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Liver transplantation in adults: Initial and maintenance immunosuppression

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INTRODUCTION

For liver transplant recipients, the goal of immunosuppression is to reduce the risk of graft rejection while minimizing the risk of recurrent liver disease and adverse effects related to immunosuppression (eg, infection). Immunosuppressive agents are initiated at the time of transplant and continued long-term as maintenance therapy. In most liver transplant centers, tacrolimus is the cornerstone of long-term immunosuppression, but the availability of alternative therapies allows for customizing the drug regimen.

This topic will discuss initiating immunosuppression following liver transplantation and maintaining long-term immunosuppressive therapy.

The following transplant issues are discussed separately:

- Diagnosis and treatment of acute T-cell mediated (cellular) rejection. (See "Liver transplantation in adults: Clinical manifestations and diagnosis of acute T-cell mediated (cellular) rejection of the liver allograft" and "Liver transplantation in adults: Treatment of acute T cell-mediated (cellular) rejection of the liver allograft".)

- Long-term management of liver transplant recipients including health maintenance and complications of immunosuppression. (See "Liver transplantation in adults: Long-term management of transplant recipients".)

- Infectious complications following liver transplantation. (See "Infectious complications in liver transplantation".)

PATHOPHYSIOLOGY OF ACUTE REJECTION

Organ rejection is a multistep process that includes the following (figure 1 and   figure 2):

- **Signal I: Alloantigen recognition** – Alloantigen recognition requires presentation of a foreign alloantigen along with a host major histocompatibility complex (MHC) molecule. Presentation is done by an antigen-presenting cell (APC). The antigen, bound to an MHC molecule, binds to the T-cell receptor. This is the first of three signals that are required for T-cell maturation and can be aborted by antilymphocyte antibodies.

- **Signal II: Lymphocyte activation (costimulation)** – T-cell activation requires costimulation, a process in which a number of ligands on the APC bind to a variety of T-cell receptors, including CD28, CD154, CD2, CD11a, and CD54. The T-cell receptor complex is internalized and binds to immunophilin. Immunophilin stimulates calcineurin, which activates nuclear factor of T-cell activation (NFAT) by removing pyrophosphate. The activated NFAT then translocates to the nucleus where it drives transcription of interleukin (IL)-2 and other cytokines. Two immunophilin targets, cyclophilin and FK-binding protein, are targets of cyclosporine and tacrolimus, respectively. Both agents block calcineurin and are known collectively as calcineurin inhibitors. (See 'Calcineurin inhibitors' below.)

- **Signal III: Clonal expansion** – Newly synthesized IL-2 is secreted by T cells and binds to IL-2 receptors on the cell surface in an autocrine fashion, stimulating a burst of cell proliferation. Basiliximab, a monoclonal antibody against the IL-2 receptor, blocks this signal. Sirolimus, which binds to the downstream mechanistic target of rapamycin (mTOR), also acts at this step. Finally, the proliferation burst can be inhibited at the level of DNA synthesis by azathioprine and mycophenolate. (See 'Alternatives to systemic glucocorticoids' below and 'Use of mechanistic target of rapamycin (mTOR) inhibitors' below.)

- **Graft inflammation** – T-cell proliferation is associated with cell-mediated cytotoxicity and secretion of cytokines, chemokines, and adhesion molecules. The secreted mediators recruit additional inflammatory cells to the graft. The result is an inflammatory milieu with additional toxic and vasoactive mediators. Glucocorticoids and anti-thymocyte globulin are therapies that inhibit this step. (See 'Glucocorticoids' below and "Liver transplantation in

adults: Treatment of acute T cell-mediated (cellular) rejection of the liver allograft", section on 'Therapy for nonresponders'.)

GENERAL PRINCIPLES

Goals — All liver transplant recipients receive immunosuppression following transplantation. The goal of immunosuppression is to lower the risk of rejection, while minimizing the risk of adverse drug effects and recurrent liver disease.

Transplant expertise — Multiple specialists are involved in the care of liver transplant recipients immediately after transplant (eg, transplant surgeon, transplant hepatologist, clinical pharmacist). After several months, the transplant center typically continues to manage the immunosuppressive agents, treat recurrent liver disease, and manage biliary complications. In addition, the transplant center may also manage adverse effects related to immunosuppression (eg, kidney disease).

Drug interactions — Some immunosuppressive agents have drug interactions that may necessitate dose adjustments (table 1). Both calcineurin inhibitors (CNIs) and mechanistic target of rapamycin (mTOR) inhibitors are metabolized by CYP3A4, a member of the cytochrome P450 enzyme system. This creates the potential for other drugs metabolized by CYP34A to cause drug-drug interactions that may result in toxic or subtherapeutic drug levels that are associated with increased risk of rejection. As examples, antifungal agents and some antibiotics inhibit CYP3A4 (table 2).

Consultation with a clinical pharmacist may help with identifying and managing interactions through dose adjustments. For more information on potential drug-drug interactions, refer to the Lexicomp drug interactions program within UpToDate.

INITIAL THERAPY

General approach — For most liver transplant recipients, the immunosuppressive regimen is center-specific and informed by the drug's mechanism of action, the available published evidence, and clinical experience.

We typically use an initial regimen consisting of triple immunosuppression with the following agents [1]:

- A glucocorticoid (see 'Glucocorticoids' below)

- A calcineurin inhibitor (CNI; usually tacrolimus) (see 'Calcineurin inhibitors' below)

- An antimetabolite (usually mycophenolate) (see 'Antimetabolite agents' below)

We maximize the level of immunosuppression in the early post-transplant period (ie, during the first three months post-transplant) when the risk of rejection is greatest. As an example, we administer a glucocorticoid intravenously immediately post-transplant and continue it for several days until transitioning to an oral glucocorticoid that is then gradually tapered over the next several weeks to months.

We use drug trough levels to titrate the dose of some immunosuppressive agents (eg, CNIs). We target higher drug levels earlier in the post-transplant course. As the duration of time after transplant increases, we aim for lower drug levels in patients without acute T-cell mediated (cellular) rejection. (See "Liver transplantation in adults: Clinical manifestations and diagnosis of acute T-cell mediated (cellular) rejection of the liver allograft".)

In general, all liver transplant recipients receive lifelong immunosuppression because the lack of immunosuppression routinely results in graft rejection and graft loss. To transition from the initial to a long-term maintenance regimen, we typically reduce the doses of the immunosuppressants. (See 'Maintenance therapy' below.)

For most recipients, we do not include an mTOR inhibitor as part of the long-term immunosuppressive regimen. However, we may use an mTOR inhibitor as an alternative agent for selected patients (eg, those intolerant of CNIs due to toxicity). (See 'When and how to modify maintentance therapy' below.)

Glucocorticoids — Systemic glucocorticoids are the cornerstone of the initial immunosuppressive regimen after transplant because they suppress antibody and complement binding, upregulate expression of interleukin (IL)-10, and downregulate T cell synthesis of IL-2, IL-6, and interferon-gamma [2-4].

 Dosing and administration — Glucocorticoid regimens vary among transplant centers, and consensus on dosing is lacking. We administer methylprednisolone in a bolus dose beginning with 1000 mg intravenously intraoperatively, followed by four days of gradually decreasing the methylprednisolone dose, and then transitioning to oral prednisone. We then gradually taper the prednisone dose with the goal of discontinuing it by approximately six months posttransplant.

An example of a glucocorticoid dosing protocol following liver transplantation is provided in the table (table 3).

Some transplant centers administer higher doses of glucocorticoids during the first four days post-transplant, followed by a more rapid glucocorticoid taper to achieve a prednisone dose of 5 mg daily by one-month post-transplant. Beginning at 6 to 12 months post-transplant, prednisone is then slowly tapered by reducing the dose in 1 mg increments every 1 to 2 months until it is discontinued. Based on clinical experience, a slow, gradual glucocorticoid taper lowers the risk of acute cellular rejection or an underlying disease flare (eg, autoimmune hepatitis).

Alternatively, some centers may continue a low-dose oral glucocorticoid indefinitely (eg, prednisone 5 mg daily).

Managing glucocorticoid-related toxicity — A major complication of glucocorticoids is increased susceptibility to infection, especially oral candidiasis, cytomegalovirus (CMV), *Aspergillus*, *Pneumocystis jirovecii* (previously referred to as *P. carinii*), and bacterial pathogens [5]. Other potential problems include impaired wound healing, hyperglycemia, hypertension, peptic ulcer disease, psychiatric conditions (eg, depression), visual changes, and osteopenia. (See "Major side effects of systemic glucocorticoids".)

The approach to managing glucocorticoid-related toxicity includes monitoring blood glucose levels and infection prophylaxis, and these issues are discussed separately. (See "Liver transplantation in adults: Treatment of acute T cell-mediated (cellular) rejection of the liver allograft", section on 'Managing glucocorticoid-related toxicity' and "Infectious complications in liver transplantation".)

Whether the benefits of withdrawing glucocorticoids outweigh the potential risks is uncertain. Thus, the decision to withdraw glucocorticoids is informed by patient characteristics (eg, risk factors for graft rejection) as well as transplant center-specific protocols. In a meta-analysis of 16 trials comparing early glucocorticoid avoidance or withdrawal with glucocorticoid-containing immunosuppression in 1347 liver transplant recipients, there were no statistically significant differences in rates of mortality, graft loss, or infections between the groups [6]. Glucocorticoid avoidance or withdrawal was associated with increased risk of acute cellular rejection (relative risk [RR] 1.33, 95% CI 1.08-1.64) and glucocorticoid-resistant rejection (RR 2.14, 95% CI 1.13-4.02). However, glucocorticoid avoidance or withdrawal was associated with lower risks of diabetes mellitus (RR 0.81, 95% CI 0.66-0.99) and hypertension (RR 0.76, 95% CI 0.65-0.90).

