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Special Article

Common issues in the management of patients in the waiting list and after liver transplantation

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ABSTRACT

The present document contains the recommendations of an expert panel of transplant hepatologists, appointed by the Italian Association for the Study of the Liver (AISF), on how to manage the most common aspects of liver transplantation: the topics covered include: new treatments for HCV in patients on the waiting list for liver transplantation; antiviral treatments in patients with HCV recurrence after liver transplantation; prophylaxis for HBV recurrence after liver transplantation; indications for liver transplantation in alcoholic liver disease; and Immunosuppressive therapy. The statements on each topic were approved by participants at the AISF Transplant Hepatologist Expert Meeting (organized by the Permanent Committee on Liver Transplantation in Mondello on 4–5 October 2015), and are graded according to the Oxford classification of levels of evidence.

1. Introduction

The present document contains the recommendations of an expert panel of transplant hepatologists, appointed by the Italian Association for the Study of the Liver (AISF), on how to manage the most common aspects of liver transplantation. The method used to develop these recommendations involved the following steps: the 5 members of the AISF Permanent Committee on Liver Transplantation chose the following main topics of interest: 1. New treatments for HCV in patients on the waiting list for liver transplantation; 2. Antiviral treatments in patients with HCV recurrence after liver transplantation; 3. Prophylaxis for HBV recurrence after liver transplantation; 4. Indications for liver transplantation in alcoholic liver disease; and 5. Immunosuppressive therapy. For each topic, a working group was selected by the members of the AISF committee that consisted of several experts plus a chairman who was one of the 5 members of the AISF committee. In all, 36 transplant hepatologists (experts) were invited to join the groups. They were chosen on the grounds of their competence, role, expertise and publications/research in the field of end-stage liver disease and liver transplantation. The experts involved in the 5 groups are listed in Appendix A. For each group, the chairman identified the relevant questions regarding clinical practice and controversial issues, which were then circulated within each working group to refine the topics and avoid duplications. The working groups independently developed their recommendations, and conducted a systematic literature search and review (using Medline/PubMed) to support all definitions and statements, grading each recommendation according to the Oxford classification of levels of evidence [1]. All working group participants and members of the Permanent Committee on Liver Transplantation took part in the AISF Transplant Hepatologist Expert Meeting organized by the committee in Mondello on 4–5 October 2015. During the first sessions at the meeting, the chairmen of the working groups presented the 5 topics, and the recommendations their group had developed on each question. This was followed by a general debate to refine the recommendations, making any necessary adjustments. At the end of this discussion, each working group met to finalize their position statements in the

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light of the input they had received. At a final general session, the working group chairmen submitted each recommendation to the approval of all 41 participants at the meeting.

2. Antiviral treatment for HCV-positive patients on the waiting list and after liver transplantation (LT)

HCV infection is the leading cause of death due to liver disease, and the most common indication for LT in the US and Europe [2,3]. Recurrent HCV infection in the graft was judged to affect all patients who undergo LT and have active HCV replication [4]. HCV-positive recipients experience a more accelerated progression of liver damage and onset of significant liver fibrosis than immune-competent patients [5], and about 30% of them develop graft cirrhosis within 5 years after LT. Severe HCV recurrence is responsible for the worse outcome in HCV-positive recipients than in patients undergoing LT for other indications [6].

The treatment options for HCV-related liver disease have been evolving rapidly since the approval of the first direct antiviral agents (DAAs), Boceprevir and Telaprevir, in 2011. The new DAAs that became available as of 2014 target different HCV genome regions: NS3, NS5A and NS5B. The NS3 inhibitors already available are Simeprevir and Paritaprevir, while Grazoprevir is expected to become available soon. The NS5A inhibitors currently available are Ledipasvir, Daclatasvir and Ombitasvir, while Elbasvir and Velpatasvir will also be available soon. Two distinct NS5B inhibitors, Sofosbuvir and Dasabuvir, are currently used in combination with NS3 and/or NS5A inhibitors.

The new DAAs are very effective and well tolerated. They have completely changed the picture of anti-HCV therapy. The vast majority of HCV-positive patients with severe liver disease can now be treated successfully either pre- or post-LT. Given their favorable profile, two different approaches can now be pursued:

- treating HCV infection before LT, while the patient is on the waiting list. This policy has some clear advantages in terms of preventing liver graft reinfection, improving liver function (to such an extent that some patients may be delisted), and facilitating post-LT management;
- treating HCV infection after LT, either soon afterwards to take advantage of the removal of the infected native liver and the consequently very low viral burden, or at the time of HCV recurrence, as done in the past.

2.1. Question 1

Which DAA or combination of DAAs can be used in cirrhotic patients listed for LT, and what are the expected sustained virological response (SVR) rates while on the list?

2.1.1. Statement

1a. Sofosbuvir, Ledipasvir, and Daclatasvir can be used in patients with cirrhosis with no need for dose adjustments whatever the functional impairment of the liver **(1b, A)**.

1b. The 3D combo (Paritaprevir/r, Ombitasvir, Dasabuvir), and 2D combo (Paritaprevir/r, Ombitasvir) should not be used in patients with moderate-to-severe hepatic impairment (Child–Pugh B and C). Simeprevir is not recommended in patients with moderate hepatic impairment (Child–Pugh B), and should be avoided in Child–Pugh C (**1b, A**). The 3D or 2D combo, and Simeprevir can be safely used in Child–Pugh A **(1b, A)**.

1c. Since Sofosbuvir requires dose adjustments in cases of an eGFR <30 mL/min (every other day), and in patients on hemodialysis, it is not yet licensed in Italy for use in these clinical conditions [4]. In cases of severe kidney impairment, treatment with Sofosbuvir (if licensed) should preferably be administered after LT. The 3D and 2D combo can be used in patients with an eGFR <30 mL/min, but only if liver function is preserved (Child–Pugh A).

1d. Virological response after DAA therapy is very high, in the order of 90%, in patients with compensated cirrhosis (Child–Pugh A) and high, in the order of 80%, in those with decompensated cirrhosis (Child–Pugh B–C). DAA therapy can therefore be considered for patients listed for LT **(1b, A)**.

2.1.2. Comment

DAAs should be used with caution in LT candidates with severely impaired liver function (Child–Pugh B and C), or severe renal dysfunction (eGFR <30 mL/min), because both of these conditions affect the metabolism of some DAAs [7]. In Italy, the AIFA (*Agenzia Italiana del Farmaco*) warns against the use of Sofosbuvir if the eGFR is <30 mL/min.

2.2. Question 2

What is the impact of DAAs on liver function and inactivation/delisting?

