

The impact of immunosuppressant therapy on the recurrence of hepatitis C post-liver transplantation

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ABSTRACT

The use of immunosuppressants to reduce the likelihood of acute graft rejections is a cornerstone in the post-transplantation management of recipients. However, these agents were always associated with increased risk of deleterious effects such as infections vulnerability and comorbidities. The objective of this review is to discuss the impact of different immunosuppression strategies used in liver transplant recipients (LTRs) on the recurrence of hepatitis C virus (HCV) infections after transplantation. Traditionally, corticosteroids were a mainstay in immunosuppressive regimens in LTRs. Several trials have suggested early tapering of corticosteroids or steroid-free immunosuppression protocols to minimize metabolic complications and other accompanied adverse events. However, there is no consistent agreement on the apparent benefit of steroid-avoidance regimens on HCV recurrence. At present, calcineurin inhibitors alone or in combination with other immunosuppressants are the standard regimen for immunosuppression in LTRs. Although the use of mycophenolate mofetil and sirolimus were sometimes associated with a significantly lower risk of liver injury as a result of HCV recurrence, they were associated with an increased risk of acute graft rejection compared to calcineurin inhibitors. Consequently, reducing the incidence of HCV recurrence in LTRs could be at the expense of other potential complications. The appropriate selection of adequate immunosuppression could diminish the associated increased risk of HCV recurrence after liver transplantation. However, further clinical studies are still pivotal to establish the appropriate/optimal immunosuppressive therapies for HCV-positive LTRs.

Keywords: Hepatitis C, Immunosuppression, Liver transplantation

Introduction

Liver transplantation has saved the lives of many patients and reduced the prevalence of chronic hepatitis.^[1] It has progressively become the standard treatment for hepatitis C virus (HCV) induced cirrhosis and end-stage liver disease in most developed countries.^[2] However, several formidable challenges still encounter liver transplant recipients (LTRs) as many factors could deleteriously affect the success of the transplanted graft and the quality of life of LTRs such as vulnerability of infections, liver condition, and comorbid diseases.^[3]

Immunosuppressive agents are among various drugs used in LTRs management. The use of immunosuppressive therapy in LTRs is always necessary to avoid acute rejection of the transplanted liver graft. Many studies have reported a strong association between the use of immunosuppressant drugs and HCV recurrence.^[4,5] A considerable health burden is attributed

to the recurrence of HCV due to the use of immunosuppressant drugs as more than half of graft injuries in LTRs were due to HCV in the first post-operative year,^[6] which might escalate up to 70% by the 3rd year after liver transplantation.^[2]

In addition to immunosuppression, other factors may also contribute to HCV recurrence after liver transplantation such as the donor age,^[7] preexisting illnesses,^[8] malnutrition,^[9] inflammatory activity,^[10] bilirubin level,^[11] cytomegalovirus infection,^[4] dual liver-kidney transplantation,^[12] HCV-positive donors,^[13] genetic elements,^[14] and post-liver transplantation antiviral treatment.^[15]

Analysis of all previous factors leading to graft injury or failure in LTRs showed that the use of immunosuppressant drugs is the most prominent cause responsible for the increased risk of HCV recurrence.^[16] Several studies have demonstrated various effects for different immunosuppressant drugs in LTRs. For example, many studies have reported a significant

increase in the frequency and severity of HCV recurrence in LTRs due to cyclosporine-based treatment, the standard immunosuppression regimen in LTRs,^[17] On the other hand, other studies implies that favorable effects are associated with for the use of mycophenolate mofetil (MMF)^[18] and Sirolimus^[19] in LTRs. However, controversial results are still reported by other researchers, who did not found significant differences in the incidence of HCV recurrence in LTRs due to different immunosuppression regimens.^[20] Reducing the consequence of recurrent HCV infection in LTRs could be achieved by proper selection of immunosuppressant drugs,^[21] or reducing overall immunosuppression.^[22] However, minimizing the risk of acute graft rejection is still the main outcome for the use of immunosuppressant drugs. Therefore, it is always necessary to find a balance between the use of immunosuppressant drugs and preventing HCV recurrence to ultimately augment the survival rate of LTRs, thus avoiding or reducing further complications.

