World Journal of Gastroenterology

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World J Gastroenterol 2024 April 7; 30(13): 1791-1800

DOI: 10.3748/wjg.v30.i13.1791

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Cellular strategies to induce immune tolerance after liver transplantation: Clinical perspectives

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Sanal MG, India

Received: December 30, 2023
Peer-review started: December 30, 2023
First decision: January 16, 2024
Revised: February 3, 2024
Accepted: March 14, 2024
Article in press: March 14, 2024
Published online: April 7, 2024

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Abstract

Liver transplantation (LT) has become the most efficient treatment for pediatric and adult end-stage liver disease and the survival time after transplantation is becoming longer due to the development of surgical techniques and perioperative management. However, long-term side-effects of immunosuppressants, like infection, metabolic disorders and malignant tumor are gaining more attention. Immune tolerance is the status in which LT recipients no longer need to take any immunosuppressants, but the liver function and intrahepatic histology maintain normal. The approaches to achieve immune tolerance after transplantation include spontaneous, operational and induced tolerance. The first two means require no specific intervention but withdrawing immunosuppressant gradually during follow-up. No clinical factors or biomarkers so far could accurately predict who are suitable for immunosuppressant withdraw after transplantation. With the understanding to the underlying mechanisms of immune tolerance, many strategies have been developed to induce tolerance in LT recipients. Cellular strategy is one of the most promising methods for immune tolerance induction, including chimerism induced by hematopoietic stem cells and adoptive transfer of regulatory immune cells. The safety and efficacy of various cell products have been evaluated by prospective preclinical and clinical trials, while obstacles still exist before translating into clinical practice. Here, we will summarize the latest perspectives and concerns on the clinical application of cellular strategies in LT recipients.

Key Words: Cellular therapy; Induced tolerance; Liver transplantation; Regulatory T cells; Regulatory dendritic cells

Core Tip: Immune tolerance after liver transplantation could significantly reduce the long-term side-effects of immunosuppressants. Compared with operational and spontaneous tolerance, induced tolerance by cellular therapy could reduce immunosuppressant dosage at early stage after transplantation. Regulatory immune cells could suppress the inflammatory response, which are widely explored in preclinical and clinical trials. So far, regulatory CD4+ T cells, mesenchymal stromal cells and regulatory dendritic cells are mostly studied. However, even the safety and tolerability of cellular therapy in transplantation recipients have been validated, the overall efficacy of tolerance induction is unsatisfactory. Detailed exploration is required in the future.

Citation: Zhou AW, Jin J, Liu Y. Cellular strategies to induce immune tolerance after liver transplantation: Clinical perspectives. *World J Gastroenterol* 2024; 30(13): 1791-1800
URL: https://www.wjgnet.com/1007-9327/full/v30/i13/1791.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i13.1791

INTRODUCTION

With development of surgical techniques and perioperative management, liver transplantation (LT) has become the most efficient treatment for end-stage liver diseases, with 75%-90% recipients owning the chance to survival over 5 years after transplantation[1-3]. Most recipients need lifelong immunosuppression to prevent acute rejection and achieve ideal long-term outcomes[4]. However, the long-term side-effects caused by immunosuppressant usage, like opportunistic infection, malignant tumor, metabolic disorders and renal dysfunction have become the dominant obstacle to the long-term survival rates and life quality of LT recipients, especially for pediatric ones[5]. When matching by gender and age, LT recipients suffer a 2.4-fold higher risk of death and a 5.8-fold higher risk of premature death than the general population [6]. Therefore, strategies facilitating reduction or discontinuation of immunosuppressant are highly desirable.

