Risk factors and management of hepatitis C recurrence after liver transplantation

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Abstract

Introduction
Liver disease associated with Hepatitis C virus infection is the most common indication for liver transplantation. Patients with detectable hepatitis C virus ribonucleic acid at the time of liver transplantation inevitably experience graft re-infection. This results in 30% of patients to develop cirrhosis in 5 years post liver transplantation, with a rate of decompensation at 1 year of 40%. Achievement of sustained virological response is associated with stabilization of fibrosis and improvement in graft survival. Standard antiviral therapies using pegylated interferon, ribavirin and retransplantation in decompensated patients were the only options for the treatment.

Direct acting antivirals such as protease inhibitors, polymerase or other non-structural protein inhibitors are new modalities of treatment of Hepatitis C. However, their use in the field of liver transplant is limited due to their safety and tolerance issues. Combination therapy with telaprevir or boceprevir added to pegylated interferon and ribavirin is anticipated to be beneficial but with increased rates of adverse effects and challenges in managing drug–drug interactions between the protease inhibitors and calcineurin inhibitors or sirolimus. The aim of this review was to discuss the risk factors and management of hepatitis C recurrence after liver transplantation.

Conclusion
Hepatitis C virus recurrence is a serious complication in liver transplant patients, where it can cause cirrhosis, graft loss and death in up to 30% of Hepatitis C virus-infected patients. Several strategies to control and minimize the Hepatitis C virus re-infection have been evolving. Direct acting antiviral represents a new era in Hepatitis C virus treatment; however, careful evaluation for drug–drug interactions, tolerance and adverse effects are required.

Introduction
Chronic hepatitis C is one of the leading causes of end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC) worldwide and the main indication for liver transplantation (LT). This reflects the changes in prioritisation of HCC for LT and an increased prevalence of HCC in the Hepatitis C virus (HCV)-infected patients1. Post LT HCV recurrence is universal in patients with detectable serum Hepatitis C virus ribonucleic acid (HCV RNA) at the time of transplantation. The 5-year graft and patient survival rates are 23% lower in HCV-infected LT recipients compared to non-HCV-infected recipients2. The most successful approach to the treatment of recurrent HCV is eradication of the HCV infection with either pre-transplant or post-transplant antiviral therapy, before hepatic decompensation occurs. Nonetheless, these patients commonly develop hepatic decompensation, and antiviral therapy is associated with poor tolerability in pre-transplant patients. Furthermore, it is associated with decreased drug efficacy and an increased risk of adverse effects in post-transplant patients3. In this article, we will review the natural history of HCV disease in LT recipients, identification of risk factors, current and future advances in the treatment of HCV recurrence.

Discussion
The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Natural history of HCV recurrence
HCV infection of the allograft occurs at the time of transplantation and HCV RNA is detectable in the first post-operative week. The natural history of HCV disease is accelerated in post-transplant recipients compared to pre-transplant patients, presenting with high HCV RNA levels3. The HCV RNA levels progressively increase and peak at the fourth post-operative month4. Acute hepatitis develops between 1 and 4 months. Chronic hepatitis develops at 2–4 months. Cases with severe HCV recurrence have been described as early as the ninth post-operative day5. About 10% of patients develop severe disease with cholestatic features with the first year post LT, which can lead to graft loss6. Between 20% and 30% of patients develop cirrhosis within 5 years after LT and the rate of decompensation is 40% within the...
Risk factors associated with the progression of HCV disease

Recipient-, donor-, and transplant-related factors contribute to the risk of recurrent cirrhosis and graft loss.

Recipient factors
Among the transplant recipients, older age is associated with reduced survival but not disease progression. Female gender, African American race, HIV co-infection are all associated with both higher rates of severe HCV disease and reduced graft survival. The risk of fibrosis is 23% higher in women compared to men. The risk of advanced fibrosis is 47% higher in African-American patients compared to non-African-American patients; however, this can be improved using African-American donors.

The graft survival rates are 53% for HIV co-infected patients compared to 74% for HCV mono-infected recipients. In co-infected patients, factors associated with worse outcome are older donor age, high donor risk index, genotype 1, combined kidney-liver transplant, body mass index <21 kg/m² and anti-HCV-positive donor. Interleukin (IL)-28B polymorphisms in recipient and donor are associated with viral response to therapy.