All these facts highlight the need for a better understanding of the impact of various immunosuppressive modalities on LTRs. The aim of this review is to provide insight into the use of immunosuppressant drugs in LTRs after liver transplantation. This review will also discuss the impact of different immunosuppression regimen strategies used in these patients and the recurrence of hepatitis C after liver transplantation. A set of relevant recommendations will be also proposed that will help both patients and health-care providers to confront the dilemma of hepatitis C recurrence after liver transplantation.

Methods (Search Strategy)

A comprehensive review of the available literature in the online database subscriptions at the King Saud bin Abdulaziz University for Health Sciences digital library was carried out using PubMed, Embase, Ovid, and Google Scholar. All relevant, accessible full-text articles published from 2005 to December 2016 were located using the following Boolean Logic combination of keywords “Immunosuppression or Immunosuppressant,” and “Hepatitis C,” and “liver transplantation.” A manual literature search for relevant randomized controlled trials and cohort studies on different immunosuppressant drugs including calcineurin inhibitors (cyclosporine and tacrolimus), mTOR inhibitors (sirolimus and everolimus), antimetabolites (azathioprine and MMF), immunoglobulin antibodies, and different members of corticosteroids was also done to include these articles in the review. Only full-text articles available in English were included.

Results and Discussion

Despite the current advances in the medical intervention of liver diseases, HCV infection recurrence, and progressive hepatic fibrosis are still occurring in a substantial proportion

of LTRs after liver transplantations. Immunosuppressant drugs were always blamed for these deleterious consequences, which are regarded as the major concern among both patients and health-care providers in the post-transplant period.^[16]

The present report reviewed the result of several randomized controlled studies that assessed the benefits and the risks associated with the use of current immunosuppressant drugs after liver transplantation in LTRs. Several factors were addressed in these studies including donor age, recipient gender, graft condition, HCV genotype, and the immunosuppression regimen used.

Few studies had claimed that there are no significant differences between patient and/or graft survival rate and the previous presumed risk factors.^[23,24] Nevertheless, numerous studies have reported a high incidence of HCV recurrence in LTRs after liver transplantation.^[13,25,26] Although these studies have established an association between immunosuppression regimens and recurrent HCV, several research outcomes have failed to confirm the variable effects of a specific immunosuppressant drug on recurrent HCV in LTRs.^[27,28] Although there was no consistency in the reported interval between liver transplantation and HCV recurrence, most studies have agreed that HCV recurrence frequently takes place between the 1st and 4th month after liver transplantation.^[29,30] In the next sections, the consequences of the immunosuppressant drugs use in LTRs are described and compared. Table 1 summarizes a summary of the results of 15 randomized controlled clinical studies retrieved from the available literature in the King Saud bin Abdulaziz University for Health Sciences digital library online databases subscriptions, published from 2005 to 2016.

The following sections summarize the impact of using current immunosuppressive regimens used in LTRs on the incidence of HCV infection recurrence, progressive hepatic fibrosis and patient and/or graft survival rate after liver transplantation.

Calcineurin inhibitors (cyclosporine and tacrolimus)

Calcineurin inhibitors have been used as a standard immunosuppressive regimen in LTRs.^[46] Both cyclosporine (CsA) and tacrolimus (TAC) are naturally occurring substances isolated from fungal origins that have been clinically approved for decreasing graft rejection of heart, kidney, liver, and bone marrow transplants.^[47] Calcineurin inhibitors interfere with production or activity of interleukin-2, thereby inhibiting immune cells activation and proliferation.^[48] They are usually used in combination with steroids with or without other immunosuppressant drugs.^[49] Unfortunately, calcineurin inhibitors are usually associated with a number of adverse effects including diabetes, hypertension, and nephrotoxicity.^[50] Numerous studies have demonstrated an established risk of progressive hepatic fibrosis as a result of HCV infection in LTRs treated with calcineurin inhibitors.^[51-53]

Table 1: Summary of results of the available randomized controlled studies in the online database subscriptions at the KSAU-HS digital library