Safely minimizing or discontinuing immunosuppressant without compromising allograft function could be an attractive strategy to improve the long-term post-LT survival[7,8]. The liver is considered a tolerogenic organ as LT recipients require less immunosuppressants and suffer lower risk of immune rejection when comparing with other solid organ recipients[9-11]. Anatomically, antigen-rich blood from the gastrointestinal tract flow through the intrahepatic sinusoids and scanned by antigen-presenting cells (APCs) and lymphocytes, while liver sinusoidal endothelial cells (LSECs) and hepatocytes act as scavenger cells contributing to the clearance of antigens[12-15]. Apoptosis of cytotoxic T lymphocyte (CTL) that induced by FasL and Programmed death ligand 1 (PD-L1) expressed by LSECs and hepatic stellate cells facilities the maintenance of the tolerogenic state[16,17]. Regulatory immune cells inside the liver like regulatory CD4+ T cell (Treg), Regulatory B cell (Breg) and regulatory dendritic cell (DCreg) also contribute to the development of tolerance by suppressing intrahepatic immune assault[18]. Traditionally, tolerance could be achieved through spontaneous, operational and induced ways. The first two means for tolerance were generally conducted in long-term follow-up recipients, while induced tolerance could be finished at early stage after transplantation, regardless of recipient's medical background, which makes it more applicable in clinical practices. Cellular strategy by infusion of *ex vivo* regulatory immune cell to create suppressive immune environment is the mainstream to achieve inducible tolerance. So far, many clinical and preclinical trials have been conducted to prove the efficacy of induced tolerance in LT recipients. Although promising preclinical and early-stage clinical results have proven the safety and feasibility of cellular therapy, its application in clinical practices requires more validation (Figure 1).

TREGS AND THE INDUCTION OF TOLERANCE

Treg is a specialized subset of CD4 T cells characterized by the high expression of FoxP3 and interleukin-2 (IL-2) receptor CD25, and low expression of IL-7 receptor CD127[19]. Based on developmental origins, CD4+ Tregs could be divided into thymic Tregs (tTregs) and peripheral Tregs (pTregs). Functionally, tTregs primarily recognize self-antigens, whereas the pTreg could recognize "non-self" pathogens like infectious antigens or gastrointestinal commensal microbiota-derived antigens[20,21]. Tregs induce immune tolerance through a variety of pathways, including direct and indirect pathways. Currently, adoptive transfer of Tregs is becoming an attractive therapy to restore self-tolerance in autoimmune diseases and preventing occurrence of graft *vs* host disease (GVHD) after hematopoietic transplantation[20,22]. Valuable information has arisen from multiple clinical trials designed to test the safety and efficacy of Treg therapy in solid organ transplantation. Infusion of peripheral polyclonal Tregs in kidney transplantation recipients had proven the safety and feasibility of Treg therapy in solid organ transplantation recipients[23-25]. The first study to describe successful withdrawn of immunosuppressant following Treg therapy was reported by Todo *et al*[26] (UMIN-000015789), in which 7 out of 10 Living donor liver transplant recipients achieved tolerance[26]. However, less than 20% of the cell product in this study was defined as Tregs, which made it difficult to determine the precise immunoregulatory mechanisms involved. Then Sánchez-Fueyo *et al*[27] evaluated the safety and applicability of autologous polyclonal Treg adoptive

