Immunosupressants

Classification

1. *Calcineurin inhibitors*

   Cyclosporine, Tacrolimus

2. *Antiproliferative drugs*

   Azathioprine , Cyclophosphamide ,Methotrexate, Chorambucil

3. *Glucocorticoids*

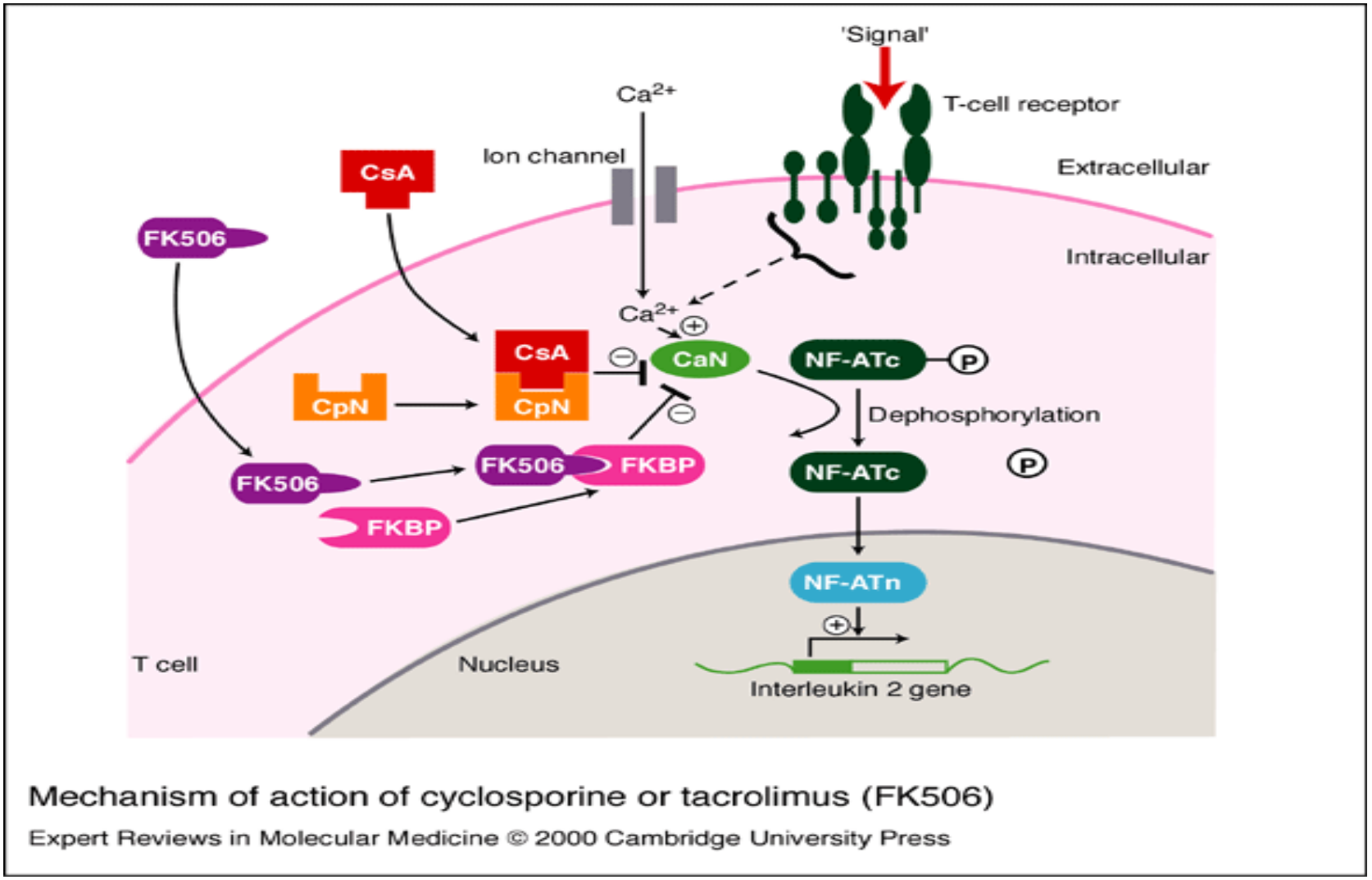
   Prednisolone and others

4. *Antibodies*

   Muromonab CD3, Antithymocyte globulin (ATG), Rho (D) immunoglobulin

Pharmacology of Cyclosporine

Cyclosporine (cyclosporin A), a cyclic polypeptide of 11 amino acids, is produced by the fungus *Beauveria nivea*.



Mechanism of action of cyclosporine or tacrolimus (FK506)

Mechanism of action

1. Cyclosporine suppresses some humoral immunity but is more effective against **T cell-dependent immune mechanisms** such as transplant rejection and some forms of auto-immunity.
2. Cyclosporine forms a complex with **cyclophilin**, a cytoplasmic-receptor protein present in target cells. This complex binds to calcineurin, **inhibiting** Ca^{2+}-stimulated **dephosphorylation of the cytosolic component of NFAT.**
3. When cytoplasmic NFAT is dephosphorylated, it translocates to the nucleus and complexes with nuclear components required for complete T-cell activation, including trans-activation of IL-2 and other lymphokine genes.
4. Calcineurin phosphatase activity is inhibited after physical interaction with the cyclosporine/cyclophilin complex.
5. This prevents NFAT dephosphorylation such that NFAT does not enter the nucleus, gene transcription is not activated, and the T lymphocyte fails to respond to specific antigenic stimulation.
6. Cyclosporine also increases expression of transforming growth factor (TGF α-), a potent inhibitor of IL-2–stimulated T-cell proliferation and generation of cytotoxic T lymphocytes (CTLs).

Pharmacokinetics

1. Cyclosporine and tacrolimus are available as oral or intravenous agents.