Reference No.	Study period	Mean Follow-up period	Immunosuppression regimen	Number patients	Median age	Gender % male	Acute hepatitis/HCV recurrent/fibrosis (%)	Results*
[31]	2006–2008	12 months	1. TAC + MMF 2. TAC + steroids	58	56.5	79.3	8.6	<ul style="list-style-type: none"> • Steroid-free regimen was associated with a better renal and cardiovascular functions
[32]	1993–2013	72 months	1. CsA or TAC 2. MMF 3. Immunosuppression withdrawn	21 15 10	54.7 50.4 52.4	80.1 73.3 80.0	42.8 40.0 0	<ul style="list-style-type: none"> • Significant increase in the fibrosis in the CNI group • Hepatitis C titers were comparable in the three groups
[33]	2000–2007	96 months	1. TAC monotherapy 2. TAC + AZA + prednisolone	52 51	48.9 50	75.0 68.6	19 11	<ul style="list-style-type: none"> • No significant differences between groups • Long-term immunosuppression with TAC, AZA resulted in slower progression to severe fibrosis compared with TAC alone
[34]	2008–2010	635.8 days	1. ATG + MMF + methylprednisolone 2. TAC + MMF + methylprednisolone	26 23	55.5 53.3	69.23 69.57	26.9 73.9	<ul style="list-style-type: none"> • MMF was discontinued 12 weeks after LT • Prednisone was discontinued after 1 year
[35]	2008–2011	12 months	1. Basiliximab + belatacept+MMF 2. Belatacept + MMF 3. Belatacept [LD] + MMF 4. TAC + MMF 5. TAC alone	50=31 48=29 49=26 53=46 50=32	54.0 53.4 55.2 53.0 54.7	78 71 63 87 84	60.9 40.4 28.6 52.0 37.5	<ul style="list-style-type: none"> • All patients received corticosteroid therapy for the first 3 months • The graft and patient survivals were higher with TAC+MMF compared to other groups
[36]	2004–2010	55 months	1. TAC + corticosteroid 2. TAC + MMF	35 40	56 59	54.3 55.0	59.4 74.2	<ul style="list-style-type: none"> • The overall 5-year patient survival rates were similar • Steroid-free regimen had no apparent impact on outcomes for HCV-positive LTRs
[37]	1999–2008	12 months	1. CsA + MMF 2. CsA	94 92	56 54	79.8 72.8	N/A	<ul style="list-style-type: none"> • Significant survival rate in MMF patients • No significant association between MMF and acute rejections
[38]	2005–2008	12 months	1. TAC + daclizumab 2. TAC + steroid	67 68	53.1 55.3	73.1 66.2	84.7 94.8	<ul style="list-style-type: none"> • HCV recurrence was slightly better with the steroid-free protocol
[39]	1991–2005	53.1 months	1. CsA 2. TAC	126 270	47.9 50.8	61.9 72.6	At 0.5 year 26.8 At 1 year 44.6 At 5 year 83.3 At 1 year 69.2 At 2 year 91.9	<ul style="list-style-type: none"> • No significant differences in the graft or patient survivals • HCV recurrence-free survival was significantly higher in the CsA group
[40]	1998–2003	60 months	1. TAC 2. MMF	70 72	49 50	50 61	60.0 54.2	<ul style="list-style-type: none"> • No significant differences in the incidence of acute rejection, progression or severity of fibrosis were detected
[41]	24	24 months	1. TAC + corticosteroid 2. MMF + TAC + corticosteroids 3. MMF + TAC, + daclizumab	77 72 143	51.3 51.6 51.3	71.4 75.0 71.9	At 1 year 48.2 At 2 year 69.5 50.4 75.9 43.0 68.1	<ul style="list-style-type: none"> • No differences in acute cellular rejection, HCV recurrence, patient survival, or graft survival rates

(Contd...)

Table 1: (Continued)

Reference No.	Study period	Mean Follow-up period	Immunosuppression regimen	Number patients	Median age	Gender % male	Acute hepatitis/HCV recurrent/ fibrosis (%)	Results*
[42]	2002–2010	24 months	1. SRL	173	53.7	76.7	At 1 year 15.3 At 2 year 30.1	• SRL had significantly less advanced fibrosis
[43]	2000–2007	53.5 months	2. HCV control	282	50.4	75.8	36.2	• No patient or graft survival differences • Prednisolone was gradually tapered and stopped between 3 and 6 months
			1. TAC monotherapy	52	48.9	75.0	31	
[44]	2001–2003	24–36 months	2. TAC + AZA + prednisolone	51	50.0	68.6	20	• Prednisone was tapered down rapidly in patients with severe side effects • No difference between the CsA and TAC groups
			1. TAC and methylprednisolone	46	59	72	35	
[45]	1998–2000	44 months	2. CsA and methylprednisolone	44	54	70	32	• No patient or graft survival differences • Steroid withdrawal was started at 3 months after liver transplantation
			1. TAC monotherapy	28	57	64.3	47	
			2. TAC and methylprednisolone	32	56	78.1	67	

