

# Asian Liver Transplant Network Clinical Guidelines on Immunosuppression in Liver Transplantation



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***Authorship page***

[Authorship]

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### *Abbreviations page*

ALTN, Asian Liver Transplant Network; ATG, anti-thymocyte globulin; AUC, area under the curve; BPAR, biopsy-proven acute rejection; CHB, chronic hepatitis B; CNI, calcineurin inhibitor; CrCl, creatinine clearance; CsA, cyclosporine; DDLT, deceased-donor liver transplantation; eGFR, estimated glomerular filtration rate; EVR, everolimus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma HCV, hepatitis C virus; IL2RA, interleukin 2 receptor antagonist; LDLT, live-donor liver transplantation; LT, liver transplantation; MDRD, Modification of Diet in Renal Disease; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; OS, overall survival; PR-TAC, prolonged release tacrolimus; RCT, randomized trials; RFS, recurrence free survival; SCr, serum creatinine; SRL, sirolimus; TAC, tacrolimus; TTC, tacrolimus trough concentration

## ***Abstract***

Most management guidelines and much of the available clinical trial evidence for immunosuppressants in liver transplantation pertain to Western practice. While evidence from Western studies may not translate to Asian settings, there is a paucity of Asian randomized controlled trials of immunosuppression in liver recipients. Nonetheless, there are notable differences in the indications and procedures for liver transplantation between Western and Asian settings. The Asian Liver Transplant Network (ALTN) held its inaugural meeting in Singapore in November 2016 and aimed to provide an Asian perspective on aspects of immunosuppression following liver transplantation. Because of their importance to outcome following liver transplantation, the meeting focused on: (1) reducing the impact of renal toxicity, (2) hepatocellular carcinoma recurrence and (3) nonadherence with immunosuppressant therapy.

## ***Main body text***

### **Introduction**

The Asian Liver Transplant Network (ALTN) is a strategic network of key opinion leaders in liver transplantation from Hong Kong, Japan, Indonesia, Singapore, South Korea, Taiwan, and the Philippines, which provides a platform for regular exchange to facilitate best clinical practice, multicenter studies/clinical trials and to establish an Asian Liver Transplant Registry. The ALTN convened its inaugural meeting in Singapore in November 2016 and the meeting aimed to provide an Asian perspective on aspects of immunosuppression following liver transplantation (LT). This document summarizes the meetings proceedings and recommendations.

LT is a standard therapy for acute and chronic end-stage liver disease of any etiology. The procedure is potentially lifesaving with survival rates following transplantation having improved significantly in the last 25 years. One-year survival rates of 82% and 87% have been reported in the European and Japanese Liver Transplant registries respectively;<sup>1, 2</sup> while 10-year survival rates range from 53% to 76%, in the USA, European and Japanese registries.<sup>1-3</sup> There are key differences regarding the indications and procedures for LT between Western and Asian settings. In the Asia Pacific region, the most common indication for LT in adults is HCC secondary to chronic hepatitis B (CHB) infection, followed by hepatitis B virus (HBV)-cirrhosis without HCC, and hepatitis C virus (HCV)-related cirrhosis without HCC. One exception is Japan, where chronic HCV infection is more common than CHB.<sup>2, 4, 5</sup> In contrast, the most common single diagnosis among adult LT recipients in the USA is chronic HCV infection (although this is declining with the introduction of new antiviral treatments); this is followed by alcoholic liver disease and malignancy.<sup>3</sup> While in Europe, cirrhosis secondary to alcoholic liver disease is the commonest indication for LT, followed by HCV-related cirrhosis and HCC.<sup>1</sup>

In Southeast Asia, Japan and South Korea, over 80% of adult LT involve partial grafts from living donors<sup>2, 6</sup> whereas in Europe and the US, 5% or fewer of adult LT are from living donors.<sup>1, 3</sup> Overall patient survival at five years is similar following live-donor liver transplantation (LDLT) and deceased-donor liver transplantation (DDLT),<sup>1, 2</sup> although LDLT is associated with high rates of biliary complications,<sup>4, 6, 7</sup> and possibly higher tumor recurrence rates in patients with HCC.<sup>4, 5, 8</sup>

The long-term survival after LT is mostly limited by recurrent disease and the side effects associated with the use of long-term immunosuppression, including malignancy, opportunistic infections, and renal failure.<sup>9-11</sup> Although LT recipients can be maintained on lower levels of immunosuppression than other solid organ transplant recipients,<sup>11, 12</sup> the challenge remains to minimize long-term complications by the prudent use of immunosuppressive drugs. Other important aspects relate to the use of immunosuppression, including the class of agent used (Table 1) and adherence to the prescribed regimen. Nonadherence can lead to inadequate immunosuppression and is associated with substantial increases in the rates of graft loss and death; poor adherence is an issue in up to 40% of LT recipients.<sup>13</sup> Because of their importance to outcome post LT, the meeting focused on the following key areas: (1) strategies to reduce renal impairment post-LT, including delaying the introduction of calcineurin inhibitors (CNIs), early minimization of CNI levels and excluding CNIs from the immunosuppression regimen; (2) evidence for the effect of immunosuppressants on HCC recurrence post-LT and their use in post-LT HCC recurrence; and (3) strategies to improve immunosuppressant adherence.

## **Materials and methods**

### **Organization of the meeting and methods**

The meeting was organized by the ALTN, consisting of 12 experts from Singapore, Hong Kong, Indonesia, Philippines and South Korea. A comprehensive literature search (QZ and YLT) was conducted in MEDLINE/Ovid, EMBASE/Ovid, Cochrane Library and National Guideline Clearinghouse to identify randomized controlled trials (RCTs) of immunosuppression in LT (published from 2000) without any language restrictions. Steroid-free immunosuppression was an exclusion criterion within the literature search. Medical subject headings MeSH/Emtree and free-text search terms was used to develop the search strategy and maximize the retrieval of current evidence. In 2151 initially identified records, there were 21 RCTs evaluating renal sparing strategies to reduce nephrotoxicity, one RCT reporting immunosuppression efficacy for LT recipients transplanted for HCC, either by subgroup or main analysis and one RCT reporting adherence/compliance of immunosuppressive agents in LT (Figure 1).

