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REVIEW ARTICLE

Liver graft rejection following immune checkpoint inhibitors treatment: a review

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Abstract

Immune checkpoint inhibitors (ICIs) have demonstrated remarkable efficacy in a variety of solid tumors; nonetheless, they have not been well investigated and are still recognized as a relative contraindication for patients with a liver transplantation (LT) history, since ICIs treatment might potentially lead to graft rejection. The program death-1 (PD-1) and the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathways are implicated in the tolerance of transplanted organ, as well as blockade of the pathways, which contribute to eliminating tumors and may inadvertently lead to peripheral transplant rejection. Currently, no guidelines are available regarding the treatment for ICIs patients with a prior LT history. Therefore, this study was carried out to review the recent studies, attempting to introduce the ICIs-related graft rejection after LT from various aspects. We believed that ICIs could be given for the well-informed patients receiving LT and developed recurrence in a controlled setting. Typically, these patients should be treated according to a clinical care path or a prospective clinical trial, so as obtain a persistent anti-tumor immune response in the meantime of avoiding graft rejection, adjust the immunosuppression, reduce the possibility of graft loss following rejection, and have the opportunity to develop biomarkers for tumor response and transplant rejection.

Keywords Graft rejection · Immune checkpoint inhibitors · Liver transplantation · Immunosuppression · Biomarkers

Abbreviations

ALT	Alanine transaminase
AST	Transaminase
CR	Complete response
CTL	Cytotoxic T lymphocytes
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DC	Dendritic cell
GIC	Graft-infiltrating cells
GVHD	Graft versus host disease
HCC	Hepatocellular carcinoma
ICIs	Immune checkpoint inhibitors
LAG3	Lymphocyte activation gene 3
LT	Liver transplantation
mTOR	Mammalian target of rapamycin
ORR	Objective response rate
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand 1
PR	Partial response
SC	Spleen cell
SOT	Solid organ transportation
TILs	Tumor infiltrating lymphocytes
TIM	T-cell immunoglobulin mucin

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Introduction

Immunotherapy using immune checkpoint inhibitors (ICIs), which can interrupt the cancer-immunity cycle and promote the tumor-specific immune cell activity without intrinsic cytotoxicity, has become the standard of care for a variety of tumors, including melanoma, lung cancer, urothelial cancer, kidney cancer, and hepatocellular carcinoma (HCC) [1–12]. For HCC patients, increasing importance has been attached to liver transplantation (LT) thanks to the advances in surgical techniques and immunosuppression regimens, resulting in the mean 1-year and 5-year survival rates of 85–90% and 70–75%, respectively [13–18]. However, about 16% HCC patients develop recurrence after LT [19–26]; besides, ICIs

can activate the alloreactive T cells and give rise to acute rejection and graft loss, but its safety and efficacy for HCC patients undergoing LT remain a source of controversy. This paper aimed to review the ICIs-related graft rejection following LT from various aspects. The major patient characteristics and outcomes are summarized in Table 1. A detailed overview of the individual liver transplant recipients is presented in Table 2.

Basic classification of ICIs

Generally, ICIs include monoclonal antibodies against cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4), programmed death-1 (anti-PD1), and PD1 ligand (anti-PD-L1). Typically, CTLA-4 is one of the B7/CD28 immunoglobulin family members, which is found on T cell surface and can transmit an inhibitory signal to T cells [1]. Additionally, anti-CTLA-4 antibodies, including ipilimumab, a fully human monoclonal antibody, can antagonize the inhibitory signals to cytotoxic T lymphocytes (CTL) at lymph node level, where tumor antigens are presented to activate CTL [27]. PD-1 is expressed in T cells, which can bind to its ligands PD-L1 and PD-L2 expressed in tumor cells as well as other immunocytes [1]. However, anti-PD1 drugs, such as pembrolizumab, nivolumab, and pidilizumab or PD-L1 agents, like MEDI4736 and MPDL3280A, act in tumor microenvironment where tumor can interact with CTL via the PD1-PDL1 axis, thereby directly targeting the mechanism by which tumors evade the immune responses [1, 27].

