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Systematic Review: antiviral therapy of recurrent hepatitis C post liver transplant

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**Systematic Review: antiviral therapy of recurrent hepatitis
C post liver transplant**

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3 **Systematic Review: antiviral therapy of recurrent**
4 **hepatitis C post liver transplant**
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For Peer Review

SUMMARY

Background

Hepatitis C viral (HCV) infection is the first cause of liver transplantation worldwide. Recurrence of infection is constant and compromises patient and graft survival.

Aim

To provide an updated review of the main treatments of recurrent HCV.

Methods

MEDLINE (1990 to August 2010) and national meeting abstract search. Search terms included hepatitis C, liver transplantation, treatment, sustained virological response. An emphasis was placed on randomized trials.

Results

Antiviral therapy based on pegylated interferon and ribavirin must be considered before liver transplantation but is poorly tolerated and has poor results in patients with cirrhosis and end-stage liver disease or hepatocellular carcinoma. Antiviral therapy can be administrated systematically early after liver transplantation, or in patients with established recurrent chronic hepatitis. Combination of pegylated interferon alfa plus ribavirin results in a sustained virological response of up to 30% in patients which histological HCV recurrence. The results of a small trial of polyclonal anti-HCV to prevent recurrence were disappointing.

Conclusion

Currently available antiviral therapy is only effective in a minority of transplanted patients infected with HCV. Specifically targeted antiviral therapies combining interferon alfa and ribavirin or a combination of antiprotease and antipolymerase components associated with a genetic prediction of antiviral response and blocking HCV cell entry should improve the long-term prognosis of recurrent hepatitis C in the near future.

Introduction

In addition to alcoholic cirrhosis, Hepatitis C virus (HCV)-related cirrhosis is, a major indication for liver transplantation (LT) worldwide. It is the second most common indication for transplantation in northern Europe and in the USA and the primary indication in countries with high HCV seroprevalence such as Italy or Spain. Indications are end-stage liver diseases and/or hepatocellular carcinoma (HCC). Patients in the former group are usually placed high on the waiting list based on the prognostic MELD score (Model for End-stage Liver Disease) (1). Patients in the latter group with preserved liver function usually wait for a long period and must be treated for HCC. After transplantation, recurrence of HCV infection occurs in almost all patients (2) (3) and is associated with reduced graft and patient survival (4) (5). However, survival of patients after transplantation who become serum HCV RNA negative during therapy was improved (6).

Recurrence of infection is immediate in recipients who are serum HCV RNA-positive at liver transplantation (7). It does not occur in the few patients who experience a sustained virological response (SVR) to antiviral therapy before transplantation. Acute hepatitis is unpredictable, frequently asymptomatic and usually appears between 1 and 6 months after LT. In less than 5 % of patients, acute recurrence is severe, corresponding to a fibrosing cholestatic hepatitis (FCH) which is also described in other settings of immunosuppression. Once established, FCH leads to liver failure in a few weeks or months. More frequently up to 20 % of patients transplanted for HCV- liver disease may have no significant lesions 5 years after LT (8) (9). Thus, changes consistent with chronic, mild hepatitis are usually observed in more than 70 % of cases in the 5 years after LT (8). A ten to 20 fold increase in HCV viral load is generally observed in the first year following LT (7), with a subsequent decrease to levels found in immunocompetent subjects.

Recurrent liver disease is clearly more aggressive after LT than in immunocompetent subjects, as progression to cirrhosis at 5 years occurs in 10 to 50 % of LT patients (9) (10) while in immunocompetent subjects decades of infection are required before cirrhosis develops. Once cirrhosis is established, the probability of liver graft failure is 42 % within 12 months (11). Theoretically,

