Immunopharmacology

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Immunosuppressive Agents

• Clinical Uses:
  – Organ transplantation.
  – Autoimmune Disorders.
  – Isoimmune Disease, e.g. hemolytic disease of newborn.
  – Prevention of cell proliferation, e.g. coronary stents, neovascular macular degeneration.
Immunosuppressive Agents

- Glucocorticoids.
- Calcineurin Inhibitors.
- Proliferation Signal Inhibitors.
- Mycophenolate Mofetil.
- Thalidomide.
- Cytotoxic Agents.
- Immunosuppressive Antibodies.
- Monoclonal antibodies.
Clinical Uses of Glucocorticoids

• First-line immunosuppressive therapy for:
  – Solid organ
  – Hematopoietic stem cell transplant recipients
  – Graft-versus-host disease (GVHD).

• Idiopathic thrombocytopenic purpura and rheumatoid arthritis.

• Bronchial asthma.
• Premedication for agents (e.g. blood products, and drugs) known to cause undesirable immune responses.
Side Effects to Glucocorticoids

- Immunodeficiency
- adrenal glands
- Hyperglycemia and abnormal Fat redistribution
- Growth failure, delayed puberty.
- Excitatory effects on central nervous system (euphoria, psychosis)
- Osteoporosis
- Cataract
- Gastric irritation and ulceration.
Drugs affecting IL-2

These drugs can be further divided into three main classes:

A. Calcineurin inhibitors (cyclosporine and tacrolimus)

B. Co-stimulation blockers (belatacept)

C. mTOR inhibitors (sirolimus and everolimus)
The immune activation cascade can be described as a three-signal model.

Signal 1 constitutes T-cell triggering at the CD3 receptor complex by an antigen on the surface of an antigen-presenting cell (APC).

Signal 2 (costimulation) occurs when CD80 and CD86 on the surface of APCs engage CD28 on T cells.

Both Signals 1 and 2 activate several intracellular signal transduction pathways one of which is the calcium-calcineurin pathway.

Production of cytokines such as interleukin (IL)-2, IL-15, CD154, and CD25.

IL-2 then binds to CD25 (IL-2 receptor) on the surface of other T cells to activate mammalian target of rapamycin (mTOR), providing Signal 3, the stimulus for T-cell proliferation.
NFATc: cytosolic Nuclear Factor of Activated T cells
Cyclosporine

- **Mechanism of action:** suppresses cell-mediated immune reactions, whereas humoral immunity is affected to a far lesser extent.

- Cyclosporine binds to a cyclophilin.
- The formed Complex binds to calcineurin.
- Calcineurin: is responsible for dephosphorylating NFATc.

- The end result is a decrease in IL-2, which is the primary chemical stimulus for increasing the number of T lymphocytes.
Therapeutic Uses

• To prevent rejection of kidney, liver, and cardiac allogeneic transplants
• Combined in a double-drug or triple-drug regimen with
  • 1. Corticosteroids
  • 2. Antimetabolite such as Mycophenolate mofetil.
• Cyclosporine may also be used for recalcitrant psoriasis.
Pharmacokinetics

• Cyclosporine may be given either orally or by intravenous (IV) infusion.

• Oral absorption is variable due to metabolism by a cytochrome P450 (CYP3A4) isoenzyme in the gastrointestinal (GI) tract and efflux by P-glycoprotein (P-gp).

• Cyclosporine is extensively metabolized, primarily by hepatic CYP3A4.

• Excretion of the metabolites is primarily through the biliary route into the feces.
Adverse Effects

• Nephrotoxicity (dose dependant) ...most common  >>>>Be careful of drug combinations

• Hepatotoxicity

• In patients taking cyclosporine, infections are common and may be life threatening.
Cyclosporine

• Nephrotoxicity.
• Hypertension.
• Hyperglycemia.
• Liver dysfunction.
• Hyperkalemia.
• Altered mental status, seizures.
• Hairsutism.
• Gum hyperplasia
• Lymphoma and other cancers (Kaposi's sarcoma, skin cancer) due to induction of TGF-β.
Cyclosporin Monitoring Parameters

• Cyclosporine trough levels.
• Serum electrolytes.
• Renal function.
• Hepatic function.
• Blood pressure.
• Serum cholesterol.
Tacrolimus

• MOA: binds immunophilin, FKBP-12 (FK-binding protein)
• Also calcineurin inhibitor, is a macrolide that is isolated from the soil fungus Streptomyces tsukubaensis.
• This drug is preferred over cyclosporine because of its
  1. increased potency
  2. decreased episodes of rejection
  3. Steroid sparing effects
Therapeutic Uses

• preventing liver and kidney rejections (along with glucocorticoids).

