Keywords: Liver transplantation; Hepatitis C virus infection; Direct-acting antiviral agents

Introduction

Chronic hepatitis C virus (HCV) infection is one of the most frequent causes of cirrhosis and represents the leading indication for liver transplantation (LT) in the USA and in many European countries [1,2]. Unfortunately, HCV infection after LT is an almost universal phenomenon in HCV-RNA positive candidates, representing a serious threat to the success of the transplant [3,4].

The natural history of HCV infection in post-transplant recipients is variable but generally more rapid and aggressive compared to non-transplanted patients. A subgroup of transplanted HCV (about 1-9%) develop a fibrotic cholestatic hepatitis, characterized by a rapid progression to graft failure and death [5], while the majority of patients (about 70%) develop acute and then chronic hepatitis [6,7]. In contrast to the natural history of primary infection, liver disease progresses more rapidly in HCV recipients, with a progression to cirrhosis in 25-30% of patients within 5-7 years after surgery [8-11]. Furthermore, about 40% will develop hepatic decompensation within one year after the diagnosis of cirrhosis [8,10]. Therefore, the majority of HCV transplanted recipients suffer an inexorably poor outcome: about 10-25% will die or require re-transplantation within 5 years post-transplant [12]. Unfortunately, the results of retransplantation in these patients are disappointing, limited by the high likelihood of a further rapid HCV recurrence [13]. As a result, the overall and graft survival of transplanted patients with HCV infection is significantly lower than that of patients without hepatitis C [14-16].

There are many factors associated with disease and graft injury progression in patients with HCV recurrence after LT, including virological, donor and host characteristics, but for most of them the role is controversial. A high HCV load (>1 MEq/L) before transplantation, HCV genotype 1b [8,17,18] older age [19], female sex [14], race and severity of disease before LT [20] are all frequently associated with severity of HCV recurrence, fibrosis progression and a poor outcome. Similarly, donor factor like older age [18], allograft fat content and prolonged warm ischemia time are all related to poor outcome [21]. In any case, the immunosuppressed status is the most important factor in the evolution towards chronic hepatitis and cirrhosis. The overall immunosuppression level and/or dramatic changes in immunosuppression probably facilitate viral replication and the outcome of HCV recurrence [22].

Considering the increasing shortage of donor organs and the accelerated progression of hepatitis C in transplant recipients, the development of effective strategies to treat HCV-recurrence are of paramount importance.

Treatment of HCV Transplanted Patients

Higher viral load, cytopenia and some degree of renal insufficiency make the treatment of HCV transplanted recipients more difficult than in immunocompetent patients. In addition, many transplanted HCV patients are previous non-responders to pre-LT antiviral therapy [23].

In order to reduce the impact of HCV recurrence on graft and patient survival, several treatment strategies have been evaluated. Antiviral therapy could be administered before transplantation to suppress viral replication and reduce the risk of recurrence. However, the tolerability of this approach is poor; therefore it is applicable only...
in subjects with compensated cirrhosis which usually represent a minority [24].

After LT, patients can be treated immediately following transplantation (pre-emptive approach) or when chronic hepatitis is diagnosed (recurrence-based approach). The former allows therapy to be initiated within the first 4-6 weeks, when serum HCV-RNA levels are characteristically low and before the presence of significant histological graft damage. However, several studies demonstrated that antiviral therapy with IFN immediately post-transplant is difficult to manage and that the efficacy is poor [25,26]. Consequently, the better current approach is to initiate antiviral treatment in the presence of histological signs of HCV recurrence. Combination therapy of interferon (IFN) and ribavirin (RBV) for 12 months has been associated with an overall sustained virological response (SVR) of about 20 to 30% [27], while the more recent standard therapy with PEG-IFN and RBV leads to SVR rates of about 30-45% [28-32]. Among the many factors that could influence the treatment response [28-36] (Table 1), the polymorphism of IL28B gene, which codes for IFN, plays a pivotal role especially in patients with genotype 1 [37,38]. In addition early virological response (EVR) is the principal predictive factor of SVR [39].