Table 1 Patient characteristics

Characteristics	Total	Non-HCC	HCC
Tumor type			
Cutaneous melanoma	7	7	0
Uveal melanoma	1	1	0
NSCLC	1	1	0
HCC recurred with pulmonary	2	0	2
HCC	9	0	9
Immunotherapy			
Nivolumab	10	1	9
Pembrolizumab	7	5	2
Ipilimumab	1	1	0
Ipilimumab + pembrolizumab	2	2	0
Liver transplant outcome			
Graft preservation	13	6	7
Graft rejection with graft failure	4	1	3
Graft rejection without graft failure/UK	3	2	1
Final outcome			
CR	2	2	0
PR	3	2	1
PD	8	3	5
Death from organ failure before evaluation	4	1	3
UK	3	1	2

Contributions of the PD-1 and the CTLA-4 signaling pathways to graft tolerance

Both the PD-1 and the CTLA-4 signaling pathways contribute to the immune tolerance of transplanted organ. Some scholars believe that PD-1 plays a crucial role in inducing and maintaining the tolerance of peripheral transplant, which is achieved through its ability to alter the balance between pathogenic and regulatory T cells; besides, it is also involved in T-cell exhaustion [28–31]. Wang et al. had utilized corresponding mAb in mice with PD-1 or PD-L1 deletion, and suggested that PD-1 could suppress gene expression in the graft, which could serve to suppress T-cell activation and proliferation, together with cytokine production, thus contributing to anergy induction in CD4 T cells after costimulation blockade and finally promoting allograft survival [32]. Meanwhile, PD-L1 expression has been recognized as a key component in graft tolerance following LT, and its high expression can provide negative feedback to create a protective shield from human T-cell responses [33–35]. Therefore, PD-1 and its ligand PD-L1 are suggested to be essential for allograft tolerance.

Moreover, Zhang et al. proposed in their research that, the interaction between CTLA-4 and its various dendritic cell (DC) ligands was pivotal to the expansion of regulatory cells (Tregs) in response to the allogeneic stimulation; besides, they had further underlined the role of CTLA-4 in promoting graft acceptance [36]. Notably, one related mechanism for such results was that CTLA-4 might antagonize the functions of T cells through inhibiting the CD28 signaling by competing for their shared ligands B7-1 and B7-2. Nevertheless, Lin et al. concluded that, CTLA-4 could still inhibit the regulation of allograft rejection even in the absence of CD28, which had thereby verified the importance of CTLA-4 from diverse perspectives [37]. On the other hand, it has been suggested in preclinical models that CTLA-4 contributes to inducing graft tolerance, but not to maintaining graft tolerance, which may suggest a lower predisposition to graft rejection in patients with a remote LT history that undergo CTLA-4 inhibitors treatment [38, 39]. Additionally, other literature using a murine model also reports that blocking CTLA-4 at the early stage following LT can lead to graft rejection, whereas blockade at the late stage seems not to affect the transplant survival, which is consistent with the above point of view [35, 38].

Additionally, available data have shown that both PD-1 and PD-L1 are essential for inducing and maintaining

Table 2 Immune checkpoint inhibitors for the treatment of solid tumor in liver transplant recipients