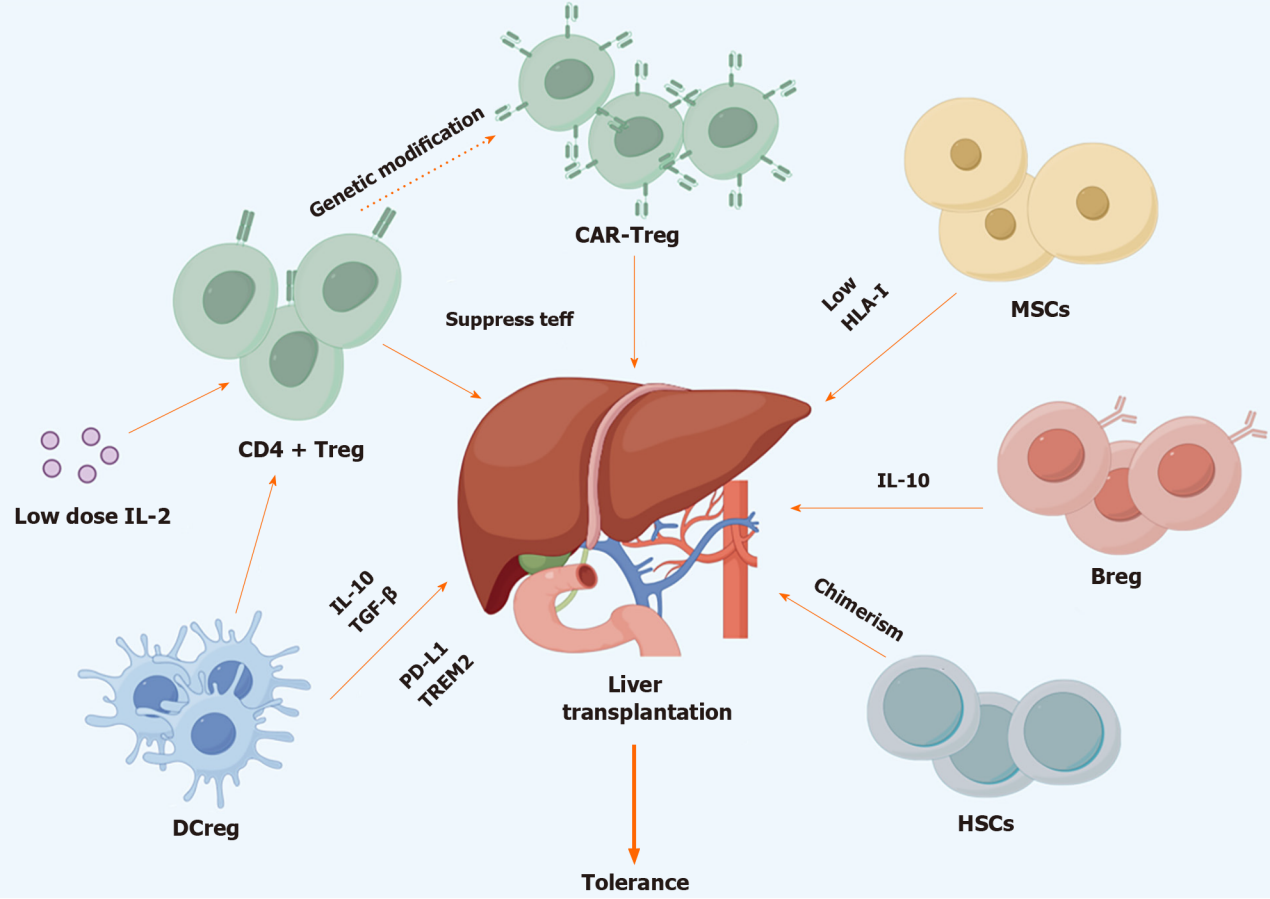

Figure 1 Cellular strategies using regulatory immune cells to induce tolerance after liver transplantation. Breg: Regulatory B cell; DCreg: Regulatory dendritic cell; HSCs: Hematopoietic stem cells; MSCs: Mesenchymal stromal cells; Treg: Regulatory CD4+ T cell; CAR: Chimeric antigen receptors; IL-2: Interleukin-2; HLA: Human leukocyte antigen; TGF-β: Transforming growth factor β; PD-L1: Programmed death ligand 1.

transfer in adult LT recipients through a phase I single-center clinical trial (ThRIL, NCT02166177)[27]. They found that Treg transfer was safe, transiently increased the amount of peripheral circulating Tregs and reduced T cell responses to donor antigens, which might facilitate the reduction or complete discontinuation of immunosuppression following LT. More recently, Tang *et al*[28] reported the results of a phase I/II trial (ARTEMIS, NCT02474199) of autologous donor alloantigen reactive Treg therapy in living donor liver transplant recipients. Four of five recipients who received sufficient infusion dosage encountered acute rejection during the process of immunosuppressant withdrawal[28]. Therefore, despite the capability of Tregs to ameliorate acute rejection in several preclinical studies, we are far from achieving induced post-LT tolerance in the clinic.

Expanding the circulating Tregs through cytokines treatment has also been tested. Since studies have suggested that Tregs have a reduced IL-2 receptor (IL-2R) signaling threshold than Teff cells, it has been hypothesized that the administration of low doses of IL-2 could preferentially activate Tregs and limit the activation of effector T cells[29,30]. In a murine skin transplantation model, IL-2 treatment with donor-specific Tregs infusion preferentially enhanced the proliferation of Tregs in skin allograft and draining lymph nodes, which prolonged skin allograft survival[31]. Lim *et al*[32] conducted the first clinical trial of using low-dose IL-2 to induce immune tolerance in adult LT recipients (NCT02949492). Although all participants achieved increased circulating Tregs after treatment, no expansion of donor-reactive Tregs or accumulation of intrahepatic Tregs was found, which was accompanied an interferon-γ dependent inflammatory response[32]. Reasons for the failure of IL-2 induced tolerance includes off-target effects of IL-2 to other immune cells, heterogeneity of IL-2 expanded Tregs and lack of intrahepatic infiltrated Tregs after treatment[33,34]. Therefore, IL-2 mutants or alternative induction approaches should be explored in the future.