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3 there is a risk of developing a new HCC on the liver graft but, to our knowledge,
4 this has never been reported.
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7 The progression of recurrent HCV is variable and the risk factors are the subject
8 of debate. Many factors have been reported to play a role before LT (genotype
9 1 (12), viral load and female gender), or after LT (time of cold or warm ischemia
10 (13), blood transfusions, steatosis on the liver graft, age of the donor, use of
11 antilymphocytes (14), co-infection with HIV (15)). Amongst these factors, donor
12 age appears to be a major indicator of a poor prognosis of recurrent hepatitis C
13 because donor-age is increasing (11) (16) . However, donor age is also
14 important in non-HCV patients (17). Data from large registries indicate that the
15 recurrence of HCV probably results in decreased survival as compared to other
16 indications (18) (19).
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19 HCV recurrence appears to have the poorest prognosis of all causes of re-
20 transplantation with a 2-year survival rate of less than 33 % (20) (21) (22).
21 Mortality is frequently high in the first year after retransplantation (21). In a study
22 by Berenguer (20), only 4 (33 %) of 12 patients who underwent retransplantation
23 for HCV cirrhosis on the first graft survived after 2 years of follow-up. Causes of
24 death were HCV cirrhosis in 2 patients, FCH in one and surgical complications
25 in 3 patients. Retrospective studies (23) (24) have shown that HCV infection is
26 an independent risk factor of mortality after retransplantation. Re-transplant
27 recipients with HCV infection had a higher death rate compared to non-HCV re-
28 transplant recipients (26.0 vs. 8.8 deaths/100 patient-years, respectively) (24).
29 One reason for this could be a delayed indication for retransplantation after
30 unsuccessful antiviral therapies (20) in patients with co-morbidities. Only one
31 retrospective study (25) did not show any significant difference between HCV
32 and non-HCV patients after retransplantation with a 3-year survival rate of 67 %
33 and 66 % respectively.
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52 53 **Methods**

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55 The information for this review was compiled by searching PubMed and
56 MEDLINE databases (1990 to 2010). The search terms used were “liver
57 transplantation”, “HCV recurrence”, “treatment of recurrence”, “randomized
58 trials”. Priority was given to randomized and controlled studies. The web of
59 science and clinical trials.gov were also searched to identify ongoing
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3 unpublished studies. Finally we selected interesting recent papers on the
4 treatment of recurrent hepatitis C.
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8 9 **Interferon-alfa and ribavirin therapy**

10 Classic antiviral therapies based on pegylated interferon-alfa and ribavirin may
11 be indicated before LT to avoid recurrence, systematically after liver
12 transplantation (pre-emptive therapy) or later once chronic hepatitis has been
13 confirmed and immunosuppression is relatively low. Before or after LT,
14 combined bitherapy has clear limitations: poor tolerance, poor efficacy and
15 serious adverse events.
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23 **Therapy before LT**

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25 In the past decade, combined therapy with interferon-alfa and ribavirin has
26 improved. An increasing number of patients with cirrhosis who would have been
27 previously excluded can now be treated thanks to pegylated interferon-alfa
28 (PEG-IFN), the use of granulocyte and erythrocyte growth factors, and dosing of
29 ribavirin. Veldt et al (26) studied 479 patients with compensated cirrhosis. One
30 hundred and forty two of these patients experienced a sustained virological
31 response (SVR) (30 %) and had significantly fewer liver-related deaths or HCC.
32 Thus this bitherapy may be tempting in candidates with compensated liver
33 disease waiting for LT due to HCC, especially those with HCV genotypes 2 or 3
34 when the waiting list is long, or if they are naive or relapsers. Another recent
35 prospective and randomised clinical trial (27) confirmed that SVR was lower in
36 patients with cirrhosis (33%) than in those with bridging fibrosis (51%-
37 p=0.0028). All patients with cirrhosis had compensated liver disease defined by
38 a Child-Pugh score <7. Tolerance to antiviral therapy was similar in patients
39 with and without bridging fibrosis or cirrhosis.
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52 In decompensated cirrhosis, therapy is less effective and even hazardous. In a
53 randomised study of 129 patients with an average MELD score of 14 by
54 Lacobellis et al (28) SVR was 43 % in patients infected with HCV genotype 2 or
55 3 and only 7 % in those infected with genotype 1. One of the goals of treating
56 decompensated patients on the waiting list is to achieve plasma HCV RNA -
57 negativity at LT. In the study by Everson (29), there was no post-transplant
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3 recurrence in 12/15 (80%) HCV RNA -negative recipients. Results were lower in
4 the study by Forns (30) suggesting that post-transplant recurrence can be
5 prevented in up to 20 % of selected patients.
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10 **Pre-emptive treatment (Table I)**

