Identifying risk profiles in liver transplant candidates and implications for induction immunosuppression

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Abstract: Changes in recipient and donor characteristics are redefining the role of induction in liver transplant recipients. Older recipients are more common, with greater concomitant comorbidity. Moderate or severe renal dysfunction is now estimated to affect 40% of liver transplant recipients. Donors are also becoming older, and other factors such as more frequent non-alcoholic fatty liver disease (NAFLD) compromise the quality of some grafts. Rejection rates are now relatively low (10%) but some patients have a markedly increased risk such as younger recipients and those undergoing re-transplantation. Induction immunosuppression is associated with a significant reduction in rejection risk but due to various factors universal induction is not justified. Steroid-free therapy without induction increases the risk of biopsy-proven acute rejection (BPAR) but randomized trials have shown that induction with an interleukin-2 antagonist receptor (IL-2RA) agent or with rabbit antithymocyte globulin (rATG) maintains immunosuppressive efficacy in steroid-free regimens. Delayed calcineurin inhibitor (CNI) initiation (e.g. to days 4-5 post-transplant) can prevent deterioration of renal function during the first year post-transplant, but requires induction with an IL-2RA agent or rATG to maintain early immunosuppressive efficacy. IL-2RA induction may be inadequate to ensure a low risk of rejection in a steroid-free regimen combined with delayed tacrolimus. Randomized trials of CNI withdrawal at month 1 post-transplant have only achieved an acceptable rate of BPAR when induction is administered. In terms of safety, an increased rate of infection does not seem to be a concern. The most recent large-scale analyses have not indicated any evidence for an increased risk of malignancy, or specifically post-transplant lymphoproliferative disease. In summary, the place of induction in the management of liver transplant patients is becoming established. Selective use in high-risk individuals to avoid graft rejection is still relevant, but the key rationale for induction is to facilitate steroid-sparing and CNI-sparing regimens to reduce long-term complications.

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Review article

Identifying risk profiles in liver transplant candidates and implications for induction immunosuppression☆

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ABSTRACT

Changes in recipient and donor characteristics are redefining the role of induction in liver transplant recipients. Older recipients are more common, with greater concomitant comorbidity. Moderate or severe renal dysfunction is now estimated to affect 40% of liver transplant recipients. Donors are also becoming older, and other factors such as more frequent non-alcoholic fatty liver disease (NAFLD) compromise the quality of some grafts. Rejection rates are now relatively low (~10%) but some patients have a markedly increased risk such as younger recipients and those undergoing re-transplantation. Induction immunosuppression is associated with a significant reduction in rejection risk but due to various factors universal induction is not justified. Steroid-free therapy without induction increases the risk of biopsy-proven acute rejection (BPAR) but randomized trials have shown that induction with an interleukin-2 antagonist receptor (IL-2RA) agent or with rabbit antithymocyte globulin (rATG) maintains immunosuppressive efficacy in steroid-free regimens. Delayed calcineurin inhibitor (CNI) initiation (e.g. to days 4—5 post-transplant) can prevent deterioration of renal function during the first year post-transplant, but requires induction with an IL-2RA agent or rATG to maintain early immunosuppressive efficacy. IL-2RA induction may be inadequate to ensure a low risk of rejection in a steroid-free regimen combined with delayed tacrolimus. Randomized trials of CNI withdrawal at month 1 post-transplant have only achieved an acceptable rate of BPAR when induction is administered. In terms of safety, an increased rate of infection does not seem to be a concern. The most recent large-scale analyses have not indicated any evidence for an increased risk of malignancy, or specifically post-transplant lymphoproliferative disease. In summary, the place of induction in the management of liver transplant patients is becoming established. Selective use in high-risk individuals to avoid graft rejection is still relevant, but the key rationale for induction is to facilitate steroid-sparing and CNI-sparing regimens to reduce long-term complications.

1. Introduction

The field of liver transplantation is changing rapidly. The number of transplants is growing annually [1], partly due to factors such as wider acceptance of expanded criteria donors (ECD) and developments in machine perfusion that are expanding the donor pool. At the same time the profile of recipients is changing due to alterations in population demographics and in selection criteria. In parallel, acute cellular

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rejection rates have fallen to little more than 10% [2], with higher recipient and donor age likely making a contribution [2,3]. Long-term graft survival rates have improved, with 10-year survival rates in the US now reaching 60% [2], although the increase in one-year survival appears to be plateauing [2]. In contrast, patient survival rates have not changed substantially in recent years [2], reflecting the growing proportion of older donors with more comorbidities [4].

These changes are mirrored in new priorities for immunosuppression that take into account the risk profiles, clinical status and comorbidities of recipients. The proportion of liver transplant patients given induction immunosuppression increased markedly after the introduction of graft allocation according to Model of End-Stage Liver Disease (MELD) and Pediatric End-Stage Liver Disease (PELD) scoring [5], and is now given to more than 30% of all adults and children [2]. One important contributing factor is that MELD-based allocation favors transplantation of patients with renal impairment, and renal-sparing regimens typically include induction (see '*Renal dysfunction and calcineurin inhibitor therapy*: *a remit for induction*'). Currently, interleukin-2 receptor antagonist (IL-2RA) induction is slightly more frequently used than T-cell depleting therapy for both adults and children undergoing liver transplantation [2].

