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Special article

Operational tolerance after liver transplantation☆

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The achievement of an immunosuppression (IS)-free state after transplantation represents the ultimate goal of any immunosuppressive regimen. While clinical operational tolerance (COT) remains the exception after other types of solid organ transplantation, several cases of COT have been described after liver transplantation (LT). Overall, the experience gained so far worldwide demonstrates that COT can be achieved safely in one quarter of selected individuals, irrespective of the immunological background of donor and recipient, patient age, indication for LT, study endpoint, length of the weaning period and of pre/post-weaning follow-up, presence or not of chimerism. However, most transplant physicians still believe that the achievement of COT is still out of reach for the majority of LT recipients because of the potential risk for transplant survival, the non-randomized nature of most of the studies reported so far, and the selective nature of the patients enrolled in such studies, making them non-representative of the whole population of LT recipients. Despite these concerns, the present article demonstrates that this attitude is potentially no longer justified, given the growing evidence that a permanent and stable IS-free state can be achieved in a proportion of individuals who have received a LT for non-immune mediated liver diseases.

Keywords: **Liver transplantation; Immunosuppression; Clinical operational tolerance**

1. Introduction

The clinical era of transplantation began on December 23rd 1954, when Dr. Joseph Murray and co-workers performed the first successful renal transplant on the Herrick twins [1]. As a result of the genetic identity between the brothers, Richard Herrick did not receive any immunosuppression (IS) after the operation, thus representing the very first case of clinical operational tolerance (COT) in solid organ transplantation (SOT). In the same year, Billingham, Brent and Medawar first introduced the term transplantation tolerance, with the report of skin graft acceptance in mice that had received neonatal injections of donor mononuclear cells [2]. More than 50 years later, COT remains an extremely difficult goal to achieve in the majority of transplant recipients. However, in liver transplantation (LT) there is a growing body of evidence that COT can be achieved safely in a proportion of recipients. In this article, we will summarize and comment on all of the cases of COT described after LT reported to date, and will demonstrate that the achievement of an IS-free state – namely, COT – is definitely possible and safe after LT. The manuscript will emphasise the clinical perspectives, and will touch only briefly on the immunological mechanisms relevant to the understanding of the IS-free state achieved in the different studies described herein where, despite improved knowledge, understanding of the

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Abbreviations: COT, clinical operational tolerance; SOT, solid organ transplantation; IS, immunosuppression; LT, liver transplantation; GVHD, graft-versus-host disease; UDCA, ursodeoxycholic acid; MSC, mesenchymal stem cells; DBMC, donor bone marrow cells.

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immune mechanisms underlying the phenomenon remains inadequate.

The cases of COT discussed will be divided into four different groups and sorted timewise according to the weaning strategy adopted. The first group identifies cases in which no tolerogenic molecule- or cell-based protocols were used, whereas the second and third groups will include cases in which tolerogenic molecule- and cell-based regimens were implemented, respectively. The cases of COT that developed after bone marrow transplantation will be included in the last group.

1.1. Definition

The authors define COT as the condition whereby a liver transplant retains function and lacks histological signs of rejection in the absence of any IS. The LT recipient in question is an immunocompetent host capable of responding to other immune challenges, including infections [3].

2. Group A: immunosuppressive drugs only

2.1. Pittsburgh – the original work

The very first cases of COT after LT were documented by Starzl and colleagues in the early 1990s [4–10]. Based on the finding that 11 LT recipients had been IS-free as a consequence of non-compliance or post-transplant lymphoproliferative disorders, the authors designed a prospective trial in which IS was intentionally withdrawn in patients experiencing IS-derived chronic toxicity. Out of 95 patients enrolled, 28 (29%, Table 1) were successfully weaned off IS after a mean time from enrollment of 2.2 years; currently, the LT recipients in this group have been off IS for an average period of 10.8 years.

Most individuals (22/28, 79%) were transplanted before the age of 18, and patients with autoimmune diseases – namely, primary biliary cirrhosis and autoimmune hepatitis – were excluded from the studies from 1997 on due to the risk for disease recurrence.

In the attempt to identify a fingerprint of tolerance in IS-free LT recipients that might enable selection of patients who may be prone to develop COT, the authors proposed a set of immunologic assays studying cytokine gene polymorphism and subsets of dendritic cells [11–14]. These parameters require validation in further randomized trials.

2.2. London

Girlanda et al. recently published the 10-year follow-up of a single arm trial in which 18 patients suffering from IS-derived chronic toxicity were enrolled and weaned off IS [15,16]. The weaning protocol was initially successful in 5 patients (28%), but only 2 of them (11%) remained completely off IS in the long term. The remaining three resumed IS for a variety of reasons; late acute rejection (1×), re-transplantation for chronic rejection (1×), and kidney transplantation for secondary end-stage renal failure (1×). Non-immune-mediated liver disorders, fewer donor-recipient HLA mismatches and no previous acute rejection were identified as parameters predictive of successful weaning, while HCV-related cirrhosis is an absolute contraindication to IS withdrawal. The London experience demonstrated that COT may be extremely difficult to maintain in the long term, as the immunologic balance between the host and the donor may be lost at any time for numerous unforeseeable reasons.

2.3. Columbus–Madison

In the attempt to define immunological parameters that identify potentially tolerant patients, Burlingham and colleagues utilized the human-to-mouse trans-vivo delayed-type hypersensitivity assay [17,18]. One of the three IS-free individuals analysed in the first study was a LT recipient and had been IS-free for 3 years, without experiencing any sign of rejection.

By observing that allograft acceptors failed to exhibit donor-reactive delayed type hypersensitivity responses when recipient leukocytes were challenged with donor antigen, although they frequently develop donor-reactive alloantibodies, the authors demonstrated that this pattern of immune responses is not due to an absence of allosensitization, but to the development of an immune mechanism that actively inhibits antidonor delayed-type (i.e., cell-mediated) immune responses. In doing so, they emphasized the fundamental concept of immune regulation, rather than immune-suppression [19].

2.4. Kyoto

Tanaka and co-workers documented their initial experience on COT in a large population of 63 pediatric recipients who received a liver graft from a living donor [20,21]. COT was achieved in 24/63 (38%) individuals, after a mean period of 23.5 (range 3–69) months. A further 23 individuals were at various stages of weaning at the time of data collection. The remaining 16 developed rejection after a mean period of 9.5 (1–63) months from initiation of tapering of IS, but the resumption of maintenance IS or the introduction of additional steroid bolus resolved the rejection.

In 2007, the same group reported on the immunological and pathological aspects of COT, as observed in a larger population of 87 IS-free pediatric LT patients, inclusive of the above mentioned 24 tolerant individuals