11 The aim of this approach is to rapidly prevent the development of chronic
12 hepatitis once the patient has been transplanted before there is biochemical
13 and histological evidence of recurrent HCV infection. Although treatment of
14 acute hepatitis is very effective in immunocompetent subjects (31) recurrent
15 hepatitis C after liver transplantation is clearly not an acute infection. In
16 contrast, immunosuppression is strong the first year after LT, which probably
17 decreases the antiviral response during this period. The initial pilot study by
18 Mazzafero et al (32) reported encouraging effects with 12-month, pre-emptive
19 treatment in 36 LT patients with a combination of non-pegylated IFN alfa and
20 ribavirin for one year, beginning within 3 weeks after LT. Serum HCV -RNA
21 clearance was obtained in 12 (33 %) patients after 37 days of treatment. At the
22 end of the one-year period all of these 12 patients remained HCV- RNA
23 negative. Dose reductions were frequent but none of the patients was
24 withdrawn from treatment and there was no graft rejection during the study.
25 Four randomized studies have evaluated monotherapy with non- Pegylated
26 (33) (34) or PEG-IFN alfa (35), and only one has evaluated the combination of
27 interferon alfa or PEG-IFN alfa plus Ribavirin (36). SVR was achieved in less
28 than 20 % in all of these studies and there were numerous side effects because
29 only a minority of patients could receive a full-dose treatment. Conversely, the
30 severity of recurrence was decreased in most of these studies. Therefore pre-
31 emptive treatment is a strategy to be explored and final results of prospective,
32 randomized studies are expected. In particular, the PHOENIX trial prospectively
33 compared pre-emptive therapy and the treatment of recurrent liver disease.
34 This as yet unpublished trial (ClinicalTrials.gov NCT00087633) measured the
35 efficacy, tolerance, and safety of PEG-IFN alfa-2a/ribavirin prophylaxis in
36 preventing recurrent allograft hepatitis C. At 10-26 weeks post-OLT, 115
37 patients were randomized to either 48 weeks of peginterferon alfa-2a plus
38 ribavirin or observation. Patients in the observation arm who developed
39 histological recurrence of HCV were treated with PEG-IFN alfa-2a/ribavirin. In
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3 the intention to treat analysis, (SVR) was achieved by 12/54 (22%) patients in
4 the prophylaxis arm and 3/14 (21%) treated patients in the observation arm. In
5 the intention to treat analysis, 34/55 (62%) patients in the prophylaxis arm
6 versus 39/60 (65%) patients in the observation arm developed recurrent
7 hepatitis C. Withdrawal during the 48-week treatment/observation period was
8 frequent: 24 patients in the prophylaxis arm and 17 patients in the observation
9 arm. Prophylactic treatment with PEG-IFN alfa-2a/ribavirin to prevent recurrent
10 hepatitis C was associated with a low rate of SVR, side-effects, and a high rate
11 of discontinuation (37).
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21 **Treatment of recurrent chronic hepatitis (Table II)**