Rational prescribing of induction demands an understanding of the evidence supporting its use in specific settings. This review considers the role of induction against the background of changing scenarios and priorities in liver transplantation. It focuses on the two agents used most widely in this context: rabbit antithymocyte globulin (rATG, Thymoglobulin®) and the IL-2RA agent basiliximab (Simulect®).

2. Evolution of donor and recipient characteristics

2.1. Donors

The average age of liver transplant donors is increasing, with more than 30% of donors in Europe now aged 60 years or older [6]. Indeed, an upper donor age limit for liver transplantation has recently been withdrawn in several countries. In addition to older age, donor quality is compromised by high body mass index (BMI) and the presence of diabetes [7], both of which are becoming more common in developed countries. The prevalence of non-alcoholic fatty liver disease (NAFLD) is rising, with one study from Italy reporting NAFLD in over 30% of donors [8]. NAFLD in the donor adversely affects graft and recipient outcomes [9] and is likely to lead to a higher rate of rejected donor livers in the future as the prevalence continues to rise. One large single-center study assessed the proportion of higher-risk grafts among 1152 liver transplants performed during 2000 to 2011, defining 'higher risk' as donation after cardiac death (DCD), donor age >60 years, donor body BMI >30 kg/m^2, donor intensive care stay >7 days, or donor serum sodium >165 mmol/L and/or donor serum bilirubin >51 μmol/L [10]. The prevalence increased from 31.8% in 2000−2003 to 40.9% in 2004−2007 and 59.1% in 2008−2011 ($p < 0.001$).

Advances in the field of machine liver perfusion, with use of dynamic preservation technology may help to improve the performance of marginal grafts with extensive steatosis or from older donors to increase rates of immediate graft function and also allow viability assessments before acceptance [11]. Improving the viability of higher-risk grafts may also lead to expanded use of DCD donation [12]. Importantly, machine perfusion can also help identify which marginal grafts do not merit transplantation, avoiding failed transplants.

2.2. Recipients

Older recipients (≥65 years) now account for more than 20% of procedures in the US [2], which as well as increasing levels of comorbidity is influencing the pattern indications for liver transplant.

Among wait-listed patients, chronic liver failure due to non-alcoholic steatohepatitis (NASH) and alcoholic liver disease, and hepatocellular carcinoma (HCC) related to hepatitis C virus (HCV) infection, are growing in frequency [13,14]. There has been a pronounced decline in HCV-related fibrosis as a cause for wait-listing and liver transplantation in the era of direct acting antiviral (DAA) therapy. Indeed, NASH is now the second most frequent cause of end-stage liver disease [15], and is likely to become the leading cause shortly as virus-related disease declines. Malignancy, including HCC related to HCV infection or NASH, is also a growing cause of liver transplantation, with a tripling in the number of patients transplanted for malignancy in the last 10 years [2].

Related to these changes and also to MELD-based allocation of donor grafts, medical urgency is increasing, with approximately 20% of US recipients now having decompensated disease at the time of transplant [2]. Patients with acute-on-chronic liver disease, which has extremely high mortality on the waiting list [2], still represent a small proportion of liver transplant recipients due to problems with identification, referral, organ availability and timing of transplantation [16] but evidence for good outcomes after transplantation [17] may promote further efforts to increase transplantation of this critically ill group [18]. Additionally, the priority given to patients with impaired renal function means that combined liver-kidney transplants now account for almost 10% of liver transplants in the US [2], further increasing the complexity of cases.

3. Risk of rejection after liver transplantation

Inclusion of induction in the immunosuppressive regimen following liver transplantation is by no means required in all cases. When a conventional regimen of calcineurin inhibitor (CNI) and steroids is given from time of transplant, possibly also with mycophenolic acid (MPA), the risk of rejection – be it T-cell mediated or humoral – should be taken into account.

3.1. Recipient and donor risk factors for rejection

Younger recipient age is a well-recognized risk factor for risk of acute cellular rejection [19,20]. Compared to patients aged 40 years, those aged 18–25 years have a three-fold increase in risk while patients aged ≥65 years have only ~70% of the risk [19]. Infants, however, have a lower risk for rejection than older children [21]. African-American race increases the risk for liver allograft rejection significantly [15,20]. The indication for liver transplantation may also play a role, with the available data suggesting that primary sclerosing cholangitis (PSC) [19,20,22] and autoimmune hepatitis (AIH) [23,24] are associated with a greater risk for acute rejection than other indications. Patients undergoing re-transplantation are more likely to experience acute rejection [19] here partly due to more frequent development of *de novo* donor-specific antibodies (*dn*DSA) [25].

There is no convincing evidence that the relative risk of acute rejection varies to any relevant degree in recipients of a living-donor graft compared to a deceased-donor graft [24], or a living-related versus living-unrelated graft [26]. Studies relating to the effect of combined liver-kidney transplantation are scarce, but no increase in rejection risk versus liver-only transplants has been shown to date [27,28].

3.2. Immunological risk factors for rejection

Positive T-cell cross-match, which occurs in approximately 7% of liver transplant procedures [29], shows a clear association with increased risk for acute rejection and lower five-year graft survival [23,30–33]. One recent study observed a four-fold increase of risk of acute rejection among recipients with a positive cross-match in a series of 413 living-donor recipients, and more frequent preservation injury [23]. Induction therapy might be clinically relevant for these patients, but T-cell cross-matching is not routinely checked in most liver transplant centers. Further studies on its role are needed.