### New Strategies

Recently, several direct-acting antiviral drugs such as protease inhibitors, polymerase and other non-structural protein inhibitors, named direct antiviral agents (DAAs), have been developed as new treatment for HCV. At the moment, only Boceprevir (BCV) and Telaprevir (TLV) have been released and approved for new treatment for HCV. At the moment, only Boceprevir (BCV) and Telaprevir (TLV) have been released and approved for treatment in LT recipients. In the USA [44], 61 LT HCV patients were treated with TLV after lead-in therapy with PEG-IFN and RBV. HCV-RNA negativization was obtained in 63% and 72% of patients, respectively. Therefore, the maintenance of stable through the discontinuation of antiviral treatment did not cause a relapse of viral replication and this patient was still HCV-RNA negative at the end of the study period. Two-thirds of patients developed cytopenia requiring RBV dose reduction, use of erythropoietin (EPO) or blood transfusion, or administration of granulocyte colony-stimulating factor (GCS-F). Moreover, patients treated with TAC experienced more side effects and more hospitalization. A reduction of individual dose of immunosuppressant drugs was necessary in all patients with a mean daily reduction dose of 2.5-fold and 22-fold for CSA and TAC, respectively. Therefore, the maintenance of stable through level of immunosuppressant emerges as a principal issue in treating transplanted patients with DAAs.

In the largest multicenter ongoing study in the USA [44], 61 LT HCV patients were treated with TLV after lead-in therapy with PEG-IFN and RBV. HCV-RNA negativization was obtained in 63% and 72% of patients, respectively. Preliminary results have been disclosed in abstract form and exclusively concern established HCV reinfection of the graft [44-51]. To the best of our knowledge there are no data about the use of DAAs in post-transplantation prophylactic or pre-emptive therapy.

So far, the available clinical experiences on the use of DAAs in LT HCV recipients are inconsistent and hampered by major methodological drawbacks, such as small study population, heterogeneous study design, different treatment schedules and follow-up periods, ongoing nature of data. In addition essential information such as the timing of treatment in respect to LT is often lacking. Keeping in mind these major limitations, the results of these few reports have been summarized in tables 2 and 3.

In the only study published in extenso, Werner et al. [43] treated 9 HCV-genotype 1 infected LT patients with a combination of TLV, PEG-IFN and RBV in association with tacrolimus (TAC; 4 patients) or cyclosporine A (CSA; 4 patients) or sirolimus (1 patient). The Authors reported efficacy and safety data after 12 weeks of treatment. At week 4 and 12, 4 (44%) and 8 (89%) patients respectively, were found to be HCV-RNA negative. However, two patients dropped out before the 12 week treatment period because of side effects even though in one case the discontinuation of antiviral treatment did not cause a relapse of viral replication and this patient was still HCV-RNA negative at the end of the study period. Two-thirds of patients developed cytopenia requiring RBV dose reduction, use of erythropoietin (EPO) or blood transfusion, or administration of granulocyte colony-stimulating factor (GCS-F). Moreover, patients treated with TAC experienced more side effects and more hospitalization. A reduction of individual dose of immunosuppressant drugs was necessary in all patients with a mean daily reduction dose of 2.5-fold and 22-fold for CSA and TAC, respectively. Therefore, the maintenance of stable through level of immunosuppressant emerges as a principal issue in treating transplanted patients with DAAs.

### Results

The results of literature search showed that there is nothing published yet in the literature but one paper on triple therapy in LT setting using DAAs [43].

As far as the administration of antiviral treatment before transplantation is concerned, DAAs has been evaluated in patients with decompensated cirrhosis. But it is unknown if this treatment is able to reduce HCV recurrence after LT. In addition, it seems that the tolerability is poor and there is a high risk of life-threatening complications [40].

After LT, almost all preliminary results have been disclosed in abstract form and exclusively concern established HCV reinfection of the graft [44-51]. To the best of our knowledge there are no data about the use of DAAs in post-transplantation prophylactic or pre-emptive therapy.

