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Achieving Sustained Virological Response in Hepatitis C Reduces the Long-Term Risk of Hepatocellular Carcinoma: An Updated Meta-Analysis Employing Relative and Absolute Outcome Measures

Methods:
Our literature search extended up to June 2015. We identified all studies that assessed the risk of HCC in patients achieving or not achieving SVR. Meta-analysis was based on a standard random-effect model. The end-point was occurrence of HCC compared between patients with and without SVR; this end-point was expressed as an odds ratio and percent reduction in risk and was also presented separately for patients with...
and without cirrhosis. All results were presented with 95% confidence intervals (CIs). The presence of any
temporal trend in these indexes was investigated by standard meta-regression.

Results:
Our search identified 25 observational studies (19,822 patients). The random-effect model fared better than
the fixed-effect model. The odds ratio of HCC for SVR versus no-SVR was 0.19 (95% CI 0.15–0.24) in
the overall series of 25 studies. The difference in this index between patients with any stage of fibrosis/
cirrhosis and those with cirrhosis was small. With regard to risk difference, the 25 studies indicated an
overall reduction of 10% (95% CI 8.00–12.0); this effect was much less pronounced in the group with any
stage of fibrosis/cirrhosis (risk difference 6.7%) than in the selected group with cirrhosis (risk difference
22%). Meta-regression showed no temporal trend.

Conclusion:
Our analysis was successful in providing an updated overview on this controversial topic. Some
pharmacoeconomic assessments are also presented to interpret the clinical results of our analysis.
Achieving Sustained Virological Response in Hepatitis C Reduces the Long-Term Risk of Hepatocellular Carcinoma: An Updated Meta-Analysis Employing Relative and Absolute Outcome Measures

Andrea Messori1 · Brigitta Badiani1 · Sabrina Trippoli1

Abstract

Background and Objectives We studied the effect of achieving sustained virological response (SVR) on the risk of developing hepatocellular carcinoma (HCC) in patients with hepatitis C receiving anti-hepatitis C virus treatment. Avoiding HCC is considered the main long-term benefit of successful antiviral treatment.

Methods Our literature search extended up to June 2015. We identified all studies that assessed the risk of HCC in patients achieving or not achieving SVR. Meta-analysis was based on a standard random-effect model. The end-point was occurrence of HCC compared between patients with and without SVR; this end-point was expressed as an odds ratio and percent reduction in risk and was also presented separately for patients with and without cirrhosis. All results were presented with 95 % confidence intervals (CIs). The presence of any temporal trend in these indexes was investigated by standard meta-regression.

Results Our search identified 25 observational studies (19,822 patients). The random-effect model fared better than the fixed-effect model. The odds ratio of HCC for SVR versus no-SVR was 0.19 (95 % CI 0.15–0.24) in the overall series of 25 studies. The presence of any temporal trend in these indexes was investigated by standard meta-regression.

Conclusion Our analysis was successful in providing an updated overview on this controversial topic. Some pharmacoeconomic assessments are also presented to interpret the clinical results of our analysis.

Key Points

We carried out a meta-analysis in patients treated for hepatitis C to evaluate the effect of sustained virological response achievement on the long-term risk of developing HCC.

After scanning the literature up to June 2015, 25 observational studies were included (19,822 patients).

Our results indicate that the achievement of SVR reduces the risk of HCC to a clinically relevant extent in patients with cirrhosis and also in patients with less severe disease.

1 Introduction

In 2013, a very comprehensive meta-analysis was published by Morgan and co-workers [1] to summarize the information on the long-term risk of developing hepatocellular carcinoma (HCC) in patients treated for hepatitis C virus (HCV) infection. After the introduction of the newest direct-acting antiviral agents (DAAs), interest in this topic
has markedly increased worldwide and several papers have been published in recent literature. Since the meta-analysis by Morgan et al. covered the literature published up to February 2012, we undertook the present work to generate a more updated meta-analytic report on this important topic.

2 Materials and Methods

Our literature search was conducted in PubMed and in Scopus and covered the period from 1 January 1990 to the present time (last search conducted on 30 June 2015). A single Boolean search term [namely, (SVR OR “sustained virological response”) AND (“hepatocellular carcinoma” OR hepatocarcinoma)] was employed. Since the number of citations retrieved through these keywords was small (less than 450 with PubMed), we analysed all of these articles individually by examining the abstract or, when necessary, their full text, and identified the clinical studies that met our inclusion criteria. These criteria included: (a) mono-infected adult patients with hepatitis C receiving treatment and classified according to the achievement of SVR; (b) patient follow-up with separate evaluation of HCC development between patients achieving and not achieving SVR; (c) information on the presence of cirrhosis in the included patients; and (d) observational design of the study. We restricted our analysis to observational studies because we were aware that no controlled studies were available. For each clinical study, we extracted the basic information needed for our analysis and the information on the primary end-point, expressed as a crude rate.