2.2.1. Statement

2a. In Child B patients, a significant improvement in Child–Pugh (>2 points) or MELD score (>3 points) can be achieved in 20–40% of cases. Although this issue is still largely unexplored, preliminary data indicate that delisting is possible in at least 15% of treated patients [8]. Further studies are also needed to identify possible predictors of delisting, and which patients might benefit most from DAA treatment **(4, C)**.

2b. A similar significant improvement in Child–Pugh or MELD score can be achieved in Child Pugh C patients with a MELD score <25, but this improvement may not suffice to enable their delisting, and it may hamper their access to LT. Further studies are required to ascertain to what extent DAA may be beneficial or detrimental to Child–Pugh C patients from an intention-to-transplant perspective **(4, C)**.

2.2.2. Comment

Excellent SVR rates and a very good safety profile can now be achieved with the new DAAs, which have virtually no contraindications, even in decompensated patients on the waiting list. Interestingly, improvements in liver function (albumin and bilirubin levels) and measures of decompensation – including the MELD and Child–Pugh scores – have been reported in patients with advanced liver disease during and shortly after treatment with Sofosbuvir/Ledipasvir [9–11], or Sofosbuvir/Daclatasvir [11–14]. There is still some uncertainty, however, as to whether there is a point of no return, whether this therapy is safe in patients with advanced liver insufficiency, and whether short-term positive effects on hepatic decompensation will translate into long-term clinical benefits [15].

2.3. Question 3

What is the impact of pre-LT treatment on post-LT HCV recurrence?

2.3.1. Statement

3a. Based on current knowledge, the prevention of post-LT HCV recurrence thanks to pre-LT DAA treatment requires a period of virological suppression of at least 30 days. Patients should therefore be placed "on hold" until this goal has been reached, providing their expected waiting time is long enough **(2b, B)**.

2.3.2. Comment

So far, this issue has only been addressed in one study by Curry et al. [16], who showed that pre-LT DAA therapy can effectively prevent HCV recurrence in 95% of Child–Pugh A patients, providing a minimum 30-day period of viral suppression before LT is granted. Though nobody yet knows whether the same results can be achieved in patients with decompensated cirrhosis (Child–Pugh B and C), data from the Solar 1 and 2 studies [2,3] are encouraging: in about 80% of patients with decompensated cirrhosis, 4 weeks of treatment with Sofosbuvir/Ledipasvir and Ribavirin can result in an HCV-RNA below the level of detection.

2.4. Question 4

Who should or should not be treated before LT?

2.4.1. Statement

4a. Based on current research and practice, pre-LT DAA treatment is not recommended in patients with high MELD scores (>25) because of safety concerns and their rapid access to LT. Post-LT DAA treatment is preferable in these patients **(5, D)**.

4b. In Child–Pugh B patients, the likelihood of clinical improvement and a regression of the signs of decompensation makes DAA treatment before LT a reasonable option because some of these patients may be delisted. In Child–Pugh C patients with a MELD <25, the decision whether to treat should be made with caution to ensure that it will not be detrimental to the patient **(4, D)**.

4c. Among patients listed with hepatocellular carcinoma (HCC), pre-LT treatment should be restricted to those expected to have to wait >3 months for LT **(5, D)**.

2.4.2. Comment

The following factors should be considered when deciding whether to treat patients before or after LT:

- the urgency of the case;
- the chances of delisting if the primary indication for LT is decompensated cirrhosis without HCC;
- cost-effectiveness considerations.

Being aware of these factors helps futile DAA treatments to be avoided.

Finally, recent conflicting evidence of a higher risk of HCC recurrence when DAA are given to patients previously treated for HCC needs to be explored in appropriately designed studies [17,18].

2.5. Question 5

Is bridging therapy a valid option?

2.5.1. Statement

5a. Bridging therapy cannot be recommended on a routine basis because of a lack of data on the issue. It might be considered in the event of an unexpected, rapid deterioration in liver function due to incidental events while on DAA therapy, particularly in patients who are still viremic. Any decision to continue DAA treatment across transplant should take into account early liver graft function, postoperative renal function, and drug-to-drug interactions **(5, D)**.

2.5.2. Comment

Very limited data are available on DAA absorption early after the surgical procedure, when liver function may be suboptimal due to ischemic reperfusion injury or an unexpectedly poor graft quality [19]. Another reason for caution concerns the potential interactions between the many drugs needed in the early post-operative period, and because of the risk of acute renal failure.

3. Antiviral treatment in patients with HCV recurrence after liver transplantation

Data emerging from registration trials and clinical practice clearly demonstrate that antiviral strategies involving new DAAs have achieved a SVR in more than 95% of LT recipients with recurrent HCV infection. This means we are now in a "new DAA era" that will substantially change our approach to the burden of HCV in the post-LT setting. The issues that remain to be clarified concern drug-to-drug interactions between DAAs and immunosuppressants, and the safety profile of DAAs in patients with advanced liver disease and/or renal insufficiency. These aspects are of paramount importance in HCV-positive LT recipients because most of them develop renal impairments post-LT due to calcineurin inhibitor toxicity.

3.1. Question 6

What are the main determinants for deciding when to start antiviral therapy for HCV recurrence?

3.1.1. Statement

6a. All patients should be treated as early as possible after LT. Patients who experience recurrent HCV infection with fibrosing cholestatic hepatitis should take higher priority.

Antiviral treatment should be started taking the following issues into account:

- clinical conditions should be stable and patients should be out of the intensive care unit;
- serum immunosuppressant levels should be stable;
- renal function must allow for the use of DAAs **(5, D)**.

6b. In patients who develop decompensated graft cirrhosis due to HCV recurrence, the first option to consider is retransplantation. Antiviral therapy should only be offered as a first option to patients with contraindications for retransplantation whose advanced liver disease represents their main risk of death **(5, D)**.

3.1.2. Comment

Before the advent of DAAs, the recommended time to start antiviral treatment for recurrent HCV infection depended on a patient's persistently elevated alanine aminotransferase levels, and on histologically-confirmed significant graft fibrosis, after rejection, biliary obstruction, and vascular damage had been ruled out. Interferon-based antiviral therapy was associated with high rates of side effects that required dose reductions or premature interruptions of the treatment in the majority of patients, as well as carrying a risk of graft rejection. Early severe HCV recurrences, w fibrosing cholestatic hepatitis, were associated with higher mortality rates and a less effective antiviral treatment. Nowadays, with the new DAAs, these conditions can be treated with good outcomes, as Forns et al. demonstrated [20]: given Sofosbuvir-based antiviral therapy, their patients with early HCV recurrence were more likely to achieve a SVR12 (73%) than patients with established cirrhosis (43%); and a larger proportion of the former patients showed clinical improvements in ascites and hepatic encephalopathy than among the patients with decompensated cirrhosis (69% vs. 45%, respectively). These results suggest that early DAA treatment for patients with recurrent HCV infection after LT may offer an advantage over waiting until patients develop more advanced fibrosis. Secondly, treating HCV infection during the first weeks after LT (i.e. within 30 days) could help to prevent HCV extrahepatic dissemination. It is well known that HCV infection is associated

with injury to organs other than the liver, leading to the onset of HCV-related extra-hepatic manifestations believed to contribute to higher morbidity and mortality rates [21]. In this setting, early HCV eradication may protect against the clinical consequences of extra-hepatic manifestations such as cryoglobulinemic vasculitis, glomerulonephritis and polyneuropathy, as well as lymphoma and diabetes. On the other hand, deferring antiviral treatment for HCV recurrence could favor the onset of irreversible organ injury [22]. Bearing in mind that a SVR12 is still unsatisfactory in DAA-treated patients with decompensated liver cirrhosis due to HCV recurrence, the retransplantation option should be considered first [9,11].