• It is also used in heart and pancreas transplants and rescue therapy in patients after failure of standard rejection therapy.

• An ointment preparation is approved for moderate to severe atopic dermatitis unresponsive to conventional therapies.
Pharmacokinetics

- Orally or IV.
- The oral route is preferable, but absorption is incomplete and variable, requiring tailoring of doses.
- Tacrolimus is subject to gut metabolism by CYP3A4/5 isoenzymes and is a substrate for P-gp. **Bioavailability ?!**

- Absorption is decreased if the drug is taken with high-fat or high-carbohydrate meals.
- The drug and its metabolites are primarily eliminated in the feces.
Adverse Effects

• Nephrotoxicity and neurotoxicity (tremor, seizures, and hallucinations) more severe than with cyclosporine

• Development of posttransplant insulin-dependent diabetes mellitus is a problem, especially in black and Hispanic patients.

• Other toxicities are similar to cyclosporine, except that tacrolimus does not cause hirsutism or gingival hyperplasia, but it can cause alopecia.

• Lower incidence of cardiovascular toxicities, such as hypertension and hyperlipidemia
Belatacept

• Costimulation blocker (2nd Generation), is a recombinant fusion protein that targets signal 2 in the immune activation cascade. It is used for long-term maintenance immunosuppressive therapy.
Mechanism of Action

Belatacept blocks CD28-mediated costimulation of T lymphocytes (signal 2) by binding to CD80 and CD86 on APCs. This prevents the downstream stimulatory signals promoting T-cell survival, proliferation, and IL-2 production.
Therapeutic Uses

- kidney transplantation in combination with basiliximab, mycophenolate mofetil, and corticosteroids.

- This drug can take the place of the calcineurin inhibitors in an effort to avoid the detrimental long-term cardiovascular, metabolic, and renal complications.

- Note: The first-generation costimulation blocker abatacept is approved for rheumatoid arthritis.
Pharmacokinetics

• The first IV maintenance immunosuppressant and is dosed in two phases.
• The initial high-dose phase is administered on a more frequent interval.
• In the maintenance phase, the dose is decreased and administered once a month.
• Monthly dosing may be beneficial in patients for whom medication compliance is an issue.
• Belatacept clearance is not affected by age, sex, race, renal, or hepatic function.
Adverse Effects

• Belatacept increased the risk of post-transplant lymphoproliferative disorder (PTLD), particularly of the central nervous system. Therefore, it is contraindicated in those patients who have never been exposed to the Epstein-Barr virus (EBV), a common cause of PTLD.

• Common adverse events include:
  • Anemia
  • Diarrhea
  • Urinary tract infection,
  • Edema.
Proliferation Signal Inhibitors (PSIs)

- Sirolimus (Rapamycin).
- Everolimus.
- Bind the circulating immunophylline FK506-binding protein 12.
- Instead of forming a complex with calcineurin, sirolimus binds to mTOR (a serine/threonine kinase), interfering with signal 3.

  - The complex inhibits interleukin-driven T-cell and B-cell proliferation as well as immunoglobulin production.
The sirolimus-FKBP complex inhibits mTOR, thereby inhibiting translation and causing T cells to arrest in the G1 phase.

mTOR increases translation of selected mRNAs that promote transition from G1 to S phase of the cell cycle.
• **Sirolimus (Rapamycin) & Everolimus.**

• Available for oral and topical administration.

• Approved for use in renal transplantation, in combination with cyclosporine and corticosteroids.

• **Sirolimus-eluting coronary stents:** The antiproliferative action of sirolimus is also valuable in cardiology where sirolimus-coated stents are used to inhibit restenosis of the blood vessels by reducing proliferation of the endothelial cells.

• Everolimus also indicated second-line treatment in patients with advanced renal cell carcinoma.
Adverse effects

• A common adverse effect of sirolimus is hyperlipidemia (elevated cholesterol and triglycerides), which may require treatment.
• The combination of cyclosporine and sirolimus is more nephrotoxic
• Others: headache, nausea and diarrhea, leukopenia, and thrombocytopenia.
• Impaired wound healing ......obese patients and those with diabetes.
Pharmacokinetics

- The drug is available as an oral solution or tablet.
- Although it is readily absorbed, high-fat meals can decrease the absorption.
- Sirolimus has a long half-life (57 to 62 hours), allowing for once-daily dosing.
- A loading dose is recommended at the time of initiation of therapy.
- Like both cyclosporine and tacrolimus, sirolimus is metabolized by the CYP3A4 isoenzyme, is a substrate for P-gp, and has similar drug interactions.
- Sirolimus also increases the concentrations of cyclosporine, and careful blood level monitoring of both agents must be done to avoid harmful drug toxicities.
Everolimus

• Everolimus is rapidly absorbed, but absorption is decreased with high-fat meals. Everolimus is a substrate of CYP3A4 and P-gp and, thus, is subject to the same drug interactions.

