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CAQ Corner: Basic concepts of transplant immunology

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BASIC CONCEPTS OF TRANSPLANT IMMUNOLOGY

Principles of the immune system

The primary role of the immune system is to provide protection from infection and to detect and destroy abnormal cells. The immune system consists of innate and adaptive immunity alongside the complement system. The innate immune system is present at birth and is not altered by future exposures to foreign antigens during one's lifetime. This is the first line of defense upon exposure to micro-organisms that are present at the location of infection or injury with an immediate non-specific inflammatory response. On the other hand, the adaptive immune system changes during one's lifetime in response to different antigen exposures. Activation and sensitization of the adaptive immune system leads to antigen-specific T lymphocytes (cellular immunity) and B lymphocytes (humoral immunity).

Activation of the immune system requires the recognition of molecules as being foreign to the body. Pathogen-associated molecular patterns (PAMPs) are highly conserved molecular components unique to micro-organisms that are not found in the human body.

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The antigen presenting cells (APCs) of the innate immune system have germline-encoded pathogen recognition receptors (PRRs) that recognize PAMPs.[1] Binding of PAMPs to PRRs leads to the destruction of the pathogen via phagocytosis and activation of transcription factors that stimulate cytokine release and triggers the inflammatory response with activation of the

Abbreviations: *ABCB1*, ATP binding cassette subfamily B member 1; Akt, protein kinase B; AMR, antibody-mediated rejection; APC, antigen presenting cell; ATP, adenosine triphosphate; Bm, memory B cell; Ca, calcium; C4d, complement fragment 4d; CNI, calcineurin inhibitor; CsA, cyclosporine A; CTLA4, cytotoxic T lymphocyte antigen 4; CYP, cytochrome P540; DAMP, damage-associated molecular pattern; DSA, donor-specific antibodies; ER, extended release; FK-506, tacrolimus; FKBP, FK506 binding protein; FOXP3, forkhead box P3; G1, gap 1 phase; G2, gap 2 phase; HLA, human leukocyte antigen; IL2, interleukin 2; IMDPH, inosine monophosphate dehydrogenase; IR, immediate release; IV, intravenous; IVIG, intravenous immunoglobulin; M, mitosis phase; MDPH, inosine mono-phosphate dehydrogenase; MHC, major histocompatibility complex; MMF, mycophenolate mofetil; MP, mercaptopurine; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T cells; PAMP, pathogen-associated molecular pattern; PC, plasma cell; P-gp, P-glycoprotein; PI3K, phos-phatidylinositol 3-kinase; PRR, pathogen recognition receptor; RAI, rejection activity index; S, synthesis phase; TCMR, T cell–mediated rejection; TCR, T cell receptor; Te, effector T cell; TG, thioguanine; T_h1, T helper 1; T_h2, T helper 2; T_h17, T helper 17; Tm, memory T cell; Treg, regulatory T cell.

complement system. Dendritic cells are the APCs that serve as messengers between the innate and adaptive immune systems.[2]

The dendritic cells process the antigen material, travel to the lymphoid tissue, and present the antigenic peptides on its cell surfaces for recognition by T cells. The inactive or naïve T cells are not able to recognize free or soluble antigens; rather, they must be presented antigens bound to the membrane-associated major histocompatibility complex (MHC) molecules on the APCs. Once the T cell receptor (TCR) recognizes and binds to the MHC complex, a cascade of events leads to T cell activation, differentiation into effector T cells, and proliferation. Naïve CD4 T cells are activated by MHC class II (MHC II), and naïve CD8 T cells are activated by MHC class I (MHC I). All nucleated cells express MHC I, whereas constitutive expression of MHC II are found on epithelial cells or APCs such as dendritic cells, macrophages, and B cells in the periphery, and inducible expression may occur in certain inflammatory conditions.[3]

T cell activation requires a TCR-mediated signal and a costimulatory signal. The first signal that stimulates the T cell is recognition of an antigenic peptide bound to an MHC molecule on the membrane of the APC by the T cell receptor on a naïve T cell. Numerous costimulatory molecules and ligands have been identified that direct the activation and differentiation into the various effector T cells.[4] One of the main costimulatory molecule-ligand signals required to prevent T cells from becoming anergic or ineffective is B7:CD28. This is further promoted by the CD40:CD40L signal that induces further expression of CD28 on T cells and the B7 protein (CD80/86) and MHC molecules on APCs. On the other hand, B7:CD28 binding increases cytotoxic T lymphocyte antigen 4 (CTLA4) expression by T cells, which competes with CD28 for binding to B7 in a negative feedback mechanism. Thus, the balance of CTLA4 and CD28 regulates ongoing T cell activation. The programmed cell death protein 1 (PD-1): programmed cell death ligand 1 (PD-L1) is a coinhibitory signaling pathway that promotes tolerance by preferentially promoting regulatory T cell (Treg) differentiation; thus, dysregulation of this signal contributes to the development of malignancies, auto-immune disorders, and infections.[5]