Alternatives to systemic glucocorticoids — Although initial immunosuppressive therapy after liver transplant typically includes systemic glucocorticoids, other agents are available for patients intolerant of glucocorticoids:

- **Monoclonal antibodies** – Monoclonal antibodies against specific cell surface proteins such as the IL-2 receptor are not typically used as first-line immunosuppressive agents in

liver transplantation. However, they have important roles as glucocorticoid- or CNI-sparing agents [7]. (See 'Alternatives to calcineurin inhibitors' below.)

Basiliximab is a monoclonal antibody against the IL-2 receptor on activated T cells. Blockade of the IL-2 receptor prevents T-cell proliferation.

For liver transplant recipients who do not tolerate glucocorticoids, we administer intravenous (IV) basiliximab 20 mg, intraoperatively, and 20 mg on postoperative day 4. This regimen is similar to basiliximab use for inducing immunosuppression in kidney transplant recipients. (See "Kidney transplantation in adults: Induction immunosuppressive therapy", section on 'Basiliximab'.)

- Budesonide – Budesonide is a glucocorticoid with limited systemic effects because of high first-pass hepatic extraction from portal venous blood. We do not use budesonide for initial immunosuppression because data from clinical studies are limited and because its modest serum concentrations are less effective for downregulating effector T cells in peripheral lymph nodes [8,9]. In a study comparing a budesonide-based regimen in 20 liver transplant recipients with a prednisone-based regimen in recipients who were matched for age, sex, autoimmune liver disease and use of anti-thymocyte globulin, budesonide was associated with lower rates of new-onset diabetes mellitus (0 versus 15 percent) and infection (0 versus 30 percent) at six months after transplant [9]. (See "Overview of budesonide therapy for adults with inflammatory bowel disease", section on 'Pharmacology'.)

Calcineurin inhibitors — For most liver transplant recipients, CNI therapy is initiated postoperatively and continued as the cornerstone of long-term maintenance therapy. We typically use tacrolimus as the first-line CNI because studies demonstrated that tacrolimus resulted in lower risk of acute cellular rejection and mortality compared with cyclosporine [10-14]. Tacrolimus is better tolerated overall and does not lower mycophenolate levels, although tacrolimus has been associated with higher rates of new onset diabetes mellitus. In a meta-analysis of 16 trials including 3813 liver transplant recipients, tacrolimus resulted in lower risk of mortality and graft loss in the first year post-transplant compared with cyclosporine (RR 0.85, 95% CI 0.73-0.99 and RR 0.73, 95% CI 0.61-0.86, respectively) [10]. However, the risk of new onset diabetes mellitus was higher with tacrolimus (RR 1.38, 95% CI 1.01-1.86).

CNIs selectively inhibit calcineurin, thereby impairing the transcription of the T cell mitogen IL-2 and other cytokines. By inhibiting cytokine gene transcription, CNIs suppress effector T cell proliferation and T cell-dependent B cell activation. (See "Kidney transplantation in adults: Maintenance immunosuppressive therapy".)

Tacrolimus (commonly-used)

Pharmacology — Tacrolimus inhibits IL-2 and interferon-gamma production and is 100 times more potent than cyclosporine. Oral bioavailability varies widely (5 to 67 percent), and an oral dose of 0.15 mg/kg results in a peak drug concentration of 0.4 to 3.7 ng/mL. Tacrolimus is metabolized in the liver by CYP3A4 and is not removed by dialysis. (See "Pharmacology of cyclosporine and tacrolimus", section on 'Mechanism of action'.)

Dosing and administration — There is wide variation in dosing between centers, although for most patients the recipient's kidney function informs the timing and dosing of initial tacrolimus therapy:

- No kidney impairment – We typically start with a low dose of 2 mg by mouth every 12 hours on postoperative day 1 and adjust the dosing to achieve a trough level of 8 to 12 ng/mL by the end of the first week post-transplant.

- Kidney impairment – For patients who meet criteria for perioperative acute kidney injury (table 4) and/or chronic kidney disease (table 5) and who did not receive a combined liver-kidney transplant, we either delay initiation of tacrolimus until at least postoperative day 2 or use an alternative agent such as basiliximab. (See 'Alternatives to systemic glucocorticoids' above and "Definition and staging criteria of acute kidney injury in adults" and "Definition and staging of chronic kidney disease in adults".)

  For patients with kidney impairment who are starting tacrolimus, we begin with 2 mg every 12 hours and adjust the dosing to achieve a lower target trough level of ≤8 ng/mL until their kidney injury improves.

For all patients, we typically obtain drug trough levels daily during the post-transplant hospitalization (table 6), and subsequent monitoring is discussed below. (See 'Monitoring' below.)

Observational data suggested that achieving target tacrolimus trough levels in the early post-transplant period was associated with improved outcomes. In a study of 493 liver transplantation recipients who were treated with tacrolimus as their primary immunosuppressive agent, a tacrolimus level >7 ng/mL at the time of a protocol liver biopsy (mean of six days after transplantation) was associated with lower rates of moderate or severe rejection compared with drug levels <7 ng/mL (24 versus 41 percent) [15]. Compared with achieving tacrolimus trough levels between 7 and 10 ng/mL within 15 days after transplant, trough levels outside the target range were associated with higher risk of graft loss after a

median follow-up of seven years (trough level <7 ng/mL: RR 2.32, 95% CI 1.28-4.16, and trough level 10 to 15 ng/mL: RR 2.17, 95% CI 1.16-4.03).

Cyclosporine — Cyclosporine is an alternative CNI for patients who have experienced or are at risk for tacrolimus-associated toxicity. (See 'Calcineurin inhibitor (CNI)-related toxicity' below.)

Pharmacology — Cyclosporine, a peptide derived from the fungus *Cylindrocarpon lucidum*, is a potent immunosuppressive agent [16]. It inhibits T-cell activation by binding intracellular cyclophilin, thus reducing calcineurin activation. Without calcineurin, the nuclear factor of activated T cells (NFAT) does not translocate to the nucleus and does not cause production of IL-2 and other cytokines. This markedly diminishes T-cell response to class I and class II antigens resulting in a significant reduction in rejection.

Formulations and dosing — Cyclosporine is available in modified and unmodified formulations (table 7). Modified cyclosporine is a microemulsion formulation that does not depend on bile salts for its absorption and, thus, has increased bioavailability and more consistent absorption. The microemulsion formulation is preferred for liver transplant recipients who may have alterations in production and delivery of bile salts into the gut due to biliary complications, drug-induced cholestasis, or acute cellular rejection.

The typical starting dose for microemulsion cyclosporine is 1 to 2 mg/kg every 12 hours. We typically obtain drug trough levels daily during the post-transplant hospitalization, and subsequent monitoring is discussed below. (See 'Monitoring' below.)

Because nonmodified oral cyclosporine depends upon bile salts for absorption, it has inconsistent bioavailability and gastrointestinal absorption patterns that limit its use. The formulations of cyclosporine are discussed in more detail separately. (See "Pharmacology of cyclosporine and tacrolimus", section on 'Cyclosporine'.)

Monitoring — The frequency of monitoring CNI trough levels varies depending on the duration of time post-transplant and transplant center protocol. We typically use the following monitoring schedule:

- Immediate post-transplant period of hospitalization: Daily CNI trough level

- Following hospital discharge until achieving target drug level with stable dose: Twice weekly CNI level

- After achieving stable dose: Weekly CNI levels for one month, then once monthly thereafter

In addition, we check drug levels if the transplant recipient develops an acute illness or starts a new medication with potential for interaction (table 1).

When measuring CNI levels, we also measure electrolytes, magnesium, and serum creatinine. We check blood pressure daily during hospitalization and with each outpatient follow-up visit.

The target trough levels vary among transplant center protocols and may be individualized based on etiology of liver disease (eg, targeting the lower end of the range for recipients with a nonimmune etiology such as those with nonalcohol-associated fatty liver disease, viral hepatitis, or alcohol-related liver disease):

- Tacrolimus – Target tacrolimus levels are listed in the table (table 6).

- Cyclosporine – During the first three to six months after transplantation, target cyclosporine trough levels range from 200 to 250 ng/mL. Between 6 and 12 months post-transplant, target trough levels range from 80 to 120 ng/mL.

Monitoring drug trough levels facilitates the goal of using the least amount of immunosuppression that prevents rejection but also minimizes the risk of long-term dose-related complications of CNIs, including kidney toxicity, hypertension, and post-transplant lymphoproliferative disorders (PTLD). (See 'Adverse effects' below and "Pharmacology of cyclosporine and tacrolimus", section on 'Side effects'.)

Adverse effects — The side effects of tacrolimus and cyclosporine are generally similar and include nephrotoxicity, hypertension, hyperkalemia, hypomagnesemia, and neurologic toxicity.

For patients on CNI therapy, we avoid potassium-sparing diuretics (eg, spironolactone, amiloride) and any potentially nephrotoxic drugs (table 1). For more detailed information on potential drug-drug interactions, refer to the Lexicomp drug interactions program.

Neurologic toxicity may include altered mental status, polyneuropathy, dysarthria, myoclonus, seizures, hallucinations, and cortical blindness [17]. Other adverse effects include hyperlipidemia, gingival hyperplasia, and hirsutism.

