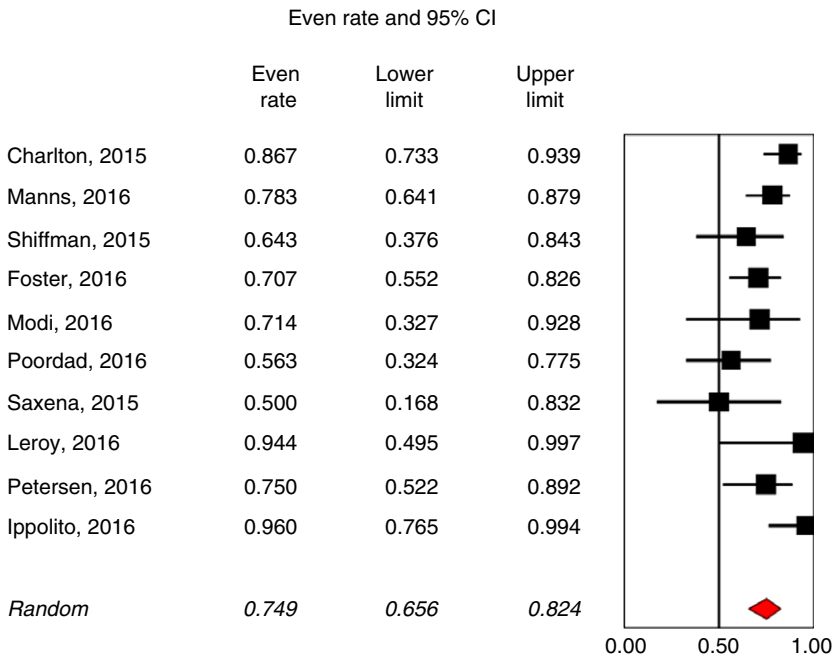

Figure 2 | Weighted estimates of sustained virological response rates after treatment of patients with Child C cirrhosis with the new direct-acting antivirals in the 10 selected studies.

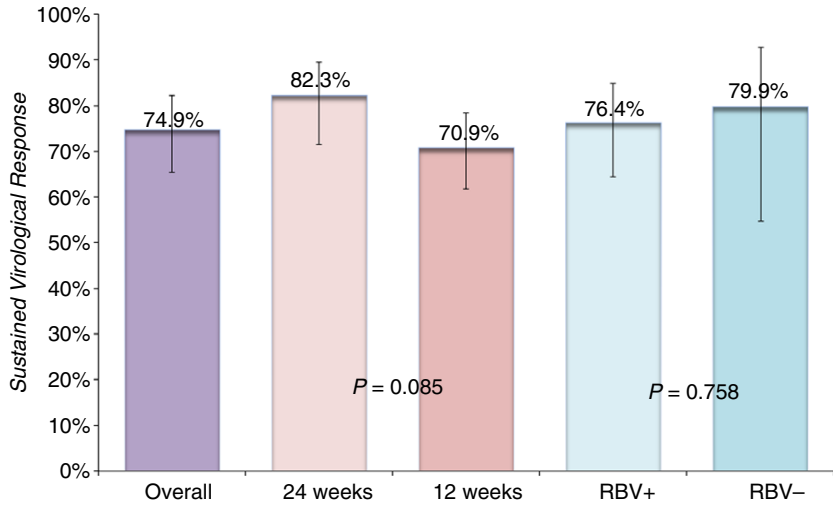

Figure 3 | Summary results of weighted estimates of sustained virological response rates according to the different therapeutic regimens with new direct acting antivirals by treatment duration (24 vs. 12 weeks) or the inclusion or not of ribavirin in the regimens.

cirrhosis with available information relapsed after cessation of therapy (12.1%). Data on functional outcome after 12 weeks of follow-up were extracted from five studies[14, 18, 21, 24] (Table 2): an improvement of ≥2 points at the post-treatment follow-up was documented in 63 of 103 patients (61.1%).

DISCUSSION

The efficacy, safety and long-term outcome of treatment with new direct acting antiviral agents of patients with Child C cirrhosis are unknown, as the low numbers of these patients enrolled in either registrative or post-marketing clinical trials do not allow conclusions to be drawn. This lack of information reflects concerns and fears regarding the treatment of such patients with peg-interferon and ribavirin: although such a therapy has been shown to be feasible,[7] the associated severe events and worsening of hepatic decompensation[25, 26] have discouraged physicians from administering interferon-based therapies to patients with Child C. These same concerns and fears also apply to the new interferon-free regimens. While these new regimens have proved safe and effective in patients with Child A and B cirrhosis,[8–10] data describing their use in Child C patients are limited. We sought to address this lack of information by conducting a systematic review of the published literature and tried to separate the results for Child C patients from those of the entire cohort of patients with cirrhosis in each trial.