Once T cells are activated, proliferation and differentiation into the various lineages are driven by the cytokine environment, costimulatory signals, and degree of antigenic burden.[4] Naïve CD8 T cells differentiate to effector cytotoxic T cells or memory T cells, whereas the naïve CD4 cells differentiate to effector helper T cells (T helper 1 [T_h1], T helper 2 [T_h2], T helper 17 [T_h17]) or Tregs. Naïve B cells differentiate to memory B cells and plasma cells that subsequently release alloantibodies. Further T cell proliferation is mediated by numerous pathways in response to the cytokine milieu. For instance, interleukin 2 (IL2) is a major signal in promoting the Janus kinase-signal transducer and activator of transcription (Jak-STAT), phosphatidylinositol 3 kinase–protein kinase B (PI3K-Akt), and mammalian target of rapamycin complex (mTORC) pathways that converge to promote de novo nucleotide synthesis and cell cycle progression.

Immune system response to organ transplantation

In liver transplantation (Figure 1), the period of ischemia followed by reperfusion leads to donor hepatocyte injury and the production of hepatic damage-associated molecular patterns (DAMPs) that creates a sterile inflammatory state triggering the innate immune system.[6] Similar to PAMPs binding to PRRs after microbial invasion, DAMPs engage with toll-like receptors that are the PRRs expressed on innate immune cells and play a critical role in the subsequent activation of dendritic cells, stimulation of cytokine production, recruitment of additional immune system cells, and mobilization of the dendritic cells.[1]

Once dendritic cells are activated, they process the DAMPs and express alloantigen bound to MHC and travel to the recipient lymphoid tissue to trigger the adaptive immune system. Recognition of MHC-bound alloantigen by the donor naïve T cells permits activation, proliferation, and further differentiation of the T cells. The cytotoxic T cells travel to the graft tissue where they are able to recognize host antigen and mediate graft injury. Although most of these effector T cells will ultimately undergo apoptosis when the antigen load decreases, a subset may persist as memory T cells posing a threat for long-term allograft survival attributed in part to their ability to be triggered by a lower antigen burden and less dependency on costimulatory signals.[7]

There are two distinct types of rejection, T cell–mediated rejection (TCMR) and antibody-mediated rejection (AMR), although the two entities may coexist.[8] Early acute TCMR is primarily mediated by the direct allorecognition pathway early after transplantation. Donor APCs with alloantigens bound to donor MHC I and II molecules engage recipient TCRs on naïve CD8 and CD4 cells, respectively, leading to activation and differentiation. The cytotoxic CD8 T cells are the main effector cells primed to travel back to the graft where they recognize allogeneic MHC molecules, resulting in injury to the vascular endothelium and bile ducts with potential for additional injury to hepatocytes in severe cases of rejection. Thus, histological examination of the liver allograft in early TCMR typically shows portal-based inflammation with a mixed infiltrate, cholangitis with inflammatory infiltration of the bile ducts, and subendothelial infiltration of the portal and hepatic venules.[9]