2. Because cyclosporine exhibits erratic bioavailability, serum levels are routinely monitored.
3. The drug undergoes slow hepatic metabolism by the cytochrome P450 system and has a long half-life.
4. Its metabolism is affected by a host of other drugs.

Adverse effects

1. Renal dysfunction, hypertension, and neurotoxicity.
2. Hyperglycemia, hyperlipidemia, and cholelithiasis.
3. Hypertriglyceridemia, hepatotoxicity, diarrhea, and myelosuppression.

Drug interactions

1.Aminoglycoside, vamcomycin, amphotericin B and NSAIDs cause nephrotoxicity.

2. Pheytoin, phenobarbitone, rifampin lower blood levels of CsA.

3. Erythromycin, ketoconazole increase toxicty

4. Potassium supplements cause hyperkalaemia.

Uses

1.Prevention and treatment of graft rejection reaction.

2. Second line drug in autoimmune diseases.

3. Aplastic anemia.

Brands

IMUSPORIN 25, 50, 100 mg soft gelatin cap.

Pharmacology of Azathioprine

Azathioprine is a purine antimetabolite. It is an imidazolyl derivative of 6-mercaptopurine

Mechanism of action

1. Following exposure to nucleophiles such as glutathione, azathioprine is cleaved to 6-mercaptopurine.
2. Which is converted to additional metabolites that inhibit *de novo* purine synthesis.
3. A fraudulent nucleotide, 6-thio-IMP, is converted to 6-thio-GMP and finally to 6-thio-GTP, which is incorporated into DNA.
4. Cell proliferation thereby is inhibited, impairing a variety of lymphocyte functions.

Pharmacokinetics

1. Azathioprine is well absorbed orally and reaches maximum blood levels within 1-2 hours after administration.
2. The $t_{1/2}$ of azathioprine is 10 minutes, while that of its metabolite, 6-mercaptopurine, is 1 hour. Other metabolites have a $t_{1/2}$ of up to 5 hours.
3. Azathioprine and mercaptopurine are moderately bound to plasma proteins and are partially dialyzable.

