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TOPIC HIGHLIGHT

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Strategies to reduce hepatitis C virus recurrence after liver transplantation

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Abstract

Hepatitis C virus (HCV) is a major health problem that leads to chronic hepatitis, cirrhosis and hepatocellular carcinoma, being the most frequent indication for liver transplantation in several countries. Unfortunately, HCV re-infects the liver graft almost invariably following reperfusion, with an accelerated history of recurrence, leading to 10%-30% of patients progressing to cirrhosis within 5 years of transplantation. In this sense, some groups have even advocated for not re-transplanting this patients, as lower patient and graft outcomes have been reported. However, the management of HCV recurrence is being optimized and several strategies to reduce post-transplant recurrence could improve outcomes, decrease the rate of re-transplantation and optimize the use of available grafts. Three moments may be the focus of potential actions in order to decrease the impact of viral recurrence: the pre-transplant moment, the transplant environment and the post-transplant management. In the pre-transplant setting, it is not well established if reducing the pre transplant viral load affects the risk for HCV progression after transplant. Obviously, antiviral treatment can render the patient HCV RNA negative post transplant but the long-term benefit has not yet been fully established to justify the cost and clinical risk. In the transplant moment, factors as donor age, cold ischemia time, graft steatosis and ischemia/reperfusion injury may lead to a higher and more aggressive viral recurrence. After the transplant, discussion about immunosuppression and the moment to start the treatment (prophylactic, pre-emptive or once-confirmed) together with new antiviral drugs are of interest. This review aims to help clinicians have a global overview of post-transplant HCV recurrence and strategies to reduce its impact on our patients.

Key words: Hepatitis C virus; Recurrence; Liver; Transplantation; Outcomes

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INTRODUCTION

Hepatitis C virus (HCV) is a major health problem that leads to chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC)[1]. HCV-cirrhosis is the most frequent indication for liver transplantation (LTx) in Europe and America[2]. Although accepted as the standard of care for end-stage liver disease[3], the progression of liver disease is variable, leading to re-transplantation and lower survival rates. Because of these results, concerns have been expressed regarding the appropriateness of re-transplantation for HCV and the optimal timing of surgery in an era of organ shortage[4].

The diagnosis of post-transplant HCV recurrence ideally should be histological, by protocol-driven biopsies as biochemical and serological markers for HCV are inaccurate in the post LTx population[5,6]. Although non-invasive procedures such as fibroscan are able to provide similar results in detecting early and rapidly progressive fibrosis, its use is not widely extended[7]. HCV re-infects the liver graft almost invariably following reperfusion[8]. Histological patterns of acute HCV appear between 4 and 12 wk post-transplant, followed by a concomitant rise in the HCV viral load[8,9]. Serum transaminases and HCV RNA levels usually settle but spontaneous viral clearance has not been observed post LTx. A healthy HCV carrier state does not ensue, and histological features of chronic HCV can be demonstrated in 70%-90% of recipients after 1 year and in 90%-95% after 5 years[10].

The natural history of recurrent HCV is accelerated in LTx recipients, with 10%-30% progressing to cirrhosis within 5 years of transplantation. When cirrhosis is present after liver transplantation, the rate of decompensation is > 40% at 1 year and > 70% at 3 years in liver transplant recipients with established cirrhosis versus < 5% and < 10%, respectively, in immunocompetent patients[10-12]. Some patients (2%-5%) develop a severe form of cholestatic fibrosing hepatitis, with extremely high levels of serum and intrahepatic HCV RNA, and histological cholestasis, the majority of which rapidly progress to graft failure and death[10].

Strategies to reduce post-transplant HCV recurrence aim to improve outcome, to decrease the rate of re-transplantation and optimize the use of available grafts. Potential areas where recurrence can be influenced are pre-transplant antiviral treatment (AVT), modifiable perioperative and donor variables, and post-transplant immunosuppression AVT regimens

PRE-TRANSPLANT STRATEGIES

The rationale

The aim of pre transplant AVT is to achieve a sustained virological response (SVR) or to clear HCV RNA at time of transplant. Low HCV RNA before transplant has been shown to be associated with a reduced risk of severe recurrence. The HCV RNA load has also been shown to be an independent factor for fibrosis progression and survival[13,14]. By reducing pre transplant viral load the severity of HCV recurrence has the potential to be reduced and patient survival improved. However, it is not established if reducing the pre transplant viral load affects the risk for HCV progression after transplant[15-17].

Historically, cirrhotic patients were not considered for AVT as it was felt they would not be able to tolerate therapy and be at risk of decompensation. Currently available AVT is also less effective when started in the presence of advanced fibrosis and cirrhosis. Pegylated interferon (PEG IFN) and Ribavirin are emerging as the standard therapy for HCV and appear to be tolerated by cirrhotic patients[18,19].

Predictors of antiviral therapy response and tolerance

Drawbacks to undertaking antiviral treatment in the pre transplant population are the prevalence of genotype 1, the side effects of IFN and Ribavirin preventing full dose from being achieved, and complications related to the underlying liver disease[18,20,21]. To achieve a SVR at transplant the patient generally will need to be observed for 24 wk after completion of the antiviral course. This is difficult to achieve and may represent too long a period for a patient on the waiting list. Predictors of viral clearance include non-genotype 1 and an early virological response[22-25]. The absence of a ⩾ 2 log10 reduction in HCV RNA between baseline and wk 4 has a strong negative predictive value[22-24,26,27]. This absence of an early virological response can be used as a guide to stopping treatment[26]. Pre transplant higher viral load has been reported as another predictor of SVR[22,25].

To make AVT more tolerable, various dosing strategies have been used including tailoring dose to liver function, shortening the duration of therapy or using haematopoietic growth factors[22,24,25]. In decompensated cirrhotics, reported rates of neutropaenia, thrombocytopaenia, anaemia, infection or liver decompensation range from 50%-60%, 30%-50%, 30%-60%, 4%-13% and 11%-20% respectively[22-25]. Child-Turcotte-Pugh (CTP) C patients are unable to tolerate a course of treatment[23,28]. The CTP score appears to be a more reliable predictor than Model for End-stage Liver Disease (MELD) for serious side effects that lead to discontinuation of therapy, hepatic decompensation or death[28].

Evidence regarding pre-transplant antiviral therapy

Over the past decade, there have been a small number of non-controlled studies that have assessed the efficacy of IFN and Ribavirin in HCV patients on the waiting list (Table 1). Many of the reported studies were designed to focus on the safety and tolerability of AVT, rather than HCV recurrence patterns and clinical course post LTx[22-24,26-31]. A number of different antiviral regimens and treatment periods have been studied. Non-pegylated IFN and Ribavirin using a low accelerating dose regime (LADR), appears to be well tolerated with 39% clearing HCV RNA on treatment and 21% with a SVR[23]. The best results have been reported with PEG IFN and Riba-

Table 1 The pre transplant hepatitis C virus antiviral therapy studies

Study	No.	Study design	Regime	Period	GFs	CTP/MELD mean	Genotype	Tx Naive	On Tx virolocal response %		SVR %		CessationTx	Dose reduction	% HCV neg post LTx[2]	Period FU postLTx
									G1/4	G2/3	G1/4	G2/3				
Massoumi *et al*[28]	90	Cohort	90-180 mcg IFNα2a + 400-1200 mg RBV *od*	8 wk	Y	6.7/11.2	77% G1/4	62%	48	67	10	29	33%	18%	40% (2/5)	9.6 mo
A2ALL LADR 2009[1]	79	Prospective semirandomised	0.75 mcg/kg per wk PEG IFNα2b + 600 mg RBV *od*	11.4-14.6 wk	NA	NA	59% G1/4	NA	NA	NA	NA	NA	NA	75% adverse event	40% (2/5)	3 mo
Everson *et al*[23]	124	Cohort	IFNα2b 1.5-3 mu x 3/wk + RBV 600-1200 mg *od*	6-12 mo	Y	7.4/11	70% G1	NA	30	83	13	50	13%	71%	80% (12/15)	6 mo
Iacobellis *et al*[24]	66	Case match	PEG IFNα2b 1 mg/kg per wk + RBV 800-1000 mg *od*	24 wk	Y	8/14.2	67% G1/4	NA	30	83	7	44	20%	40%	0% (0/0)	30 mo
Crippin *et al*[30]	15	Randomised	IFNα2b 1-3 mu *od*/wk ± RBV 400 mg *bd*	12 wk	N	11.9/NA	73% G1	NA	18	10	NA		NA	87% adverse event (study closed)	0% (0/0)	1 mo
Thomas *et al*[27]	20	Cohort	IFNα2b 5 mu *od*	14 mo	Y	12/13/2010	67% G1	100%	56	100	NA		0%	0%	33% (4/12)	33.6 mo
Forns *et al*[22]	30	Cohort	IFNα2b 3 mu *od* + RBV 800 mg *od*	12 wk	Y	50% CTP A, 50% B/C	83% G1	80%	30	82	NA		25%	63%	67% (6/9)	46 wk
Carrion 2009	51	Case match	PEG IFNα2a 180 mcg/wk + RBV 800-1200 mg *od*	15 wk	Y	48% CTP A, 43% B	88% G1/4, 10% G2/3	NA	47		20		43%	49%	67% (10/15)	6 mo
Tekin *et al*[31]	20	Cohort	PEG IFNα2a 135 mcg/wk + RBV 1-1.2 g *od*	48 wk	N	30% CTP A, 70% B	All G1b	NA	45	-	30	-	40%	65%	33% (1/3)	14 mo

[1]Not published presented at American Association for the Study of Liver Diseases 2009. Substudy of Adult to Adult Living Donor Liver Transplant Study (A2ALL) low accelerated dose regime (LADR); [2]% hepatitis C virus (HCV) neg post LTx = Patient No. HCV neg post LTx/HCV neg at LTx (actual patient nos). GFs: Growth factors; CTP: Child Turcotte Pugh; MELD: Model for End Stage Liver Disease; Tx: Treatment; SVR: Sustained virological response; neg: negative; LTx: Liver transplant; FU: Follow up, mcg: Micrograms; IFN: Interferon; RBV: Ribavirin, *od*: Once daily; *bd*: Twice daily; Y: Yes; N: No NA: Not available.

virin, with a SVR of up to 50% depending on genotype. The trials reporting more favourable SVR often had restrictive entry criteria such as patients with clinical, biochemical or haematological evidence of decompensation being excluded. A further factor adding to the variation in SVR reported was the selection of patients who were treatment naïve or previous responders[16,32].

Overall nearly one third of patients stopped treatment due to side effects, and the remaining patients often required dose reduction to improve tolerability. The actual number of patients who were HCV RNA negative coming to transplant was small. Of the responders, up to 80% remained HCV RNA negative after transplant[22,23,26] but long-term follow up was limited. From the available data, in the selected few, AVT can render the patient HCV RNA negative post transplant but the long-term benefit has not yet been fully established to justify the cost and clinical risk.

Who to treat?