The extent of HLA mismatching is a clear risk factor [23,30,34]. One meta-analysis of four studies found the risk ratio for acute rejection to be 0.77 in patients with 0–2 mismatches compared to a reference group of patients with 3–6 mismatches [34]. Shindoh *et al.* found HLA-DR mismatch, specifically, to be an independent risk factor for acute cellular rejection (odds ratio [OR] 2.99; $p = 0.013$) after living-donor liver transplantation [23]. However, the ubiquity of HLA mismatching in liver transplantation [35] means that decision-making about induction is not generally influenced by the number of HLA mismatches.

Awareness of the impact of DSA in liver transplantation is growing, with recent studies in adult patients estimating the incidence of preformed and *dn*DSA to be 13–15% [25,36] and 8–9% [36–38], respectively. Rates are higher in children [39]. Although data are limited, liver transplant recipients with preformed or *dn*DSA appear to be at increased risk for antibody-mediated rejection (AMR) [25,40,41] compared to DSA-negative individuals. The liver may be relatively resistant to AMR, however, due to its large size and sinusoidal microvascular bed, secretion of high levels of soluble HLA and phagocytosis by Kupffer cells in the liver, and the organ's regenerative capacity in response to injury [42]. More evidence is awaited on the implications of DSA, and particular DSA classes, in liver transplant patients before DSA monitoring is routinely performed in this setting.

4. Other factors affecting induction decision-making

In recent years, clinician decision-making processes in immunosuppression have been increasingly guided by the need to minimize early- and long-term CNI-related adverse events. Induction plays a pivotal role in supporting both steroid-sparing and CNI-sparing regimens after liver transplantation, as discussed below. Certain types of patient are likely to gain particular benefits from such regimens.

Older age, as expected, negatively impacts survival rates [1,43,44], partly due to an increased risk of infectious death [20,45]. Post-transplant infections are also more frequent in patients with higher MELD scores [45,46]. For older or critically ill individuals with an increased risk for infection early after transplantation, minimization of immunosuppression is paramount and could be facilitated by induction. Malignancy prior to transplantation [47] and transplantation with malignancy as the primary indication [1,48] are associated with a relevant increase in tumor-related mortality and CNI minimization can be prudent in this setting. Where recipients are at increased risk of infection or malignancy, use of induction to support rapid tapering or withdrawal of CNI therapy to achieve a low-intensity maintenance regimen may be beneficial.

5. Induction and outcomes: findings from large-scale analyses

A small number of registry analyses and meta-analyses have evaluated outcomes according to whether induction was administered, and the type of agent used [5,49,50]. Data, however, are typically based on populations transplanted no later than the 2000s.

Regarding risk for acute rejection, a Cochrane analysis found that induction of any type was associated with a clear benefit when analyzed across 1918 liver transplant patients in 16 randomized clinical trials, calculating a relative risk of 0.85 (95% confidence interval [CI] 0.75; 0.96) versus no induction [50]. A meta-analysis which included only pediatric liver transplant recipients ($n = 431$) also found a significant reduction in acute rejection in patients given induction versus controls [51].

Evidence concerning graft and patient survival is more complex since so many factors contribute. In a registry analysis of over 60,000 patients transplanted up to 2008, Moonka *et al.* observed significantly higher graft survival up to five years post-transplant (69.5% versus 66.2%, $p < 0.001$) in the subgroup given induction of any type versus those without induction [5]. Five-year patient survival was also superior (74.8% versus 72.4%, $p < 0.001$). The differences in survival rates emerged by year 1 and remained stable thereafter, supporting an early beneficial effect of induction (Fig. 1). Although the positive impact of induction remained persistent on multivariate analysis, a residual selection bias cannot be ruled out in such analyses. A Cochrane analysis of 19 randomized trials which compared any induction versus no induction has also been carried out, but inevitably involved far fewer patients ($n = 2067$) with shorter follow-up [50]. In that analysis, there was no significant effect of induction on either graft or patient survival although there was a trend to improved graft survival [50]. In US registry analyses comparing graft and patient survival according to whether patients received rATG/ATG or IL-2RA induction [5,49], there was a strong trend towards superior outcomes with rATG/ATG versus IL-2RA therapy. However, numbers were relatively low and no firm conclusions can be drawn.

6. Steroid-free immunosuppression: the role of induction

Peri-operative intravenous steroids are universally prescribed for liver transplantation to ameliorate ischemia-reperfusion injury (IRI) [52], block innate and adaptive immunity and enhance regulatory T-cell activity [53]. For post-operative oral steroid therapy, however, protocols and dose levels vary widely. While steroid withdrawal at various time points during the first year post-transplant is common [54], 'steroid-free' therapy – i.e. no oral steroid therapy – remains uncommon after liver transplant procedures [54].

A meta-analysis of randomized trials in liver transplant populations found no significant difference in graft or patient survival for steroid-free versus standard steroid regimens, but rates of cytomegalovirus (CMV) infection and mean cholesterol levels were significantly lower with steroid-free therapy, and there was a trend to less frequent hypertension [55]. Evidence concerning an effect on recurrence of HCC is mixed [56,57]. Potential long-term effects, such as limiting the risks for post-transplant diabetes, may be the most pressing reasons for seeking steroid-free therapy. Steroid-free regimens are not advisable in patients with autoimmune disorders such as PSC or AIH which require maintenance steroid therapy.