Late acute TCMR is mediated by the indirect allorecognition pathway. In this process, donor allogeneic antigens are taken up by the recipient APCs,
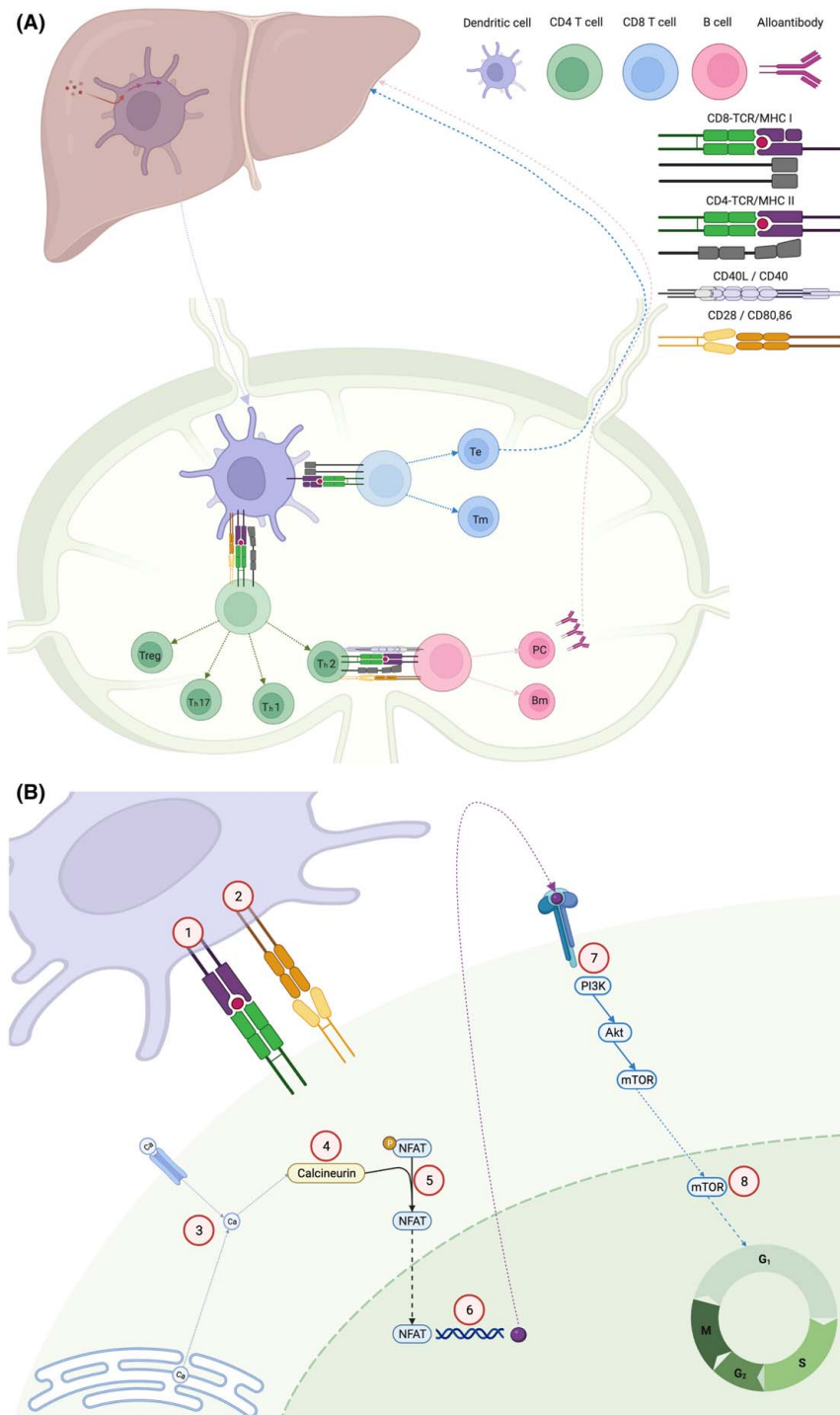
FIGURE 1 Immune response to transplantation. (A) The APCs responsible for T cell activation are the dendritic cells. Direct allorecognition is responsible for acute rejection, wherein donor APCs with donor MHC molecules travel from the donor organ to lymphoid tissue. Indirect allorecognition occurs later, wherein recipient APCs have processed the alloantigens and present them on recipient MHC molecules. Allorecognition and subsequent T cell activation is dependent on TCR recognition of MHC I and II by the naïve CD8 and CD4 cells, respectively. CD8 cells differentiate into cytotoxic effector cells and memory cells. CD4 cells differentiate into subpopulations depending on the costimulatory signals and cytokine environment present. B cells process alloantigens and display these on MHC II molecules that are recognized by T_h2 CD4 cells with maturation into antibody-producing plasma cells and memory B cells. (B) (1) TCR recognition of alloantigen bound to MHC II on APC (Signal 1); (2) costimulation with various proteins and ligands (Signal 2)—B7 protein (CD80 or CD86) on the APC membrane-binding CD28 on T cell surface is one of the main costimulatory signals necessary for T cell activation; (3) Signals 1 and 2 are both necessary for T cell activation, which increases intracellular calcium; (4) increased calcium concentration activates calcineurin; (5) activated calcineurin dephosphorylates NFAT; (6) NFAT is then able to enter the nucleus and upregulate transcription of numerous cytokines, including IL2; (7) IL2 binds to IL2 receptor (Signal 3), leading to activation of PI3K/Akt/mTOR pathway; and (8) mTOR is one of the regulators in the cell cycle progression and proliferation. Created with BioRender.com.

processed, and presented to T cells by self-MHC molecules. There is also a semidirect pathway in which donor MHC molecules remain intact in exosomes that are taken up by the recipient APCs, and alloantigens are subsequently presented bound to donor MHC on the recipient APC surface membrane.[10] Activation, proliferation, and differentiation of the T cells with long-term immune response occurs in a similar process as the direct pathway. Late TCMR is more likely to be associated with steroid-resistant rejection compared to early TCMR with worse patient and graft survival.[11]