AZA: Azathioprine, MMF: Mycophenolate mofetil, TAC: Tacrolimus, CsA: Cyclosporine A, SRL: Sirolimus, ATG: Antithymocyte globulin, LD: Low dose

However, a number of studies have reported that the severity of HCV recurrence after liver transplantation was not correlated to the specific calcineurin inhibitors used (i.e., TAC vs. CsA), yet, it could be correlated with the overall prolonged excessive immunosuppression.^[44] The long-term use of triple therapy of TAC, AZA, and steroid was associated with a slower progression of HCV cirrhosis in LTRs in comparison with TAC monotherapy.^[33] Several other studies have also showed no significant difference in HCV recurrence or in the graft and patient survivals between CsA and TAC used as maintenance immunosuppression.^[17,44] However, a newer study has reported a higher HCV recurrence-free survival in LTRs patients using CsA by the 12th month after liver transplantation.^[39]

On the other hand, recent studies have suggested reducing HCV infection relapse by adding antiviral regimen to eradicate HCV infections (e.g., interferon alfa-2b plus ribavirin) can significantly improve consequences for LTRs who are receiving calcineurin inhibitors,^[54,55] with better outcomes in patients receiving CsA than TAC.^[12] Although no significant differences were reported between the two calcineurin inhibitors in either the graft or patient survival rates, the HCV recurrence was significantly lower in the CsA group than in the TAC group.^[39] This could be attributed to the inhibitory effect of TAC, but not CsA, on interferon cellular signal transducers, which can contribute to the increased severity of HCV after liver transplantation.^[56] Unlike TAC, CsA possesses additional suppressive effects on HCV replication as described, which could further clarify the enhanced outcome of CsA compared to TAC.^[57] However, controversial details are been reported by some randomized controlled studies regarding the differential effect of calcineurin inhibitors on graft or patient survival and HCV recurrent in LTRs.^[52,58,59]

Antimetabolites (azathioprine and MMF)

Azathioprine (AZA), a prodrug of mercaptopurine, is a cytotoxic antimetabolite immunosuppressant used to prevent acute graft rejection since 1960s.^[60] AZA interferes with purines metabolism which impedes lymphoid cells proliferation.^[61] It is usually used in combination with other immunosuppressants, mainly calcineurin inhibitors and corticosteroids.^[43] Although AZA has shown a significant benefit in kidney-transplant recipients, it has been largely replaced by MMF in most transplant centers in 1990s due to its myelosuppression toxicity.^[62] MMF, on the other hand, has shown to be highly effective as an immunosuppressant, alone or in combination with steroids in most grafts recipients with tolerable side effects.^[63] MMF is a semisynthetic derivative of a fungal antibiotic and a prodrug of mycophenolic acid, which deter proliferation of both T and B lymphocytes and cytotoxic T cells by inhibiting the *de novo* synthesis of purines.^[64]

Unlike calcineurin inhibitors, many studies have reported that MMF-treated patients showed significantly lower risk

for acute graft rejection and recurrence of HCV infection and thus lesser hepatic fibrosis.^[40,65] MMF has also been currently used to minimize calcineurin inhibitor dosing to decrease nephrotoxicity following liver transplantation.^[40] Furthermore, several studies have revealed a significantly improved renal and cardiovascular functions in LTRs who exchange immunosuppression regimen from calcineurin inhibitors to MMF monotherapy.^[53,66] In addition, it has been reported that LTRs receiving MMF monotherapy are at lower risk of developing cancer compared to those using calcineurin inhibitors maintenance therapy.^[67]