Nephrotoxicity and other adverse effects related to CNIs are discussed in more detail separately:

- (See "Cyclosporine and tacrolimus nephrotoxicity".)
- (See "Kidney function and non-kidney solid organ transplantation", section on 'Liver transplantation'.)
- (See "Pharmacology of cyclosporine and tacrolimus", section on 'Side effects'.)

Alternatives to calcineurin inhibitors — For patients with pretransplant kidney disease in whom we wish to limit the use of CNIs, we generally use antibody preparations in the immediate post-transplant period. We use basiliximab, a IL-2 receptor inhibitor that reduces proliferation and maturation of activated T cells [7].

Dosing and administration for basiliximab in liver transplantation is based on dosing recommendations in kidney transplant recipients, and this is discussed separately. (See "Kidney transplantation in adults: Induction immunosuppressive therapy", section on 'Basiliximab' and 'Alternatives to systemic glucocorticoids' above.)

The use of IL-2 receptor inhibitors for initial immunosuppression in liver transplant recipients is supported by data from clinical trials and observational studies [7,18-21]. In a trial comparing an induction regimen of basiliximab, glucocorticoids, and mycophenolate with standard triple agent regimen (ie, glucocorticoid, tacrolimus, and mycophenolate) in 89 liver transplant recipients, there were no significant differences in patient survival, graft dysfunction, infection rate or type, or wound healing between regimens [21]. However, the rate of developing kidney impairment was lower with the regimen containing basiliximab (7 versus 19 percent).

Antimetabolite agents — Antimetabolite agents (eg, mycophenolate mofetil [MMF], mycophenolic sodium, azathioprine) inhibit the proliferation of T and B lymphocytes by interfering with DNA synthesis from nucleic acids. Antimetabolite agents may be used in combination with a CNI or as CNI- or glucocorticoid-sparing agents.

Although published evidence of superiority over azathioprine is lacking, MMF is the first-line antimetabolite agent in most liver transplant centers [22]. An important exception is that we do not use MMF or mycophenolate sodium in females of childbearing potential because of teratogenicity, unless they are on long-acting contraception, have undergone a surgical sterilization procedure, or have infertility. We use azathioprine in such patients because long-term safety data demonstrated that azathioprine does not have adverse effects on fertility or pregnancy outcomes. (See "Mycophenolate: Overview of use and adverse effects in the treatment of rheumatic diseases" and "Safety of rheumatic disease medication use during pregnancy and lactation".)

Mycophenolate (commonly-used) — Mycophenolate is widely used for preventing rejection in transplant recipients:

- **Pharmacology** – Mycophenolic acid (MPA) is produced by several species of the fungus *Penicillium*. While MPA is poorly absorbed, two oral prodrugs with superior gut absorption are available in the United States: the 2-morpholinoethyl ester, mycophenolate mofetil (MMF, CellCept), and mycophenolate sodium (Myfortic). Both drugs are converted to

antiproliferative MPA in the liver and eliminated predominantly by glucuronidation and urinary excretion [23].

MPA inhibits inosine monophosphate dehydrogenase (IMPDH), the rate limiting step in purine synthesis, preventing formation of guanosine monophosphate (GMP). Cells depleted of GMP cannot synthesize guanine triphosphate (GTP) or deoxy-guanine triphosphate (d-GTP) for DNA synthesis and, therefore, cannot replicate. Most mammalian cells can maintain GMP levels through the purine salvage pathway. However, lymphocytes lack a key enzyme of the guanine salvage pathway (hypoxanthine-guanine phosphoribosyltransferase) and cannot compensate for the MPA-induced block. As a result, MPA selectively inhibits the proliferation of both B and T lymphocytes [24].

- **Safety** – The most common adverse effects are bone marrow suppression and gastrointestinal symptoms, including abdominal pain, ileus, nausea, vomiting, and oral ulcerations. These symptoms are generally dose-related and improve with temporary or permanent dose reduction.

  Mycophenolate is not associated with either neurotoxicity or nephrotoxicity.

- **Dosing** – Typical dosing for MMF (Cellcept) is 1 g, orally, every 12 hours. Patients may tolerate the drug better when they initiate therapy with a dose of 250 to 500 mg every 12 hours and gradually increase to 1 g twice daily. Alternatively, MMF can be initially dosed at 500 mg four times daily. Mycophenolate sodium (Myfortic) is formulated as 360 mg tablets and is typically given as two tablets (720 mg) orally every 12 hours. Food may interfere with absorption of both drugs; thus, they should be taken one hour before or two hours after meals.

- **Monitoring** – We measure a complete blood count in one week after starting therapy to evaluate for cytopenia. If there is no evidence of bone marrow suppression, we measure a complete blood count every eight weeks. We do not use serum mycophenolate concentrations to guide dosing adjustments.

- **Efficacy** – The use of immunosuppression regimens containing mycophenolate is supported by clinical trials and observational studies [25-29]. In a trial including 565 liver transplant recipients, mycophenolate therapy resulted in lower rates of biopsy-proven acute rejection or graft loss at six months post-transplant compared with azathioprine (38.5 versus 47.7 percent) [29]. In a study including 30 adult liver transplant recipients who were treated with an immunosuppressive regimen of tacrolimus and mycophenolate, patient and graft survival rates after two years were 87 and 84 percent, respectively [30].

Data suggest that mycophenolate monotherapy may be an effective and safe maintenance regimen for selected recipients (eg, those with kidney impairment) [26,31,32]. In a trial comparing long-term MMF therapy alone with CNI-based immunosuppression in 150 liver transplant recipients, the rates of chronic rejection, patient survival, and graft survival were not significantly different after five years [31]. There was a nonsignificant trend toward higher rates of acute rejection with MMF alone (11 versus 3 percent), but all patients with acute rejection were successfully treated with glucocorticoid therapy. There were no significant differences between regimens in rates of *de novo* malignancy or other adverse cardiovascular, gastrointestinal, or neurologic effects. In a trial including 56 liver transplant recipients with CNI-related kidney injury, conversion to MMF monotherapy resulted in lower serum creatinine levels and improved glomerular filtration rates (GFR) after 12 months compared with CNI therapy [26].

Azathioprine — We use the antimetabolite azathioprine for patients who do not tolerate mycophenolate and for female patients who are pregnant or may become pregnant (ie, those without effective long-acting contraception, surgical sterilization, or infertility):

- **Pharmacology** – Azathioprine is a prodrug of 6-mercaptopurine, which is further metabolized into 6-thioguanine nucleotides (6-TGNs) that inhibit purine synthesis. By preventing *de novo* synthesis of purines, 6-mercaptopurine interferes with RNA and DNA synthesis required for replication of T and B cells.

- **Dosing** – Azathioprine is typically given at a dose of 1.5 to 2.0 mg/kg daily, up to a maximum dose of 200 mg daily [33]. Assessing thiopurine methyltransferase metabolite (TPMT) enzyme activity reduces the risk of toxicity associated with absence of TPMT. In addition, measuring levels of 6-TGNs can help optimize dosing of azathioprine. Pretreatment testing prior to azathioprine use is discussed in detail separately. (See "Thiopurines: Pretreatment testing and approach to therapeutic drug monitoring for adults with inflammatory bowel disease", section on 'Pretreatment evaluation'.)

- **Safety** – Adverse effects of azathioprine include bone marrow suppression, nausea, vomiting, pancreatitis, hepatotoxicity, and neoplasia. (See "Pharmacology and side effects of azathioprine when used in rheumatic diseases", section on 'Adverse effects'.)

  Azathioprine has been used safely during pregnancy. (See 'Pregnancy and lactation' below.)

  Monitoring – The approach to laboratory and therapeutic drug monitoring with azathioprine therapy is discussed in detail separately. (See "Thiopurines: Pretreatment testing and approach to therapeutic drug monitoring for adults with inflammatory bowel

disease", section on 'Routine laboratory monitoring' and "Thiopurines: Pretreatment testing and approach to therapeutic drug monitoring for adults with inflammatory bowel disease", section on 'Therapeutic drug monitoring'.)

- **Efficacy** – Historically, azathioprine was used for immunosuppression in liver transplant recipients; however, data from randomized trials to support its efficacy are lacking.

Investigational therapies — Other therapies have been examined for initial immunosuppression, but none has been sufficiently studied to be recommended for use:

- Rabbit anti-thymocyte globulin – Rabbit anti-thymocyte globulin (rATG) has been studied in liver transplant recipients in order to delay initiation of CNIs and potentially preserve kidney function. In a trial including 55 liver transplant recipients that compared rATG induction therapy plus initiating tacrolimus on postoperative day 10 with a standard tacrolimus regimen that was initiated on postoperative day 2, there were no significant differences in estimated glomerular filtration rate (GFR), biopsy-proven acute rejection, or infections between groups [34].

MAINTENANCE THERAPY

General approach — Beyond the initial period of three months post-transplant, the risk of complications related to intensive immunosuppression outweighs the benefit because the risk of graft rejection decreases over time [35,36]. For most recipients with stable graft function and normal liver enzymes, lower doses of immunosuppressive agents are generally well tolerated. Factors informing individualized medication adjustments include the etiology of primary liver disease, recipient characteristics such as kidney function, time from transplant, center-specific protocols, and achieving CNI target trough levels.

As an example, an initial regimen consisting of a glucocorticoid, tacrolimus, and mycophenolate in a recipient who has stable graft function and no kidney disease is gradually transitioned to a maintenance regimen by continuing the gradual glucocorticoid taper, titrating the tacrolimus dose to a lower drug level range (table 6), and continuing mycophenolate at the fixed dose. The maintenance regimen is usually achieved within six months post-transplant. (See 'Glucocorticoids' above and 'Calcineurin inhibitors' above.)