With regard to assessment of methodological quality, two reviewers (B.B. and S.T.) applied the Cochrane Collaboration tool [2] to evaluate the risk of bias in the studies included in our analysis. This tool assesses six domains (random sequence generation, concealment of allocation, blinding of participants and personnel, incomplete data, selective outcome reporting of outcomes, and other sources of bias). Studies with adequate procedures in all domains were considered to have a low risk of bias.

For our statistical analysis, we employed a standard model of traditional pair-wise meta-analysis [3]. Since we anticipated the presence of heterogeneity, the random-effect version of the model was employed.

Fig. 1 PRISMA diagram of the literature search based on PubMed. Other sources for identification of further articles included EMBASE and Scopus. The last search was done on 30 June 2015. The other sources that allowed us to identify the subgroup of additional 77 citations included the reference lists of included studies and the information reported in a previous meta-analysis. Studies were excluded because they lacked a design in line with our analysis or because they did not report the information needed for our analysis.
In all of our analyses, the results were presented in duplicate according to the relative outcome measure (i.e. odds ratio of HCC for the comparison of SVR vs. no-SVR) and the absolute one (i.e. percent reduction in the occurrence of HCC for the same comparison). As pointed out elsewhere, this duplicate presentation of the results is more informative than that based on a single outcome measure [4].

All of our analyses were conducted by using the software package Open Meta- Analyst (version 4.16.12, Tufts University, http://tuftscaes.org/open_meta/).

### 3 Results

Our literature search is summarized in Fig. 1 according to the PRISMA schematic representation. After the initial selection of 432 articles in PubMed and 696 in Scopus, we examined the full text of 62 articles and we finally identified 25 studies that met our inclusion criteria [5–29]. These observational studies included a total of 19,822 patients.

Table 1 summarizes the main characteristics of these 25 studies. In general, these studies showed a very similar design to one another. One potential source of heterogeneity in this clinical material was the region of origin, race and, in particular, the distribution of fibrosis/cirrhosis reflecting in most cases a lack of criteria for patient selection. The clinical material was therefore representative of a real-world setting.

With regard to the methodological quality of these studies, their observational design did not make them fully suitable for being described as having a low risk of bias; this type of design was the main source of potential bias, while the other items were low risk. Because of this uncertainty, we decided not to present the results of the Cochrane scoring system, preferring this narrative examination.

### Table 1 Main characteristics of the 25 included observational studies

<table>
<thead>
<tr>
<th>First author and year of publication</th>
<th>Country of origin</th>
<th>Patients achieving SVR</th>
<th>Patients not achieving SVR</th>
<th>Disease severity</th>
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SVR sustained virological response, HCC hepatocellular carcinoma
The results of our random-effect model meta-analysis based on the end-point of odds ratio are shown in Fig. 2. A significant heterogeneity was found in the patient subgroup with any stage of fibrosis/cirrhosis (p = 0.029) and not in the remaining patients (p = 0.148). In the overall series of 25 observational studies, the odds ratio was 0.19 (95 % CI 0.15–0.24). This outcome measure was quite similar in the patient subgroup with any stage of fibrosis/cirrhosis (odds ratio 0.21; 95 % CI 0.17–0.27) and in those with cirrhosis (odds ratio 0.15; 95 % CI 0.08–0.27).

The results of our random-effect model meta-analysis based on the end-point of risk difference are shown in Fig. 3. A significant heterogeneity was found in both patient subgroups (p < 0.001 in both analyses). In the overall series of 25 observational studies, the risk difference was 10 % (95 % CI 8.00–12.0). This absolute effect was much less pronounced in the patient subgroup with any stage of fibrosis/cirrhosis (risk difference 6.7 %; 95 % CI 5.1–8.3) than in the patient subgroup with cirrhosis (risk difference 22 %; 95 % CI 13.3–30.6).

Meta-regression showed no significant temporal trends (Fig. 4). The regression coefficients were −0.015 (95 % CI −0.072 to 0.042; p = 0.60) in the case of the odds ratio and −0.009 (−0.021 to 0.004; p = 0.17) in the case of risk difference.