### Table 1: Predictive factors associated with SVR.

| Author              | Predictive factors in univariate analysis                                                                 | Predictive factors in multivariate analysis                                                                 | SVR   |
|---------------------|-----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|-------|
| Dumortier [28]      | Completion of therapy, genotype non-1, VR at 3 months                                                                                                           | NA                                                                                                         | 45%   |
| Biselli [29]        | VR at 1 and 6 months                                                                                                                                            | NA                                                                                                         | 45%   |
| Berenguer [30]      | Use of EPO, VR at 3 months, adherence to therapy                                                                                                                | VR at 3 months                                                                                               | 50%   |
| Nuemann [31]        | NA                                                                                                         | Baseline viremia < 1.000.000 UI/ml                                                                 | 36%   |
| Sharma [32]         | Low baseline viremia, higher dose of antiviral, longer therapy duration, EVR, EPO, anemia                                                                   | None                                                                                                         | 37%   |
| Crespo [33]         | IL28B CC genotype with either low VL, young donor age, cyclosporine A -based immunosuppression                                                          | HCV genotype 2, total dose PEG-IFN                                                                     | 69%   |
| Picciotto [34]      | HCV genotype 2, higher dose of antivirals, absence of cirrhosis                                                                                                  | HCV genotype 2, total dose PEG-IFN                                                                     | 28%   |
| Oton [35]           | Baseline HCV RNA, 2-4 years after LT, VR at 1-3 months                                                                                                       | Baseline HCV RNA, 2-4 years after LT, VR at 1-3 months                                                                                                | 44%   |
| Roche [39]          | EVR, completion of treatment, VL before therapy, genotype non-1                                                                                           | EVR                                                                                                         | 38%   |

**Abbreviations:** SVR: Sustained Virological Response; HCV: Hepatitis C Virus; RNA: Ribonucleic Acid; LT: Liver Transplantation; VR: Virological Response; PEG-IFN: Peglated-interferon; NA: Not Available; EVR: Early Virological Response; EPO: Erythropoietin; IL28B: Interleukin 28B; VL: Viral Load
(16%) prematurely stopped treatment because of an early virological failure in 6 and severe adverse events in 4. During triple therapy 37% of patients required transfusions and 33% developed renal failure. Growth factors were used in 77% and RBV dose reduction was needed in 33% of patients. Required transfusions and 33% developed renal failure.

In five French LT Centres [47] an ongoing study analyzed the effect of triple therapy (PEG-IFN/RBV + TLV or BCV) in 25 LT patients with HCV genotype 1 both naïves and non responders to a previous period with PEG-IFN and RBV in 12 weeks. HCV-RNA negativization was obtained in 15%, 68% and 55% of cases after 4, 12 and 24 weeks, respectively. Severe adverse events included 2 cases of acute rejection and 1 death due to sepsis. As usual, cytopenia was extremely common, requiring EPO in 19 patients, blood transfusion in 8 patients and 5 TLV patients (45%) after 4 weeks and in 11 BCV patients (79%) and 8 TLV patients (73%) after 12 weeks. Two patients died (1 TLV, 1 BCV) for sepsis. Most common side effect was anemia (64%) so that about 90% in each group received EPO. Even in this series the dose of immunosuppressive drugs needed to be reduced, in particular in TLV patients.

The preliminary results obtained in a further group of 10 patients with recurrent hepatitis C after LT treated for a maximum of 24 weeks with PEG-IFN/RBV plus TLV in an ongoing US single centre study [48] showed a 4 week virological response of 22% (2 out of 9). The immunosuppressant regimen was CSA in 15 patients and TAC in 10. Mean follow-up was about 20 weeks. A virological response was observed in 6 BCV patients (43%) and 5 TLV patients (45%) after 4 weeks and in 11 BCV patients (79%) and 8 TLV patients (73%) after 12 weeks. Two patients died (1 TLV, 1 BCV) for sepsis. Most common side effect was anemia (64%) so that about 90% in each group received EPO. Even in this series the dose of immunosuppressive drugs needed to be reduced, in particular in TLV patients.

The preliminary results obtained in a further group of 10 patients with recurrent hepatitis C after LT treated for a maximum of 24 weeks with PEG-IFN/RBV plus TLV in an ongoing US single centre study [48] showed a 4 week virological response of 22% (2 out of 9). The three patients who completed 12 weeks of therapy were all HCV-RNA negative as well as the only patient who reached week 24. The only reported data on adverse events were anemia (20%), leukopenia (10%) and depression (20%). No information on their severity was described.