Experts were invited to review the search findings and drafted statements. They were also given the opportunity to provide comments and suggest additional items that may not have been included when developing the initial list of statements. Statements required 80 % agreement from the panel (i.e., agreement among 8 of 11 experts) in order to accept or omit a statement during construction of the final list of statements. Statements not meeting 80 % agreement were modified according to feedback provided by the expert panel and redistributed to the panelists for round 2. As no Asian RCT addressing the 3 key areas was identified, we extended our literature search criteria to include non-RCT Asian studies and found an additional 956 records, of which 6 were deemed appropriate and included to supplement the guidelines.

## Level of evidence

The studies used as a basis for this consensus are graded in relation to the quality of evidence according to the Oxford Centre of Evidence-Based Medicine 2011 Levels of Evidence and the clinical experience of the authors (Table 2).<sup>14, 15</sup>

## Results

### Summary of Recommendations

#### Recommendation 1

##### Delaying the introduction of calcineurin inhibitors

- Use of induction agents is recommended for preservation of renal function regardless of the patient's renal function at the time of transplantation. (Level 2, Grade A)
- IL2RAs may be the preferred induction agent. (Level 2, Grade A)

#### Recommendation 2

##### Calcineurin inhibitor minimization: mycophenolate mofetil

- MMF in combination with reduced CNI is recommended in liver transplant recipients with or without evidence of post-liver transplant renal impairment. (Level 2, Grade A)

#### Recommendation 3

##### Calcineurin inhibitors minimization: mTOR inhibitors

- Use of mTOR inhibitors in combination with reduced dose CNIs is recommended for preservation of renal function. (Level 2, Grade A)

#### **Recommendation 4**

##### **Immunosuppression in liver transplant recipients transplanted for HCC**

- High CNI exposure (trough levels: tacrolimus >10 µg/L or cyclosporine >300 µg/L), especially in the early post-liver transplant period should be avoided if possible. (Level 2, Grade B)
- Inclusion of a mTOR inhibitor to a CNI-based immunosuppression regimen allows for CNI reduction and ~~is preferred~~ can be considered. (Level 2, Grade A)
- If mTOR inhibitor were unavailable or not tolerated, use of mycophenolate may be an alternative for CNI minimization. (Level 5, Grade D)

#### **Recommendation 5**

##### **Immunosuppression in liver transplant recipients with post-transplant HCC recurrence**

- Addition of a mTOR inhibitor and CNI minimization is recommended. (Level 4, Grade C)

## Recommendation 6

### Immunosuppression adherence

- Intensive medication counseling by a transplant medication specialist is recommended for all transplant patients to promote adherence. (Level 2, Grade B)
- A designated transplant pharmacist is recommended to provide comprehensive pharmaceutical care. (Level 2, Grade B)
- Simplifying medication to reduce pill burden and dosing frequency is recommended to improve medication adherence. (Level 2, Grade A)
- Health information technology platforms could be adopted to promote adherence. (Level 2, Grade B)

IL2RAs, interleukin 2 receptor antagonists; MMF, mycophenolate mofetil; CNI, calcineurin inhibitors; mTOR, mammalian target of rapamycin

### Minimizing immunosuppressant-related renal complication

Renal insufficiency is an increasingly complication of LT, with LT recipients having the second highest incidence of post-transplant chronic renal failure, including end-stage renal disease (5-year cumulative incidence of 18%-22%)<sup>11, 16</sup>, which is largely due to nephrotoxic effects of CNIs.<sup>16, 17</sup> Acute CNI-induced nephrotoxicity results from vasoconstriction in the afferent arterioles causing a decrease in renal blood flow and urine output. Renal function usually improves once the CNI is stopped; however, prolonged CNI-induced vasoconstriction may lead to chronic/irreversible nephrotoxicity. Two-thirds of deaths after LT occur after the first year post-transplant and renal insufficiency is the strongest predictor of late mortality following LT.<sup>10</sup> Because of the potential medium-and long-term consequences of CNI-toxicity, the use of renal sparing immunosuppression protocols such as delayed CNIs

introduction, early CNIs minimization, or CNI-free regimens, both during the induction and maintenance periods following LT, have been introduced over the past decade.<sup>10, 16</sup>

### **Delaying the introduction of calcineurin inhibitors**

Delaying the introduction of a CNI beyond the immediate post-operative phase may help decrease its negative impact on renal function during a period when the kidneys are particularly susceptible to CNI acute injury.<sup>16</sup> This can be achieved with induction therapy – a prophylactic, perioperative course of intensive immunosuppression given to prevent acute rejection in the first months post-operatively.<sup>18</sup> Induction therapy is being increasingly used in LT to facilitate steroid avoidance as well as to minimize CNI exposure.<sup>9, 19</sup>

Two types of antibodies are commonly used for inducing immunosuppression in LT: the non-depleting interleukin 2 receptor antagonists (IL2RAs) that block the IL-2 dependent expansion of effector T cells (daclizumab, which has been withdrawn from the market, and basiliximab) and the T-cell depleting anti-thymocyte globulin (ATG). The panel reviewed four RCTs that investigated the use of an IL2RA as part of a renal sparing strategy post-LT. In each of these studies, at least one arm involved using an IL2RA together with MMF and corticosteroids followed by the delayed introduction of tacrolimus on day 5 at reduced (tacrolimus trough concentration (TTC)  $\leq$  8 ng/L) or standard dose (Table 3).<sup>20-23</sup> Overall, these studies showed improved renal function and less renal dysfunction in renal sparing strategy arm compared with a standard tacrolimus regimen, without compromising tolerability or efficacy in terms of biopsy-proven acute rejection (BPAR) rates and patient survival.<sup>20-23</sup>

Although two retrospective cohort studies of ATG induction with delayed CNI reported lower rejection rates and a beneficial effect on renal function,<sup>24, 25</sup> subsequent RCTs found that ATG induction with either standard or reduced dose tacrolimus failed to show any beneficial effects on renal function and was associated with higher acute rejection and leukopenia rates.<sup>26, 27</sup>

### **Recommendation 1**

#### **Delaying the introduction of calcineurin inhibitors**

- Use of induction agents is recommended for preservation of renal function regardless of the patient's renal function at the time of transplantation. (Level 2, Grade A)
- IL2RAs may be the preferred induction agent. (Level 2, Grade A)

