Immunosuppressant Medications

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Presentation outline

- **Evolution of immunosuppressive therapies**
- **Common indications for immunosuppression**
- **Discussion of immunosuppressive drug classes**
- **Prophylaxis, Immunization and Pregnancy considerations**

Goals of immunosuppressive therapies

- **Prevent allograft rejection after transplant**
- **Control baseline inflammatory disease**
- **Prevent and/or treat disease flares**

- **Minimize adverse effects**
- **Avoid infectious complications**

Indications

- **Solid organ and bone marrow transplantation**

- **Autoimmune disease**

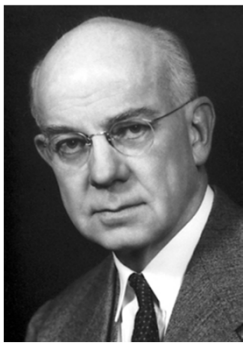
Rheumatoid arthritis	Multiple sclerosis	Psoriasis	SLE
Crohn's disease	Ulcerative colitis	Behcet's	FSGS
Myasthenia gravis	Ankylosing spondylitis	Sarcoidosis	

- **Asthma**

- **Pre-20th century attempts at transplantation**
  - **300 B.C.: Pien Chi'ao, Chinese physician**
  - **3rd century A.D.: Cosmas & Damian**
  - **"biochemical barrier to transplantation" Ernst Unger (1909)**
- **1910s – use of cytotoxic medications**
- **1950s – sublethal total-body irradiation**
- **1954 – successful kidney transplant between identical twins**

