

Vesalius SCALpel™ : Transplant (see also: VID 125, 606)

Immunology

general

- TNF stimulated by endotoxin
- NK cells large granular lymphocytes, non-A or B
- interferons antiproliferative, block viruses
- chemokines (30 known) = LMW cytokines: recruit immune cells

hypersensitivity

- 4 types of hypersensitivity
 - 1 immediate: IgE (food, hay fever, anaphylaxis)
 - 2 cytotoxic: IgG, IgM + cell-bound antigen (ABO, Rh, Graves, myasthenia)
 - 3 immune complex: IgG, IgM (serum sickness, RA, glomerulonephritis)
 - 4 delayed: previous sensitized T cell (CD4 + helpers) (contact dermatitis)

3 major components:

- 1 antigen presenting cell (APC): dendritic cells, macrophages
 - phagocytizes antigen
 - antigen broken down in lysosomal system
 - peptide fragments presented on cell surface as major histocompatibility complex (MHC) class II
 - HLA = a major histocompatibility complex (MHC) antigen
 - also secretes IL-1
- 2 humoral: B lymphocytes, antibody mediated
 - B cells mature to plasma cells, present preformed/existing antibodies
 - responsible for early/hyperacute rejection
 - ABO, HLA incompatibility
- 3 cellular: T lymphocytes (thymus), cell mediated
 - T cell + CD3 surface marker/receptor = T cell-receptor (TCR) complex
 - recognizes and binds to antigen (MHC) on antigen presenting cell
 - requires 2nd co-stimulatory signal
 - T cell stimulated to produce cytokine IL-2
 - drives clonal expansion of that T cell subset to recognize that specific antigen
 - IL-2 also stimulates B cell humoral response
 - T-cells direct further immune response, infiltrate graft and destroy target cells
 - primary mediator of transplant rejection

TARGET OF MOST IMMUNOSUPPRESSION

immune mediators/cytokines

- soluble messengers, communicate between cells, regulate immune responses
- interleukin 1 & 2: primary regulators of initial immune response

Clinical immunosuppression

- 1 deplete lymphocyte population/destroy lymphocytes
 - e.g. thymoglobulin, alemtuzumab

- 2 inhibit/supress lymphocyte activity, prevent stimulation signals
 - e.g. tacrolimus, cyclosporine
- 3 block lymphocyte proliferation
 - interfere with nucleic acid synthesis
 - block metabolic pathway
 - e.g. mycophenolate mofetil

Pre-transplant matching

two major matches: ABO compatibility and HLA antibodies

ABO

human immune competence based primarily on preformed humoral antibodies
 compatibility necessary for orgs that express ABO antigens (kidney, heart)
 ABO antibodies attack target antigen in endothelium, thrombosis, necrosis,
 hyperacute rejection

acquired antibodies against human leukocyte antigens (HLA system)

humoral and cell immunity loci on chromosome 6
 elicited by: transfusion, pregnancy, previous transplant
 complement dependent
 cytotoxic to tissues with corresponding surface antigens
 microcytotoxicity test on lymphocytes
 if antibody present lymphocytes die
 flow cytometry for antibodies more sensitive
 if positive, higher rate of early rejection
 circulating preformed antibodies may be neutralized
 remove with plasmapheresis & IgG

hyperacute rejection now rare because of this testing

Rejection

hyperacute

mediated by pre-formed B-cell antibodies to ABO, HLA 1
 complement activation
 rare now with screening
 positive X-match (PRA panel) absolute contraindication to kidney transplant
 liver relatively resistant v kidney, heart, lung, pancreas
 immediate as soon as flow restored, minutes to hours
 vascular endothelial damage, leakage, thrombosis, organ turns black
 remove organ promptly

acute

30% of transplants experience acute rejection
 most common 1st 3-6mo
 most clinical immunosuppression directed at acute rejection
 cytotoxic T-cell subset
 can begin 1-3w after transplant

treatment

increase dose of immunosuppressant that the pt is on
steroid pulse is first line (more than 80% will respond)
if steroids fail, then antibody treatment, graft biopsy, consider antibody-mediated rejection
each episode increases the risk of chronic rejection
each treatment and duration increases the risk of infection and malignancy

infection

1st month common post op infections
after 1mo unusual environmental low pathogenicity organisms
reactivation latent (usually viral, CMV most) infections
highest risk 6-12w post transplant
Rx & prophylactic acyclovir, gancyclovir
other viral agents: Ebstein-Barr, human herpes virus 6 (HHV-6), hepatitis A, B, C, HIV
other prophylaxis: pneumovax, hep B
nystatin for oral/esophageal fungus

