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REVIEW

Posttransplant complications in the setting of acute-on-chronic liver failure and considerations regarding immunosuppression

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INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a dynamic syndrome defined by acute decompensation of known cirrhosis and associated extrahepatic organ failures. The pathogenesis is based on intense systemic inflammation and oxidative stress, often precipitated by proinflammatory events such as infection or alcoholic hepatitis.[1] Liver transplantation is the definitive treatment for patients with ACLF; however, the majority of patients on the waiting list (>50%–75%) die of severe comorbidities, active infection, or alcoholism.[2] Patients with ACLF grades 1 through 3 (82.3%–86.2%) had similar 1-year posttransplant survival rates compared with patients without ACLF (90%).[3] Two or three immunosuppressive agents are commonly used in the immediate posttransplant period and are reduced to monotherapy once the patient's liver function has adequately recovered. Calcineurin inhibitors (CNIs) are potent immunosuppressive agents that impair nuclear factor of active T cells (NFAT) and suppress interleukin-2 (IL-2) transcription and T cell activation.[4] However, inhibition of the calcineurin and NFAT isoforms pathways gives rise to other toxicities, such as infection, nephrotoxicity, metabolic/cardiovascular complications, neurotoxicity, and malignancy (Table 1).

POSTTRANSPLANT COMPLICATIONS IN ACLF

ACLF liver transplant recipients (LTRs) have a higher incidence of posttransplant complications compared with patients without ACLF (74%–100% versus 51.2%). The highest risk is infectious complications, which persist beyond the first year as the leading cause of mortality in ACLF LTRs (37.6%) compared with malignancy (28.6%) in non-ACLF LTRs. ACLF LTRs shared similar complications rates on other short- and long-term complications in non-ACLF LTRs[5] (Table 2).

Infections

The mortality rate from infection was reported to be 33.7% in ACLF LTRs compared with 6.6% in non-ACLF LTRs.[6] Risk factors for posttransplant infection-related mortality included age >60 years, diabetes, and number of pretransplant organ failures.[5] It was observed that approximately one-third of lethal sepsis cases in the ACLF LTRs were from the same infection focus pretransplant, suggesting incomplete resolution of infection. Bacterial infection accounts for most of the infectious complications, followed by viral and fungal infections.[3] Although studies are lacking in the understanding of innate and adaptive immune system function in patients with ACLF, it has been postulated that the immune system function might be similar to what was observed in patients with sepsis, whereby the initial activation of the immune system in ACLF might be followed by a period of immunosuppression/immunoparesis, further exacerbated by bone marrow suppression from superimposed infection. In addition, the use of immunosuppressive medications posttransplant further inhibits immune

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TABLE 1 Immunosuppressive drugs used in liver transplantation

Class	Agents	Mechanism of action	Main adverse effects
Pharmacological agents			
CNIs	Cyclosporine Tacrolimus	Inhibits calcineurin phosphatase and T cell activation	Nephrotoxicity, hypertension, diabetes, neurotoxicity
Corticosteroids	Prednisone Methylprednisolone	Inhibits cytokine transcription by antigen-presenting cell	Diabetes, osteopenia, hyperlipidemia, hypertension
mTOR inhibitors	Sirolimus Everolimus	Inhibits target of rapamycin and IL-2–driven T cell proliferation	Hyperlipidemia, thrombopenia, hepatic artery thrombosis
Purine synthesis inhibitor (antagonist)	Mycophenolate acid Azathioprine 6-Mercaptopurine	Inhibits purine and DNA synthesis, preventing proliferation of T and B cells	Bone marrow toxicity, gastrointestinal disturbances (e.g. diarrhea, nausea, abdominal pain)
Biological agents			
ATG	ATG	Blocks T cell membrane proteins and causes altered function, lysis, and prolonged T cell depletion	Cytokine release syndrome (e.g. fever, diarrhea, hypotension, shortness of breath), serum sickness
Anti-CD3 monoclonal antibodies	OKT3	Causes T cell depletion and receptor modulation and interferes with signal 1	Cytokine release syndrome, pulmonary edema, acute renal failure, gastrointestinal disturbances
Anti–IL-2 alpha-chain receptor antibodies	Basiliximab Daclizumab	Blocks IL-2 receptor on activated T cells and inhibits IL-2–induced T cell activation	Hypersensitivity reactions
Anti-CD52 monoclonal antibodies	Campat 1-H Alemtuzumab	Binds to CD52 on all B and T cells and thymocytes, causing cell lysis and prolonged depletion	Cytokine release syndrome, idiosyncratic pancytopenia, thyroid disease