	Age	Sex	Transplant to malignancy/ICIs (years)	IST before ICIs	IST during ICIs	Malignancy	Treatment before initiation of ICIs	ICIs (cycles)	Outcomes (TTR) (PFS)	OR	OF	Reasons for transplantation	Cause of death
Morales et al. [53]	67	M	1/10	Tacrolimus + MMF/mTOR inhibitor + MMF (after metastatic HCC was diagnosed)	Low-dose sirolimus (1 mg)	Melanoma/metastatic HCC	Chemotherapy (paclitaxel) + palliative radiotherapy to the hip	Ipilimumab (4)	PR(3 months) (10 months[a])	No	–	HCC	–
Ranganath et al. [51]	59	F	7/8	Tacrolimus (1 mg)	Tacrolimus (< 3.1 ng/ml)	Melanoma	Adjuvant interferon + local radiation	Ipilimumab (4) Pembrolizumab (2 mg/kg) (after PD)	PD	No	–	Cirrhosis (due to α1-trypsin deficiency)	UK
Kuo et al. [1]	62	F	5/5	Prednisone + tacrolimus (4 mg) + MMF	Low-dose sirolimus (1 mg) + MMF (500 mg 2xpd)	MPNST like melanoma	–	Ipilimumab(4) Pembrolizumab (25)	PR (3 months) (17 months[a])	No	–	HCC	–
Schvartsman et al. [54]	35	M	15/18	Tacrolimus	Tacrolimus	Melanoma	Chemotherapy (carboplatin + paclitaxel)	Pembrolizumab (2)	CR (UK) (6 months[a])	No	–	Biliary atresia	–
Tio et al. [48]	63	F	UK	UK	Cyclosporine	Melanoma	UK	Pembrolizumab (1)	Death due to OF (3 weeks after start ICIs)	Yes	Yes	NS	OF (18 days after start ICIs)
Dueland et al. [61]	67	F	1.5/1.5	Sirolimus + MMF	Prednisone (10 mg)	Ocular melanoma	UK	Pembrolizumab (1 mg/kg)	PD	Yes	No	Liver metastasis	PD
Biondani et al. [55]	54	M	12/13	Tacrolimus + prednisone + MMF	Everolimus + tacrolimus+ prednisone(60–5 mg)	NSCLC	Surgery + adjuvant chemotherapy (cisplatin–vinorelbine)	Nivolumab	PD	No	–	Hepatitis C	PD
DeLeon et al. [50]	54	M	5/UK	UK	MMF + everolimus	Melanoma	UK	Pembrolizumab (9.5 months)	CR (21 months[a])	No	–	HCC	–
DeLeon et al. [50]	63	M	3/UK	UK	MMF + prednisone	Melanoma	UK	Pembrolizumab (1)	UK	Yes	No	HCC	–
DeLeon et al. [50]	56	M	2/UK	UK	Tacrolimus	HCC	UK	Nivolumab (6)	PD	No	–	HCC	Probably PD
DeLeon et al. [50]	55	M	7/UK	UK	Sirolimus + MMF	HCC	UK	Nivolumab (5)	PD	No	–	HCC	Probably PD
DeLeon et al. [50]	34	F	3/UK	UK	Tacrolimus	HCC	UK	Nivolumab	PD	No	–	HCC	Probably PD
DeLeon et al. [50]	63	M	1/UK	UK	Tacrolimus	HCC	UK	Nivolumab	UK[b]	No	–	HCC	MOF
DeLeon et al. [50]	68	M	1/UK	UK	Sirolimus	HCC	UK	Nivolumab	UK[b]	Yes	UK	HCC	PD
De Toni et al. [63]	41	M	1/UK	UK	Tacrolimus (1 mg)	HCC	TACE + microwave ablation	Nivolumab (15)	Dissociated response (7 months) PD hereafter	No	–	HCC	PD
Varkaris et al. [62]	70	M	6/8	Tacrolimus	Low-dose (50%) tacrolimus	HCC	Sorafenib	Pembrolizumab	PD	No	–	HCC	PD

Table 2 (continued)

	Age	Sex	Transplant to malignancy/ICIs (years)	IST before ICIs	IST during ICIs	Malignancy	Treatment before initiation of ICIs	ICIs (cycles)	Outcomes (TTR) (PFS)	OR	OF	Reasons for transplantation	Cause of death
Gassmann et al. [41]	53	F	2/2	Prednisone + MMF(1 to 2 g/d) + everolimus 1 mg/d	Everolimus + MMF	HCC recurred with pulmonary	Sorafenib	Nivolumab(1)	Death due to OF (2 weeks after start ICIs)	Yes	Yes	HCC	OF (2 weeks after start ICIs)
Friend et al., [42]	14	M	1/UK	UK	Tacrolimus (4 mg)	Fibrolamellar HCC	Sorafenib + gemcitabine + oxaliplatin	Nivolumab(1)	Death due to OF (5 weeks after start ICIs)	Yes	Yes	HCC	OF (5 weeks after start ICIs)
Friend et al., [42]	20	M	3/UK	UK	Sirolimus (2 mg)	Fibrolamellar HCC	Sorafenib + capecitabine monotherapy	Nivolumab (2)	Death due to OF (4 weeks after start ICIs)	Yes	Yes	HCC	OF (4 weeks after start ICIs)
Rammohan et al. [56]	57	M	4/5	Tacrolimus + MMF + steroid	Tacrolimus + MMF + steroid + mTOR inhibitor	HCC recurred with pulmonary	Sorafenib	Pembrolizumab	Complete radiological resolution	No	–	HCC	–