#### **Technical remarks**

1. IL2RAs or ATG can be used as induction agents.
2. The use of induction agents may be of greater benefit to patients with impaired baseline renal function as compared to patients with normal baseline renal function.
3. ATG may lead to higher rates of acute rejection and leukopenia and IL2RAs appear to have a more favourable side effect profile.
4. In an induction regimen, the following strategies can be considered:
  - a. Delayed CNI introduction – at day 5
  - b. CNI dose reduction– aiming for a tacrolimus trough concentration of  $\leq 8 \mu\text{g/L}$
  - c. Delayed CNI introduction combined with CNI dose reduction

## Calcineurin inhibitors minimization/elimination using mycophenolate mofetil

Mycophenolic acid, the active compound of mycophenolate mofetil (MMF), is a reversible purine synthase inhibitor with anti-proliferative activity against T cells and B cells. In targeting a different step in the rejection cascade, the synergistic effect of the combination enables a reduction in the CNI dose. Table 4 summarizes the randomized studies utilizing MMF to reduce or eliminate CNIs.<sup>28-34</sup> In all of the four studies looking at minimizing CNIs, switching to a reduced CNI dose was associated with significant improvement in renal function without an increase in the risk of acute graft rejection.<sup>28-31</sup> Only in one study did patients receiving the reduced CNI regimen have a significantly lower rate of BPAR (30%) compared with those on full dose CNI regimen (46%);  $P=0.024$ .<sup>30</sup> In most of these trials, TTC were maintained at  $<8 \mu\text{g/L}$  at 3 months. Similar findings were observed in Asian cohort studies. In a large Chinese retrospective single centre study looking at 940 LT recipients, incidence of renal dysfunction was lower in a group with TTC of  $\leq 8 \text{ ng/L}$  in combination with MMF compared with higher TTC groups. Interestingly, this renal sparing effect was less pronounced in a group with TTC of  $< 8 \text{ ng/L}$  but without co-administration of MMF.<sup>35</sup> In a separate retrospective study by the same Chinese centre, TTC of  $> 8 \text{ ng/L}$  and lack of MMF were identified as independent risk factors of renal dysfunction progression.<sup>36</sup>

With CNI elimination strategies, there was also significant improvement in renal function; however, this appeared to be associated with an increased risk of acute rejection (Table 4).<sup>32-</sup>

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Of note, the dose of MMF in these studies was in the range of 2-3 g/day, which may not be tolerated by Asian recipients. A Korean study had shown that up to 74% of liver recipients developed MMF related adverse events even at a reduced dose of 1 g/day and 42% of the patients required dose reduction within the first year after LDLT with  $<3\%$  rate of BPAR.<sup>37</sup> In

several other Asian cohort studies, standard dosage of MMF as part of immunosuppression protocol was reported to be in the range of 1 – 1.5g per day, without any observed increase in expected BPAR.<sup>35, 36, 38, 39</sup>

## **Recommendation 2**

### **Calcineurin inhibitor minimization: mycophenolate mofetil**

- MMF in combination with reduced CNI is recommended in liver transplant recipients with or without evidence of post-liver transplant renal impairment.  
(Level 2, Grade A)

### **Technical remarks**

1. Recommended dose of MMF is between 1000-3000 mg/day. However, a lower dose of 500-1000 mg/day may be considered and better tolerated among Asian recipients.
2. MMF can be used in combination with reduced-dose CNIs in patients with post-LT renal impairment to prevent the progression of the renal impairment.
3. MMF can be used in combination with reduced-dose CNIs in patients with normal renal function post LT to prevent the onset of renal impairment.
4. The target tacrolimus trough concentration should be  $\leq 8 \mu\text{g/L}$  at 3 months post-transplant when using a reduced-dose strategy
5. Use of MMF alone without a CNI can lead to an increased risk of acute rejection.

### **Calcineurin inhibitors minimization/elimination using mTOR inhibitors**

The mTOR inhibitors, sirolimus, and everolimus block the IL-2 and IL-15 induction of proliferation of T cells and B cells.<sup>40</sup> Because mTOR inhibitors were considered non-nephrotoxic at the dose used post-LT, it was thought these might replace CNIs in LT recipients with renal dysfunction. However, the use of sirolimus is controversial. Studies on the conversion of CNI's to sirolimus to improve renal function have shown conflicting data (Table 5).<sup>41-46</sup> Also, sirolimus conversion has been associated with higher BPAR rates than

with continued CNI.<sup>41, 43, 45, 46</sup> Further, *de novo* use of sirolimus with reduced-dose tacrolimus resulted in a high rate of graft loss, sepsis, and death when compared with standard doses of tacrolimus, leading to the premature termination of one prospective randomized trial.<sup>46</sup> Data for everolimus with CNI withdrawal or reduction are more encouraging (Table 6).<sup>47-50</sup> The large PROTECT study indicated the potential usefulness of early everolimus-based CNI-free immunosuppression following LT.<sup>49</sup> In this study, patients receiving CNI-free immunosuppression had better renal function compared with those on CNI after 12 months, with comparable patient and graft outcomes; this benefit was maintained after five years' follow up.<sup>49, 51</sup> Also in a prospective, randomized, multicenter, open-label study, LT recipients receiving an everolimus plus reduced tacrolimus regimen were found to have a significantly superior estimated glomerular filtration rate (eGFR) at month 12 compared with tacrolimus control ( $P<0.001$ ). This benefit of everolimus plus reduced tacrolimus was maintained at three years' follow up with comparable efficacy to tacrolimus control with no late safety concerns. However, the randomization to tacrolimus elimination arm in this study was stopped prematurely due to significantly higher rates of treated BPAR.<sup>50, 52</sup> While everolimus should generally be initiated 30 days post-LT, a recent propensity score matching study showed that introduction of everolimus as early as day 15 was feasible with reasonable safety profile.<sup>53</sup>

### **Recommendation 3**

#### **Calcineurin inhibitors minimization: mTOR inhibitors**

- Use of mTOR inhibitors in combination with reduced dose CNIs is recommended for preservation of renal function. (Level 2, Grade A)