If liver enzymes begin to rise with dose and/or regimen adjustments, we return to the previously successful dose or regimen of immunosuppression. If the liver enzymes remain elevated, we obtain a liver biopsy to assess for features of acute cellular rejection or other cause

of inflammation. (See "Liver transplantation in adults: Clinical manifestations and diagnosis of acute T-cell mediated (cellular) rejection of the liver allograft".)

Duration of therapy — In general, liver transplant recipients receive lifelong immunosuppression because of the increased risk of rejection and graft loss after discontinuing immunosuppression.

Some center-specific protocols for recipients transplanted for autoimmune liver disease use higher CNI trough levels, dual therapy with an antimetabolite, and/or maintenance glucocorticoid therapy to prevent rejection and recurrent autoimmune liver disease. However, data from a meta-analysis of two observational studies did not support long-term use of glucocorticoids to prevent rejection, graft loss, or patient mortality related to recurrent autoimmune hepatitis [37]. (See 'Calcineurin inhibitors' above.)

Some data suggest that a few, highly selected recipients develop immune tolerance to the graft, usually after a prolonged, stable period (ie, years) of immunosuppression. These recipients may tolerate withdrawal of immunosuppression without developing rejection [38-40]. In contrast, there have been unpublished case reports of graft rejection and patient mortality among recipients who stopped immunosuppression without medical supervision, despite having stable graft function for many years post-transplant.

Preliminary studies suggest that gradually weaning and discontinuing immunosuppression may be possible for a group of carefully selected liver transplant recipients [39,40]. In a study including 77 liver transplant recipients who met specific criteria (ie, history of either hepatitis C virus or nonimmune, nonviral liver disease; use of single-drug immunosuppression at one to two years post-transplant; stable kidney function; and absence of rejection on liver biopsy), gradual, systematic reduction of immunosuppression resulted in immunosuppressive doses of <50 percent of baseline doses in 52 recipients (68 percent) and complete withdrawal of immunosuppression for ≥1 year in 10 recipients (13 percent) [40]. However, attempts to discontinue long-term immunosuppression outside well-established protocols should be avoided until methods to select patients with graft immune tolerance are developed and validated.

Studies of biomarkers may lead to the ability to predict whether a recipient is likely to develop immune tolerance and can tolerate withdrawal of immunosuppression; however, specific predictive models are not yet available.

WHEN AND HOW TO MODIFY MAINTENANCE THERAPY

In most liver transplant recipients, a stable maintenance immunosuppressive regimen is established within six months after transplantation. However, some recipients may require modification of the maintenance regimen due to complications, such as drug toxicity, acute cellular rejection, infection, or other clinical event, such as pregnancy or surgery. We discuss these special patient populations below.

It is important to emphasize that adjustments to the immunosuppressive regimen should be made in consultation with the recipient's transplant team.

Calcineurin inhibitor (CNI)-related toxicity — Although CNIs are the cornerstone of maintenance immunosuppression in liver transplantation, some recipients do not tolerate these agents due to kidney injury or other adverse effects (eg, neurotoxicity, leukopenia). The risk of post-transplant kidney injury has been exacerbated by the MELD-based organ allocation system, which favors recipients with higher serum creatinine levels indicative of acute and/or chronic kidney injury. (See "Model for End-stage Liver Disease (MELD)".)

Modifying the existing regimen — Selecting a strategy to minimize the use of CNIs is based on the available published data, transplant center-specific protocols, clinical experience, and type and severity of CNI-related adverse effects [41] (see 'Use of mechanistic target of rapamycin (mTOR) inhibitors' below):

- For patients with CNI-related kidney toxicity, we either lower the CNI dose and initiate a mechanistic target of rapamycin (mTOR) inhibitor or substitute an mTOR inhibitor for the CNI. The use of an mTOR inhibitor is supported by a pooled analysis of two trials including 772 liver transplant recipients that compared a regimen of everolimus plus lower dose tacrolimus (target level 3 to 5 ng/mL) with standard dose CNI therapy [42]. After 24 months, the everolimus-based regimen resulted in better kidney function, and there were no significant differences in rates of acute rejection, graft loss, or mortality between the groups.

- For patients with non-kidney-related adverse effects that can be attributed to CNI therapy, our approach takes into account the severity and timing of the adverse effects. As an example, if a patient experiences a severe adverse event such as seizure activity related to tacrolimus (despite achieving target trough levels), we discontinue tacrolimus. After seizure prophylaxis has been given, we may either reintroduce tacrolimus at a lower dose or switch to cyclosporine. For patients with less severe side effects (eg, nausea), we reduce the CNI dose by 25 to 50 percent.

The optimal timing for initiating mTOR inhibitor therapy and reducing the dose or withdrawing the CNI is uncertain. However, we do not initiate mTOR inhibitors prior to postoperative day 30

after transplantation because of increased risk of hepatic artery thrombosis and poor wound healing in the early post-transplant period [43]. (See 'Use of mechanistic target of rapamycin (mTOR) inhibitors' below.)

Use of mechanistic target of rapamycin (mTOR) inhibitors — The mTOR inhibitors used in liver transplantation include everolimus and sirolimus. Although mTOR inhibitors facilitate dose reduction or discontinuation of CNIs, mTOR inhibitors are associated with adverse events such as bone marrow suppression and poor wound healing [44-50]. As a result, mTOR inhibitors are used as second-line immunosuppressive agents. (See 'Modifying the existing regimen' above.)

In addition, we generally do not initiate mTOR inhibitors earlier than 30 days post-transplant because of an increased risk of hepatic artery thrombosis and wound healing complications in the postoperative period [50,51]. The pharmacology, formulations, dosing, pharmacokinetics, drug interactions, and adverse effects associated with mTOR inhibitors are discussed in detail separately. (See "Pharmacology of mammalian (mechanistic) target of rapamycin (mTOR) inhibitors".)

Issues related to mTOR inhibitors in liver transplant recipients are summarized as follows [44,52]:

- **Pharmacology** – mTOR inhibitors bind to the FK binding protein and presumably modulate the activity of intracellular mTOR to inhibit IL-2-mediated signal transduction necessary for proliferation of activated T- and B-cells. mTOR inhibitors are metabolized by CYP3A4, 3A5, and 2C8. As a result, there are risks of drug interactions with azoles, macrolides, antiepileptic agents, antiviral agents, and grapefruit juice (table 1).

- **Dosing** – For liver transplant recipients who are converting from a CNI to mTOR inhibitor monotherapy, most transplant centers use everolimus with initial dosing of 1 mg twice daily and a target trough level of 6 ng/mL [53]. An alternative option is sirolimus with initial dosing of 1 to 2 mg daily and target trough level of 8 to 12 ng/mL.

- **Monitoring** – We monitor complete blood count, electrolytes, kidney function, glucose, and liver enzymes once a month. We check spot urine protein-to-creatinine ratio (calculator 1) at baseline, one month, six months, one year, and once yearly thereafter. We measure fasting lipids at baseline, at every three months for the first year, and then twice a year. We discontinue the mTOR inhibitor if the patient develops nephrotic range proteinuria (ie, protein excretion >3.5 g/24 hours) and/or severe hypertriglyceridemia (serum triglyceride level >500 mg/dL).

- **Adverse effects** – The adverse effects of mTOR inhibitors have contributed to their positioning as second-line immunosuppressive agents [44-50].

  We avoid the use of mTOR inhibitors during the first 30 days after liver transplant because in the postoperative period mTOR inhibitors have been associated with hepatic artery thrombosis, delayed wound healing with incisional hernias, and graft loss [50].

  Long-term adverse effects of mTOR inhibitors include hyperlipidemia, bone marrow suppression, mouth ulcers, skin rash, albuminuria, and pneumonia.

  The dose-dependent nature of side effects of mTOR inhibitors is discussed separately. (See "Pharmacology of mammalian (mechanistic) target of rapamycin (mTOR) inhibitors", section on 'Adverse effects'.)

- **Efficacy** – The beneficial effect of mTOR inhibitors on kidney function is supported by some clinical trials and observational studies, but the risk of adverse events remains a concern [51,54-61]. Overall, none of the studies have shown improvement in patient or graft survival with regimens that included mTOR inhibitors. In a trial including 188 liver transplant recipients who initially received basiliximab induction therapy and mycophenolate, patients were randomly assigned at four weeks post-transplant to receive either everolimus plus tapering doses of tacrolimus until discontinuation or a standard-dose tacrolimus regimen. After 24 weeks, the everolimus-based regimen resulted in improvement in estimated glomerular filtration rate (1.1 mL/min/1.73 m^2 versus -13.3 mL/min/1.73 m^2) [51]. However, rates of biopsy-proven acute rejection were higher with the everolimus regimen (10 versus 2 percent). In a study including 140 liver transplant recipients, introducing everolimus in the early postoperative period (day 8) plus minimizing tacrolimus use was associated with higher rates of wound healing complications at three months compared with a standard dose tacrolimus-based regimen (18 versus 0 percent) [55].

  The timing of initiating mTOR inhibitors has also been linked to changes in recipient's kidney function. In a study including 1045 recipients who were switched from tacrolimus to everolimus, initiating everolimus at >12 months post-transplant was associated with lower rates of improved kidney function at 36 months compared with initiating everolimus within three months (21 versus 55 percent) [56]. These data may suggest that CNI-induced kidney disease is more reversible in its earlier stages. (See "Kidney transplantation in adults: Maintenance immunosuppressive therapy".)