3.2. Question 7

Should per protocol liver biopsies be maintained in the surveillance of liver fibrosis progression?

3.2.1. Statement

7a. Other than for scientific research purposes, no per protocol liver biopsies are indicated in patients who achieve a SVR and have no signs of liver injury **(3b, C)**.

7b. Liver biopsy remains an important tool for the histological assessment of abnormal liver function **(1c, A)**.

3.2.2. Comment

Per protocol liver biopsy has traditionally been considered the reference method for assessing tissue damage and the progression of hepatic fibrosis in patients with recurrent HCV infection [23]. Pathologists have developed robust scoring systems for staging liver fibrosis, such as the semi-quantitative METAVIR score [24], but several non-invasive tests for assessing the severity of graft fibrosis have been introduced in clinical practice in recent years. Gambato et al. [25] showed that measuring liver stiffness is useful both for stratifying patients by their risk of progression and for predicting HCV-related outcomes in recurrent hepatitis C. Bignulin et al. likewise demonstrated that measuring the acoustic radiation force impulse is highly accurate in ruling out significant graft fibrosis due to HCV recurrence [26]. The systematic use of non-invasive tests to monitor graft fibrosis will be of particular interest with a view to confirming in larger series whether the achievement of SVR is associated with the regression of liver fibrosis in the long term [27].

3.3. Question 8

Are there antiviral regimens to be favored, in relation to particular HCV genotypes, for treating HCV recurrence?

3.3.1. Statement

8a. Antiviral regimens should be selected according to the HCV genotype. To treat early HCV recurrence, 12 weeks of antiviral treatment based on Sofosbuvir and NS5A inhibitors (with or without Ribavirin) is preferable to Paritaprevir/Ritonavir plus Ombitasvir (with or without Dasabuvir) – unless the patient has severe renal failure – due to the former's milder drug–drug interactions (5, D).

3.3.2. Comment

In the early weeks after LT, patients are usually given several different drugs in addition to their immunosuppressive medication, so transplant hepatologists should pay attention to drug-to-drug interactions when deciding to use DAAs [28]. Given the relatively recent introduction of DAAs in clinical practice, further clinically significant drug–drug interactions are likely to be discovered in the near future. An unexpected example that emerged only very recently concerns the onset of symptomatic bradycardia when Amiodarone was co-administered with Sofosbuvir in combination with Daclatasvir, Simeprevir or Ledipasvir [29]. As for the duration of antiviral treatments, a short course of antiviral therapy should be preferred to optimize patient adherence [30].

3.4. Question 9

Should Ribavirin always be maintained?

3.4.1. Statement

9a. The benefit of using Ribavirin in HCV-positive liver recipients was not clearly demonstrated in randomized trials. Data deriving from studies conducted on immune-competent patients indicate that, when treating HCV genotype 1 and 4 infections with 12-week antiviral regimens, Ribavirin could be maintained if the treatment involves Sofosbuvir plus Ledipasvir and Daclatasvir. Combinations of Paritaprevir/Ritonavir plus Ombitasvir and Dasabuvir, or Sofosbuvir plus Simeprevir for genotype 1b, can be used without Ribavirin, but these combinations are responsible for important drug–drug interactions. A combination of Sofosbuvir plus Daclatasvir can be used without Ribavirin to treat HCV genotype 2 for 12 weeks. Ribavirin should be maintained when treating patients with genotype 3 with advanced liver disease. A prolonged 24-week treatment with Ribavirin should be considered for patients who failed previous DAA regimens **(1c, B)**.

9b. A longer (24-week) antiviral treatment should be preferred for treating genotypes 1, 3 and 4 in patients in whom Ribavirin is contraindicated or poorly tolerated **(4, B)**.

Renal impairment is a common complication of treatment with calcineurin inhibitors, which are used as the backbone immunosuppressant in LT patients. Ribavirin is a synthetic nucleoside analog metabolized by the liver and excreted by the kidney, so higher serum levels of Ribavirin and its metabolites are seen in patients with renal impairment. LT patients tend to have more side effects, particularly hemolytic anemia, which in many cases necessitate dose reductions or discontinuation of this drug. Antiviral treatment schedules without Ribavirin with a demonstrated efficacy against recurrent HCV infection are consequently needed. For the purpose of treating HCV recurrence, the optimal duration of antiviral treatments and the need for Ribavirin are still controversial issues because no studies have been performed to answer the question of whether or not Ribavirin is necessary, particularly in 12-week antiviral regimens and in cases of non-genotype 2 HCV infection. It is largely accepted, and recommended in current clinical guidelines, that Ribavirin should be used in 12-week treatment schemes, or patients should be treated without Ribavirin for 24 weeks [31]. In kidney transplant recipients with F0–F2 METAVIR chronic hepatitis C, the combination of Sofosbuvir plus Ledipasvir without Ribavirin has been associated with very high SVR12 rates, suggesting that Ribavirin may not be essential in LT recipients with mild disease [32].

3.5. Question 10

How should antiviral treatment efficacy and safety be monitored?

3.5.1. Statement

10a. The efficacy of antiviral treatment is judged mainly on the grounds of a serum HCV-RNA measurement (using high-sensitivity real-time PCR) obtained 12 weeks after stopping the treatment **(1a, A)**.

10b. Since HCV protease inhibitors have important drug–drug interactions with calcineurin inhibitors, serum levels of immunosuppressive drugs should be checked frequently. Serum levels of hemoglobin, creatinine clearance, and liver function tests should

be considered the mainstay for monitoring the safety of antiviral treatment **(3a, C)**.

3.5.2. Comment

In the less recent clinical trials, a SVR with interferon-based regimens was defined as HCV-RNA serum levels below a designated threshold 24 weeks after stopping the therapy (SVR24). More recently, the regulatory authorities changed this definition of a SVR to mean the absence of HCV-RNA in the serum 12 weeks after stopping the treatment (SVR12), considered a valid marker of a patient cured of any HCV infection. The concordance between SVR12 and SVR24 was recently assessed adopting new DAA regimens [33].