Chronic TCMR develops after recurrent, severe, or persistent episodes of TCMR. Previously formed memory T cells may contribute to chronic allograft rejection with lower activation thresholds.[12] Additional risk factors include an underlying autoimmune etiology of liver disease, tacrolimus (FK-506)-free immunosuppression regimen, repeat transplantation, and medication noncompliance. In comparison to acute TCMR, the portal inflammation is less prominent with lymphoplasmacytic infiltrate, obliterative arteriopathy, and eventually irreversible bile duct loss with fibrosis over time.[9]

Antibody-mediated rejection (AMR) may result from preformed or de novo donor-specific antibodies (DSA) to donor human leukocyte antigen (HLA) antigens. In the pathways described previously, activated B cells differentiate to memory B cells and plasma cells which produce de novo antibodies. MHC II expression in the liver is relatively low but may be upregulated after injury, which increases the likelihood of DSA binding, complement fixation, and subsequent cellular toxicity.[13] Risk factors for chronic AMR include preservation injury, prior episodes of TCMR in the setting of inadequate immunosuppression, and any recurrent or new chronic liver disease. Of note, the presence of DSA is not independently diagnostic of AMR. Liver histology is needed for the diagnosis with complement fragment 4d (C4d) staining, indicating the presence of complement activation on the vascular endothelium.[8]

In acute AMR, the recipient has preexisting antibodies to the donor antigens that bind to the endothelium of the graft vessels. This is typically caused by ABO-incompatible grafts or the presence of preformed anti-HLA alloantibodies from prior transplantation, transfusion, or pregnancy. This can be avoided with appropriate cross-matching or preemptive desensitization protocols, although testing for preformed DSA is not standard protocol at many liver transplant centers. Although the management of rejection may vary by center with individualized protocols, general principles recommended by the International Liver Transplantation Society are shown in Figure 2.[14]

Immune tolerance

Immune tolerance refers to a state in which the immune system does not respond to a specific antigen. As it relates to liver transplantation, this is a state in which any type of rejection may be avoided. In fact, the liver is considered an immunologically privileged organ, and some patients may achieve operational tolerance, a state of stable graft function without the use of any maintenance immunosuppression.[15] Numerous immunosuppression withdrawal studies have been conducted with a 20%–30% success rate of achieving operational tolerance, although the rates vary greatly due to differences in study design and patient populations. Common factors that appear to be important in achieving operational tolerance are nonautoimmune liver diseases (autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis) as the indication for transplant, older age at time of transplant, greater amount of time elapsed after transplant, and a liver biopsy lacking subclinical evidence of acute or chronic rejection prior to weaning of immunosuppression.[16]

Regulatory T cells are CD4+ CD25^{high} lymphocytes that express the transcription factor forkhead box P3 (FOXP3) and play a critical role in immune tolerance.[17] Natural Treg cells differentiated in the thymus are vital in maintaining self-tolerance. In the allorecognition pathways, naïve CD4 T cells may produce effector cytotoxic and helper cells alongside induced Treg cells, a subset of CD4+ CD25− FOXP3− T cells converted to CD4+ CD25^{high} FOXP3+ cells. Tregs play a key role in allograft tolerance by diminishing the activation, differentiation, and function of effector T cells. CD25 is the high-affinity alpha chain of the IL2 receptor with constitutively high expression on Tregs that leads to IL2 depletion and the suppression of other IL2-dependent processes including proliferation. Additional roles of Tregs include the secretion of cytokines that inhibit proliferation and cytotoxic enzymes that induce apoptosis, depletion of adenosine triphosphate (ATP) that is necessary for proliferation, and endocytosis of the CD80/86 ligands that are needed as a costimulatory signal for T cell activation and proliferation.[18]

IMMUNOSUPPRESSIVE AGENTS

The pharmacotherapies (Table 1) available for preventing organ rejection are primarily focused on altering the adaptive immune response by interfering with one of the three signals of the alloimmune response to prevent T cell activation or proliferation at various steps (Figure 1).