It is estimated that 93% of listed HCV patients have a MELD ⩽ 18, equivalent to CTP ⩽ 7 suggesting that the majority of listed patients have stable liver function and should tolerate AVT[16]. Recommendations of the International Liver Transplant Society consensus conference (ILTS) for the selection of HCV cirrhotic patients for IFN based treatment, is to consider therapy when MELD ⩽ 18/CTP ⩽ 7, to use selectively when MELD 18-25/CTP 8-11 and avoid when MELD > 25/CTP > 11[16], as High MELD/CTP have an unacceptable risk of complication[23,28,30].

HCV genotype may influence the severity of HCV recurrence. European centres have reported worse outcome in genotype 1b, which may be related to host immune re-

sponse[33] but this has not been verified in American studies. However, genotype is the major determinant of response to treatment. Genotypes 2 and 3 should be considered for treatment, whereas the benefit of treating genotype 1 has not been fully established.

Patients who are previous non responders to IFN and Ribavirin are not suitable as the likelihood of achieving undetectable HCV RNA is very low < 10%. Prior relapsers would be suitable for treatment as their response would be predicted to be high[34]. The ideal group for waiting list AVT are patients who are previous responders, are treatment naïve or low MELD/CTP. Typically these are patients with living donors, or have compensated cirrhosis and HCC. Living Donor Liver Transplant (LDLT) recipients typically have a lower MELD than patients with decompensated cirrhosis awaiting deceased donor liver transplantation (DDLT).

Treatment regimens

Cytopenia is more common and severe with PEG IFN compared to non PEG IFN and thus, has to be balanced against higher virological response rates observed with PEG IFN. A LADR has been recommended by ILTS, as it is thought to be better tolerated in the cirrhotic patient[16,23]. Starting doses of IFN α2b 1.5 million units three times a week, PEG IFN α2b 0.5 μg/kg per week or PEG IFN 2α 90 μg per week, all with ribavirin 600 mg/d have been recommended. The dose of ribavarin should be reduced in renal impairment. Close monitoring of haematological and biochemical parameters is required, with dose adjustments being made every two weeks to allow full dose treatment to be achieved as tolerated by the patient. Patients with no virological response after 12 wk should have therapy discontinued[26]. Estimated duration of treatment is 6 mo for genotype 2 and 3, and 12 mo for genotype 1[16]. Treating for one year may not be practicable and the best group to treat is those with low MELD scores (< 18) who would be more likely to complete the treatment. LDLT recipients are a perfect group to be treated as the transplant can be timed according to HCV RNA clearance. A minimum of 12 wk, but up to 24 wk prior to LDLT is recommended[16].

Haematological growth factors

IFN is associated with cytopenia though bone marrow suppression, whereas Ribavirin can cause anaemia by a combination of haemolysis and bone marrow suppression. Patients developing anemia during HCV therapy often have inappropriately poor serum erythropoietin responses probably related to their underlying liver disease[35]. Patients with cirrhosis receiving AVT have a high incidence of haematological side effects[30]. To try and counter this Granulocyte-Colony Stimulating Factor (G-CSF) and erythropoietin (EPO) analogues have been used to avoid antiviral dose reduction with the aim of maintaining a good virological response. Severe anemia develops in about 10% of treated patients, and requires close monitoring of hemoglobin and RBV dose reduction, which may compromise sustained virologic response[36]. The impact of haematological growth factors on avoiding complications or improving virological response has not been clearly demonstrated. Aggressive use of bone marrow analogues to allow continued AVT or to avoid a dose reduction has not translated into higher treatment success rates[28,37-39].

DONOR AND PERI-TRANSPLANT FACTORS

Donor age

Several donor factors have been identified that influence HCV recurrence, impacting on both graft and patient survival. Age has been the most widely studied. Berenguer *et al*[40]. identified donor age higher than 60 years as a risk factor for developing cirrhosis [HR = 1.02 (1.008-1.05)] and worse graft survival [HR = 1.05 (1.03-1.07)]. Other studies have demonstrated a relationship between accelerated fibrosis and poorer outcome in grafts from older donors[41,42]. Machicao *et al*[41] and Wali *et al*[42] reported that donors aged 50 years or more, had a median fibrosis progression rate of 2.7 units/year and time to cirrhosis of 2.2 years post transplant. In contrast, Samonakis *et al*[43] found that absence of maintenance steroids and azathioprine but not donor age influenced severity of HCV recurrence. Lake *et al*[44] analyzed data from the American Scientific Registry of Transplant Recipients, looking at the effect of donor age on the outcome of 778 hepatitis B, 3463 hepatitis C and 7429 non-viral recipients. Donor age was not a risk factor for HBV recipients, but was the strongest predictor for graft loss in HCV recipients. The risk was identifiable with donors > 40 years [HR = 1.67 (1.34-2.09); $P < 0.001$] and > 60 years [HR = 2.21 (1.73-2.81); $P < 0.001$]. Donor age was also a strong predictor for graft loss in non-viral recipients, although the age range was higher (> 60 years) and the statistical strength was lower than for HCV recipients [HR = 1.89 (1.61-2.23); $P < 0.001$]. Donor age (> 50 years) was also found to be a strong factor in determining the likelihood of AVT success as measured by SVR[45]. Although there are no clear data defining the donor age at risk of severe HCV recurrence, donors over 60-70 years are generally regarded as higher risk.

Donor graft steatosis

The influence of donor microvesicular steatosis on HCV recurrence is not addressed in the literature, possibly because it is regarded as a mild and reversible condition[46]. Nevertheless, a recent study has reported that microvesicular steatosis increased the risk of initial poor graft function (IPF) (OR = 1.38 per 1 SD = 9.3%; $P < 0.021$)[47] and work is required to establish if it influences HCV recurrence.

The adverse influence of donor macrovesicular steatosis on graft and patient outcome has been widely studied[48-50]. Two recent publications reported that macrosteatotic grafts were safe to use in HCV recipients. Botha *et*

al[51] found that recipients receiving mildly macrosteatotic grafts (< 15% in their classification) had a good outcome, although only 3 out of 113 donors had macrosteatosis greater 30%. Burra *et al*[52] reached the same conclusion, although they classified mild macrosteatosis as < 30% and only 5 patients in their series had macrosteatosis > 30%. The small number of macrosteatotic grafts assigned to HCV recipients in these series makes it difficult to draw firm conclusions. In contrast, Briceño *et al*[53] reported that donor graft macrosteatosis (> 30%) was a risk factor for more frequent, earlier and severe HCV recurrence post LTx. Their study had 29 recipients receiving a moderately (30%-60%) and 19 recipients receiving a severely (> 60%) steatotic graft, although lack of protocolized biopsies was a limitation to this study[54], they reported a clear relationship between donor graft steatosis > 30%, earlier viral recurrence and the development of a more severe graft fibrosis.

The significance of acquired post-LTx macrosteatosis and HCV recurrence is unclear. Baiocchi *et al*[55] in 1998 suggested that macrosteatosis was highly specific for HCV recurrence and sensitive in detecting HCV disease recurrence, at 3 and 12 mo, but with low specificity and not genotype-related. However, Machicao *et al*[56] found that macrosteatosis developing after LTx did not predict severity of HCV recurrence in the first 12 mo. The development of macrosteatosis is influenced by several factors, including body mass index (BMI), immunosuppression, alcohol and diabetes. When the factors behind macrosteatosis development in the LTx population are fully elucidated its relationship to HCV recurrence may become clearer.

Type of graft

Garcia-Retortillo *et al*[57] reported an analysis of 117 LTx in 116 HCV recipients, of which 22 were LDLT. Type of transplant was the only independent predictor of severe recurrence (OR = 2.5; 95%CI: 1.13-5.68; $P = 0.025$) and the 2-year probability of severe recurrence was higher in LDLT compared to DDLT (45% *vs* 22%, $P = 0.019$). Suggested mechanisms, to explain the more aggressive HCV recurrence observed after LDLT, included shared HLA matching, the type of immunosuppression, a higher incidence of biliary complications, and the effect of liver regeneration. However, a prospective controlled trial by Shiffman *et al*[58] using protocol liver biopsies in 23 LDLT and 53 DDLT found no association between graft type and HCV recurrence in terms of recipient and graft survival or fibrosis progression over 3 years. Guo *et al*[59] reported similar results from a retrospective study of 15 LDLT and 52 DDLT, with no difference in histological HCV recurrence rates or graft survival over 2 years. Similar short-term results have also been reported by Schmeding *et al*[60]. with first-year fibrosis rates and graft survival being similar between DDLT and LDLT.

Split liver transplantation shares with LDLT the issue of liver regeneration as a possible risk factor for HCV recurrence, but reported studies show no difference in histological recurrence of HCV or in survival between recipients of deceased donor whole and split livers[61,62]. These studies share the limitation that donors suitable for split grafts are usually younger than 40 years and this may be an important confounding factor.

A recent study from Selzner *et al*[63] on 46 LDLTs and 155 DDLTs followed up with protocol biopsies showed that the mean fibrosis stage (Metavir) was significantly higher at 12 to 48 mo post LTx, and the rate of fibrosis progression tended to be faster after DDLT than LDLT (0.19 *vs* 0.11 stage/year, $P < 0.05$). In multivariate analysis, donor age was the only variable independently associated with both surrogate outcomes. Thus, donor age > 45 years carried a relative risk of 8.17 (95%CI: 2.6-25.5, $P = 0.001$) for reaching fibrosis stage 3 or 4 at 2 years post LTx, suggesting that donor age rather than graft type determines progression of recurrent HCV.

HCV positive donors and co-infections

The increasing organ shortage has necessitated the use of both older and HCV+ organs. There are a small number of studies examining the use of HCV+ grafts. Donor Hepatitis C status does not seem to affect graft or recipient survival and using HCV+ livers for transplantation in HCV+ recipients seems to safely expand the organ donor pool[64]. Interestingly, a recent study has analyzed the effect of HCV+ donors stratified by age. Demonstrating a negative impact of older donor age (> 50 years) on survival and fibrosis progression in patients transplanted with HCV+ organs. According to the current evidence, using HCV+ grafts from young donors (< 50 years) for HCV recipients can produce good results, but further experience is required to establish the validity of this approach[65].

The influence of co-infections on HCV recurrence has been investigated by a number of groups. Humar *et al*[66] studied cytomegalovirus (CMV) and human herpesvirus-6 (HHV-6). No correlation was found between CMV or HHV-6 serum peak and HCV viral load. But on subgroup analysis HHV-6 infection was associated with the development of more severe recurrence (hepatitis and/or fibrosis score > 2). Also, fibrosis scores at last follow up were higher in patients with CMV disease or HHV-6 infection. Burak *et al*[67] have also identified CMV co-infection as a risk factor for graft failure and severe fibrosis on biopsy. Considering that CMV infection occurs in approximately one quarter of HCV-infected LTx recipients, CMV donor and recipient status may be an important modifiable factor to consider.