Table 2 | Characteristics of Child C cirrhotic patients, enrolled in the studies selected for the meta-analysis

	Regimen	Ribavirin	Duration of therapy (weeks)	Total no. of patients	No. of patients with SVR12	No. of patients who relapsed	≥2 points improvement in MELD score
Charlton, 2015	SOF/LDV	Yes	12	22	19	1	8/18
		Yes	24	23	20	2	6/20
Manns, 2016	SOF/LDV	Yes	12	21	17	3	12/16
		Yes	24	25	19	1	13/19
Shiffmann, 2015	SOF/SMV	No	12	14	9	5	–
Foster, 2016	SOF/DAC or LDV	Yes	12	41	29	–	–
Modi, 2016	SOF/SMV	No	12	7	5	–	–
Poordad, 2016	SOF/DAC	Yes	12	16	9	–	7/13
Saxena, 2016	SOF/SMV	±	12	6	33	–	–
Leroy, 2016	SOF/DAC	No	24	8	8	–	3/4
Petersen, 2016	SOF/DAC	±	24	20	15	–	–
Ippolito, 2016	SOF/DAC	Yes	24	6	5	1	3/6
		No	24	5	5	–	4/5
	SOF/LDV	Yes	24	3	3	–	3/3
		No	24	7	7	–	3/7
	SOF/SMV	Yes	12	2	2	–	1/2
		No	12	2	2	–	–

We pooled the therapeutic results for 228 Child C patients, the largest collection of such patients evaluated to date. The weighted average SVR12 rate was 74.9% (95% CI: 65.6–82.4%) in the 228 patients treated with the new direct acting antiviral agents in 10 studies. Eight of the surveyed studies had a prospective design, which further validates the observed outcome data. However, we must evaluate this rate carefully because this is an unusual population, as the majority of patients were genotype 1 and previously exposed to peg-interferon plus ribavirin. Nevertheless, this remarkable SVR12 rate indicates that this particular setting of HCV-infected patients should not be denied treatment with the new therapeutic regimens.

Although of relevance to physicians caring for these patients, the average SVR rate seen in this investigation is lower than that reported in patients with Child A and B cirrhosis. We tried to explore whether the different schedules adopted in the original investigations might have impacted on the SVR rate in these patients. As indicated in Figure 3, neither duration of treatment (whether 24 or 12 weeks), nor the addiction of ribavirin seemed to make a difference. Numerically higher SVR12 rates were seen when therapy was administered for 24 weeks (82.3% vs. 70.9%), but this difference is likely due to the fact that more patients administered 12 weeks of treatment received therapy with the less effective schedule, that is sofosbuvir in combination with simeprevir. Indeed, the individual therapeutic regimens administered to patients resulted in some variation in the SVR12 rates: 65.4% (95% CI: 46.8–80.2) in patients treated with sofosbuvir and simeprevir, 76.0% (95% CI: 54.4–89.3) in those treated with sofosbuvir and daclatasvir, and 83.0% (95% CI: 73.4–89.6) in those treated with sofosbuvir and ledipasvir. The reasons for the choice of the regimens in the original investigations are unknown, but appeared to be dependent on when the various direct acting antiviral drugs were made available to physicians. On the Italian market, the combination of sofosbuvir and simeprevir was licensed first, followed by sofosbuvir with daclatasvir, and then by sofosbuvir and ledipasvir. Because these regimens were not randomised in the original investigations, we cannot compare their respective efficacies. However, we note that there was a 17% difference in SVR12 rates between sofosbuvir/simeprevir and sofosbuvir/ledipasvir, so a formal clinical trial comparing these therapeutic schedules is urgently required. In the meanwhile, the data presented here indicate that patients with Child C cirrhosis should be treated with sofosbuvir and ledipasvir, irrespective of ribavirin, for 12 weeks.

A further argument against treating these patients concerns the long-term benefit of therapy, as antiviral treatment in end-stage liver disease might be futile and only marginally affect prognosis. After successful therapy, the MELD score will improve in one-third of patients with cirrhosis, deteriorate in one-third and remain stable in one-third.[27] Of note, in the present investigation, an improvement of ≥2 points in the MELD

score was seen in 61.1% of the Child C patients during follow-up. Unfortunately, the MELD score was only available for 103 of the 228 treated Child C patients, but the percentage of patients with an improved MELD score was remarkable. The difference seen between our data and previous studies on post-treatment benefit in patients with decompensated cirrhosis[22, 23] may be partially be due to the characteristics of the investigated patients: our survey was restricted to Child C patients, while in previous studies the majority of cases had Child B cirrhosis. About 50% of our patients with cirrhosis presented with a MELD score >15 at baseline, and the higher the MELD scores at baseline the more likely an improvement is seen at the post-treatment evaluation.