Another approach to induce tolerance using Tregs is to generate antigen specific Treg cells by introducing synthetic chimeric antigen receptors (CARs) or engineered T cell receptors, enabling direct antigen recognition in the context of an antigen-major histocompatibility complex (MHC)-peptide complex[20]. In murine model, engineered CAR-Tregs with the ability to directly recognize allogeneic MHC class II molecules could facilitate the long-term acceptance of MHC-mismatched allograft[35]. Human CAR-Tregs targeting the human leukocyte antigen (HLA)-A2 could prevent HLA-A2-positive cells mediated xenogeneic GVHD in mouse models[36]. A multicenter phase I/II clinical trial aiming to evaluate the safety and tolerability of autologous anti-HLA-A2 CAR-Tregs in LT recipients (LIBERATE, NCT05234190) had been launched in Europe, while no further results had been reported so far. Since autologous CD4+ T cells and DCs played an important role in mediated posttransplant rejection, CAR-Treg targeting CD83, which was mainly expressed on alloreactive conventional CD4+ T cells and proinflammatory DCs had been proven to be efficient in preventing GVHD after

hematopoietic cell transplantation[37]. Another target protein for CAR-Tregs therapy is GAD65, which had been proved efficient to suppress CTLs in diabetes and islet transplantation mouse model[38]. However, since some studies of CAR effector T cells suggested that the density of the antigen recognized by the CAR must be high on the target cell to trigger activation, the efficiency of CAR-Tregs in the induction of tolerance still need more exploration[39].

DENDRITIC CELLS AND TOLERANCE INDUCTION

Dendritic cells (DCs) are potent APCs linking the innate and adaptive immune process[40]. DCregs are characterized by reduced expression of MHC and co-stimulatory molecules (like CD80 and CD86), and increased level of death-inducing ligands (FasL) and co-inhibitory ligands (PD-L1)[4,41]. Functionally, DCregs are able to produce anti-inflammatory cytokines [IL-10 and Transforming growth factor β (TGF-β)] and impede T cell proliferation[42,43]. Unlike conventional DCs in secondary lymphoid tissue, intrahepatic DCs display tolerogenic properties. Intrahepatic DCs express comparatively low levels of Toll-like receptor 4, leading to limited adaptive immune response[44-46]. DCs express human leukocyte Ig-like receptor B family members result suppression of T cell responses[47]. Murine model indicated that Flt3 and DAP12 regulated liver myeloid DCs maturation and tolerance[46,48]. Meanwhile, donor-derived plasmacytoid DCs express high levels of DAP12, TREM2 and PD-L1 to attenuate graft-infiltrating effector T cell responses, enhance CD4+ Tregs function and promote spontaneous acceptance of allografts[49]. Therefore, application of tolerogenic DCs or DCregs could be an alternative approach to reach the goal of induced tolerance after LT.

The safety and feasibility of autologous DCreg therapy have been confirmed in autoimmune disorders, including rheumatoid arthritis, type I diabetes and Crohn's disease[50-52]. Many studies in murine transplantation model have confirmed the ability of donor derived DCs to function immunoregulatory properties and enhance organ allograft survival[53,54]. A clinically relevant nonhuman primate model also confirmed the safety and efficacy of donor derived DCs in prolonging MHC mis-matched renal allograft survival[55]. Angus W Thomson performed the first-in-human prospective study of donor-derived DCregs in LT recipients (NCT03164265), which proved the safety of DCreg therapy and changes of immune status after infusion[42]. However, no increase of tolerance rates in LT recipients has been observed so far[56]. One possible reason is the short-lived survival of donor DCreg after infusion, which may be killed by the NK cells. Meanwhile, the influence of donor derived DCreg to the immune status of the recipients is unclear. Even though circulating Treg/Teff ratio witness increase after DCreg infusion, whether the change is sufficient to induce tolerance is questionable. Therefore, although DCs are critical in the balance between allograft rejection and tolerance, extensive data from clinical trials and mechanism study are required before translating DCreg therapy into clinical practice in LT recipients.

