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Modification of immunosuppressive therapy as risk factor for complications after liver transplantation

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A B S T R A C T

Management of complications post-liver transplantation (LT) includes immunosuppressive manipulations with the aim to reduce the overall burden of immunologic suppression and compensate for renal, cardiovascular, metabolic toxicities, and for the increased oncologic risk. Two approaches can be implemented to reduce immunosuppression-related adverse events: *upfront* schedules tailored to the pretransplant individual patient's risk profile versus *downstream* modifications in the event of immunosuppression-related complications. *Upfront* strategies are supported by evidence originating from prospective randomized trials and consist of triple/quadruple schedules whereby calcineurin inhibitors (CNI)-exposure is reduced with combination of anti-CD25 monoclonal antibodies, antimetabolites and corticosteroids. Quadruple regimens allow for staggering of CNI introduction and higher renal function in the early term, but their superiority in the long term has not yet been established. A more recent *upfront* schedule contemplates early (4 weeks) introduction of mammalian target of rapamycin inhibitor (mTORi) everolimus and allows for reduction of CNI up to 4 years posttransplantation. Incorporation of mTORi has the potential to prolong time to recurrence for patients with hepatocellular carcinoma. However, as suggested by the available evidence, *downstream* immunosuppressive manipulations are more frequently adopted in clinical practice. These encompass CNI replacement and immunosuppression withdrawal. Switching CNI to mTORi monotherapy is the option most commonly adopted to relieve renal function and compensate for posttransplant malignancies. Its impact is dependent on interval from transplantation and underlying severity of renal impairment. Introduction of mTORi is associated with longer overall survival for patients with extrahepatic posttransplant malignancies, but results are awaited for recurrences of hepatocellular carcinoma. Immunosuppression withdrawal seems feasible (70%) in very long term survivors (>10 years), but is not associated with reversal of immunosuppression-related complications. Awaiting novel immunosuppressive drug categories, integration of *upfront* strategies with the aim to reduce CNI-exposure and a low threshold for adjustment in the posttransplant course are both advisable to improve long-term outcomes of LT.

Introduction

Immunosuppression plays a key role in achieving favorable outcomes after liver transplantation (LT), but is also the source of significant morbidity. Introduction of calcineurin inhibitors (CNI), cyclosporine (CsA) and tacrolimus (TAC), has resulted in considerable advancements with reduction of acute rejection (AR) rates and improvements in short-term graft survival [1,2]. With current CNI-based schedules, the risk of posttransplant AR is estimated between 5% and 20% within 1 year after surgery, while 1-year graft survival exceeds 85–90% in most international registries [3]. However, improvements in short-term outcomes have not been mirrored by long-term results [3].

Whilst early posttransplant morbidities consist of complications related to surgery, infections and poor graft quality, extrahepatic morbidities contribute to graft attrition rates in the long term, and arise from renal, cardiovascular, and metabolic toxicities produced

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Abbreviations

AE	adverse event(s)
AR	acute rejection
BPAR	biopsy proven acute rejection
CI	confidence interval
CNI	calcineurin inhibitor
CrCl	creatinine clearance
CsA	cyclosporine
cGFR	calculated GFR
EC	enteric coated
EC-MPS	enteric-coated mycophenolate sodium
eGFR	estimated GFR
EVR	everolimus
GFR	glomerular filtration rate
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
LT	liver transplant
MELD	model for end-stage liver disease
MMF	mycophenolate mofetil
MPA	mycophenolic acid
MPS	mycophenolate sodium
mTOR	mammalian target of rapamycin
mTORi	mTOR inhibitors
RCT	randomized clinical trial
sCr	serum creatinine
SIR	sirolimus
TAC	tacrolimus

by CNIs [4–8]. In recipients surviving more than 1 year, malignancies account for 22% of deaths, while renal insufficiency is strongly associated with increased overall mortality (HR: 4.10, 95% CI: 2.87–5.86; P<0.001) [9]. In times when most liver grafts are allocated on a patient basis, as per the model for end-stage liver disease (MELD) scoring system, the goal of current immunosuppressive schedules is twofold: to maintain long-term efficacy and reduce CNI-related toxicities [10].