Our investigation may have some limitations. Although the present collection represents the largest series to date of patients with Child C cirrhosis, in several sub-analyses the size of the investigated cohort limited our ability to draw conclusions. For instance, we cannot compare the different regimens because the reasons for choosing the regimen are not known: about three quarters of the patients received a combination of sofosbuvir with ledipasvir, and only a minority the other three currently available regimens. A second issue is that the patients included in the three largest studies[12, 13, 19] had an upper age limit of 63 years, so we do not have sufficient evidence to recommend treatment for older subjects. We tried to retrieve information on safety of the new antivirals administered to Child C patients, being aware of reports on the risk of hepatic decompensation following this therapy.[28, 29] In 2015, the FDA issued a warning against the administration of the new antivirals in patients with Child B and C cirrhosis, based on 26 cases of worsening liver failure.[30] Unfortunately, data on the safety of antiviral treatments and mortality during therapy in Child C patients in the original studies could not been analysed, as this information could not be extracted from the information from entire populations. Nutt et al. have reported that the overall incidence of hepatic decompensation in patients with cirrhosis treated with the newer direct antivirals was higher in those treated with sofosbuvir/simeprevir than in those treated with sofosbuvir/ledispavir.[31] We acknowledge this lack of data as a major limitation of the present investigation. Finally, the majority of treated patients in this analysis were infected with HCV genotype 1 and so the results refer to this subset of patients but may not apply to HCV genotypes 3 and 4. Despite these concerns, the overall SVR12 rates in this study are reassuring for patients with Child C cirrhosis.

In conclusion, the outcomes of the studies analysed in this review provide evidence for the effectiveness of the new interferon-free regimens for patients with Child C cirrhosis: their efficacy together with the remarkable improvement in post-treatment MELD scores indicate this subgroup of patients with severely impaired liver function should be treated. There is an urgent need to conduct a formal observational trial to evaluate the efficacy, safety and post-treatment outcome of the new protease inhibitors in patients with Child C cirrhosis.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. The impact of treatment duration (24 or 12 weeks) on sustained virological response to direct acting antivirals in patients with Child C cirrhosis.

Figure S2. Sustained virological response to the administration of the new antivirals in patients with Child C cirrhosis when ribavirin was or not included in the therapeutic regimens

Figure S3. Sustained virological response rates to the administration of direct acting antiviral agents in patients with Child C cirrhosis by treatment duration (24 or 12 weeks) and ribavirin administration (yes or no)

Figure S4. Sustained virological response rates by treatment regimens in patients with Child C cirrhosis.

Figure S5. Effect of treatment duration (24 or 12 weeks) in patients with Child C cirrhosis who received therapy with sofosbuvir and ledipasvir.

AUTHORSHIP

Guarantor of the article: A. Andriulli

Author contributions: Antonio Massimo Ippolito declares that there are no known conflicts of interest associated with this publication. The statistic analysis was drawn by MR Valvano. The Medline search was conducted by Guarino Maria, Antonio Massimo Ippolito and Filomena Morisco. Marta Librandi, Nicola Andriulli, Monica Greco, Annabianca Amoruso, Angelo Iacobellis, Grazia Niro, and Nicola Caporaso have contributed to the scientific discussion of the data. Angelo Andriulli wrote and developed the paper. Antonio Massimo Ippolito declares that there are no known conflicts of interest associated with this publication.

All authors approved the final version of the manuscript.

ACKNOWLEDGEMENTS

Declaration of personal and funding interests: None.