MESENCHYMAL STROMAL CELLS AND TOLERANCE INDUCTION

Mesenchymal stromal cells (MSCs) are nonhematopoietic multipotent and self-renewing cells with the ability to differentiate into mesodermal lineages like chondrocytes, adipocytes and osteocytes[57]. Surface marker profiles of MSCs include high expression of CD73, CD105 and CD90, and negative expression of CD45, CD34, and CD19[58]. Under normal conditions, MSCs express low levels of HLA-I molecules and do not express HLA-II nor co-stimulatory molecules, which renders MSCs immunoregulatory and anti-inflammatory properties[57,59]. Meanwhile, MSCs can be isolated from diverse tissues and are easy to cultivate, expand and store without losing clinical applicability *in vitro*[60,61]. In murine models, MSCs polarize both naïve and memory T cells toward Foxp3+ Treg phenotype and induce long-term graft acceptance[62-64]. Based on the preclinical results, lots of clinical trials have been conducted to study the therapeutical potentials of MSCs. Several pilot studies have proved that donor-derived bone marrow MSCs combined with a sparing dose of immunosuppressant dosage could maintain normal allograft function and don't increase the acute rejection occurrence in kidney transplantation recipients[65,66]. Yves Beguin performed the first human phase I clinical trial (NCT01429038) exploring the safety and tolerability of third-party MSCs infusion in LT recipients[67]. This study showed no toxicity, but a single MSC infusion was not sufficient to allow discontinuition of immunosuppression. Casiraghi *et al*[68] further revealed that MSCs infusion in LT recipients prior to transplantation was safe and could induce positive changes in peripheral immunoregulatory T and NK cells, but no tolerance data was reported[68]. The MYSTEP1 trial (NCT02957552) is the first clinical trial aiming to investigate the safety and feasibility of donor-derived NSCs in pediatric LT recipients, while no further data is available so far[69]. Pre-clinical studies in transplantation models exhibited a comparable capacity of autologous and allogeneic MSCs to induce Treg expansion and prolong allograft survival[70]. A single-center prospective clinical trial (NCT00658073) to inoculated living kidney transplantation recipients with bone marrow derived autologous MSCs revealed that autologous MSCs therapy resulted in lower incidence of acute rejection, decreased risk of opportunistic infection and better estimated renal function[71]. Modifications of MSCs like cytokine pretreatment, genetic modification or three-dimensional culture can improve the immunoregulatory capacity of MSCs and may be an effective approach to improve the regulatory capacity of MSCs under transplantation circumstance[72]. In rat LT model, infusion of TGF-β overexpressing or HO-1 transduced MSCs could induce a local immunosuppression in liver grafts, ameliorate the acute rejection and reduce the overall mortality[73,74]. However, no genetic modified MSCs have been applied in clinical trial so far. More detailed study to the molecular mechanism to the regulatory feature of MSCs is required before its clinical application (Table 1).

Table 1 Clinical trials using cellular therapy to induce tolerance after liver transplantation

Ref.	Cellular products	Sample size/stage	Recipients	Status	Trial ID
Todo *et al*[26]	Donor derived Treg	10/Phase I/II	Adult	7/10 recipients reached tolerance	UMIN-000015789
Sánchez-Fueyo *et al*[27]	Recipient derived polyclonal Treg	6/Phase I	Adult	Safe for recipients, not test tolerance	NCT02166177
Tang *et al*[28]	Recipient derived darTreg	5/Phase I/II	Adult	4/5 encountered acute rejection	NCT02474199
Lim *et al*[32]	IL-2 infusion	5/Phase I/II	Adult	All suffered rejection	NCT02949492
Sánchez-Fueyo *et al*[91]	CAR-Treg targeting HLA-A2	18-70/Phase I/II	Adult	Recruiting	NCT05234190
Tran *et al*[92]	Donor derived DCreg	13/Phase I/II	Adult	Safe for recipients, no tolerance tested	NCT03164265
Detry *et al*[67]	Third party MSCs	10/Phase I/II	Adult	Safe for recipients, no tolerance achieved	NCT01429038
Casiraghi *et al*[68]	Third party MSCs	10/Phase I/II	Adult	Safe for recipients	NCT01429038

Treg: Regulatory CD4+ T cell; IL-2: Interleukin-2; CAR: Chimeric antigen receptors; HLA: Human leukocyte antigen; DCreg: Regulatory dendritic cell; MSCs: Mesenchymal stromal cells.