The safety and efficacy profiles of the new DAA regimens were investigated in patients with HCV recurrence, including those with fibrosing cholestatic hepatitis [9,14,34–36]. Although DAAs are generally considered safe in such patients, who are difficult to treat, serum levels of immunosuppressants and hemoglobin (especially if a regimen includes Ribavirin), creatinine clearance and liver function should be checked routinely throughout the treatment and monitored closely afterwards because the achievement of a SVR has been associated with an accelerated liver metabolism of immunosuppressants, leading to the risk of their serum levels dropping.

3.6. Question 11

Which antiviral regimens should be adopted in cases of previous treatment failure?

3.6.1. Statement

11a. A 24-week retreatment with combinations of Sofosbuvir plus Ribavirin and an NS3 (where NS5A inhibitors have failed), or an NS5A inhibitor (where NS3 inhibitors have failed) seems to be a reasonable rescue strategy if antiviral retreatment cannot be deferred **(3b, B)**.

11b. A retreatment strategy guided by genetic analyses of drug resistance can be proposed for patients with less advanced liver disease in whom combinations based on polymerase plus NS3 inhibitors have failed. There is a stronger recommendation for the performance of genetic analyses of resistance before retreatment in patients in whom a combination based on polymerase plus NS5A inhibitors has failed **(5, D)**.

3.6.2. Comment

The treatment of HCV infection with DAAs is associated with high rates of SVR. The factors associated with any failures of this treatment include advanced liver fibrosis, previous failure to respond to DAAs, higher baseline viral loads and the presence of viral particles with resistance-associated substitutions (RAS). These RAS can occur in different genotypes and subtypes if the NS3, NS5A and NS5B regions of HCV, either at the baseline or (more often) as a result of the failure of DAA treatment. Genetic testing is becoming increasingly common nowadays for patients unresponsive to different combinations of DAAs. One study was conducted on 14 patients infected with HCV genotype 1 failing to respond to Sofosbuvir plus Ribavirin for 24 weeks, who were retreated with Sofosbuvir plus Ledipasvir for 12 weeks, and all patients achieved a SVR [37]. This cohort included seven patients with advanced fibrosis/cirrhosis. The S282T variant was transiently detectable in one patient after initial therapy with Sofosbuvir and Ribavirin was stopped, while wild-type NS5B polymerase sequences were observed in all the other patients [37]. In another study, patients infected mainly with HCV genotype 3 who achieved no SVR after 12–24 weeks of Sofosbuvir plus Ribavirin were retreated with either PEGylated interferon with Ribavirin and Sofosbuvir for 12 weeks, or with Sofosbuvir plus Ribavirin for 24 weeks. An interim analysis conducted as part of this study showed that the conventional triple therapy was very effective (SVR12 92%), while the SVR rate after another course of the Sofosbuvir plus Ribavirin combination therapy was only 63% [38]. One patient infected with HCV genotype 1 not responding to Sofosbuvir plus Ledipasvir after 8 weeks was successfully retreated using the same regimen with the addition of Ribavirin for 24 weeks, despite the presence of highly resistant NS5A RAVs (per esteso prima?) and a S282T variant responsible for a marked resistance to Sofosbuvir [39]. On the other hand, 41 patients in whom 8–12 weeks of Sofosbuvir plus Ledipasvir, with or without Ribavirin, had failed were given salvage treatment with Sofosbuvir plus Ledipasvir for 24 weeks, achieving an overall SVR rate of 71%. In the subgroup of 11 patients unresponsive to 12 weeks of the previous treatment, only 5 (45%) achieved a SVR, and the presence of NS5A RAVs was associated with treatment failure [39]. Further studies are ongoing to investigate salvage therapies in patients not responding to DAAs. For the time being, the guidelines recommend waiting to see the results of ongoing clinical studies before retreating patients without severe liver disease, or considering their retreatment with a different class of DAAs, and checking their genetic analyses of resistance, particularly for patients urgently needing retreatment [7].

4. Prophylaxis for HBV recurrence after liver transplantation

Remarkable improvements have been made in the outcome of patients transplanted for hepatitis B virus (HBV) in the past two decades. Using standard therapies, the vast majority of transplant recipients are protected against recurrent HBV infection after liver transplantation, and patients transplanted for HBV have a 5-year survival in excess of 80%, which is currently the benchmark for LT performance in adults [40]. These impressive results reflect the success of prophylactic therapies in preventing graft reinfection as well as the greater efficacy of antiviral drugs for managing recurrent post-LT HBV disease. It is crucial to consider the risk of HBV recurrence in order to plan effective strategies against HBV reactivation post-LT. Risk factors associated with high rates of HBV reactivation are a high viral load prior to the transplant, HBeAg positivity, HIV co-infection, non-compliance, HCC at the time of the transplant, and drug resistance [41,42]. Hepatitis B immunoglobulins (HBIG) have been the core component of HBV prophylaxis since the landmark study by Samuel et al. in 1991, who showed that HBV recurrence could be prevented by the long-term administration of HBIG in 80% of non-viremic transplant patients [43,44]. When the first oral antiviral drug against HBV (Lamivudine) became available, antiviral monotherapy was attempted as an alternative, but failed to maintain results on a par with those achieved by HBIG in terms of HBV recurrence. Thereafter, long-term HBIG and nucleos(t)ide analogues (NAs) became the standard prophylaxis for all patients, whatever their replication status at the time of transplantation [45–47]. High doses of intravenous (iv.) HBIG were often used initially, making this prophylaxis expensive, but the more recent adoption of lower doses of HBIG combined with NA(s) has made the treatment just as effective and less costly, particularly when long-term prophylaxis with intramuscular (im.) or subcutaneous (sc.) low-dose HBIG is combined with more potent third-generation NAs (Entecavir, Tenofovir) [48]. Although combination prophylaxis has proved very successful, some limitations of HBIG are recognized. It requires parenteral administration, for instance, which is inconvenient for patients and care providers. But the feasibility of HBIG-free strategies is still debated, either because of the particular characteristics of large published cohort, or because of different definitions of HBV recurrence (the historical persistence or reappearance of HbsAg vis-à-vis the reappearance of HBV-DNA

despite antiviral treatment), and the potential residual risk of HCC in immunocompromised patients after the reappearance of HBsAg. Some authors suggested in the past that it might be safe to interrupt HBIG after LT in selected patients (those who undergo LT with undetectable HBV-DNA) [51], and others more recently proposed completely withdrawing HBV prophylaxis after at least 6 years of post-LT follow-up in recipients with undetectable serum and total intrahepatic HBV-DNA, and covalently closed circular DNA at the time of their transplant [52].

4.1. Question 12

Which is the best prophylactic regimen for preventing HBV recurrence after LT in HBV+ recipients?