Burton and Everson [49] evaluated the effect of the introduction of TLV after a 4-week lead-in phase with PEG-IFN and RBV in 12 LT patients with HCV genotype 1. Patients were treated for 12 weeks with triple therapy and then all patients received an additional 36 week period with PEG-IFN/RBV. By week 4, 11/12 (91%) patients reached an undetectable viral load even if two cases of resistance to TLV with a

### Table 2: Preliminary data about virological response during triple therapy in post-liver transplantation.

| Patients[n] | Werner [43] | Burton [44] | Aqel [45] | Pungpapong [46] | Coilly [47] | McCashland [48] | Burton [49] | Kwo [50] | de Oliveira [51] |
|-------------|-------------|-------------|-----------|-----------------|-------------|-----------------|-------------|---------|-----------------|
| Regimen     |             |             |           |                 |             |                 |             |         |                 |
| - BCV       | 0           | 0           | 9         | 23              | 28          | 0               | 14          | 11      | 10              |
| - TLV       | 0           | 0           | 0         | 23              | 28          | 0               | 14          | 11      | 10              |
| 4 week lead-in phase | 0% | NA | 100% | NA | 76% | NA | 100% | NA | 100% | NA |
| Fibrosis [Ishak score] | NA | 43% | [>3] | NA | NA | NA | 84% | [>3] | 30% | [>2] |
| Cholestatic hepatitis | 11% | 10% | NA | 16% | NA | NA | NA | NA | NA |
| IS therapy | - Tacrolimus | 44% | 27% | 0% | 0% | 60% | 40% | 0% | 60% |
| - Cyclosporine | 44% | 63% | 100% | 0% | 100% | 100% | 63% | 100% | 100% |
| HCV-RNA genotype | 1 | 1 | 1 | 1a | 1 | 1 | 1 | 1 |

### Table 3: Preliminary data about adverse events and their management during triple therapy in post-liver transplantation.

| Patients[n] | Werner [43] | Burton [44] | Aqel [45] | Pungpapong [46] | Coilly [47] | McCashland [48] | Burton [49] | Kwo [50] | de Oliveira [51] |
|-------------|-------------|-------------|-----------|-----------------|-------------|-----------------|-------------|---------|-----------------|
| - Hematological AEs | 66% | 100% | NA | 100% | NA | 100% | 50% | 50% | 100% |
| - Skin rash [mild] | 33% | NA | NA | 11% | NA | 4% | NA | 58% | NA |
| - Kidney failure | 11% | 33% | NA | 4% | NA | 8% | NA | NA | 17% |
| - Death | 0% | 3% | NA | 0% | 0% | 0% | 0% | 0% | 0% |
| - Acute rejection | 0% | 3% | NA | 7% | NA | 0% | 0% | 0% | 0% |

### Management

| - RBV reduction | 78% | 46% | NA | 82% | 52% | 100% | 83% | 100% | NA |
| - EPO | 66% | NA | NA | 68% | 92% | NA | 61% | 86% | NA |
| - Blood transfusion | 66% | 37% | NA | 39% | 8% | 21% | 56% | 86% | NA |
| - Growth factor | 22% | 77% | 100% | 14% | NA | NA | NA | 86% | NA |
| - Hospitalized | 44% | 18% | NA | 14% | NA | NA | 25% | NA | 17% |

### Abbreviations:

- BCV: Boceprevir; TLV: Telaprevir; HCV: Hepatitis C Virus; IS: Immunosuppressive; NA: Not Available
rise of viremia were reported. About side effects, 42% patients required blood transfusion and 25% were hospitalized.

Other 2 very small series (less than 10 patients each) [50,51] analyzed the effect of the association PEG-IFN/RBV with TLV in transplanted patients with HCV genotype 1. The rates of virological response at 12 weeks ranged from 33 to 100%, but it is not clear how many patients completed 12-weeks of treatment.

To complete the description of available data on DAAs in LT setting, it is worth mentioning the use of a new potent replication inhibitor of HCV named dataclatavir in association with PEG-IFN and RBV for 24 weeks in a single patient who developed recurrent cholestatic hepatitis C after liver retransplantation obtaining a complete SVR without serious adverse event [52].