4 Discussion

The short-term benefit of a successful anti-HCV treatment is the achievement of SVR. In turn, SVR is expected in the long term to show a benefit consisting of improved survival and/or reduced risk of HCC. The present study was focused only on evaluating whether treatment reduces the long-term risk of HCC and, more importantly, if this long-term benefit differs between patients with severe versus mild disease.
Our meta-analysis was successful in providing an updated synthesis on the association between SVR achievement and reduced risk of developing HCC. These data have important practical implications because, owing to budget constraints, regulatory decisions in most countries have restricted the reimbursement of the newest DAAs to patients with more severe disease and have excluded those with mild disease.

According to our results, growing evidence indicates that treating patients with less severe disease determines a documented clinical benefit (Figs. 2, 3); despite the relatively small magnitude of the benefit, this could justify an extended reimbursability of DAAs as some jurisdictions have recently advocated [30].

We chose to express the benefit of the analysis by employing both relative measures of outcome and absolute ones [4]. Relative measures are those most commonly used, but their disadvantage is that they do not provide any information on cost effectiveness. Absolute measures on the other hand correlate with value-based pharmacoeconomic indexes and therefore allow a more thorough interpretation of the results.

Reducing the risk of HCC by an absolute 6.7% in patients with any stage of fibrosis/cirrhosis allows, for example, the calculation of the number needed to treat (NNT), which is around 15; this means that, for every 15 patients achieving SVR, one case of HCC would be avoided in this unselected population. This balance of benefits is even more favourable for patients with cirrhosis in whom the NNT is remarkably low (absolute risk reduction 22%; number need to treat 4.5).

Avoiding these cases of HCC has favourable pharmacoeconomic consequences because direct costs are reduced. The NNT is helpful for expressing this result in quantitative terms, and so some examples of pharmacoeconomic calculations are examined in detail.

If one accepts the assumption that each case of HCC generates a lifetime cost of £22,826 (data from Hartwell...
et al. [31]), the savings in direct costs per patient related to HCC are the following: (a) when the NNT is 15, £22,826/15 = £1522, and (b) when the NNT is 4.5, £22,826/4.5 = £5072. On the other hand, the cost per patient of sofosbuvir is around £35,000 [32], and so the above data indicate that the reduced risk of HCC does not compensate for the cost of the treatment when the newest DAAs are considered. However, the cost of treating HCC is also rapidly rising. According to Camma` et al. [33], incorporating a targeted agent such as sorafenib in the treatment of HCC (cost per 200-mg capsule €31.8; daily dose 800 mg; treatment duration 6 months [33]) increases the drug cost by approximately €23,000 (i.e. £16,330); hence, the savings in avoiding one case of HCC in the era of targeted therapies would be around £20,000 [33] and not as low as £5000 as in our initial estimate.

Reducing the risk of HCC is not the only favourable effect of achieving SVR. The main factor is that the achievement of SVR has also been postulated to prolong survival [34] because of the presence of both hepatic and extra-hepatic benefits. This would have profound pharmacoeconomic consequences because, according to current cost-effectiveness thresholds, the gain of 1 year is valued at £35,000 (and the gain of 1 month at £2500). Hence, in purely speculative terms, a reduction in the risk of HCC (even when valued at only £5000 according to the our initial estimate) combined with a gain of at least 1 year in survival (valued at £30,000) could justify, for example, the cost of sofosbuvir. In fact, while this gain is still to be fully demonstrated, the avoidance of some direct costs (other than those implicated in HCC) has a sound basis and would be the final factor leading the base-case value of avoided costs per patient beyond a figure of £35,000 per patient required by the newest agents (or at least by sofosbuvir). Clearly, the pharmacoeconomic profile of drug costs is favourable when the costs avoided as a result of the achievement of SVR and from related benefits (normalized to one patient) are greater than those required to treat the patients (normalized to one patient).

In comparison with the meta-analysis published by Morgan et al. in 2013 [1], our analysis included a number of studies published more recently and also had the advantage of expressing the results according to relative and absolute outcome measures. This allowed us to offer some pharmacoeconomic interpretations of the results which are important because of the high cost of current anti-HCV treatments.

5 Conclusions

In conclusion, our meta-analysis confirms that the achievement of treatment-related SVR exerts a significant protective effect on the development of HCC among HCV-infected persons at all stages of fibrosis and among those with advanced liver disease.
Virological Response in Hepatitis C and Risk of Hepatocellular Carcinoma

Compliance with Ethical Standards

Source of funding None.

Conflict of interest All authors declare no conflicts of interest.

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