REFERENCES

1. D'Amico G, Pasta L, Morabito A, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception color study of 494 patients. *Aliment Pharmacol Ther* 2014; **39**: 1180–93.
2. Jacobson JM, Davis GL, El-Serag H, et al. Prevalence and challenges of liver diseases in patients with chronic hepatitis C infection. *Clin Gastroenterol Hepatol* 2010; **8**: 924–33.
3. Petta S, Maida M, Macaluso FS, et al. Hepatitis C virus infection is associated with increased cardiovascular mortality: a meta-analysis of observational studies. *Gastroenterology* 2016; **150**: 145–155.
4. Morgan TR, Ghany MG, Kim HY, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. *Hepatology* 2010; **52**: 833–44.
5. Van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012; **308**: 2584–93.
6. Morisco F, Granata R, Stroffolini T, et al. Sustained virological response: a milestone in the treatment of chronic hepatitis C. *World J Gastroenterol* 2013; **19**: 2793–8.
7. Iacobellis A, Ippolito A, Andriulli A. Antiviral therapy in hepatitis C virus cirrhotic patients in compensated and decompensated condition. *World J Gastroenterol* 2008; **14**: 6467–72.
8. Boccaccio V, Bruno S. Management of HCV patients with cirrhosis with direct acting anti-virals. *Liver Int* 2014; **34** (suppl 1): 38–45.
9. Reddy KR, Lim JK, Di Bisceglie AM, et al. All-oral direct-acting antiviral therapy in HCV-advanced liver disease is effective in real-world practice: observations through HCV-TARGET database. *Aliment Pharmacol Ther* 2017; **45**: 115–26.
10. Faria R, Woods B, Griffin S, et al. Prevention of progression to cirrhosis in hepatitis C with fibrosis: effectiveness and cost effectiveness of sequential therapy with new direct-acting anti-virals. *Aliment Pharmacol Ther* 2016; **44**: 866–76.
11. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.2 (updated September 2009). The Cochrane Collaboration, 2008. Available from http://handbook.cochrane.org.
12. Wilson EB. Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc* 1927; **22**: 209–12.
13. Greenland S. Quantitative methods in the review of epidemiologic literature. *Epidemiol Rev* 1987; **9**: 1–30.
14. Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. *Gastroenterology* 2015; **149**: 649–59.
15. Manns M, Samuel D, Gane EJ, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. *Lancet Infect Dis* 2016; **16**: 685–97.
16. Shiffman ML, James AM, Long AG, Alexander PC. Treatment of chronic HCV with sofosbuvir and simeprevir in patients with cirrhosis and contraindications to interferon and/or ribavirin. *Am J Gastroenterol* 2015; **110**: 1179–85.
17. Saxena V, Nyberg L, Pauly M, et al. Safety and efficacy of simeprevir/sofosbuvir in hepatitis C-infected patients with compensated and decompensated cirrhosis. *Hepatology* 2015; **62**: 715–25.
18. Poordad F, Schiff ER, Vierling JM, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. *Hepatology* 2016; **63**: 1493–505.
19. Foster G, Irving WL, Cheung MCM, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol* 2016; **64**: 1224–31.
20. Modi AA, Nazario H, Trotter JF, et al. Safety and efficacy of simeprevir plus sofosbuvir with or without ribavirin in patients with decompensated genotype 1 hepatitis C cirrhosis. *Liver Transplant* 2016; **223**: 281–6.
21. Pol S, Bourliere M, Lucier S, et al. Safety and efficacy of daclatasvir-sofosbuvir in HCV genotype 1-monoinfected patients. *J Hepatol* 2017; **66**: 39–47.
22. Petersen J, Welzel T, Herzer K, et al. Daclatasvir plus sofosbuvir with or without ribavirin for the treatment of chronic HCV infection in patients with decompensated cirrhosis: results of an European multicentre compassionate use program. *Dig Liv Dis* 2017 (under revision)
23. Cheung MC, Walker AJ, Hudson BE, et al. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol* 2016; **65**: 741–7.
24. Ippolito AM, Milella M, Messina V, et al. HCV clearance after direct-antivirals in cirrhotic patients by stage of liver impairment: the ITAL-C network study. *Dig Liv Dis* 2017 (under revision).
25. Bruno S, Shiffman ML, Roberts SK, et al. Efficacy and safety of peginterferon alfa-2a (40KD) plus ribavirin in patients with advanced fibrosis and cirrhosis. *Hepatology* 2010; **51**: 388–97.
26. Carrion JA, Martinez-Bauer E, Crespo G, et al. Antiviral therapy increases the risk of bacterial infections in HCV infected cirrhotic patients awaiting liver transplantation: a retrospective study. *J Hepatol* 2009; **50**: 719–28.
27. Deterding K, Höner Zu Siederdissen C, Port K, et al. Improvement of liver function parameters in advanced HCV-associated liver cirrhosis by IFN-free antiviral therapies. *Aliment Pharmacol Ther* 2015; **42**: 889–44.
28. Stine JG, Intagliata N, Shah NL, et al. Hepatic decompensation likely attributable to simeprevir in patients with advanced cirrhosis. *Dig Dis Sci* 2015; **60**: 1031–5.
29. Welker MW, Luhne S, Lange CM, et al. Lactic acidosis in patients with hepatitis C virus cirrhosis and combined ribavirin/sofosbuvir treatment. *J Hepatol* 2016; **64**: 790–9.
30. FDA Drug Safety Communication: FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie. Available at: http://www.fda.gov/Drugs/Drugs Safety (accessed 31 October 2016).
31. Butt AA, Ren Y, Marks K, et al. Do directly acting antiviral agents for HCV increase the risk of hepatic decompensation and decline in renal function? Results from ERCHIVES *Alimentar Pharmacol Ther* 2017; **45**: 150–9.