Recently, an immense favorable profile has been revealed for MMF immunosuppression without aggravating the progression of hepatic fibrosis in LTRs, which was comparable to those patients who have been successfully withdrawn from immunosuppression treatment.^[32] Moreover, an improved patient survival has also reported when MMF was added to the calcineurin inhibitors standard immunosuppressive therapy.^[37] Despite the apparent benefit of MMF in LTRs, it has recently reported an increased risk of acute graft rejection in calcineurin inhibitor-free MMF maintenance therapy in LTRs.^[68] In addition, several other studies have failed to demonstrate superior clinical benefits for MMF over AZA in LTRs.^[69-71]

mTOR Inhibitors (sirolimus and everolimus)

Sirolimus (SRL), also known as rapamycin, is an mTOR Inhibitor, which was approved by the U.S. Food and Drug Administration in 1999 for post-transplant immunosuppression in graft recipients.^[72] SRL is a macrolide antibiotic derived from *Streptomyces hygroscopicus* that inhibit T cell proliferation.^[73] Similar to the MMF, SRL has been shown to be a safe alternative to calcineurin inhibitors in kidney transplant recipients due to its lower risk of nephrotoxicity.^[74]

SRL has been occasionally used as a potent immunosuppressive agent in LTRs in combination with lower doses of CsA^[75] and/or corticosteroids^[76] and thereby lowering potential adverse effects. SRL-based immunosuppression has demonstrated a prominent safety profile and lower risk of progressive hepatic fibrosis in LTRs.^[19,42] Moreover, it has been recently demonstrated that conversion from calcineurin inhibitors to mTOR inhibitors could assist in immunosuppressant withdrawal in LTRs with better tolerance.^[77]

The incidence of HCV recurrence in patients treated with SRL-based immunosuppression has been assessed by many studies. Some recent studies have reported no significant difference in the timing or severity of HCV recurrence or in the patient or graft survival rates in LTRs treated with SRL as the primary immunosuppressive agent.^[20,78,79] On the other hands, few studies have reported significantly lower risk of liver fibrosis,^[19,42] and higher survival rates in SRL-based immunosuppression in LTRs due to lower rates of HCV recurrence after liver transplantation.^[80] However,

a contradictory result has been also shown where SRL was associated with inferior outcome in LTRs in comparison with calcineurin inhibitors.^[81]

On the other hand, the use of SRL could have a favorable effect in LTRs with hepatocellular carcinoma, since SRL has demonstrated additional antineoplastic actions.^[82,83] Such potential anticancer property could be of a great benefit in LTRs inhibiting tumor growth and protecting against the emergence of new malignant tumors, a known hazard of immunosuppressant agents.^[79,84]

However, in November 2009, FDA issued a “black box warning” for the use of SRL in stable LTRs,^[85] which was based on the results of a prematurely terminated phase 3 clinical trial conducted by sirolimus (Rapamune®) manufacturer, Wyeth-Pfizer.^[86] The trial data revealed a high incidence rates of graft loss, and hepatic artery thrombosis/portal vein thrombosis, in addition to a substantial increase in mortality in LTRs.^[87] Therefore, it is not recommended to use SRL monotherapy in stable LTRs undergoing maintenance immunosuppressive therapy due to the aforementioned associated risks.

Similarly, everolimus, a 40-O-(2-hydroxyethyl) derivative of SRL, has demonstrated a potent and comparable immunosuppressive efficacy to TAC in LTRs,^[88,89] with significantly lower adverse effects in comparison with the standard immunosuppression therapy in liver transplantation (i.e., calcineurin inhibitors), particularly nephrotoxicity.^[90] This also permitted the early reduction or withdrawal of calcineurin inhibitors in LTRs especially in cases of renal dysfunction.^[91] However, Saliba and Nevens have reported a slight reduction in liver fibrosis progression and HCV replication in HCV-positive LTRs who were treated with everolimus therapy with an early reduction of the standard TAC regimen.^[92] Similarly to SRL, everolimus also exhibited an effective antineoplastic effect in patients with recurrent or new malignancies especially those with hepatocellular carcinoma, thus providing an additional benefit in LTRs.^[93]

Corticosteroids

Traditionally, corticosteroids were the main immunosuppressive regimen in organ transplant recipients. They are frequently used as an induction treatment after liver transplantation and, in combination with other immunosuppressants, to maintain immunosuppression^[94] and to prevent and treat acute graft rejections.^[95] However, steroid-resistant acute graft rejection was always a source of concern as patients who had steroid-resistant rejection are at higher risk of severe recurrent HCV infection after liver transplantation compared to patients with no steroid-resistant rejection and thus requiring alternative therapies.^[96]

