TRANSPALNTATION

DEFINITIONS

- ***Transplantation*** is the process of transferring an organ, tissue, or cell from one place to another.
- An ***organ transplant*** is a surgical procedure in which a failing organ is replaced by a functioning one.
- The organ is transplanted either ***orthotopically*** (implanted in the same anatomic location in the recipient as it was in the donor)
- or ***heterotopically*** (implanted in another anatomic location). Orthotopic transplants require the removal of the diseased organ (heart, lungs, liver, or intestine); in heterotopic transplants, the diseased organ is kept in place (kidney, pancreas).

Types of transplant

According to the degree of immunologic similarity between the donor and recipient, transplants are divided into three main categories:

- (a) ***An autotransplant*** is the transfer of cells, tissue, or an organ from one part of the body to another part in the same person, so no immunosuppression is required. This type of trans- plant includes skin and vein, bone, cartilage, nerve, and islet cell transplants.
- (b) ***An allotransplant*** is the transfer of cells, tissue, or an organ from one person to another of the same species. The immune system of the recipient recognizes the donated organ as a foreign body, so immunosuppression is required in order to avoid rejection.
- (c) ***A xenotransplant*** is the transfer of cells, tissue, or an organ from one organism to another from a different species. To date, animal-to-human transplants are still experimental proce- dures, given the very complex immunologic and infectious issues that have yet to be solved.

TRANSPLANT ANTIGENS

In humans, these antigens make up the human leukocyte antigen (HLA) system. The antigen-encoding genes are located on chromosome 6. Two major classes of HLA antigens are recognized. They differ in their structure, function, and tissue distribution.

- ***Class I antigens*** (HLA-A, HLA-B, and HLA-C) are expressed by all nucleated cells.
- ***Class II antigens*** (HLA-DR, HLA-DP, and HLA-DQ) are expressed by antigen- presenting cells (APCs) such as B lymphocytes, dendritic cells, macrophages, and other phagocytic cells.

CLINICAL REJECTION

Graft rejection is due to a complex interaction of different parts of the immune system, including B and T lymphocytes, APCs, and cytokines.

- ***Hyperacute rejection***, a very rapid type of rejection, results in irreversible damage and graft loss within minutes to hours after organ reperfusion. It is triggered by preformed antibodies against the donor's HLA or ABO blood group antigens.
- ***Acute rejection***, the most common type of rejection, usually occurs within a few days or weeks post transplant. According to the mechanism involved, it is further divided into cellular (T-cell–mediated) rejection, humoral (antibody-mediated) rejection, or a combination of both.

CLINICAL REJECTION

- ***Chronic rejection*** is a slow type of rejection. It can manifest within the first year posttransplant, but most often progresses gradually over several years. The mechanism is not well under- stood, but the pathologic changes eventually lead to fibrosis and loss of graft function. With advances in immunosuppression, this relatively rare form of rejection is becoming more common.

CLINICAL IMMUNOSUPPRESSION

- A successful transplant is a balance between the recipient's immune response, the donor's allograft, and pharmacologic immunosuppression. Immunosuppressive regimens are very **2** important to graft and patient survival posttransplant.
- ***Immunosuppression*** has evolved from the use of aza- thioprine and steroids in the 1960s and 1970s to the develop- ment, in the 1980s, of cyclosporine, which increased allograft survival.10,11 The introduction of tacrolimus and mycophenolate mofetil (MMF) in the 1990s further changed the field of trans- plantation, enabling a variety of combinations to be used for immunosuppression

Immunosuppressive drugs by grouping

Immunophilin binders

- Calcineurin inhibitors Cyclosporine Tacrolimus
- Noninhibitors of calcineurin Sirolimus

Antimetabolites

- Inhibitors of de novo purine synthesis Azathioprine Mycophenolate mofetil

Biologic immunosuppression

- Polyclonal antibodies Atgam
- Antithymocyte immunoglobulin Monoclonal antibodies
- Muromonab-CD3 Basiliximab Belatacept Alemtuzumab Rituximab Bortezomib Eculizumab