1. Signal 1: Alloantigen recognition. MHC-bound alloantigen on APC interacts with TCR of the naïve T cells.
2. Signal 2: Costimulatory signals. Numerous signaling pathways have been identified. One of the important costimulatory signals for activation is the interaction of CD80/86 on APCs with CD28 on T cells.
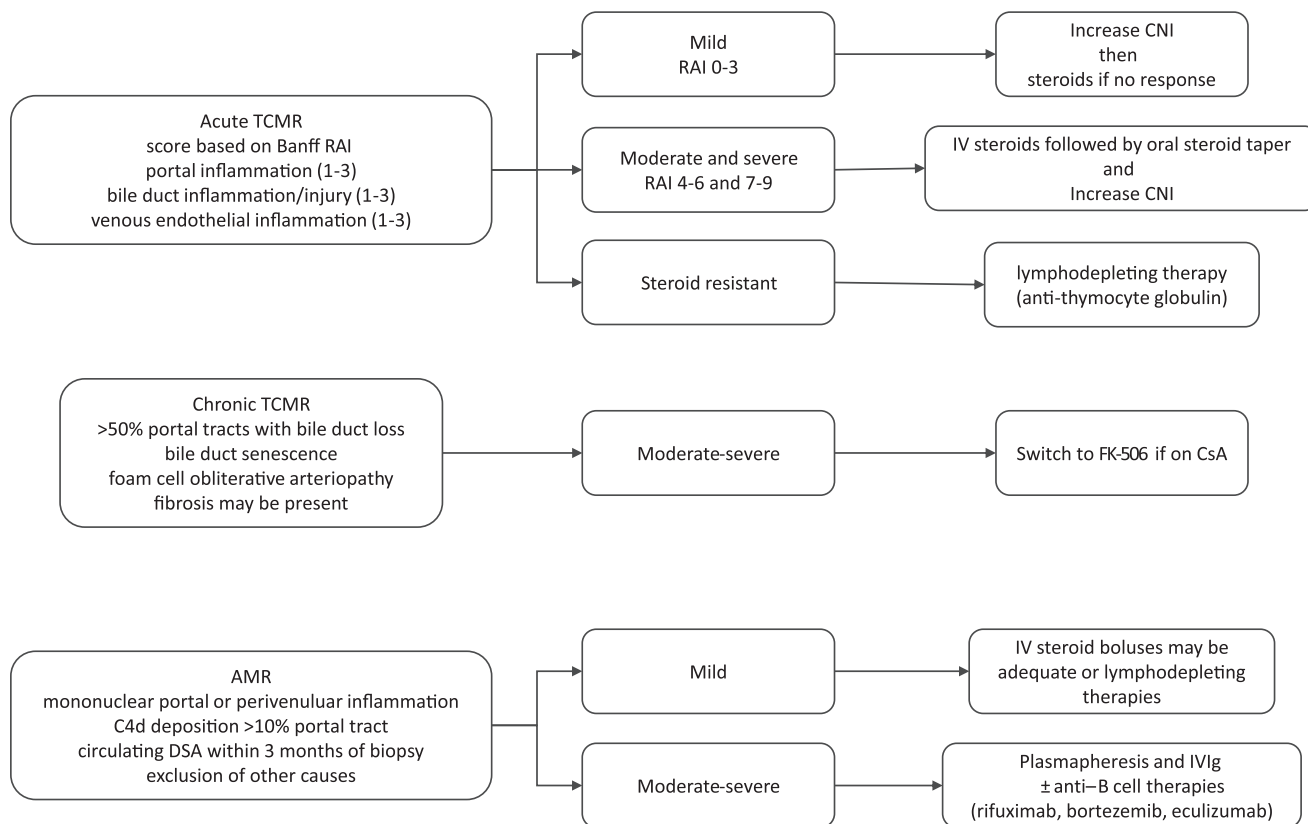
FIGURE 2 Management of rejection. Liver biopsy is required to make the diagnosis of any type of rejection. Severity of acute TCMR is stratified based on the Banff RAI.[8] Mild acute TCMR may respond to an increase in CNI goal levels or oral steroids if needed. Moderate and severe TCMR require treatment with IV steroids followed by a steroid taper alongside an increase in CNI goal levels. Steroid-resistant TCMR are treated with lymphodepleting antibody therapy. Management of chronic TCMR is difficult and often progresses with cholestasis and fibrosis despite treatment. Use of FK-506 is most ideal in these patients if not limited by adverse effects. For AMR, a diagnosis requires the presence of classic histologic features, C4d staining, circulating DSA, and exclusion of alternative causes. The goal of treatment for AMR is removal of the DSA.

Increased cytoplasmic calcium activates calcineurin, which then dephosphorylates and activates nuclear factor of activated T cells (NFAT). The activated NFAT then translocates into the nucleus and upregulates transcription of IL2 genes.

3. Signal 3: Cytokine-mediated differentiation and proliferation. One of the proinflammatory cytokines IL2 is a major growth factor necessary for proliferation and differentiation to effector cells. IL2 binds to IL2 receptor (CD25) on T cells and activates numerous signaling pathways that ultimately promote the mammalian target of rapamycin (mTOR) signal necessary for cell cycle progression alongside de novo purine synthesis.Strategies for induction therapy vary by transplant center and may include the use of corticosteroids or antibody therapies. Although induction therapy has not historically been standard protocol, its use has increased over time because of the increased number of patients with renal dysfunction at the time of transplant and the need to delay the introduction of calcineurin inhibitor (CNI) therapy.[19] Basiliximab is a monoclonal antibody against the IL2 receptor that blocks T cell proliferation by removing the necessary stimulating growth factor. Rabbit antithymocyte globulin is a polyclonal antibody to multiple antigen receptors on T cells that is prepared from the plasma of rabbits after immunizing them with human T cells. For this reason, there is a significant potential for infusion reactions, anaphylaxis, and serum sickness.