Pregnancy and lactation — Adjustments to maintenance immunosuppression during pregnancy and lactation are informed by the relative drug safety, the risk of rejection if the drug

is discontinued, and the available data [62,63] (see "Safety of rheumatic disease medication use during pregnancy and lactation"):

- **Pregnancy** – For transplant recipients who are or may become pregnant, mycophenolate (ie, MMF or mycophenolate sodium) and mTOR inhibitors are contraindicated. Mycophenolate should be stopped at least six weeks prior to attempts at conceiving due to high reported rates of spontaneous abortion (45 percent) and risk of congenital anomalies such as orofacial, esophageal, cardiac, and kidney malformations [64-66]. If pregnancy occurs within six weeks of mycophenolate use, it should be reported to the Mycophenolate Risk Evaluation and Mitigation Strategy (Mycophenolate REMS).

  Mycophenolate can safely be switched to azathioprine without increased risk of graft rejection. Azathioprine is considered safe for use during pregnancy in both transplant and non-transplant populations [65,67].

  CNIs are considered to be safe during pregnancy based on data suggesting no increased risk of congenital anomalies [68]. While low birthweight and prematurity have been linked to CNI use, maternal comorbidities may have been confounding factors. Tacrolimus levels should be monitored every two to four weeks during pregnancy because the increase in circulating volume during pregnancy can lead to lower drug levels [69].

  Professional society guidance supports the use of glucocorticoids during pregnancy and lactation [70]. Although earlier data suggested an increased risk of orofacial cleft for infants whose mothers were treated with glucocorticoids during pregnancy, subsequent studies did not find increased risk of this abnormality [71,72].

  Preconception counseling, timing of pregnancy, and pregnancy outcomes in liver transplant recipients are discussed separately. (See "Pregnancy in women with pre-existing chronic liver disease", section on 'Liver transplantation'.)

- **Lactation** – Azathioprine, CNIs, and glucocorticoids are considered safe for breastfeeding because studies have shown low or undetectable drug levels in breast milk or infant serum [73-76]. However, mycophenolate and mTOR inhibitors should be avoided during breast feeding due to limited data on drug levels in breast milk and potential adverse effects on infants.

Patients undergoing non-transplant surgery — Most liver transplant recipients undergoing elective surgery do not require adjustment of maintenance immunosuppression. However, special considerations during the perioperative period include:

- **Drug interactions** – We carefully check for potential drug interactions with medications given perioperatively (eg, antimicrobials or antifungals). The recipient's transplant team should be consulted prior to making any changes to the immunosuppressive regimen. (See 'Drug interactions' above.)

- **Drug administration** – The route of administration for immunosuppressant drugs may need to be modified if the patient cannot tolerate oral medication. However, intravenous administration of calcineurin inhibitors (CNIs) should be avoided because it is associated with a higher risk of kidney toxicity. We consult with a transplant pharmacist when adjusting the route of drug administration.

- **Adjusting immunosuppressive drug doses** – Dosing adjustments for the following drug classes may be indicated:

  - mTOR inhibitors – We typically discontinue mTOR inhibitors at least one month prior to elective surgery because they are associated with poor wound healing. While the mTOR is being held, we usually use tacrolimus with or without an antimetabolite to maintain immunosuppression.

    Urgent surgery should not be delayed due to use of an mTOR inhibitor; however, discontinuing the mTOR inhibitor after surgery is appropriate. For patients who undergo urgent surgery, selecting an alternative immunosuppressive agent involves input from the surgical and liver transplantation teams. (See 'Use of mechanistic target of rapamycin (mTOR) inhibitors' above and "Pharmacology of mammalian (mechanistic) target of rapamycin (mTOR) inhibitors", section on 'Adverse effects'.)

  - Glucocorticoids – For recipients on glucocorticoid therapy, the need for perioperative glucocorticoid coverage is determined by the duration and dose of maintenance glucocorticoid therapy, the likelihood of underlying suppression of the hypothalamic-pituitary-adrenal (HPA) axis, and the surgical procedure. However, stress dose glucocorticoids are rarely necessary. Management of surgical patients taking glucocorticoids is discussed in more detail separately. (See "The management of the surgical patient taking glucocorticoids".)

Patients who develop infection — For transplant recipients who develop infection, the approach to adjusting immunosuppression varies among transplant centers, but it is generally based on the severity of infection (see "Infection in the solid organ transplant recipient"):

- For patients with acute infection requiring hospitalization who have sepsis or organ dysfunction, we typically reduce the doses of antimetabolite and/or CNI, with the dosing

adjustments guided by severity of illness and comorbidities (eg, kidney injury, myelosuppression).

- For patients with acute infection requiring hospitalization but who do not have sepsis or organ dysfunction, we usually reduce the dose of immunosuppressants if they are at higher risk of developing severe infection (eg, advanced age, comorbidities).

- For patients with uncomplicated, community-acquired infection (eg, cystitis, bronchitis), we usually do not adjust the maintenance regimen.

For recipients with an opportunistic infection, regardless of severity (eg, cytomegalovirus [CMV]), we typically decrease the CNI dose by 25 percent and/or decrease the antimetabolite dose by 25 to 50 percent. CMV viremia in solid organ transplant recipients is often a sign of excessive immunosuppression, and this is discussed separately. (See "Clinical manifestations, diagnosis, and management of cytomegalovirus disease in kidney transplant patients", section on 'Reduction of immunosuppression'.)

For liver transplant recipients with COVID-19, adjustments to immunosuppression are individualized and based on COVID-19 severity, the specific regimen used, time post-transplant, and estimated risk of graft rejection [77-81]. These issues are discussed separately. (See "COVID-19: Issues related to solid organ transplantation", section on 'Active COVID-19 in solid organ transplant recipients'.)

Some antimicrobial agents have the potential for drug interactions with immunosuppressive agents (table 1). For more detailed information on potential drug-drug interactions, refer to the Lexicomp drug interactions program within UpToDate.

Patients with a new cancer — For recipients who develop a new cancer after liver transplantation, we typically reduce maintenance immunosuppression to optimize response to cancer treatment and to reduce the risk of infection. Optimal management of such patients requires a multidisciplinary team approach by oncology, transplant hepatology, and pharmacy. Adjusting maintenance immunosuppression in patients with a post-transplant malignancy is discussed separately. (See "Malignancy after solid organ transplantation" and "Malignancy after solid organ transplantation", section on 'Reduction in immunosuppression'.)

Liver transplant recipients who are diagnosed with cancer can usually be managed with the same therapeutic protocols used to treat nontransplant patients with cancer. However, an important exception is immune checkpoint inhibitor (ICI) therapies (ie, cytotoxic T-lymphocyte antigen 4, programmed cell death 1 and programmed cell death 1 ligand antibodies), which have been associated with increased risk of graft rejection. In a systematic review of 83 solid

organ transplant recipients who were treated with ICIs, allograft rejection was reported in 33 patients (40 percent) [82]. Whether there is an immunosuppressive strategy that will help mitigate risk of ICI-related rejection is uncertain without compromising the efficacy of ICIs. However, preliminary data suggested that mTOR inhibitors were associated with lower risk of rejection in transplant recipients receiving ICI therapy [83-85]. Selecting an immunosuppressive strategy in recipients with *de novo* cancer is individualized and informed by the estimated risk of graft rejection, risk of cancer-related mortality, the available evidence, and multidisciplinary input. (See "Malignancy after solid organ transplantation", section on 'Management'.)

Patients with recurrent hepatitis C virus — The availability of highly effective direct-acting antivirals (DAAs) has greatly reduced the need for HCV treatment after liver transplantation. However, for liver transplant recipients with HCV viremia, we typically use a DAA-based therapy that minimizes the risk of drug interaction with the immunosuppressive regimen [86-91]. Specific drug interactions are listed in the table (table 8). Drug interactions can also be checked through the Lexicomp drug interactions program included with UpToDate.

DAA regimens containing a protease inhibitor have the potential to increase drug levels of CNIs and mTOR inhibitors. Thus, CNI levels should be monitored closely after starting antiviral therapy (table 8). For patients receiving DAA therapy, we measure tacrolimus levels weekly for the first four weeks and every two to four weeks thereafter during treatment. In addition, the rate of CNI clearance may increase as HCV replication declines. Management of HCV infection in liver transplant recipients is discussed separately. (See "Hepatitis C virus infection in liver transplant candidates and recipients", section on 'Post-transplant antiviral therapy'.)

Patients with hepatocellular carcinoma (HCC) — Some data have suggested that the mTOR inhibitor sirolimus suppresses tumor growth and may be beneficial for recipients with history of hepatocellular carcinoma (HCC) [92-96]. In a meta-analysis of three trials and 14 cohort studies including recipients with history of HCC, mTOR inhibitors were associated with increased likelihood of overall survival at five years post-transplant compared with no mTOR use (trials: RR 1.13, 95% CI 1.02-1.26 and cohort studies: RR 1.17, 95% 1.10-1.24) [96]. The clinical implications of these data remain unclear because most studies included in the meta-analysis were observational and subject to selection bias. Additionally, protocols for long-term immunosuppression at most transplant centers do not use sirolimus as monotherapy and typically add a second immunosuppressive agent when discontinuing CNI. (See 'Use of mechanistic target of rapamycin (mTOR) inhibitors' above and "Overview of treatment approaches for hepatocellular carcinoma".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Liver transplantation".)

SUMMARY AND RECOMMENDATIONS

- **Pathophysiology of acute rejection** – Organ rejection is a multistep process that includes alloantigen recognition, lymphocyte activation, clonal expansion, and graft inflammation (figure 1 and figure 2). (See 'Pathophysiology of acute rejection' above.)