OTHER CELLULAR STRATEGIES TO INDUCE TOLERANCE

Infusion of hematopoietic stem cells (HSCs) to create mixed chimerism could establish donor-specific tolerance and retain immunocompetence for primary immune responses[75,76]. Kawai *et al*[77] conducted the first successful application of mixed chimerism in tolerance induction in human kidney transplantation[77]. Four of five recipients who received combined bone marrow and kidney transplants from HLA single-haplotype mismatched living related donors and nonmyeloablative preparative regimen discontinued all immunosuppressive therapy with normal renal function. Patients with end stage renal disease and hematologic malignancies are thought as the most suitable candidates for combined bone marrow and kidney transplant[78]. The idea of hematopoietic chimerism to achieve graft tolerance has also been explored in LT recipients. Spontaneous complete hematopoietic chimerism could be found in deceased donor LT recipient even without HSCs transplant and tolerance was achieved[79]. Tryphonopoulos *et al*[80] reported that donor bone marrow cell infusion had no influence on the overall survival rates or tolerance of adult LT recipients[80]. Kim *et al*[81] and Hartleif *et al*[82] indicated that LT with myeloablative HSC transplant could establish full tolerance in both pediatric and adult recipients, but the life-threatening complication of GVHD couldn't be avoided[81-83]. Thus, the current dilemma of HSC therapy is that intense myeloablative or non-myeloablative conditioning therapy may not be tolerated by transplantation recipient, while lacking conditioning therapy could compromise the therapeutic efficiency of donor HSC infusion[80]. Therefore, careful selection of recipients might be the key to the safety and efficiency of HSCs therapy.

Bregs are immunosuppressive cells that express immune regulatory cytokines, like IL-10, TGF-β and IL-35, and support immunological tolerance[84]. In autoimmune disease mice model, the most widely investigated Breg population comprises the IL-10 producing B10 cells which could modulate T cell function[85]. It was found that B lymphocytes could interact with allo- and autoreactive effector cells, while selective manipulation of B cell function rather than depletion could be a promising approach to promote tolerance to allografts[86]. In murine heart and islet transplantation models, combined treatment with anti-CD45RB and anti-ICAM/LFA/TIM1 facilitated allograft acceptance *via* B-cell dependent mechanism[86,87]. A possible explanation is that B cells act as Treg inducing antigen presenting cells to promote Tregs function during this process. Single-cell RNA sequencing data of transplanted murine kidney revealed a shifting from a T cell-dominant to a B cell-rich population at 6 months after transplant with an increased Breg signature, implicating a key role of Bregs in the maintenance of allograft tolerance[88]. Analysis to stable renal transplantation recipients also revealed that B cells from tolerant patients had lower numbers of plasma cells and secreted more IL-10, which reduced production of proinflammatory cytokines and promoted transplantation tolerance[89,90]. However, so far, no clinical trial using Bregs to induce tolerance after transplantation have been conducted. One of the challenges is the lack of lineage marker for Bregs, which impedes the *in vitro* and *ex vivo* isolation and expansion of Bregs. Another problem is the unclear underlying mechanism of Bregs in the process of tolerance induction. Therefore, Breg induced tolerance has a long way to go before translation into clinical practice.

CONCLUSION

Immune tolerance is one of the most promising approaches to avoid the long-term side-effects of immunosuppressants in LT recipients. Cellular therapy could be applied before and after transplantation, which could induce early tolerance. So far, many clinical trials have demonstrated the feasibility and safety of cellular therapies for autoimmune diseases,

hematopoietic stem cell transplantation and solid organ transplantation. However, most clinical results for cellular induced tolerance after LT are still very preliminary. The most obstacle is how to improve the efficiency of induced tolerance by cellular therapy. Detailed study to underlying mechanisms of immunoregulatory immune cells, genetic modification and optimal infusion dosage should be conducted in the future.

FOOTNOTES

Co-first authors: Ai-Wei Zhou and Jing Jin.

Author contributions: Zhou AW and Jin J collected the literature, wrote the initial manuscript, conceptualized the table and figure and contributed equally to this work; Yuan L conceptualized the structure of the text, critically revised the manuscript and read and approved the final version of the manuscript.

Supported by the National Natural Science Foundation of China, No. 82000586 and No. 82241221; and Shanghai Immune Therapy Institute.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: China

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S-Editor: Li L
L-Editor: A
P-Editor: Yu HG

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