## Technical remarks

1. mTOR inhibitors should be used in combination with reduce-dose CNIs – conversion of CNIs to mTOR inhibitors may lead to higher acute rejection rates.
2. In general, mTOR inhibitors should only be introduced 30 days after transplantation. However, in patients with early severe CNI toxicities without option of alternative immunosuppressant, careful initiation of everolimus may be considered from as early as day 15 post liver transplantation.
3. *De novo* use of mTOR inhibitors cannot be recommended at this time until results from ongoing studies are published.
4. Everolimus may be preferred over sirolimus in liver transplant patients with the aim to preserve renal function

## Immunosuppression and HCC recurrence

### The effect of immunosuppressants on post-LT HCC recurrence

LT is a potentially curative option for selected HCC patients; however, HCC recurrence rates of up to 20% have been reported, usually during the first two years post-LT.<sup>54, 55</sup> The use of immunosuppressive drugs may increase risk of HCC recurrence and tumor's aggressiveness. Indeed, CNIs have been shown to have pro-oncogenic effects in experimental models and clinical studies.<sup>56-59</sup> In experimental models, CNIs increased the production of TGF- $\beta$  in a dose-dependent fashion and promoted cancer progression by a direct cellular effect that is independent of their effect on the host's immune cells.<sup>56</sup>

Risk of HCC recurrence post LT appears to be related to high blood levels of CNIs, particularly in the early post-transplant period rather than to the type of CNI. Two retrospective analyses from a single Italian study showed a dose-dependent CNI effect on post-LT HCC recurrence.<sup>57, 58</sup> In the first study, 10% of 70 recipients treated with

cyclosporine-based regimens had HCC recurrence, which was associated with high cyclosporine exposure (CsA–AUC [trough] divided by the time of exposure to the drug: 278 µg/L in recurrent vs. 170 µg/L in tumor-free patients;  $P<0.001$ ). Cyclosporine exposure was the only independent predictor of tumor recurrence in the multivariate analysis.<sup>57</sup> The second study reviewed 139 HCC patients who received LT. HCC recurred in 20% of the 60 patients receiving tacrolimus and 11% of the 79 patients receiving cyclosporine. The optimal cut-off values of exposure identified with receiver operating characteristic analysis to categorize the risk of recurrence were 10 µg/L for tacrolimus and 220 µg/L for cyclosporine. High CNI trough concentrations (tacrolimus >10 µg/L or cyclosporine>220µg/L) increased HCC recurrence rates five- to six-fold.<sup>58</sup>

Timing of high CNI exposure could also impact on post-LT HCC recurrence. Rodríguez-Perálvarez et al analyzed 219 consecutive patients transplanted for HCC and showed that higher exposure to CNIs within the first month after LT (mean trough concentrations: tacrolimus >10 µg/L or cyclosporine >300 µg/L), but not thereafter, was associated with increased risk of HCC recurrence (28% vs. 15% at 5 years;  $P=0.007$ ).<sup>59</sup> These findings suggest that early CNI minimization should be preferred in LT recipients transplanted for HCC to minimize tumor recurrence.

In observational studies, antimetabolites (MMF and azathioprine), IL2RA and monoclonal antibodies have not been associated with increased post-LT HCC recurrence.<sup>57, 59</sup> While these western studies also did not identify corticosteroids use as a risk factor, a China Liver Transplant Registry study showed significantly better overall and recurrence free survival among within Milan criteria recipients who received steroid-free immunosuppression than those who received steroid post-operatively.<sup>60</sup> A retrospective review of 412 patients found that use of ATG or anti-CD3 antibody (OKT3) was independently associated with HCC recurrence ( $P=0.005$ ).<sup>61</sup>

In addition to being immunosuppressive, mTOR inhibitors have an anticancer effect. As a serine/threonine protein kinase of the phosphoinositide-3-kinase-related kinase family, it regulates several oncogenic processes which are important in HCC, including cell growth, proliferation and differentiation, tumorigenesis, and angiogenesis. Altered expressions of the mTOR pathway have been reported in 50% of HCCs, while the activation of the mTOR pathway is related to the presence of less differentiated tumors, earlier recurrence, and poorer survival outcomes.<sup>62</sup> A number of cohort studies suggest that patients who receive a mTOR inhibitor in combination with a CNI may have a lower HCC recurrence risk and improved overall survival compared with a standard CNI regimen.<sup>63</sup> Meta-analyses of observational reports have supported these findings as well.<sup>63, 64</sup> Also, in three randomized open-label trials that assessed the renal sparing effect of *de novo* mTOR inhibitor therapy, there was a numerically lower rate of HCC recurrence by 1-3 years post-transplant in patients given a mTOR inhibitor versus the control arm.<sup>43, 48, 52</sup>

The SiLVER (Sirolimus in Liver Transplant Recipients with HCC) study is the only prospective, randomized trial comparing recurrence-free survival (RFS) for mTOR inhibitor-containing and mTOR inhibitor-free immunosuppression in post-LT patients with HCC.<sup>65</sup> In this open-label trial, 525 LT recipients were randomized (1:1) 4 to 6 weeks after transplantation to receive a mTOR inhibitor-free immunosuppression regimen or one incorporating sirolimus. After eight years, patients receiving the mTOR inhibitor had a numerically higher but not statistically significant long-term RFS (70% vs. 65%) and overall survival (OS, 75% vs. 68%). However, there was a significant benefit with sirolimus in the first five years after transplantation with significantly improved RFS in the first three years and significantly improved OS out to 5 years. In subgroup (Milan criteria-based) analyses, low-risk (within Milan criteria) rather than high-risk (outside Milan criteria, no cirrhosis or salvage LT) HCC, younger recipients (age  $\leq 60$ ) and recipients who did not receive any HCC

treatment prior to LT benefited most from sirolimus. A small proportion of patients (n=50) in the SiLVER study received sirolimus monotherapy and this may offer a further advantage. Those patients receiving monotherapy had higher RFS (83%) and OS (85%) rates versus sirolimus-combination therapy patients (68% and 72%, respectively), but the number of patients was insufficient for meaningful statistical analysis.<sup>65</sup>