22 In many transplantation centres, antiviral treatment is delayed until there is
23 histological evidence of recurrent hepatitis. Definition of histological HCV
24 recurrence can range from simple lobular hepatitis (F0) to more severe, chronic
25 hepatitis with fibrosis, as well as the relatively rare, but severe, fibrosing
26 cholestatic hepatitis (38). This therapeutic approach has been reported in 8
27 small, randomised trials (35) (38) (39) (40) (41) (42) (43) (44). Antiviral
28 treatment was begun between 6 and 60 months after liver transplantation. All of
29 the results of trials using IFN-alfa monotherapy were disappointing with less
30 than 12 % of SVR and no benefit in treated patients (40) (42) (35). In contrast,
31 in studies with the combination of IFN-alfa and Ribavirin (41) (45) (46) (43)
32 and, more recently PEG-IFN plus ribavirin (47) (48) (49) (50) (51) (52) (6)
33 (38) (53), SVR was achieved in between 20 % (43) and 30 % (38) respectively.
34 Improvement in necroinflammatory activity and fibrosis was more likely in
35 patients who achieved SVR with combination therapy, and the likelihood of
36 developing cirrhosis was significantly reduced compared to patients who did not
37 achieve SVR (54). Finally, recent, unpublished reports suggest that 5-year
38 survival rates are higher in patients who achieve SVR, as well as in those who
39 experience relapse than in non -responders (96 % and 93 % versus 83 %) (55).
40 Predictors of SVR seem to be the same as in the non-transplant setting. In a
41 retrospective study Hanouneh et al (56) found that a rapid virological response
42 (e.g. undetectable viral load at week 4) was a good predictor of SVR with a very
43 high specificity and positive predictive value. Four other studies (50) (51) (38)
44 (57) confirmed that most, if not all, patients who achieved SVR had a virological
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3 response at week 12. The second important factor affecting treatment response
4 was obviously viral genotype with a poor response in genotype 1 patients (48)
5 (56). Another important factor is the presence of FCH, which is almost incurable
6 with IFN bitherapy (38).
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10 Another strong predictor of SVR is adverse events. There were fewer dose
11 reductions in patients with SVR (57). Thrombocytopenia, neutropenia, or
12 anaemia may require a dose reduction, discontinuation or stopping therapy.
13 These effects were very common with therapy in all trials, leading to cessation
14 of therapy in up to 43 % of treated patients (43). The prospective study by
15 Calmus (58) clearly demonstrated that ribavirin was mandatory throughout the
16 entire course of treatment. Fortunately the use of G-CSF and EPO has
17 improved tolerance to treatment, reducing cytopenia so that antiviral therapy
18 can be maintained.
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28 **Rejection induced by interferon alfa (Table III)**

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30 Chronic rejection was initially described with monotherapy using non-pegylated
31 IFN-alfa (8). It seems to be far less frequent (<5%) with combined therapies.
32 Ribavirin, which has immunomodulatory effects, could explain the lower rate of
33 rejection. Better patient selection, improvement of immuno suppressive
34 regimens and careful histological follow-up also probably play a role in the low
35 rate of rejection.
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42 **Immunosuppression and HCV (Table IV)**

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44 During the first post-transplant months, serum HCV-RNA levels increase when
45 immunosuppression is the highest. The relationship between HCV recurrence,
46 its severity and the type of immunosuppressive regimen remain unclear.
47 Because the distinction between recurrent hepatitis and rejection is far from
48 clear-cut, the effect of immunosuppression on recurrent hepatitis is difficult to
49 assess. It has been clearly established that the induction of immunosuppression
50 through antilymphocyte antibodies is deleterious (14).
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54 Two meta-analyses (59) (60) have shown that steroid-free protocols are
55 significantly better in limiting the recurrence of HCV [R.R = 1.15 (1.01, 1.13)],
56 acute graft hepatitis [O.R = 3.15 (1.18, 8.40)] and treatment failure [O.R = 1.87
57 (1.33, 2.63)] (60).
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3 Cyclosporine A (CyA) has been shown to suppress in cultured hepatocytes, the
4 replication of HCV through the interaction of cyclophilin A and the NS2 viral
5 protein (61). Most prospective (62) (63) (64) (65) studies suggest that there is
6 no difference between cyclosporine-based regimens and tacrolimus-based
7 regimens for liver histology or long-term graft survival. A meta-analysis (66) of
8 randomised clinical trials did not find any statistically significant difference in
9 mortality, graft survival, acute rejection or FCH between the two
10 immunosuppressive regimens. On the other hand, 3 studies have suggested
11 that SVR rates were higher in patients receiving cyclosporine compared to
12 those receiving mycophenolate mofetil (MMF) or tacrolimus (67) (68) (38). A
13 recent report from Italy has confirmed that cyclosporine may be associated with
14 a higher rate of SVR compared to tacrolimus in patients receiving IFN alfa-
15 based combination therapy for recurrent hepatitis C after liver transplantation
16 (39.5 % versus 13.2 %) (69).