Where steroid-free therapy is planned, induction with rATG or an IL-2RA agent is generally adopted to maintain immunosuppressive potency. In a meta-analysis of 10 randomized trials published up to 2007, Segev *et al.* found that the relative risk of biopsy-proven acute rejection (BPAR) was increased by 31% when no induction was given in steroid-free regimens, but was reduced by 32% versus standard steroid therapy when induction (or mycophenolate mofetil [MMF]) was added [55].

6.1. IL-2RA induction

A randomized trial of steroid-free therapy in 602 deceased-donor liver transplant patients showed that IL-2RA induction with daclizumab achieved a similar level of BPAR to ongoing MMF therapy when either was given with tacrolimus (19.7% versus 16.2%) [58]. Drug-related adverse events and bacterial infections were, as would be expected, more frequent in the MMF group. In that trial, tacrolimus levels were relatively high compared to today's practice (10–20 ng/mL to week 6, then <10 ng/mL thereafter). Using lower tacrolimus exposure (mean 9 ng/mL to month 6), another randomized trial in 157 patients found that a steroid-free combination of daclizumab with MMF and tacrolimus achieved a lower rate of BPAR than standard tacrolimus/steroid therapy (11.5% versus 26.6%, $p < 0.05$) [59]. The efficacy of daclizumab with both MMF and tacrolimus in a steroid-free regimen (targeting tacrolimus 9–11 ng/mL) was again shown to lower the rate of BPAR versus tacrolimus/steroids, and also versus tacrolimus/MMF/steroids in a randomized trial of 312 patients published by Klintmalm *et al.* in 2005 [60]. A similar observation was reported in the recent randomized DIAMOND study of 844 liver transplant patients, where basiliximab induction with tacrolimus and MMF was associated with 12.1% BPAR at one year compared to 17.9% for tacrolimus and MMF, both in a

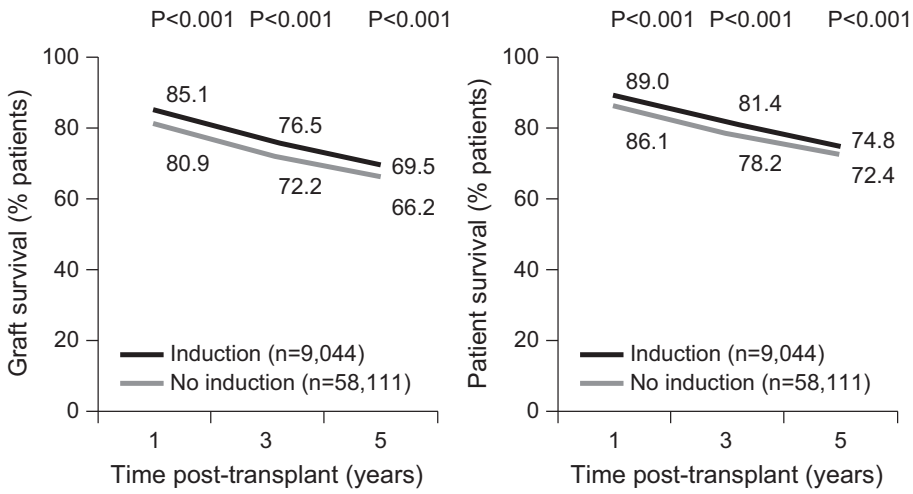

Fig. 1. Observed graft and patient survival in primary liver transplant recipients enrolled with the United Network of Organ Sharing (OPTN) database up to 2008, according to whether induction of any type was given or not [5].

steroid-free regimen ($p = 0.016$) (Fig. 2) [61]. The results from the DIAMOND study are relevant today since tacrolimus exposure (<10 ng/mL from week 2 onwards) is comparable to current practice.

Results from the DIAMOND study showed that delaying tacrolimus until day 5 was associated with 16.8% BPAR compared to 12.1% with immediate tacrolimus, a difference that was statistically significant ($p = 0.039$) but of minor clinical relevance (Fig. 2) [61].

6.2. rATG induction

A randomized trial of steroid-free therapy using rATG induction (1.5 mg/kg on days 0 and 1) with tacrolimus and MMF showed a similar rate of BPAR versus tacrolimus, MMF and oral steroids (25% versus 31%), but fewer patients required pulsed steroids in the rATG/steroid-free cohort (6.6% versus 50.0%, $p = 0.03$) [62]. As in many of the steroid-free trials using IL-2RA induction, tacrolimus exposure was higher than currently (10–12 ng/mL to month 3). One retrospective analysis of prospectively collected data, published in 2015, assessed rATG with delayed tacrolimus at more modern exposure levels (6–8 ng/mL), MMF and no oral steroids [63]. At a mean follow-up of 43 months, 22.8% patients had experienced BPAR, with pulsed steroids required in 6.6% [63]. Delayed tacrolimus in a steroid-free regimen appears feasible with rATG and MMF therapy.

Only one study, of a retrospective design, has compared rATG versus basiliximab in liver transplant patients managed with steroid-free therapy [64]. rATG was the induction agent of choice ($n = 322$), with basiliximab given in cases of persistent post-operative hemodynamic instability, persistent cardiac arrhythmias or pulmonary hypertension ($n = 273$). All patients were given tacrolimus starting from day 4 (10–12 ng/mL to month 3, then 3–5 ng/mL) with MMF given only to patients with renal dysfunction to support low-exposure tacrolimus [64]. BPAR was less frequent at final follow-up in the rATG group (18% versus 27%) with a reduced risk for graft loss, but selection bias limits interpretation. However, it seems reasonable to conclude that rATG induction enables steroid-free therapy with tacrolimus and MMF after liver transplantation, and may permit delayed tacrolimus initiation in this context.