4.1.1. Statement

12a. Nowadays, the best prophylactic regimen – in terms of safety and efficacy – is a combination of third-generation NAs (Entecavir, Tenofovir) plus low-dose HBIG. All transplant centers in Italy adopt this approach in patients transplanted for HBV-related liver disease **(5, B)**.

4.1.2. Comment

Recent data emerging from a retrospective study conducted in Far East Countries indicate that monotherapy with third-generation NAs (Entecavir) is effective in preventing recurrent HBV infection after LT in HBeAg+ recipients (the rate of recurrence was 4–5%) [49,50]. These findings suggest that the current use made of third-generation NAs can minimize the need for HBIG and prove more cost-effective in the long term, but prospective data from dedicated clinical trials will be needed to enable an informed decision on whether to adopt a regimen with third-generation NAs alone (and no HBIG).

4.2. Question 13

What is the recommended dose of iv. HBIG to administer perioperatively after LT (in the anhepatic phase and 1st postoperative week)?

4.2.1. Statement

13a. The most widely adopted regimen involves the use of 10.000 IU iv. in the anhepatic phase, then 5.000 IU iv. daily until day 7 after LT. Some Italian centers are currently using smaller amounts of HBIG in this perioperative phase, however, with unchanged long-term results, in terms of efficacy **(5, B)**.

4.2.2. Comment

The high iv. dosages of HBIG still used in the perioperative phase at many centers probably come from the time when HBIG were used without NAs, or combined with first-generation NAs (Lamivudine) [51,52]. Now that third-generation NAs (Entecavir, Tenofovir) have become available, lower doses of HBIG can be used in the perioperative phase too. There has been encouraging recent evidence to suggest that administering iv. HBIG based not on preset dosage regimens, but on HBsAg quantification during the initial post-operative clinical course, can maintain a protective anti-HBs titer while saving on the total amount of HBIG required.

4.3. Question 14

What is the recommended long-term prophylaxis regimen, in terms of route and timing of HBIG administration?

4.3.1. Statement

14a. Lifelong combined NAs + HBIG prophylaxis is administered to prevent HBV recurrence after LT. The currently adopted regimen for this prophylaxis combines third-generation NAs (Entecavir, Tenofovir) with low-dose parenteral HBIG. The im. and sc. routes of HBIG administration have proved equally effective in providing protection, and they can be used starting from shortly after the LT procedure. For long-term protection, the anti-HBs titer should be kept at around 100 IU **(5, B)**.

4.3.2. Comment

Lifelong prophylaxis with NAs and HBIG to maintain an anti-HBs titer of around 100 IU is currently managed using two different approaches. Some centers deliver it *on demand* (the amount and timing of HBIG administrations being based on anti-HB titers), while others prefer a fixed schedule (usually 2000 IU a month, irrespective of the patient's anti-HBs titer). The two approaches seem to assure the same clinical efficacy and safety, but their cost-effectiveness is unknown and studies are needed to clarify this issue.

4.4. Question 15

What is the recommended long-term prophylaxis regimen for preventing HBV reactivation after LT in recipients of anti-HBc+ grafts?

4.4.1. Statement

15a. Long-term mono-prophylaxis with NAs (Lamivudine) is mandatory in recipients of anti-HBc+ grafts to prevent HBV reactivation after LT. There is evidence from several sources to suggest that HBIG is not helpful in this clinical setting, so they should not be used **(5, B)**.

4.4.2. Comment

Recipients of anti-HBc+ grafts are usually given lifelong mono-prophylaxis with NAs (Lamivudine) [53–55]. It has been suggested, however, that this prophylaxis might be withdrawn a few years after LT in certain subgroups of patients (depending on their serological HBV status pre-transplant, i.e. patients with an anti-HBcAb+/anti-HBsAb+ profile). A dedicated controlled study will be needed before this approach can be translated into clinical practice.

5. Indications for liver transplantation for alcoholic liver disease

Alcoholic liver disease is the second most common indication for LT, accounting for approximately 20% of all primary transplants in Italy, 40% in Europe and about 25% in the United States. Although outcomes of LT for alcohol-related liver disease are comparable with those of LT for other etiologies, transplant hepatologists and clinicians have to face several challenging issues when considering patients with alcoholic liver disease for LT. It is hard to say whether the length of the period of pre-LT abstinence has a specific role in predicting post-LT abstinence, or whether it is more useful to identify patients whose condition will improve with abstinence, and who will survive without LT. Most transplant programs demand 6 months of abstinence before considering a patient suitable for LT, but the patient's psycho-social assessment seems more important for identifying potential risk factors of alcohol relapse and establishing the real likelihood of long-term abstinence after LT. Acute alcoholic hepatitis is considered a contraindication for LT at most transplant centers, though early LT in selected patients with a first episode of severe alcoholic hepatitis unresponsive to steroid

therapy has been shown to improve survival. The LT option should therefore be explored within strict criteria in this setting.

5.1. Question 16

Is a 6-month period of abstinence required before a patient can be considered eligible for liver transplantation?

5.1.1. Statement

16a. Patients with alcohol-related cirrhosis (with or without HCC):

- the six-month period of abstinence is an arbitrary definition, but remains a valid criterion for this subset of patients, mainly because it enables the liver's potential for functional improvement to be assessed **(4, C)**;
- all patients should undergo a multidisciplinary assessment with an addiction specialist, psychiatrist, psychologist and/or social worker to identify risk factors for non-adherence before and after LT **(5, D)**;
- if patients' liver disease has not stabilized within 6 months, they can be considered for LT;
- if their liver function deteriorates, LT is indicated even without 6 months of abstinence **(5, D)**.

16b. Patients with alcohol-related cirrhosis (+/− HCC) with a life expectancy of less than 6 months:

- all patients should undergo a multidisciplinary assessment with an addiction specialist, psychiatrist, psychologist and/or social worker to identify risk factors for non-adherence before and after LT (5, D).

5.1.2. Comment

The rationale behind this strategy is to consider the period of abstinence before LT as a tool for avoiding LT in patients whose liver function will improve with abstinence alone, and identifying patients at higher risk of post-LT alcohol relapse. This approach can be applied to patients with a life expectancy beyond 6 months. For patients with a shorter life expectancy, the 6-month period of abstinence is not mandatory, and other parameters should be considered to judge the risk of post-LT alcohol relapse. Some of the most important are family and social support, prior psychiatric comorbidities, unsuccessful attempts at rehabilitation, and a family history of alcoholism [56].

5.2. Question 17

How should abstinence be monitored while patients are on the waiting list?

5.2.1. Statement

17a. Carbohydrate deficient transferrin (CDT) assays are not useful for assessing alcohol consumption during the required period of abstinence **(4, C)**.