From these preliminary data, tolerance and the risk of severe adverse events emerges as a major concern in the use of DAAs in LT patients. LT patients are particularly exposed to several side effects due to the standard therapy based on PEG-IFN/RBV, in particular to haematological toxicity leading to a dose reduction in almost 70% of patients and premature termination in almost 30% [53]. In addition, it is not completely understood if antiviral treatment in transplanted patients might increase the risk of acute rejection [26,54]. Consequently, the addition of a third drug, such as DAAs, could increase the incidence and severity of side effects thus reducing the applicability of this new therapeutic strategy. Indeed, in non-transplanted patients it has been shown that RBV-induced anemia as well as PEG-IFN associated neutropenia and thrombocytopenia could be exacerbated by the addition of TLV and BCV, probably with a mechanism leading to a bone marrow suppressive effect [55,56]. Moreover, TLV and BCV are specifically associated with several adverse dermatological events, like generalized pruritus with eczematiform lesions and anorectal disorders [57,58]. These data suggest a careful monitoring and management of LT patients under treatment with triple antiviral therapy.

One of the major problem in the use of DAAs in LT is represented by interaction with immunosuppressive drugs, in particular with calcineurin inhibitors both cyclosporine (CSA) and tacrolimus (TAC), CYC and TAC are substrate of both cytochrome P450A 3A (TAC). CYC and TAC are substrate of both cytochrome P450A 3A (CYP3A), the primary enzyme responsible for their metabolism and P-glycoprotein (P-gp), a transmembrane transporter. TLV and BCV are both CYP3A4 substrates and inhibitors and have the potential to saturate or inhibit P-gp in the gut, so they could increase calcineurin inhibitor levels and the systemic exposure to these agents [59].

Garg et al. [60] evaluated the effect of TLV on the pharmacokinetic of a single dose of CSA and TAC in healthy volunteers. CSA maximum observed plasma concentration (Cmax) increased about 1.4 fold, the area under the curve (AUC) increased approximately 4.6 fold and mean t1/2 increased 4-fold. The effect was greater with TAC: dose normalized Cmax increased about 9.3 fold, AUC increased approximately 70-fold and the main t1/2 approximately 5-fold. Hulskotte et al. [61] demonstrated that concomitant BCV increased the AUC and Cmax of CSA of 2.7 and 2.0 respectively and increased the AUC and Cmax of TAC of 17 and 9.9, respectively. Coilly et al. reported an estimated oral clearance reduction by 50% with CSA and about 80% with TAC [62,63]. It cannot be excluded that in transplant recipients the potential interactions between calcineurin inhibitor and TLV or BCV could be higher and more variable than that seen in healthy volunteers, thus reducing their potential use in HCV recurrence after LT.

Conclusion

On the basis of these scanty data it is difficult to draw any conclusion. The few and preliminary data on the use of DAAs in LT patients are neither consistent nor conclusive. Due to the lack of consistent data, it is not possible to quantify the efficacy in terms of SVR, the tolerability and the adverse event profile of DAAs for the treatment of recurrent HCV infection after LT. Similarly, at the moment there are no indications about the potential predictors of SVR. It has to be underlined that in this particular setting, given the potential clinical benefits, the availability of clinical data on these new potent HCV inhibitors is urgently needed. For the moment there is no indication to their use in LT patients and the tolerability and the potential interaction with calcineurin inhibitors still represent a major drawback. Larger and well done clinical studies are urgently needed.