Since their introduction, CNIs have become the cornerstone for maintenance immunosuppression due to the marked improvements in graft and patient survival in comparison with other available immunosuppression medications.[20] The mTOR inhibitors or antiproliferative agents may be used with CNIs for synergistic effects in those with increased immunological risk, or they may be used to allow minimization of the CNI dose. The CNIs, cyclosporine A (CsA) and FK-506, form a complex with the cytoplasmic receptor proteins cyclophilin and FK506 binding protein (FKBP)–12, respectively. These complexes bind to and inhibit calcineurin activity, leading to an interference of Signal 2 by limiting the transcription of cytokines, most notably IL2, which are necessary for cell proliferation. Although the CNIs have similar mechanisms of action, FK-506 is the preferred agent because of the lower rates of TCMR, including steroid-

TABLE 1 Pharmacology of immunosuppressive medications

	Mechanism of action	Pharmacokinetics
Corticosteroids		
Methylprednisolone (Solumedrol) Prednisone (Deltasone)	Inhibits cytokine production by T cells and APCs, suppresses migration of leukocytes, and suppresses antibody and complement binding	Metabolism: active metabolite prednisolone Half life: 2–4 h Excretion: urine
Antibody therapies		
Basiliximab (Simulect)	Monoclonal antibody to CD25 (IL2 receptor alpha chain)	Half life: 7.2 days
Rabbit antithymocyte globulin (Thymoglobulin)	Polyclonal antibody with multiple antigen receptors on T cells	Half life: 2–3 days
CNIs		
CsA (modified: Neoral, Gengraf; nonmodified: Sandimmune)	Forms a complex with cyclophilin → binds to and inhibits calcineurin → blocks translocation of NFAT to the nucleus → decreased production of IL2 and other cytokines → inhibits activation of T cells that are dependent on IL2	Metabolism: CYP3A4/5 Half life: 5–18 h (modified) 10–27 h (nonmodified) Excretion: biliary via P-gp
FK-506 (IR: Prograf; ER: Envarsus)	Forms a complex with FKBP-12 → binds to and inhibits calcineurin → blocks translocation of NFAT to the nucleus → decreased production of IL2 and other cytokines → inhibits activation of T cells that are dependent on IL2	Metabolism: CYP3A4/5 Half life: 11.5 h (IR) 23–39 h (ER) Excretion: biliary via P-gp 100 times more potent than CsA
mTOR inhibitors		
Sirolimus (Rapamune)	Forms a complex with FKBP-12 → binds to mTOR and inhibits its activity → prevents transduction signal mediated by IL2 to direct cell proliferation	Metabolism: CYP3A4/5 Half life: 46–78 h Excretion: biliary via P-gp
Everolimus (Zortress)	Forms a complex with FKBP-12 → binds to mTOR and inhibits its activity → prevents transduction signal mediated by IL2 to direct cell proliferation	Metabolism: CYP3A4/5 Half life: 30 h Excretion: biliary via P-gp
Antiproliferative agents		
MPA prodrugs (mycophenolate mofetil: Cellcept; mycophenolate sodium: Myfortic)	Inhibits IMPDH → inhibits de novo purine synthesis needed for lymphocyte proliferation	Metabolism: hydrolyzed to free MPA (active metabolite), conjugated by glucuronyl transferase Half life: 18 h Excretion: urine
Azathioprine (Imuran)	Converted to 6-MP and 6-TG → inhibits IMPDH → inhibits de novo purine synthesis needed for lymphocyte proliferation	Metabolism: metabolized to 6-MP, deactivated by xanthine oxidase Half life: 3–5 h Excretion: urine

Abbreviations: APC, antigen presenting cell; CNI, calcineurin inhibitor; CsA, cyclosporine A; CYP, cytochrome P540; ER, extended release; FK-506, tacrolimus; FKBP-12, FK506 binding protein 12; IL2, interleukin 2; IR, immediate release; IMDPH, inosine monophosphate dehydrogenase; MP, mercaptopurine; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T cells; P-gp, P-glycoprotein; TG, thioguanine.

resistant rejection, when compared with CsA.[21] Although CNIs are superior to the other maintenance immunosuppressive agents at preventing rejection, they also have notable adverse effects. For instance, the CNIs stimulate endothelin and transforming growth factor β, which contribute to the nephrotoxic effects and may also drive tumorigenic properties.[22]

