Hot Topics In Hepatitis C Virus Treatment:
Recommendations From an AISF/SIMIT/SIMAST Expert Opinion Meeting

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1. INTRODUCTION

Hepatitis C virus (HCV) infection is a major health problem in Italy. Current estimates indicate that the number of chonically viremic HCV carriers exceeds 1.5 million (3% of the population), with most of the infected subjects being more than 50 years old. HCV infection is the main cause of cirrhosis and hepatocellular carcinoma in Italy and the main indication for liver transplantation.

National recommendations for the treatment of HCV have not been updated since 2003, when regimens based on the combination of pegylated interferons and ribavirin were adopted. However, treatment responses have varied widely in real-life practice, and it is becoming increasingly clear that there is a need for a new therapeutic approach to specific clinical situations. In particular, it is urgently necessary to improve success rates in difficult to treat and unresponsive HCV patients and limit treatment duration in those with highest probabilities of response. Furthermore, the management of special patient categories originally excluded from phase III clinical trials needs to be optimised.

These considerations prompted the organisation of an Expert Opinion Meeting with the aim of fine-tuning recommendations for the treatment of HCV infection on an individual basis. This was held in Naples in June 2008 and was endorsed by:

- the Italian Association for the Study of the Liver (Associazione Italiana per lo Studio del Fegato: AISF)
- the Italian Society of Infectious and Tropical Diseases (Società Italiana per lo studio delle Malattie Infettive e Tropicali: SIMIT)
- the Italian Society for the Study of Sexually Transmitted Diseases (Società Italiana per lo studio delle Malattie Sessualmente Trasmissibili: SIMAST).

This report summarises the proceedings of the meeting and its shared conclusions on orientations.

2. METHODS

The aim of this document is to provide clinical practice guidelines defining the best management of individual categories of HCV patients, including those originally excluded from phase III clinical trials and thus not covered by the current guidelines, because the lack of published data concerning some particular aspects of HCV therapy has led to heterogeneous indications and treatment modalities.

The format of recommendations through practice guidelines was chosen because our main objective was to offer clinically-oriented readers practical suggestions for managing "difficult" HCV patients. To do this, a Promoting Committee of AISF, SIMIT and SIMAST members identified multidisciplinary panels of 4-6 experts on nine controversial aspects of HCV infection (acute hepatitis, short or extended treatment, non-responders and relapsers, cirrhosis, liver transplantation and immunosoppressed subjects, HCV/HIV co-infection, HCV/HBV ± HDV co-infection, elderly patients, and normal ALT levels). Each group analysed the literature and within three months presented a first draft of recommendations for review and suggestions to an external panel of clinicians acting as referees. A redrafted document was then discussed again with the referees during a public debate, after which the clinical practice guidelines were prepared.

The recommendations were drawn up using the levels of the Oxford Centre for Evidence-Based Medicine (Philips B, Ball C, Sackett D *et al*., Oxford Centre for Evidence-Based Medicine http://cebm.net/levels_of_evidence.asp#levels), with the quality of the evidence backing any statement being scored as follows:

I) a systematic review or meta-analysis of randomised controlled trials (RCTs) and/or an individual RCT with narrow confidence intervals

II) a systematic review or meta-analysis of cohort studies or an individual cohort study, including a low quality study (<80% follow-up)

III) a systematic review or meta-analysis of case-control studies or an individual case-control study

IV) case series, and poor quality cohort or case-control studies

V) expert opinion or consensus conference

The grade (i.e. strength) of recommendation was based on the quality of evidence:

Grade A) Consistent with level 1 studies

Grade B) Consistent with level 2 or 3 studies, or extrapolations from level 1 studies

Grade C) Consistent with level 4 studies, or extrapolations from level 2 and 3 studies

Grade D) Consistent with level 5 evidence or troublingly inconsistent studies at any level

3.1. TREATMENT OF ACUTE HEPATITIS C

(Group coordinated by Teresa Santantonio)

3.1.1 Background

On the basis of data provided by the Italian National Surveillance System for Acute Viral Hepatitis (SEIEVA), HCV infection is responsible for about 10% of cases of acute viral hepatitis. The incidence of acute HCV infection has decreased over the years and is now about 1/100,000 subjects per year [1], but this figure is probably underestimated because it mainly refers to symptomatic patients and it is known that the majority of acute HCV cases are asymptomatic and therefore elude clinical observation.

The current major risk factors for HCV transmission are intravenous drug use and viral exposure during medical procedures (endoscopy, surgery, dental treatment, dialysis, etc) [2,3].

There is no serological marker for a definite diagnosis of primary HCV infection, but the presence of documented HCV RNA or anti-HCV seroconversion (a negative test within the previous six months) is considered the gold standard for distinguishing acute hepatitis C (AHC) from the reactivation of chronic hepatitis C [4]. In patients with increased alanine aminotransferasi (ALT) levels and positive HCV RNA, but without documented HCV RNA or anti-HCV seroconversion, the diagnosis of AHC is based on the presence of at least two of the following criteria:

- ALT levels >10 times the upper normal limit
- Known or suspected exposure to HCV or the presence of a risk factor associated to HCV transmission within the previous six months
- The exclusion of all other causes of acute liver damage (HAV, HBV, HDV, hepatotoxicity, autoimmune liver disease).

3.1.2 Management

Most AHC patients are asymptomatic, and the disease generally has a mild clinical course, with rare cases of severe cholestasis or fulminant hepatitis. However, it has a high rate of chronicity (50-85%), with spontaneous virus clearance occurring in only about 30% of patients [5-13]. A number of studies have demonstrated that a strong and multispecific immune cellular response is an important host factor for spontaneous viral eradication [14].

Symptomatic disease, female gender, a young age, HCV genotype 3 or the clearance of HCV RNA within four weeks of clinical onset have all been associated with spontaneous viral clearance, but none of these parameters accurately predicts the spontaneous resolution of AHC [8-11,13,15]. In patients with self-limiting AHC, HCV generally clears during the first three months [3,9-11]. The onset of AHC is defined as the time of the detection of increased ALT levels or HCV RNA. In some patients, HCV viremia persists despite ALT normalisation and there is some, albeit limited, evidence that they may experience a late relapse, which suggests that viremic patients with normal ALT levels three months after clinical onset should be considered for antiviral treatment [9,10].

Most published studies have evaluated the efficacy of conventional interferon (IFN) monotherapy and, more recently, that of pegylated interferons (Peg IFNs), although the latter are not specifically licensed for use in AHC. These studies were generally open-label, non-comparative trials with small patient populations that differed widely in terms of their designs, patient characteristics and treatment regimens. Nevertheless, it has

been found that IFN monotherapy is effective in reducing the risk of progression to chronicity as it leads to higher rates of disease resolution and viral clearance than those observed in untreated patients. In addition, the rate of response to short-course IFN monotherapy is higher in AHC patients than in patients with chronic hepatitis C [13,14,16,17].

Using IFN monotherapy to treat AHC is therefore recommended by national and international guidelines [18-20], but it is still not standardised because of the difficulty in organising large-scale clinical trials to define how and when to treat [21].

Standard and PEG IFN monotherapy

A number of small clinical trials have investigated using IFN alpha or beta at a dose of 3-6 MU three times a week for 4-24 weeks [9,10,22-34] (Table 1), and the most recent meta-analysis by Licata *et al*. definitely demonstrated that IFN monotherapy significantly increased the probability of obtaining sustained viral response (SVR) in comparison with no treatment (risk difference 49%) [35]. Moreover, the SVR rate is higher at higher weekly doses, thus indicating the need for higher IFN doses during the first month of therapy [35]. Jaeckel *et al*. found that 98% of patients treated with an induction regimen of IFN alpha 2b (5 MU/day for four weeks followed by 5 MU three times weekly for a further 20 weeks) obtained a SVR that was confirmed by a median long-term follow-up of 135 weeks [27,36]. In this study, patients were treated for a median of 35 weeks after diagnosis of AHC. Other studies have evaluated the efficacy of early treatment with high-dose IFN (5-10 MU/day) and shorter treatment durations (8 weeks), reporting SVR rates of 75-83% [26,30]. The meta-analysis by Licata *et al*. showed that delaying therapy up to 60 days after disease onset did not reduce the probability of obtaining a favourable response to standard IFN monotherapy [35]. Overall, the published data indicate that AHC can be effectively managed by administering conventional IFN alpha for 4-24 weeks, starting immediately after diagnosis or at the end of an 8-week observational period. Higher daily IFN doses during the first month seem to be the best treatment option.

Pegylated IFN monotherapy studies

More recent studies have investigated the efficacy of pegylated IFN (Peg-IFN) monotherapy using different strategies in terms of treatment initiation, dose and duration (Table 2) [37-46]. The published data indicate that Peg-IFN monotherapy leads to high SVR rates similar to those obtained using conventional IFN with the additional patient benefit of the administration of a single weekly dose. Response to treatment administered 8-12 weeks after clinical onset was similar to that obtained with earlier administration. In patients with a rapid virological response, the duration of treatment can be reduced.

IFN and Peg-IFN plus ribavirin

The efficacy of combining standard IFN with ribavirin (RBV) has been investigated in a limited number of small studies [9,10,29]. According to the published data, combination therapy does not seem to be necessary for the treatment of AHC as the addition of RBV does not increase response in comparison with IFN monotherapy.

The efficacy of Peg-IFN and Peg-IFN plus ribavirin has been compared in only one randomised controlled clinical trial whose results showed no significant difference in response (80% *vs* 85%) [37].

Predictive factors

Unlike chronic hepatitis C, the response of AHC to IFN therapy does not seem to be affected by viral genotype [9,25-27,31,39,40,46].

Side effects

Standard IFN monotherapy is well-tolerated even in patients with high ALT levels and jaundice, and the reported side effects are similar to those observed in patients with chronic hepatitis C [9,27,30,38,39,40,42,46].

Treating ACH in hemodialysis patients

The few observational studies of hemodialysis patients treated with conventional IFN or Peg-IFN have reported SVR rates of 57-86% [47-51].

Treating AHC in HIV-positive patients

The SVR rates observed in studies of limited numbers of HIV-positive patients range from 0% to 71% [52-56], but the findings may have been confounded by questions such as treatment adherence, the quality of the AHC diagnosis and the simultaneous use of substances of abuse.

Post-exposure prophylaxis

No evidence supports the early use of IFN to prevent infection after accidental exposure to HCV as most accidentally exposed subjects will not develop the infection [57]. Furthermore, there are no data showing the efficacy of IFN in preventing the development of AHC. The best option therefore seems to be treatment only for subjects developing AHC in order to prevent its progression to chronicity.

3.1.3 State-of-the-art and open questions

Overall, published studies demonstrate that IFN is effective in preventing the progression of AHC to chronicity. The higher response rate to early IFN treatment in comparison with that observed in chronic hepatitis C patients underlines the importance of identifying and treating subjects with AHC, which is why surveillance programmes designed to monitor high-risk populations are the best approach.

Randomised and controlled clinical trials would be useful to define the best time to start treatment, the dose and duration of therapy, and the possible role of ribavirin in HIV-positive subjects who are unlikely to respond to IFN alone. Further studies are needed to clarify possible predictors of response, individualised therapy, and how to treat special populations such as hemodialysed and HIV-positive patients.

3.1.4 Statements

1. A definite diagnosis of AHC should be based on the presence of HCV RNA in the serum of a previously HCV-negative patient or seroconversion from a negative anti-HCV test (in the previous six months) to a positive anti-HCV test. In the absence of documented seroconversion, the diagnosis should be based on the presence of at least two of the following criteria: a) ALT levels >10 times the upper normal limit; b) known or suspected exposure to HCV within the previous six months; c) the exclusion of all other causes of acute liver damage (A-III).
2. When no precise diagnosis of AHC can be made, a liver biopsy should be considered in order to exclude a reactivation of chronic hepatitis C (B-VI).
3. An average of only 30% of AHC patients experience spontaneous viral clearance, which primarily occurs during the three months following the clinical onset of the disease (B-III).

4. All patients with AHC should be considered for treatment in order to prevent progression to chronic hepatitis C (A-I).