Donor factors
Older donor age is associated with progressive HCV disease and graft loss, and the risk increases with age. There is a 67% higher rate of graft loss for donors aged 41–50 years, 86% higher rate of graft loss for donors aged 51–60 years, and 221% higher rate of graft loss for donors over 60 years of age; so, it is recommended not to use elderly donors. Recipients from anti-HCV-positive antibody donors do not have worse outcome compared to recipients from anti-HCV-negative donors, although donor age more than 45 years is associated with a 58% increased risk of advanced fibrosis.

Donation after cardiac death (DCD) for LT has been increasing mainly because of the shortage of organ donors. Donation after brain death (DBD) is associated with inferior graft survival in HCV recipients compared to non-HCV recipients. Additionally, DCD in HCV recipients showed no difference in graft survival in relation to non-HCV patients. Living and deceased donors have similar post-transplant outcomes and is dependent on the transplant centre’s experience with living donors.

IL-28B gene polymorphisms
IL-28 modulates CD 8 T cell function, and has interferon-like antiviral properties. Both recipient and donor IL-28B gene polymorphisms are associated with viral response to therapy. Decreased fibrosis and SVR to HCV therapy were 100% if both recipient and donor were CC genotype; whereas SVR was only 25% if neither donor nor recipient had CC genotype. However, the IL-28B genotype did not seem to play a role in the overall survival in these patients. Additionally, IL-28B gene polymorphisms affect post-transplant outcomes like the time to recurrence, HCV RNA titres, histological progression, alanine aminotransferase levels and development of HCC. The complex interactions between the donor and recipient IL-28 B gene polymorphisms may also affect outcomes not related to HCV infection like the acute cellular rejection and metabolic disease like post-transplant diabetes mellitus. Routine IL-28 genotyping of recipients and donors may allow for the identification of patients who are at higher risk of developing severe and progressive disease.

Transplant-related factors
HCV transplant patients with evidence of early preservation injury on biopsy are associated with poorer survival outcomes than non-HCV transplant patients with preservation injury or HCV transplant patients without preservation injury. Organ cold and warm ischaemia are other risk factors associated with the severity of recurrence. CMV infection at the time of transplantation is associated with severe fibrosis in patients with HCV infection, and may warrant an extended course of CMV prophylaxis for the CMV-negative recipient and the CMV-positive donor group.

Treatment of acute rejection is associated with HCV disease severity, so mild rejection is not recommended to be treated, especially with corticosteroid boluses and anti-lymphocyte preparations, but with increased maintenance of immunosuppression. Acute cellular rejection and progressive fibrosis are associated with YKL-40 genotypes. Post-LT diabetes mellitus and steatosis, which are actually influenced by the immunosuppressive choices, are associated with a higher risk of progressive fibrosis in HCV recurrence patients.

Viral factors
High pretransplant viral load and HCV genotype 1b are associated with increased severity in HCV disease and also poor graft survival (Table 1). Eradicating HCV before LT would have a major impact on decreasing the incidence of recurrent HCV and its complications.

Role of immunosuppressive agents
Immunosuppressive regimen is directly related to the HCV recurrence for two reasons. First reason is that the degree and composition of the immunosuppressive agents influence the progression of fibrosis. The second reason is the potential drug–drug interactions between the immunosuppressive agents and the direct antiviral agents (DAAs).

Induction therapy
Antithymocyte globulin: The use of rabbit antithymocyte globulin (ATG)
initially gained popularity, but later waned off when several centres reported conflicting results when compared to steroids during induction. A recent study conducted by Uemura et al. analysed 16,898 adult primary LT patients from United Network for Organ Sharing (UNOS) database, who received ATG alone, ATG and steroids, daclizumab alone or steroids alone as induction immunosuppression. The use of ATG with steroids in HCV patients was associated with inferior graft survival compared with daclizumab or steroids alone. 

Alemtuzumab is an anti-CD52 monoclonal antibody that acts on mature lymphocytes but not stem cells. When used with low-dose tacrolimus (Tac) and compared to Tac and steroids in adult LT patients, there was no difference in patient and graft survival, but there was a significant benefit in rejection rates and decreased nephrotoxicity. 