7. Renal dysfunction and calcineurin inhibitor therapy: a remit for induction

7.1. Prevalence and risk factors for renal dysfunction

Liver cirrhosis can induce renal dysfunction via renal hypoperfusion, with the risk for acute tubular necrosis if left untreated, compounded by hepatorenal syndrome in advanced liver disease [65,66]. Introduction of MELD-based allocation criteria inevitably led to an increase in renal dysfunction among liver transplant recipients [67], with one US study reporting moderate or severe chronic kidney disease (chronic kidney disease [CKD] stage ≥3) in 40% of cases [68]. Hepatorenal syndrome resolves after transplantation, but progressive post-transplant deterioration of renal function is widespread. End-stage renal disease affects up to 10–20% of patients by five years post-transplant [69,70], increasing the risk of hospitalization two-fold [71] and the risk of death by as much as three-fold [72].

The risk of renal dysfunction after liver transplantation is closely associated with pre-transplant renal status [68,73]. Conventional risk factors for renal deterioration also apply, notably diabetes [68,72] and older age [72]. One of the few modifiable variables is chronic CNI-related nephrotoxicity with its hallmark signs of arteriolar hyalinosis, interstitial fibrosis and glomerular sclerosis [74]. Even in the era of low-dose tacrolimus, long-term CNI-related distortions to renal architecture are common [75]. Since almost all patients receive CNI therapy after liver transplantation, few studies have been able to assess the clinical impact. In the ICEBERG study, a multicenter retrospective analysis of 402 adult liver transplant patients who survived for at least two years after transplantation, 368 patients were

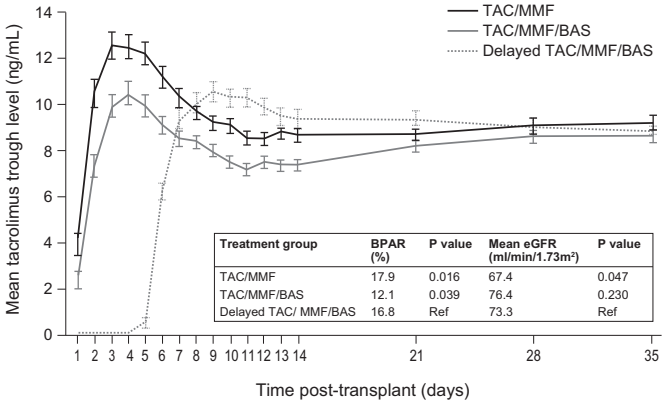

Fig. 2. Mean tacrolimus trough concentration and clinical outcomes at month 6 post-transplant in the randomized DIAMOND trial of 844 primary liver transplant recipients [61]. All patients received prolonged-release tacrolimus (5−15 ng/mL to week 7 and 5−12 ng/mL thereafter) with MMF (2 g/day to week 2 and 1 g/day thereafter) and were randomized to (i) no additional therapy (ii) basiliximab induction or (iii) basiliximab with delayed introduction of tacrolimus until day 5. BAS, basiliximab; BPAR, biopsy-proven acute rejection; eGFR, estimated GFR; MMF, mycophenolate mofetil; TAC, tacrolimus

given CNI therapy (155 cyclosporine, 149 tacrolimus) and 64 were managed with CNI-free regimens [76]. On multivariate analysis, the risk of chronic renal dysfunction was more than two-fold higher in CNI-treated patients (hazard ratio [HR] 2.31; 95% CI 1.05, 5.07; p = 0.037). The effect is dose-dependent. A study of 57 pediatric liver transplants found that the cyclosporine trough concentration was a significant time-dependent predictor for development of CKD (stage ≥3) [77]. High CNI exposure has also been shown to increase the risk of acute renal injury after liver transplantation by more than two-fold [78].

7.2. Induction to facilitate CNI minimization

A key role for induction therapy after liver transplantation is to facilitate CNI sparing. Recipients at high risk for post-transplant CKD are clear candidates for CNI-sparing regimens. In fact, it could be argued that CNI minimization should be applied broadly in an attempt to preserve long-term renal function after liver transplantation. Various CNI minimization regimens have been explored to help preserve long-term renal function after liver transplantation, the majority of which have included induction.

7.2.1. Delayed CNI initiation

Several studies published in 2005–2010 investigated use of delayed CNI initiation, to reduce the early renal insult immediately post-transplant [79–83]. Calmus *et al.* undertook a two-year randomized trial of tacrolimus, MMF and oral steroids in which 199 primary liver transplants with acceptable renal function (serum creatinine ≤180 μmol/L) were randomized to tacrolimus started on day 1 without induction, or on day 5 with daclizumab induction [79]. Performed during the early 2000s, the study used a tacrolimus target level of 10–20 ng/mL to week 5 then 5–15 ng/mL. Rates of BPAR were similar between groups, but despite a trend to improved renal function (eGFR) at month 6 in the delayed tacrolimus/daclizumab group eGFR was comparable by month 12 [79]. In a similar population, Yoshida *et al.* also randomized patients to immediate or delayed (day 4) tacrolimus with daclizumab, both with MMF and steroids, but this time tacrolimus exposure was also lower in the delayed-initiation group during month 1 [81]. BPAR rates were similar between groups, but despite an early renal benefit from delayed/reduced tacrolimus was again lost by month 6. A longer-term renal benefit was achieved by Neuberger *et al.* in a cohort of 517 primary liver transplant patients with serum creatinine ≤200 μmol/L at time of transplant [80]. In this three-arm study, patients were given tacrolimus (>10 ng/mL to month 1) with steroids, tacrolimus (≤8 ng/mL) with MMF and steroids, or tacrolimus from day 5 (≤8 ng/mL) with daclizumab induction and steroids. The daclizumab-treated group had the lowest tacrolimus exposure until month 3, with significantly better preservation of renal function at year 1, and significantly less frequent early treated BPAR (Fig. 3). As described above, when basiliximab was used to support steroid-free therapy with delayed tacrolimus in the DIAMOND study, there was only a minor difference in the incidence of BPAR compared to immediate tacrolimus (Fig. 2) [61]. To summarize, IL-2RA induction with delayed tacrolimus does not compromise immunosuppressive efficacy and can improve early renal function.