Duclos-Vallée *et al*[68] reported poorer survival of co-infected HIV/HCV patients (35 patients) than that of HCV mono-infected patients (44 patients). The 2 and 5 years survival rates were 73% and 51% in co-infected, and 91% and 81% in mono-infected patients, respectively. Additionally, fibrosis-free survival rates were markedly low in co-infected patients after the second year post-transplant, whereas the majority of mono-infected patients only experienced mild recurrent hepatitis. These

results are similar to our series, in which 5 of 7 HCV-infected patients died after LT at 95-784 d (median 161 d), of whom 4 patients died of recurrent HCV infection and sepsis, despite antiviral therapy in 3[69]. Longer follow-up in larger series is required before a conclusive directive can be provided for HCV/HIV co-infected patients requiring LT and the advent of more effective anti-viral therapy may transform the outlook for this group.

Ischemia-reperfusion injury

Ischemia-reperfusion injury (IRI) is a result of several peri-operative factors that can define the extended criteria donor. Factors influencing the severity of IRI include donor status (cardiac or brain death), cold and warm ischemia time, donor age, preservation solution and technical factors during retrieval. Other factors influencing IRI are type of reperfusion used and graft-related quality factors such as macrosteatosis. Because of the complexity of IRI, its inclusion in multivariate analysis usually becomes a confounding factor that is difficult to study. A study from Watt *et al*[70] showed worse survival outcome in HCV recipients receiving grafts with preservation injury (PI). The 1- and 3-year survival rates for these 2 groups were 78% and 59% in HCV-PI(+) versus 100% and 88% in HCV-PI(-). In addition, more patients in the PI(+) group had progressed to stage 3 or 4 fibrosis, compared to the group with no PI (-) (43% *vs* 9%, $P = 0.02$). In 2008, Killackey *et al*[71] reported a significant correlation between peak alanine transaminase (ALT) and the severity of IRI on reperfusion biopsy among 477 HCV recipients (of which 44 were LDLT). However, there was no correlation between the severity of IRI and the incidence or timing of histologic HCV recurrence or incidence of acute cellular rejection (ACR). Briceño *et al*[72] also looked at the effect of marginal donor variables on outcome in HCV recipients and IRI was a prognostic factor on univariate analysis. The same group additionally reported that, when moderate to severe IRI was associated with macrovesicular steatosis > 30%, graft survival was decreased[53]. This association has not been previously reported and deserves further study.

Immunological factors

The role of human leukocyte antigen (HLA) matching between donor and recipient in post-transplant rejection and survival has been widely studied. It has been proven to increase graft survival after kidney, heart, and other organ transplants In contrast, HLA matching is not routinely performed in LTx because its importance remains unclear. A recent meta-analysis of over 16 studies found that good HLA compatibility reduces the incidence of ACR but had no influence on graft outcomes[73].

Early acute rejection and steroid bolus treatment are considered as risk factors for HCV recurrence[74]. Langrehr *et al*[75] published a retrospective analysis on 165 LTx in HCV recipients with complete donor/recipient HLA typing, analyzing HCV recurrence and outcome. In this study it was shown that HLA matching reduced rejection episodes, but the severity of fibrosis progression within the first year after LTx was enhanced. Interestingly, this did not result in impaired survival in the better-matched grafts. Belli *et al*[76] reported on the association of MHC alleles and donor/recipient mismatch with the occurrence and the severity of recurrent HCV, drawing two conclusions. Firstly, a fully mismatched donor/recipient pair at the DRB1 locus was associated with HCV recurrence and severity. And secondly, donor age, full HLA-DRB1 donor-recipient mismatch, and HLA B14, were independent risk factors for the development of severe fibrosis.

Balan *et al*[77] studied HLA mismatch in a cohort of 883 LTx recipients. Overall graft survival decreased according to the total mismatch score and there was a negative effect of mismatching at the A locus on patient survival. Interestingly, there was a subgroup with DR-locus mismatch with increased recurrence of autoimmune hepatitis and primary biliary cirrhosis, while mismatch in the A locus was associated with recurrence of HCV ($P = 0.01$, HR = 1.6) and primary sclerosing cholangitis ($P = 0.03$, HR = 2.9). Yoshizawa *et al*[78] reported two cases of LDLT between identical twins. Despite the avoidance of immunosuppression, a rapid increase in serum HCV RNA and histological recurrence of HCV by 1 mo was observed. The contribution of HLA mismatch to HCV recurrence remains unclear and other immunological factors may be involved. To date, cytokine gene polymorphisms in allograft tumor-necrosis-factor β (TNF-β), Interleukin 16 (IL-16)[79], TGF-β, IL-10, and INF-γ[80] have been proposed as novel markers to predict the severity of HCV recurrence. The innate lymphocyte population of CD56+ lymphocytes, NK and NT cells provide an important first line of defense against viral infection. Rosen *et al*[81] showed that the number of CD56+ lymphocytes and NK cells in peripheral blood prior to LTx was significantly lower in recipients who developed severe HCV recurrence compared to those with mild histological recurrence. There was no association between NK and viral levels, suggesting that the severity of HCV recurrence is independent of viral level and high levels of CD56+ lymphocytes are protective against recurrence More work is required to confirm the genetic components that contribute to both NK cell-mediated control of HCV recurrence and to liver injury in the transplant setting[82,83].

Recent research emphasizes the important part that host genetics play in the ability to clear acute HCV infection and to achieve SVR. Polymorphism of the IL-28B gene, which encodes the endogenous antiviral cytokine IFN-λ, are associated with SVR and natural viral clearance[84]. The prevalence of the rs8099917 G allele in HCV/HIV-1 co-infected patients is strongly associated with treatment failure in HCV genotype 1-infected patients[85]. These polymorphisms may well serve, at least in the start, as a predictor of achieving SVR.

Diabetes mellitus

Diabetes and insulin resistance have been associated with progression of fibrosis[86]. Hyperinsulinemia may cause

direct stimulation of hepatic stellate cell mitogenesis and synthesis of collagen[87]. The synergy between donor age and recipient diabetes as a factor for aggressive HCV recurrence was observed by Foxton *et al*[88] who reported that patients with diabetes receiving a liver from a donor older than 55 years was associated with an 8.38-fold risk of progression to severe fibrosis.

In 2008, Hanouneh *et al*[89] performed an analysis on liver biopsies to assess the impact of metabolic syndrome (MS). Overall median rate of fibrosis progression was 0.08 units per month. On univariate analysis, high HCV RNA at 4 mo post LTx, diabetes, CMV, and MS were associated with progression of fibrosis, whereas on multivariate analysis, MS was independently associated with fibrosis progression 1 year after LTx [OR = 6.3 (1.4-28.7); P = 0.017].

More recently, Veldt *et al*[90] evaluated the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) to identify insulin-resistant recipients at risk for rapid fibrosis progression after LTx. They found that when this index was elevated (> 2.5) there was a risk for rapid fibrosis progression and treatment with insulin had no effect on the fibrosis progression rate, suggesting that there might be a role for treatment with insulin sensitizing agents.

The association between immunosuppression with tacrolimus, HCV and post-transplant diabetes or impaired fasting glucose has been reported[91]. The choice of immunosuppressive treatment might be decided on the basis of the patient's pretransplantation status.

POST-TRANSPLANT IMMUNOSUPPRESSION AND ANTIVIRAL TREATMENT

Anhepatic initiated therapy

Thymoglobulin induction: Thymoglobulin is an antithymocyte polyclonal antibody that depletes the T cell pool and can be used as an induction immunosuppressant agent during the anhepatic phase. By pre-treating with thymoglobulin and minimizing immunosuppression, cellular host immunity against HCV re-infection may be improved[92]. A retrospective study on the use of thymoglobulin induction found that lower levels of Tacrolimus were achieved but HCV recurrence rates were similar between patients who had received thymoglobulin induction therapy and tacrolimus versus tacrolimus and steroids. However, HCV RNA loads were significantly lower in the thymoglobulin group[93]. More work is required to see whether this observation is clinically significant and alters the pattern of HCV post transplant recurrence.

Adoptive immunotherapy: HCV viral levels post often exceed pre LTx, as immunosuppression suppresses the host response to HCV replication. Adoptive immunotherapy has been studied in a phase 1 trial where lymphocytes extracted from liver allograft perfusate were able to mount an anti HCV response. Activated liver allograft-derived NK cells were isolated from the perfusate (IL-2 stimulated and anti-CD3 monoclonal antibody treated to deplete T cells), and injected intravenously into the transplant recipient. Early data from the pilot study reported lower HCV RNA titers at one month post-transplant, but the effect was transient[94]. Augmentation of the NK cell response, which plays a pivotal role in innate immunity, may be an alternative approach to preventing HCV recurrence and is an area of active research[95].

Post-transplant immunosuppression

Immunosuppression is considered to be a major factor in accelerated HCV recurrence and has been an area of extensive research. The immunosuppression strategy in HCV LTx recipients was evaluated in 81 LTx programs in an international survey. The most common regimen used (41%) was based on triple therapy [Tacrolimus, Mycophenolate Mofetil (MMF) and steroids]. Steroid-free protocols were used by 7.4% of transplant groups, while 11% discontinued steroids within a week, 56% within three months and 98% within the first year[96].

Steroids: High dose steroid boluses to treat rejection increase viremia and may lead to premature HCV recurrence. It has been shown that HCV recurrence is associated with the number of rejection episodes[97]. Although the data on increased HCV viral load with steroid bolus is convincing, the effect of steroid maintenance remains controversial. Moreover, a rapid reduction in steroid dosage may be harmful for HCV recurrence[98]. Interestingly, Vivarelli *et al*[99] reported that it is the way that steroids are administered what impacts the recurrence; in fact while rapid steroids tapering and withdrawal exert a negative effect, low-dose steroid maintenance in the first 24 post-operative months seems to reduce the severity of HCV recurrence, in particular the degree of fibrosis associated with recurrent hepatitis.

The link between steroids and viral replication has prompted many centres to practice steroid withdrawal. However there is a lack of robust data showing the efficacy of this approach. A meta-analysis of 13 trials[100] showed that steroid avoidance was associated with lower HCV recurrence (RR = 0.90, P = 0.03), although no individual trial reached statistical significance. The heterogeneity, short-term follow-up and relatively small size of many of the trials, as well as the lack of information on steroid dosage, make conclusions less robust. Larger multicenter trials are required to clarify the influence of steroid-free regimens on HCV recurrence.

Calcineurin inhibitors: The association between oversuppression and HCV progressive disease is well recognized. However, the effect of different calcineurin inhibitors (CNIs) on HCV replication and/or progression of recurrent HCV remain controversial. Cyclosporine A (CsA) has been found to inhibit HCV replication *in vitro* while tacrolimus does not[101]. But the effect of CsA on

HCV replication *in vivo*, in the setting of LTx is not clear. A meta-analysis comparing tacrolimus to CsA-based immunosuppression in HCV recipients[102] assessed the clinical, virological, and histologic post-transplant outcomes. A total of 5 randomized control trials (1995-2006) which included 366 patients were analyzed. No significant differences in mortality, graft survival, biopsy proven ACR, steroid resistant ACR or fibrosing cholestatic hepatitis between the regimens was found. But the use of different immunosuppression regimens, an era-effect, and the lack of protocol liver biopsies limit this meta-analysis.