Other

- Corticosteroids

Summary of the main immunosuppressive drugs

DRuG	MECHANISM OF ACTION	ADvERSE EFFECTS	CLINICAL uSES	DOSAGE
Cyclosporine (CSA)	Binds to cyclophilin Inhibits calcineurin and IL-2 synthesis	Nephrotoxicity Tremor Hypertension Hirsutism	Improved bioavailability of microemulsion form	Oral dose 5 mg/kg per day (given in two divided doses)
Tacrolimus (FK506)	Binds to FKBP Inhibits calcineurin and IL-2 synthesis	Nephrotoxicity Hypertension Neurotoxicity GI toxicity (nausea, diarrhea)	Improved patient and graft survival in (liver) primary immunosuppression and rescue therapy Used as mainstay of maintenance protocols	IV 0.015 mg/kg per day as continuous infusion PO 0.05 mg/kg per day (given every 12 h)
Mycophenolate mofetil	Antimetabolite Inhibits enzyme Nec essary for de novo purine synthesis	Leukopenia GI toxicity	Effective for primary immunosuppression in combination with tacrolimus	1 g bid PO
Sirolimus	Inhibits lymphocyte effects driven by IL-2 receptor	Thrombocytopenia Increased serum cholesterol/LDL Poor wound healing	May allow early withdrawal of steroids and decreased calcineurin doses	2–4 mg/d, adjusted to trough drug levels
Corticosteroids	Multiple actions Anti-inflammatory Inhibits lymphokine production	Cushingoid state Glucose intolerance Osteoporosis	Used in induction, maintenance, and treatment of acute rejection	Varies from milligrams to several grams per day Maintenance doses, 5–10 mg/d
Azathioprine	Antimetabolite Interferes with DNA and RNA synthesis	Thrombocytopenia Neutropenia Liver dysfunction	Used in maintenance protocols or if intolerance to mycophenolate mofetil	1–3 mg/kg per day for maintenance
Belatacept	T-cell blocker	Increased risk of bacterial infections	New drug for maintenance immunosuppression in renal transplants only	5–10 mg/kg per day infusion

FKBP = FK506-binding protein; GI = gastrointestinal; IL = interleukin; IV = intravenous; LDL = low-density lipoprotein; PO = oral

Side effects and drug interactions of the main immunosuppressive drug

	COMMON SIDE EFFECTS	OTHER MEDICATIONS THAT INCREASE BLOOD LEVELS	OTHER MEDICATIONS THAT DECREASE BLOOD LEVELS	OTHER MEDICATIONS THAT POTENTIATE TOXICITY
Cyclosporine (CSA)	Hypertension, nephrotoxicity, hirsutism, neurotoxicity, gingival hyperplasia, hypomagnesemia, hyperkalemia	Verapamil, diltiazem, clarithromycin, azithromycin, erythromycin, azole antifungals, protease inhibitors, grapefruit juice	Isoniazid, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort	Nephrotoxicity: ganciclovir, aminoglycosides, NSAIDs, ACE-Is, and ARBs
Tacrolimus (FK506)	Hypertension, nephrotoxicity, alopecia, hyperglycemia, neurotoxicity, hypomagnesemia, hyperkalemia	Verapamil, diltiazem, clarithromycin, azithromycin, erythromycin, azole antifungals, protease inhibitors, grapefruit juice	Isoniazid, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort	Nephrotoxicity: ganciclovir, aminoglycosides, NSAIDs, ACE-Is, and ARBs
Sirolimus	Thrombocytopenia and neutropenia, elevated cholesterol, extremity edema, impaired wound healing	Verapamil, diltiazem, clarithromycin, azithromycin, erythromycin, azole antifungals, protease inhibitors, grapefruit juice	Isoniazid, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort	—
Mycophenolate mofetil	Leukopenia, thrombocytopenia, GI upset	—	Cholestyramine, antacids	Bone marrow suppression: valganciclovir, ganciclovir, TMP-SMX
Corticosteroids	Hyperglycemia, osteoporosis, cataracts, myopathy, weight gain	—	—	—
Azathioprine	Leukopenia, anemia, thrombocytopenia, neoplasia, hepatitis, cholestasis	—	—	Bone marrow suppression: allopurinol, sulfonamides

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; NSAID = nonsteroidal anti-inflammatory drug; TMP-SMX = trimethoprim-sulfamethoxazole