- **General principles** – All liver transplant recipients receive immunosuppression following transplantation (see 'General principles' above):

  - **Goal of immunosuppression** – The goal of immunosuppression is to lower the risk of rejection while minimizing the risk of adverse drug effects and recurrent liver disease.

  - **Drug interactions** – Some immunosuppressive drugs, such as calcineurin and mechanistic target of rapamycin (mTOR) inhibitors, are metabolized by the cytochrome P450 (eg, CYP3A4) enzyme system. Potential drug interactions affecting these agents, along with recommendations for alternatives, monitoring, and/or dose adjustments are listed in the tables (table 1 and table 2).

- **Initial immunosuppression** – For most liver transplant recipients, the immunosuppressive regimen is center-specific and informed by the drug's mechanism of action, the available published evidence and clinical experience. We suggest an initial regimen consisting of triple immunosuppression with the following agents (**Grade 2C**):

  - A glucocorticoid (see 'Glucocorticoids' above)

  - A calcineurin inhibitor (usually tacrolimus) (see 'Calcineurin inhibitors' above)

  - An antimetabolite (usually mycophenolate) (see 'Antimetabolite agents' above)

  We maximize the level of immunosuppression in the early post-transplant period when the risk of rejection is greatest (ie, perioperative period until approximately three months post-transplant).

- **Maintenance therapy** – We use long-term maintenance immunosuppression for liver transplant recipients because of the increased risk of graft rejection and graft loss without immunosuppression. Factors informing the specific maintenance regimen and dosing include the risk of graft rejection, risk of adverse drug effects, etiology of primary liver

disease, recipient characteristics (eg, kidney function), and center-specific protocols. (See 'General approach' above.)

Some liver transplant recipients develop complications or other conditions that are indications for modifying the maintenance regimen. A discussion of these special populations includes (see 'When and how to modify maintentance therapy' above):

- Pregnancy and lactation. (See 'Pregnancy and lactation' above.)

- Recipients with CNI-related toxicity. (See 'Calcineurin inhibitor (CNI)-related toxicity' above.)

- Recipients who develop infection. (See 'Patients who develop infection' above.)

- Recipients undergoing nontransplant surgery. (See 'Patients undergoing non-transplant surgery' above.)

- Recipients with a new cancer. (See 'Patients with a new cancer' above.)

Adjustments to the immunosuppressive regimen should be done in consultation with the liver transplant team.

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Topic 4586 Version 39.0

GRAPHICS

The three signals of T cell activation
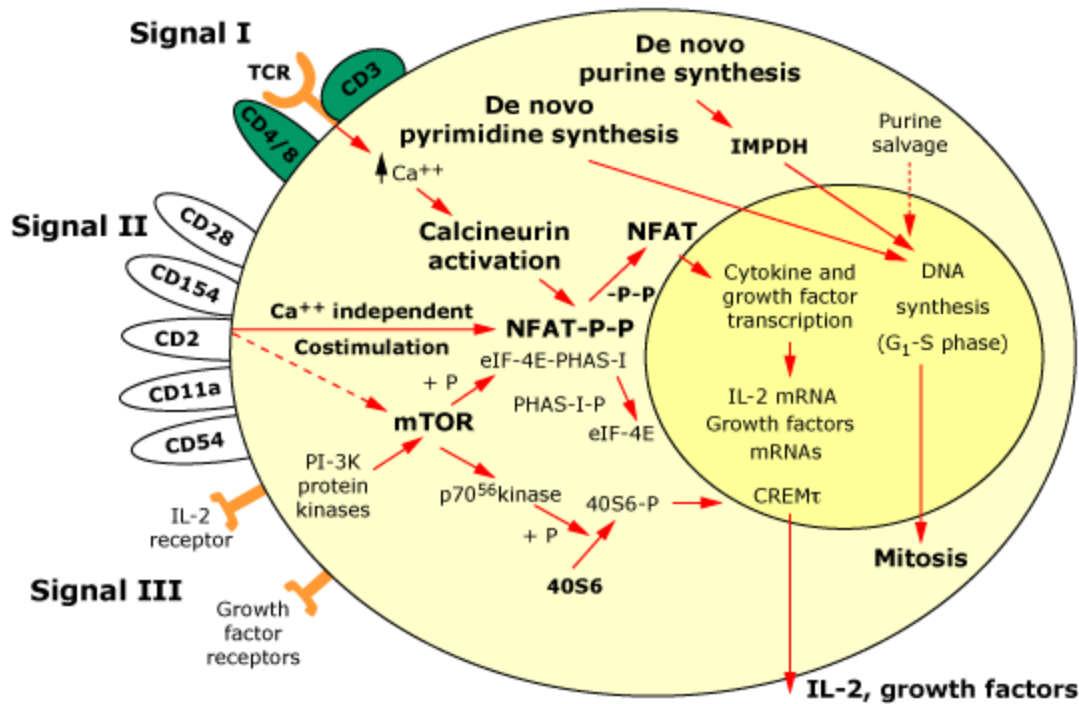
Signal I: Antigen presentation by APC to the T cell receptor.

Signal II: Costimulation - binding of additional APC ligands to specific T cell receptors.

Signal III: Newly synthesized IL-2 and growth factors feed back on T cell membrane receptors, causing clonal expansion of newly activated T cells.
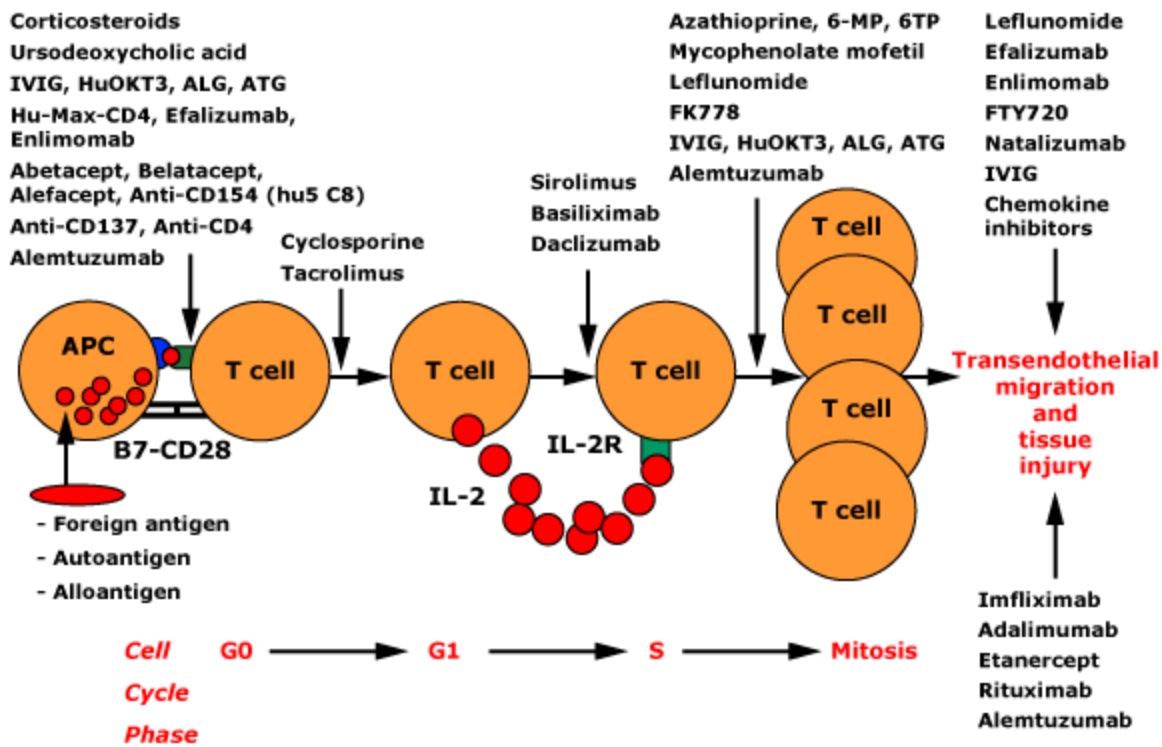

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Graphic 54486 Version 2.0

Overview of T cell activation and proliferation showing the site of action of available and experimental immunomodulatory agents

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Graphic 60525 Version 1.0

Examples of common drug interactions of immunosuppressants used in solid-organ transplant: Cyclosporine, tacrolimus, sirolimus, and everolimus

Common types of drug interactions	Examples of interacting drugs	Approach to management in the absence of appropriate noninteracting alternatives
Coadministration of drugs that inhibit CYP3A metabolism and/or P-gp efflux can **increase immunosuppressant serum concentrations**, leading to significant toxicities.	- Amiodarone - ART-boosting agents (eg, ritonavir, cobicistat) - Azole antifungals (eg, fluconazole, posaconazole, voriconazole) - HIV protease inhibitors (eg, atazanavir, nelfinavir, saquinavir) - Macrolide antibiotics - Non-dihydropyridine calcium channel blockers - Ombitasvir-paritaprevir-ritonavir with or without dasabuvir (an HCV, direct-acting antiviral regimen) - Grapefruit juice	- Closely monitor immunosuppressant concentrations and signs of toxicity (eg, tremors and headaches). - Substantial, including preemptive, dose reduction of immunosuppressant drug may be needed (eg, on average, only 25% of the standard dose of cyclosporine is required if administered concomitantly with HIV protease inhibitors). - Some combinations are considered contraindicated according to product labeling; refer to appropriate topic reviews for detail. - Lists of CYP3A and P-gp **inhibitors** are provided as separate tables within UpToDate.
Coadministration of drugs that induce CYP3A metabolism and/or P-gp efflux pumping can **decrease immunosuppressant serum concentrations**, increasing the risk of organ rejection.	- Antiseizure medications, enzyme inducing (eg, carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone) - Enzalutamide - Nafcillin - Rifamycins (eg, rifabutin, rifampin, rifapentine) - St. John's wort	- Closely monitor immunosuppressant serum concentrations and signs of organ rejection. - Significant immunosuppressant dose increases may be needed. - Enzyme induction can require up to 2 weeks to achieve maximum effect and persists for up to 2 weeks after discontinuation of the interacting medication. Clinically significant effects can occur within hours to days of starting a CYP inducer.