Adverse effects

1. Bone marrow suppression, including leukopenia (common), thrombocytopenia (less common), and/or anemia (uncommon).
2. Increased susceptibility to infections (especially varicella and herpes simplex viruses)
3. Hepatotoxicity, alopecia, GI toxicity, pancreatitis, and increased risk of neoplasia.

Drug Interactions

Azathioprine + Allopurinol cause leukopenia, thrombocytopenia, and anemia as a result of myelosuppression.

Uses

1. It is indicated as an adjunct for prevention of organ transplant rejection and in severe rheumatoid arthritis.
2. Autoimmune diseases.

Brands

IMURAN, TRANSIMUNE 50mg tab

Pharmacology of Glucocorticoids Prednisolone

Mechanism of Action

1. Glucocorticoids causes lyses and induce the redistribution of lymphocytes, causing a rapid, transient decrease in peripheral blood lymphocyte counts.
2. Steroids bind to receptors inside cells; either these receptors, glucocorticoid-induced proteins, or interacting proteins regulate the transcription of numerous other genes.
3. Glucocorticoids curtail activation of NF-B, which increases apoptosis of activated cells.
4. Key pro-inflammatory cytokines such as IL-1 and IL-6 are down regulated.T cells are inhibited from making IL-2 and proliferating.
5. The activation of cytotoxic T lymphocytes is inhibited.

Adverse effects

1. Growth retardation in children,
2. Avascular necrosis of bone, osteopenia,
3. Increased risk of infection, poor wound healing, cataracts, hyperglycemia, and hypertension.

Uses

1. Combined with other immunosuppressive agents to prevent and treat transplant rejection.
2. Treatment of graft-versus-host disease in bone-marrow transplantation.
3. Treat auto-immune disorders such as rheumatoid and other arthritides, systemic lupus erythematosus, systemic dermatomyositis, psoriasis, asthma and other allergic disorders, inflammatory bowel disease, inflammatory ophthalmic diseases, auto-immune hematological disorders, and acute exacerbations of "Multiple Sclerosis".

Brands

DELTACORTRIL, HOSTACORTIN 5,10 mg tab

Pharmacology of Antibodies Muromonab CD3

Mechanism of Action

1. Muromonab-CD3 binds to the chain of CD3, a monomorphic component of the T-cell receptor complex involved in antigen recognition, cell signaling, and proliferation. Antibody treatment induces rapid internalization of the T-cell receptor, thereby preventing subsequent antigen recognition.
2. Muromonab-CD3 also reduces function of the remaining T cells, as defined by lack of IL-2 production and great reduction in the production of multiple cytokines, perhaps with the exception of IL-4 and IL-10.

Adverse drug reaction

1. The major side effect of anti-CD3 therapy is the "cytokine release syndrome" syndrome typically begins 30 minutes after infusion of the antibody (but can occur later) and may persist for hours.
2. Skin reactions and cardio-respiratory and central nervous system (CNS) disorders, including aseptic meningitis.
3. Potentially fatal pulmonary edema, acute respiratory distress syndrome, cardiovascular collapse, cardiac arrest, and arrhythmias have been described.

Uses

Muromonab-CD3 is indicated for treatment of acute organ transplant rejection

Immunostimulants

Levamisole

1. Levamisole (ERGAMISOL) was synthesized originally as an anthelmintic but appears to "restore" depressed immune function of B lymphocytes, T lymphocytes, monocytes, and macrophages.

2. Its only clinical indication was as adjuvant therapy with 5-fluorouracil after surgical resection in patients with Dukes' stage C colon cancer .