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18 Finally in a randomised trial in 2002 Jain et al (70) concluded that there was no
19 difference in HCV recurrence, patient survival or rejection between a regimen of
20 tacrolimus and tacrolimus plus MMF. However another retrospective report (71)
21 showed that the addition of MMF at discharge to tacrolimus-based
22 immunosuppression was associated with improved long-term outcomes after
23 liver transplantation in patients with HCV.
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40 **Treatment of HCV -recurrence in HIV-HCV co-infected patients**

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42 With the introduction of highly active antiretroviral therapies, replication of HIV
43 is controlled and liver transplantation is feasible. The main difficulty after LT in
44 these cases is severe recurrence of HCV (15).
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47 HIV infection accelerates the progression of recurrent HCV (72) and probably
48 affects survival in transplanted co-infected patients (73) (74). Some studies
49 have shown that recurrent HCV in these patients increased the incidence of
50 FCH, a leading cause of mortality (73) (72). HCV recurrence increases the
51 mitochondrial toxicity of antiretrovirals which is not observed in HIV-HBV co-
52 infected patients (75). However because of the significant toxicities and drug-
53 to-drug interactions of nucleoside reverse transcriptase inhibitors in
54 combination with ribavirin, with drug-to-drug interaction of HIV protease
55 inhibitors with HCV protease inhibitors and calcineurin-inhibitors, new
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3 antiretrovirals without these interactions could be attractive therapeutic
4 alternatives for post-liver transplantation.
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7 There are few studies on the treatment of recurrent HCV in co-infected patients
8 and all of them are uncontrolled and non-randomized with small patient
9 populations. Castells et al (76) investigated the efficacy of early antiviral
10 treatment for recurrent HCV in co-infected patients. Treatment with PEG-IFN
11 alfa 2b and ribavirin was administered for 24 to 48 weeks when histological
12 recurrence was observed. Three of the 5 patients presented with severe
13 cholestatic hepatitis. Antiviral treatment was initiated a median of 12 weeks
14 after LT. SVR was only achieved in one patient. The antiretroviral regimen was
15 not modified in any of the patients. Moreover, acute rejection or mitochondrial
16 toxicity was not observed. In contrast, in the study by Wojcik (74), four co-
17 infected patients with recurrent HCV after LT received peg-IFN plus ribavirin for
18 6 to 12 months. FCH hepatitis was diagnosed in 2 patients. At the end of the
19 treatment, all patients were HCV-RNA negative with improved histology.
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31 **Specific targeted antiviral therapies (STAT-C)**

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33 Specific targeted antiviral therapies directed against protease, polymerase or
34 other non structural proteins will certainly change the prognosis of recurrent
35 hepatitis C after LT. The two molecules directed against viral protease NS3 in
36 the most advanced stages of development (telaprevir and boceprevir) combined
37 with classic bitherapy have been shown to increase the SVR in naïve patients,
38 relapsers and non responders (77) (78) (79). Although these treatments will be
39 soon available to immunocompetent patients no reports exist for transplanted
40 patients. STAT-C induced rapid selection of the escape mutant and must be
41 used in combination with classical bitherapy. Interaction with
42 immunosuppressive drugs and additional adverse events will probably limit the
43 use of this treatment. Another very interesting perspective is the combination of
44 antiprotease and antipolymerase molecules without interferon-alfa or ribavirin
45 (80) which was tested in immunocompetent patients in a short-term trial.
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58 **Prediction of SVR in liver transplant patients**

59 Large genome-wide association studies of immunocompetent patients infected
60 with genotype 1 HCV and treated in controlled trials by classic pegylated