ICIs immune checkpoint inhibitors, *CR* complete response, *HCC* hepatocellular carcinoma, *IST* immunosuppressive therapy, *MMF* mycophenolate mofetil, *MPNST* malignant peripheral nerve sheath tumor, *mTOR* mammalian target of rapamycin, *NSCLC* non-small cell lung cancer, *OF* organ failure, *OR* organ rejection, *PD* progressive disease, *PFS* progression-free survival, *PR* partial response, *TACE* transarterial chemoembolization, *TTR* time to response, *UK* unknown

[a]Ongoing at time of publication of case report

[b]Discontinuation before restaging

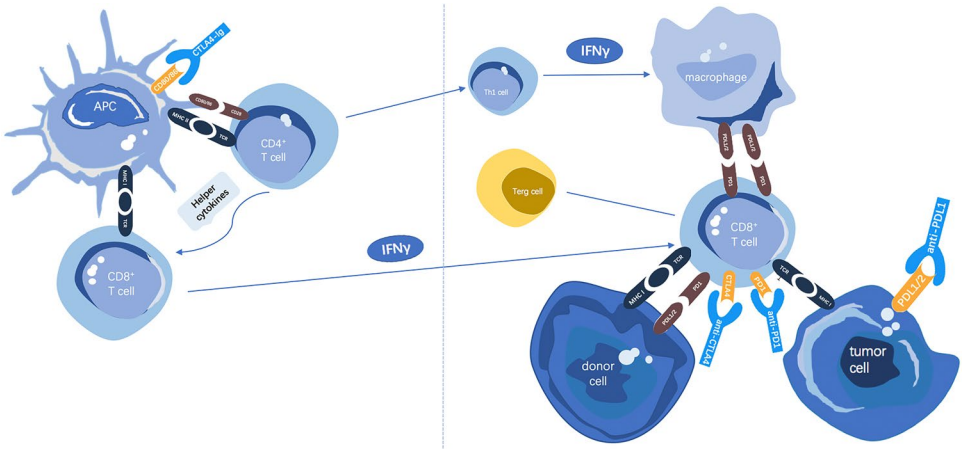

Fig. 1 Role of cytotoxic T-lymphocyte-associated protein 4 and programmed death ligand 1 in tumor and organ rejection

allograft tolerance, meanwhile, CTLA-4 also exerts a crucial role in graft tolerance (Fig. 1), which may at least partially account for less application of ICIs in patients with recurrence following LT.

The occurrence of ICIs-related graft rejection in the transplant recipients

With regard to the incidence of rejection among the transplant recipients treated by ICIs, Ijaz et al. reported that about 23% and 14% cases were reported with acute rejection, while 9% would suffer from chronic rejection [40]. In another study by Gassmann et al. on liver allograft failure following nivolumab treatment, graft loss or acute rejection was described in 13 (45%) out of 29 patients undergoing transplantation across all checkpoint inhibitors, as well as in 3 (37%) of 11 patients receiving LT specifically [41]. At the same time, nivolumab had been recognized to increase the risk of rejection compared with ipilimumab and pembrolizumab [41]. Overall, the risk of ICI-related graft rejection was reported to be 25% after LT and 29–54% following solid organ transportation (SOT) [40, 41].

Of the 20 patients discussed in this review, 7 patients (35%) experienced graft rejection when treated with ICIs. It is worth mentioning that 4 of 10 (40%) patients receiving nivolumab experienced liver graft rejection, in contrast with 3 of 9 (33%) receiving pembrolizumab, while none of the patients receiving ipilimumab suffered graft rejection. Interestingly, no rejection occurred in patients treated with two kinds of ICIs. Graft rejection is potentially life-threatening, and there were 5 (38%) cases of death secondary to graft failure.

The occurrence time of ICIs-related graft rejection

Graft rejection appears to be an early ICIs adverse event, which occurs earlier than most other autoimmune adverse events that typically peak at 6–14 weeks after the initiation of therapy, and the median time to rejection mentioned in previous case reports is 8 days (range 5–63 days) [42–47]. In this review, patients usually develop liver graft rejection 2 to 3 weeks after ICIs treatment.