malignancy

most low grade, skin cancers, viral-associated tumors
HPV: cervical cancer
hep B/C: hepatocellular
HSV-8 (herpes): Kaposi's sarcoma
EBV (Ebstein-Barr): post transplant lymphoproliferative disorders (PTLD)
mimics mono: fever, night sweat, tonsillar enlargement
difficult to diagnose
transplanted organ involved only 20%
66% one site, 75% extranodal (kidney, bowel, liver, mediastinum, lung, skin)
lymphomas make up 22% of cancers in transplant pts
most (90%) B-cell, most 1st & 2nd y
30% regress w treatment, 50% mortality
CD20 widely expressed on B lymphocytes
Rx: rituximab = anti CD20 antibody
Rx: decrease dose of immunosuppressive, usual cancer Rx
(intensive chemo with CHOP)

chronic rejection

months to years
B & T-cell mediated
most common cause of graft loss after 1st year

cardiovascular disease

immunosuppression drugs exacerbate cardiovascular disease, atherosclerosis
frequent cause of death after 1st year (less than graft loss, infection)
steroids, cyclosporin

Immunosuppression agents

induction: deplete lymphocytes or inhibit IL-2

antithymocyte globulin (ALG)

depletes lymphocytes, mainly T-cells, polyclonal antibody
profound and prolonged depletion, well tolerated
may be used for steroid resistant acute rejection

alemtuzamab

depletes T-cells, monoclonal antibody (CD52)
profound and prolonged depletion, well tolerated
may be used for steroid resistant acute rejection

OKT3

monoclonal (mouse) antibody to T/CD3+ immune complex
binds CD3, blocks activation of cytotoxic t-cell subset
lymphocytes then destroyed like ALG
profound immunosuppression, similar problems
decreases T-cells in 30-60m

used for induction (rarely) and acute rejection
serum sickness, anaphylaxis, rare (5%) flash pulmonary edema

IL-2 antibodies block IL-2 receptors

specific to activated T-cell subset (major activity)
also block subset of B-cells with IL-2 receptors and some APC cells
humanized and chimeric antibodies
e.g. Daclizimab, Balixamab
less immunogenic than ALG and OKT3
eliminates allergy and serum sickness, infection, malignancy

Maintenance immunosuppression

steroids

mechanism:

steroid enters cell, binds to cytosolic receptors
complex migrates into nucleus, retards gene transcription
decrease T-cell cytokine production (IL-1,2)
decrease number of circulating lymphocytes

suppress chronic and acute inflammation

azothioprine/immuran

maintenance, was most widely used until cyclosporine and tacrolimus
precursor of 6MP converted in liver, nucleoside analogue
incorporated into purine biosynthetic pathway
blocks DNA/RNA synthesis which decreases lymphocyte proliferation and clonal
expansion

complications due to purine biosynthetic block

bone marrow suppression, profound leukopenia, major side effect, dose related
pancreatitis

hepatotoxicity: small vessel veno-occlusive disease
arthralgia

mycophenolate mofetil/Cellcept/inosine monophosphate dehydrogenase

safe, easy, has replaced azothioprine

competitive reversible inhibitor of purine synthesis enzyme necessary for guanosine monophosphate (GMP) production

lymphocytes are the only cells that require GMP synthesis

lymphocyte specific, limited toxicity

inhibits both B and T-cell populations

few side effects allow higher long-term dosing regimens

complications: GI intolerance, nausea, vomiting, diarrhea

marrow suppression at hi dose

cyclosporine (CSA)/sandimmune, neoral

fungal metabolite

metabolized in liver by cytochrome P-450 system

caution drug/drug interaction: many drugs impair P-450 metabolism

binds cyclophilin (CyP, intracellular molecule), complex binds and inhibits calcinurin

inhibiting calcinurin phosphatase enzyme which inhibits cytokine gene

transcription blocking synthesis of IL-1 and 2 which inhibits lymphocyte

activity and proliferation

complications

nephrotoxicity: limiting side effect, dose related

hepatotoxicity, occasional severe hypertension, hyperlipidemia

hyperkalemia, hirsutism, gingival hyperplasia, breast fibroadenoma,

tremor/neurotoxicity (aphonia), diabetes

tacrolimus/FK506

fungal metabolite

structurally different from CSA, but similar mechanism of action

binds to FK506 binding protein (FKBP) similar to CyP

complex inhibits calcinurin, block synth IL-1,2

inhibits lymphocyte activity and proliferation

100X more potent than CSA

maintenance, refractory rejection, salvage

complications similar to CSA

nephrotoxicity: limiting side effect, dose related

glucose intolerance (more DM than CSA), neurotox, hypomagnesemia,

alopecia, (less hyperlipidemia and hypertension)