1950 Nobel Prize in Physiology or Medicine

Edward Calvin Kendall

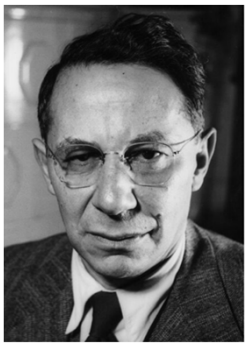


Biochemist

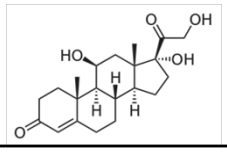
Philip Showalter Hench

Rheumatologist

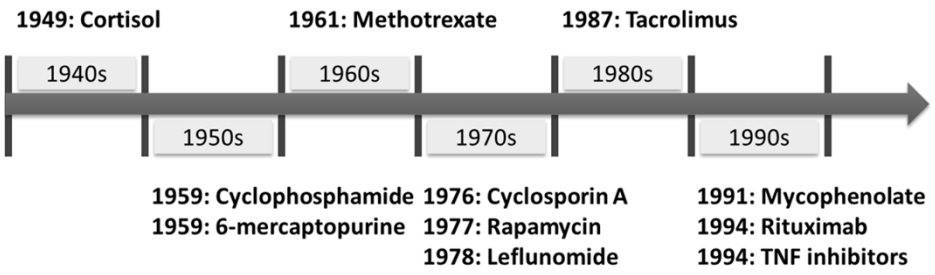
Tadeusz Reichstein



Chemist



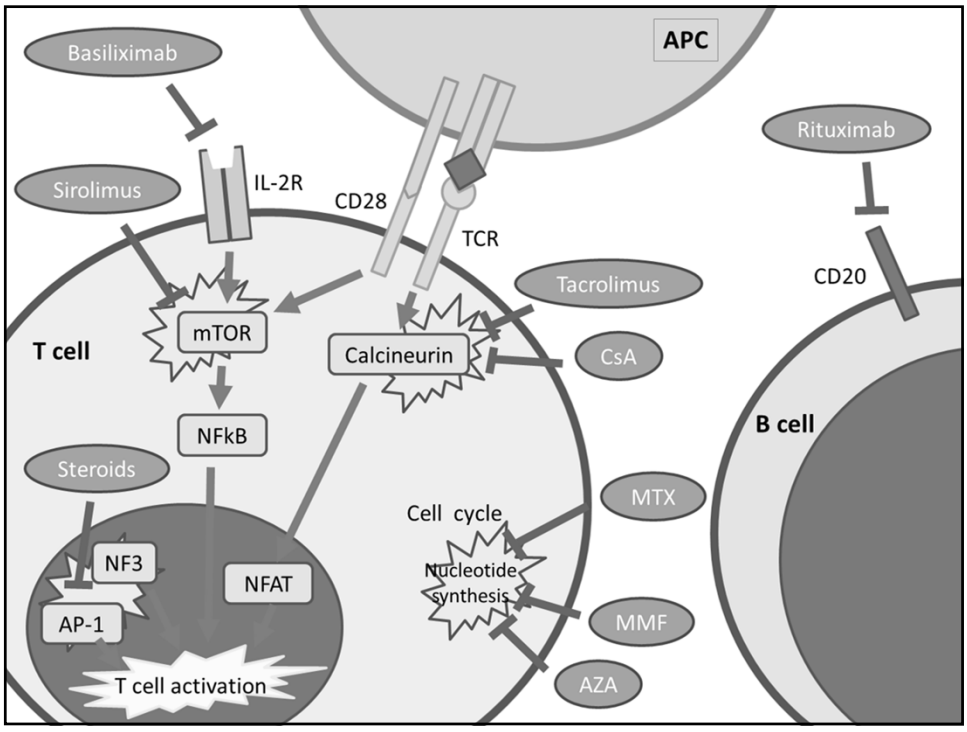
History of Immunosuppression



1959: Cyclophosphamide
1959: 6-mercaptopurine

1976: Cyclosporin A
1977: Rapamycin
1978: Leflunomide

1991: Mycophenolate
1994: Rituximab
1994: TNF inhibitors



Immunosuppressant Medications

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Corticosteroids

- **Nonspecific anti-inflammatory affects both B and T cell lines**

Medication	Activity		Duration of Action (hours)	Equipotent Dose (mg)
	Glucocorticoid	Mineralocorticoid		
Hydrocortisone	1	1	8-12	20
Prednisone	4	0.8	18-36	5
Methylprednisolone	5	0.5	18-36	4
Dexamethasone	30	0	36-54	0.75
Fludrocortisone	10	125	18-36	N/A

- **Do not discontinue abruptly (≥ 7 days)**

***Indian J. Dermatol. Venereol. Leprol.* 2007;73(4):218-221.**

Corticosteroids

Adverse Effects

- Nausea/vomiting
  - Give with food
- Increased appetite
- Hyperglycemia
- Confusion, nervousness, depression, mood changes
- Insomnia
- Edema
- Gout
- Osteoporosis
  - Consider calcium/vitamin D supplement
- Hyperlipidemia
- Hypertension
- Impaired wound healing

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e9d6774e-45f6-419f-b388-8dfb4dd34944

Disease-modifying Antirheumatic Drugs (DMARDs)

- Methotrexate
  - Inhibits cytokine production and purine biosynthesis = reduction in inflammation
  - 1st line in the treatment of RA
  - Available PO, IV, subQ
  - Onset of action: 3-4 weeks
  - Typically dosed once a week or split dosing (>15mg/week)
  - Renally eliminated

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8f1260de-b60c-4f0e-8af6-0e957b0a281b

DMARDs

- Methotrexate
  - Adverse effects: nausea/vomiting/diarrhea, thrombocytopenia, leukopenia, ↑ LFTs, pulmonary fibrosis
  - Can induce folic acid deficiency
    - Give with 1mg/day to reduce adverse effects
  - Monitoring
    - CBC w/platelets, LFTs every 1-2 months
    - Levels rarely obtain, usually reserved for high dose (hematologic malignancies)

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8f1260de-b60c-4f0e-8af6-0e957b0a281b

DMARDs

- Sulfasalazine
  - Sulfapyridine ↓ erythrocyte sedimentation rate and C-reactive protein
  - Used in RA (combination), IBD, spondyloarthritis
  - Available PO
  - On set of action: 4- 9 weeks
  - Dose: 500 mg daily x 1 week then ↑ the dose by 500 mg daily on a weekly basis until a dose of 2 g daily (divided doses) is achieved

Arthritis Rheum. 2008;59:762.
Br J Rheumatol. 1997;36:382.