#### **Recommendation 4**

##### **Immunosuppression in liver transplant recipients transplanted for HCC**

- High CNI exposure (trough levels: tacrolimus >10 µg/L or cyclosporine >300 µg/L), especially in the early post-liver transplant period should be avoided if possible. (Level 2, Grade B)
- Inclusion of a mTOR inhibitor to a CNI-based immunosuppression regimen allows for CNI reduction and can be considered. (Level 2, Grade A)
- If mTOR inhibitor were unavailable or not tolerated, use of mycophenolate may be an alternative for CNI minimization. (Level 5, Grade D)

#### **Technical remarks**

1. The inclusion of a mTOR inhibitor in the immunosuppression regimen appears to confer a short-term benefit on overall survival (up to 5 years) and HCC recurrence (up to 3 years) in LT recipients with HCC, especially for those who are <60 years old, within Milan criteria or HCC treatment-naïve. There are insufficient data currently to recommend mTOR inhibitor monotherapy in this setting.
2. Use of T cell-depleting agents (ATG/OKT3) may increase post-LT HCC recurrence.
3. While robust evidence is lacking, corticosteroids free immunosuppression seems to be associated with better overall as well as recurrence free survival among Asian recipients with HCC and may be considered in this setting.

4. To date, there is no evidence to suggest that antimetabolites (MMF and azathioprine) and IL2RA monoclonal antibodies influence post-LT HCC recurrence.

### **Immunosuppressants in post-liver transplant HCC recurrence**

Post-LT HCC recurrence occurs in 16% of recipients and remains a big challenge with very limited evidence to guide optimal management.<sup>55</sup> Median time to post-LT HCC recurrence is around 13 months, and median overall survival is 13 months. HCC recurrence may be treated with surgery or local ablation for resectable or early lesions or systemic therapy (including sorafenib) for unresectable lesions.<sup>54</sup> The only clinical evidence suggesting a potential benefit of mTOR inhibitors following HCC recurrence post LT is from retrospective studies and case reports. A meta-analysis of 61 such studies found that surgical resection improved survival (median 42 months) for localized resectable HCC recurrence. When there was a systemic recurrence, the use of sorafenib combined with a mTOR inhibitor improved survival (median 18.2 months) compared with sorafenib alone (median 12.1 months) and best supportive care (median 3.3 months).<sup>55</sup> However, sorafenib, especially when combined with a mTOR inhibitor, was frequently associated with severe side effects that required dose reduction or discontinuation; six out of 23 studies reported severe adverse events with the combination; including four deaths.<sup>55</sup>

#### **Recommendation 5**

##### **Immunosuppression in liver transplant recipients with post-transplant HCC recurrence**

- Addition of a mTOR inhibitor and CNI minimization is recommended. (Level 4, Grade C)

## Technical remarks

1. Combination of mTOR inhibitor with sorafenib is associated with serious adverse events and should only be administered by experienced physicians.

## Immunosuppressant adherence post-liver transplantation

Nonadherence, defined as ‘deviation from the prescribed medication regimen sufficient to influence adversely the regimen’s intended effect’,<sup>66</sup> has been identified as a significant issue in LT recipients; it carries an increased risk of graft rejection and potential graft loss.<sup>13</sup> A meta-analysis of studies on post solid organ transplant found nonadherence rates of 22.6 cases per 100 person-years.<sup>67</sup> Among adult liver transplant patients, the reported rates of nonadherence vary from 15% to 40% and may be up to four times higher in pediatric and adolescent transplant recipients.<sup>13</sup>

Risk factors for nonadherence that have been identified in adult LT recipients include high medication costs, psychiatric disorders, the conviction that the medication is harmful and side effects of immunosuppressive therapy.<sup>13</sup> A study conducted in Singapore showed that younger age and longer post-transplant duration of >5 years as independent predictors of non-adherence.<sup>68</sup> Because there are likely to be many factors at play, multilevel approaches are needed to promote adherence, including simplified drug regimens, reducing costs and addressing the patient behavior.<sup>17, 70</sup> Although overcoming cost barriers may be beyond the scope of the clinician, designing medically appropriate simplified drug regimens is feasible. Addressing behavioral factors requires more than just patient education, rather it needs individualized approaches taking into account the patient’s lifestyle, cultural factors and belief systems with regular follow-up and continuity of care.

Despite nonadherence being an acknowledged problem among adult LT recipients, the literature on the topic is limited. Most studies are small and use a wide range of methods to measure adherence. There is, however, some evidence for a multilevel approach. In a prospective randomized controlled trial, Klein et al. investigated the effectiveness a pharmaceutical care program, comprising one-to-one intensive medication education, written medication information, resolution of identified drug-related problems and simplified drug regimens.<sup>70</sup> Fifty LT recipients were randomized 1:1 to pharmaceutical care vs. traditional of care. An objective medication event monitoring systems were used to determine adherence supported by other direct and indirect methods. The study found that pharmaceutical care of LT patients led to a significant increase in compliance with immunosuppressive therapy; 90% compared with 81% in the control group ( $P=0.015$ ). Moreover, patients in the intervention group were more likely to achieve target blood levels (78% vs. 51% within range).<sup>70</sup> Other observational studies have shown that educational interventions, and measures to simplify regimens also can improve adherence.<sup>13</sup>

Medication management for transplant patients can be challenging due to the narrow therapeutic index of immunosuppressive medications, high potential for adverse effects, significant drug interactions, and the high cost of medications, resulting in the need for intense monitoring. Pharmacists trained in the area of transplantation are uniquely equipped to handle the complex pharmacotherapy associated with transplantation. Professional organizations have published guidelines that strongly recommend inclusion of a transplant pharmacist in the care of the transplant patient, including the United Network for Organ Sharing (UNOS);<sup>71</sup> the United States Centers for Medicare and Medicaid Services;<sup>72</sup> the Joint Commission International (JCI);<sup>73</sup> the American Society of Transplantation (AST);<sup>74</sup> the International Society for Heart and Lung Transplantation (ISHLT);<sup>75</sup> and the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group.<sup>76</sup>

There are a number of observational studies indicating that a prolonged-release once-daily tacrolimus formulation can improve adherence compared with the twice-daily tacrolimus regimen.<sup>77-80</sup> Patients also tend to prefer the once-daily formulation.<sup>77, 78, 80, 81</sup> In addition, a retrospective study of European Liver Transplant Registry data reported improved graft and patient survival with once-daily tacrolimus compared with twice-daily.<sup>82</sup> The authors hypothesized that the improvements were related to improved adherence to treatment and reduced variability of tacrolimus exposure with the prolonged-release, once-daily formulation.<sup>82</sup>