5. Delaying treatment for 8-12 weeks after disease onset allows the identification of subjects in whom the infection spontaneously resolves, thus avoiding unnecessary therapy (A-II).

6. AHC treatment is based on IFN monotherapy, which leads to high sustained virological response rates (>90%) (I-A). IFN/ribavirin combination therapy is not more effective than IFN monotherapy in AHC patients, although it is more effective in chronic hepatitis C patients (A-II).

7. Pegylated interferon monotherapy may be the best therapeutic option as its efficacy is comparable with that of standard IFN monotherapy (A-III); however, the Italian Medicines Agency only allows the use of conventional IFN alpha to treat AHC.

8. An induction regimen with daily doses of conventional IFN is associated with higher SVR rates (III-A). When using Peg-IFN alpha-2b, the recommended 1.5 μg/kg/week dose should be administered (A-III).

9. The optimal duration of IFN monotherapy seems to be 24 weeks, but a shorter course may be as effective (B-III). A 12-week course of Peg-IFN is effective in patients with undetectable HCV RNA levels by week 4 (B-III).

10. The response of AHC to IFN therapy does not seem to be affected by viral genotype or pre-treatment viral load (B-III).

11. There is currently no indication for administering IFN as post-exposure prophylaxis or for the treatment of subjects with primary HCV infection without and clinical signs of disease (B-VI).

3.2. INDIVIDUALISED THERAPY FOR CHRONIC HEPATITIS C

(Group coordinated by Alfredo Alberti)

3.2.1 Background

The current standard of care (SOC) for the treatment of chronic hepatitis C and HCV-related compensated cirrhosis is the combination of a pegylated IFN (Peg-IFN alpha2a or Peg-IFN alpha2b) and ribavirin. On the basis of the evidence-based data produced by randomised clinical trials, current treatment guidelines recommend administering this therapy for 48 weeks to patients infected by HCV-1 (HCV-1a or HCV-1b) or HCV-4, and for 24 weeks to thoase infected by HCV-2 or HCV-3.

The same guidelines recommend stopping antiviral therapy after 12 weeks in HCV-1 or HCV-4 infected patients if their HCV-RNA levels have not decreased by at least 2 $\log_{10}$ in comparison with baseline on the basis of solid evidence showing that such patients have little or no likelihood of achieving a sustained viral response (SVR) when treated for 48-52 weeks. No similar recommendations have been proposed for patients with HCV-2 and HCV-3 infection.

Using the current SOC regimens and adequate doses of Peg-IFN and ribavirin, SVR rates are as high as 70-85% in patients with HCV-2 or HCV-3, intermediate in those with HCV-4, and lower (~50%) in patients with HCV-1. Recent data indicate that patients with HCV-2 and HCV-3, traditionally considered a "easy-to-treat" category, have different SVR rates and should be considered separately, although doses and treatment duration have not yet been identified for the two genotypes.

A number of virus- and host-related variables have been identified as influencing SVR rates in HCV-infected subjects. In addition to the HCV genotype, baseline viremia levels are certainly important in the case of patients infected by HCV-1 and HCV-3, although less so for those infected by HCV-2. The host-related factors include age, alcohol intake, the stage of liver disease, obesity and, obviously, treatment adherence. A number of co-morbidities also affect SVR rates, above all HBV and HIV co-infections and the metabolic syndrome with insulin resistance, but also any associated condition that reduces adherence to adequate PEG-IFN or ribavirin dosing.

There is good reason to believe that the current SOC of HCV therapy, with its two fixed 48- or 24-week regimens based on the infecting HCV genotype, is not ideal and may lead to the over-treatment of the most easily treated patients and the under-treatment of those are more difficult to treat. Grouping HCV-1 and HCV-4 cases as difficult to treat and always requiring 48 weeks's treatment, and HCV-2 and HCV-3 cases as easy to treat and best suited to a 24-week regimen, is an oversimplification that may facilitate a pragmatic approach to HCV therapy but is rather weak on biological and evidence-based grounds. This situation has led to growing interest in the possibility of further individualising treatment duration in patients with chronic hepatitis C by means of response-guided therapy (RGT), an approach supported by the fact the early kinetics of the virological response (i.e. the rapidity and degree of HCV-RNA decay in serum during the first 4-12 weeks of treatment) allows the categorisation of treated patients on the basis of their "susceptibility" to HCV eradication and the definition of more individualised treatment durations regardless of the infecting HCV genotype.

3.2.2 Principles of treatment

HCV-1 patients

A number of studies have compared SVR rates in HCV-1 infected patients treated for 24 or 48 weeks. In a randomised study of Peg-IFN alpha2a in patients with HCV-1 in which the duration of treatment was based on a rapid viral response (RVR: negative HCV RNA [<50 IU/mL] by week 4), Ferenci *et al*. [58] observed an intention to treat-SVR rate of 75%. In an open, non-randomised cohort study of patients treated with Peg-IFN alpha2b for 24 weeks, Zeuzem *et al*. [59] found that the SVR rate in those with HCV-1 and a low baseline viral load (<600,000 IU/mL) was only 50% as against to a historical control value of 71% with 48 weeks' therapy, but a subgroup analysis of the patients with an RVR indicated an SVR rate of 88% *vs* 91%. Despite the weak study design and the retrospective nature of the subgroup analysis, these results were deemed adequate to grant an indication for 24-week treatment in HCV-1 patients with a low baseline viral load and RVR.

Janssen *et al*. [60] retrospectively analysed the results of Peg-IFN alpha2a registration trials, and found that patients with a rapid virologic response (RVR) had similar SVR rates when treated for 24 or 48 weeks (88% and 91%); an RVR was seen in 16% of the HCV-1 patients but this was reduced in the presence of high baseline viremia, HCV-1a, and advanced liver fibrosis.

Mangia *et al*. [61] compared the results of a randomised study of HCV-1 infected patients treated with Peg-IFN alpha2a or Peg-IFN alpha2b on a fixed 48-week schedule, and those observed in patients whose duration of therapy was based on the time to HCV RNA negativity. When patients with an RVR were considered, the SVR rate was 87.1% in those treated for 48 weeks and 77.2% in those treated for 24 weeks; this difference was not statistically significant mainly because of the limited number of patients. Relapse rates were higher in the patients with high baseline viremia levels (>400.000 IU/mL).

Other studies have compared treating HCV-1 patients for 48 and 72 weeks in an attempt to identify those who may benefit from a longer treatment duration than that foredeen in the current SOC. Berg *et al*. [62] compared Peg-IFN alpha2a combined with a fixed 800 mg dose of ribavirin and found no difference in SVR rates between 48 and 72 weeks; however, a retrospectives analysis showed that the SVR rates with both regimens were similar in patients with an RVR or a complete early virological respons (cEVR: HCV RNA positive at week 4 but negative at week 12), but significantly higher with 72 weeks (46% *vs* 33%) in the patients with a partial EVR (pEVR: HCV RNA positive at week 4 and 12, but a $\geq$2 $\log_{10}$ decrease from baseline at week 12). Similar findings were reported by Sanchez-Tapias *et al*. [63], who found that the SVR rates in HCV-1 patients with a pEVR were 16% when treated for 48 weeks and 44% when treated for 72 weeks, and these differences were also confirmed by a small study of Ferenci *et al*. [64] in which the corresponding figures were 31% and 77%.

All three studies found that 72 weeks' treatment offered no benefit over 48 weeks' treatment in terms of SVR rates in patients with a cEVR or without an EVR. They also confirmed the extremely low likelihood of an SVR in patients without an EVR regardless of of the duration of treatment.

HCV-2

A number of studies have investigated whether patients with HCV-2 or HCV-3 (or a subgroup of them) can be treated with Peg-IFN and ribavirin for less than the current SOC of 24 weeks without reducing SVR rates.

Most of them pooled HCV-2 and HCV-3 patients, although they should be analysed separately because of the growing evidence that they respond differently to Peg-IFN plus ribavirin.

The studies have assessed shortening the treatment schedule to 12, 14 or 16 weeks, but their findings are limited by the heterogeneity of their designs, the use of different cut-off values to define virological response at different time points, the use of different doses of ribavirin in combination with different types of Peg-IFN, and their small patient populations (particularly when it is wanted to consider HCV-2 and HCV-3 separately).

The studies assessing the possibility of shortening treatment in HCV-2 patients had designs based on allocation or randomisation by RVR. Mangia *et al*. [65] found no difference in SVR when the patients with an RVR were treated for 12 or 24 weeks (87% *vs* 89%), and similar results were obtained by von Wagner *et al*. [66] (SVR: 95% after both 16 and 24 weeks' therapy) and Dalgard *et al*. [67,68] (93% after 14 weeks *vs* 97% after 24 weeks).

On the other hand, the subgroup analysis of HCV patients developing an RVR in the large "ACCELERATE" clinical trial [69] showed that the SVR rate was lower after 16 weeks that after 24 weeks of therapy (80% *vs* 91%), although this study did not allocate the patients to short or standard treatment on the basis of RVR.

All of these studies confirm that the presence of an RVR is associated with high SVR rates, whereas its absence reduces the likelihood of an SVR after 24 weeks of treatment to <50%.

HCV-3

The same studies also analysed patients with HCV-3, and all of them found that an RVR was highly predictive of SVR. However, some of them found that the RVR and SVR rates in the HCV-3 patients were different from and generally about 10% lower than those observed in the HCV-2 patients, thus confirming that the two genotypes respond differently to treatment with Peg-IFN plus ribavirin.

In the study by Mangia *et al*. [65], 77% of the HCV-3 patients with an RVR achieved an SVR when treated for 12 weeks, as against 100% of those treated for 24 weeks. Response rates after 24 weeks were better than those after 14 weeks (92% vs 84%) in the study by Dalgard *et al*. [67], whereas von Wagner *et al*. [66] found no difference between 16 weeks and 24 weeks of treatment (76% *vs* 75%) and the same was true of the "ACCELERATE" study [69] (84% *vs* 89%). These heterogeneous results mainly reflect the small size of the study populations, the different study designs, the different types of Peg-IFN, and the different ribavirin doses.

All of the studies indicated that an RVR is associated with high SVR rates, whereas the absence of an RVR reduces the probability of an SVR to <50%. The RVR and SVR rates were significantly lower in the patients with high baseline viremia levels and in those with advanced fibrosis or cirrhosis.

3.2.3 Statements

HCV-1

1. In patients with HCV-1, an RVR is an important predictor of a SVR (A-I)

2. In patients with HCV-1, the absence of an EVR is an important predictor of unresponsiveness, with a very high negative predictive value. Therapy should therefore be stopped in the absence of an EVR (at least a 2 log reduction in HCV RNA levels in comparison with baseline) (A-I)

3. The duration of Peg-IFN and ribavirin treatment can be reduced to 24 weeks in some HCV-1 patients (A-II). To do this safely without compromising SVR rates, all of the following conditions should be fulfilled:

    * baseline HCV RNA <600.000 IU/mL

* an RVR after four weeks of treatment
* optimal adherence to the Peg-IFN and ribavirin doses
* the absence of major co-factors known to reduce response (HBV or HIV co-infection, obesity and metabolic syndrome, advanced liver fibrosis or cirrhosis)

4. Patients with HCV-1 and a pEVR should be treated for 72 weeks in order to maximise the chance of an SVR. The decision to prolong therapy in these patients should take individual side effects, the quality of life and the patient's motivation into account (A-I)
5. Patients with HCV-1 and without an RVR but with a cEVR should be treated for 48 weeks (A-I)
6. All patients should received standard doses of Peg-IFN alpha2a or alpha2b and weight-based doses of ribavirin as SOC (A-II)
7. Using higher Peg-IFN and/or ribavirin doses to improve SVR rates in patients with HCV-1 is still experimental and cannot be recommended in clinical practice (A-II)