In the LIS2T trial, immunosuppression regimens based on CsA or tacrolimus were compared according to HCV status[103]. All patients received a combination of either CsA (n = 250) or tacrolimus (n = 245) with steroids and some additionally received azathioprine (AZA). The incidence of ACR was similar in patients receiving combination therapy with AZA, whether with CsA or tacrolimus, independent of the HCV status. In HCV patients, death or graft loss was higher with tacrolimus (16%) compared to CsA (6%) ($P < 0.03$). The HCV recurrence rate was similar for tacrolimus and CsA but time to histological diagnosis of recurrence was longer with CsA than with tacrolimus (100 ± 50 d *vs* 70 ± 40 d; $P < 0.05$).

On the basis of current data, it is not possible to conclude that CsA by itself has a significant effect on viral replication or on the course of HCV recurrence. However, choice of CNI may influence the efficacy of AVT. As co-treatment with IFN and CsA has been shown to achieve greater inhibition of HCV replication and higher SVR rates compared to IFN alone[104]. Furthermore, SVR after IFN therapy has been found to be higher with CsA compared to tacrolimus (46% *vs* 27%; $P = 0.03$)[105]. In a pilot study[106], 38 patients with HCV recurrence receiving PEG IFN α2a and Ribavirin were randomized to continue tacrolimus or to be switched to CsA. CsA led to a modest decrease in HCV RNA levels and appeared to enhance the antiviral response to IFN and Ribavirin, but there was no difference in SVR. However this study was limited by small sample size and randomization at transplant rather than at time of significant HCV recurrence. Further randomized trials are needed to establish whether the presently available CNIs affect HCV recurrence.

Post-transplant antiviral treatment

Prophylactic therapy: Treatment with neutralizing antibodies is effective in patients transplanted for HBV, but currently there is no evidence that this strategy is effective in preventing HCV recurrence. Both polyclonal and monoclonal anti-envelope antibodies can capture and neutralize HCV in vitro[107-109]. The main target for neutralizing antibodies appears to be the various epitopes in the E2 envelope glycoprotein. HCV antibody therapy starts in the anhepatic phase and then is continued for 12 to 14 wk after transplant. Three trials[110-112] comparing high dose HCV antibody vs. low dose HCV antibody were included in a Cochrane meta-analysis[113]. There was no difference in patient and graft survival, virological response or fibrosis on histology. Discontinuation of therapy occurred in up to 35% of patients with high dose antibody and 17% with low dose antibody. Considering both the lack of clinical benefit and occurrence of side effects, there is currently no evidence to recommend prophylactic HCV antibody.

Pre-emptive therapy: Antiviral therapy after transplantation but before clinical evidence of reinfection. HCV recurrence manifests in the first 6 mo post LTx. Initiation of AVT in the early post transplant period has been proposed as a potentially more effective way of preventing it. Pre-emptive therapy refers to the initiation of AVT within 2 to 8 wk after LTx when the viral load is low and histological damage is absent[114]. However, only those patients who are well after transplant and without severe complications can receive AVT. In the general population, AVT with PEG IFN for acute HCV hepatitis can achieve high SVR rates, but in transplant patients the rate is lower at 8%-39%. The high levels of immunosuppression early post LTx make AVT less effective and dose reduction or discontinuation due to adverse events is common (up to 57% of cases)[114].

Several trials have assessed the efficacy of the pre-emptive AVT. IFN, PEG IFN and Ribavirin, alone or in combination. At present, there is no standard timing of commencement of pre-emptive treatment. It has been applied very early post LTx (as soon as patients can tolerate food), to 4-6 wk after transplant. A meta-analysis which included randomized trials assessing the use of pre-emptive AVT showed no benefit in terms of survival, graft rejection, virological response or histological changes. The proportion of patients who discontinued treatment was 31% for PEG IFN, 29% for IFN and 9% for Ribavirin. Currently, there is no evidence to recommend pre-emptive AVT to prevent HCV re-infection.

Antiviral therapy after evidence of reinfection: Directed AVT after evidence of HCV recurrence represents the mainstay of management in HCV post transplant. Most LTx centers commence AVT once liver biopsy demonstrates significant histological damage and therapy with PEG IFN and Ribavirin aims to achieve SVR as this has been associated with improved survival, reduced risk of graft failure and reduced risk of developing complications.

The therapeutic efficacy and side effects of different AVT in patients with HCV re-infected grafts have been compared in a Cochrane review[115]. Eleven trials including 389 LTx were analyzed. Dose reduction or discontinuation due to adverse effects or patient choice, was required in 87.5% and 42.9% respectively. All the trials had high-risk bias and none of them reported decompensation rates or quality of life. The antiviral regimens and dosages, the interval between the LTx and the beginning of the treatment and the duration of the therapy were heterogeneous in all trials. There was no difference in the mortality, graft rejection or re-transplantation between

the intervention and control arms. Nevertheless, a higher SVR (48% *vs* 0%) and improvement in fibrosis occurred in the treatment group of PEG IFN and ribavarin[116]. In the comparison between two doses of PEG IFN (1.5 mg/kg per week *vs* 0.5 mg/kg per week) plus ribavirin, higher rates of SVR were achieved in the high-dose group (63% *vs* 22%). Despite there being no difference in the main outcomes, SVR has been shown to reduce mortality rates in observational studies and it is worthwhile performing further studies to assess this.

Data evaluating the effect of AVT on disease progression are scarce and results are controversial. However, it has been demonstrated that AVT with PEG IFN and ribavirin achieves higher SVR rates in mild HCV recurrence than in severe HCV recurrence[116]. AVT tolerability is a major issue as only 30% of transplant patients reach target dose and duration. Dose reduction of PEG IFN and ribavirin are needed in 39% and 45% respectively, with discontinuation of treatment in 26%. Close monitoring is required and growth factors help to avoid dose reduction/discontinuation due to cytopenia.

A recent study attempted to determine the most cost effective timing for AVT (PEG IFN and ribavirin) in advanced liver disease infected with HCV genotype 1 and concluded that treatment of patients with compensated cirrhosis was the most cost effective[117]. Four different treatment strategies in a hypothetical cohort of 4000, 55 years old, treatment naïve cirrhotics with a 17 year follow-up, were analyzed in a Markov model. The authors concluded that treatment of advanced post LTx recurrence is more cost-effective than no treatment, but it gave less survival benefit at greater cost in comparison with patients treated during compensated cirrhosis.

New drugs for HCV recurrence treatment

In view of the current results of standard antiviral therapy, there is a need to improve treatment strategies. The recent knowledge of the HCV life cycle and of structural features of the HCV proteins has supported the development of many promising directly acting antiviral agents, or "specifically targeted anti-viral therapy for hepatitis C" (STAT-C) compounds. Many of these STATs are currently in phase I -Ⅲ development and will significantly change treatment options for HCV infection in the near future.

Compounds targeting HCV polyprotein procession: ns3/4a protease inhibitors: These compounds provide a high anti-viral efficacy but a low genetic barrier to resistance. However, the frequency of resistance development can be reduced by the additional administration of peg-IFN and Ribavirin. Many of these compounds are under development, however telaprevir (VX-950) and boceprevir (SCH 503034) which are the most advanced HCV NS3 protease inhibitors, have already entered phase-Ⅲ clinical development and are expected to be approved in 2011/2012[118]. Most protease inhibitors and polymerase inhibitors are HCV genotype 1 specific. The PROVE 3 trial[119] has shown that telaprevir is highly effective in the treatment of HCV genotype-1 nonresponders or relapsers. In contrast, addition of boceprevir to standard treatment only revealed a minor impact on SVR rates in non-responders, but further trials are awaited. In addition to telaprevir and boceprevir, many NS3/4A inhibitors with promising anti-viral activities are currently investigated in phase I and II trials.

Compounds targeting HCV replication: (1) HCV NS5B polymerase inhibitors. Nucleoside analogue inhibitors (NIs) [valopicitabine (NM283), R7128, R1626, PSI-7851 or DX184]. Since these compounds can mimic the natural substrates of the polymerase, they are incorporated into the growing RNA chain and tackle the active site of NS5B, then causing direct chain termination. NIs are potentially effective against different genotypes, in contrast to NS3⁄4A inhibitors. There is a relatively high genetic barrier in the development of resistances to NIs. Valopicitabine was the first NI investigated in patients with chronic hepatitis C, but its activity was low. More effective NIs are under development; (2) Non-nucleoside analogues inhibitors (NNIs). These drugs can bind to different allosteric enzyme sites, which results in conformational protein change before the elongation complex is formed. Their application results more frequently in resistance development compared to Nis; and (3) NS5A/NS4B inhibitors. NS4B displays RNA-binding properties that are crucial in HCV-RNA replication. In vitro inhibition of NS4B has been shown to compromise HCV replication significantly. NS5A protein contributes in the regulation of HCV replication[120]. No clinical data on resistance to these compounds have been reported, and thus, results studies using multiple dose and combination therapy have to be awaited.

Conclusion and keypoints

HCV recurrence is a major concern when transplanting HCV+ patients. Several strategies to try and prevent graft infection or, if already infected, to reduce recurrence severity are available.

In the pre-transplant setting, AVT aims to achieve HCV RNA negativity at time of transplant. Presently available antivirals can produce HCV RNA negativity in highly selected patients and undetectable HCV RNA or SVR at time of transplant may influence recurrent HCV.

Probably, the most important strategy in the peri-transplant, especially in an era of organ shortage, is ideal donor-to-recipient matching. Factors like donor age, donor steatosis, recipient co-infections and recipient insulin resistance increase the risk of HCV recurrence and decrease global outcome. Interestingly, the type of graft or using young HCV+ donors does not appear to increase the risk. The role of IRI and HLA mismatch needs to be explored more, although available evidence supports the minimization of both.

In the post-transplant setting, there is no evidence for the use of HCV antibody therapy and adoptive im-

munotherapy is still experimental. Steroid boluses and ACR are factors associated with recurrence, and steroid free immunosuppression maintenance appears to reduce recurrence. Presently available CNIs appear to have equivalent influence on HCV recurrence but CsA in combination with AVT may produce a greater inhibition of HCV replication. Directed AVT after histological evidence of HCV recurrence is the mainstay of management, with no evidence supporting pre-emptive AVT. In the future it is strictly necessary to find out whether SVR can be achieved by combination therapies of different STAT-C compounds without PEG IFN and ribavirin. Future clinical trials need to address whether a long-term suppression of HCV replication or even SVR can be achieved with such direct antiviral combination therapies. The results of LTx for HCV will hopefully continue to improve as a greater understanding of the factors influencing recurrence is achieved.

