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# The Importance of Regulatory T Cells for the Tolerance Maintaining After Liver Transplantation

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## ABSTRACT

In some cases, spontaneous inhibition of immunological reactivity in transplantation, which is responsible for the graft rejection, has been observed, a phenomenon mediated by a specific T cell population defined as regulatory T cells (Tregs). This mini-review discusses the impact of Treg cells on the in initiation and maintenance of operational tolerance after liver transplantation, the Treg cells as a biomarker for post-transplantation tolerance assessment, and the novel approach of adoptive transfer of Treg cells after liver transplantation. Currently, the data are limited and do not allow for extensive comments. However, by virtue of the immunological background, Tregs are promising as diagnosing and therapeutic application that gives hope for successful liver transplantation.

## KEYWORDS

T Regulatory Cells; Treg Cells; FoxP3; liver Transplantation; Operational Tolerance; Immunosuppressive Drugs.

## INTRODUCTION

Immunological mechanisms in transplantation are complex and in most cases are directed towards effector reactions, leading to the graft rejection. From clinical point of view, the control of this effector reaction and the establishment of immune tolerance towards graft is ensured by the immunosuppressive therapy. However, in some cases the immune system of the recipient spontaneously develops immune tolerant milieu, a phenomenon mediated by a specific T cell population defined as regulatory T cells (Tregs) [1].

### Characteristics of Treg cells

The extensive research during last decade identified several subsets of T cells with regulatory properties. Among them of most importance for the establishment of immune tolerance are natural (nTregs) and inducible (iTregs) cells. Unlike iTregs, which originate from circulating naïve T cells and are involved mainly in the regulation of inflammation and immune responses to various pathogens in the periphery [2,3], nTregs are educated and selected into the thymus directly from T-cells precursors. Those cells that recognize their own antigens with high-avidity undergo clonal deletion or transform into Tregs by increasing the expression of a FoxP3 transcription factor. When nTregs leave the thymus, they are functionally active and with stable expression of FoxP3. In contrast, iTregs are population, which depends on various factors in the environment [2,4].

Currently, two mechanisms used by Tregs for inducing tolerance are known. The contact-dependent pathway is mediated by the expression of specific molecules on the surface of Tregs, like CTLA-4 / CD80-86 and PD-1 / PD-L1, and the activa-

tion of inhibitory signals on the target cell [5]. By the contact-independent mechanism, Tregs suppress the target cell via the potent immunosuppressive effect of IL-10, TGF-β, IL-34, and IL-35 perforin and granzymes and/or competing with effector cells for the available IL-2 in the surrounding area [6]. All of the described mechanisms are crucial in establishing tolerance after transplantation.

## Treg cells and operational tolerance after liver transplantation

The outcome of transplantation depends on the establishment of post-transplantation immune tolerance. It is induced by the application of immunosuppressive regimen that should be followed by patients. However, in some cases of treatment interruption, the immune system of the recipient is able to control graft rejection by it self. This status is defined as Operation tolerance. Although it is observed in kidney transplantation also, the operational tolerance is attributed mainly to the liver transplantation.

The liver has particular tolerogenic characteristics that distinguish it from other solid organs and are consequences of anatomical, biochemical and immunological features. Among them are: i) liver immune cells, incl. lymphocytes and liver parenchymal cells, ii) blood flow - systematically introducing huge range of antigens to the liver immune cells, and iii) liver cells metabolism. In addition, a number of factors of natural and acquired immunity are synthesized in the liver as complement components, acute phase proteins, cytokines, and chemokines [7-9]. The unique anatomic together with the specific cellular community suggest that the immunologic approach after the surgical operation in liver transplantation might be different from those in other solid organ transplantations.

A good example confirming it is the operational tolerance. Although several immune subsets were reported associated with it, like NK and YδTcells [10], Treg cells are considered as the principal one [11]. A number of studies have shown that prolonged high percentages of Tregs were seen in patients with operational tolerance alone and this observation did not depend on the immunosuppressive therapy administered in adults and children [12]. Other immunosuppressive mechanisms were shown to work in concert with the above-mentioned subsets. For example, the non-classical HLA class I molecule HLA-G was associated with a decreased incidence of the liver graft acute rejection. From the other hand, the high expression of HLA-G on circulating monocytoid dendritic cells from tolerant recipients has been correlated with the increased expression of Foxp3 in T cells. This is an example of a two-way process (Tregs and HLA-G) for inducing tolerance, which are mutually potentiated [13].

## Treg cells and immunosuppressive therapy after liver transplantation

From the immunosuppressive therapy, Everolimus alone has a stimulating effect on Treg cells [14, 15]. While plasma levels of the immunosuppressive drugs are the subject of clinical laboratory and pharmacology, the degree of immunosuppression is determined by the swing between activation and tolerance [15, 16]. Thus, Treg cells could be employed as a biomarker for post-transplantation tolerance. The ONE Study has already offered a specific Tregs analysis algorithm [17]. Barcelona Consensus (2016) on immunosuppressive therapy also listed Tregs as one of the possible indicators of graft rejection and control of the effectiveness of immunosuppressive therapy [18]. Some authors showed that in patients after liver transplantation the percentage of Tregs was increased significantly reaching values close to or greater than those in healthy subjects at the end of the first week after surgery [19]. We also found such tendency at the end of the first week after liver transplantation (unpublished our data).

## Adoptive transfer of Treg cells after liver transplantation

Over the past few years, Tregs have been on focus not only as a diagnostic tool but also for therapeutic purposes in transplantation. At present, several studies employing Treg cells transfer in solid organ and hematopoietic stem cell transplantations are ongoing [1]. The aim of this novel therapeutic approach is to increase the number of regulatory T cells in the recipients to achieve immune tolerance and reduce the possibility of rejection. For the first time, a protocol for isolation of Tregs according to the requirements of GMP was performed in 2006 [20, 21], and adoptive Tregs transfer in 2009 [22]. Cells can be isolated from peripheral blood or umbilical cord. In most laboratories, Tregs are sorted by the CliniMACS system (CliniMACS TM Instruments, Miltenyi Biotec Bergisch Gladbach, Germany) under sterile conditions, multiplied by specific stimulation and re-injected into the patient. The second option is a flow cytometric sorting. Currently, three centers have been authorized for this operations - two in the USA (University of Minnesota, USA [23]; University of California, USA [24] and one in Europe - University of Gdansk, Poland [22].

Interestingly, of the currently ongoing eleven studies, four are for Tregs in liver transplantation. Despite the fact that they are still at an early stage, and there are many issues regarding the amount and frequency of injection of the cells, the adoptive transfer of regulatory T cells is a promising therapeutic approach [1].

## Conclusion remarks

In conclusion, it is already known that regulatory T cells are es-

sential for providing an immune-friendly environment in liver transplants. Moreover, their measurement in the peripheral blood could be useful as a diagnostic tool for early detection of graft rejection. The possibility of an adoptive transfer of regulatory T cells is a very new approach to transplantation therapy in humans. Currently, the data are limited and do not allow for extensive comments. However, by virtue of its immunological background, the evaluation and functions of Treg cells for diagnostic and follow up of immune state in liver transplantation, as well as eventual therapeutic approach, gives hope for a successful application in transplantation practice

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