HCV-2 and HCV-3

1. The SOC for the treatment of patients with HCV-2 and HCV-3 is the combination of standard doses of Peg-IFN alpha 2a or alpha 2b and weight-based doses of ribavirin given for 24 weeks (A-I)
2. Patients with HCV-2 or HCV-3 and an RVR have a very high chance of achieving an SVR (A-I)
3. The duration of treatment can be shortened to 12-16 weeks in a subgroup of patients with HCV-2 who have developed RVR. To do this safely without compromising SVR rates, all the following conditions should be fulfilled: the presence of an RVR; the absence of advanced fibrosis, cirrhosis or any other co-factor/comorbidity known to reduce the efficacy of antiviral therapy (including HIV, HBV co-infection, obesity, metabolic syndrome); and adequate adherence to Peg-IFN and ribavirin. Shortening therapy should be considered particularly in the presence of side effects that may be expected to worsen with continued treatment (A-II)
4. The duration of treatment can be shortened to 12-16 weeks in a subgroup of patients with HCV-3 who have developed an RVR. To do this safely without compromising SVR rates, all of the following conditions should be fulfilled: low baseline viremia levels (<600,000 IU/mL); the presence of an RVR; the absence of advanced fibrosis, cirrhosis, severe steatosis, or any other co-factor/co-morbility known to reduce the efficacy of antiviral therapy (including HIV, HBV co-infection, obesity, metabolic syndrome); and adequate adherence to Peg-IFN and ribavirin. Shortening therapy should be considered particularly in the presence of side effects that may be expected to worsen with continued treatment (A-II)
5. Although the SVR rates obtained by means of 24 weeks' treatment in HCV-2 and HCV-3 patients without an RVR are comparatively low, none of the available data support the use of a longer treatment duration (C-II)
6. The rates of response to retreatment in HCV-2 and HCV-3 patients with an EVR who relapse after a short treatment course are currently unknown. None of the available data support the use of a longer treatment duration (C-II)

3.3. RETREATMENT OF NON-RESPONDERS AND RELAPSERS

(Group coordinated by Antonio Craxì)

3.3.1 Background

Since the early 2000s, at least 50% of chronic hepatitis C patients have failed to respond to treatment with standard interferon alpha (IFN alpha) and ribavirin combination therapy and there is still a large cohort of non-responders (i.e. subjects with detectable serum HCV RNA three or six months after the start of therapy). The clinical course of the disease seems to be worse in these patients, leading to an accelerated progression towards end-stage liver disease [70] and the development of hepatocellular carcinoma [71]. An effective retreatment regimen is therefore a major goal in their long-term management.

A number of studies of retreatment with Peg-IFN plus ribavirin in patients failing to respond to the combination of standard or pegylated IFN and ribavirin have been published [72-91]. However, their results are inconclusive or conflicting because of the relatively small study populations, and difficult to generalise because of differences in patient characteristics, study designs including relapsers and non-responders, and different IFN and ribavirin doses in the first course and retreatment regimens.

3.3.2 Methods

We made a meta-analysis in accordance with the QUOROM statement [92] by retrieving trials from the Cochrane Controlled Trials Register, the Cochrane Library, MEDLINE and ENBASE using the following medical subject headings: chronic hepatitis C, non-responders, interferon and ribavirin, pegylated interferon, retreatment, clinical trial. The search was carried out in May 2008, without a lower date limit on the search results.

3.3.3 Statistical analyses

Pooled SVR estimates were calculated using random-effects logistic regression analysis after applying sample weights based on sample size as implemented in the PROC NLMIXED command of SAS version 8.1 software (SAS Institute, Cary, NC, USA). Trial heterogeneity was assessed using Pearson's chi-squared test. The assumption of heterogeneity implied by the use of random-effect models was justified by the differences in patient characteristics and study designs.

3.3.4 Results

Description of the studies

After reviewing the titles and abstracts, 20 articles were considered to fulfil the inclusion criteria and were selected for review. The main features of the trials included in the meta-analysis are shown in Table 3. Twelve, which accounted for 1571 patients (30.9%), were reported as full papers [72-83], and eight studies, which accounted for 3508 patients (69.1%), were abstracts [84-91]. Three of the full-length papers did not report the number of participating centres; the others all involved between two and 23 centres. Eighteen were prospective cohort studies; two were randomized controlle trial (RCTs) [90-91].

Sustained virological response rate (SVR)

The retreatment regimens and SVR rates are shown in Table 4. The regimens varied widely in terms of the type of Peg-IFN (alpha-2a or alpha-2b); the dose of Peg-IFN alpha-2b (50-300 μg/week); and the dose of ribavirin (800-1400 mg/day). The duration of retreatment was 48 weeks in all but one trial [91].

Figure 1 shows the SVR rates in the different studies. The 20 studies involved a total of 5079 patients, and the estinated pooled SVR rate was 16% (95% CI 6-33%). The magnitude of the treatment effect was remarkably heterogeneous (chi-squared test for heterogeneity 159.5 with 19 DF; $p<0.0001$). The proportion of patients who achieved an SVR differed widely from 6% [88] to 32% [84].

Only six trials provided data concerning SVR rates by genotype (genotype 1 *vs* genotype non-1) [75-78,80,81]. The estimated pooled SVR rate in the subgroups of these six studies was 15.6% for genotype 1 (95% CI 12.4-19.4%) and 33.9% for genotype non-1 (95% CI 25.8-43.1%) ($p=0.0001$).

3.3.5 Statements

Concerning retreatment with a 48-week course of pegylated IFN plus ribavirin in non-responders to standard or pegylated IFN and ribavirin combination therapy, the available evidence is sufficient to conclude that:

1. The low levels of overall efficacy and tolerability, and the inconsistent SVR rates argue against the indiscriminate retreatment of all non-responders to combination therapy (B-III)
2. Restricting retreatment to patients infected with HCV genotype 2 or 3 optimises the potential benefit (A-III)
3. The use of a stopping rule after 12-24 weeks of retreatment avoids unnecessarily long and unsuccessful treatments (A-III)
4. Given the low probability of clinical benefit, the decision to retreat subjects infected with HCV genotype 1 should be assessed on an individual basis (C-III)

3.4. ANTIVIRAL TREATMENT IN HCV-RELATED CIRRHOSIS

(Group coordinated by Savino Bruno)

3.4.1 Background

Cirrhotic patients have a significant risk of developing hepatic decompensation within a decade, and a 1-4% yearly risk of developing hepatocellular carcinoma (HCC) during the first five years after diagnosis [93]. HCV-related cirrhosis is now the most common reason for liver transplantation [94]. Recent studies have shown that achieving a sustained virological response (SVR) is associated with a reduction in liver-related mortality and complications, including HCC in patients with HCV-induced compensated cirrhosis [70].

In the landmark phase III trials assessing combined pegylated interferon (Peg-IFN) and ribavirin (RBV) therapy, 15-30% of the patients showed signs of severe liver disease, and SVR rates were calculated by pooling all of those with bridging fibrosis (Knodell score F3) and complete cirrhosis (Knodell score F4), thus including patients at very different stages of liver disease ranging from marginal bridging fibrosis to compensated cirrhosis. As these last represented no more than 6% of the patients distributed in the different arms of the studies, no reliable conclusions have yet been reached concerning the safety and efficacy of both Peg-IFN alpha2b and Peg-IFN alpha2a plus RBV in patients with HCV-induced cirrhosis. Moreover, the SVR rates according with "easy-to-treat" (2a/c and 3a) and/or "difficult-to-manage" genotypes (1a, 1b and 4) in this subset of patients are poorly investigated. Finally, the reliability of baseline and on-treatment predictors of response together with the efficacy of the SOC schedule of treatment currently used in subjects with mild to moderate fibrosis needs to be assessed in cirrhotics by dedicated studies.

The following classification of patients with HCV-induced cirrhosis was used in assessing the results:

- Patients with "histologically proven" cirrhosis without esophageal varices (Child class A5 to 6) identified by stages 5 and 6 of Ishak's score, and stage 4 of the Metavir and Knodell scores
- Patients with "compensated" cirrhosis with or without esophageal varices (including Child class B7) identified by a clinical or histological diagnosis of cirrhosis; bilirubin and albumin levels of <2 mg/dL and >2.8 g/dL; a prothrombin time of >60%; HVPG >5 mmHg; esophageal varices and/or platelet levels of >100,000/dL; and a bipolar spleen diameter of <13 cm without any previous episode of decompensation or evidence of HCC
- Patients with "decompensated" cirrhosis: (Child class B8 or more) defined by any evidence of previous decompensation (ascites, esophageal bleeding, portal encephalopathy, jaundice).

The achievement of an SVR, defined as undetectable RNA levels (<50 IU/mL) six months after the end of antiviral therapy, is a reliable prognostic marker in patients with HCV-induced cirrhosis regardless of the stage. SVR is associated with a reduction in: 1) decompensation, occurrence of HCC, and mortality in patients with histologically proven cirrhosis without esophageal varices [70]; 2) event rates in patients with esophageal varices [96]; and 3) mortality in patients at a decompensated stage of the disease [97].

3.4.2 Methods

For the purposes of this analysis, MEDLINE was used to identify studies published between 2001 and 2008, and further studies were located by means of a manual search using references from the retrieved articles. Abstracts were selected for the period from the 2005 AASLD meeting to the 2008 EASL meeting (DDW, AASLD, EASL, APASL, AISF). All studies of antiviral treatment in patients with chronic hepatitis C were

considered eligible if they were published in English; included adult patients; used combination antiviral treatments (Peg-IFN alpha2a/alpha 2b + ribavirin) in naïve and non-responding patients; and the analyses were made of and/or stratified for patients with a histological or clinical diagnosis of cirrhosis.
On the basis of the above criteria, 11 papers [98-108] and eight abstracts [109-116] were considered.

3.4.3 Statements

1. For patients with "histologically proven" cirrhosis without esophageal varices (Child class A5 to 6):
   - The SVR rate in naïve patients ranges from 25% to 76% (A-I)
   - The SVR rate in previous non-responders is approximately 10% (A-III)
   - Achieving an SVR is more frequent in patients with genotypes 2 or 3 (76-78% and 17-55%) than in patients with genotype 1 (25%, range 24-27%) (A-I)
   - A rapid virological response (RVR), early virological response (EVR) and genotype are the main predictors of an SVR (A-I)
   - The rate of treatment withdrawal is higher than in patients without cirrhosis (A-II)
   - Bone marrow toxicity (but not other toxicities) is more frequent than in patients without cirrhosis (A-II)
   - The achievement of an SVR is associated with a decrease in the decompensation rate, liver-related deaths, and the occurrence of HCC (A-I)
   - Three-years long "maintenance" therapy with Peg-IFN alpha 2a/b monotherapy did not reduce the rate of decompensation, HCC and mortality (A-I)
   - Given the lack of studies comparing a standard duration (48 weeks) with short duration treatment (24 weeks) in patients with "easy-to-treat" genotypes (2 and 3), and extended treatment (72 weeks) in patients with "difficult-to-treat" genotypes (1 and 4), no indication can be given concerning individual genotype subpopulations of cirrhotic patients
   - Clinical gain is extremely relevant as an SVR is associated with a significantly better outcome (A-I)
   - Naïve patients should be given antiviral therapy because of the high rate of SVRs (A-I)
   - Due to the low rate of SVR, it is nowadays not advisable to re-treat non-responder patients *(A-I).*
   - Non responders patients should not be treated with three-years long "maintenance" therapy (A-I)

2. For patients with "compensated" cirrhosis with or without esophageal varices (including Child class B7):
   - The SVR rate is approximately 20% (A-III)
   - The achievement of an SVR is more frequent in patients with genotypes 2 or 3 (50% and 60%) than in patients with genotype 1 (10-18%) (A-III)
   - Baseline predictors of an SVR are genotype and albumin levels; on-treatment predictors of are an RVR and EVR (A-III)
   - The rate of treatment withdrawal is similar to those observed in patients with "histologically proven" cirrhosis without esophageal varices (A-III)
   - The rate of bone marrow toxicity is similar to that of patients with "histologically proven" cirrhosis without esophageal varices (A-III)
   - The achievement of an SVR is associated with a significant decrease in the rates of decompensation and HCC (A-III)

- There are no data concerning the optimal duration of therapy as all of the patients were treated for 48 weeks
- Patients can be treated mainly if they are infected by an “easy-to-treat” genotype (A-II)
- Clinical gain is relevant as an SVR is associated with a significantly better outcome (A-III)