17b. Where available, urinary ethyl glucuronide (uEtG) assay should always be performed in stable cirrhotic patients **(4, C)**.

17c. The frequency of monitoring by the addiction specialist, psychologist and/or psychiatrist can vary, at the discretion of the various specialists **(5, D)**.

5.2.2. Comment

Transplant hepatologists and clinicians involved in the care of patients with alcoholic liver disease should focus on detecting any form of alcohol use during the assessment process or while patients are on the waiting list for LT. Among the screening tools available, CDT assay is of limited use because it is unable to identify the intake of small quantities of alcohol, and serum levels are often unpredictable because of the interference of hyperbilirubinemia [57]. Instead, uEtG assay is considered a reliable and useful screening tool in the LT setting [58,59] as it is detectable even after the consumption of very small amounts of ethanol (<10 g), and for up to 80 h after the last drink was ingested [60].

5.3. Question 18

Is a patient with polysubstance abuse and end-stage liver disease a potential candidate for liver transplantation?

5.3.1. Statement

18a. Smoking and the use of cannabinoids and methadone do not make LT absolutely contraindicated, but patients with polysubstance abuse need to be adequately assessed by a multidisciplinary team (addiction specialist, psychiatrist, psychologist, social worker) to examine how they used these substances and their potential dependence **(2b, B)**.

18b. The active use of opioids, cocaine and synthetic drugs is an absolute contraindication for LT **(2b, B)**.

5.3.2. Comment

Although smoking is not considered an absolute contraindication for LT, it should be mandatory for patients to stop smoking before LT because it is associated with higher post-transplant morbidity and mortality rates.

5.4. Question 19

What is appropriate for the management of alcohol and/or other substance use/abuse before liver transplantation?

5.4.1. Statement

19a. Anti-craving therapy options are limited before LT, but gamma-hydroxybutyric acid (GHB), Baclofen and Topiramate can be used in cirrhotic patients **(3, C)**.

19b. Individual or group-based psychological support should be offered to these patients, including specialist help with the management of alcohol-related problems or psychiatric disorders, and self-help groups **(4, C)**.

19c. Hepatological outpatient visits should be scheduled according to the severity of a patient's liver disease:

- at least every 3 months for stable disease;
- at least once a month for unstable/severe liver disease **(4, C)**.

5.4.2. Comment

New studies are needed to improve our knowledge in this field, to define a follow-up protocol that should be adopted by all transplant centers in Italy, and to nurture collaborations with services outside the hospital, including self-help groups, mental health services, and drug addiction services.

5.5. Question 20

Is acute alcoholic hepatitis, as a first episode of decompensation in patients with chronic liver disease, an indication for liver transplantation?

5.5.1. Statement

20a. Patients with acute alcoholic hepatitis, as a first episode of decompensation in chronic liver disease, and not responding

to steroid therapy can only be considered for LT if the following conditions are met **(2b, B)**:

- total consensus of the paramedical and medical staff;
- no comorbidities;
- social integration;
- supportive family members;
- psychiatric assessment and addiction profile.

Non-responders to steroid therapy are identified on the grounds of a Lille score ≥0.45 or worsening liver function by day 7 **(1b, A)**.

Patients unsuitable for steroid therapy, with a MELD score >30, can only be considered for LT if they meet the above criteria **(2b, B)**.

5.5.2. Comment

It has been demonstrated that early LT for severe acute alcoholic hepatitis only has potential as a therapeutic option for patients not responding to steroid therapy if specific, strict selection criteria are met [61]. Sequential infection screening before steroid therapy is an efficient way to identify patients at high risk of developing infections [62]. Antibiotic therapy can be administered as an adjuvant to steroids in the setting of severe acute alcoholic hepatitis [63]. Studies are warranted on the usefulness of fungal prophylaxis before LT in the light of reported deaths due to aspergillosis. Further multicenter studies are needed to explore this controversial issue properly.

20b. The diagnosis of acute alcoholic hepatitis is based mainly on a clinical examination, but a transjugular liver biopsy should be obtained, where the option is available, at highly-experienced centers **(4, C)**.

A histological diagnosis is not required for steroid therapy **(4, C)**.

Any presence of infections and/or sepsis should always be ruled out before starting steroid therapy **(2b, B)**.

Steroid therapy should be administered to patients with a discriminant factor (DF) ≥32 and should be based on methylprednisolone 40 mg/day **(2b, B)**.

When patients are potential candidates for LT, steroid therapy should always be provided at a liver transplant center **(5, D)**.

5.5.3. Comment

Although acute alcoholic hepatitis is considered a clinical syndrome and its diagnosis is often based on clinical and biochemical findings, the role of liver biopsy in establishing a diagnosis of alcoholic hepatitis remains controversial. This is due to the higher risk of bleeding in such patients as they often present with coagulopathy and thrombocytopenia. Transjugular liver biopsy is consequently preferable, if available, since the procedure is safe even in patients with a low platelet count [64]. In our opinion, a histological diagnosis is not a prerequisite for steroid therapy at experienced centers, though this attitude is not perfectly in line with the EASL Clinical Practice Guidelines on Liver Transplantation [65].

5.6. Question 21

What is the correct follow-up after LT?

5.6.1. Statement

21a. A post-LT assessment by the addiction specialist, psychologist and/or psychiatrist (depending on availability at the transplant center) is strongly recommended, at intervals suited to the patient's characteristics and transplant center variables. The high risk of de novo tumors in these patients warrants a strict, regular follow-up **(5, C)**.

21b. This is mandatory for patients transplanted with potential risk factors for post-LT alcohol relapse **(5, C)**.

21c. Anti-craving therapy is feasible in the post-LT setting **(5, D)**.

5.6.2. Comment

An adequate post-LT follow-up is crucial in order to contain the rate of alcohol relapse. This should include assessment by the addiction specialist, psychologist and/or psychiatrist, and should focus on patients with specific pre-LT risk factors for post-LT alcohol relapse. Pharmacological therapy can be considered after LT.

5.7. Question 22

Is graft dysfunction due to alcohol relapse a potential indication for liver re-transplantation?

5.7.1. Statement

22a. Graft dysfunction due to alcohol relapse is considered a contraindication for liver re-transplantation **(2b, B)**.

5.7.2. Comment

To date, only a few cases have been reported of liver re-transplantation for graft dysfunction due to alcohol relapse.