The mechanism of ICIs treatment in inducing graft rejection

At present, the mechanism of graft rejection resulted from B7/CTLA-4 and PD1/PD-L1 blockade remains largely unclear. Some scholars believe that rejection following PD-1/PD-L1 blockade is related to the activation of cellular immunity via the $CD8^+$ effector cells, as well as the down-regulation of regulatory T cells [30]. On the flip side, Li et al. stated based on the murine model that, the allospecific proliferative responses, anti-donor CTL and natural killer (NK) cell activities in the graft-infiltrating cells (GICs) and spleen cells(SCs), together with the serum levels of interferon-γ (IFN-γ) and interleukin-2 (IL-2) in recipients treated with anti-CTLA-4 mAb, were markedly increased compared with those in control mice; therefore, they concluded that CTLA-4 blockade could promote the donor-specific T-cell activation, cytotoxicity, and Th1 polarization; protect alloreactive T cells from apoptotic death; and induce acute rejection of liver allograft [30].

In addition to T-cell-mediated rejection, some scholars have also provided the evidence of T-cell- and antibody-mediated rejection, and further explain that the latter may have been a secondary phenomenon, since the former is known to activate the costimulatory ligands and cytokines to trigger the humoral response [44].

Factors affecting the occurrence of ICIs-related graft rejection following LT

PD-1 inhibitors versus CTLA-4 inhibitors

Compared with PD-1 inhibitors, CTLA-4 inhibitors are associated with lower risks of rejection and graft loss in patients undergoing LT [39, 48]. For instance, Kittai et al. had reviewed the existing literature and pointed out that graft rejection developed in four out of the eight patients receiving anti-PD-1 therapy, but it was not detected in the four patients treated with anti-CTLA-4 therapy, which had further corroborated data obtained from the mouse model data suggesting that the PD-1 pathway played a more dominant role in allograft immune tolerance than the CTLA-4 pathway [49]. In addition, Friend et al. demonstrated that the anti-PD-1 antibody would lead to increased graft versus host disease (GVHD) compared with that of anti-CTLA-4, and that combining these two antibodies would result in more severe GVHD than anti-PD-1 antibody treatment alone, thus supporting this theory [44]. However, DeLeon et al. reported that one out of the four patients receiving CTLA-4 inhibitors treatment alone had suffered from graft rejection, which might be ascribed to the inadequate immune suppression, since only prednisone was administered to the patient [50]. Consequently, it remains unclear so far about whether anti-PD-1 or anti-CTLA-4 therapy will lead to an increased risk of graft rejection, and the detailed mechanisms should be explored in more research.

Recurrent tumor type after LT

Various tumor types can occur following LT, including HCC, melanoma, non-small cell lung carcinoma, and cutaneous squamous-cell carcinoma. Among them, malignant melanoma, which is more commonly seen in organ transplant recipients than in general population, may be associated with immunosuppressive therapy [54]. Compared with HCC, melanoma patients after LT seem to have favorable outcomes and reduced graft rejection after ICIs treatment. Bruyn et al. had described in their paper that, of the 7 melanoma patients treated with ICIs following OLT, 3 had partial response (PR), 2 had complete response (CR), and 2 had progressive disease (PD); notably, no significant graft rejection was observed in all patients [52]. Meanwhile, several reports have mentioned the absence of graft rejection in melanoma patients undergoing ICIs treatment after LT [51, 53, 54]. Such distinct difference in treatment outcomes and graft rejection rate between HCC and melanoma patients might be attributed to the sensibility of HCC and Melanoma to ICIs [52]. As a result, it is advisable that melanoma patients may be more suitable for ICIs treatment after LT, who would develop less graft rejection during treatment than that in recurrent HCC patients.

Detailed report on the effects of various pathological subtypes on graft rejection in recurrent HCC patients that receive LT is lacking at present. Friend et al. reported two patients with fibrolamellar HCC after LT, and found that both of them had developed graft rejection, which might potentially speculate that graft rejection was more common in such tumor type than in typical HCC [44]. At the moment, no enough cases are available to discuss the relation between graft rejection and the type of recurrent liver tumor, meanwhile, the specific mechanism remains unclear.