3. For patients with decompensated cirrhosis:
    - The SVR rate is approximately 20% (B-III)
    - The achievement of an SVR is more frequent in patients with genotypes 2 or 3 (43% cumulatively) than in patients with genotype 1 and 4 (approximately 7%) (B-III)
    - The rate of severe side effects (mainly infections) is significantly higher than in untreated patients (B-III)
    - The achievement of an SVR may be associated with improved decompensation in comparison with untreated patients or non-responders, thus delaying the need for a liver transplant. Further studies are needed to confirm these data (C-III)
    - There are no data concerning the optimal duration of therapy as all of the patients were treated for six months
    - These patients should generally not be treated outside trials in the transplant setting

4. For patients with cirrhosis and HIV co-infection:
    - Treatment can be successful (A-I)
    - The management of anti-HCV therapy is difficult in this setting (A-III)
    - Anti-HIV treatment can delay the onset of decompensation and improve the response to anti-HCV therapy (A-I)
    - Nucleosides analogues must be used cautiously as in the case of patients without cirrhosis (B-I)
    - Disease progression can be slowed by achieving an SVR (A-III)

3.5. TREATMENT OF HCV REINFECTION AFTER LIVER TRANSPLANTATION

(Group coordinated by Stefano Fagiuoli)

3.5.1 Background

HCV-related end-stage liver disease (ESLD) is the main indication for liver transplantation, accounting for 30-40% of the cases in most centres worldwide. Post-transplantation HCV is virtually universal in the carriers of active infection (i.e. those who are positive for HCV RNA). Histologically recurrent disease can be documented in 80-90% of recipients five years after transplantation, 50-60% of whom will develop clinically relevant chronic liver disease. Within the same time-frame, evolution towards cirrhosis can be expected in 25-30% of recipients. More than 35% of the graft losses in patients receiving a transplanted liver because of HCV-related ESLD are due to disease recurrence. After the development of cirrhosis, the mean time to first decompensation can be less than one year, significantly shorter than that observed during the natural course of the disease. This rapid evolution is the main reason for the significantly higher mortality in HCV-related liver transplantations in comparison with non-HCV indications (Fig. 2).

Antiviral treatment of the recurrence of HCV after liver transplantation should be proposed only by a hepatologist who is expert in both chronic HCV hepatitis and liver transplantation, in agreement with the referring Liver Transplant Centre.

3.5.2 Methods

For the purposes of this analysis, studies were identified from papers published between 1994 and 2008, and entered in PUBMED, Cochrane and EMBASE, and further studies were located manually using the references given in the retrieved articles. No abstracts were selected. All studies of antiviral treatment in patients with chronic hepatitis C were considered eligible provided that they were published in English; included adult patients, concerned antiviral treatment in liver transplant recipients and the analyses were made of and/or stratified for patients with a histological or clinical diagnosis of cirrhosis.

References in Liver Transplantation: 118 papers

References in HIV: 55 papers

(117-234)

3.5.3 Definitions and statements

Definition of recurrent HCV infection:

HCV-RNA positivity after liver transplantation (A-III)

Definition of the recurrence of HCV-related liver disease

HCV-RNA positivity with a histological pattern suggesting/consistent with HCV-related liver disease (A- III)

3.5.4 Principles of treatment and statements

The recurrence of HCV-related disease after liver transplantation significantly reduces graft and patient survival (Fig.1) (A-III)

Two approaches can be considered:

a) Pre-emptive therapy: “very early” treatment of graft reinfection (within 4-6 weeks of transplantation) before the virological, clinical or histological features of HCV develop.

This approach is not advisable because of the risk of acute and chronic rejection and the poor tolerance of patients mainly due to three factors: incomplete recovery, the presence of other risk factors and the fact that immunosuppression is not at maintenance level and the immune system can therefore be affected by the use of immunomodulators such as interferons (IFNs). Moreover, pre-emptive therapy expose a large number of patients who will not develop liver disease to unnecessary treatment (A-III) [139, 171, 178, 183, 193, 200].

b) Antiviral treatment of HCV-related liver disease: treatment is proposed when fibrosis has already started to progress (stage ≥F2). This approach offers some advantages over pre-emptive therapy insofar as it identifies patients with developing disease and the patients are less immunosuppressed and in better clinical condition, and should therefore be more tolerant of antiviral drugs (B-III) [117, 127, 131, 136].

Inclusion criteria for antiviral therapy:

- HCV RNA positivity
- Histology consistent with recurrent HCV and fibrosis stage ≥F2 (Scheuer)
- Absence of rejection, biliary obstruction and vascular damage (B-III)

On the basis of the available data, it is difficult to identify the best time to start antiviral therapy: the ideal time should be matched with the ideal patient. Some data suggest that early treatment is associated with a better response (B-III) [117, 124, 145].

The well-known contraindications listed for immunocompetent patients also apply to immunosuppressed patients with even greater caution being required in the case of transplant patients with previous episodes of acute or chronic rejection, steroid-resistant acute rejection, high autoantibody titres. The risk/benefit ration of possible antiviral treatment should be carefully evaluated in each case (C-V) [121, 122, 125, 128, 138, 146, 149, 153, 160, 163, 176, 187, 198, 208, 214, 231].

The published studies used four different antiviral schedules: A) ribavirin monotherapy; B) standard or pegylated IFN monotherapy; C) standard IFN + ribavirin; and D) pegylated IFN + ribavirin.

Combined therapy (C or D) is currently recommended and the most widely used is pegylated IFN + ribavirin (A-III) [130, 131, 132, 159, 167, 177, 180, 184, 186, 192, 194, 199, 201, 202, 205, 210, 213, 216-220, 222-225, 226-228, 230, 232-234].

There is no evidence of any difference in the efficacy or tolerability of Peg-IFN alpha2a and Peg-IFN alpha2b after liver transplantation (A-III).

The suggested dose is

- Peg-IFNα2a: 180 μg/week s.c; Peg-IFNα2b: 1.5 μg/week s.c.
- Ribavirin 1000-1200 mg/day p.o.

No data support the efficacy of dose reductions or escalations and so they are not recommended (D-VI) [169].

There is little evidence that higher Peg-IFNα doses are more efficacious than standard doses and so they are not recommended (D-VI) [140].

The ribavirin doses used in most of the studies are lower than those recommended for non-transplant patients [120, 155, 215].

The difficulty in reaching and maintaining high doses of ribavirin is mainly due to concomitant renal impairment and anemia (B-III) [197, 209, 221].

It must be stressed that renal impairment may lead to higher blood drug levels when the same dose is administered, thus interfering with the evaluation of side effects and efficacy [172].

The most widely used antiviral treatment schedule is 48 weeks (B-III) [212].

The absence of an early virological response (EVR, defined as a reduction in HCV RNA of <2 log after 12 weeks) significantly predicts non-response to treatment (NPV= 95-100%; PPV=50-60%). For this reason the therapy should be stopped, although there are still insufficient data to define this approach partially because of the lack of a precise definition of the primary objective of antiviral treatment after liver transplantation (C-II) [124, 154, 164, 226].

There are a few published anedotical reports concerning the rate of treatment compliance to antiviral treatment in liver transplanted patients (B-VI) [135, 150].

On the basis of a cohort study, compliance is greater in the patients achieving an SVR (B-III).

The most common side effects of antiviral therapy are anemia, leukopenia and thrombocytopenia, which have been reported in more than 50% of treated patients. It should be noted that many transplanted patients have an enlarged spleen that persists long after transplantation; however, the inclusion criteria are the same as those used in the case of immunocompetent patients.(WBC >3.000/mm^3, Hb >10 mg/dL, Plts >45,000) (A-II) [129, 134, 141, 143, 157, 162, 174, 179, 182, 204].

Growth factors

The use of growth factors should make it possible to prolong antiviral treatment, thus limiting the need for a dose reduction and ensuring a better quality of life (A-II) [183, 206, 158].

There are no data supporting the use of growth factors to obtain an SVR (C-III) [214].

No cut-off in Hb or neutrophil values have been established for the use of growth factors. In usual practice, erythropoietin is administered when Hb is <10g/dL and/or the reduction in Hb is ≥2g/dL, and growth factors are used when neutrophils are <500/mm^3 (C-III) [133, 156, 170].

The usual erythropoietin dose is 10,000 U x 3-4/week s.c.

The usual dose of G-CSF is 300 µg x 1-2/week s.c.

None of these schedules have been validated in the liver transplant setting (C-VI) [119, 168].

3.5.5 Outcomes and statements

Definition of a virological response

The definition of virological response is the same as that used for immunocompetent patients, although there are very few published studies regarding liver transplant patients:

- ETR (early treatment response): HCV RNA negative at the end of treatment
- SVR (sustained virological response): HCV RNA negative six months after the end of treatment
- RVR (rapid virological response): HCV RNA negative after four weeks of treatment
- EVR (early virological response): HCV-RNA negative after 12 weeks of treatment (A-II)

SVR is usually reported in 30-35% of cases, rarely above 40%, depending on the genotype.

Definition of a histological response

An improvement of at least one level in staging score (B-I) [161].

The data are insufficient to confirm the association between an SVR and an improved fibrosis score (C-VI) [148, 150, 181, 185, 203].

Usefulaulness and applicability of histological criteria

A histological response still cannot really be defined because of the potential presence of multiple co-factors In the post-transplant setting (immunsuppression, drug toxicity, immunological phenomena such as acute and chronic rejection, metabolic syndrome, etc.) (C-VI) [134, 142, 144, 152, 166, 188].

Definition of a complete response

Negative HCV RNA and normal transaminase levels at the and of treatment. However, this definition has some limitations mainly due to the need to exclude other risk factors affecting liver function despite negative HCV RNA (A-I).

Factors predicting a virological response

Genotypes 2 or 3 are associated with a virological response.more frequently than the other genotypes (B-VI) [165].

RVR and EVR: there is no consensus that they can be used in the post-transplant setting, although some recent retrospective studies have shown that EVR predicts a virological response (B-IV).

Treatment non-compliance seems to be the main factor responsible for a reduced response in the transplant setting (A-III) [147].

Impact of antiviral treatment on long-term outcomes

Some studies have found no correlation between an SVR and the progression of fibrosis after antiviral treatment. It is still debated whether this due to the lack of data or the presence of co-factors related to liver transplant patients (C-IV) [173, 175, 189, 191, 195, 196, 207].

3.5.6.Pre-transplant antiviral treatment and statements

All patients with decompensated liver cirrhosis should be evaluated for liver transplantation (A-III). Antiviral treatment can be considered in stable patients whose decompensation is easily controlled by therapy while they are on the transplant waiting list. Antiviral treatment should only be proposed by expert hepatologists or in clinical trial protocols approved by an Ethics Committee (C-VI). The use of growth factors is possible during the treatment of these patients (A-IV).

Antiviral treatment of patients co-infected by HIV and HCV after liver transplantation

(coordinated by P. Grossi)

3.5.7. Rationale

In this era of highly active antiretroviral therapy (HAART), hepatocellular carcinoma and end-stage cirrhosis due to hepatitis C virus (HCV) are increasing causes of mortality among subjects infected by human immunodeficiency virus (HIV). Access to organ transplantation may be their only option, but HIV infection was an exclusion criteria until a few years ago. One major concern was that administering iatrogenic immunosuppression to an already immunocompromised individual would increase the risk of opportunistic infections and accelerate HIV-related disease, but the recent significant increase in the life expectancy of HIV-infected subjects receiving HAART has meant that various centres throughout the world now offer them liver, kidney, kidney-pancreas, heart and lung transplantations. Despite the limited number of transplanted patients worldwide and the shortness of the follow-up of a great number of them, ongoing studies confirm that the short-term results in selected patients are comparable with those observed in non HIV-infected liver transplant (OLT) recipients [235-240].

The rapid reappearance of HCV infection after liver transplantation in recipients with HCV/HIV co-infection led to significant concerns that HIV/HCV co-infected patients are at risk of poorer outcomes than other HIV-positive recipients [241-243]. A recent analysis of data from the United Network for Organ Sharing (UNOS) database has shown that OLT recipients with HIV/HCV co-infection have a significantly lower rate of survival than those infected with HCV alone (P=0.006), and a significantly higher mortality rate (P=0.003) [244,245].

The shortage of liver donors makes it important to determine prognosis (survival and histology) and the factors contributing to the severity of recurrent liver disease in this new indication for OLT.