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3 interferon alfa and ribavirin showed that the DNA polymorphism of the IL28
4 gene, a type-I cytokine involved in the antiviral response, is a powerful predictor
5 of SVR (81). As a result of this major finding the SVR can be predicted for
6 genotype 1 as well as genotype 3 HCV patients. Moreover, favourable
7 polymorphisms seem to correspond to a higher expression of this cytokine in
8 the liver. Liver transplantation is an interesting model since the polymorphisms
9 of both the recipient and the donor could be involved. Very recent small series
10 in patients with recurrent HCV after LT, suggest that donor or recipient IL28B
11 genotypes could predict SVR with PEG-IFN/RBV therapy. The first published
12 series on this subject (82) suggested that recipient and donor IL28B status are
13 related to SVR after LT. Larger series are clearly required to determine the
14 respective role of donor or recipient polymorphisms. If the donor genotype is
15 really predictive, livers from donors with favorable polymorphisms could be
16 directed to HCV recipients.
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30 **Blockage of HCV cell entry**

31 Viral entry is required for the initiation, spread, and maintenance of infection,
32 making it an attractive target for antiviral strategies. The first way to block entry
33 is obviously by neutralizing HCV. Chimpanzees inoculated with infectious
34 plasma (83) and more recently immunodeficient mice harboring human
35 hepatocytes (84) are the two animal models for HCV. More recently, the JFH1
36 HCV strain (85) which can infect hepatocyte cell lines (Huh7) has been used to
37 test viral neutralization of clinical sera (86) (87). Antibody-mediated
38 neutralization has also been suggested in chimpanzees (88) or in patients
39 receiving different preparations of polyclonal immunoglobulins (89). During the
40 chronic phase of HCV infection, most HCV-infected patients develop high-titer
41 cross-neutralizing antibodies (85) (90). However, the small trial using
42 polyclonal anti-HCV preparations (HCIG) after LT was shown to be both
43 innocuous and ineffective (91).
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54 Another exiting approach is to block cell entry at the level of cell receptors. The
55 tight junction protein claudin-1 (CLDN1) has been shown to be necessary for
56 entry of HCV into the cell. Monoclonal antibodies against the HCV entry factor
57 CLDN1 has been shown to be effective in a model of cultured human
58 hepatocytes (92) and might be effective in preventing HCV recurrence after
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3 liver transplantation as well as in limiting viral spread in chronically infected
4 patients. The potential drawback of this new approach could be the side-effects
5 induced by antibodies directed against these cell receptors. The major
6 advantage of this approach is that the selection of viral mutations is unlikely.
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10 Blocking either viral or cell receptors could be ineffective in case of high viral
11 load. Neutralizing anti-HBs (HBIG) in HBV does not prevent post-LT recurrence
12 in patients with high viral load at LT while HBIG has been shown to be effective
13 in patients with either spontaneous low HBV viremia or those receiving
14 antiretroviral therapy. Hypothetically, neutralization and reduction of viral load
15 could prevent recurrent HCV infection.
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22 **Conclusions**

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24 While waiting for the commercialisation of STAT-C what can be proposed to
25 HCV patients receiving LT in 2010? Before liver transplantation, in patients with
26 a favourable genetic IL28b polymorphism, HCV genotypes 2 or 3 or patients
27 who have relapsed, combined therapy should be attempted combined with
28 growth factors and careful follow-up. This is especially difficult but feasible in
29 patients with high MELD scores. It is also difficult in patients with compensated
30 cirrhosis on the LT waiting list for hepatocellular carcinoma. However, due to
31 the long waiting time in case of low MELD scores, in HCC patients priority is
32 given to treatment of HCC, which is difficult to combine with antiviral therapies.
33 Although the final results of the Phoenix trial have not yet published, there is no
34 clear indication for pre-emptive therapy after liver transplantation.
35 Immunosuppression must be administered excluding anti-lymphocyte
36 antibodies, with rapid tapering of steroids and cyclosporin instead of tacrolimus.
37 Classic therapy should be attempted in patients with early recurrence, liver
38 fibrosis, without rejection, favourable viral genotypes or the IL28B
39 polymorphism. Finally, we must emphasize the importance of systematically
40 assessing liver histology in case of recurrent hepatitis C. Indeed, non invasive
41 procedures after liver transplantation have not been well studied, and cannot
42 identify associated rejection which is a central issue both before and during
43 interferon-alfa therapies.
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TABLE I:

PREEMPTIVE TREATMENT: PROSPECTIVE AND RANDOMISED STUDIES

Study	Transplantation treatment interval (weeks)	Antiviral therapy, time	N	Withdrawals	Virological response	Histological results	Adverse events
Singh et al Transplantation 1998	<2	IFN 3MU tiw vs <i>no treatment</i> 24 weeks	24	nd	0 in both groups	HCV recurrence: 50% in the IFN group vs 42% in the control group (NS) No difference in severity of recurrence	IFN group: Leukopenia (17%) asthenia (33%)
Sheiner et al Hepatology 1998	<2	IFN 3MU tiw vs <i>no treatment</i> 48 weeks	71	discontinuation: 14%	ETR: IFN 17% control: 5% NS	Incidence of early recurrence reduced in IFN group: 26% vs 54% in control group (p=.017)	IFN group: Thrombocytopenia (17%)
Shergill et al American journal of Transplantation 2005	<6	IFN 3MU tiw OR Peg-IFN 1,5 µg/kg vs IFN + Ribavirin 600 to 1-1,2mg/day 48 weeks	44	discontinuation: 41%	SVR: IFN 4,54% IFN+RIB 18,2% NS	nd	27% serious adverse events 11 received growth factors Hemolytic anemia with Ribavirin
Chalasani et al Hepatology 2005	<3	Peg-IFN 180µg/week vs <i>no treatment</i> 48 weeks	54	Withdrawals:31% Dose reductions: 42%	SVR: IFN: 8% No treatment: 0 NS	HAI score and fibrosis are lower in IFN group But not significant	IFN group: Thrombocytopenia or anemia 9%

Abbreviations:
N: number of patients, IFN: Interferon, Peg: pegylated, tiw: three times weekly, ETR: undetectable hepatitis C virus RNA at the end of treatment, SVR: sustained virological response, HAI: histology activity index, nd: not defined, ns: not statistically significant.

TABLE II:

TREATMENT OF HEPATITIS C RECURRENCE: PROSPECTIVE AND RANDOMISED STUDIES

	Study	Transplantation treatment interval (months)	Antiviral therapy, time	N	Genotype 1	Discontinuation (n)	ETR	SVR	Histological results	Adverse events
IFN vs Ribavirin monotherapy	Gane et al Hepatology 1998	> 6	IFN 3 MU tiw vs Ribavirin for 12 weeks	30	47%	2 in ribavirin group	IFN group: 46% Rib group: 17% p=ns	0	Reduction of inflammation: 21% in IFN group vs 64% in Rib group, p=0.05 No improvement of fibrosis	anemia leukopenia
IFN monotherapy	Cotler et al Transplantation 2001	> 7	IFN (3MU/day) vs no treatment for 48 weeks	12	33%	2 discontinuation in IFN group	IFN group: 4 (50%) Control group: 0	IFN: 1 (12.5%) Control group: 0	improvement in HAI score in the treated group p=0.04	Asthenia Depression
	Chalasanani et al Hepatology 2005	< 60	Peg-IFN 180µg/week vs no treatment for 48 weeks	67	77%	10 (30%) in treated group	IFN group : 9 (27%) Control group: 0	IFN group: 4 (12%) Control group: 0	HAI score and fibrosis lower in the treated group but not significant	Flu like symptoms
IFN monotherapy vs bitherapy	Angelico et al J Hepatol 2007	< 12	Peg-IFN (180µg/week) vs Peg-IFN + Ribavirin for 48 weeks	42	83%	Withdrawals: Monotherapy: 6/21 Bitherapy: 7/21 Dose reductions: Monotherapy: 7 Bitherapy: 8	Monotherapy: 76 Bitherapy: 71	Monotherapy: 38 Bitherapy: 33	Improvement necro-inflammatory score: Monotherapy: 7/11(64) Bitherapy: 2/10(20) Improvement fibrosis score: Monotherapy: 5/11(45) Bitherapy: 2/10(20)	Headache Asthenia Thrombocytopenia Hemolytic anemia
Bitherapy with IFN	Kizikisik et al Transpl Proc 1997	nd	Ribavirin +/- IFN (3MU tiw) vs no treatment for 12 weeks	19	nd	1 (17%) in treated group	0 in each group	0 in each group	nd	nd
	Ghalib et al Hepatology 2000	> 5	IFN (6MU tiw) + Ribavirin for 24 weeks vs 48 weeks	10	80%	5 completed treatment	24 weeks group: 3/3 48 weeks group: 1/2	24 weeks group: 1/3 48 weeks group: 1/2	nd	Flu like symptoms mild fatigue
	Samuel et al Gastroenterology 2003	> 48	IFN (3 MU tiw) + Ribavirin vs no treatment for 48 weeks	52	83%	12/28 (43%) in treated group	Treated group: 32% Control group: 0 p=.02	Treated group: 21% Control group: 0 p=.04	No significant histologic improvement	Anemia Psychiatric disorders 1 chronic rejection
Bitherapy with Peg-IFN	Carrion et al Gastroenterology 2007	> 6	Peg-IFN (1,5µg/kg/week) + Ribavirin vs no treatment for 48 weeks	81	90%	Treatment interruptions 39% Dose reductions 49/54	nd	Treated group: 18 (33%) Control group: 0	Liver fibrosis progressed >1 stage in 70% of control group versus 39% of treated group p<0.01	Anemia Asthenia, fever
Abbreviations: N: number of patients, IFN: Interferon, Peg: pegylated, tiw: three times weekly, ETR: undetectable HCV RNA at the end of treatment, SVR: sustained virological, HAI: Histological Activity Index ; nd: not defined, ns: not statistically significant.										