Assessment of immune checkpoint regulators in liver biopsies

Another relevant point is whether immune checkpoint regulators expressed in liver biopsies are related to the occurrence of graft rejection. Specifically, Munker et al. had evaluated three available biopsies from liver transplant recipients with acute graft rejection, and their results suggested that each of them had elevated PD-L1 expression, whereas all the four biopsies from patients without rejection were not positive in PD-L1 staining, which had strongly supported that PD-L1 expression might predict graft rejection [2]. In another study, the authors had investigated patients with sufficient pathological specimens of liver allograft tissues and tumor tissues that underwent PD-L1 staining, and evaluated the tumor-infiltrating lymphocytes (TILs), the results of which suggested that PD-L1 expression could be detected in allograft lymphocytes among all cases with graft rejection in the cohort, thus further speculating that the combined expression of TILs and PD-L1 might be a more reliable predictor of the response to PD-1 inhibitors compared with PD-L1 expression alone [50]. However, biopsies from transplant patients with rejection were obtained after ICIs exposure, which could not be debarred that positive PD-L1 staining might reflect a consequence of liver graft rejection [2]. In summary, it is recommended that graft liver biopsies should be performed routinely prior to initiating ICIs treatment in liver transplant recipients, and that PD-L1 staining and TILs evaluation ought to be taken into consideration, especially for determining whether a PD1/PD-L1- or a CTLA4-blocking agent should be employed.

The dose and administration time of ICIs

It remains to be investigated about the relationship between the dose of ICIs and liver graft rejection. As suggested in the currently available articles, most patients receiving LT have received ICIs at a dose of 3 mg/kg, and some of them have experienced graft rejection while others have not [44, 55, 56]. Ipilimumab at a dose of 5 mg/kg was once applied

to 15 patients, in whom the objective response rate (ORR) was reported as 23%, and liver graft rejection was seen in 6 patients (including 1 acute and 5 chronic), indicating that increasing the antibody dose could enhance the efficacy, but more patients were susceptible to the risk of GVHD [57]. On the other hand, the influence of dose on liver graft rejection remains unclear at present. Davids et al. as well as Bashey et al. proposed in their studies that, the observed lower incidence of graft rejection at a lower dose (3 mg/kg) might be related to the long interval between transplantation and ICIs administration [58, 59]. Consequently, it is suggested that the interval between ICIs administration and transplantation can also affect the occurrence of liver graft rejection. Moreover, some researchers report that patients receiving nivolumab at a relatively early stage after LT with the median interval of 8.5 months have experienced graft rejection. In contrast, patients who do not develop graft rejection after ICIs exposure are then administered nivolumab at a later stage after LT, with the median time interval of 28.5 months [60]. In another study by DeLeon et al., liver graft rejection occurred in patients receiving ICIs at an interval of 1.1 years following LT, but it was not observed in patients receiving ICIs at an interval of 7.8 years, which was also consistent with the above theory [50]. Additionally, it is also suggested that clinicians should be cautious when considering ipilimumab treatment during the first few years after LT [61]. Existing evidence has suggested that the risk of ICIs-induced graft rejection can be minimized in patients with a longer interval from LT to the initiation of ICIs treatment, and that such an interval may be extended through administrating reasonable immunosuppressive medication and appropriately applying the approved first-line conventional medicine. Noteworthily, a close follow-up should be performed during the first-line conventional treatment period, so as to recognize the signs of disease progression early. Moreover, once the disease has progressed, the decision to initiate ICIs treatment should be made in a timely manner, so that the efficacy of ICIs can be extended as soon as possible.

Immunosuppressive therapy

According to some researchers, immunosuppression may potentially exert a detrimental part in determining the efficacy of ICIs, since the intact T-cell response is required for their effects [2, 62]. In recurrent patients following transplantation, the dose of immunosuppressive agents is usually reduced before initiating the ICIs treatment, so as to avoid the potential interference of immunosuppressants with the anti-tumor effects of ICIs, but it may also increase the risk of graft rejection [1, 63]. Previous case reports indicate that patients can respond to cancer immunotherapy irrespective of the immunosuppression [50]. Nevertheless, it remains unsatisfactory that neither the significant ICIs treatment effect nor the graft rejection exist in recurrent patients after transplantation [63]. Thereby, it is unknown about whether immunosuppressive therapy will dampen the effectiveness of cancer immunotherapy; besides, immunosuppressive therapy seems to exert two-way regulation between graft rejection and tumor response.