Numerous reports have described negative outcomes for corticosteroids with a substantial increase in HCV replication,^[97]

and graft hepatitis.^[98] In a retrospective observational study, repeated methylprednisolone pulse therapy was associated with significantly higher risks of HCV-related graft loss than single steroid pulse therapy.^[99] Moreover, several studies have reported direct proportionality between the intensity of steroids immunosuppression boluses and recurrence of HCV.^[24,100]

Consequently, several clinical studies have tried to minimize the use of corticosteroids in an attempt to reduce the recognized adverse effects associated with the prolonged use of corticosteroids. Most of the reports on steroid-sparing immunosuppression protocols have revealed favorable consequences by reducing infection rates and metabolic complications in LTR after liver transplantation.^[100-103] It has been suggested that a reduction of the HCV recurrence after liver transplantation could be attained by slow tapering of corticosteroids or with a steroid-free immunosuppression protocol.^[38] Additional benefits for steroid-free immunosuppressive regimens with either TAC-or MMF-based therapies in LTRs have also been reported including preserved renal function and reduced cardiovascular risk.^[31]

Some studies, however, reported contradictory findings or found no significant differences after steroid withdrawal during short-term follow-up.^[41,45,104] For example, a recent randomized, multicenter clinical trial reported no apparent benefit for steroid-avoidance regimens on the outcome of HCV recurrence in patients received TAC plus corticosteroid versus TAC plus MMF regimen and with similar overall 5-year survival rates.^[36] Peculiarly, other reports suggested a reduction in the severity and HCV recurrence could be attained by long-term treatment with high daily doses of corticosteroids which were slowly tapered off over several months after liver transplantation and thereby increasing survival in LTRs.^[24]

Immunoglobulin (antibodies)

Immunoglobulins were initially introduced in immunosuppression practice of graft recipients to improve overall survival and to avoid the risk of long-term adverse effects and complications of the standard immunosuppression regimens, such as calcineurin inhibitors.^[105]

Monoclonal antibodies

Muromonab-CD3, which targets the CD3 receptor on mature T lymphocytes, was the first murine monoclonal antibody to be approved for immunosuppression in patients who showed episodes of steroid-resistant rejection after graft transplantation.^[106] Studies had reported a substantial increase in the risk and severity of HCV recurrence in Muromonab-CD3 treated-LTRs, which eventually progressed to hepatic fibrosis and cirrhosis.^[13,107] The use of Muromonab-CD3 has dramatically declined lately due to the availability of alternative treatments with improved efficacy and fewer adverse effects.

Basiliximab is another immunosuppressive monoclonal antibody that was approved by FDA in 1998 for use in kidney recipients to prevent acute cellular rejection following organ transplantation. Basiliximab interferes with the interleukin-2 receptor known as CD25 antigen, and thus inhibiting T-lymphocyte proliferation.^[108] At present, basiliximab has been frequently used in LTRs as an induction immunosuppressive treatment, showing superb efficacy and safety profile since it allows the early withdrawal of corticosteroids and reduction of calcineurin inhibitors, especially in renal insufficiency patients.^[109] The addition of basiliximab to standard immunosuppressive therapies (CsA, AZA, and corticosteroids) has improved the outcome in LTRs by reducing the incidence of acute rejection without significantly increasing adverse effects.^[110,111] Although it has recently reported that basiliximab-induced immunosuppression was associated with a lower acute rejection in HCV-positive LTRs, neither the incidence of HCV recurrence has reduced, nor the patient survival rates have enhanced.^[112]

Polyclonal antibodies

Thymoglobulin or the anti-thymocyte globulin (ATG) has recently become the primary treatment for acute steroid-resistant rejection.^[113] A lower frequency of HCV recurrence has been reported in LTRs patients on ATG in comparison to TAC-based immunosuppression during the induction phase of immunosuppression. Nevertheless, ATG-based immunosuppression has not shown better graft and/or patient survival outcomes, rather, it was associated with a significantly higher frequency of fungal infections.^[34] Moreover, no significant difference has been displayed in the graft and patient survivals or in the severity of recurrent HCV in LTRs who were using either Muromonab-CD3 or ATG immunoglobulins.^[96]