no gingival hyperplasia or hirsutism

sirolimus/rapamycin

macrolid antibiotic, structurally similar to tacrolimus

binds FKBP, different mechanism of action than tacrolimus & cyclosporine

blocks IL-2 signals to nucleus, blocking lymphocyte proliferation

inhibits growth-factor stimulated lymphocyte proliferation

effects synergistic with CSA and tacrolimus, can be used in combination

can be used as single agent for low risk

side effects:

no nephrotoxicity
increases triglycerides cholesterol and liver enzymes
decreases platelets and WBCs

Drug protocols: 2 components

induction

most regimens include 3 drugs

hi dose steroids, CSA or FK506, azathioprine or mycophenylate, OKT3 or ALG (less common now), lymphocyte depletion or anti-IL-2 antibodies
steroids

maintenance

lo dose steroids; CSA or FK506, azathioprine or mycophenylate
most drugs tapered to lo dose after 6mo to 1y
steroids can often be stopped or only used for rejection episodes

Kidney transplant

transplant increases life expectancy 2X dialysis

diabetics more benefit than non

only 20% 5y survival on dialysis

6 antigen match (0 antigen mismatch) 52% 10y graft survival, no match 37%

living donor 94% 1y v 88% cadaver

continuous pulsatile perfusion preferred preservation method high risk cadaver kidney

early vascular thrombosis renal TP manifested by no urine: reimplant

25% of renal TP reactivate herpes zoster within 6 mo

predictors of long term graft failure: etiology of recipient's renal failure, number of acute rejection episodes, creatinine @ 6mo

BK polyoma virus

90% endemic in donor kidneys, 5% recipient nephropathy, 50% loss of function

two types: BK nephropathy, JC leukoencephalopathy

increasing creatinine over weeks, inflammation different from rejection

more common with mycophenolate & tacrolimus, switch to cyclosporine

usually indicative of over-immunosuppression, treat with gradual decrease in immunosuppression

cidofovir a treatment option

Liver transplant

indications: hepatitis C (20%), alcoholic cirrhosis (18%), primary biliary cirrhosis (10%), unspecified/cryptogenic (10%), sclerosing cholangitis (9%), acute hepatic necrosis (6%), hepatocellular carcinoma

end stage liver disease 90% 1y mortality

if alcoholic is abstinent 6mo, good TP candidate

APACHE II best predictor of 1y survival after liver TP

emergency transplant in fulminant liver failure

transplant before irreversible brain damage
sepsis and multiple organ failure contraindications
hepatorenal syndrome: splanchnic vasodilatation, decreased SVR, intense renal arteriolar vasoconstriction (osmolality, lytes mimic hypovolemia)
temporary benefit vasopressin analog (desmopressin/DDAVP) to reverse splanchnic vasodilatation
reversible with liver transplant
hepatocellular cancer in decompensated cirrhotics
3% risk/y of HCC with hepatitis C
contraindications to transplant: >2 tumors, tumor > 5cm, extrahepatic mets
in operative candidates transplant is best chance for long term survival
absolute contraindications: uncorrectable cardiopulmonary disease, irreversible pulmonary hypertension, pressor-dependent hypotension, recent intracranial hemorrhage, HIV/AIDS, uncontrolled sepsis, extrahepatic malignancy, inability to comply with treatment, (age > 60 alone not a contraindication), metastatic colon cancer
pulmonary hypertension hi risk ventilatory failure immediately after reperfusion
eight predictors of liver transplant survival: age of donor and recipient, creatinine, pro time, bili, hx of prior transplant, warm ischemia time (min), cold ischemia time (hrs)
(AST, sex and hepatitis C not predictors)
hepatitis C most common cause of end stage liver disease in US
80% chronic hep C after acute illness
20-30% of all liver transplant pts
universal reinfection of the graft into C+ pts, earlier cirrhosis
C+ donor into C+ recipient same survival as C- donor
CMV exacerbates chance of failure from hepatitis C
hep B transplant rare recurrence of infection, excellent outcome
severe untreated contraindication to liver TP
hepatic artery thrombosis and acute rejection most common causes of early graft loss
4% incidence adults, 6% children: 50% need retransplant
35% incidence acute rejection reactions

pancreatic transplant reverses the early secondary complications of diabetes

Small bowel: large amount of lymphoid tissue
require high dose immunosuppression
high (20%) incidence of lymphoma, fatal CMV infection