IL-2 receptor antibodies (basiliximab and daclizumab): Induction with basiliximab or ATG is effective in controlling acute rejection at 1 year of LDLT (living donor LT) but may increase the risk of HCV recurrence. Basiliximab used alone or in combination with steroids for induction showed that a steroid-free therapy is associated with a significantly lower treatment failure rate, although histological recurrence rate of HCV was similar in the two groups. A number of studies have been conducted where daclizumab is used in the steroid-free protocol along with Tac and mycophenolate mofetil (MMF) versus Tac, MMF and corticosteroids and no differences in fibrosis were identified. However, there was a significant association between ACR and fibrosis stage at 1 year. As a follow-up of the HCV-3 study, there was no statistical difference in the incidence of ACR, HCV RNA levels, HCV recurrence or patient or graft survival, and these results suggest that a corticosteroid-free regimen of Tac and MMF following daclizumab induction is safe and effective in HCV(+) LT recipients.

Maintenance therapy
Calcineurin inhibitors (CNI), Tac and cyclosporine (CsA) are the currently used main agents. In vitro, CsA is noted to have antiviral property due to Cyclophilin A as the main protein, but its effect in vivo seems questionable. Several studies have compared Tac and CsA regarding the patient and graft survival as endpoints and have shown no difference. A recent study by Irish et al. retrospectively analysed 8809 chronic HCV LT recipients from the UNOS/Organ Procurement and Transplantation Network (OPTN), who received either Tac or CsA as maintenance immunosuppression prior to discharge. Endpoints were death, graft failure and graft failure due to recurrent disease and ACR. Propensity score-adjusted results suggest that CsA-treated patients are at an increased risk of patient death and graft failure [hazard ratio (HR) = 1.17; 95% CI = 1.01 – 1.36 and HR = 1.19; 95% CI = 1.04 – 1.35, respectively] and biopsy-confirmed AR (HR = 2.03; 95% CI = 1.54 – 2.67) compared to Tac-treated patients. While considering histologic HCV recurrence, fibrosis, cholestatic hepatitis, several studies have shown no significant differences.

Azathioprine and MMF: A retrospective study in 2005 studied 3463 HCV post-LT patients from Scientific Registry of Transplant Recipients. Researchers compared LT recipients discharged on Tac, MMF and steroids with the group receiving only Tac and steroids, and found that MMF had no impact on the rate of graft loss due to HCV recurrence, though they had less ACR and better patient and graft survival rates. The benefit of MMF on azathioprine is based on very few studies and the results are not conclusive.
However, the overall degree of immunosuppression may have an impact on the HCV recurrence rather than the independent action of each drug. There is a need for additional trials and analysis.

Mammalian target of rapamycin inhibitors (sirolimus and everolimus): Sirolimus slowed progression and fibrosis in LT recipients with recurrent HCV disease.\(^\text{34-35}\).

**Role of steroids**

Steroids were mainly used either as bolus therapy for the treatment of ACR or for maintenance immunosuppression. The use of steroid boluses to treat ACR should be avoided, as it worsens the progression of fibrosis, increases rate and decreases time of HCV recurrence. It also increases the frequency of acute hepatitis and high risk of early transplant mortality.\(^\text{34}\). The role of steroids in maintenance therapy remains debated, as aforementioned. A steroid-free immunosuppressive regimen was safe and effective, but did not show any advantage for HCV recurrence compared to traditional regimen.\(^\text{37-38}\). The undesirable side-effects of steroids like post-LT diabetes mellitus, hypertension, increased cardiovascular risk, increased risk of infection and bone disease are leading to minimised use of steroids at several transplant centres.

**Diagnosis and monitoring**

The diagnosis of HCV reinfection is established by persistently detectable HCV RNA in the serum after LT and demonstration of hepatitis in the liver biopsy. Non-invasive tests have a role in the monitoring of HCV recurrence, but liver biopsy is the gold standard diagnostic test.\(^\text{39}\). Liver enzymes can be elevated post LT preservation injury, acute and chronic rejection, biliary complications and steatohepatitis; so, liver biopsy is the only test to rely on.\(^\text{3}\) It is imperative to monitor the histological progression of the disease, as this will aid in appropriate intervention of antiviral therapy. Treatment at earlier stage of fibrosis is associated with higher likelihood of achieving sustained viral clearance.\(^\text{40}\).