DMARDs

- Sulfasalazine
  - Adverse effects
    - Hepatotoxicity, rash
      - Usually occur within the first 12 weeks of treatment
    - Dose related: nausea/vomiting/diarrhea, headache, leukopenia
  - Monitoring
    - Glucose-6-phosphate dehydrogenase (G6PD) before initiating therapy
    - CBC, LFTs every 1-2 months and after increasing dose

Br J Rheumatol. 1997;36:382.

DMARDs

- Hydroxychloroquine
  - ↓ cytokine production, lymphocyte proliferation, and autoantibody production
  - Used in lupus and RA
  - Available PO
  - Onset of action: 1-3 months
  - Dose
    - Lupus: 200mg – 400mg (daily or divided doses)
    - RA: 400mg – 600mg (daily or divided doses)

Br J Rheum. 1997;36:799-805.

DMARDs

- Hydroxychloroquine
  - Adverse effects
    - Corneal deposits, retinopathy
    - Pruritic maculopapular lesions, hyperpigmentation,
    - Dose related: nausea/vomiting/diarrhea, headache
  - Monitoring
    - Eye examination at baseline and yearly
    - No routine lab monitoring required

DMARDs

- Leflunomide
  - Inhibits T-cell proliferation and production of B lymphocytes by inhibiting the production of multiple tyrosine kinase
  - Interferes with viral assembly
  - Used in RA, Crohn's disease, psoriatic arthritis, transplant (active BK virus or CMV)

Immunopharmacology. 2000;47:291-298

DMARDs

- Leflunomide
  - Available PO
  - Onset of action: 3-4 weeks
  - Dose
    - RA
      - 100mg daily x 3 days then 20mg daily or 10-20mg/daily without loading dose
    - Transplant
      - 100mg daily x 3 days then 20-60mg daily

American Journal of Transplantation. 2011;11:1079-1084
Immunopharmacology. 2000;47:291-298

DMARDs

- Leflunamide
  - Adverse effects
    - Nausea/vomiting/diarrhea, alopecia
    - Leukopenia, anemia, thrombocytopenia
  - Monitoring
    - CBC and LFTs monthly initially then every 8 weeks
    - Teriflunomide (leflunomide metabolite) can be monitored in transplants: target goal > 50,000ng/mL

American Journal of Transplantation. 2011;11:1079-1084
Dialysis & Transplantation. 2011;40:102-107
Immunopharmacology. 2000;47:291-298

Biologic DMARDs

- Growing field
  - Kinase inhibitors
  - TNF alpha inhibitors
  - IL-6 receptor inhibitors
  - T cell costimulatory modulators
- Used in RA, Crohn's disease, psoriatic arthritis
- Typically available subq or IV
- Risk of infection and malignancy

Rheumatology. 2012; 51:37-43.

Antimetabolites

- Mycophenolate
  - Interferes with purine synthesis→↓T-cell and B-cell proliferation
  - Used in transplant immunosuppression, autoimmune hepatitis, lupus nephritis

Pharmacotherapy. 1997;17:1178-1197.

Antimetabolites

- Mycophenolate
  - Available PO (tablets, capsules, liquid) and IV
  - Dosing
    - Cellcept (mycophenolate mofetil): 500mg-1500mg Q12H
    - Myfortic (mycophenolate sodium): 360mg-1080mg Q12H
    - Conversion: Myfortic 720mg = Cellcept 1000mg

Pharmacotherapy. 1997;17:1178-1197.