The results of one very small study of HCV-positive and HIV-negative transplant recipients suggest that the rate of HCV clearance is better when they receive post-transplantation, pre-emptive therapy with interferon and ribavirin [246]; however, the complexity of the drug interactions and toxicities invariably present in such patients make pre-emptive therapy extremely challenging in the early post-transplant period [247]. For all of these reasons, the current recommendations for HIV/HCV co-infected recipients are no different from those for HIV-negative recipients. Table 7 summarises the results of studies evaluating the effectiveness of the combined Peg-IFN and ribavirin treatment of HCV re-infection in HIV+ OLT recipients.

HCV treatment should be started when there is histological evidence of progressive or severe recurrence. Although combined IFN and ribavirin treatment has proved to be more efficacious, caution and dose adjustments of both INF and ribavirin are extremely important in co-infected patients. Furthermore, adjunctive growth factor therapy is almost always necessary to correct drug-induced anemia, lymphopenia and thrombocytopenia.

In conclusion, the recurrence of HCV infection after OLT is more severe in co-infected patients and made more difficult by the low SVR rate induced by INF-based therapies. However, the overall results of OLT in HIV/HCV co-infected patients are satisfactory in terms of survival, and can be improved by the earlier referral of these patients to a liver transplant unit, the use of new drugs effective against HCV, and the avoidance of drug toxicity.

3.5.8. Statements

1. The post-OLT recurrence of HCV infection is almost universal regardless of whether the patient is also infected by HIV, but some studies suggest that it tends to be more severe and occurs earlier in patients with HIV co-infection (A-III).
2. HCV recurrence is currently the most important cause of death (A-III).
3. Antiviral treatment for HCV infection in HIV+ OLT recipients requires the joint efforts of a multidisciplinary team including experts in HCV treatment and infectious disease specialists with experience in treating HIV-infected patients and transplant recipients closely collaborating with the transplant centre (A-VI).
4. In the case of HCV-positive and HIV-negative OLT recipients, no published data suggest that the rates of HCV clearance are better when the recipients receive post-transplantation pre-emptive therapy with interferon and ribavirin (B-III). Furthermore, the complexity of the drug interactions and toxicities invariably present in HIV co-infected patients makes pre-emptive therapy in the early post-transplant period extremely challenging. For these reasons, the current recommendations for HIV/HCV co-infected recipients are no different from those for HIV-negative recipients. HCV treatment should be started when there is biochemical and/or histological evidence of progressive or severe recurrence (B-III)
5. Although the best time for treatment has not yet been determined, early HCV therapy (four weeks after OLT) exclusively based on the documented recurrence of HCV RNA may improve graft and patient survival (C-VI)
6. The schedule of combined INF and ribavirin treatment is the same as that used for OLT recipients infected by HCV alone (B-III).
7. Caution and ribavirin dose adjustments are extremely important in patients with concurrent renal insufficiency (A-III).
8. HCV RNA is cleared more slowly in HIV/HCV co-infected patients than in those with HCV infection alone (A-III).
9. In HIV/HCV co-infected OLT recipients, a significant biochemical response despite a reduction in the HCV load of less than 2-$\log_{10}$ at week 12 is considered sufficient to continue antiviral treatment (C-V)
10. Treatment must be prolonged for at least 48 weeks, regardless of the genotype and the rapidity of HCV RNA clearance (C-VI)
11. Adjunctive growth factor therapy is almost always necessary to correct drug- induced anemia, neutropenia and thrombocytopenia (B-V)
12. The simultaneous administration of didanosine and ribavirin is contraindicated because of the high risk of lactic acidosis (A-V)

13. There is no consensus concerning the drugs and recommended doses for maintenance immunosuppression: tacrolimus/cyclosporine with or without mofetil mycophenolate or azathioprine; steroids or not; rapid or slow steroid tapering (C-V)

3.6. TREATMENT OF HIV/HCV CO-INFECTION

(Group coordinated by Raffaele Bruno)

3.6.1 Background

Information on liver fibrosis staging is important for making therapeutic decisions in co-infected patients, but a liver biopsy is not mandatory for decisions concerning the treatment of chronic HCV infection. Current therapy is particularly recommended in patients with a high likelihood of achieving a sustained virological response (SVR): i.e. those infected by genotypes 2 or 3, and those infected with genotype 1 if the viral load is low (<400,000-600,000 IU/mL) [2]; in the case that a liver biopsy or non-invasive tests of hepatic fibrosis (e.g. transient elastometry, FibroScan, Echosens, Paris, France) have demonstrated lower grades of liver fibrosis (F0-F1), treatment can be deferred regardless of HCV genotype. It is especially important to assess the stage of liver disease in patients unlikely to achieve an SVR [248].

The standard weekly doses of Peg-IFN alpha2a and Peg-IFN alpha2b are respectively 180 mg/kg and 1.5 mg/kg. A weight-adjusted ribavirin (RBV) daily dose of between 1000 mg (weight <75 kg) and 1200 mg (weight >75 kg), given in two administrations, is recommended for all genotypes [5,6] If chronic hepatitis C is detected early in the course of HIV infection (before the start of HAART), HCV treatment is advised but, if a co-infected patient is severely immunodeficient (a CD4+ cell count of less than 200 cells/mL), this should be improved by highly active antiretroviral therapy (HAART) before starting anti-HCV treatment. Patients with relative CD4 counts of 25% are more likely to achieve an SVR than those with lower percentages [249]. Rapid Virological Response (RVR) at week 4 is correlated with higher SVR rate. If no early virological response (a reduction of at least 2 $\log_{10}$ in HCV RNA in comparison with baseline) is achieved by week 12, HCV treatment should be discontinued as an SVR is unlikely [250].

During the course of PEG-IFN alpha plus RBV therapy, didanosine is contraindicated [251], and stavudine and zidovudine should be avoided if possible. The role of abacavir is currently uncertain, but cohort data suggest that SVR rates are lower in patients receiving abacavir-containing HAART [252], possibly because abacavir impairs RBV phosphorylation.

3.6.2 Statements

1. HCV treatment makes it possible to eradicate HCV within a defined period, which is potentially advantageous for the subsequent management of patients with HIV. All such patients should therefore be considered for treatment when its benefits outweigh the risks (A-IV)
2. HCV therapy is particularly recommended in patients who are highly likely to achieve a sustained virological response (SVR): i.e. those with genotypes 2 or 3, and those with genotype 1 provided that their viral load is low (<400,000-600,000 IU/ml) (A-I)
3. If a liver biopsy or non-invasive test demonstrates low grades of liver fibrosis (F0-F1), treatment can be deferred regardless of the HCV genotype (A-VI)
4. If chronic hepatitis C is detected early in the course of HIV infection (before the start of HAART), HCV treatment is advisable (A-VI)
5. If a co-infected patient is severely immunodeficient (CD4 count <200 cells/mL), the CD4 count should be improved by HAART before starting anti-HCV treatment. Patients with relative CD4 counts of 25% are more likely to achieve an SVR than those with lower percentages (A-IV)

6. Combined Peg-IFN and weight-based ribavirin treatment is the SOC for HCV infection. The standard weekly doses of Peg-IFN alpha2a and Peg-IFN alpha2b are respectively 180 mg/kg and 1.5 mg/kg. A weight-adjusted RBV daily dose of between 1000 mg (weight <75 kg) and 1200 mg (weight >75 kg), given in two administrations, is recommended for all genotypes. The recommended duration of treatment for all genotype is 48 weeks except for genotype 1 patients not achieving an HCV-RNA negative at week 4 and a drop more than two log of HCV-RNA at week 12 which should be treated for 72 weeks (A-I)

7. If no early virological response (a reduction of at least 2 $\log_{10}$ in HCV-RNA in comparison with baseline) is achieved by week 12, HCV treatment should be discontinued as an SVR is unlikely (A-I)

8. Patients with genotypes 2 or 3, low viral loads (<400 000 U/ml) and mild fibrosis in whom HCV RNA becomes undetectable in four weeks (a rapid virological response) may need only 24 weeks of therapy, but this can increase the relapse rate (A-III)

9. HIV/HCV co-infection may suggest starting antiretroviral therapy early (CD4 counts of 350-500 cells/mm^3) because the therapy itself and higher CD4 counts may slow the progression of liver disease. (B-III)

10. During Peg-IFN plus ribavirin therapy, didanosine is contraindicated, and stavudine and zidovudine should be avoided if possible. (I-A)

11. The role of abacavir is currently uncertain, but cohort data suggest that SVR rates are lower in patients receiving abacavir-containing HAART, possibly because abacavir impairs RBV phosphorylation (B-III)

12. In HIV/HCV co-infected patients, liver function tests should be performed one month after starting therapy, three and six months later, and then every three months. (A-VI)

13. Antiretroviral therapy should be promptly withdrawn in the case of: 1) lactic acidosis; 2) hypersensitivity reactions; 3) liver function test results >10 times the upper normal limit or five times the values observed before therapy; or 4) jaundice or signs of liver decompensation (A-VI)

3.7. TREATMENT OF HCV/HBV ± HDV CO-INFECTION

(Group coordinated by Giovanni Battista Gaeta)

3.7.1 Background

Between 1% and 2% of patients with chronic HCV infection are co-infected by HBV, and are usually negative for HbeAg, although the prevalence of HBV co-infection is more significant in high-risk patients (HIV co-infected subjects and IVDUs) [253,254].

The impact of the timing of acute HBV and/or HCV infection on the development of the chronic co-infection (acute co-infection by both viruses, HBV superinfection in chronic HCV carriers, HCV superinfection in chronic HBV carriers) is uncertain. Studies enrolling small numbers of patients do not allow any conclusions to be drawn, apart from the fact that the superinfecting virus tends to suppress the replication of the pre-existing virus. Cross-sectional studies of chronic HCV/HBV co-infection have shown reciprocal inhibition, usually with a negative effect of HCV on HBV [255-261]. The only prospective study performed so far found that the replicative status of one or both viruses may vary over time in at least 30% of patients [262], which is very important when defining individual therapeutic approaches.

Of the 14 therapeutic studies identified [263-277], twelve enrolled a limited number of patients (range 5-42), and one 161 patients [276]. The drugs used were: a) recombinant IFN monotherapy (6 studies, 82 patients); b) IFN+ribavirin (5 studies, 114 patients); c) IFN+lamivudine (one study, 8 patients); and e) Peg-IFN+ribavirin (2 studies of respectively 161 and 19 patients). Only one study was randomised [16], and two are only described in abstract form [264,276].

Combined IFN and ribavirin (RBV) treatment leads to sustained virological response rates similar to those observed in subjects with HCV monoinfection, but there is still a lack of comparative studies. Only one non-randomised study has analysed both HBV/HCV co-infected patients (n=161; 97 infected with HCV genotype 1) and HCV monoinfected subjects (n=160; 110 infected with HCV genotype 1) treated with Peg-IFN alpha2a and ribavirin, and found the same sustained virological response rate in the two groups: HbsAg clearance was observed in 10% of the patients six months after the end of treatment [276].

HCV suppression has been associated with HBV reactivation in some patients regardless of the treatment received.

3.7.2 Statements for HCV/HBV co-infection

- The virological profiles of patients with chronic HCV/HBV co-infection must be defined before starting therapy by determining HCV RNA and HBV DNA levels every two months for one year (A-II)
- Standard dose and duration Peg-IFN+RBV treatment is the SOC if HCV replication is detectable (B-II)
- HBV reactivation may occur during SOC therapy, and so HBV DNA levels must be monitored every three months during treatment.
- Treatment with anti-HBV nucleos(t)ide analogues must be considered in the case of constant or fluctuating HBV replication (HBV DNA >2000 IU/mL, the presence of anti-HBc IgM) during the pre-treatment time or in the case of reactivation during Peg-IFN+RBV therapy (B-III). The choice of the analogue must take toxicity data into account the in the case of concomitant therapy with Peg-IFN+RBV (A-II). Telbivudine should not be administered with Peg-IFN.