**Histopathology features of recurrent HCV**

Recurrent HCV can manifest as multiple presentations: (1) Acute hepatitis presents with apoptotic hepatocytes, lobular disarray, spotty inflammation, and portal mononuclear inflammation. (2) Chronic hepatitis presents after 2–3 months, with initial portal-based fibrosis and then accelerated fibrosis.\(^\text{40}\). (3) Severe cholestatic hepatitis (CH) presents with hepatocyte ballooning, spotty acidophilic bodies, kupffer cell hypertrophy and prominent cholestasis. Here, early perisinusoidal fibrosis rapidly progresses to bridging fibrosis and cirrhosis. It is due to direct cytotoxic effect of HCV.\(^\text{41}\). It is seen in 2–9% of HCV disease in post-LT patients.\(^\text{41}\). Onset is rapid within the first 6 months after LT, with very high HCV RNA >10 million IU/ml, high bilirubin >6 mg/dl and high liver function tests. Progressive graft failure occurs within 2–12 months if untreated with antiviral therapy.\(^\text{41}\). (4) Plasma cell hepatitis presents with perivenular inflammation, necrosis and plasma cell-rich infiltrate, likely representing de novo autoimmune disease or a variant of alloimmune response.\(^\text{42}\).

This is seen in patients treated with interferon-based therapy. There may be elevation of autoimmune markers and manifestation of other autoimmune diseases. It can progress rapidly leading to graft loss, so early intervention with discontinuation of interferon and optimising immunosuppression is necessary.\(^\text{42}\).

**Non-invasive tests to assess severity of fibrosis**

Ultrasound hepatic elastography has 98% sensitivity and 84% specificity, and area under receiver operating curve (AUROC) was 0.98 for the presence or absence of cirrhosis and has 83% sensitivity and 83% specificity, and AUROC of 0.90 for defining significant fibrosis. Hence, its utility is limited in detecting early stages of fibrosis when antiviral therapy is recommended. However, ultrasound elastography is useful for assessing transition to cirrhosis, especially when complementing to serum liver fibrosis markers.\(^\text{43}\).

**Prognostic tests**

Identifying rapidly progressive HCV disease is essential, as this is helpful for guiding antiviral therapy. Liver biopsy with stage 2 fibrosis, hepatic venous gradient >6 mmHg at 12 months, and hepatic elastography with liver stiffness value >9.0 kPa at 6 months are good predictors for progressive fibrosis(Table 2).\(^\text{44-45}\).

### Table 2 Prognostic tests for severe post-transplant HCV recurrence\(^\text{44-45}\)

<table>
<thead>
<tr>
<th>Type of test</th>
<th>When to assess (months)</th>
<th>Predictors for cirrhosis and hepatic decompensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver biopsy</td>
<td>12</td>
<td>Stage 2 fibrosis</td>
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<tr>
<td>Hepatic elastography</td>
<td>6</td>
<td>LSM &gt; 9.0 kPa</td>
</tr>
<tr>
<td>Hepatic venous pressure gradient (HPVG)</td>
<td>12</td>
<td>HVPG &gt; 6</td>
</tr>
<tr>
<td>Serum fibrosis markers</td>
<td>12</td>
<td>Serum hyaluronic acid, serum procollagen type III N terminal peptide, tissue inhibitor of metalloproteinase, all &gt;2</td>
</tr>
<tr>
<td>Or serum markers</td>
<td>5</td>
<td>Serum hyaluronic acid &gt;90 µg/L and YKL-40 &gt; 2000 µg/L</td>
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Differential diagnosis

Differentialiating recurrent HCV from mild-to-moderate rejection is the main problem, as inappropriate treatment can lead to adverse outcomes. Several parameters like time from LT, degree of immunosuppression,HCV RNA levels, and degree of biochemical abnormalities in addition to histopathology are considered to differentiate the two. Ancillary investigations like anti-HCV core titres, immunoperoxidase staining for HCV antigens were also reported, but are not in widespread use. C4d, a marker of complement activation, has a specificity of 90% and sensitivity of 68% in distinguishing ACR from HCV recurrence. About 25 genes associated with major histocompatibility complexes 1 and 2, T cell activation, apoptosis and insulin growth factor (IGF) 1 and 2 were found to be overexpressed in patients with ACR. Recently, specific microRNA expression signatures that can differentiate between slow and fast fibrosis in HCV recurrence, HCV and ACR have been demonstrated. Specifically, profibrogenic miRNAs that regulate through IGF1 receptor and vascular endothelial growth factor (VEGF) pathways were identified, which could help differentiate between HCV recurrence and ACR; however, larger translational studies are required to validate their routine use on post-LT patients.