Furthermore, belatacept, a fusion immunoglobulin Fc fragment that selectively inhibits T-cell activation, has been also approved FDA in 2011 to prevent acute graft rejection in adult patients receiving a kidney transplant in combination with basiliximab induction, MMF, and corticosteroids.^[114] However, the use of belatacept in LTRs is not recommended because it was frequently associated with significantly higher death rates, acute graft rejections and even infections compared to the TAC- or MMF-based immunosuppression.^[35] Therefore, the potential benefits of any of these immunoglobulins over the standard immunosuppression regimens in LTRs is still controversial.

Recommendations

Although immunosuppressant agents have been widely employed after organ transplantations in various clinical settings to reduce acute grafts rejections, HCV recurrence is still a major concern in LTRs with the potential to lead to progressive liver injury and fibrosis. The significant association of immunosuppressive therapies with the severity of liver injury due to HCV recurrence has been extensively reported

by numerous clinical studies. This negative impact could be a reflection of an overall excessive immunosuppression rather than the direct effect of a specific immunosuppressive agent. Therefore, reducing the intensity of immunosuppression in HCV patients following liver transplantation to maintain adequate host immune responses could enhance the outcome of liver transplantation by decreasing the opportunity of HCV recurrence and thus improving both graft and patient survivals.

Viral infections, including cytomegalovirus infection, are common risk factors for severe HCV recurrence in LTRs, which is usually associated with graft injury.^[4] Several strategies have been proposed and applied to manage viral infections either before or after liver transplantation. Preventative antiviral therapy, particularly peginterferon alfa and ribavirin were usually considered for at least 3 months following liver transplantation to manage HCV recurrence in LTRs.^[115,116] Valganciclovir is also commonly used for both prophylaxis and treatment of viral infections in LTRs.^[117] However, a relatively recent study has failed to demonstrate any clear benefit for early antiviral therapy with peginterferon alfa plus ribavirin after liver transplantation.^[118] Therefore, due to their modest efficacy in the immunosuppressed LTRs routine prophylactic antiviral treatments after liver transplantation for HCV should not always be considered, taking into consideration their potential adverse side effects and drug interactions.^[30]

Many studies have also identified corticosteroid therapy as a major risk factor for HCV recurrence and the progress of liver graft failure as discussed earlier. Therefore, steroid-sparing immunosuppression has been suggested and employed in LTRs to avoid their adverse events and to reduce the risk of HCV-induced graft injury. However, limiting corticosteroids usage was not always associated with reducing the risk of HCV recurrence as the results of most of these studies were inconclusive or contradictory.^[36,104]

Finally, the large variation in immunosuppression regimens among different health-care centers in addition to the differences in the methodology used by available clinical studies restrained the authors from performing statistical comparisons. Furthermore, there is little or no consensus in the reported consequences of different immunosuppression regimens in these studies. Such variations in outcomes could be due to heterogeneity of these studies and other confounding factors that could have been overlooked leading to potentially biased perceived effects. Therefore, more prospective studies on different immunosuppressant protocols should be performed to verify the effect of immunosuppressants on recurrent HCV in LTRs.

Conclusion

Although the optimal immunosuppressive therapy for HCV-positive LTRs has not been established yet, an adequate immunosuppression is certainly required to prevent acute

cellular rejection of the transplanted graft. Therefore, the appropriate choice of safe, yet potent immunosuppressant regimens in LTRs could diminish such potential consequences and help to evade the need for repeated dosing of corticosteroids, thus reducing the likelihood of the associated adverse effects. The early use of effective antiviral prophylactic treatments could eventually reduce the recurrent of HCV and have favorable effects in LTRs by avoiding the abrupt changes in immunosuppression. Moreover, avoiding what is so-called “over-immunosuppression” could potentially reduce HCV recurrence and other unfavorable outcome in LTRs, thus increasing the patient survival rate after liver transplantation. However, further clinical studies are indispensable to understand the complexity of HCV recurrence in LTRs to determine the ideal immunosuppression strategies form an aging acute rejection and to improve the outcome after liver transplantation.

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