- In patients in whom the replication of both viruses is initially active, therapy with Peg-IFN alone can be continued in the case of a non-response of HCV after 12 weeks of therapy (a reduction in HCV RNA of <2 log_{10}) if the response of HBV is good (B-III)

3.7.3 Statements for HDV co-infection

Multiple infection by HCV, HBV and HDV can induce severe disease [278] and increase the risk of hepatocellular carcinoma [279] (II-A). This report emphasises the need for antiviral therapy, but only few and inconclusive are currently available concerning treatment schedules and efficacy.

1. Patients with HCV/HBV/HDV co-infection should be repeatedly monitored by testing for HCV RNA, HBV DNA, anti HDV IgM and HDV RNA in order to identify who to treat and and how (A-II)
2. Virological evaluations are recommended every two months during a one-year period of observation [262] (B-II)
3. Treatment is indicated in patients with persistent viremia, ALT levels above the normal upper limit, and liver histology showing significant fibrosis (an Ishak score of at least S2) [281] (B-II)
3. Treatment with Peg-INF+RBV is suggested in patients with active HCV (A-III). If no early virological response (a reduction of at least 2 log_{10} in HCV RNA in comparison with baseline) is achieved by week 12, RBV can be discontinued and Peg-INF alone administered for 48-72 weeks. The duration of Peg-INF therapy should also be defined by evaluating HDV replication on the basis of HDV RNA measurements [282] (B-III)
4. During Peg-IFN+RBV therapy especially frequent blood tests are recommended in cirrhotic patients because of the risk of bone marrow toxicity and the need for a dose adjustment [283] (B-III)
5. Treatment with nucleos(t)ide analogues should be considered in patients with triple HCV/HCV/HDV infection and active HBV replication (HBV DNA >2000 UI/ml and anti-HBc IgM positive) (B-II)

3.8. TREATMENT OF HCV INFECTION IN ELDERLY PATIENTS

(Group coordinated by Giorgio Francesco Antonucci)

3.8.1 Background

In countries such as Italy and Japan, the epidemiology of HCV infection is characterised by increasing prevalence with aging [284-287], unlike in the USA where a recent survey has shown a 0.9% prevalence of HCV infection in people aged >60 years and a peak incidence (>4.0%) between 40 and 49 years of age [288].

3.8.2 Clinical studies and results in elderly patients

Data from meta-analyses and large-scale, randomised clinical trials of hepatitis C treatment have shown that an age of >40 years is an independent predictor of reduced efficacy [289-292]. However, the majority of these studies excluded patients aged >65 years, thus making it difficult to know whether the efficacy of HCV treatments in such patients is any different [293].

A multicentre retrospective analysis by AISF found that 775 out of 1544 HCV-infected patients aged 65 years or more (50.2%) were excluded from treatment, 318 (41%) exclusively on the grounds of old age [294]. This finding may be at least partially explained by the lack of clinical trial data.

Previous AISF Guidelines (2003) state that elderly HCV-infected patients may be treated on a case-by-case basis taking into account the severity of their liver disease and the presence of co-morbidities. Moreover, they also state that only older patients with a life expectancy of >5 years should be treated [295].

Table 8 shows the response rates observed in elderly patients with different HCV genotypes in published studies [294,296,297,298-301]. Taken together, these suggest that sustained virologic response (SVR) rates tend to be lower in the elderly. However, direct comparison is difficult because the studies used different age classifications and different treatment schedules.

Two independent Italian retrospective studies have recently provided data concerning patients with chronic HCV hepatitis aged 65 years or more [294,296]. One single-centre retrospective study considered the efficacy and safety of combined pegylated interferon (Peg-INF) alpha plus ribavirin (RBV) treatment in 153 patients, including 30 (19.6%) aged 65 years or more. Among the elderly patients, the overall SVR rate was 70%: 36% among the 11 patients infected by genotypes 1 or 4, and 89.5% among those infected by genotypes 2 or 3. After adjusting for potential confounders, the analysis showed that patients aged >40 years were significantly less likely to achieve an SVR; the SVR rates were similar in the patients aged 40-49 years, 50-64 years and >65 years.

Three studies have highlighted the effect of age on SVR rates taking into account the different HCV genotypes (Table 8). In their prospective study, Iwasaki *et al*. observed a a trend towards lower SVR rates in patients aged >60 years infected by genotype 1 (p=0.094) [300], and two other studies found that HCV genotypes 2 or 3 were independent predictors of an SVR after adjusting for potential confounders, including age [296,301].

In line with these results, three recent clinical trials evaluating the efficacy of different schedules of combination Peg-IFN alpha therapy in HCV patients infected by genotypes 2 or 3 found no association between age and SVRs [302-304]. The Italian single-centre study observed that the effect of age was maintained only in the subgroup of patients infected with HCV genotypes 1 or 4 [296].

Table 9 shows the frequency of adverse events among elderly patients [296,294,297,298-301]. Adverse reactions to INF seem to be more frequent in older patients. The incidence of RBV-induced hemolytic anemia increases with age [305,306], and dose reductions or discontinuation are more frequent in patients aged >55 years [297,300,305]. The reduced efficacy of treatment in elderly patients [297,307,308] may be partly related to less adherence to the SOC protocol.

Pre-existing co-morbidities may also contribute to the reduced tolerability associated with aging [300,305,307]. In the AISF study, 53.2% of the enrolled patients suffered from hypertension, 19.5% had diabetes, 11.8% were affected by psychiatric disorders, and 10.8% had ischemic heart diseases [294].

3.8.3. Response assessment and predictors

Recently published cohort studies of elderly patients with chronic hepatitis evaluate treatment efficacy on the basis of the recommendations in the current practice guidelines [296,297,309]. Remarkably, the Italian single-centre study found a higher relapse rate among the patients infected by genotypes 1 or 4 who were aged >40 years [296]. A recently published clinical trial evaluating the effect of different treatment durations on the basis of undetectable HCV RNA levels in patients infected with HCV genotype 1 found that an age of >45 years was an independent predictor of HCV RNA positivity after 12 weeks of treatment [302]. It is worth noting that this trial enrolled 696 patients aged 18-70 years, of whom 536 (77%) were more than 45 years old, thus suggesting that HCV RNA negativity after 12 weeks of treatment may better predict an SVR in the elderly than a 2 $\log_{10}$ reduction in viremia levels.

3.8.4 Statements

1. HCV-infected subjects aged 65 years or more should be considered elderly patients (A-I)
2. Treatment is indicated in elderly patients, who are at increased risk of developing severe liver disease (B-IV)
3. Peg-IFN plus weight-based ribavirin is the SOC for elderly patients with chronic hepatitis C; the treatment schedules and doses are the same as those recommended for younger patients (B-III)
4. Treatment decisions In elderly patients should be individualised on the basis of the severity of liver disease, HCV genotype, the presence of co-morbidities (particularly those related to aging), and the likelihood of severe side-effects. Elderly patients with little or no liver fibrosis, and those with a life expectancy of less than five years should not be treated (B-III)
5. When possible, co-morbidities should be controlled by appropriate treatment before starting HCV therapy (A-III)
6. The predictors of response and the criteria used to assess treatment success are the same in elderly and younger patients (B-III)

3.9. TREATMENT OF PATIENTS WITH NORMAL ALT LEVELS

(Group coordinated by Claudio Puoti)

3.9.1 Rationale

It must be stressed that the upper normal alanine aminotransferase (ALT) limit varies between studies and between tests performed in different laboratories because of technical reasons and different reference populations [310-314]. Furthermore, the ALT reference ranges currently used in clinical practice underestimate the actual frequency of liver disease in this subset of patients as current evidence suggests that existing 'normal' ALT thresholds are too high and should be lowered by 25-30%, thus setting the "optimal" ALT threshold at 30 U/L for males and 20 U/L for females [312]. Finally, given the typically fluctuating pattern of ALT levels in chronic HCV infection, only more stringent tests can distinguish subjects with persistently normal ALT values (PNALT) from those in temporary biochemical remission. The definition of PNALT should be based on at least nine ALT determinations carried out every two months over an 18-month observation period.

The earliest guidelines [315,316] discouraged interferon (IFN) treatment in patients with PNALT except in clinical trials because most have low-grade liver fibrosis and are at low risk of disease progression, because of the cost and side effects of therapy, and because of the low response rates to IFN monotherapy (<10-15%) with a risk of ALT flares in up to 50% of patients during treatment. On the other hand, it has been stressed that these patients often have features traditionally associated with a good therapeutic response, such as mild histological lesions, and there is a prevalence of females and genotype non-1 infection. Finally, given the possibility of ALT flares during follow-up (which invariably accelerate the progression of fibrosis and the worsening of histological activity), the opportuneness of deferring therapy has been questioned because of the possible risk of disease worsening.

The introduction of the new combination of pegylated IFN (Peg-IFN) plus ribavirin (RBV) has led to overall response rates of more than 50%, and a favourable risk/benefit ratio even in patients with benign or slowly progressing disease. One multicentre, randomised study [310] of Peg-INF alpha2a (180 μg weekly) plus ribavirin (800 mg daily) for 24 or 48 weeks in patients with PNALT found an overall sustained virological response (SVR) rate of 30% in those treated for 24 weeks and 52% in those treated for 48 weeks. The response rates in genotype 1b carriers were respectively 13% and 40% and, in those harbouring genotype 2 or 3, they were 72% and 78%. The adverse reactions were no different from those observed in patients with high ALT levels. During treatment, ALT levels did significantly decrease from baseline only in the patients with an SVR. It should also be stressed that ALT levels actually increased during the one-year follow up period in more than 50% of the untreated PNALT patients in this placebo-controlled study. Furthermore, the subjects with HCV-1 were treated with a fixed RBV dose (800 mg/day) that is lower than that universally recommended for such patients (1000-1200 mg/day, depending on body weight). Simulation studies suggest that the SVR rate significantly increases in HCV-1 patients with PNALT when the standard weight-adjusted dose of RBV is administered [317]. A more recent Italian retrospective multicentre study observed an SVR rate of 67% in HCV-1 patients with PNALT treated for 48 weeks with standard RBV doses [319] .

An *ad hoc* AISF Committee [318] and a more recent Medical Position Statement on the Management of Hepatitis C by the American Gastroenterological Association (AGA) [320] have noted that "decision analyses in patients with biochemically and histologically mild chronic hepatitis C have led to the conclusion

that, even in this population, antiviral therapy is cost-effective. Clinicians may rely in their decision making on individual patient features, including patient motivation and perspective, genotype, relative histologic activity and fibrosis, duration of HCV infection, age, occupation, symptoms, and so on. Recommendation category: I". Whether antiviral therapy is really cost-effective in HCV patients with PNALT has not yet been clearly proven. The possibility of even severe ALT flares among genotype 2 carriers, leading to progressive fibrosis and disease worsening, should be taken into account.

In patients not receiving antiviral treatment, periodic measurements of ALT levels and adequate lifestyles should be recommended. In particular, overweight and the use of alcohol should be strongly discouraged [321-323].

3.9.2 Statements

1. Due to the fluctuating pattern of ALT levels in patients with chronic hepatitis C, only more stringent tests will make it possible to distinguish subjects with persistently normal ALT values (PNALT) from those in transient biochemical remission. The definition of PNALT should be based on at least nine ALT determinations made at intervals of at least two months over an 18-month observation period. The optimal ALT threshold should be set at 30 U/L for males and 20 U/L for females (B-II)
2. HCV carriers with PNALT may receive antiviral treatment with Peg-IFN plus RBV using the same algorithms and protocols as those recommended for HCV patients with abnormal ALT levels (A-II). The Italian Medicines Agency restricts this prescription indication to Peg-IFN alpha2a.
3. Decision making should rely on individual characteristics such as genotype, histology, age, potential disease progression, the probability of viral eradication, patient motivation, the desire for pregnancy, co-morbidities, co-factors, etc (A-VI)
4. Antiviral treatment might be offered without the need for liver biopsy in patients with a high likelihood of achieving an SVR (e.g. an age of <50 years + easy-to-treat HCV genotype + low viral load), in the absence of any contraindication and co-factors of poor responsiveness (A-VI).
5. In patients aged 50-65 years, and in those with a reduced likelihood of achieving an SVR, a liver biopsy may be used to evaluate the need for therapy, with treatment being recommended only for patients with more severe fibrosis (>F2) and a higher possibility of response, depending on the HCV genotype (A-VI).
6. Biopsy and therapy are not recommended in therapy elderly (>70 years). These patients should be recommended to adopt lifestyle changes and undergo periodic ALT determinations (D-VI).
7. Non-invasive assessments of fibrosis can be used to detect changes over time and consequently indicate the need for biopsy or treatment on an individual patient basis.
8. In patients not receiving antiviral treatment, periodic ALT measurements and adequate lifestyles should be recommended. In particular, overweight and the use of alcohol should be strongly discouraged.