6. Immunosuppressive therapy

As a general concept, a transplanted liver is better "tolerated" by the recipient than other organs, so liver recipients are maintained on lower levels of immunosuppression than other organ transplant recipients. In a small percentage of selected LT recipients, the allograft may even survive long after immunosuppressant therapy has been withdrawn. Rejection of transplanted livers is nonetheless a diagnostic challenge and there is an ongoing search for reliable and readily-available early markers of this condition. Immunosuppression protocols used at liver transplant centers differ widely and there is a general tendency for individual recipient-tailored immunosuppression, generally based on different indications for LT and comorbidities. Concerning the indications for LT, HCC and recipient serum HCV RNA positivity (though the latter will become rare in future due to pre-LT pharmacological HCV clearance) are two conditions that could, in principle, influence immunosuppressive strategies. As for pre- and/or post-transplant comorbidities, renal dysfunction, metabolic syndrome (or single components thereof, such as obesity, diabetes, hypertension and dyslipidemia) and post-LT de novo neoplasms could also dictate the choice of different immunosuppression protocols.

6.1. Question 23

What are the suggested regimens for administering steroids by recipient pre-transplant diagnosis and post-transplant follow-up?

6.1.1. Statement

23a. Based on the available evidence, steroid-free immunosuppression after LT should be considered in all LT recipients except for patients transplanted for autoimmune hepatitis, primary biliary cholangitis, or primary sclerosing cholangitis **(1a, A)**.

6.1.2. Comment

Except in patients with autoimmune hepatitis, primary biliary cholangitis or primary sclerosing cholangitis, the routine use of steroids in the first 6 months after LT does not improve graft or patient survival [66,67], and it is associated with a higher incidence of CMV infection and more severe HCV recurrences after LT [68–70].

6.2. Question 24

When should a calcineurin-sparing/withdrawal strategy be adopted in the case of renal dysfunction, and how should this strategy be implemented?

6.2.1. Statement

24a. In patients with pre-LT renal dysfunction, it is advisable to delay the introduction of calcineurin inhibitors (CNIs), or to reduce the dose of CNIs and add mycophenolic acid (MMF) or enteric-coated mycophenolate sodium (EC-MPS), and/or IL-2 receptor antibodies **(1b, A)**.

24b. In patients who develop renal failure after LT, a combination of MMF or EC-MPS and reduced-dose Tacrolimus (TAC) is recommended **(1a, A)**.

24c. A valid alternative is a combination of Everolimus (EVE) with reduced-dose TAC **(1b, B)**.

6.2.2. Comment

In patients with pre-LT renal dysfunction, the delayed introduction or reduced doses of CNIs under the protection of MMF and/or IL-2 receptor antibodies is associated with an improvement in renal function in the short and mid-term, with no increase in the risk of liver rejection [71]. In patients who develop renal failure after LT a combination of MMF and reduced-dose TAC has proved a safe and effective approach to ameliorating renal dysfunction [72–75]. Gastrointestinal symptoms in LT recipients are more common with MMF treatment than with EC-MPS, and conversion from MMF to EC-MPS leads to symptom improvement [76–80].

Compared with standard therapy, a combination of EVE with reduced-dose TAC as a de novo (within 1 month of the transplant) or as a conversion immunosuppressive regimen is associated with an equally effective immunosuppression and no renal toxicity. The risks of adverse wound healing events with EVE is associated with the administration of a loading dose. Using lower doses of EVE without a loading dose is not associated with any increased risk of wound healing complications. No conclusive data are available on the impact of EVR on wound healing in the event of its de novo use after LT [81,82].

6.3. Question 25

What are the immunosuppressive strategies for HCV-RNA+ recipients?

6.3.1. Statement

25a. Either TAC-based or cyclosporine (CsA)-based immunosuppression can be used in HCV-infected patients after LT **(1a, A)**.

25b. Steroid-free immunosuppression is safe in HCV-positive LT recipients **(1a, B)**.

6.3.2. Comment

Neither the HCV recurrence-related mortality, graft loss and retransplantation rates, nor the incidence of histological HCV recurrence, is associated with the choice of CNIs administered [81]. Steroid-free immunosuppression is safe in HCV-positive LT recipients and does not increase the risk of rejection or of fibrosis progression [82].

6.3.3. Question 26

What are the immunosuppressive strategies for patients transplanted for HCC?

6.4. Statement

26a. Both CyA and TAC reportedly raise the post-LT risk of HCC recurrence in a dose-dependent manner [4].

26b. There is no strong evidence for the use of immunosuppressive regimens based on mammalian target of rapamycin inhibitors (mTORi) to reduce HCC recurrences **(2b, B)**, but they do seem to reduce the rate of HCC recurrence in low-risk (Milan Criteria in criteria) patients **(1a, B)**.

6.4.1. Comment

It is still not clear which immunosuppressive therapy is best to reduce HCC recurrences, despite the anti-proliferative effect of mTORi and the positive effect of CNI weaning [83]. Although there is no strong evidence for the use of mTORi-based immunosuppressive regimens [84], the SILVER study has suggested a lower HCC recurrence rate in low-risk patients (Milan in criteria) [85].

6.5. Question 27

Which immunosuppressive strategies are appropriate when a de novo neoplasm develops after LT?

6.5.1. Statement

27a. The risk of de novo malignancy is 2–4 times higher in transplant recipients. The types of cancer with the highest standardized incidence ratio after LT related to viral infections originate from the immune system **(2b)**.

27b. The incidence of the overall cancer is lower when mTORi immunosuppression regimens are adopted, but there is no strong evidence to support the use of mTORi to reduce the incidence of the overall cancer **(2b, B)**.

6.5.2. Comment

For the time being, there is no strong evidence to indicate which is the best immunosuppressive therapy in cases of de novo neoplasms post-LT [84,86], so minimizing immunosuppression, screening and avoiding risk factors remain the main recommendations for managing the risk of de novo malignancies [87].

6.6. Question 28

Which immunosuppressive strategies are appropriate in cases of metabolic syndrome?

6.6.1. Statement

28a. Based on the currently available evidence, there is no specific immunosuppressive therapy for managing patients with metabolic syndrome (MS). It is reasonable to consider tailored therapies according to each patient's single MS components, especially in the event of diabetes and hypertension **(2b, B)**.

6.6.2. Comment

The prevalence of MS is high (38%–50%), and rising among post-LT patients, and is associated with a higher likelihood of cardiovascular and cerebrovascular events [88]. Different types of immunosuppression (TAC vs. CsA vs. others) assessed at 1 year, and corticosteroid use in the first 3–6 months were not significantly associated with the subsequent onset of MS [89,90]. In the case of diabetes (considered as a separate MS component), only methylprednisolone boluses emerged as independent risk factors for the onset of post-LT diabetes [91]. A meta-analysis of sixteen prospective, randomized comparative studies reported a 13.4% incidence of new-onset diabetes in patients after solid organ transplantation, with a higher incidence in patients receiving TAC than in those given CsA (16.6% vs. 9.8%). This trend was observed across

renal, liver, heart and lung transplant groups [92]. The association between BMI and/or obesity at 1 year and type of immunosuppression (TAC vs. CsA vs. others) was not found statistically significant [93]. Hypertension occurs with both types of CNI, but more commonly with CsA, compared with which TAC was found associated with a lower incidence of hypertension and cardiovascular disease [89]. Early conversion from CNI therapy to either Sirolimus or Everolimus is associated with higher serum triglyceride and cholesterol levels [94,95].