Two large retrospective studies have compared outcomes using rATG with delayed tacrolimus versus control groups given tacrolimus immediately post-transplant [82,83]. In both studies, oral steroids were given at least to month 3 [82,83]; one included low-dose MMF (1 g/day) to month 6 [82]. The two studies showed that rATG with delayed tacrolimus initiation significantly reduced the rate of BPAR at one year versus standard therapy – and renal function was significantly better at 1 year [82,83]. Interestingly, a large-scale Organ Procurement and Transplantation Network (OPTN) analysis of 1720 liver transplant patients performed up to 2005 found that use of rATG versus no induction was associated with a 2.2-fold increase in recovery of renal function after liver transplantation in patients with pre-transplant CKD (p = 0.022), possibly related to delayed CNI exposure [84]. Although randomized trials are lacking, these findings are encouraging.

7.2.2. Reduced CNI exposure

One randomized trial, published by Boudjema *et al.* in 2011, compared reduced-exposure tacrolimus started immediately after transplantation with concurrent MMF and steroids versus standard-exposure tacrolimus and steroids [85]. No induction was given. The rate of clinically-suspected acute rejection was 30% in the reduced-tacrolimus/MMF group versus 46% in controls, but without biopsy confirmation it is difficult to assess the efficacy of the investigational arm. A renal benefit was seen in the reduced-tacrolimus group [85]. Use of a mammalian target of rapamycin (mTOR) inhibitor also appears effective supporting reduced CNI exposure without the need for induction. The randomized H2304 study demonstrated that an early switch (at month 1) to reduced-exposure CNI with the mTOR inhibitor everolimus, plus steroids, appears feasible without induction [86] while retrospective data have indicated that *de novo* everolimus with reduced-exposure tacrolimus from the day of transplant can also offer adequate immunosuppressive potency [87,88]. Both approaches improved renal outcomes without requiring induction [86,87].

7.2.3. CNI withdrawal

Randomized trials have assessed the effect of early CNI withdrawal (~1 month post-transplant), with introduction of an mTOR inhibitor [86,89–91]. The two randomized trials which included induction (both using basiliximab) showed no increase in BPAR after CNI discontinuation [89,90]. In marked contrast, in the H2304 study where no patient received induction, recruitment to the tacrolimus withdrawal arm was discontinued due to excess BPAR [86]. Similarly, in the Spare The Nephron study where only 29.4% of patients received induction, BPAR was significantly higher after tacrolimus withdrawal [91]. The evidence seems clear-cut that without induction, the risk of BPAR increases significantly with early switch from CNI to mTOR inhibitor therapy and induction therapy is prudent (Table 1).

Reviewing the available evidence, renal function during the first year post-transplant may be optimized by delaying CNI therapy until day 4 or 5, potentially with steroid-free therapy or early steroid withdrawal, but induction is necessary to protect against rejection. Where CNI therapy is to be withdrawn, for example around month 1, induction also appears favorable. Reduced-exposure CNI with adjunctive use of MPA or

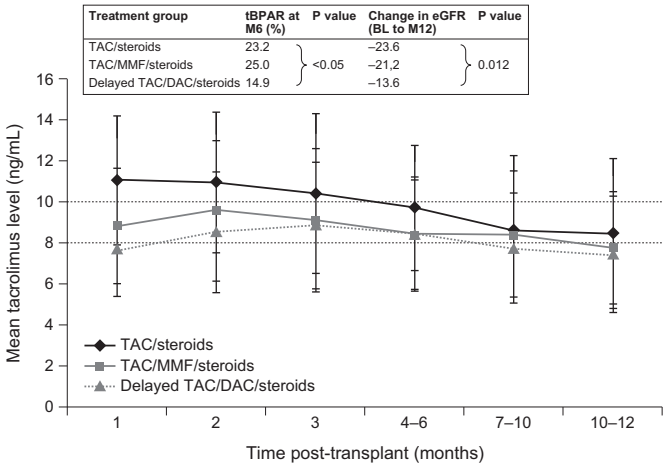

Fig. 3. Mean tacrolimus trough concentration and clinical outcomes in a randomized trial of 517 primary liver transplant recipients [80]. Patients received (i) tacrolimus (>10 ng/mL to month 1 then according to local practice) with oral steroids (ii) tacrolimus ≤8 ng/mL with MMF (dosed at 2 g/day to week 1) and steroids or (iii) tacrolimus ≤8 ng/mL with daclizumab induction and oral steroids. BL, baseline; DAC, daclizumab; eGFR, estimated GFR (mL/min/1.73 m^2); M6, month 6; M12, month 12; MMF, mycophenolate mofetil; TAC, tacrolimus; tBPAR, treated biopsy-proven acute rejection

an mTOR inhibitor, with steroids, may not require induction to maintain efficacy. However, if any early CNI minimization approach is planned with a steroid-free regimen, induction should be given.