References

1. Adam R, Holl E (2009) Liver transplantation: the current situation. Semin Liver Dis 29: 3-18.
2. Kim WR, Stock PG, Smith JM, Heimbach JK, Skeans MA, et al. (2011) OPTN/STRT Annual Data Report: liver. Am J Transplant 13: 73-102.
3. Rodriguez-Luna H, Douglas DD (2004) Natural history of hepatitis C following liver transplantation. Curr Opin Infect Disease 17: 363-371.
4. Wright TL, Donegan E, Hsu HH, Ferrell L, Lake JR, et al. (1992) Recurrent and acquired hepatitis C viral infection in liver transplant recipients. Gastroenterology 103: 317-322.
5. McCaughan GW, Zekry A (2004) Mechanisms of HCV reinfection and allograft damage after liver transplantation. J Hepatol 40: 368-374.
6. Guerrero RB, Batts KP, Burgart LJ, Barrett SL, Germer JJ, et al. (2000) Early detection of hepatitis C allograft reinfection after orthotopic liver transplantation: a molecular and histologic study. Mod Pathol 13: 229-237.
7. Sreekumar R, Gonzalez-Koch A, Moar-Kendler Y, Batts K, Moreno-Luna L, et al. (2000) Early identification of recipients with progressive histologic recurrence of hepatitis C after liver transplantation. Hepatology x 32: 1125-1130.
8. Berenguer M, Ferrell L, Watson J, Prieto M, Kim M, et al. (2000) HCV-related fibrosis progression following liver transplantation: increase in recent years. J Hepatol 32: 673-684.
9. Feray C, Gigou M, Samuel D, Paradis V, Wilber J, et al. (1994) The course of hepatitis C virus infection after liver transplantation. Hepatology 20: 1137-1143.
10. Berenguer M, Prieto M, Raymon JM, Mora J, Pastor M, et al. (2000) Natural history of clinically compensated hepatitis C virus-related graft cirrhosis after liver transplantation. Hepatology 2000: 32: 852-858.
11. Berenguer M, Lopez-Labrador FX, Wright TL (2001) Hepatitis C and liver transplantation. J Hepatol 35: 666-678.
12. Charlton M, Seaberg E, Wiesner R, Everhart J, Zetterman R, et al. (1998) Predictor of patient and graft survival following liver transplantation for hepatitis C. Hepatology 3: 823-830.
13. Watt KDS, Lydem ER, McCashland TM (2003) Poor survival following liver retransplantation: is hepatitis C to blame? Liver Transpl 9: 1019-1024.
14. Forman LM, Lewis DJ, Berlin JA, Feldman HI, Lucey MR (2002) The association between hepatitis C infection and survival after orthotopic liver transplantation. Gastroenterology 122: 889-896.
15. Multimer DJ, Gunson B, Chen J, Berenguer J, Neuhaus P, et al. (2006) Impact of donor age and year of transplantation on graft and patient survival following liver transplantation for hepatitis C. Hepatology 43: 103-110.
16. Berenguer M, Prieto M, Raymon JM, Mora J, Pastor M, et al. (2000) Natural history of clinically compensated hepatitis C virus-related graft cirrhosis after liver transplantation. Hepatology 2000: 32: 852-858.
17. Davies SE, Portmann BC, O'Grady JG, Ailis PM, Chaggar K, et al. (1991) Hepatocellular histological findings after transplantation for chronic hepatitis B virus infection, including a unique pattern of fibrosing cholestatic hepatitis. Hepatology 13: 150-157.
18. Feray C, Gigou M, Samuel D, Paradis V, Mishiro S, et al. (1995) Influence of
the genotypes of hepatitis C virus on severity of recurrent liver disease after liver transplantation. Gastroenterology 108: 1088-1096.

19. Berenguer M, Prieto M, San Juan F, Rayon JM, Martínez F, et al. (2002) Contribution of donor age to the recent decrease in patient survival among HCV-infected liver transplant recipient. Hepatology 36: 202-2010.

20. Charlton M, Seaberg E, Wisnew R, Everhart J, Zetterman R, et al. (1998) Predictors of patient and graft survival following liver transplantation for hepatitis C. Hepatology 28: 823-830.

21. Burak KW, Kremers WK, Battos KP, Wisnew RH, Rosen CB, et al. (2002) Impact of cytomegalovirus infection, year of transplantation and donor age and outcomes after liver transplantation for hepatitis C. Liver Transpl 8: 362-369.

22. McCaughan GW, Zekry A (2000) Effects of immunosuppression and organ transplantation on the natural history and immunopathogenesis of hepatitis C virus infection. Transpl Infect Dis 2: 166-185.

23. Davis JL, O’Leary JG (2012) Use of protease inhibitors in live transplant recipients. Gastroenterology and Hepatology 8: 183-184.

24. Bruno S, Shiffman ML, Roberts SK, Gane EJ, Messinger D, et al. (2010) Efficacy and safety of peginterferon-alfa 2a plus ribavirin in hepatitis C patients with advanced fibrosis and cirrhosis. Hepatology 51: 388-397.

25. Sherrill AK, Khalili M, Straley S, Bollinger K, Roberts JP, et al. (2005) Applicability, tolerability and efficacy of preemptive antiviral therapy in hepatitis C infected patients undergoing liver transplantation. Am J Transplant 5: 118-124.

26. Chalasani N, Manzarbela C, Ferenci P, Vogel W, Fontana JR, et al. (2005) Peginterferon alfa-2a for hepatitis C after liver transplantation: two randomized, controlled trials. Hepatology 41: 289-296.