• It has a much shorter half-life than sirolimus and requires twice-daily dosing.

• Everolimus increases drug concentrations of cyclosporine, thereby enhancing the nephrotoxic effects of cyclosporine, and is, therefore, recommended to be used with reduced doses of cyclosporine.
Everolimus side effects

• An additional adverse effect noted with everolimus is angioedema, which may increase with concomitant use of angiotensin-converting enzyme inhibitors.

• There is also an increased risk of kidney arterial and venous thrombosis, resulting in graft loss, usually in the first 30 days posttransplantation.
Azathioprine

• The first agent to achieve widespread use in organ transplantation.

• It is a prodrug that is converted first to 6-mercaptopurine (6-MP) and then to the corresponding nucleotide, thioinosinic acid.
Azathioprine

• Prodrug of mercaptopurine.
• Metabolized by Xanthine oxidase (so dose is reduced when given with allopurinol).
• Antimetabolite: interferes with purine nucleic acid metabolism, and consequently will destroy and inhibit lymphoid cell proliferation stimulated by antigens.
• Blocks cellular immunity as well as primary and secondary serum antibody responses.
Azathioprine

- Used in renal allograft, acute glomerulonephritis, SLE, RA, Crohn’s Disease, MS, and ITP.

- Toxicity:
  - Bone marrow suppression.
  - Skin rashes, fever.
  - N, V, D.
  - Hepatic dysfunction and jaundice.
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Drug Interactions

• Concomitant use with angiotensin-converting enzyme inhibitors or cotrimoxazole in renal transplant patients can lead to an exaggerated leukopenic response.

• Allopurinol, an agent used to treat gout, significantly inhibits the metabolism of azathioprine. Therefore, the dose of azathioprine must be reduced. Nausea and vomiting are also encountered.
Mycophenolate mofetil

• Replaced azathioprine because of its safety and efficacy in prolonging graft survival.

• Uses: heart, kidney, and liver transplants.

• As an ester, it is rapidly hydrolyzed in the GI tract to mycophenolic acid.

• This is a potent, reversible, noncompetitive inhibitor of inosine monophosphate dehydrogenase, which blocks the de novo formation of guanosine phosphate.

• Deprives proliferating T and B cells of a key component of nucleic acids.
Mycophenolate inhibits IMP dehydrogenase, blocking the formation of GMP. GMP is a key precursor required for nucleic acid synthesis. Blocking the formation of GMP deprives rapidly proliferating T and B cells of this precursor.
Pharmacokinetics

• Mycophenolic acid is quickly and almost completely absorbed after oral administration.

• The glucuronide metabolite is excreted predominantly in urine.

• Concomitant administration with antacids containing magnesium or aluminum, or with cholestyramine, can decrease absorption of the drug.
Adverse effects

• GI adverse effects: (most Common) diarrhea, nausea, vomiting, and abdominal pain.

• High doses of mycophenolate mofetil are associated with a higher risk of CMV infection.
Thalidomide

- Historical sedative drug withdrawn in 1960s because of its teratogenicity (Phocomelia).
- Inhibits angiogenesis.
- Antiinflammatory.
- Inhibits tumor necrosis factor-alpha (TNF-α)
- Reduces phagocytosis by neutrophils.
- Increases production of IL-10
- Enhances cell-mediated immunity via interaction with T cells.
Thalidomide

• Use continued only for leprosy.

• Very successful in multiple myeloma.

• Clinical trials in other diseases:
  myelodysplastic syndrome, AML, graft-versus-host disease, and solid tumors.
Thalidomide

• **Toxicity:**
  – Teratogenicity.
  – Peripheral neuropathy.
  – Constipation.
  – Rash.
  – Fatigue.
  – Hypothyroidism.
  – DVT.