Technologies to support adherence have both increased and improved. This has created innovative ways to remind patients to take medications at prescribed times and to monitor adherence. Examples include customizable messaging systems that contact patients by phone, email or text message, electronic pill bottles and caps and mobile phone apps. A prospective study of 41 pediatric/adolescent LT recipients (median age 15 years) reported that sending text message reminders to the primary medication administrator (patient or caregiver) significantly improved medication adherence and reduced rejection episodes. The mean SD tacrolimus significantly decreased from 3.46 µg/L before the study to 1.37 µg/L ( $P<0.005$ ) and the number of acute cellular rejection episodes decreased from 12 to 2 during the study ( $P=0.02$ ).<sup>83</sup>

## **Recommendation 6**

### **Immunosuppression adherence**

- Intensive medication counseling by a transplant medication specialist is recommended for all transplant patients to promote adherence. (Level 2, Grade B)
- A designated transplant pharmacist is recommended to provide comprehensive

pharmaceutical care. (Level 2, Grade B)

- Simplifying medication to reduce pill burden and dosing frequency is recommended to improve medication adherence. (Level 2, Grade A)
- Health information technology platforms could be adopted to promote adherence. (Level 2, Grade B)

### **Technical remarks**

1. Intensive medication counselling should be provided to all transplant patients and their caregivers, by a qualified healthcare professional and should include information on: dosage regimens, indications and side effects of the medications, potential drug-drug and drug-food interactions, protective measures while on immunosuppressants, and the importance of adherence to immunosuppressive regimens and the consequences of nonadherence.
2. Frequent medication reconciliation at transitions of care should be performed to identify patients who are at high risk for nonadherence or risk of nonadherence.
3. Prolonged- or extended- release medication formulations should be considered whenever possible to enable once-daily dosing of medications.
4. With the widespread use of technology, mobile apps, instant messaging and social media platforms can be used to send patient reminders and to promote patient engagement in their care process.

### **Concluding remarks and future direction**

While there is a general lack of prospective randomized trials of immunosuppressants in Asian liver recipients, these ALTN guidelines were developed based on a comprehensive review of existing literature while taking into consideration common LT practices in Asia. There is an urgent need for more prospective Asian-centric immunosuppression in LT trials,

in particular to address: (1) CNI-minimization comparing MMF with mTOR inhibitors to determine the preferred renal-sparing strategy; (2) optimal immunosuppression regimen guided by predictive biomarkers to minimize post-LT HCC recurrence; (3) efficacy of adherence-enhancing interventions following implementation of the recommended multilevel approaches.

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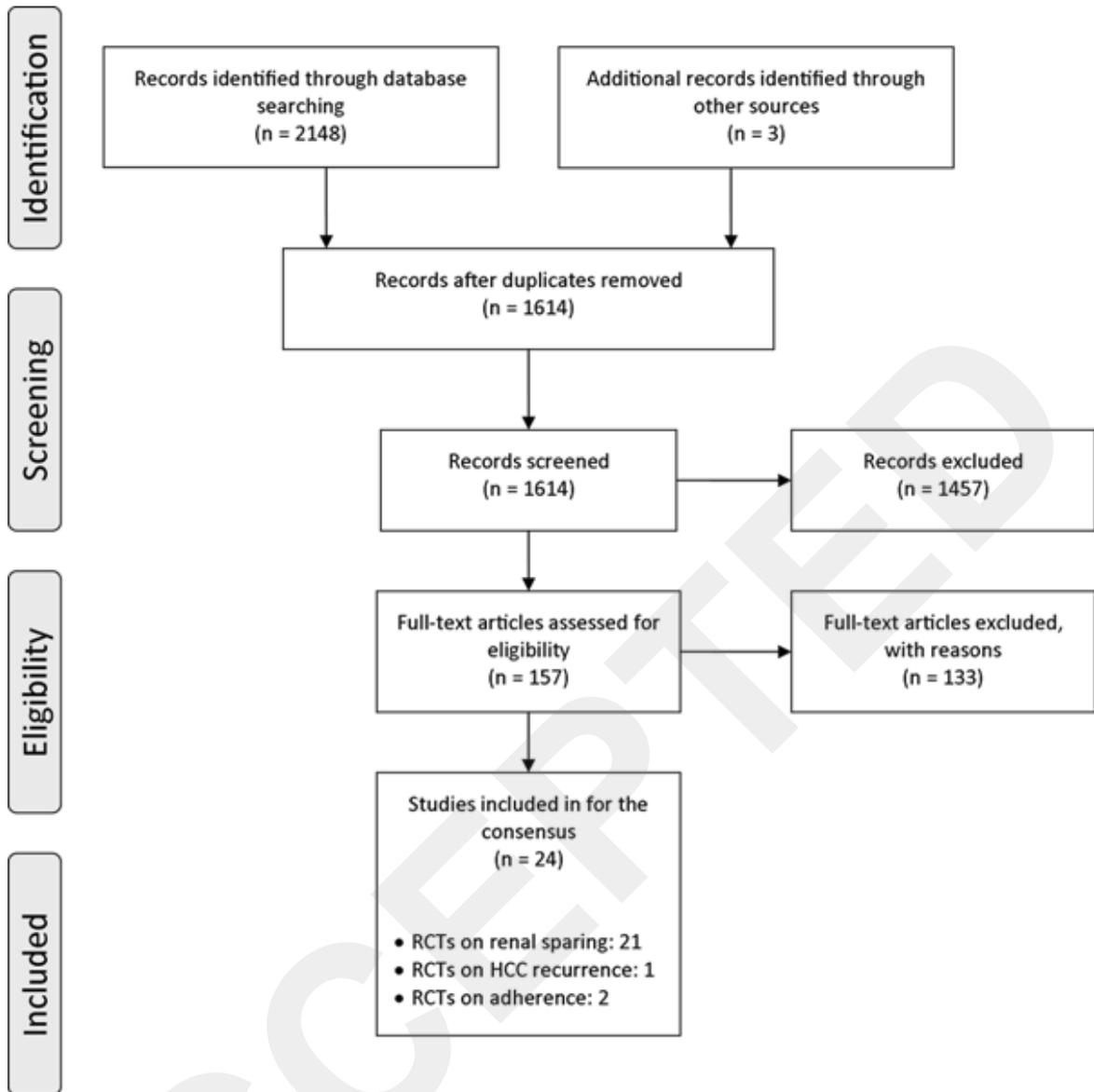
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## Tables

