xenotransplantation with genetically modified organs of nonhuman origin (e.g., swine).

POSTOPERATIVE COURSE AND MANAGEMENT

IMMUNOSUPPRESSIVE THERAPY

The introduction in 1980 of cyclosporine as an immunosuppressive agent contributed substantially to the improvement in survival after liver transplantation. Cyclosporine, a calcineurin inhibitor, blocks early activation of T cells and is specific for T cell functions that result from the interaction of the T cell with its receptor and that involve the calcium-dependent signal transduction pathway. As a result, the activity of cyclosporine leads to inhibition of lymphokine gene activation, blocking interleukins 2, 3, and 4, tumor necrosis factor a, and other lymphokines. Cyclosporine also inhibits B cell functions. This process occurs without affecting rapidly dividing cells in the bone marrow, which may account for the reduced frequency of posttransplantation systemic infections. The most common and important side effect of cyclosporine therapy is nephrotoxicity. Cyclosporine causes dose-dependent renal tubular injury and direct renal artery vasospasm. Following renal function is therefore important in monitoring cyclosporine therapy, perhaps even a more reliable indicator than blood levels of the drug. Nephrotoxicity is reversible and can be managed by dose reduction. Other adverse effects of cyclosporine therapy include hypertension, hyperkalemia, tremor, hirsutism, glucose intolerance, and gingival hyperplasia.

Tacrolimus, a macrolide lactone antibiotic isolated from a Japanese soil fungus, *Streptomyces tsukubaensis*, has the same mechanism of action as cyclosporine but is 10–100 times more potent. Initially applied as "rescue" therapy for patients in whom rejection occurred despite the use of cyclosporine, tacrolimus was shown to be associated with a reduced frequency of acute, refractory, and chronic rejection. Although patient and graft survival are the same with these two drugs, the advantage of tacrolimus in minimizing episodes of rejection, reducing the need for additional glucocorticoid doses, and reducing the likelihood of bacterial and cytomegalovirus (CMV) infection has simplified the management of patients undergoing liver transplantation. In addition, the oral absorption of tacrolimus is more predictable than that of cyclosporine, especially during the early postoperative period when T-tube drainage interferes with the enterohepatic circulation of cyclosporine. As a result, in most transplantation centers, tacrolimus has now supplanted cyclosporine for primary immunosuppression, and many centers rely on oral rather than IV administration from the outset. For transplantation centers that prefer cyclosporine, a better-absorbed microemulsion preparation is available.

Although more potent than cyclosporine, tacrolimus is also more toxic and more likely to be discontinued for adverse events. The toxicity of tacrolimus is similar to that of cyclosporine; nephrotoxicity and neurotoxicity are the most commonly encountered adverse effects, and neurotoxicity (tremor, seizures, hallucinations, psychoses, coma) is more likely and more severe in tacrolimus-treated patients. Both drugs can cause diabetes mellitus, but tacrolimus does not cause hirsutism or gingival hyperplasia. Because of overlapping toxicity between cyclosporine and tacrolimus, especially nephrotoxicity, and because tacrolimus reduces cyclosporine clearance, these two drugs should not be used together. Because 99% of tacrolimus is metabolized by the liver, hepatic dysfunction reduces its clearance; in primary graft nonfunction (when, for technical reasons or because of ischemic damage prior to its insertion, the allograft is defective and does not function normally from the outset), tacrolimus doses have to be reduced substantially, especially in children. Both cyclosporine and tacrolimus are metabolized by the cytochrome P450 IIIA system, and, therefore, drugs that induce cytochrome P450 (e.g., phenytoin, phenobarbital, carbamazepine, rifampin) reduce available levels of cyclosporine and tacrolimus; and drugs that inhibit cytochrome P450 (e.g., erythromycin, fluconazole, ketoconazole, clotrimazole, itraconazole, verapamil, diltiazem, danazol, metoclopramide, the HIV protease inhibitor ritonavir, and the HCV protease inhibitors telaprevir and boceprevir) increase cyclosporine and tacrolimus blood levels. Indeed, itraconazole is used occasionally to help boost tacrolimus levels. Like azathioprine, cyclosporine and tacrolimus appear to be associated with a risk of lymphoproliferative malignancies (see below), which may occur earlier after cyclosporine or tacrolimus than after azathioprine therapy. Because of these side effects, combinations of cyclosporine or tacrolimus with prednisone and an antimetabolite (azathioprine or mycophenolic acid, see below)—all at reduced doses—are preferable regimens for immunosuppressive therapy.