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Tables

Table 1 Treatment of acute hepatitis C with conventional IFN alpha.

Author	Country	Journal	Study	No. of treated patients / controls	Median time to therapy	IFN α	Schedule	Duration	ITT SVR (%)
Genesca [22]	Spain	Gut, 1993	RCT	15/13	NA	2b	3 MU tiw	3 mos	73 *vs* 31
Alberti [23]	Italy	Viral Hepat Liver Dis, 1994	NRCT	11/10	4 mos after onset	2a	6 MU tiw	16-24 wks	64 *vs* 20
Lampertico [24]	Italy	Hepatology, 1994	RCT	22/16	NA	2b	3 MU tiw	12 wks	39 *vs* 0
Hwang [25]	Taiwan	J Hepatol, 1994	RCT	16/17	8 wks after ALT elevation	2b	3 MU/tiw	12 wks	44 *vs* 13
Vogel [26]	Austria	Dig Dis Sci, 1996	NRNCT	24	NA	2b	10 MU/day	up to ALTn (max 6wks)	75
Jaeckel [27]	Germany	NEJM, 2001	NRNCT	44	35 days after onset	2b	5 MU/day; 5 MU/tiw	24 wks	98
Fabris [28]	Italy	AJG, 2002	RCT	8 6	NA	2b	3 MU/tiw; 3 MU/day	12 wks 36 days	37 33
Rocca [29]	France	Gastroenterol Clin Biol, 2003	NRNCT	5 mono 8 combi	NA	2b	3-6 MU/day or tiw ± RBV**	2.5-12 mos	80 mono 100 combi
Santantonio [9]	Italy	Dig Liv Dis, 2003	NRNCT	11	6 mos after onset	2b	5 MU/tiw 3 MU/tiw	24 wks 24 wks	82
Gerlach [10]	Germany	Gastroenterol, 2003	NRNCT	10	1-26 mos after onset	IFNa	3-5 MU/tiw	24-52 wks	70
Delwaide [30]	Belgium	Al Phar Ther, 2004	NRCT	28/16^	55 days after onset	2b	5 MU/die	8 wks	75 *vs* 19
Nomura [31]	Japan	Hepatology, 2004	RCT	15 15	8 wks-1 year after onset	Ly*	6 MU/die, 6 MU/tiw	4 wks 20 wks	100 53

Pimstone [32]	USA	Ann Int Med, 2004	NRNCT	7	14-20 wks after exposure	2b	5 MU/day 3 MU/tiw	12 wks 40 wks	100

RCT = randomised controlled trial; NRCT = non-randomised controlled trial; NRNCT = non-randomised non-controlled trial; ITT = Intention To Treat; SVR = Sustained Virological response; ^historical series of untreated patients; *Lymphoblastoid IFN; **RBV = ribavirin; NA = not applicable

Table 2. Treatment of acute hepatitis C with pegylated IFN

Author	Country	Year	Journal	Study	No. of patients	Median time to treatment	Peg-IFN	Schedule	Duration	ITT SVR (%)
Kamal [37]	Egypt, Germany	2004	Hepatology	RCT	40*T* 14*C*	12 wks	a-2b/a-2a a-2b/a-2a±RBV	1.5/kg/wk 180/wk ±800mg/10.6mg/ kg/day	24 wks	85 combi 80 mono 36*C*
Broers [38]	Switzerland	2005	J Hepatol	NRNCT	14	6 wks (1-50)	a-2b	1.5/kg/wk	24 wks	57
Santantonio [39]	Italy	2005	J Hepatol	NRNCT	16	12 wks	a-2b	1.5/kg/wk	24 wks	94
Wiegand [40]	Germany	2006	Hepatology	NRNCT	89	27 days (5-131)	a-2b	1.5/kg/wk	24 wks	71 ITT 89 PP
Kamal [41]	Egypt, Germany, USA	2006	Gastro-enterol	RCT	129	8 wks 12 wks 20 wks	a-2b	1.5/kg/wk	12 wks	95 92 76
Kamal [42]	Egypt, Germany, USA	2006	Hepatology	RCT	102*T* 30*C*	8-12 wks	a-2b	1.5/kg/wk	8 wks 12 wks 24 wks	68 82 91
De Rosa [43]	Italy	2006	J Antimicrob Chemother	NRNCT	19	31 days (0-116)	a-2b	1,06-1.66/kg/wk	12 wks	74
De Rosa [44]	Italy	2006	Antiviral Therapy	NRNCT	19	34 days (7-116)	a-2b	1.06-1.66/kg/wk	12 wks	74
De Rosa [45]	Italy	2007	Clin Infect Dis	NRNCT	23	13.5 days (0-166)	a2b	1-1.6/kg/wk	12 wks	74
Calleri [46]	Italy	2007	J Viral Hep	NRNCT	46	15 days (1-90)	a2b	1-1.5/kg/wk	12 wks	72

RCT = randomised controlled trial; NRNCT = non-randomised non-controlled trial; *T* = treated; *C* = controls; ITT= Intention To Treat; SVR= Sustained Viral Response; PP= Per Protocol

Table 3. Patient and study characteristics of the trials included in the meta-analysis

Study (reference)	Sample n	Centres n	Males %	Mean age yrs	Mean BMI kg/m^2	Cirrhosis %	Genotype 1 %	First treatment stopping rule Timing of qualitative HCV-RNA determination (wks)
FULL PAPERS (n = 12)								
Shiffman M.L., 2004 (3)	385	10	73	50	29.7	39	N.R.	12
Krawitt E.L., 2005 (4)	94	13	69	46	29	18	N.R.	24
Jacobson I.M., 2005 (5)	219	19	74	49.5	N.R.	39 (F3-F4)	N.R.	12
Taliani G., 2006 (6)	140	14	77.3	49.3	26.1	22	78	12
Mathew A., 2006 (7)	96	7	74	N.O.	N.R.	N.R.	100	N.R.
Parise E., 2006 (8)	97	14	84	48	N.R.	37	71	N.R.
Sherman M., 2006 (9)	167	18	70.5	47.2	27.5	18.6	89	24
Ciancio A., 2006 (10)	81	N.R.	74	50	24.9	8.6	81	24
Maynard M., 2006 (11)	99	23	N.R.	46.8	N.R.	0	83.7	23
Moucari R., 2007 (12)	101	2	66.3	49.8	26.3	N.R.	76.2	12
Diago M., 2007 (13)	72	N.R.	77.7	41.8	26.2	N.R.	N.R.	24
Cheruvatthath R., 2007 (14)	20	N.R.	60	50.2	30.3	N.R.	95	12
ABSTRACTS (n = 8)								
Gross J.B., 2003 (17)	110	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
Lawitz E.J., 2003 (18)	317	N.R.	N.R.	N.R.	N.R.	N.R.	6	N.R.
Teuber G., 2003 (19)	240	N.R.	68	45.5	N.R.	N.R.	N.R.	N.R.
Gitlin N., 2004 (15)	31	N.R.	61	N.R.	N.R.	32	93	12
Gaglio P., 2005 (16)	454	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
White C., 2005 (20)	60	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
Poynard T., 2006 (21)	1354	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
Marcellin, 2008 (22)	942	13	N.R.	N.R.	N.R.	N.R.	N.R.	12

N.R.: not reported; wks: weeks; yrs: years

Table 4. Sustained virological response rates and retreatment regimens

FULL PAPERS (n = 12)				
Study (reference)	**Peg-IFN µg/wk + ribavirin mg/day**	**SVR n/t (%)**	**SVR genotype 1 n/t (%)**	**SVR genotype non-1 n/t (%)**
Shiffman M.L., 2004 (3)	α2a 180 + 1000/1200	46/385 (12)	N.R.	N.R.
Krawitt E.L., 2005 (4)	α2b 100/150 + 1000	17/94 (18)	N.R.	N.R.
Jacobson I.M., 2005 (5)	α2b 100/150 + 800/1000/1200	17/219 (7)	N.R.	N.R.
Taliani G., 2006 (6)	α2b 150 + 1000/1200	28/140 (20)	21/110 (19)	7/30 (23)
Mathew A., 2006 (7)	α2b 50-150 + 1000/1200	14/96 (15)	14/96 (15)	N.R.
Parise E., 2006 (8)	α2a 180 + 800	25/97 (26)	12/69 (17)	13/28 (46)
Sherman M., 2006 (9)	α2a 180 + 800	36/167 (22)	29/148 (20)	7/19 (37)
Ciancio A., 2006 (10)	α2a 180 + 1000/1200	24/81 (30)	N.R.	N.R.
Maynard M., 2006 (11)	α2b 150 + 800/1200	16/99 (16)	10/82 (12)	6/17 (35)
Moucari R., 2007 (12)	α2b 150 + 1000/1200	13/101 (13)	6/77 (8)	7/24 (29)
Diago M., 2007 (13)	α2a 360/270/180—›180 + 1000/1200	20/72 (28)	N.R.	N.R.
Cheruvatthath R., 2007 (14)	α2a 1.5 w.b. —› α2b 180 + 1000/1200	2/20 (10)	N.R.	N.R.
TOTAL		258/1571(16)	92/582 (16)	40/118 (34)
ABSTRACTS (n = 8)				
Gross J.B., 2003 (17)	α2b 150/300 + 800/1400	9/110 (8)	N.R.	N.R.
Lawitz E.J., 2003 (18)	α2b 150+100/100 +1000-1200/800	23/317 (7)	N.R.	N.R.
Teuber G., 2003 (19)	α2b 100 + 800	15/240 (6)	N.R.	N.R.
Gitlin N., 2004 (15)	α2a 180 + 1000/1200	10/31 (32)	N.R.	N.R.
Gaglio P., 2005 (16)	α2b 150 + 100/1400	64/454 (14)	N.R.	N.R.
White C., 2005 (20)	α2b 300 + 1400	15/60 (25)	N.R.	N.R.
Poynard T., 2006 (21)	α2b 150 + 800/1400	311/1354 (23)	N.R.	N.R.
Marcellin, 2008 (22)	α2a 180/360+180 + 1000-1200	112/942 (12)	N.R.	N.R.
TOTAL		559/3508 (16)	N.R.	N.R.

N.R.: not reported; wk: week; yrs: years; SVR: sustained virological response; N/T: number/total

Table 5: Results of combined Peg-IFN and ribavirin therapy after liver transplantation

TABLE 1. Comparison of Studies to Treat Posttransplantation HCV With Peginterferon and Ribavirin

References	Year	N	GT1 (%)	Dosing	D/C (%)	Dose reduce (%)	Growth factors	REJ (%)	VR (%)	SVR (%)
Dumortier et al.[15]	2004	20	80	PEG: 0.5-1.0 μg/kg/week	20	30		25	GT1:44	45
				RVN: 400-1200 mg/day		81			GT2-3:100	
Castells et al[16]	2005	24	100	PEG: 1.5 μg/kg/week	0	25		4	58	35
				Ribavirn: 600 mg/day	13	58				
Neff et al.[17]	2004	29 Naive	97	PEG: 1.5 μg/kg/week	0	66	N: 35	?	Naive: 38	21
		28 NR	100	Ribavirn: 400-1200 mg/day		39	E: 44		NR: 32	7
Neumann et al.[18]	2006	25	80	PEG: 1.0 μg/kg/week	4	PEG: 52	N: 44	0	68	36
				Ribavirn: 600 mg/day		RVN: 36	E: 36			
Babatin et al.[19]	2005	13	N/A	PEG: 0.5-1.0 μg/kg/week	N/A	N/A	N/A	23	N/A	31
				Ribavirin: 0-1200 mg/day						
Berenguer et al.[20]	2006	36	93	PEG: NS	37	35	N: 33	9	46	31
				Ribavirin: NS		45	E: 25			60
Oton et al.[21]	2006	55	91	PEG: 1.5 μg/kg/week or 180 μg/week	29	13	N: 15	2	67	GT1:40
				Ribavirin: 800-1200 mg/day		47	E: 38			GT2-3:100
Sharma et al.[22]	2007	35	77	PEG: 1.5 μg/kg/week or 180 μg/week	43	48	N: 17	11	54	GT1:33
				Ribavirin: 800 mg/day		52	E: 20			GT2-3:50

NOTE: Superscripted numbers indicate reference numbers.
Abbreviations: NR, nonresponder; PEG, peginterferon; N, neupogen; E, epoetin alfa; GT, genotype; REJ, rejection.