3. Because of its risk for fatal agranulocytosis, levamisole was withdrawn from the U.S. market in 2005.

Thalidomide

1. Indicated for the treatment of patients with erythema nodosum leprosum and multiple myeloma.
2. In addition, it has orphan drug status for mycobacterial infections, Crohn's disease, HIV-associated wasting, Kaposi sarcoma, lupus, myelofibrosis, brain malignancies, leprosy, graft-versus-host disease, and aphthous ulcers.
3. Thalidomide has been reported to decrease circulating TNF- in patients with erythema nodosum leprosum but to increase it in patients who are HIV seropositive.
4. Alternatively, it has been suggested that the drug affects angiogenesis. The anti–TNF- effect has led to its evaluation as a treatment for severe, refractory rheumatoid arthritis.

Lenalidomide

1. Lenalidomide (REVLIMID), 3-(4-amino-1-oxo 1,3-dihydro-2H-isoindol-2-yl) piperidine-2,6-dione, is a thalidomide analog with immunomodulatory and anti-angiogenic properties.
2. Lenalidomide is FDA approved for the treatment of patients with transfusion-dependent anemia due to low- or intermediate risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

Bacillus Calmette-GuéRin (BCG)

1. Live BCG (TICE BCG, THERACYS) is an attenuated, live culture of the bacillus of Calmette and Gu é rin strain of *Mycobacterium bovis* that induces a granulomatous reaction at the site of administration.
2. By unclear mechanisms, this preparation is active against tumors and is indicated for the treatment and prophylaxis of carcinoma *in situ* of the urinary bladder and for prophylaxis of primary and recurrent stage Ta and/or T1 papillary tumors after transurethral resection.
3. Adverse effects include hypersensitivity, shock, chills, fever, malaise, and immune complex disease.

Recombinant Cytokines

Interferons

1. The interferons bind to specific cell-surface receptors that initiate a series of intracellular events: induction of certain enzymes, inhibition of cell proliferation, and enhancement of immune activities, including increased phagocytosis by macrophages and augmentation of specific cytotoxicity by T lymphocytes.
2. Recombinant IFN--2b (INTRON A) is obtained from *Escherichia coli* by recombinant expression.
3. IFN-2b is indicated in the treatment of a variety of tumors, including hairy cell leukemia, malignant melanoma, follicular lymphoma, and AIDS-related Kaposi sarcoma.
4. It also is indicated for infectious diseases, chronic hepatitis B, and condylomata acuminata.
5. Flu-like symptoms, including fever, chills, and headache, are the most common adverse effects after IFN--2b administration.
6. All interferons carry a boxed warning regarding development of pulmonary hypertension.

IFN--1b

1. A recombinant polypeptide that activates phagocytes and induces their generation of oxygen metabolites that are toxic to a number of microorganisms.
2. It is indicated to reduce the frequency and severity of serious infections associated with chronic granulomatous disease and to delay the time to progression in severe malignant osteopetrosis. Adverse reactions include fever, headache, rash, fatigue, GI distress, anorexia, weight loss, myalgia, and depression.

IFN--1a

1. A 166–amino acid recombinant glycoprotein, and IFN--1b (BETASERON), a 165–amino acid recombinant protein, have antiviral and immunomodulatory properties.
2. They are FDA- approved for the treatment of relapsing MS to reduce the frequency of clinical exacerbations (see "Multiple Sclerosis"). The mechanism of their action in MS is unclear. Flu-like symptoms (e.g., fever, chills, myalgia) and injection-site reactions have been common adverse effects.

Interleukin-2

1. **Human recombinant IL-2** is produced by recombinant DNA technology in *E. coli*.
2. It has the following *in vitro* biological activities of native

   IL-2: enhancement of lymphocyte proliferation and growth of IL-2-dependent cell lines, enhancement of lymphocyte-mediated cytotoxicity and killer cell activity, and induction of IFN- activity.
3. Is indicated for the treatment of adults with metastatic renal cell carcinoma and melanoma.
4. Serious cardiovascular toxicity resulting from capillary leak syndrome.
5. Hypotension, reduced organ perfusion, and death may occur.
6. An increased risk of disseminated infection