8. Ischemia-reperfusion injury: a role for rATG?

The question of whether intraoperative rATG administration can ameliorate IRI is intriguing. Interest was triggered by a randomized trial of kidney transplant patients by Goggins *et al*., which demonstrated that intraoperative rATG reduced the rate of delayed graft function and improved early graft function [92]. A randomized single-center trial in 22 liver transplant patients has compared no induction versus rATG, given as three 1.5 mg/kg doses (one administered anhepatically at the start of the transplant procedure, and then on days 2 and 4) [93]. Clinically there was less evidence of IRI in the rATG group, with significantly lower mean alanine transaminase (ALT) levels on day 2. Data from a non-human primate model has suggested that rATG may exert a protective effect by reducing leukocyte adhesion via down-regulation of leukocyte chemokine receptors and reducing inflammation and tissue damage in reperfused tissues [94,95]. *In vitro* evidence has shown that rATG inhibits leukocyte migration to chemotactic signals [96]. A retrospective analysis of recipients of DCD liver grafts has also indicated that rATG may offer a protective effect on the biliary epithelium, reducing ischemic stricture formation for grafts transplanted from DCDs [97].

Any effect of rATG on IRI would require intraoperative, anhepatic administration. As a note of caution, a non-randomized case study which assessed the use of a high single intraoperative dose of rATG (3 mg/kg) in 16 liver transplant patients found evidence of cytokine syndrome and other side effects [98]. A lower intraoperative dose (e.g. 1.5 mg/kg) would be advisable.

9. Safety issues in liver transplantation

Two main safety issues are of potential concern in relation to induction: the risk for infection and risk for post-transplant malignancies.

A Cochrane analysis published in 2014 which included 1424 patients from 11 randomized trials of induction (of any type) versus no induction found no effect of induction on risk of infections overall (relative risk 0.90 [95% CI 0.76; 1.06]) [50]. The same analysis, based on 1543 patients in 10 randomized trials, showed no difference in risk of CMV infection (relative risk 1.24 [95% CI 0.93; 1.67]) [50]. There was no increase in infections or CMV infections when IL-2RA induction and rATG induction were considered separately, although patient numbers were low for rATG (n = 115) [50]. Individual studies of IL-2RA induction [79–81] or rATG [82,83] with delayed CNI initiation have reported no effect on infection rates with either category of induction. Infections do not seem to be a concern when considering use of induction after liver transplantation.

Concern about the risk of non-Hodgkin's lymphoma (NHL) in patients given lymphocyte-depleting induction arose following a Collaborative Transplant Study of kidney transplants, spanning the period 1985–2004 [99]. However, a more recent analysis from the same group, involving 38,311 kidney transplants from 2004–2013, found no increase in risk of NHL compared to no induction [100], likely reflecting exclusion of older lymphocyte-depleting agents (e.g. OKT3) and lower doses of ATG. The relative rarity of NHL, and more generally post-transplant lymphoproliferative disease (PTLD), means that randomized trials are too small to provide meaningful data, but a Cochrane analysis of induction generally found no increase in malignancy overall or PTLD associated with induction after liver transplantation (Table 2) [50]. When the analysis was repeated specifically for studies of IL-2RA induction or rATG, no increase in malignancy or in PTLD was seen with either type of induction (Table 2). Thus, although accurate assessment of malignancy rates is challenging, there is no evidence for an induction-related increase in risk. Based on modern dosing, levels of rATG (e.g. a cumulative dose of no more than 7.5 mg/kg, and frequently lower, over a maximum of five days) do not appear to influence the risk of post-transplant PTLD or malignancy.

Evidence relating to recurrence of HCV in patients given induction versus no induction, while limited, has not suggested an effect [50]. Any studies that have found a significant difference in fact showed a lower risk for recurrence under rATG versus no induction [101] or versus no induction/basiliximab [102], possibly through a CNI-sparing effect. In light of the recent introduction of DAA, however, the topic is of less interest.

There are almost no valid data comparing HCC recurrence with or without induction [103].

Table 1
Summary of rejection risk in randomized controlled trials of reduced-exposure CNI or early CNI withdrawal in liver transplantation.

Study	Population (all adults)	n	Induction	CNI minimization group	Control group	BPAR after RND	P value
Reduced CNI exposure							
H2304 [86]	Primary tx deceased donor eGFR ≥30	719	None	Everolimus reduced TAC steroids to ≥6 months	Standard TAC steroids to ≥6 months	4.1% vs 10.7%	0.005
Boudjema 2011 [85]	Primary tx deceased donor SCr ≥130 μmol/L	195	None	Reduced TAC MMF steroids	Standard TAC steroids	30% vs 46% (not biopsy-confirmed)	0.024
CNI withdrawal							
PROTECT [89]	≤70 years primary tx acceptable renal function no rejection	203	BAS	Day 30: switch from TAC or CsA to EVR (by month 4) ±Steroids	TAC or CsA ±Steroids	17.7% vs 15.3%	n.s.
Masetti 2010 [90]	Primary tx deceased donor CIT ≤12 h	78	BAS	Day 10: switch from CsA to EVR by day 30 steroids to week 5	CsA steroids to week 5	5.7% vs 7.7%	n.s.
H2304 [86]	Primary tx deceased donor eGFR ≥30	719	None	Day 30: switch from TAC to EVR (by month 4) steroids to ≥6 months	TAC steroids to ≥6 months	19.9% vs 10.7%	Recruitment to TAC withdrawal arm stopped due to high BPAR
Spare the nephron [91]	No steroid-resistant rejection or ≥1 BPAR eGFR ≥30	293	29.4% of patients[a]	Weeks 4–12: started sirolimus, TAC or CsA stopped MMF ± steroids	TAC or CsA MMF ± steroids	12.2% vs 4.1%	0.02