TABLE 2 Post–liver transplant complications

Short term (<6 months)	Long term (>6 months)
Surgical	
• Postoperative hemorrhage • Vascular complications (hepatic artery thrombosis, portal vein thrombosis, hepatic venous obstruction) • Biliary tract complications (bile leak or fistula, biliary stricture)	• Biliary anastomotic stricture • Vascular stricture • Hepatic artery thrombosis • Incisional hernia
Medical	
• Hemodynamic complications • Infection (bacterial, viral, fungal) • Respiratory failure • Renal dysfunction • Neurological	• Renal dysfunction or failure • Posttransplant metabolic syndrome (hypertension, diabetes, obesity, and dyslipidemia) • Cardiovascular disease • Metabolic bone diseases • Infection • Neurological • Malignancy
Allograft	
• Primary nonfunctional or poor function • Acute cellular rejection • Recurrent viral hepatitis • Drug hepatotoxicity	• Chronic rejection • Disease recurrence

reconstitution, causing a protracted immune dysfunction. Patients with ACLF are also known to be more prone to multidrug-resistant pathogens and invasive fungal infections[7] (Table 3).

Malignancy

Malignancy was observed to be the predominant cause of death after 1 year posttransplant in non-ACLF LTRs

TABLE 3 Infectious causes of death within 1 year of liver transplantation in patients with ACLF grade 3

	<3 months posttransplant	3–12 months posttransplant
Bacterial peritonitis	2.8%	3.1%
Pneumonia	3.2%	2.5%
Sepsis	72.4%	76.1%
Fungal	7.6%	3.1%
Mixed	1.9%	1.3%
Opportunistic	1.6%	1.3%
Viral	0.8%	1.3%
Other	9.6%	11.3%

(28.5%) compared with ACLF LTRs (18.4%–21.6%).[5] Posttransplant malignancy can either be de novo, donor related, or recurrent cancer. Nonmelanoma skin cancer is the most common *de novo* malignancy with an overall incidence rate of 16%–22.5%. Other common malignancies include posttransplant lymphoproliferative disorders and oropharyngeal, esophageal, and vulvar cancer.[8] CNIs and azathioprine have direct oncogenic effects, impair immunosurveillance, and increase the incidence of virally induced malignancies. On the contrary, mammalian target of rapamycin (mTOR) inhibitors and mycophenolate mofetil demonstrate antiproliferative effects that may lead to a decreased risk for malignancy.

Acute and chronic renal failure

The presence of chronic kidney disease (stage ≥3) was significantly higher in ACLF LT after 1 year compared with the non-ACLF LTRs, but it was not significantly different between the two groups after 5 years.[5] Posttransplant renal failure is closely related to CNI use. CNIs activate the renin-angiotensin system, which results in acute, dose-dependent, and often reversible nephrotoxicity. However, with sustained excessive exposure there can be irreversible damage and chronic nephrotoxicity.[9]

Posttransplant metabolic syndrome: hypertension, diabetes mellitus, obesity, and dyslipidemia

The overall prevalence rate of posttransplant metabolic syndrome (PTMS) is 43%–58%. Little data exist to compare the rate of metabolic complications between ACLF and non-ACLF LTRs. Preexisting diabetes mellitus (DM), posttransplant weight gain, and immunosuppression (CNI and corticosteroids) are the major contributory factors for PTMS. Both CNIs and corticosteroids increase the risks of posttransplant DM via decreased peripheral insulin sensitivity, insulin production and release, and increased hepatic gluconeogenesis. CNIs (cyclosporine > tacrolimus) increase sympathetic tone (i.e. leading to vasoconstriction) and cause sodium-dependent volume expansion, resulting in hypertension. Sirolimus causes the most significant dyslipidemia among all immunosuppressants (up to 55%).[10]

MANAGEMENT OF POSTTRANSPLANT COMPLICATIONS

Aggressive infection management and judicious antimicrobial and antifungal prophylaxes are paramount to improve short- and long-term survival in ACLF LTRs. A lower target CNI concentration or delayed initiation of CNI could be considered in patients with ACLF to reduce acute kidney injury. It is important to modulate immunosuppressive agents and optimize preexisting risk factors for metabolic syndrome and cardiovascular disease. The type, intensity, and duration of immunosuppressive therapy can influence the rate of carcinogenesis; hence the management should include careful selection of immunosuppressive agents, prophylaxis against infection-related malignancies, and use of intensive targeted screening programs.

CONCLUSION

In conclusion, ACLF LTRs are at a higher risk for posttransplant infectious complications, which are intensified by the use of immunosuppressive therapy. Despite this, ACLF LTRs have excellent short-term outcome and acceptable long-term survival. Rigorous infection management and judicious modulation of immunosuppression are of critical importance to improve short- and long-term survival in this highly vulnerable patient population.

CONFLICT OF INTEREST

Nothing to report.

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