		■ Lists of CYP3A and P-gp **inducers** are provided as separate tables within UpToDate.
Coadministration of nephrotoxic drugs with cyclosporine or tacrolimus can cause **additive or synergistic kidney injury**.	■ Aminoglycosides ■ Amphotericin B ■ Colchicine ■ Nonsteroidal anti-inflammatory drugs (NSAIDs)	■ Concomitant administration of cyclosporine and tacrolimus with other potentially nephrotoxic drugs should be avoided. ■ Suggested dose adjustments for use with colchicine are available in the Lexicomp drug interactions database included within UpToDate.
Coadministration of drugs that increase serum potassium with cyclosporine or tacrolimus may cause **severe hyperkalemia**.	■ ACE inhibitors/ARBs ■ Amiloride ■ Spironolactone ■ Triamterene ■ Trimethoprim, trimethoprim-sulfamethoxazole (cotrimoxazole)	■ Closely monitor serum potassium levels.
Coadministration of cyclosporine with sirolimus can **increase sirolimus concentrations**.	■ Cyclosporine	■ Separate administration of sirolimus from cyclosporine by 4 hours; give sirolimus at a consistent time with respect to cyclosporine. ■ Closely monitor immunosuppressant serum concentrations.
Coadministration of statin drugs with cyclosporine can **increase statin levels and risk of myotoxicity**.	■ Atorvastatin ■ Lovastatin ■ Pitavastatin ■ Rosuvastatin ■ Simvastatin	■ Pravastatin and fluvastatin are preferred due to decreased interactions. ■ Tacrolimus may be preferred over cyclosporine in patients receiving statin therapy. ■ Cyclosporine and simvastatin should not be used together. ■ Some combinations are considered contraindicated or statin daily dose limits are recommended in the product labeling; refer to the Lexicomp drug interactions database included within UpToDate for detailed information.

- **Important note:** The interactions listed in this table illustrate some of the common types of interactions with immunosuppressive drugs; this is **not** a complete list, and many other significant drug interactions can occur. When initiating or altering drug therapy, use of a drug interactions database, such as Lexicomp drug interactions, is advised.
- Cyclosporine, tacrolimus, sirolimus, and everolimus are highly dependent upon CYP3A metabolism for clearance and are also substrates of P-gp drug efflux pump. Some interactions can lead to subtherapeutic or dangerously toxic levels of immunosuppressant concentrations.
- When appropriate noninteracting alternatives are readily available, consider modifying treatment to avoid combined use with potent metabolic inhibitors/inducers or agents known to have additive toxicities with immunosuppressants.
- Drug therapy should be managed by transplant specialists with expertise in therapeutic drug monitoring, and doses should be adjusted based upon measurement of immunosuppressant concentrations, particularly whenever drug therapy is altered. If there are any concerns about the safety of a given medication or supplement, they should be discussed with the patient's transplant center prior to initiation.

CYP: cytochrome P450 metabolism; P-gp: P-glycoprotein drug efflux pump; ART: HIV antiretroviral therapy; HIV: human immunodeficiency virus; HCV: hepatitis C virus; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker.

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Graphic 110436 Version 19.0

Cytochrome P450 3A (including 3A4) inhibitors and inducers

Strong inhibitors	Moderate inhibitors	Strong inducers	Moderate inducers
- Adagrasib - Atazanavir - Ceritinib - Clarithromycin - Cobicistat and cobicistat-containing coformulations - Darunavir - Idelalisib - Indinavir - Itraconazole - Ketoconazole - Levoketoconazole - Lonafarnib - Lopinavir - Mifepristone* - Nefazodone - Nelfinavir - Nirmatrelvir-ritonavir - Ombitasvir-paritaprevir-ritonavir - Ombitasvir-paritaprevir-ritonavir plus dasabuvir - Posaconazole - Ritonavir and ritonavir-containing coformulations - Saquinavir - Tucatinib - Voriconazole	- Amiodarone¶ - Aprepitant - Berotralstat - Cimetidine¶ - Conivaptan - Crizotinib - Cyclosporine¶ - Diltiazem - Duvelisib - Dronedarone - Erythromycin - Fedratinib - Fluconazole - Fosamprenavir - Fosaprepitant¶ - Fosnetupitant-palonosetron - Grapefruit juice - Imatinib - Isavuconazole (isavuconazonium sulfate) - Lefamulin - Letermovir - Netupitant - Nilotinib - Ribociclib - Schisandra - Verapamil	- Apalutamide - Carbamazepine - Enzalutamide - Fosphenytoin - Lumacaftor - Lumacaftor-ivacaftor - Mitotane - Phenobarbital - Phenytoin - Primidone - Rifampin (rifampicin)	- Bexarotene - Bosentan - Cenobamate - Dabrafenib - Dexamethasone^Δ - Dipyrone - Efavirenz - Elagolix, estradiol, and norethindrone therapy pack[◇] - Eslicarbazepine - Etravirine - Lorlatinib - Mitapivat - Modafinil - Nafcillin - Pexidartinib - Rifabutin - Rifapentine - Sotorasib - St. John's wort

- For drug interaction purposes, the inhibitors and inducers of CYP3A metabolism listed above can alter serum concentrations of drugs that are dependent upon the CYP3A subfamily of liver enzymes, including CYP3A4, for elimination or activation.
- These classifications are based upon US Food and Drug Administration (FDA) guidance.[1,2] Other sources may use a different classification system resulting in some agents being classified differently.
- Data are for systemic drug forms. Degree of inhibition or induction may be altered by dose, method, and timing of administration.
- Weak inhibitors and inducers are not listed in this table with exception of a few examples. Clinically significant interactions can occasionally occur due to weak inhibitors and inducers (eg, target drug is highly dependent on CYP3A4 metabolism and has a narrow therapeutic index). Accordingly, specific interactions should be checked using a drug interaction program such as the Lexicomp drug interactions program included within UpToDate.
- Refer to UpToDate topics on specific agents and indications for further details.

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* Mifepristone is a significant inhibitor of CYP3A4 when used chronically (eg, for hyperglycemia in patients with Cushing syndrome); not in single-dose use.

¶ Classified as a weak inhibitor of CYP3A4 according to FDA system.[1]

Δ Classified as a weak inducer of CYP3A4 according to FDA system.[1]

◇ The fixed-dose combination therapy pack taken in the approved regimen has moderate CYP3A4 induction effects. When elagolix is used as a single agent, it is a weak CYP3A4 inducer. Norethindrone and estradiol are not CYP3A4 inducers.

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2. *US Food & Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at: FDA.gov website.*

Graphic 76992 Version 95.0

An approach to glucocorticoid dosing for patients after liver transplantation

Time after transplant	Glucocorticoid dosing
Day 0 (intraoperatively)	Methylprednisolone 1000 mg IV once
Day 1	Methylprednisolone 50 mg IV twice daily
Day 2	Methylprednisolone 40 mg IV twice daily
Day 3	Methylprednisolone 30 mg IV twice daily
Day 4	Methylprednisolone 20 mg IV twice daily
Days 5 to 7	Prednisone 20 mg orally once daily
Days 8 to 30	Prednisone 15 mg orally once daily
During month 2	Prednisone 10 mg orally once daily
During month 3	Prednisone 7.5 mg orally once daily
During month 4	Prednisone 5 mg orally once daily
During month 5	Prednisone 2.5 mg orally once daily
During month 6	Prednisone 2.5 mg orally once every other day
At 6 months	Discontinue prednisone

This table provides an example of a glucocorticoid-tapering regimen for an adult patient following liver transplantation. Glucocorticoid regimens vary among transplant centers, and consensus on dosing is lacking.

IV: intravenously.

Graphic 141340 Version 2.0

Criteria for acute kidney injury

	RIFLE[1]	AKIN[2]	KDIGO[3]
Diagnostic criteria*			
		Increase in serum creatinine of ≥0.3 mg/dL or ≥50% within 48 hours OR Urine output of <0.5 mL/kg/hour for >6 hours	Increase in serum creatinine of ≥0.3 mg/dL within 48 hours or ≥50% within 7 days OR Urine output of <0.5 mL/kg/hour for >6 hours
Staging criteria			
Risk (RIFLE) or stage 1 (AKIN/KDIGO)	Increase in serum creatinine to 1.5 times baseline OR Urine output of <0.5 mL/kg/hour for 6 to 12 hours	Increase in serum creatinine of ≥0.3 mg/dL or to 150 to 200% baseline OR Urine output of <0.5 mL/kg/hour for 6 to 12 hours	Increase in serum creatinine of ≥0.3 mg/dL or 1.5 to 1.9 times baseline OR Urine output of <0.5 mL/kg/hour for 6 to 12 hours
Injury (RIFLE) or stage 2 (AKIN/KDIGO)	Increase in serum creatinine to 2 times baseline OR Urine output of <0.5 mL/kg/hour for 12 to 24 hours	Increase in serum creatinine to 200 to 300% baseline OR Urine output of <0.5 mL/kg/hour for 12 to 24 hours	Increase in serum creatinine to 2 to 2.9 times baseline OR Urine output of <0.5 mL/kg/hour for 12 to 24 hours
Failure (RIFLE) or stage 3 (AKIN/KDIGO)	Increase in serum creatinine to 3 times baseline OR Increase in serum creatinine by >0.5 mg/dL to >4 mg/dL OR Urine output of <0.3 mL/kg/hour for >24	Increase in serum creatinine to >300% baseline OR Increase in serum creatinine by >0.5 mg/dL to ≥4 mg/dL OR Urine output of <0.3 mL/kg/hour for >24	Increase in serum creatinine to ≥3 times baseline OR Increase in serum creatinine of ≥0.3 mg/dL to ≥4 mg/dL[¶] OR Urine output of <0.3 mL/kg/hour for ≥24

	hours or anuria for >12 hours OR Initiation of kidney replacement therapy	hours or anuria for >12 hours OR Initiation of kidney replacement therapy	hours or anuria for ≥12 hours OR Initiation of kidney replacement therapy
Loss (RIFLE)	Need for kidney replacement therapy for >4 weeks		
End stage (RIFLE)	Need for kidney replacement therapy for >3 months		

RIFLE: risk, injury, failure, loss, ESKD; AKIN: Acute Kidney Injury Network; KDIGO: Kidney Disease: Improving Global Outcomes; ESKD: end-stage kidney disease.