Mycophenolic acid, a nonnucleoside purine metabolism inhibitor derived as a fermentation product from several *Penicillium* species, is another immunosuppressive drug being used for patients undergoing liver transplantation. Mycophenolate has been shown to be better than azathioprine, when used with other standard immunosuppressive drugs, in preventing rejection after renal transplantation and has been adopted widely as well for use in liver transplantation. The most common adverse effects of mycophenolate are bone marrow suppression and gastrointestinal complaints.

In patients with pretransplantation renal dysfunction or renal deterioration that occurs intraoperatively or immediately postoperatively, tacrolimus or cyclosporine therapy may not be practical; under these circumstances, induction or maintenance of immunosuppression with antithymocyte globulin (ATG, thymoglobulin) or monoclonal antibodies to T cells, OKT3, may be appropriate. Therapy with these agents has been especially effective in reversing acute rejection in the posttransplantation period and is the standard treatment for acute rejection that fails to respond to methylprednisolone boluses. Available data support the use of thymoglobulin induction to delay calcineurin inhibitor use and its attendant nephrotoxicity. IV infusions of thymoglobulin may be complicated by fever and chills, which can be ameliorated by premedication with antipyretics and a low dose of glucocorticoids. Infusions of OKT3 may be complicated by fever, chills, and diarrhea, or by pulmonary edema, which can be fatal. Because OKT3 is such a potent immunosuppressive agent, its use is also more likely to be complicated by opportunistic infection or lymphoproliferative disorders; therefore, because of the availability of alternative immunosuppressive drugs, OKT3 is now used sparingly.

Sirolimus, an inhibitor of the mammalian target of rapamycin (mTOR), blocks later events in T cell activation, is approved for use in kidney transplantation, but is not approved for use in liver transplant recipients because of the reported association with an increased frequency of hepatic artery thrombosis in the first month posttransplantation. In patients with calcineurin inhibitor–related nephrotoxicity, conversion to sirolimus has been demonstrated to be effective in preventing rejection with accompanying improvements in renal function. Because of its profound antiproliferative effects, sirolimus has also been suggested to be a useful immunosuppressive agent in patients with a prior or current history of malignancy, such as HCC. Side effects include hyperlipidemia, peripheral edema, oral ulcers, and interstitial pneumonitis. Everolimus is a hydroxyethyl derivative of sirolimus that, when used in conjunction with low-dose tacrolimus, also provides successful protection against acute rejection, with decreased renal impairment compared to that associated with standard tacrolimus dosing. Everolimus and sirolimus share a similar adverse events profile; therefore, neither of these agents is approved for routine use in liver allograft recipients.

The most important principle of immunosuppression is that the ideal approach strikes a balance between immunosuppression and immunologic competence. In general, given sufficient immunosuppression, acute liver allograft rejection is nearly always reversible. On one hand, incompletely treated acute rejection predisposes to the development of chronic rejection, which can threaten graft survival. On the other hand, if the cumulative dose of immunosuppressive therapy is too large, the patient may succumb to opportunistic infection. In hepatitis C, pulse glucocorticoids or OKT3 use accelerate recurrent allograft hepatitis. Further complicating matters, acute rejection can be difficult to distinguish histologically from recurrent hepatitis C. Therefore, immunosuppressive drugs must be used judiciously, with strict attention to the infectious consequences of such therapy and careful confirmation of the diagnosis of acute rejection. In this vein, efforts have been made to minimize the use of glucocorticoids, a