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REFERENCES

1 **Lauer GM**, Walker BD. Hepatitis C virus infection. *N Engl J Med* 2001; **345**: 41-52 [PMID: 11439948 DOI: 10.1056/NEJM200107053450107]
2 **Neumann UP**, Berg T, Bahra M, Puhl G, Guckelberger O, Langrehr JM, Neuhaus P. Long-term outcome of liver transplants for chronic hepatitis C: a 10-year follow-up. *Transplantation* 2004; **77**: 226-231 [PMID: 14742986 DOI: 10.1002/lt.21644]
3 **Ramírez S**, Pérez-Del-Pulgar S, Forns X. Virology and pathogenesis of hepatitis C virus recurrence. *Liver Transpl* 2008; **14** Suppl 2: S27-S35 [PMID: 18825723]
4 **Llado L**, Castellote J, Figueras J. Is retransplantation an option for recurrent hepatitis C cirrhosis after liver transplantation? *J Hepatol* 2005; **42**: 468-472 [PMID: 15763328 DOI: 10.1016/j.jhep.2005.01.014]
5 **Pelletier SJ**, Iezzoni JC, Crabtree TD, Hahn YS, Sawyer RG, Pruett TL. Prediction of liver allograft fibrosis after transplantation for hepatitis C virus: persistent elevation of serum transaminase levels versus necroinflammatory activity. *Liver Transpl* 2000; **6**: 44-53 [PMID: 10648577 DOI: 10.1016/S1527-6465(00)80032-5]
6 **Gane EJ**, Portmann BC, Naoumov NV, Smith HM, Underhill JA, Donaldson PT, Maertens G, Williams R. Long-term outcome of hepatitis C infection after liver transplantation. *N Engl J Med* 1996; **334**: 815-820 [PMID: 8596547 DOI: 10.1056/NEJM199603283341302]
7 **Carrión JA**, Navasa M, Bosch J, Bruguera M, Gilabert R, Forns X. Transient elastography for diagnosis of advanced fibrosis and portal hypertension in patients with hepatitis C recurrence after liver transplantation. *Liver Transpl* 2006; **12**: 1791-1798 [PMID: 16823833 DOI: 10.1002/lt.20857]
8 **Ballardini G**, De Raffele E, Groff P, Bioulac-Sage P, Grassi A, Ghetti S, Susca M, Strazzabosco M, Bellusci R, Iemmolo RM, Grazi G, Zauli D, Cavallari A, Bianchi FB. Timing of reinfection and mechanisms of hepatocellular damage in transplanted hepatitis C virus-reinfected liver. *Liver Transpl* 2002; **8**: 10-20 [PMID: 11799480 DOI: 10.1053/jlts.2002.30141]
9 **Gane EJ**, Naoumov NV, Qian KP, Mondelli MU, Maertens G, Portmann BC, Lau JY, Williams R. A longitudinal analysis of hepatitis C virus replication following liver transplantation. *Gastroenterology* 1996; **110**: 167-177 [PMID: 8536853 DOI: 10.1053/gast.1996.v110.pm8536853]
10 **Gane EJ**. The natural history of recurrent hepatitis C and what influences this. *Liver Transpl* 2008; **14** Suppl 2: S36-S44 [PMID: 18825724 DOI: 10.1002/lt.21646]
11 **Sánchez-Fueyo A**, Restrepo JC, Quintó L, Bruguera M, Grande L, Sánchez-Tapias JM, Rodés J, Rimola A. Impact of the recurrence of hepatitis C virus infection after liver transplantation on the long-term viability of the graft. *Transplantation* 2002; **73**: 56-63 [PMID: 11792978 DOI: 10.1097/00007890-200201150-00010]
12 **Berenguer M**, Prieto M, Rayón JM, Mora J, Pastor M, Ortiz V, Carrasco D, San Juan F, Burgueño MD, Mir J, Berenguer J. Natural history of clinically compensated hepatitis C virus-related graft cirrhosis after liver transplantation. *Hepatology* 2000; **32**: 852-858 [PMID: 11003634 DOI: 10.1053/jhep.2000.17924]
13 **Charlton M**. Natural history of hepatitis C and outcomes following liver transplantation. *Clin Liver Dis* 2003; **7**: 585-602 [PMID: 14509528 DOI: 10.1016/S1089-3261(03)00046-1]
14 **Terrault NA**, Berenguer M. Treating hepatitis C infection in liver transplant recipients. *Liver Transpl* 2006; **12**: 1192-1204 [PMID: 16868944 DOI: 10.1002/lt.20865]
15 **Charlton M**, Seaberg E, Wiesner R, Everhart J, Zetterman R, Lake J, Detre K, Hoofnagle J. Predictors of patient and graft survival following liver transplantation for hepatitis C. *Hepatology* 1998; **28**: 823-830 [PMID: 9731579 DOI: 10.1002/hep.510280333]
16 **Wiesner RH**, Sorrell M, Villamil F. Report of the first International Liver Transplantation Society expert panel consensus conference on liver transplantation and hepatitis C. *Liver Transpl* 2003; **9**: S1-S9 [PMID: 14586888 DOI: 10.1053/jlts.2003.50268]
17 **Roche B**, Samuel D. Antiviral therapy in HCV-infected cirrhotics awaiting liver transplantation: A costly strategy for mixed virological results. *J Hepatol* 2009; **50**: 652-654 [PMID: 19231019 DOI: 10.1016/j.jhep.2009.01.008]
18 **Heathcote EJ**, Shiffman ML, Cooksley WG, Dusheiko GM, Lee SS, Balart L, Reindollar R, Reddy RK, Wright TL, Lin A, Hoffman J, De Pamphilis J. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. *N Engl J Med* 2000; **343**: 1673-1680 [PMID: 11106716 DOI: 10.1056/NEJM200012073432302]
19 **Manns MP**, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358**: 958-965 [PMID: 11583749 DOI: 10.1016/S0140-6736(01)06102-5]
20 **Wright TL**. Treatment of patients with hepatitis C and cirrhosis. *Hepatology* 2002; **36**: S185-S194 [PMID: 12407593 DOI: 10.1053/jhep.2002.36812]
21 **Abergel A**, Hezode C, Leroy V, Barange K, Bronowicki JP, Tran A, Alric L, Castera L, Bernard PH, Henquell C, Lafeuille H, Ughetto S, Darcha C, Chevallier M, Martineau N, Dubost S, Randl K, Dhumeaux D, Bommelaer G, Bonny C. Peginterferon alpha-2b plus ribavirin for treatment of chronic hepatitis C with severe fibrosis: a multicentre randomized controlled trial comparing two doses of peginterferon alpha-2b. *J Viral Hepat* 2006; **13**: 811-820 [PMID: 17109680 DOI: 10.1111/j.1365-2893.2006.00768.x]
22 **Forns X**, García-Retortillo M, Serrano T, Feliu A, Suarez F, de la Mata M, García-Valdecasas JC, Navasa M, Rimola A, Rodés J. Antiviral therapy of patients with decompensated cirrhosis to prevent recurrence of hepatitis C after liver