Table1. Classifications and indications for immunosuppressant agent used post-liver transplantation

Agent	Indications
<b>Corticosteroid</b> Prednisone Prednisolone	Induction of immunosuppression Treatment of acute cellular rejection Maintenance of immunosuppression
<b>Calcineurin inhibitor</b> Tacrolimus Cyclosporine	Maintenance of immunosuppression
<b>Anti-metabolite</b> Mycophenolate mofetil/mycophenolic acid Azathioprine	Maintenance of immunosuppression Treatment of rejection (only mycophenolate mofetil)
<b>mTOR inhibitor</b> Sirolimus Everolimus	Maintenance of immunosuppression Treatment of rejection Possible use in malignancies
<b>T cell depleting polyclonal antibody</b> Anti-thymocyte globulin	Induction of immunosuppression Treatment of steroid-resistant rejection
<b>IL2RA monoclonal antibody</b> Basiliximab Daclizumab (withdrawn from the market)	Induction of immunosuppression Treatment of steroid-resistant rejection

Table 2. Levels of evidence for the recommendations and the grading of the recommendations.<sup>18,19</sup>

Level of Evidence	Objectives of the included evidence	
	Treatment Benefits	Prognosis
Level 1	Systematic review of randomized trials or n-of-1 trials	Systematic review of inception cohort studies
Level 2	Randomized trial or observational study with dramatic effect	Inception cohort studies
Level 3	Non-randomized controlled cohort/follow-up study	Cohort study or control arm of randomized trial
Level 4	Case-series, case-control studies, or historically controlled studies	Case-series or case-control studies, or poor quality prognostic cohort study
Level 5	Mechanism-based reasoning	Not applicable

Grades of recommendation	Descriptor	Qualifying Evidence
A	Strong recommendation	Level 1 evidence or consistent findings from multiple studies of levels 2 or 3.
B	Recommendation	Levels 2, 3, or 4 evidence and findings are generally consistent.
C	Option	Levels 2, 3, or 4 evidence, but findings are inconsistent.
D	Option	Level 5 evidence: little or no systematic empirical evidence.

Table 3. Randomized controlled studies of IL2RA induction agents in combination with mycophenolate mofetil (MMF) and tacrolimus (TAC): effect on follow-up renal function

Study	Regimen (number of patients in each arm)	Follow-up, months	Renal measure	Baseline renal function	Follow-up renal function	BPAR, %	Comment
Yoshida, 2005 <sup>26</sup>	A. TAC [initial trough: 10 to 15 µg/L] + MMF + steroids (76)	6	eGFR	73 mL/min	70 mL/min <sup>a</sup> (median)	28	Superior renal function with delayed-reduced-dose TAC only in early (6 months) post-transplant period
	B. Reduced TAC [trough: of 4 to 8 µg/L, day 5] + daclizumab + MMF + steroids (72)	6		71 mL/min	75 mL/min (median)	23	
Neuberger, 2009 <sup>27</sup>	A. TAC [trough: >10 µg/L]+ steroids (183)	12	eGFR change	94 mL/min	-25 mL/min <sup>b</sup>	28	Superior renal function with delayed-reduced -dose TAC
	B. Reduced TAC [trough: ≤8 µg/L] + MMF + steroids (170)	12		96 mL/min	-23 mL/min	29	
	C. Reduced TAC [trough: ≤8 ng/L, day 5] + daclizumab + MMF + steroids (172)	12		87 mL/min	-15 mL/min	19	
Calmus, 2010 <sup>28</sup>	A. TAC [trough: 10-20 µg/L]+ MMF + steroids (101)	6	SCr	88 µmol/L	114 µmol/L	18	Numerically better eGFR with delayed TAC. Trend towards improved function more apparent in those with SrC ≤ 100 µmol/L
	B. TAC [trough levels 10-20 µg/L, day 5] + daclizumab + MMF + steroids (98)	6		91 µmol/L	113 µmol/L	19	
Trunecka, 2015 <sup>29</sup>	A. PR-TAC (0.2mg/kg/day) + MMF (289)	6	eGFR	91 mL/min	67 mL/min <sup>c</sup>	18	Superior renal function with reduced-dose PR-TAC and delayed PR-TAC
	B. Reduced PR-TAC (0.15-0.175mg/kg/day) + MMF + basiliximab (291)	6		89 mL/min	76 mL/min	12 <sup>c</sup>	
	C. PR-TAC (0.2mg/kg/day, day 5) + MMF +	6		90 mL/min	73 mL/min	17	

	basiliximab (277)						
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BPAR= biopsy-proven acute rejection; eGFR = estimated glomerular filtration rate using Modification of Diet in Renal Disease (MDRD) formula; MMF= mycophenolate mofetil; PR-TAC: prolonged release tacrolimus; SCr= serum creatinine; TAC= tacrolimus

<sup>a</sup> eGFR: A significantly different vs. B at 6 months ( $P<0.05$ )

<sup>b</sup> Decrease in eGFR: A significantly different vs. C ( $P<0.05$ )

<sup>c</sup> eGFR: A significantly different vs. B and C ( $P<0.05$ ); BPAR: B significantly different vs. A and C ( $P<0.05$ )

ACCEPTED

Table 4. Randomized studies of calcineurin inhibitor (CNI) minimization/elimination using mycophenolate mofetil (MMF): effect on follow-up renal function