In particular, no standard is available currently to select and administrate immunosuppressive agents for patients receiving ICIs treatment after LT. The existing limited cases show that a wide variety of immunosuppressive medications have been applied in transplant recipients during ICIs treatment. Consequently, it is difficult to ascertain the precise contribution of each individual immunosuppressive agent to preventing graft rejection. In the cases reported so far, the immune status of patients prior to the administration of ICIs has not been described in detail yet. We recommended that patients scheduled to receive ICIs treatment after LT should be routinely performed tests, such as the count of NK cells, B cells, memory T cells, regulatory T cells and the subsets by flow cytometry. The CD4/CD8 ratio should also be assessed to determine the ideal state that is the most conducive to the effect of ICIs without affecting the graft function.

After receiving ICIs treatment, the immunosuppressive regimen in most transplant patients is not changed, but the dose will be adjusted. Nevertheless, it remains unclear about which combination of immunosuppressive agents can better preserve graft function and adapt the immunotherapy to get rid of tumor. Biondani et al. had reported a patient receiving LT that developed no adverse events after employing ICIs, and it was deduced that pre-emptive corticosteroids, together with the combination of tacrolimus and everolimus, might have prevented from the hepatic immune-related adverse events [55]. Meanwhile, whether prophylactic use of steroids alone can reduce the risk of rejection also represents a source of controversy. Some investigators reckon that pre-treatment with steroids can be attempted in the absence of contraindications, but others believe that glucocorticoids themselves do not appear to be effective on preventing from the graft rejection when receiving ICIs. It has been reported that the use of a single immunosuppressive medication in patients during ICIs treatment will not cause graft rejection. It is supposed from the scant cases that low doses of multiple immunosuppressants can contribute to preventing rejection; meanwhile, mammalian target of rapamycin (mTOR) inhibitors, which have antiproliferative and antiangiogenic effects and are associated with increased survival for patients receiving LT for HCC, are often one of the combinations [52, 64].

Immunosuppression is usually diminished before the initiation of ICIs treatment, due to the diversity of the previously reported immunosuppressants. Nonetheless, it can hardly come up with the best immunosuppression strategy. As a result, more comprehensive studies should be carried

out to seek a more optimal immunosuppressive regimen that can benefit the transplant patients with relapse during ICIs treatment.

A prior history of GVHD

A prior history of GVHD appears to be positively correlated with an increased risk of graft rejection for patients treated with PD-1 blockers for the recurrent disease. In the studies reported by Herbaux et al. and Haverkos et al., respectively, a majority of (6/6 and 12/17, respectively) patients who developed ICIs-related graft rejection had a prior history of GVHD, which had strongly supported the above points [60, 65]. Consequently, the initiation of ICIs should be carefully considered for liver transplant recipients with a history of GVHD.

To sum up, it has been found by investigators that, a higher drug dose, a shorter interval between ICIs exposure and LT, and a prior history of GVHD are positively correlated with the response to and the risk of graft rejection. However, the effects of other factors on ICIs-related graft rejection in LT recipients remain to be further examined, such as the gender and age of patients, the pathological type of primary liver tumor, the number of metastatic sites, prior sorafenib therapy, donor type, type and time of ischemia during LT, and the hepatitis virus infection status of the transplanted liver postoperatively.

Identification of the immune-related hepatitis and ICIs-related liver graft rejection

Checkpoint inhibition-related hepatitis is a kind of immune-related side effect, which will result in the mildly elevated levels of aspartate transaminase (AST) and alanine transaminase (ALT), as well as bilirubin on occasion [4, 66–68]. As a result, for patients treated with ICIs after LT, attention should be paid to identify hepatitis and graft rejection once an increasing trend is noted in liver function tests. Unlike rejection caused by ICIs, immune-mediated hepatitis will occur at a later stage, mostly 6–14 weeks after treatment initiation, which is rarely related to the life-threatening hepatic injury. Meanwhile, immune-related hepatitis is usually asymptomatic and detected through routine blood tests [26]. In addition, the immune-related hepatotoxic effects are frequently reported in patients treated with CTLA-4 inhibitors relative to those under PD-1 inhibitors treatment, while graft rejection is more commonly seen in liver transplant recipients treated with PD-1 inhibitors [66]. With regard to the pathological features, the former is characterized by acute lobular hepatitis, accompanying with isolated or confluent necrosis and the predominantly lymphocyte infiltration, while the latter mainly manifests as portal tract inflammation dominated by a mixed infiltrate with interface activity, bile duct injury and endotheliitis, along with acute cellular rejection [41]. Taken together, the possibility of immune-induced hepatitis should be considered in transplant patients with abnormal liver functions after ICIs exposure, and a liver biopsy may help to identify these two, regardless of the differences between hepatitis and graft rejection.