The mTOR inhibitors, sirolimus and everolimus, form a complex with FKBP-12 that binds to mTOR and halts cell-cycle progression. Although they bind the same protein as FK-506, the formed complex does not block calcineurin. Blocking mTOR inhibits vascular endothelial growth factor expression and angiogenesis needed for wound healing. Thus, mTOR inhibitors should be avoided after transplant until all surgical wounds have healed. The antiproliferative effects may also provide antineoplastic benefits. Everolimus used in conjugation with reduced FK-506 early after transplant leads to superior renal function without compromising immune control.[23]

The antimetabolites include azathioprine and the mycophenolic acid (MPA) prodrugs, mycophenolate mofetil (MMF) and mycophenolate sodium. They

TABLE 2 Adverse effects of the maintenance immunosuppressive medications

	FK-506	CsA	mTOR inhibitors	MPA	Azathioprine	Corticosteroids
Nephrotoxicity	++ Hyperkalemia Hypomagnesemia	++ Hyperkalemia Hypomagnesemia	+ Proteinuria	−	−	−
Diabetes mellitus	++	+	−	−	−	++
Dyslipidemia	+	+	++	−	−	+
Hypertension	++	++	+	−	−	+
Weight gain	+	+	−	−	−	++
Myelosuppression	+	+	++	++	++	−
Infection	+	+	+	+	+	+
Neurologic	++	+	−	−	−	+
Gastrointestinal	+	+	+	++	+	+
Osteoporosis	+	+	−	−	−	+
Impaired wound healing	−	−	++	−	−	+
Malignancy	+	+	−	+	+	−
Pregnancy class	C	C	C	D Teratogenic	D	C
Dermatologic	+ Hair loss	+ Hair growth Gingival hyperplasia	+ Rash Mouth ulcers	−	−	+ Hirsutism

Abbreviations: CsA, cyclosporine A; FK-506, tacrolimus; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin.

prevent lymphocyte proliferation by inhibiting de novo purine synthesis. Similar to mTOR inhibitors, the use of MPA allows for lower CNI dosing. Azathioprine is not often used in liver transplantation but may be selected to substitute MPA in pregnancy or in select cases of plasma-cell rich rejection. Whereas the nephroprotective benefit of using everolimus is limited to the first year after transplant, there is evidence showing improvement in renal function with the use of MMF and reduced CNI doses even beyond a year after transplant.[24]

Pharmacology and drug interactions

The CNIs and mTOR inhibitors are primarily metabolized by the cytochrome P540 (CYP) 3A4/5 pathways in the liver and intestine. Genetic polymorphisms in CYP3A4 and CYP3A5 affect the activity and metabolism of drugs that are dependent on this pathway for elimination.[25] Concomitant use with drugs or substances that induce or inhibit the enzymes can lead to decreased or increased immunosuppression concentrations, respectively.

The P-glycoprotein (P-gp)-1 pump is a membrane transporter that affects the absorption and excretion of medications.[25] On the apical membrane of the intestinal cells, P-gp can pump drugs back into the gut lumen before absorption across the basolateral membrane. Thus, drug bioavailability is affected by genetic polymorphisms of the ATP binding cassette subfamily B member 1 (*ABCB1*) gene that encodes P-gp. On the biliary epithelium, the pump is needed for the biliary excretion of medications and their metabolites. Similar to CYP3A, P-gp inducers or inhibitors of this pump can cause decreased or increased immunosuppression levels, respectively.

Although not an exhaustive list for all potential drug–drug interactions, the following lists provided by the US Food and Drug Administration include drugs that are categorized as strong or moderate CYP3A or P-gp inducers or inhibitors that affect levels of substrates such as CNI and mTOR inhibitors.[26]

Coadministration decreases levels of CNI and mTOR inhibitors:

- Anticonvulsants: phenytoin, carbamazepine, phenobarbital, primidone
- Antibiotics: rifampin
- Antivirals: efavirenz, etravirine
- Antineoplastics: apalutamide, enzalutamide, mitotane
- Others: St John's Wort, bosentanCoadministration increases levels of CNI and mTOR inhibitors:

- Macrolide antibiotics: clarithromycin, erythromycin, telithromycin
- Azole antifungals: fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
- Calcium channel blockers: diltiazem, verapamil
- Protease inhibitors: boceprevir, danoprevir, indinavir, lopinavir, nelfinavir, ombitasvir, paritaprevier, ritonavir, saquinavir, telaprevir, tipranavir

- Cardiac medications: amiodarone, dronedarone, propafenone, quinidine, ranolazine
- Antineoplastics: crizotinib, idelalisib, imatinib, lapatinib
- Psychiatrics: aprepitant, fluvoxamine, nefazodone, tofisopam
- Others: grapefruit juice, ciprofloxacin, conivaptan, CsA

Other common drug interactions include those that have the potential to work synergistically with the immunosuppressive agents to cause worsening of its adverse effects. These may include medications that cause nephrotoxicity, myelosuppression, hyperkalemia, or metabolic syndrome.