Treatment of HCV recurrence

The goal of the treatment is to attenuate liver-related complications and graft failure. Two approaches are used: the pre-transplant therapy and the post-transplant antiviral therapy, which can be early, within first 6 months post LT, or delayed when there is evidence of significant fibrosis.

Pretransplant antiviral therapy

Pre-transplant antiviral therapy is given with an intent of preventing the graft infection either by achieving an SVR before LT or by achieving undetectable HCV RNA for >8 weeks before LT.

Patients with compensated or mildly decompensated cirrhosis are candidates for the treatment. Treatment of patients with severe decompensated disease, with an MELD score >18 and Child-Pugh Class B or C is contraindicated due to high risk of complications. In mildly decompensated disease, therapy is discontinued in 20–35% of patients due to adverse effects. The risk of infectious complications is high in the first 30 days post LT compared to untreated patients. This risk worsens in patients with high Child-Pugh/MELD score, ascites and low baseline albumin. Several factors predict the response to antiviral therapy like baseline HCV RNA, genotype 2 or 3, receipt of growth factors, duration and adherence to therapy.

Severe adverse effects have been reported with the combination of PI to PEG-IFN and RBV compared to standard therapy in wait list patients. Anaemia, infection-related complicaion and death were reported to be higher with PI.

Post-transplant antiviral treatment

Post-transplant antiviral therapy is given either as early pre-emptive antiviral therapy or as delayed, when evidence of fibrosis is present. Early treatment is considered when there is CH or rapidly progressive disease. The goal is achievement of a sustained virological clearance, as it improves histology as well as graft survival in majority of patients. Antiviral treatment at a mild histologic disease, stage 1–2 fibrosis report higher SVR compared to advanced fibrosis 3–4. SVR rates are about 30% for genotype 1 and 30–100% for genotype 2 and 3. Predictors for SVR are genotype, IL-28B gene polymorphisms with the donor IL-28 B status being more important, viral response and pre-treatment viral load (Table 3). Early virological response is the principal factor for predicting SVR.

Undetectable HCV RNA at 4 weeks likely predicts an SVR of >80% by 48 weeks; conversely, failure to achieve an undetectable HCV RNA by 12 weeks is associated with <2% chance of SVR at 48 weeks.

Role of DAAs

Combination therapy with PI, PEG-IFN and RBV will presumably improve SVR rates, but tolerability is a major concern. Both telaprevir and boceprevir are strong CYP3A4/5 inhibitors. Consequently, they increase the bioavailability of the CNI, CsA and Tac. The dosage of CsA and Tac needs to be reduced when PI

Table 3 Factors influencing sustained virologic response with standard therapy

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
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<tr>
<td>HCV genotype</td>
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<tr>
<td>Baseline viral load</td>
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<tr>
<td>Degree of baseline fibrosis</td>
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<tr>
<td>IL-28B gene polymorphisms in donor and recipient</td>
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<td>Body weight in recipient</td>
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<td>Gender of recipient</td>
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<td>Donor age</td>
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<td>Prior antiviral therapy</td>
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<td>Adherence of antiviral therapy</td>
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<td>Duration of antiviral therapy</td>
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<td>Rapid virological response</td>
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<td>Early virological response</td>
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<td>Use of growth factors</td>
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is given and increased when PI is stopped. Intense monitoring of the CNI levels is necessary to assess the risk of toxicity or rejection due to improper dosage. PI does not need any dose adjustment. A recent study on boceprevir showed that an estimated oral clearance was reduced by 50% with CsA and up to 80% with Tac.