Management of ICIs-related liver graft rejection

More discussion is required to manage the ICIs-related liver graft rejection. Acute graft rejection can be alleviated after the application of high-dose steroids in 70–80% cases [41]. In addition, increasing the dose of oral immunosuppressive agents should also be taken into consideration [41]. However, for most patients that have already been reported, the above treatment cannot result in clinical improvement, and most of these patients end up with death due to graft failure [41, 42]. Besides, infliximab, together with the anti-thymocyte globulin, has also been employed to treat liver transplant recipients who suffer from ICIs-induced graft rejection, but high-dose steroid treatment cannot achieve satisfactory efficacy; besides, alternative treatments are often not allowed in view of the rapid clinical deterioration of such patients [26, 69]. Plasmapheresis has been reported to be utilized to treat acute humoral rejection after LT, but it may not relieve the T-cell-mediated immune rejection following ICIs treatment. Nevertheless, plasmapheresis, which can remove the checkpoint inhibitors from the circulation, may be potentially beneficial and can thereby be recommended for eligible patients [41, 70]. There is still no relevant report about whether there are differences in the treatment method and therapeutic effect between ICIs-mediated rejection and non-ICIs-mediated rejection for patients with rejection following LT. In other words, it remains unclear about whether the administration of ICIs can affect the treatment for graft rejection.

Conclusions/expectations

Typically, it is still challenging to determine the optimal ICIs treatment and immunosuppressive therapy for liver transplant recipients. Notably, the administration of ICIs after LT can potentially induce the risk of graft rejection, nevertheless, such risk can be reduced through pre-assessment and rational application, so that patients under such situation can get the most benefit. However, one important limitation of this review is that the sample size of clinical reports is very small and most studies are case reports, which can

be explained that most solid organ transplant recipients are routinely excluded from immunotherapy clinical trials. More researches should be carried out to make the results more convincing.

It is crucial to define the biomarkers to predict therapeutic effects and graft rejection, which is highlighted by a growing number of recent studies focusing on ICIs treatment in recurrent patients after transplantation. As mentioned above, assessing PD-L1 expression and TILs in liver biopsies may predict the risk of graft rejection; besides, additional intratumoral factors, including tumor mutational burden and CD8+T-cell density that are functionally related to PD-L1 expression and to each other, have also been identified as the biomarkers to predict the outcomes of anti-PD1 therapy, which may be beneficial to predict the risk of graft rejection [71]. Genetic sequencing can be performed on patients discussed in this study if further research is available, in which oncogenic mutations or mutational load are used as the potential biomarkers to predict the response to checkpoint blockade and graft rejection [72–74].

CTLA-4 and PD-1 blockades have attracted extensive attention, a growing list of additional checkpoint receptors and ligands has been targeted clinically, and recurrent patients after transplantation may gain better therapeutic effects and less graft rejection through adjusting such checkpoint receptors and ligands. For instance, T-cell immunoglobulin mucin receptor 3 (TIM3), B7H3, CD39, CD73, lymphocyte activation gene 3(LAG3) and the adenosine A2a receptor, are mostly targeted in conjunction with the PD-1 pathway blocking antibodies [75–78]. However, such clinical trials are in the early stage, and no validated biomarkers are available at present to predict which LT recipients will benefit most from the dual blockade of these molecules.

On the other hand, in liver transplant recipients that receive ICIs treatment, graft failure can hardly be avoided in the event of graft rejection. Therefore, it should be further investigated about the way to treat liver transplant patients with ICIs-induced graft rejection under emergency situation and to prevent the rejection-induced graft failure.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organisation or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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