Study	Regimens (number of patients in each arm)	Time post LT, months	Follow-up, months	Renal measure	Baseline renal function	Follow-up renal function	BPAR, %
Cicinnati, 2007 <sup>34</sup>	MMF + CNI <50% of initial dose (50)	72	12	SCr	168 µmol/L	142 µmol/L <sup>a</sup>	0
	CNI initial dose maintained (25)	65			161 µmol/L	172 µmol/L	0
Beckebaum, 2009 <sup>35</sup>	MMF + reduced dose CNI (60)	12-199	12	eGFR	40 mL/min	49 mL/min <sup>a</sup>	0
	CNI initial dose maintained (30)				41 mL/min	39 mL/min	0
Boudjema, 2011 <sup>36</sup>	MMF + reduced dose CNI (95)	0	12	eGFR	101 mL/min	90 mL/min <sup>b</sup>	30 <sup>b</sup>
	TAC standard dose maintained (100)				99 mL/min	78 mL/min	46
Pageaux, 2006 <sup>37</sup>	MMF + CNI <50% of initial dose (27)	>60	12	SCr	172 µmol/L	143 µmol/L <sup>a,b</sup>	0
	CNI >75% of initial dose (29)				175 µmol/L	182 µmol/L	0
Reich, 2005 <sup>38</sup>	MMF + CNI <50% of initial dose (18)	~ 12	12	eGFR	46 mL/min CsA	64 mL/min CsA	9
					47 mL/min TAC	60 mL/min TAC <sup>a</sup>	14
	MMF [CNI withdrawn] (20)	~ 16	12		35 mL/min CsA	58 mL/min CsA <sup>a</sup>	38
					55 mL/min TAC	56 mL/min TAC	14
Schlitt, 2001 <sup>39</sup>	MMF [CNI withdrawn] (14)	90	6	SCr	168 µmol/L	124 µmol/L <sup>a,b</sup>	21 <sup>b</sup>
	CNI maintained (14)	76*			139 µmol/L	136 µmol/L	0
Schmeding, 2011 <sup>40</sup>	MMF [CNI withdrawn] (75)	68	60	eGFR	59 mL/min	51% GFR improved <sup>a,c</sup>	11
	CNI maintained (75)	59			70 mL/min	4% GFR improved <sup>c</sup>	3

BPAR= biopsy-proven acute rejection; CNI = cyclosporine or tacrolimus; CsA = cyclosporine; eGFR = estimated glomerular filtration rate using the Cockcroft-Gault or MADR formula; LT = liver transplantation; MMF = mycophenolate mofetil; SCr= serum creatinine; TAC= tacrolimus

<sup>a</sup> Significant improvement from baseline at follow up, *P* at least<0.05

<sup>b</sup> Significant difference between groups at follow up, *P* at least<0.05

<sup>c</sup> Percent of patients with >20% improvement in GFR

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Table 5. Randomized studies of calcineurin inhibitor (CNI) elimination with conversion to sirolimus (SRL): effect on follow-up renal function

Study	Regimens (number of patients in each arm)	Time post LT, months	Follow-up, months	Renal measure	Baseline renal function	Follow-up renal function	BPAR, %
Watson, 2007 <sup>43</sup>	SRL conversion (13)	36	3	eGFR change	50 mL/min	+ 6.7 mL/min <sup>a b</sup>	18 <sup>b</sup>
	CNI maintained (14)	60	3		47 mL/min	+ 0.6 mL/min	0
Eisenberg, 2009 <sup>44</sup>	SRL conversion (8)	50	12	SCr	137 µmol/L	119 µmol/L <sup>a</sup>	0
	CNI maintained (8)	30	12		117 µmol/L	125 µmol/L	0
Teperman, 2013 <sup>45</sup>	SRL conversion (148)	~ 2	12	eGFR % change	54 mL/min	20% <sup>b</sup>	12 <sup>b</sup>
	CNI maintained (145)	~ 2	12		51 mL/min	1.2%	4
Shenoy, 2007 <sup>46</sup>	SRL conversion (20)	6-132	12	CrCl	64 mL/min	72 mL/min	5
	CNI maintained (20)	12-144	12		60 mL/min	58 mL/min	5
Abdelmalek, 2012 <sup>47</sup>	SRL conversion (393)	48	12	eGFR change	66 mL/min	-4.5 mL/min	46 <sup>b</sup>
	CNI maintained (214)	48	12		66 mL/min	-3.0 mL/min	13
Asrani, 2014 <sup>48</sup>	SRL + reduced dose TAC [trough: 4-11 µg/L] (108)	0	24		-	-	26 <sup>b</sup>
	TAC standard dose [trough: 7-15 µg/L] (111)	0	24		-	-	13

BPAR= biopsy-proven acute rejection; CNI = cyclosporine or tacrolimus; CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate using the Cockcroft-Gault or MDRA formula; LT = liver transplantation; SCr= serum creatinine; SRL: sirolimus; TAC= tacrolimus

<sup>a</sup> Significant improvement from baseline at follow up, at least  $P < 0.05$

<sup>b</sup> Significant difference between groups at follow up, at least  $P < 0.05$

Table 6. Randomized studies of calcineurin inhibitor (CNI) minimization/elimination using everolimus (EVR): effect on follow-up renal function

Study	Regimens (number of patients in each arm)	Time post-Tx, months	Follow-up, months	Renal measure	Baseline renal function	Follow-up renal function	BPAP, %
De Simone, 2009 <sup>49</sup>	EVR with CsA reduction/elimination (72)	39	6	CrCl	51 mL/min	53 mL/min	1
	CsA maintained (73)	35	6		50 mL/min	53 mL/min	1
Masetti, 2010 <sup>50</sup>	EVR conversion (52)	1	12	eGFR	82 mL/min	88 mL/min <sup>a</sup>	6
	CsA maintained (26)	1	12		75 mL/min	60 mL/min	8
Fischer, 2012 <sup>51</sup>	EVR conversion (101)	1.5	11	eGFR	78 mL/min	80 mL/min <sup>a</sup>	18
	CNI maintained (102)	1.5	11		75 mL/min	72 mL/min	15
De Simone, 2012 <sup>52</sup>	EVR conversion (231) discontinued	1	11	eGFR	83 mL/min	81 mL/min	20 <sup>a</sup>
	EVR + TAC reduced (245)	1	11		81 mL/min	81 mL/min <sup>a</sup>	4
	TAC maintained (243)	1	11		79 mL/min	70 mL/min	11

BPAP= biopsy-proven acute rejection; CNI = cyclosporine or tacrolimus; CrCl = creatinine clearance; CsA = cyclosporine; eGFR = estimated glomerular filtration rate using MDRA formula; EVR: everolimus; LT = liver transplantation; TAC= tacrolimus

<sup>a</sup> Significant difference between groups at follow up, at least  $P < 0.05$