In a case report, daclatasvir, an NSSA inhibitor, is elucidated to have minimal drug–drug interactions and CNI levels were stable throughout the treatment without alterations in the CNI dosage. A recent study showed amelioration of viral response rates in patients with advanced fibrosis, non-responders, and patients with CH while using triple therapy. The rapid virologic response (RVR) at 4 weeks of triple therapy was 43% with boceprevir and 45% with telaprevir. The early virologic response (EVR) at 12 weeks was 71% with boceprevir and 73% with telaprevir. The CsA dose was reduced by 1.3-fold with boceprevir and 4-fold with telaprevir, and the Tac dose was reduced by 5-fold with boceprevir and 35-fold with telaprevir.

**Complications and tolerability of antiviral therapy**

Several immunological complications have been reported with interferon-based therapy like acute rejection, chronic rejection, and autoimmune-like hepatitis/plasma cell hepatitis, with an incidence of 7.2%. Patients developing these complications had a lower graft survival rate of 38.5% compared to treated patients without immune-mediated complications with a graft survival rate of 85.6%. High alkaline phosphatase at the time of initiation of treatment and lack of SVR are the important predictive factors for immunological complications. Another major issue with antiviral therapy is tolerance. Haematological toxicity secondary to haemolysis and infections are common with PEG-INF and RBV. These adverse effects have led to reduction in dosage and discontinuation of antiviral therapy and amplification of immunosuppression. DAAs cause dermatological side-effects and worsen anaemia, with a 20% increase in the incidence and severity of anaemia. Serious infections leading to death have also been reported. Future use of second-generation DAA and PEG-INF free regimens should optimistically improve tolerance and complications.

**Retransplantation**

Retransplantation (reLT) is usually the sole option for transplant patients with complications of recurrent cirrhosis. The 1-year graft survival among reLT patients is 63–70%. Highly selected eligibility criteria are used for reLT, although they vary at different LT programmes. The most common criteria for not considering reLT are recurrent HCV within 6 months, fibrosing CH and renal dysfunction. Various scores for risk stratification have been created to identify patients with high mortality before considering reLT. This situation might evolve in future with the development of neoteric antiviral drugs.

**Conclusion**

HCV recurrence is a serious complication in liver transplant patients where it can cause cirrhosis, graft loss and death in up to 30% of HCV-infected patients. Several strategies to control and minimise the HCV re-infection have been evolving. Modulation of the recipient-, donor-, and transplant-related factors, and early diagnosis and treatment of CMV have demonstrated improved outcomes. It is beneficial to curtail immunosuppression with T cell-depleting therapies and pulsed corticosteroid therapy for the treatment of acute cellular rejection, although it complicates the choice of immunosuppression. As cirrhosis can progress rapidly, it is crucial to identify and treat these patients.

PEG-INF and RBV treatment had been the standard of care, but the preliminary data on DAA like PI/polymerase/non-structural protein inhibitors seems promising. The DAA represents a new era in HCV treatment; however, careful evaluation for drug–drug interactions, tolerance and adverse effects is required.

**Abbreviations list**

ATG, antithymocyte globulin; AUROC, area under the receiver operating curve; Boce, Boceprevir; CH, cholestatic hepatitis; CNI, calcinurin inhibitors; CsA, cyclosporine; CYP, cytochrome; DAA, direct acting antiviral; DBD, donation after brain death; DCD, donation after cardiac death; EPO, erythropoietin; ESLD, end-stage liver disease; EVR, early virologic response; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HLA, human leucocyte antigen; HPVG, hepatic venous pressure gradient; IGF, insulin growth factor; IL-28, interferon-28; LT, liver transplantation; MELD, model of end-stage liver disease; MMF, mycophenolate mofetil; OPTN, Organ Procurement and Transplantation Network; PEG-INF, pegylated interferon; PI, protease inhibitors; RBV, ribavirin; reLT, retransplantation; RNA, ribonucleic acid; RVR, rapid virologic response; SVR, sustained virologic response; Tac, tacrolimus; tela, telaprevir; UNOS, United Network for Organ Sharing; VEGFA, vascular endothelial growth factor.

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autoimmune hepatitis) is a variant of rejection and may lead to a negative outcome in patients with hepatitis C virus. Liver Transpl. 2008 Jun;14(6):861–71.

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