* AKIN and KDIGO provided both diagnostic and staging criteria. RIFLE provided a graded definition of AKI that is implicit in the staging criteria.

¶ In patients <18 years, stage 3 AKI is also defined by KDIGO as a decrease in estimated glomerular filtration rate (eGFR) to <35 mL/min/1.73 m^2.

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1. *Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure-definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8:B204. Copyright © 2004 BioMed Central Ltd.*
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3. *Kidney Disease: Improving Global Outcomes (KDIGO). Acute Kidney Injury Work Group. KDIGO clinical practice guidelines for acute kidney injury. Kidney Int Suppl 2012; 2:1.*

Graphic 83168 Version 14.0

Definition and criteria for chronic kidney disease

Definition:	
Chronic kidney disease is defined based on the presence of either kidney damage or decreased kidney function for three or more months, irrespective of cause.	
Criteria	**Comment**
Duration ≥3 months, based on documentation or inference	Duration is necessary to distinguish chronic from acute kidney diseases. • Clinical evaluation can often suggest duration • Documentation of duration is usually not available in epidemiologic studies
Glomerular filtration rate (GFR) <60 mL/min/1.73 m^2	GFR is the best overall index of kidney function in health and disease. • The normal GFR in young adults is approximately 125 mL/min/1.73 m^2; GFR <15 mL/min/1.73 m^2 is defined as kidney failure • Decreased GFR can be detected by current estimating equations for GFR based on serum creatinine (estimated GFR) but not by serum creatinine alone • Decreased estimated GFR can be confirmed by measured GFR, measured creatinine clearance, or estimated GFR using cystatin C
Kidney damage, as defined by structural abnormalities or functional abnormalities other than decreased GFR	Pathologic abnormalities (examples). Cause is based on underlying illness and pathology. Markers of kidney damage may reflect pathology. • Glomerular diseases (diabetes, autoimmune diseases, systemic infections, drugs, neoplasia) • Vascular diseases (atherosclerosis, hypertension, ischemia, vasculitis, thrombotic microangiopathy) • Tubulointerstitial diseases (urinary tract infections, stones, obstruction, drug toxicity) • Cystic disease (polycystic kidney disease)
	History of kidney transplantation. In addition to pathologic abnormalities observed in native kidneys, common pathologic abnormalities include the following: • Chronic allograft nephropathy (non-specific findings of tubular atrophy, interstitial fibrosis, vascular and glomerular sclerosis) • Rejection • Drug toxicity (calcineurin inhibitors) • BK virus nephropathy • Recurrent disease (glomerular disease, oxalosis, Fabry disease)
	Albuminuria as a marker of kidney damage (increased glomerular permeability, urine albumin-to-creatinine ratio [ACR] >30 mg/g).*

- The normal urine ACR in young adults is <10 mg/g. Urine ACR categories 10-29, 30-300 and >300 mg are termed "mildly increased, moderately increased, and severely increased" respectively. Urine ACR >2200 mg/g is accompanied by signs and symptoms of nephrotic syndrome (low serum albumin, edema and high serum cholesterol).

- Threshold value corresponds approximately to urine dipstick values of trace or 1+, depending on urine concentration

- High urine ACR can be confirmed by urine albumin excretion in a timed urine collection

Urinary sediment abnormalities as markers of kidney damage, for example:

- RBC casts in proliferative glomerulonephritis

- WBC casts in pyelonephritis or interstitial nephritis

- Oval fat bodies or fatty casts in diseases with proteinuria

- Granular casts and renal tubular epithelial cells in many parenchymal diseases (non-specific)

Imaging abnormalities as markers of kidney damage (ultrasound, computed tomography and magnetic resonance imaging with or without contrast, isotope scans, angiography).

- Polycystic kidneys

- Hydronephrosis due to obstruction

- Cortical scarring due to infarcts, pyelonephritis or vesicoureteral reflux

- Renal masses or enlarged kidneys due to infiltrative diseases

- Renal artery stenosis

- Small and echogenic kidneys (common in later stages of CKD due to many parenchymal diseases)

* Albumin-to-creatinine ratio (ACR) conversion factor 1.0 mg/g = 0.113 mg/mmol.

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Graphic 80632 Version 3.0

Tacrolimus levels for adult liver transplant recipients

Time posttransplant	Target tacrolimus trough level
0 to 4 weeks	8 to 12 ng/mL
4 to 12 weeks	6 to 10 ng/mL
Beyond 12 weeks	5 to 8 ng/mL

The approach to tacrolimus dosing is generally informed by the time posttransplant, patient characteristics (eg, etiology of liver disease), and transplant center protocol. We use drug trough levels to titrate the tacrolimus dose. We typically target higher drug levels earlier in the posttransplant course and adjust the target drug concentration levels as the duration of time after transplant increases. Target drug levels also vary by transplant center protocol and by individual patient. Refer to UpToDate content on the pharmacology, dosing, and safety of tacrolimus for additional details.

Graphic 141246 Version 1.0

Cyclosporine and tacrolimus preparations

Cyclosporine non-modified
Oral
Capsules: Liquid filled – 25 mg, 50 mg, 100 mg (Sandimmune and generics)
Solution: 100 mg/mL in 50 mL bottles
Topical
Ophthalmic emulsion: 0.05% in 0.4 mL vials (Restasis)
Parenteral
Concentrate for injection: For IV infusion 50 mg/mL in 5 mL ampules
Cyclosporine modified (microemulsion)
Oral
Capsules: 25 mg, 100 mg (Neoral and generics)
Solution: 100 mg/mL in 50 mL bottles
Tacrolimus
Oral
Immediate-release capsules: 0.5 mg, 1 mg, 5 mg (Prograf)
Extended-release capsules: 0.5 mg, 1 mg, 5 mg (Astagraf XL)
Extended-release tablet: 0.75 mg, 1 mg, 4 mg (Envarsus XR)
Topical
Ointment: 0.03 and 0.1% in 30 g, 60 g, 100 g tubes (Protopic)
Parenteral
Concentrate for injection: For IV infusion 5 mg/mL in 1 mL ampules

Formulation descriptions are for products available in the United States, Canada, and some other countries. Consult local product information before use.

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Graphic 57518 Version 12.0

Drug interactions between immunosuppressive agents and direct-acting antiviral agents for HCV infection

	Tacrolimus	Cyclosporine	Sirolimus	Everolimus	Azathioprine	N
Sofosbuvir	✓	✓	✓	✓	✓	
Ledipasvir-sofosbuvir	✓	✓	✓	Monitor levels*	✓	
Sofosbuvir-velpatasvir	✓	✓	✓	Monitor levels*	✓	
Daclatasvir	✓	✓	✓	Monitor levels*	✓	
Glecaprevir-pibrentasvir	Monitor levels¶	If cyclosporine dose >100 mg/day, not recommended	Monitor levelsΔ	Monitor levels*	✓	
Elbasvir-grazoprevir	Monitor levels¶	Not recommended	Monitor levelsΔ	Monitor levels*	✓	
Sofosbuvir-velpatasvir-voxilaprevir	✓	Not recommended	Monitor levelsΔ	Monitor levels*	✓	
Simeprevir	Monitor levels¶	Not recommended	Monitor levelsΔ	Monitor levels*	✓	
Ombitasvir-paritaprevir-ritonavir with or without dasabuvir	Avoid; if used, lower tacrolimus dose to 0.5 mg every 7 days and monitor levels	Avoid; if used, lower cyclosporine to one-fifth dose and monitor levels	Not recommended	Not recommended	✓	

Overall, data informing the likelihood of drug interactions between direct-acting antivirals and immunosuppressive agents are limited. Most recommendations are based on expected pharmacokinetics.

The checkmark indicates no expected interactions that warrant change in management.

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* Levels of everolimus may be increased with concurrent administration and should be followed, with dose adjustments as necessary. Conversely, everolimus may increase concentrations of

simeprevir and daclatasvir.

¶ Levels of tacrolimus may be increased with concurrent administration and should be followed, with dose adjustments as necessary.

Δ Levels of sirolimus may be increased with concurrent administration and should be followed, with dose adjustments as necessary.

Graphic 118768 Version 2.0

simeprevir and daclatasvir.

¶ Levels of tacrolimus may be increased with concurrent administration and should be followed,

Contributor Disclosures

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