Immunosuppression regimens

Management of liver transplant patients requires balancing the need to prevent graft rejection while minimizing the extensive adverse effect profiles of the immunosuppressive agents (Table 2).[27] Tailoring the immunosuppression regimen to the individual patients takes into consideration the indication for transplantation, renal function, history of malignancy, and metabolic comorbidities.

Attempting immunosuppression minimization is recommended for all patients who have not had prior AMR, steroid-resistant TCMR, repeat transplantation, immune-mediated liver disease prior to transplant, or a dual-organ transplant. In the absence of high immunologic risk, conversion to monotherapy is ideal if possible. Steroids are rarely used beyond the first 3 months after transplant because of the significant adverse effect profile, and some centers may implement steroid-sparing induction regimens to avoid any steroid use. In patients who meet the criteria for management with CNI monotherapy, trough levels 3 months after transplant are 6–10 ng/ml for FK-506 and 150–200 ng/ml for CsA with slow tapering until 12 months after transplant at which time the goal trough levels are less than 5 ng/ml for FK-506 and 100 ng/ml for CsA.[14] Dual therapy with the addition of an mTOR inhibitor or MMF may be needed in patients at high immunologic risk or patients with renal dysfunction to accommodate lower CNI levels. In the appropriately selected candidate, monotherapy with mTOR inhibitor may be possible with trough levels 3–8 ng/ml.

KEY POINTS/TAKEAWAY FOR BOARDS

1. The immune system's response to organ transplantation is a complex interplay between the innate and adaptive immune systems. Targets for immunosuppressive therapies in liver transplantation focus on modulation of the adaptive immune system.
2. T cell activation requires antigen recognition presented by MHC molecules to TCR (Signal 1) and costimulatory signals (Signal 2), which is followed by T cell differentiation and proliferation (Signal 3).
3. Early TCMR is mediated by the direct allorecognition pathway that involves donor APCs, whereas late TCMR is mediated by the indirect or semidirect allorecognition pathway that is mediated by the recipient APCs.
4. AMR may result from preformed or de novo DSA. In liver transplantation, DSA to Class II HLA are more likely to be the culprit of injury in AMR.
5. Immune tolerance (normal graft function and liver histology without the use of immunosuppression) generally depends on the balance between regulatory and effector T cells and may be achieved in a select group of liver transplant recipients.
6. FK-506 is the preferred first-line agent for maintenance immunosuppression. Early reduction of FK-506 with the use of everolimus may lead to improved renal outcomes. Use of MMF with reduced FK-506 may continue to have improved renal outcomes beyond a year after transplant.
7. CYP3A4/5 and P-gp-1 inducers and inhibitors are the main causes for drug–drug interactions with the CNIs and mTOR inhibitors.

QUESTIONS

1. A 36-year-old man with a history of alcohol-related cirrhosis received a deceased donor liver transplant from an ABO-compatible donor. His postoperative course was unremarkable until Day 12, when aminotransferases began to rise. Liver biopsy showed features consistent with early T cell–mediated rejection. He was treated with intravenous (IV) solumedrol and increased tacrolimus goal levels. Liver enzymes start to rise again a week later, and the donor-specific antibodies are detected at high titers. What is the next best step?
   A. Repeat IV solumedrol boluses
   B. Add mycophenolate mofetil
   C. Start plasmapheresis and rituximab
   D. Review liver biopsy for signs of antibody-mediated rejection
   E. List for a repeat transplant

2. Which of the following immunosuppressive agents is least likely to contribute to the development of non-alcoholic related steatohepatitis after transplant?
   A. Tacrolimus
   B. Everolimus
   C. Mycophenolate mofetil
   D. Prednisone
   E. Cyclosporine

3. A 58-year-old woman with a history of alcohol-related cirrhosis underwent a transplant 3 months ago. She had hepatorenal syndrome prior to transplant but did not qualify for a simultaneous liver–kidney transplant. Her current glomerular filtration rate is 40 mL/min/1.73m^2. She is on a renal-sparing immunosuppressive protocol with tacrolimus and everolimus. She remains on prophylactic therapy with valganciclovir and trimethoprim/sulfamethoxazole. She presents suddenly to the emergency room with abdominal pain. Examination reveals an incarcerated hernia. Which of the following medication should be discontinued?

    A. Tacrolimus
    B. Everolimus
    C. Valganciclovir
    D. Trimethoprim/sulfamethoxazole
    E. None of the above

4. Which of the following will increase tacrolimus concentrations?

    A. CYP3A4 inhibitor
    B. CYP3A4 inducer
    C. P-gp inhibitor
    D. P-gp inducer
    E. 1 and 3
    F. 1 and 4

CONFLICT OF INTEREST

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