• **Lenalidomide**

• **CC-4047 (Actimid).**
  – Are much less toxic derivatives.
**Immunosuppressive Antibodies**

- Molecular Biology >>>> Monoclonal Antibodies.
- **Humanized Antibodies**: “-umab” or “-umab”.
  - Replacing most of the regions, but keeping only the variable, antigen-specific regions intact.
- **Chimeric Antibodies**: “-imab” or “-ximab”.
  - Less complete replacement of the murine components.
Immunosuppressive Antibodies

• Antilymphocyte & Antithymocyte Antibodies.
• Muromonab.
• Immune Globulin Intravenous.
• Rh\textsubscript{0}(D) Immune Globulin Micro-Dose.
• Hyperimmune Immunoglobulins.
Rh\textsubscript{o}(D) Immune Globulin Micro-Dose.

• One of the earliest major advances in immunopharmacology.

• Concentrated (15%) solution of human IgG containing a higher titer of antibodies against the Rh\textsubscript{o}(D) antigen of the red cell.

• Given, to the mother, within 24-72 hours after the birth of an Rh-positive infant.

• Infant’s red cells are cleared from circulation before the mother can generate a B-cell response against the Rh\textsubscript{o}(D) antigen.

• This will protect against future hemolysis.
Muromonab-CD3 (OKT3)

- Muromonab-CD3 is a murine (mouse) monoclonal antibody that is directed against the glycoprotein CD3 antigen of human T cells.

- Muromonab-CD3 was the first monoclonal antibody approved for clinical use in 1986, indicated for the treatment of corticosteroid-resistant acute rejection of kidney, heart, and liver allografts.

- The drug has been discontinued from the market due to the availability of newer biologic drugs with similar efficacy and fewer side effects.
Basiliximab

• The antigenicity and short serum half-life of the murine monoclonal antibody have been averted by replacing most of the murine amino acid sequences with human ones by genetic engineering.

• Basiliximab [is said to be “chimerized” because it consists of 25% murine and 75% human protein.

• “Humanized” monoclonal antibodies (for example, trastuzumab used for breast cancer, have a smaller stretch of nonhuman protein.

• Basiliximab is approved for prophylaxis of acute rejection in renal transplantation in combination with cyclosporine and corticosteroids. It is not used for the treatment of ongoing rejection.
Basiliximab

• An anti-CD25 antibody that binds to the α chain of the IL-2 receptor on activated T cells and, thus, interferes with the proliferation of these cells.

• Blockade of this receptor foils the ability of any antigenic stimulus to activate the T-cell response system.

• Basiliximab is given as an IV infusion. The serum half-life of basiliximab is about 7 days.

• Usually, two doses of this drug are administered—the first at 2 hours prior to transplantation and the second at 4 days after the surgery. The drug is generally well tolerated, with GI toxicity as the main adverse effect.
MONOCLONAL ANTIBODIES (MABs)

Antitumor MABs

Alemtuzumab is a humanized IgG 1 with a kappa chain that binds to CD52 found on normal and malignant B and T lymphocytes, NK cells, monocytes, macrophages, and a small population of granulocytes.
Currently, alemtuzumab is approved for the treatment of B-cell chronic lymphocytic leukemia in patients who have been treated with alkylating agents.
MABs Used to Deliver Isotopes to Tumors

Arcitumomab is a murine Fab fragment from an anti-carcinoembryonic antigen (CEA) antibody labeled with technetium 99m (99m Tc) that is used for imaging patients with metastatic colorectal carcinoma (immunoscintigraphy) to determine extent of disease.

CEA is often upregulated on tumor in patients with gastrointestinal carcinomas. The use of the Fab fragment decreases the immunogenicity of the agent so that it can be given more than once; intact murine monoclonal antibodies would elicit stronger HAMA.
MABs Used to Deliver Isotopes to Tumors

Capromab pendetide is a murine monoclonal antibody specific for prostate specific membrane antigen. It is coupled to isotopic indium (\(^{111}\)In) and is used in immunoscintigraphy for patients with biopsy-confirmed prostate cancer and post-prostatectomy in patients with rising prostate specific antibody level to determine extent of disease.
MABs Used to Deliver Isotopes to Tumors

Ibritumomab tiuxetan is an anti-CD20 murine monoclonal antibody labeled with isotopic yttrium (90 Y). The radiation of the isotope coupled to the antibody provides the major antitumor activity. Ibritumomab is approved for use in patients with relapsed or refractory low-grade, follicular, or B-cell non-Hodgkin’s lymphoma, including patients with rituximab-refractory follicular disease. It is used in conjunction with rituximab in a two-step therapeutic regimen.