EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Immunosuppression minimization *vs.* complete drug withdrawal in liver transplantation

Maria-Carlota Londoño[1], Antoni Rimola[1], John O'Grady[2], Alberto Sanchez-Fueyo[2,*]

[1]*Liver Unit, Hospital Clinic Barcelona, IDIBAPS, CIBEREHD, University of Barcelona, Barcelona, Spain;* [2]*Institute of Liver Studies, King's College Hospital, Denmark Hill, King's College London, London, UK*

Summary

Despite the increase in long-term survival, liver transplant recipients still exhibit higher morbidity and mortality than the general population. This is in part attributed to the lifelong administration of immunosuppression and its associated side effects. Several studies reported in the last decades have evaluated the impact of immunosuppression minimization in liver transplant recipients, but results have been inconsistent due to the heterogeneity of study designs and insufficient sample sizes. On the other hand, complete immunosuppression withdrawal has proven to be feasible in approximately 20% of carefully selected liver transplant recipients, especially in older patients and those with longer duration after transplantation. The long-term risks and clinical benefits of this strategy, however, also need to be clarified. As a consequence, and despite the general perception that a large proportion of liver recipients are over-immunosuppressed, it is currently not possible to derive evidence-based guidelines on how to manage long-term immunosuppression to improve clinical outcomes. Large clinical trials of drug minimization and/or withdrawal focused on clinically-relevant long-term outcomes are required. Development of personalized medicine tools and a deeper understanding of the pathogenesis of idiopathic inflammatory graft lesions will be pre-requisites to achieve these goals.

Background

Long-term survival after solid organ transplantation has increased during the last decades [1] due to improvements in surgical technique, peri-operative care, and more efficient immunosuppressive (IS) drugs. However, transplant recipients still exhibit higher morbidity and mortality than the general population [2]. One of the main causes are co-morbidities negatively influenced by chronic IS drug usage [3–8]. The high prevalence of IS related toxicity and the fact that liver allograft rejection seldom impacts on clinical outcomes suggest that most liver recipients are likely to be over-immunosuppressed [9,10]. One of the most significant side effects of IS drugs is calcineurin inhibitor (CNI) nephrotoxicity, which contributes to the high rate of chronic renal failure observed in liver transplant recipients and is associated with the need to institute renal replacement therapies and with high mortality [11,12]. Minimization (or complete withdrawal) of immunosuppression, particular CNIs, may overcome these problems. The clinical opportunity is more tangible in the liver than in other transplantation settings due to the greater capacity of the liver allograft to cope with the cytolytic effects of alloimmune responses [13,14]. The potential benefits of IS minimization or withdrawal, however, still need to be balanced with the risks and inconveniences of prompting liver allograft rejection. This assessment has to take into account the fact that the individual recipient immunoreactivity evolves over time.

Over the past two decades, multiple studies on IS minimization have been reported in the liver transplantation literature. In parallel, a number of IS withdrawal trials have been performed. While the results of some of these studies have been promising, due to their heterogeneity and relatively small sample sizes, they have failed to provide truly generalizable information. As a consequence, we still lack evidence-based guidelines on how to reduce IS to improve clinical outcomes, and therefore, the long-term therapeutic management of liver transplant recipients remains an empirical practice. We review the benefits and limitations of the different strategies employed in liver transplantation to minimize or withdraw IS in an attempt to provide a framework to critically assess and/or design future studies in the field.

Immunosuppression minimization

In the absence of accurate tools to determine the optimal level of immunosuppression required by each individual patient, it is difficult to objectively define "immunosuppression minimization". A commonly used definition is the administration of the lowest amount of immunosuppression compatible with a rejection-free state [15]. The IS levels required to prevent rejection, however, vary greatly, not only between different individuals, but also

Keywords: Immunosuppression minimization; Immunosuppression withdrawal; Liver transplantation.
Received 3 January 2013; received in revised form 15 March 2013; accepted 2 April 2013

* Corresponding author. Address: Institute of Liver Studies, King's College Hospital, Denmark Hill, London SE5 9RS, UK. Tel.: +44 2032993305.
E-mail address: sanchez_fueyo@kcl.ac.uk (A. Sanchez-Fueyo).

Abbreviations: IS, immunosuppression; CNI, calcineurin inhibitor; HCV, hepatitis C virus; RCT, randomized clinical trial; ATG, anti-thymocyte globulin; MMF, mofetil mycophenolate; mTOR, mammalian target of rapamycin; RISET, reprogramming the immune system for the establishment of tolerance; US, United States.

Table 1. Strategies to minimize immunosuppression.

Reference	Minimization strategy	N	Study design	Rejection	Impact on co-morbidities
Margarit *et al*., [26]	Steroid avoidance	60	Randomized TAC *vs*. TAC + steroids	Acute rejection 39 *vs*. 32%; *p* = n.s.	No differences in survival rate and infections
Samonakis *et al*., [24]	Steroid avoidance	56	Randomized TAC *vs*. TAC + steroids + AZA	Acute rejection 70 *vs*. 86%; *p* = n.s.	No differences in renal function, metabolic complications and survival rate
Lerut *et al*., [25]	Steroid avoidance	156	Randomized TAC *vs*. TAC + steroids	Acute rejection 20 *vs*. 23%; *p* = n.s. Steroid resistant 13 *vs*. 3%; *p* = 0.04	No differences in renal function, metabolic complications and PTLD
Herrero *et al*., [27]	MMF	11	Progressive CNI reduction (6 patients free of CNI)	Acute rejection 2 episodes	Improvement in renal function in patients free of CNI
Schlitt *et al*., [28]	MMF	28	MMF replacement *vs*. CNI	Acute rejection 3 *vs*. 0 episodes	Significant improvement in renal function in MMF patients. No differences in lipid profile and blood pressure
Orlando *et al*., [30]	MMF	42	Conversion to MMF	Acute rejection 9 patients	Renal function improved in 89% of the patients. Cholesterol and triglycerides decreased in 76% of the patients. Blood pressure improved 80% of the patients
Abdelmalek *et al*., [36]	Sirolimus	607	Randomized (2:1) Conversion to sirolimus *vs*. CNI	Acute rejection 11 *vs*. 6%; *p* = 0.02	No differences in renal function or patients and graft survival
De Simone *et al*., [40]	Everolimus	719	Randomized 1 month after LT TAC + everolimus *vs*. everolimus *vs*. TAC	Acute rejection 4 *vs*. 11%; *p* = n.s. Everolimus monotherapy was early terminated due to high rate of acute rejection (19%)	Improvement in renal function
Fischer *et al*., [39]	Everolimus	203	Randomized 1 month after LT everolimus *vs*.TAC	Acute rejection 15 *vs*. 18%	No differences in renal function, infection or metabolic complications

TAC, tacrolimus; AZA, azathioprine; PTLD, post-transplant lymphoproliferative disorder; CNI, calcineurin inhibitor; LT, liver transplant; n.s., not significant.