6.7. Question 29

How should acute, late acute, and chronic rejection be diagnosed?

6.7.1. Statement

29a. Blood concentrations of immunosuppressive drugs should be assayed as standard procedure **(4, B)**.

29b. Generic TAC and MMF can be used safely as a conversion from original branded drugs **(4, C)**.

29c. In LT recipients with an unexplained graft dysfunction, a biopsy should be obtained to rule out acute rejection **(3, B)**.

29d. The value of searching for preformed (i.e. pre-LT) donor-specific antibodies (DSAs) in the serum is still controversial because its role in immune-mediated liver damage is not clear **(4, C)**.

29e. Persistent DSA positivity may be associated with early and severe acute antibody-mediated rejection (ABMR) **(2b)**.

29f. Complement component 4d (C4d) staining in liver biopsy should only be used in selected cases when isolated or predominantly ABMR is suspected **(4, C)**.

6.7.2. Comment

The use of generic TAC and MMF has proved safe and cost-effective as a strategy for conversion from original branded drugs. Data on the de novo use of generic immunosuppressants after LT are still not conclusive [96–98].

DSAs occur in up to 15% of LT recipients, but disappear after the procedure in most patients [94,99].

De novo DSAs develop in 8–14% of LT recipients, depending on how soon after the operation the assay is performed and on the mean fluorescence intensity cut-off used to define DSA positivity. De novo DSA development may be associated with acute antibody-mediated rejection [100,101].

DSAs detected in maintenance LT patients are associated with a higher risk of acute rejection and a shorter allograft survival [99,101–103].

C4d staining is not specific for any particular liver graft injury and can only provide additional information to consider in the context of other pathological and clinical features. It may be a marker of isolated ABMR (a rare occurrence in liver grafts), or of antibody-mediated injury associated with acute cellular rejection, or an aspecific finding in other graft diseases (chronic hepatitis, bile duct or vascular injuries). Diffuse C4d positivity as a sign of ABMR in more than 50% of the vascular compartment [104].

Promising results have emerged from eosinophil counts (which have revealed a strong association with moderate-severe acute cellular rejection), CD4 function tests (used to identify over-immunosuppression, but not under-immunosuppression), and anti-HLA donor-specific antibody assays (to diagnose acute antibody-mediated rejection) [99,105–107].

6.8. Question 30

Is there a role for an Italian multicenter clinical trial on drug minimization and/or withdrawal?

6.8.1. Statement

30a. There is a role for such trial because the withdrawal of immunosuppression to induce operational tolerance should be managed at liver transplant centers with specific experience of this matter, selecting patients with a long time having elapsed since LT and with a normal liver function **(2b, A)**.

6.8.2. Comment

Spontaneous operational tolerance (i.e. the complete withdrawal of immunosuppression) is feasible in nearly 20% of LT patients receiving a whole cadaveric organ, and is associated with a reduction of immunosuppression-related side effects and complications [108,109]. The time elapsing after LT is a major factor influencing spontaneous operational tolerance, which is rarely seen in patients transplanted less than 6 years earlier, and more common (79% of cases) in those transplanted more than 10 years before [110]. To demonstrate the real clinical utility of operational tolerance, large multicenter studies will be needed, using a panel of different biomarkers (including NK cells and their related transcripts, serum levels of hepcidin and ferritin and graft-derived cell-free DNA) is needed to assess immunological suppression adequately, and thus modify immunosuppressive treatments according to patients' needs [111–113].

7. Conclusion

The aim of this position paper prepared by the AISF's Permanent Committee on Liver Transplantation is to provide recommendations for orienting the clinical activity of transplant hepatologists managing patients on the waiting list for LT and after their transplantation in real-life clinical practice. The recommendations concern 5 of the most common issues in liver transplantation, including how to manage patients with hepatitis C, hepatitis B, and alcoholic liver disease, and immunosuppression.

It is well known that HCV-related liver disease is the most common indication for LT. HCV recurrence after LT was considered inevitable until recently, but the newly-developed, very effective and well tolerated antiviral drugs for treating patients before and after LT have completely changed the scenario of anti-HCV therapy in this setting.

HBV-related liver disease is a standard indication for LT. With current antiviral therapy before the transplant and HBV prophylaxis afterwards, the HBsAg recurrence rate in the long-term follow-up is lower than 10% of cases, and the 5-year survival rate exceeds 80% of cases. The prophylaxis adopted at different liver transplant centers varies considerably, however, and there is still much debate as to which drugs or drug combinations, routes of administration, and protective anti-HBs titers should be used, and for how long this prophylaxis is necessary.

Alcoholic liver disease represents the second most common indication for LT and still poses a challenge for transplant hepatologists. Most (if not all) liver transplant centers in Italy demand a 6-month period of abstinence before adding patients with alcoholic liver disease to the waiting list for LT. A pre-transplant psycho-social assessments to identify potential risk factors of alcohol relapse after LT is not routinely performed at all centers. Acute alcoholic hepatitis, which may develop on top of chronic liver disease, is still considered a contraindication for LT at most transplant centers, even though early LT in carefully selected patients with a first episode of severe alcoholic hepatitis failing to respond to steroid therapy has been shown to improve survival.

Finally, there is the general, transversal topic of immunosuppression and the diagnosis and treatment of immune-mediated disorders following LT. Despite nearly 30 years of experience with LT in Italy, approaches differ widely from one liver transplant cen-

ter to another. Some centers adopt the same immunosuppressive regimen whatever the etiology of liver disease, while others follow different regimens for patients transplanted for viral hepatitis or hepatocellular carcinoma. As concerns any pre-transplant comorbities, such as renal dysfunction, metabolic syndrome or single components of MS, such as obesity, diabetes, hypertension and dyslipidemia, there is no homogeneity in the immunosuppression protocols adopted post-LT. The same appears to apply in the case of de novo tumors developing after the transplant, and the diagnosis and treatment of liver dysfunctions occurring due to immune-mediated damage is even more complicated.

As mentioned earlier, this position paper has been prepared to assist transplant hepatologists assessing candidates for liver transplantation, and to help them manage transplanted patients correctly. We hope it will also be useful for the purpose of broadening the discussion to other healthcare providers potentially interested and/or involved in the continuously-evolving process of organ donation and liver transplantation.

Conflict of interest

None declared.

Appendix A.

Group 1 — New treatment for HCV in patients on the waiting list for liver transplantation

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Group 4 — Indications for liver transplantation for alcoholic liver disease

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Group 5 — Immunosuppressive therapy

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