TABLE III:

REJECTION IN PROSPECTIVE AND RANDOMISED TRIALS

	Study	Antiviral therapy, time	Acute rejection	Chronic rejection
Preemptive treatment	Singh et al Transplantation 1998	IFN vs no treatment 24 weeks	ns	nd
	Sheiner et al Hepatology 1998	IFN vs no treatment 48 weeks	ns	0
	Shergill et al American journal of Transplantation 2005	IFN OR Peg-IFN vs IFN + Ribavirin 48 weeks	18/44 (41%) overall	nd
	Chalasani et al Hepatology 2005	Peg-IFN vs no treatment 48 weeks	12% vs 21 % ns	nd
Treatment of recurrent hepatitis	Cotler et al Transplantation 2001	IFN vs no treatment for 48 weeks	1/6 (17%) in treatment group vs 0 in control group	nd
	Chalasani et al Hepatology 2005	Peg-IFN vs no treatment for 48 weeks	12% treated group vs 0% in control group (p=0.11) ns	nd
	Angelico et al J Hepatol 2007	Peg-IFN vs Peg-IFN + Ribavirin for 48 weeks	Monotherapy: 3/21 (14%) Bitherapy: 1/21 (4%)	nd
	Kizikisik et al Transpl Proc 1997	Ribavirin +/- IFN vs no treatment for 12 weeks	4/6 (67%) in treated group vs 3/13 (23%) in control group	1/6 in treated group
	Samuel et al Gastroenterology 2003	IFN + Ribavirin vs no treatment for 48 weeks	0	1/28 in treated group ns
	Carrion et al Gastroenterology 2007	Peg-IFN + Ribavirin vs no treatment for 48 weeks	5 (9%) in treated group vs 0 in control group	nd

Abbreviations:
IFN: Interferon, Peg: pegylated, nd: not defined, ns: not statistically significant.

Table IV

IMMUNOSUPPRESSION AND HCV RECURRENCE, PROSPECTIVE AND RANDOMISED TRIALS

Immunosuppression regimen	Study	N	HCV recurrence	Rejection	Patient Survival
Tacrolimus vs CsA	Mueller et al 1995	121	nd	60% vs 28% p=0.05	No difference
	Zervos et al 1998	50	No difference	24% vs 50% ns	No difference
	Martin et al 2004	79	No difference	No difference	nd
	Berenguer et al 2006	90	No difference	No difference	No difference

Abbreviations:
N: number of patients, CsA = Cyclosporine A, T = Tacrolimus, ns: not statistically significant, nd: not define

For Peer Review

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	