Over the last decade, much has been done in the experimental and clinical setting to mitigate toxicities associated with use of CsA and TAC and tailor immunosuppression to the individual patient's clinical risk. Most immunosuppression schedules currently include antimetabolites (mycophenolic acid (MPA) derivatives) or less frequently induction agents (anti-CD25 monoclonal antibodies) [11]. The association of TAC and mycophenolate mofetil (MMF) currently represents 75% of initial immunosuppressive regimens, and use of MMF is reported in about 45% of maintenance patients at 1 and 2 years after transplantation [10]. Reduction of CNI exposure with addition of MMF is associated with comparable efficacy and lessened cardiovascular and renal toxicities versus standard-exposure schedules [8,12], while *ab initio* CNI-free regimens are limitedly implemented in clinical practice due to a higher risk of treatment failure [13].

Incorporation of mammalian target of rapamycin (mTOR) inhibitors, everolimus (EVR) and sirolimus (SIR), in reduced-exposure CNI-based schedules is a further approach to address the issues related to long-term patient and graft survival. mTORi and CNIs act on different sites of the T-cell activation pathway [14]. EVR and SIR are selective inhibitors of the mTOR complex, which is a serine–-threonine kinase with a key role for cell metabolism and functions [14]. Over the last decade, mTORi have received substantial attention, since they are associated with a more favorable renal profile versus CNIs and have shown anti-proliferative properties in experimental and clinical studies, with a potential for reduction of recurrent or *de novo* posttransplant malignancies [15,16].

Tailoring of immunosuppressive schedules has a definite role in improving the results of LT and is the most common strategy to harness short-term and long-term immunosuppression-related adverse events (AE) [10]. To that regard, two approaches can be implemented in clinical practice in: *upfront* strategies, whereby an immunosuppressive regimen is delivered based on pretransplant and/or intraoperative risk factors versus *downstream* policies, these latter consisting of adjustments in the presence of AEs (Table 1). The current paper reviews the available literature with the aim of defining the immunosuppressive strategies which might contribute to reduce the posttransplant attrition rates, especially in regards to the toxicities associated with use of CNIs.

The choice of the ideal immunosuppressive regimen: *upfront* strategies

Ab initio CNI-free immunosuppression: is it possible?

Due to the burden of CNI-related toxicity, one approach that has spurred interest in the clinical community is to eliminate CNIs immediately after transplantation (Table 2). However, *ab initio*, CNI-free schedules are largely impractical [13]. CNIs have a pivotal role in achieving early-term posttransplant efficacy, and their elimination has variably been associated with a heightened risk of AR of the liver graft [13]. A group of biological agents available for kidney transplantation have received considerable attention in view of early elimination of CNI from immunosuppressive schedules after LT. However, anti-IL2R (anti-CD25) monoclonal antibodies, basiliximab (BAX) and daclizumab (no longer in use), have not allowed for CNI elimination, and pilot experiences on sparing CNIs with basiliximab induction failed due to a higher risk of posttransplant AR [17]. Currently, anti-IL2R antibodies are mainly used to facilitate liver engraftment and delay introduction or reduce exposure of CNIs in the early posttransplant course [18]. Similarly, anti-thymocyte globulins (ATG) have not resulted in early CNI withdrawal. A recent multicenter Spanish trial on ATG-facilitated TAC weaning 3 months after transplantation has failed due to a higher incidence of AR in the study versus the control arm [19]. AR occurring during the first 3 months after transplantation was more frequent in the ATG group (52.4% vs. 25%), and late AR episodes occurred in all recipients in whom weaning was attempted [19]. Other biologicals have shown a high incidence of treatment failure and their development in LT was eventually halted. The international, multicenter, phase-2 trial on anti-CD28 (belatacept) after LT was discontinued due to a higher incidence of AR (44%) for patients on a more intensive regimen (high-dose anti-CD28 + BAX + MMF, and corticosteroids), and to inferior graft survival (67%) for patients on less intensive regimen (low-dose anti-CD28 + MMF, and corticosteroids) within 1 year after transplantation [20].

mTORi have sporadically been used to avoid CNI administration, and a limited number of patients have been reported in the international literature. The PATRON07 was a single-arm, two-step trial of CNI-free immunosuppression with BAX + MMF and corticosteroids followed by delayed introduction of SIR in patients with renal impairment. In a total of 27 patients included, incidence of biopsy proven AR (BPAR) was 18.5%; SIR was switched to CNI in 44% patients by one year, and the 1-year overall survival was 93% [13]. A similar, exploratory trial on 29 LT recipients (CILT) with use of EVR *in lieu* of SIR was preliminary reported in the literature, but its final results are not yet available [21]. Recently, Manzia et al. reported