27. Wang CS, Ko HY, Yoshida EM, Marra CA, Richardson K (2006) Interferon-based combination anti-viral therapy for hepatitis C virus after liver transplantation: a review and quantitative analysis. Am J Transplant 6: 1568-1599.

28. Dumortier J, Scoazec JY, Chevalier P, Boillot O (2004) Treatment of recurrent hepatitis C after liver transplantation: a pilot study of peginterferon alfa-2b and ribavirin combination. J Hepatol 40: 669-674.

29. Biselli M, Andreone P, Gramenzi A, Lorenzini S, Loggi E, et al. (2006) Pegylated interferon plus ribavirin for recurrent hepatitis C infection after liver transplantation in naive and non-responder patients on a stable immunosuppressive regimen. Dig Liver Dis 38: 27-32.

30. Berenguer M, Palau A, Fernandez A, Benlloch S, Aguilera V, et al. (2006) Efficacy, predictors of response and potential risk associated with antiviral therapy in live transplant recipients with recurrent hepatitis C. Liver Transpl 12: 1067-1076.

31. Neumann U, Puhl G, Bahra M, Berg T, Langreher JM, et al. (2006) Treatment of patients with recurrent hepatitis C after liver transplantation with peginterferon alfa-2b plus ribavirin. Transplation 82: 43-47.

32. Sharma P, Marrero JA, Fontana RJ, Greenson JK, Conjevaram H, et al. (2007) Sustained virologic response to therapy of recurrent hepatitis C after liver transplantation is related to early virologic response and dose adherence. Liver Transpl 13:1100-1108.

33. Crespo G, Carrion JA, Coto-Llerena M, Marizo S, Lenz S, et al. (2012) Combinations of simple baseline variables accurately predict sustained virological response in patients with recurrent hepatitis C after liver transplantation. J Gastrointes. 34.

35. Pickolto FP, Trittio G, Lanza AG, Addario L, De Luca M, et al. (2007) Sustained virologic response following treatment for hepatitis C in liver transplant recipients with chronic hepatitis C infection. Hepatology 51: 150-159.

36. Cunha NS, da Cunha MJ, de Morais NB, de Souza M, de Araujo LF, et al. (2006) Peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C after liver transplantation: a randomized study. Gastroenterology 134: 642-650.

37. Sukowski MS, Reddy R, Afshna MH, Bisceglie AM, Zeuzem S, et al. (2011) Anemia had no effect on efficacy outcomes in treatment-naive patients who received telaprevir based regimen on the ADVANCE and ILLUMINATE phase 3 studies. J Hepatol 54: S195S.

38. Sukowski MS, Poodrad F, Manns MP, Bronowicki JP, Reddy KR et al. (2011) Anemia during treatment with peginterferon alfa-2b/ribavirin with or without boceprevir is associated with higher SVR rates: analysis of previously untreated patients and previous-treatment failure patients. J Hepatol 54: S194.

39. Lubbe J (2008) Dermatological side effects. Hot Topics Viral Hep 9: 29-35.
58. Hezode C (2012) Boceprevir and telaprevir for the treatment of chronic hepatitis C: safety management in clinical practice. Liv Int 32: 32-38.

59. Kiser JJ, Flexner C. Direct-acting antiviral agents for hepatitis C virus infection. Annu Rev Pharmacol Toxicol.;53:427-445.

60. Garg V, van Heeswijk R, Lee JE, Alves K, Nadkami P, Luo X (2011) Effect of Telaprevir on the pharmacokinetics of cyclosporine and tacrolimus. Hepatology 54: 20-27.

61. Hulskotte E, Gupta S, Xuan F, van Zutven M, O’Mara E, et al. (2012) Pharmacokinetics interaction between the hepatitis C virus protease inhibitor boceprevir and cyclosporine and tacrolimus in healthy volunteers. Hepatology 56: 1622-1630.

62. Coilly A, Furlan V, Roche B, Barau C, Noël C, et al. (2012) Pratical management of boceprevir and immunosuppressive therapy in liver transplant recipients with hepatitis C virus recurrence. Antimicrob Agents Chemoter 56: 5728-5734.

63. Coilly A, Roche B, Samuel D (2013) Current management and perspectives for HCV recurrence after liver transplantation. Liver Int 33: 56-62.