Modified from: Schiffman, Liver Transplantation 2007

Table 6: Expert management

Staging disease recurrence

The histological staging criteria are the same as those used for natural infection. The most frequently used histological scores in the transplant setting are Metavir, Scheuer, Ishak and Ludwig-Batt.

A subgroup of HCV transplanted patients (1-9%) may develop fibrosing cholestatic hepatitis characterised by a severe cholestasis index and high viremia levels in the presence of immunosuppression. Its histological features are little lymphomonocytic infiltration, sinusoidal fibrosis, and hepatocyte ballooning suggesting a cytopathic effect of the virus (B-III).

Managing immunosuppression

There are no studies confirming the superiority of one immunosuppressive schedule over another in HCV-positive recipients (C-II).

There is no agreement regarding the steroid maintainence regimen after liver transplantation, particularly during antiviral treatment (C-III).

Antiviral treatment may be followed by acute rejection episodes requiring the administration of steroid boluses (B-II).

There is no indication for modifying the immunosuppressive regimen during antiviral therapy (except for withdrawing mofetil mycophenolate as it may worsen the effect of ribavirin on red blood cells) (B-VI).

Table 7. Summary of studies evaluating the effectiveness of Peg-INF + ribavirin in treating HCV re-infection in OLT recipients

Study	Year	HIV/HCV co-infected patients		HCV-infected controls	
		No. of cases	*SVR No. (%)*	*No. of cases*	*SVR No. (%)*
Fung et al. (14.)	*2004*	*12*	*2 (17)*		
Duclos-Vallèes et al. (15)	*2006*	*13*	*2 (15)*		
de Vera et al. (9)	*2006*	*15*	*4 (27)*	*27*	*7 (28)*
Vennarecci et al. (16)	*2006*	*9*	*0 (0)*		
Castells et al. (17)	*2007*	*5*	*1 (20)*	*9*	*1 (11)*
Wojcik et al. (12)	*2007*	*4*	*4 (100)*		
Spanish study (18)	*2008*	*16*	*4 (25)*		
Duclos-Vallèes et al. (10)	*2008*	*19*	*3 (16)*		
Total		*93*	*20 (21.5)*		

Table 8. Studies evaluating the effect of age on SVR rates

Author, year	**Study design**	**No. of pts**	**Drugs**	**Duration, weeks**	**Age, years**	**SVR rate, %**	**Effect of age on SVR rates**
Antonucci, 2007[12]	Retrospective	153 (74 genotype 1 or 4; 79 genotype 2 or 3)	Peg-IFN α + RBV	24/48	48 (25-75)°	68.6	Four age groups: <40, 40-49, 50-64, ≥65 40-49 (OR 0.16; 95%CI 0.05-0.59); 50-64 (OR: 0.13; 95%CI 0.03-0.49); ≥65 (OR 0.21; 95%CI 0.05-0.91) Total SVR=70% (36% genotype 1 or 4; 89% genotype 2 or 3). Genotype 2 or 3 associated with SVR at multivariable analysis (OR 10.99; 95% CI 4.26-28.63). Age groups ≥40 had similar odds of achieving an SVR (p=0.71). The effect of age on SVR was maintained only in the 74 patients infected by genotype 1 or 4 (p=0.046)
Andreone, 2008[13]	Retrospective	756 (183 genotype 1 or 4; 174 genotype 2 or 3)[§]	IFN; IFN+RBV; Peg-IFNα+RBV	NA	72 (65-92)	30	SVR in all pts=35.7%; IFN=11.6%; IFN+RBV=20.1; peg-IFNα+RBV=68.3%

Thabut, 2006[16]	Retrospective	166	IFN; IFN+RBV; Peg-IFNα; Peg-IFNα+RBV	NA	NA	18.8	Two age groups: 65-80, >80 SVR associated with peg-IFNα+RBV (AOR: 5.4, 95%IC: 1.6-18.6) Comparison with pts <65 years: NA.
Alessi, 2003[18]	Retrospective	154	IFNα			19.0	Two age groups: <60, ≥60 years. SVR rates similar in the two groups.
Bacosi, 2002[19]	RCT	119	AH; IFNα-n_3 IFNα-n_3+AH	48	≥65	26.1	Comparison with pts <65 years: NA
Iwasaki, 2006[20]	Prospective	208 (136 genotype 1; 72 genotype 2)	IFNα-2b+RBV	24	54.5±10.4*	37.0	Three age groups: <50, 50-59, ≥60 Total SVR in patients ≥60=32%; genotype 1=16%; genotype 2 or 3=65% A trend to lower SVR rate in pts ≥60 (p=0.078) and patients ≥60 with genotype 1 (p=0.094).
Kumada, 2006[21]	Observational	288 (219 genotype 1; 37 genotype 2)	IFN + RBV	30/40	53.8 ±11.1*	36.5	Two age groups: <65, ≥65. A trend to lower SVR rate in pts ≥65 (p=0.08) Non-1 genotypes associated with SVR at multivariable analysis(OR 21.24; 95% CI 6.54-82.78)

SVR: sustained virological response; RCT: randomised clinical trial; Peg-IFN: pegylated interferon; RBV: ribavirin; NA: not available; °median (range); [§]available for 357 patients; *mean value±SD

Table 9. Studies evaluating the effect of age on side effects

Author, year	Study design	No. of pts	Drugs	Duration, weeks	Age, years	Effect of age on side effects
Antonucci, 2007[12]	Retrospective	153	Peg-IFN α + RBV	24/48	48 (25-75)°	Four age groups: <40, 40-49, 50-64, ≥65. Dermatitis was significantly more frequent in elderly patients (p=0.01). Neutropenia, thrombocytopenia, and grade 3 or 4 side effects were more frequent in patients ≥65, but the difference was not statistically significant. The frequency of dose reductions and treatment discontinuations was not different among the age groups.
Andreone, 2008[13]	Retrospective	756	IFN; IFN+RBV; Peg-IFNα+RBV	NA	72 (65-92)	Malaise: 24%; anemia: 11%; neutropenia: 11%; dyspepsia: 8%; cough: 7%; pruritus: 7%; anorexia5%; depression: 4%.
Thabut, 2006[16]	Retrospective	166	IFN; IFN+RBV; Peg-IFNα; Peg-IFNα+RBV	NA	NA	Two age groups: 65-80, >80. Dose reductions in 7% and discontinuations in 20% of treated pts. No serious adverse events reported.
Alessi, 2003[18]	Retrospective	154	IFN α			Two age groups: <60, ≥60. A trend to more frequent major side effects in pts ≥60 (p=0.07).
Bacosi, 2002[19]	RCT	119	AH; IFNα-n_3 IFNα-n_3+AH	48	≥65	In the IFNα-n_3 and IFNα-n_3+AH groups, major side effects were fever/malaise, insomnia, weight loss, depression.
Iwasaki, 2006[20]	Prospective	208	IFNα-2b+RBV	24	54.5 ±10.4*	Three age groups: <50, 50-59, ≥60. Discontinuations and dose reductions more frequent in pts ≥60 (p<0.001). Decreased appetite, retinal hemorrhage and neutropoenia were the main adverse events. An age of <60 associated with adherence at multivariable analysis.
Kumada, 2006[21]	Observational	288	IFN+RBV	30/40	53.8 ±11.1*	Two age groups: <65, ≥65 Dose reductions (p=0.045) and discontinuations (p=0.041) more frequent in pts ≥65.

SVR = sustained virological response; RCT = randomised clinical trial; Peg-IFN = pegylated interferon; RBV = ribavirin; °median (range); §available for 357 patients; * mean values±SD

Figures

Fig 1. Forest plot of the sustained virologic response rates described in 12 full-length papers and eight abstracts

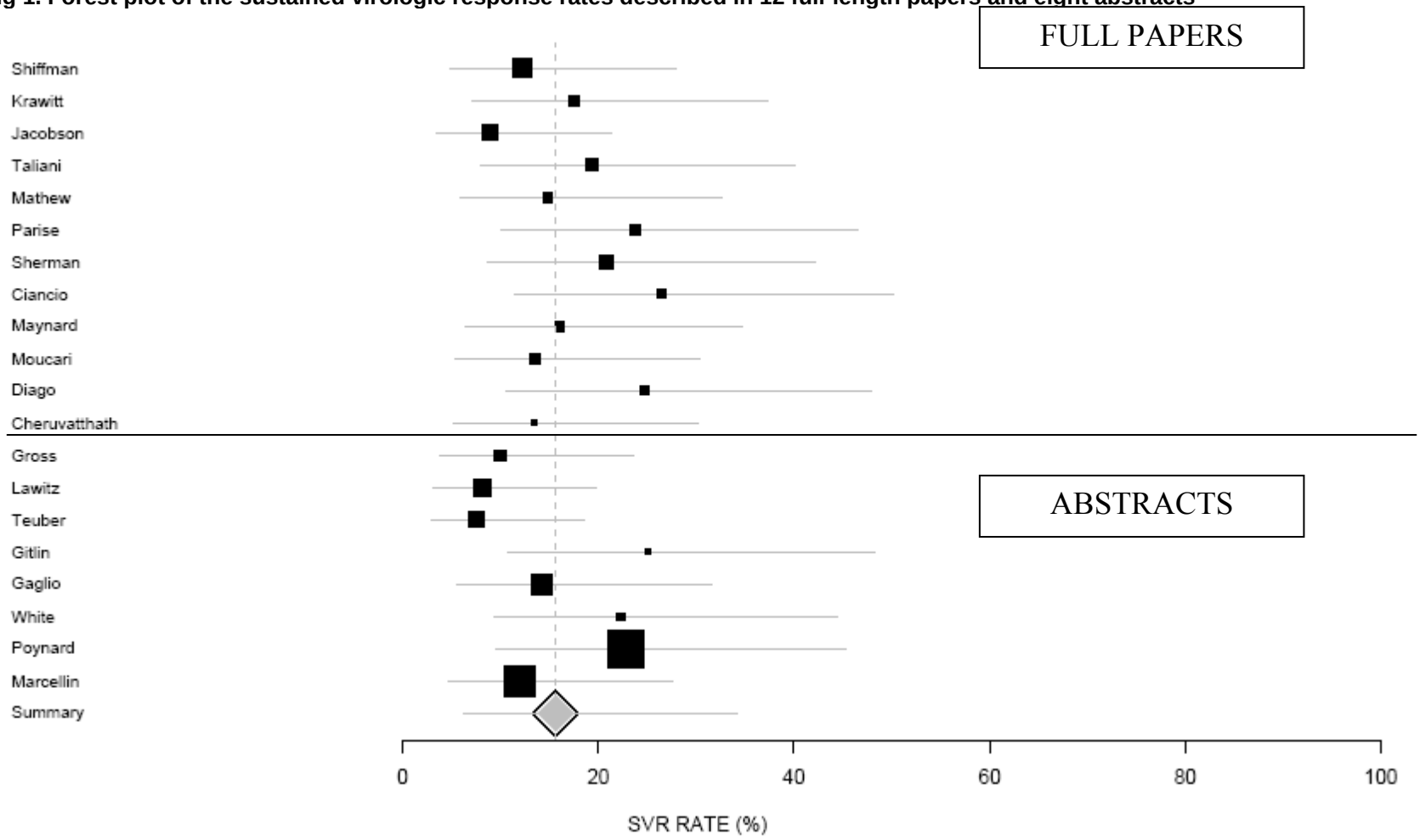

Fig 2. (vedi 3.5.1)