BAS, basiliximab; BPAR, biopsy-proven acute rejection; CIT, cold ischemia time; CNI, calcineurin inhibitor; CsA, cyclosporine; eGFR, estimated GFR; EVR, everolimus; MMF, mycophenolate mofetil; n.s., not significant; RND, randomization; SCr, serum creatinine; TAC, tacrolimus; tx, transplantation

[a] rATG n = 36; IL-2RA n = 50

10. Future perspectives

The place of induction in the management of liver transplant patients is becoming established. With acute rejection now affecting only one in ten liver transplant recipients, universal application of induction therapy as an 'add-on' to standard therapy is not justified on the grounds of lowering rejection rates. Exceptions apply, of course, for example patients undergoing re-transplantation or those with a positive T-cell cross-match, in whom addition of induction appears advisable. The key rationale for induction in liver transplantation protocols is to facilitate reduction or elimination of CNI therapy or steroids in order to minimize long-term complications. In appropriate patients, steroid-free therapy is a highly appealing option in order to alleviate the burden of chronic steroid-related adverse events such as diabetes, hypertension and osteopenia and induction is necessary to ensure effective immunosuppression with steroid-free regimens in the early post-transplant phase. Preservation of renal function, increasingly recognized as a key clinical objective, may be assisted by delayed CNI introduction and this demands effective induction to cover the interval until adequate CNI blood concentrations are reached. Similarly, if early CNI withdrawal is attempted induction is strongly advisable. Where low-exposure CNI therapy is employed, induction seems less important but potentially useful.

As the role of induction has clarified, it has raised more questions to answer. For example, what dosing regimen is appropriate for rATG in critically ill patients – is reduced dosing sufficient, or indeed beneficial? How do the immunological effects of rATG and IL-2RA induction differ based on systematic immune monitoring, for instance in terms of different types of regulatory cells? Undertaking randomized trials in transplantation is now becoming challenging since conventional endpoints such as acute rejection are less relevant, and the rapid evolution of management practices means that the time required to plan, perform and complete large studies often means that findings are irrelevant at the point of completion. Frequently, adequate statistical power cannot be achieved in this era of high success rates. Analyses of international or large national transplant registries may help address these problems, and further refine our understanding of how best to use induction in the context of liver transplantation.

Conflicts of interest

Umberto Cillo has served as a member of advisory boards, and received speaker's honoraria and travel support, from Astellas, Novartis, Sanofi, Bayer, Johnson &Johnson and Medtronics.

Wolf O. Bechstein has served on advisory boards of Astellas, Gilead, and TEVA, and has received speaker's honoraria from Astellas, Baxter, Gilead, Integra, MCI, Medica, Medupdate, MSD Sharp & Dohme, Sanofi Genzyme, and TEVA.

Gabriela Berlakovich has received speaker's and advisory board honoraria from Sanofi, MSD, Astellas, Sandoz, Teva and Chiesii.

Philipp Dutkowski has no conflicts of interest to declare.

Frank Lehner has served as a member of advisory boards, and received speaker's honoraria and travel support, from Novartis, Astellas, Sanofi, Neovii, Roche and Chiesi.

Silvio Nadalin has served as a member of advisory boards, and received speaker's honoraria and travel support, from Novartis, Teva, Sanofi and Chiesi.

Faouzi Saliba has received speaker honoraria and/or research grants from Novartis, Astellas, Roche, Genzyme, Gilead, Merck Sharp & Dohme, Gambro, Baxter, Chiesi and Vital Therapies.

Hans J. Schlitt is a member of Advisory Boards for Humedics and Chiesi, and has received speaker's honoraria and travel support from Novartis, Roche, B.Braun and Eisai.

Johann Pratschke has served as a member of advisory boards, and received speaker's honoraria and travel support, from Astellas, Chiesi, Sanofi, Neovii, Johnson &Johnson and Medtronics.

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Table 2
Cochrane analysis of relative risk for malignancy or PLTD with any induction, or specifically with IL-2RA or rATG induction, versus placebo/no induction (controls) [50].

	Any malignancy			PTLD		
	No. studies/no. patients	Induction vs controls	RR (95% CI)	No. studies/no. patients	Induction vs controls	RR (95% CI)
[Any induction]	12/1682	2% vs 3%	0.91 (0.49, 1.69)	9/985	1% vs 1%	1.08 (0.26, 4.46)
IL-2RA induction	7/1302	2% vs 2%	1.27 (0.58, 2.77)	4/605	1% vs 1%	1.00 (0.20, 4.89)
rATG	2/115	5% vs 10%	0.56 (0.15, 2.09)	2/115	0% vs 0%	–

CI, confidence interval; IL-2RA, interleukin-2 receptor antagonist; PTLD, post-transplant lymphoproliferative disease; rATG, rabbit antithymocyte globulin; RR, relative risk.

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