transplantation. *J Hepatol* 2003; **39**: 389-396 [PMID: 12927925 DOI: 10.1016/S0168-8278(03)00310-6]
23 **Everson GT**, Trotter J, Forman L, Kugelmas M, Halprin A, Fey B, Ray C. Treatment of advanced hepatitis C with a low accelerating dosage regimen of antiviral therapy. *Hepatology* 2005; **42**: 255-262 [PMID: 16025497 DOI: 10.1002/hep.20793]
24 **Iacobellis A**, Siciliano M, Perri F, Annicchiarico BE, Leandro G, Caruso N, Accadia L, Bombardieri G, Andriulli A. Peginterferon alfa-2b and ribavirin in patients with hepatitis C virus and decompensated cirrhosis: a controlled study. *J Hepatol* 2007; **46**: 206-212 [PMID: 17125876 DOI: 10.1016/j.jhep.2006.08.020]
25 **Di Marco V**, Almasio PL, Ferraro D, Calvaruso V, Alaimo G, Peralta S, Di Stefano R, Craxì A. Peg-interferon alone or combined with ribavirin in HCV cirrhosis with portal hypertension: a randomized controlled trial. *J Hepatol* 2007; **47**: 484-491 [PMID: 17692985 DOI: 10.1016/j.jhep.2007.04.020]
26 **Carrión JA**, Martínez-Bauer E, Crespo G, Ramírez S, Pérez-del-Pulgar S, García-Valdecasas JC, Navasa M, Forns X. Antiviral therapy increases the risk of bacterial infections in HCV-infected cirrhotic patients awaiting liver transplantation: A retrospective study. *J Hepatol* 2009; **50**: 719-728 [PMID: 19217183 DOI: 10.1016/j.jhep.2008.11.015]
27 **Thomas RM**, Brems JJ, Guzman-Hartman G, Yong S, Cavaliere P, Van Thiel DH. Infection with chronic hepatitis C virus and liver transplantation: a role for interferon therapy before transplantation. *Liver Transpl* 2003; **9**: 905-915 [PMID: 12942451 DOI: 10.1053/jlts.2003.50166]
28 **Massoumi H**, Elsiesy H, Khaitova V, Peterson B, Norkus E, Grewal P, Liu L, Chang C, Bach N, Schiano TD. An escalating dose regimen of pegylated interferon and ribavirin in HCV cirrhotic patients referred for liver transplant. *Transplantation* 2009; **88**: 729-735 [PMID: 19741473 DOI: 10.1097/TP.0b013e3181b2e0d1]
29 **Helbling B**, Jochum W, Stamenic I, Knöpfli M, Cerny A, Borovicka J, Gonvers JJ, Wilhelmi M, Dinges S, Müllhaupt B, Esteban A, Meyer-Wyss B, Renner EL. HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon alpha-2a and ribavirin. *J Viral Hepat* 2006; **13**: 762-769 [PMID: 17052276 DOI: 10.1111/j.1365-2893.2006.00753.x]
30 **Crippin JS**, McCashland T, Terrault N, Sheiner P, Charlton MR. A pilot study of the tolerability and efficacy of antiviral therapy in hepatitis C virus-infected patients awaiting liver transplantation. *Liver Transpl* 2002; **8**: 350-355 [PMID: 11965579 DOI: 10.1053/jlts.2002.31748]
31 **Tekin F**, Gunsar F, Karasu Z, Akarca U, Ersoz G. Safety, tolerability, and efficacy of pegylated-interferon alfa-2a plus ribavirin in HCV-related decompensated cirrhotics. *Aliment Pharmacol Ther* 2008; **27**: 1081-1085 [PMID: 18346186 DOI: 10.1111/j.1365-2036.2008.03680.x]
32 **Hadziyannis SJ**, Sette H, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; **140**: 346-355 [PMID: 14996676]
33 **Féray C**, Caccamo L, Alexander GJ, Ducot B, Gugenheim J, Casanovas T, Loinaz C, Gigou M, Burra P, Barkholt L, Esteban R, Bizollon T, Lerut J, Minello-Franza A, Bernard PH, Nachbaur K, Botta-Fridlund D, Bismuth H, Schalm SW, Samuel D. European collaborative study on factors influencing outcome after liver transplantation for hepatitis C. European Concerted Action on Viral Hepatitis (EUROHEP) Group. *Gastroenterology* 1999; **117**: 619-625 [PMID: 10464137 DOI: 10.1016/S0016-5085(99)70454-3]
34 **Terrault NA**. Hepatitis C therapy before and after liver transplantation. *Liver Transpl* 2008; **14** Suppl 2: S58-S66 [PMID: 18825697 DOI: 10.1002/lt.21624]
35 **Gogu SR**, Beckman BS, Wilson RB, Agrawal KC. Inhibitory effects of zidovudine in erythroid progenitor cells. Reversal with a combination of erythropoietin and interleukin-3. *Biochem Pharmacol* 1995; **50**: 413-419 [PMID: 7646543 DOI: 10.1016/0006-2952(95)00134-L]
36 **Russmann S**, Grattagliano I, Portincasa P, Palmieri VO, Palasciano G. Ribavirin-induced anemia: mechanisms, risk factors and related targets for future research. *Curr Med Chem* 2006; **13**: 3351-3357 [PMID: 17168855 DOI: 10.2174/092986706778773059]
37 **Afdhal NH**, Dieterich DT, Pockros PJ, Schiff ER, Shiffman ML, Sulkowski MS, Wright T, Younossi Z, Goon BL, Tang KL, Bowers PJ. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. *Gastroenterology* 2004; **126**: 1302-1311 [PMID: 15131791 DOI: 10.1053/j.gastro.2004.01.027]
38 **Del Rio RA**, Post AB, Singer ME. Cost-effectiveness of hematologic growth factors for anemia occurring during hepatitis C combination therapy. *Hepatology* 2006; **44**: 1598-1606 [PMID: 17133490 DOI: 10.1002/hep.21409]
39 **Soza A**, Everhart JE, Ghany MG, Doo E, Heller T, Promrat K, Park Y, Liang TJ, Hoofnagle JH. Neutropenia during combination therapy of interferon alfa and ribavirin for chronic hepatitis C. *Hepatology* 2002; **36**: 1273-1279 [PMID: 12395340 DOI: 10.1053/jhep.2002.36502]
40 **Berenguer M**, Prieto M, San Juan F, Rayón JM, Martinez F, Carrasco D, Moya A, Orbis F, Mir J, Berenguer J. Contribution of donor age to the recent decrease in patient survival among HCV-infected liver transplant recipients. *Hepatology* 2002; **36**: 202-210 [PMID: 12085366 DOI: 10.1053/jhep.2002.33993]
41 **Machicao VI**, Bonatti H, Krishna M, Aqel BA, Lukens FJ, Nguyen JH, Rosser BG, Satyanarayana R, Grewal HP, Hewitt WR, Harnois DM, Crook JE, Steers JL, Dickson RC. Donor age affects fibrosis progression and graft survival after liver transplantation for hepatitis C. *Transplantation* 2004; **77**: 84-92 [PMID: 14724440 DOI: 10.1097/01.TP.0000095896.07048.BB]
42 **Wali M**, Harrison RF, Gow PJ, Mutimer D. Advancing donor liver age and rapid fibrosis progression following transplantation for hepatitis C. *Gut* 2002; **51**: 248-252 [PMID: 12117889 DOI: 10.1136/gut.51.2.248]
43 **Samonakis DN**, Triantos CK, Thalheimer U, Quaglia A, Leandro G, Teixeira R, Papatheodoridis GV, Sabin CA, Rolando N, Davies S, Dhillon AP, Griffiths P, Emery V, Patch DW, Davidson BR, Rolles K, Burroughs AK. Immunosuppression and donor age with respect to severity of HCV recurrence after liver transplantation. *Liver Transpl* 2005; **11**: 386-395 [PMID: 15776454 DOI: 10.1002/lt.20344]
44 **Lake JR**, Shorr JS, Steffen BJ, Chu AH, Gordon RD, Wiesner RH. Differential effects of donor age in liver transplant recipients infected with hepatitis B, hepatitis C and without viral hepatitis. *Am J Transplant* 2005; **5**: 549-557 [PMID: 15707410 DOI: 10.1111/j.1600-6143.2005.00741.x]
45 **Berenguer M**, Aguilera V, Prieto M, Ortiz C, Rodríguez M, Gentili F, Risalde B, Rubin A, Cañada R, Palau A, Rayón JM. Worse recent efficacy of antiviral therapy in liver transplant recipients with recurrent hepatitis C: impact of donor age and baseline cirrhosis. *Liver Transpl* 2009; **15**: 738-746 [PMID: 19562707 DOI: 10.1002/lt.21707]
46 **Fishbein TM**, Fiel MI, Emre S, Cubukcu O, Guy SR, Schwartz ME, Miller CM, Sheiner PA. Use of livers with microvesicular fat safely expands the donor pool. *Transplantation* 1997; **64**: 248-251 [PMID: 9256182 DOI: 10.1097/00007890-199707270-00012]
47 **Cieślak B**, Lewandowski Z, Urban M, Ziarkiewicz-Wróblewska B, Krawczyk M. Microvesicular liver graft steatosis as a risk factor of initial poor function in relation to suboptimal donor parameters. *Transplant Proc* 2009; **41**: 2985-2988 [PMID: 19857657 DOI: 10.1016/j.transproceed.2009.08.019]
48 **Verran D**, Kusyk T, Painter D, Fisher J, Koorey D, Strasser S,

Stewart G, McCaughan G. Clinical experience gained from the use of 120 steatotic donor livers for orthotopic liver transplantation. *Liver Transpl* 2003; **9**: 500-505 [PMID: 12740794 DOI: 10.1053/jlts.2003.50099]

49 **Briceño J**, Padillo J, Rufián S, Solórzano G, Pera C. Assignment of steatotic livers by the Mayo model for end-stage liver disease. *Transpl Int* 2005; **18**: 577-583 [PMID: 15819807 DOI: 10.1111/j.1432-2277.2005.00091.x]

50 **Adinolfi LE**, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology* 2001; **33**: 1358-1364 [PMID: 11391523 DOI: 10.1053/jhep.2001.24432]

51 **Botha JF**, Thompson E, Gilroy R, Grant WJ, Mukherjee S, Lyden ER, Fox IJ, Sudan DL, Shaw BW, Langnas AN. Mild donor liver steatosis has no impact on hepatitis C virus fibrosis progression following liver transplantation. *Liver Int* 2007; **27**: 758-763 [PMID: 17617118 DOI: 10.1111/j.1478-3231.2007.01490.x]

52 **Burra P**, Loreno M, Russo FP, Germani G, Galligioni A, Senzolo M, Cillo U, Zanus G, Fagiuoli S, Rugge M. Donor livers with steatosis are safe to use in hepatitis C virus-positive recipients. *Liver Transpl* 2009; **15**: 619-628 [PMID: 19479805 DOI: 10.1002/lt.21761]

53 **Briceño J**, Ciria R, Pleguezuelo M, de la Mata M, Muntané J, Naranjo A, Sánchez-Hidalgo J, Marchal T, Rufián S, López-Cillero P. Impact of donor graft steatosis on overall outcome and viral recurrence after liver transplantation for hepatitis C virus cirrhosis. *Liver Transpl* 2009; **15**: 37-48 [PMID: 19109846 DOI: 10.1002/lt.21566]

54 **Yilmaz N**, Shiffman ML. Impact of the donor liver with steatosis in patients with hepatitis C virus: not so FAst. *Liver Transpl* 2009; **15**: 4-6 [PMID: 19109836 DOI: 10.1002/lt.21661]

55 **Baiocchi L**, Tisone G, Palmieri G, Rapicetta M, Pisani F, Orlando G, Casciani CU, Angelico M. Hepatic steatosis: a specific sign of hepatitis C reinfection after liver transplantation. *Liver Transpl Surg* 1998; **4**: 441-447 [PMID: 9791153 DOI: 10.1002/lt.500040613]

56 **Machicao VI**, Krishna M, Bonatti H, Aqel BA, Nguyen JH, Weigand SD, Rosser BG, Hughes C, Dickson RC. Hepatitis C recurrence is not associated with allograft steatosis within the first year after liver transplantation. *Liver Transpl* 2004; **10**: 599-606 [PMID: 15108251 DOI: 10.1002/lt.20107]

57 **Garcia-Retortillo M**, Forns X, Llovet JM, Navasa M, Feliu A, Massaguer A, Bruguera M, Fuster J, Garcia-Valdecasas JC, Rimola A. Hepatitis C recurrence is more severe after living donor compared to cadaveric liver transplantation. *Hepatology* 2004; **40**: 699-707 [PMID: 15349910 DOI: 10.1002/hep.20357]

58 **Shiffman ML**, Stravitz RT, Contos MJ, Mills AS, Sterling RK, Luketic VA, Sanyal AJ, Cotterell A, Maluf D, Posner MP, Fisher RA. Histologic recurrence of chronic hepatitis C virus in patients after living donor and deceased donor liver transplantation. *Liver Transpl* 2004; **10**: 1248-1255 [PMID: 15376308 DOI: 10.1002/lt.20232]

59 **Guo L**, Orrego M, Rodriguez-Luna H, Balan V, Byrne T, Chopra K, Douglas DD, Harrison E, Moss A, Reddy KS, Williams JW, Rakela J, Mulligan D, Vargas HE. Living donor liver transplantation for hepatitis C-related cirrhosis: no difference in histological recurrence when compared to deceased donor liver transplantation recipients. *Liver Transpl* 2006; **12**: 560-565 [PMID: 16555313 DOI: 10.1002/lt.20660]

60 **Schmeding M**, Neumann UP, Puhl G, Bahra M, Neuhaus R, Neuhaus P. Hepatitis C recurrence and fibrosis progression are not increased after living donor liver transplantation: a single-center study of 289 patients. *Liver Transpl* 2007; **13**: 687-692 [PMID: 17457911 DOI: 10.1002/lt.21138]

61 **Humar A**, Horn K, Kalis A, Glessing B, Payne WD, Lake J. Living donor and split-liver transplants in hepatitis C recipients: does liver regeneration increase the risk for recurrence? *Am J Transplant* 2005; **5**: 399-405 [PMID: 15644001 DOI: 10.1111/j.1600-6143.2004.00704.x]

62 **Lawal A**, Ghobrial R, Te H, Artinian L, Eastwood D, Schiano TD. Comparison of hepatitis C histological recurrence rates and patient survival between split and deceased donor liver transplantation. *Transplant Proc* 2007; **39**: 3261-3265 [PMID: 18089367 DOI: 10.1016/j.transproceed.2007.08.106]

63 **Selzner N**, Girgrah N, Lilly L, Guindi M, Selzner M, Therapondos G, Adeyi O, McGilvray I, Cattral M, Greig PD, Grant D, Levy G, Renner EL. The difference in the fibrosis progression of recurrent hepatitis C after live donor liver transplantation versus deceased donor liver transplantation is attributable to the difference in donor age. *Liver Transpl* 2008; **14**: 1778-1786 [PMID: 19025914 DOI: 10.1002/lt.21598]

64 **Marroquin CE**, Marino G, Kuo PC, Plotkin JS, Rustgi VK, Lu AD, Edwards E, Taranto S, Johnson LB. Transplantation of hepatitis C-positive livers in hepatitis C-positive patients is equivalent to transplanting hepatitis C-negative livers. *Liver Transpl* 2001; **7**: 762-768 [PMID: 11552208 DOI: 10.1053/jlts.2001.27088]

65 **Khapra AP**, Agarwal K, Fiel MI, Kontorinis N, Hossain S, Emre S, Schiano TD. Impact of donor age on survival and fibrosis progression in patients with hepatitis C undergoing liver transplantation using HCV+ allografts. *Liver Transpl* 2006; **12**: 1496-1503 [PMID: 16964597 DOI: 10.1002/lt.20849]

66 **Humar A**, Kumar D, Raboud J, Caliendo AM, Moussa G, Levy G, Mazzulli T. Interactions between cytomegalovirus, human herpesvirus-6, and the recurrence of hepatitis C after liver transplantation. *Am J Transplant* 2002; **2**: 461-466 [PMID: 12123213 DOI: 10.1034/j.1600-6143.2002.20511.x]

67 **Burak KW**, Kremers WK, Batts KP, Wiesner RH, Rosen CB, Razonable RR, Paya CV, Charlton MR. Impact of cytomegalovirus infection, year of transplantation, and donor age on outcomes after liver transplantation for hepatitis C. *Liver Transpl* 2002; **8**: 362-369 [PMID: 11965581 DOI: 10.1053/jlts.2002.32282]

68 **Duclos-Vallée JC**, Féray C, Sebagh M, Teicher E, Roque-Afonso AM, Roche B, Azoulay D, Adam R, Bismuth H, Castaing D, Vittecoq D, Samuel D. Survival and recurrence of hepatitis C after liver transplantation in patients coinfected with human immunodeficiency virus and hepatitis C virus. *Hepatology* 2008; **47**: 407-417 [PMID: 18098295 DOI: 10.1002/hep.21990]

69 **Norris S**, Taylor C, Muiesan P, Portmann BC, Knisely AS, Bowles M, Rela M, Heaton N, O'Grady JG. Outcomes of liver transplantation in HIV-infected individuals: the impact of HCV and HBV infection. *Liver Transpl* 2004; **10**: 1271-1278 [PMID: 15376307 DOI: 10.1002/lt.20233]

70 **Watt KD**, Lyden ER, Gulizia JM, McCashland TM. Recurrent hepatitis C posttransplant: early preservation injury may predict poor outcome. *Liver Transpl* 2006; **12**: 134-139 [PMID: 16382465 DOI: 10.1002/lt.20583]

71 **Killackey MT**, Gondolesi GE, Liu LU, Paramesh AS, Thung SN, Suriawinata A, Nguyen E, Roayaie S, Schwartz ME, Emre S, Schiano TD. Effect of ischemia-reperfusion on the incidence of acute cellular rejection and timing of histologic hepatitis C virus recurrence after liver transplantation. *Transplant Proc* 2008; **40**: 1504-1510 [PMID: 18589139 DOI: 10.1016/j.transproceed.2008.03.101]

72 **Briceño J**, Ciria R, Pleguezuelo M, Naranjo A, Sánchez-Hidalgo J, Ruiz-Rabelo J, López-Cillero P, Luque A, de la Mata M, Rufián S. Contribution of marginal donors to liver transplantation for hepatitis C virus infection. *Transplant Proc* 2007; **39**: 2297-2299 [PMID: 17889169 DOI: 10.1016/j.transproceed.2007.07.069]

73 **Lan X**, Zhang MM, Pu CL, Guo CB, Kang Q, Li YC, Dai XK, Deng YH, Xiong Q, Ren ZM. Impact of human leukocyte antigen mismatching on outcomes of liver transplantation: a meta-analysis. *World J Gastroenterol* 2010; **16**: 3457-3464

[PMID: 20632452 DOI: 10.3748/wjg.v16.i27.3457]
74 **Gallegos-Orozco JF**, Yosephy A, Noble B, Aqel BA, Byrne TJ, Carey EJ, Douglas DD, Mulligan D, Moss A, de Petris G, Williams JW, Rakela J, Vargas HE. Natural history of post-liver transplantation hepatitis C: A review of factors that may influence its course. *Liver Transpl* 2009; **15**: 1872-1881 [PMID: 19938138 DOI: 10.1002/lt.21954]
75 **Langrehr JM**, Puhl G, Bahra M, Schmeding M, Spinelli A, Berg T, Schönemann C, Krenn V, Neuhaus P, Neumann UP. Influence of donor/recipient HLA-matching on outcome and recurrence of hepatitis C after liver transplantation. *Liver Transpl* 2006; **12**: 644-651 [PMID: 16555324 DOI: 10.1002/lt.20648]
76 **Belli LS**, Burra P, Poli F, Battista Alberti A, Silini E, Zavaglia C, Fagiuoli S, Prando D, Espadas de Arias A, Boninsegna S, Tinelli C, Scalamogna M, de Carlis L, Pinzello G. HLA-DRB1 donor-recipient mismatch affects the outcome of hepatitis C disease recurrence after liver transplantation. *Gastroenterology* 2006; **130**: 695-702 [PMID: 16530511 DOI: 10.1053/j.gastro.2005.11.013]
77 **Balan V**, Ruppert K, Demetris AJ, Ledneva T, Duquesnoy RJ, Detre KM, Wei YL, Rakela J, Schafer DF, Roberts JP, Everhart JE, Wiesner RH. Long-term outcome of human leukocyte antigen mismatching in liver transplantation: results of the National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database. *Hepatology* 2008; **48**: 878-888 [PMID: 18752327 DOI: 10.1002/hep.22435]
78 **Yoshizawa A**, Takada Y, Fujimoto Y, Koshiba T, Haga H, Nabeshima S, Uemoto S. Liver transplantation from an identical twin without immunosuppression, with early recurrence of hepatitis C. *Am J Transplant* 2006; **6**: 2812-2816 [PMID: 16939511 DOI: 10.1111/j.1600-6143.2006.01531.x]
79 **Kimball P**, Baker M, Fisher RA. Allograft TNFbeta and IL16 polymorphisms influence HCV recurrence and severity after liver transplantation. *Liver Transpl* 2006; **12**: 247-252 [PMID: 16447204 DOI: 10.1002/lt.20611]
80 **Tambur AR**, Ortegel JW, Ben-Ari Z, Shabtai E, Klein T, Michowiz R, Tur-Kaspa R, Mor E. Role of cytokine gene polymorphism in hepatitis C recurrence and allograft rejection among liver transplant recipients. *Transplantation* 2001; **71**: 1475-1480 [PMID: 11391238 DOI: 10.1097/00007890-200105270-00020]
81 **Rosen HR**, Doherty DG, Madrigal-Estebas L, O'Farrelly C, Golden-Mason L. Pretransplantation CD56(+) innate lymphocyte populations associated with severity of hepatitis C virus recurrence. *Liver Transpl* 2008; **14**: 31-40 [PMID: 18161829 DOI: 10.1002/lt.21265]
82 **Golden-Mason L**. Natural killer cells play divergent roles in shaping the outcome of hepatitis C virus recurrence following liver transplantation. *Liver Transpl* 2009; **15**: 357-359 [PMID: 19326413 DOI: 10.1002/lt.21701]
83 **de Arias AE**, Haworth SE, Defeo TM, Poli F. Natural killer cells in hepatitis C virus recurrence following liver transplantation: what role do they play? *Expert Rev Gastroenterol Hepatol* 2009; **3**: 329-332 [PMID: 19673619 DOI: 10.1586/egh.09.29]
84 **Pearlman BL**. The IL-28 genotype: how it will affect the care of patients with hepatitis C virus infection. *Curr Gastroenterol Rep* 2011; **13**: 78-86 [PMID: 21080244 DOI: 10.1007/s11894-010-0161-9]
85 **Aparicio E**, Parera M, Franco S, Pérez-Alvarez N, Tural C, Clotet B, Martínez MA. IL28B SNP rs8099917 is strongly associated with pegylated interferon-α and ribavirin therapy treatment failure in HCV/HIV-1 coinfected patients. *PLoS One* 2010; **5**: e13771 [PMID: 21048934 DOI: 10.1371/journal.pone.0013771]
86 **Knobler H**, Schihmanter R, Zifroni A, Fenakel G, Schattner A. Increased risk of type 2 diabetes in noncirrhotic patients with chronic hepatitis C virus infection. *Mayo Clin Proc* 2000; **75**: 355-359 [PMID: 10761489 DOI: 10.4065/75.4.355]
87 **Svegliati-Baroni G**, Ridolfi F, Di Sario A, Casini A, Marucci L, Gaggiotti G, Orlandoni P, Macarri G, Perego L, Benedetti A, Folli F. Insulin and insulin-like growth factor-1 stimulate proliferation and type I collagen accumulation by human hepatic stellate cells: differential effects on signal transduction pathways. *Hepatology* 1999; **29**: 1743-1751 [PMID: 10347117 DOI: 10.1002/hep.510290632]
88 **Foxton MR**, Quaglia A, Muiesan P, Heneghan MA, Portmann B, Norris S, Heaton ND, O'Grady JG. The impact of diabetes mellitus on fibrosis progression in patients transplanted for hepatitis C. *Am J Transplant* 2006; **6**: 1922-1929 [PMID: 16780550 DOI: 10.1111/j.1600-6143.2006.01408.x]
89 **Hanouneh IA**, Feldstein AE, McCullough AJ, Miller C, Aucejo F, Yerian L, Lopez R, Zein NN. The significance of metabolic syndrome in the setting of recurrent hepatitis C after liver transplantation. *Liver Transpl* 2008; **14**: 1287-1293 [PMID: 18756451 DOI: 10.1002/lt.21524]
90 **Veldt BJ**, Poterucha JJ, Watt KD, Wiesner RH, Hay JE, Rosen CB, Heimbach JK, Janssen HL, Charlton MR. Insulin resistance, serum adipokines and risk of fibrosis progression in patients transplanted for hepatitis C. *Am J Transplant* 2009; **9**: 1406-1413 [PMID: 19459812 DOI: 10.1111/j.1600-6143.2009.02642.x]
91 **Sánchez-Pérez B**, Aranda Narváez JM, Santoyo Santoyo J, Fernández-Aguilar JL, Suárez Muñoz MA, González-Sánchez AJ, Pérez Daga JA, Ramírez Plaza CP, Carrasco Campos J, Jiménez Mazure C, Becerra Ortíz R. Influence of immunosuppression and effect of hepatitis C virus on new onset of diabetes mellitus in liver transplant recipients. *Transplant Proc* 2008; **40**: 2994-2996 [PMID: 19010171 DOI: 10.1016/j.transproceed.2008.08.116]
92 **McCaughan GW**, Zekry A. Impact of immunosuppression on immunopathogenesis of liver damage in hepatitis C virus-infected recipients following liver transplantation. *Liver Transpl* 2003; **9**: S21-S27 [PMID: 14586891 DOI: 10.1053/jlts.2003.50269]
93 **De Ruvo N**, Cucchetti A, Lauro A, Masetti M, Cautero N, Di Benedetto F, Dazzi A, Del Gaudio M, Ravaioli M, Di Francesco F, Molteni G, Ramacciato G, Risaliti A, Pinna AD. Preliminary results of a "prope" tolerogenic regimen with thymoglobulin pretreatment and hepatitis C virus recurrence in liver transplantation. *Transplantation* 2005; **80**: 8-12 [PMID: 16003226 DOI: 10.1097/01.TP.0000164349.54297.95]
94 **Ohira M**, Ishiyama K, Tanaka Y, Doskali M, Igarashi Y, Tashiro H, Hiraga N, Imamura M, Sakamoto N, Asahara T, Chayama K, Ohdan H. Adoptive immunotherapy with liver allograft-derived lymphocytes induces anti-HCV activity after liver transplantation in humans and humanized mice. *J Clin Invest* 2009; **119**: 3226-3235 [PMID: 19805910 DOI: 10.1172/JCI38374]
95 **Pawlotsky JM**, Chevaliez S. Preventing hepatitis C virus recurrence in liver transplant recipients: a role for adoptive immunotherapy? *Hepatology* 2010; **51**: 1072-1076 [PMID: 20198701 DOI: 10.1002/hep.23579]
96 **Gedaly R**, Clifford TM, McHugh PP, Jeon H, Johnston TD, Ranjan D. Prevalent immunosuppressive strategies in liver transplantation for hepatitis C: results of a multi-center international survey. *Transpl Int* 2008; **21**: 867-872 [PMID: 18498313 DOI: 10.1111/j.1432-2277.2008.00699.x]
97 **Sheiner PA**, Schwartz ME, Mor E, Schluger LK, Theise N, Kishikawa K, Kolesnikov V, Bodenheimer H, Emre S, Miller CM. Severe or multiple rejection episodes are associated with early recurrence of hepatitis C after orthotopic liver transplantation. *Hepatology* 1995; **21**: 30-34 [PMID: 7806166 DOI: 10.1002/hep.1840210107]
98 **Berenguer M**, Aguilera V, Prieto M, San Juan F, Rayón JM, Benlloch S, Berenguer J. Significant improvement in the outcome of HCV-infected transplant recipients by avoiding rapid steroid tapering and potent induction immunosuppression. *J Hepatol* 2006; **44**: 717-722 [PMID: 16487616 DOI:

10.1016/j.jhep.2006.01.005]
99 **Vivarelli M**, Burra P, La Barba G, Canova D, Senzolo M, Cucchetti A, D'Errico A, Guido M, Merenda R, Neri D, Zanello M, Giannini FM, Grazi GL, Cillo U, Pinna AD. Influence of steroids on HCV recurrence after liver transplantation: A prospective study. *J Hepatol* 2007; **47**: 793-798 [PMID: 17928091 DOI: 10.1016/j.jhep.2007.07.023]
100 **Segev DL**, Sozio SM, Shin EJ, Nazarian SM, Nathan H, Thuluvath PJ, Montgomery RA, Cameron AM, Maley WR. Steroid avoidance in liver transplantation: meta-analysis and meta-regression of randomized trials. *Liver Transpl* 2008; **14**: 512-525 [PMID: 18383081 DOI: 10.1002/lt.21396]
101 **Nakagawa M**, Sakamoto N, Enomoto N, Tanabe Y, Kanazawa N, Koyama T, Kurosaki M, Maekawa S, Yamashiro T, Chen CH, Itsui Y, Kakinuma S, Watanabe M. Specific inhibition of hepatitis C virus replication by cyclosporin A. *Biochem Biophys Res Commun* 2004; **313**: 42-47 [PMID: 14672695 DOI: 10.1016/j.bbrc.2003.11.080]
102 **Berenguer M**, Royuela A, Zamora J. Immunosuppression with calcineurin inhibitors with respect to the outcome of HCV recurrence after liver transplantation: results of a meta-analysis. *Liver Transpl* 2007; **13**: 21-29 [PMID: 17192906 DOI: 10.1002/lt.21035]
103 **Levy G**, Villamil F, Samuel D, Sanjuan F, Grazi GL, Wu Y, Marotta P, Boillot O, Muehlbacher F, Klintmalm G. Results of lis2t, a multicenter, randomized study comparing cyclosporine microemulsion with C2 monitoring and tacrolimus with C0 monitoring in de novo liver transplantation. *Transplantation* 2004; **77**: 1632-1638 [PMID: 15201658 DOI: 10.1097/01.TP.0000129095.51031.42]
104 **Inoue K**, Sekiyama K, Yamada M, Watanabe T, Yasuda H, Yoshiba M. Combined interferon alpha2b and cyclosporin A in the treatment of chronic hepatitis C: controlled trial. *J Gastroenterol* 2003; **38**: 567-572 [PMID: 12825133]
105 **Firpi RJ**, Zhu H, Morelli G, Abdelmalek MF, Soldevila-Pico C, Machicao VI, Cabrera R, Reed AI, Liu C, Nelson DR. Cyclosporine suppresses hepatitis C virus in vitro and increases the chance of a sustained virological response after liver transplantation. *Liver Transpl* 2006; **12**: 51-57 [PMID: 16382464 DOI: 10.1002/lt.20532]
106 **Firpi RJ**, Soldevila-Pico C, Morelli GG, Cabrera R, Levy C, Clark VC, Suman A, Michaels A, Chen C, Nelson DR. The use of cyclosporine for recurrent hepatitis C after liver transplant: a randomized pilot study. *Dig Dis Sci* 2010; **55**: 196-203 [PMID: 19798576 DOI: 10.1007/s10620-009-0981-3]
107 **Triyatni M**, Vergalla J, Davis AR, Hadlock KG, Foung SK, Liang TJ. Structural features of envelope proteins on hepatitis C virus-like particles as determined by anti-envelope monoclonal antibodies and CD81 binding. *Virology* 2002; **298**: 124-132 [PMID: 12093180 DOI: 10.1006/viro.2002.1463]
108 **Tarr AW**, Owsianka AM, Timms JM, McClure CP, Brown RJ, Hickling TP, Pietschmann T, Bartenschlager R, Patel AH, Ball JK. Characterization of the hepatitis C virus E2 epitope defined by the broadly neutralizing monoclonal antibody AP33. *Hepatology* 2006; **43**: 592-601 [PMID: 16496330 DOI: 10.1002/hep.21088]
109 **Bartosch B**, Dubuisson J, Cosset FL. Infectious hepatitis C virus pseudo-particles containing functional E1-E2 envelope protein complexes. *J Exp Med* 2003; **197**: 633-642 [PMID: 12615904 DOI: 10.1084/jem.20021756]
110 **Willems B**, Ede M, Marotta P, Wall W, Greig P, Lilly L, Kneteman N, Wong W, Roy A, Marleau D, Scudamore C, Yoshida E, Rinfret A. Anti-HCV human immunoglobulins for the prevention of graft infection in HCV-related liver transplantation, a pilot study. *J Hepatol* 2002; **36**: S96A [DOI: 10.1016/S0168-8278(02)80095-2]
111 **Schiano TD**, Charlton M, Younossi Z, Galun E, Pruett T, Tur-Kaspa R, Eren R, Dagan S, Graham N, Williams PV, Andrews J. Monoclonal antibody HCV-AbXTL68 in patients undergoing liver transplantation for HCV: results of a phase 2 randomized study. *Liver Transpl* 2006; **12**: 1381-1389 [PMID: 16933235 DOI: 10.1002/lt.20876]
112 **Davis GL**, Nelson DR, Terrault N, Pruett TL, Schiano TD, Fletcher CV, Sapan CV, Riser LN, Li Y, Whitley RJ, Gnann JW. A randomized, open-label study to evaluate the safety and pharmacokinetics of human hepatitis C immune globulin (Civacir) in liver transplant recipients. *Liver Transpl* 2005; **11**: 941-949 [PMID: 16035063 DOI: 10.1002/lt.20405]
113 **Gurusamy KS**, Tsochatzis E, Davidson BR, Burroughs AK. Antiviral prophylactic intervention for chronic hepatitis C virus in patients undergoing liver transplantation. *Cochrane Database Syst Rev* 2010; (12): CD006573 [PMID: 21154370]
114 **Peveling-Oberhag J**, Zeuzem S, Hofmann WP. Antiviral therapy of chronic hepatitis C in patients with advanced liver disease and after liver transplantation. *Med Microbiol Immunol* 2010; **199**: 1-10 [PMID: 19902246 DOI: 10.1007/s00430-009-0131-8]
115 **Gurusamy KS**, Osmani B, Xirouchakis E, Burroughs AK, Davidson BR. Antiviral therapy for recurrent liver graft infection with hepatitis C virus. *Cochrane Database Syst Rev* 2009; (1): CD006803 [PMID: 19160303]
116 **Carrión JA**, Navasa M, García-Retortillo M, García-Pagan JC, Crespo G, Bruguera M, Bosch J, Forns X. Efficacy of antiviral therapy on hepatitis C recurrence after liver transplantation: a randomized controlled study. *Gastroenterology* 2007; **132**: 1746-1756 [PMID: 17484872 DOI: 10.1053/j.gastro.2007.03.041]
117 **Saab S**, Hunt DR, Stone MA, McClune A, Tong MJ. Timing of hepatitis C antiviral therapy in patients with advanced liver disease: a decision analysis model. *Liver Transpl* 2010; **16**: 748-759 [PMID: 20517909]
118 **Lange CM**, Sarrazin C, Zeuzem S. Review article: specifically targeted anti-viral therapy for hepatitis C - a new era in therapy. *Aliment Pharmacol Ther* 2010; **32**: 14-28 [PMID: 20374226 DOI: 10.1111/j.1365-2036.2010.04317.x]
119 **McHutchison JG**, Manns MP, Muir AJ, Terrault NA, Jacobson IM, Afdhal NH, Heathcote EJ, Zeuzem S, Reesink HW, Garg J, Bsharat M, George S, Kauffman RS, Adda N, Di Bisceglie AM. Telaprevir for previously treated chronic HCV infection. *N Engl J Med* 2010; **362**: 1292-1303 [PMID: 20375406 DOI: 10.1056/NEJMoa0908014]
120 **Kanda T**, Imazeki F, Yokosuka O. New antiviral therapies for chronic hepatitis C. *Hepatol Int* 2010; **4**: 548-561 [PMID: 21063477 DOI: 10.1007/s12072-010-9193-3]

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