Antimetabolites

- Mycophenolate
  - Adverse effects
    - Nausea/vomiting/diarrhea
      - May be less with mycophenolate sodium (Myfortic)
    - Leukopenia, thrombocytopenia
    - Headache
    - Hypertension
  - Monitoring
    - CBC monthly
    - No correlation between drug levels and prevention of rejection/efficacy and toxicity

Antimetabolites

- Mycophenolate
  - REMS program
    - Risk of taking mycophenolate and pregnancy
      - Increased risk of miscarriage in the 1st trimester
      - Increased risk of congenital malformations
    - https://www.mycophenolaterems.com/

Antimetabolites

- Azathioprine
  - Inhibits purine synthesis
  - Used in RA, transplant immunosuppression, lupus, IBS
  - Available PO and IV (been on backorder)
  - Dose
    - 1-3 mg/kg/day or 50-150mg daily

https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/016324s034s035lbl.pdf

Antimetabolites

- Azathioprine
  - Adverse effects
    - Leukopenia, thrombocytopenia (dose dependent)
    - Nausea/vomiting
      - Give with food
  - Monitoring
    - CBC monthly
    - No correlation between drug levels and prevention of rejection/efficacy and toxicity

https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/016324s034s035lbl.pdf

Calcineurin Inhibitors

- Cyclosporine (CSA)
  - Inhibits activation of T-cells
  - Used in transplant immunosuppression, ulcerative colitis, lupus, RA, psoriasis
  - Available PO (capsule, oral solution) and IV
  - Dosing
    - Neoral (modified cyclosporine) is not bioequivalent to Sandimmune (cyclosporine)
      - Absorption of Sandimmune can be erratic; increased bioavailability with Neoral
    - 1-5 mg/kg/day (divided into BID dosing)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050715s035,050716s038lbl.pdf

Calcineurin Inhibitors

- CSA
  - Drug interactions (inhibitor and substrate of CYP3A4 and P-glycoprotein)
    - CYP3A4
      - Inhibitors: atorvastatin, amlodipine, amiodarone, fluconazole, etc.
      - Inducers: carbamazepine, phenytoin, rifampin, phenobarbital
    - Grapefruit and grapefruit juice (↑ CSA levels)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050715s035,050716s038lbl.pdf

Calcineurin Inhibitors

- CSA
  - Adverse effects
    - More nephrotoxicity but less neurotoxicity than tacrolimus (tremor, seizures)
    - Hypertension, hyperlipidemia
    - Hair growth

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050715s035,050716s038lbl.pdf

Calcineurin Inhibitors

- CSA
  - Monitoring
    - Chem-7 and BP every 2 weeks for the first 3 months then monthly
    - Troughs and C2 levels (2 hours post dose) have been used
    - Important to clarify goals

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050715s035,050716s038lbl.pdf

Calcineurin Inhibitors

- Tacrolimus (TAC)
  - Inhibits activation of T-cells
  - Used in transplant immunosuppression, RA, Crohn's disease, psoriasis
    - Shown to have better outcomes than cyclosporine in transplant immunosuppression
  - Available PO (capsule, extended release capsule) and IV

J Heart Lung Transplant. 2001;20:734-738.

Calcineurin Inhibitors

- Tacrolimus (TAC)
  - Dosing
    - Oral: 0.05-0.15 mg/kg/day in two divided doses
    - IV: 0.01-0.02 mg/kg/24 hours (continuous infusion)
  - Drug interactions (inhibitor and substrate of CYP3A4 and P-glycoprotein)
    - CYP3A4
      - Inhibitors: atorvastatin, amlodipine, amiodarone, fluconazole, etc.
      - Inducers: carbamazepine, phenytoin, rifampin, phenobarbital
    - Grapefruit and grapefruit juice (↑ TAC levels)

J Heart Lung Transplant. 2001;20:734-738.

Calcineurin Inhibitors

- TAC
  - Adverse effects
    - Neurotoxicity (tremors and seizures)→more common in TAC vs CSA
    - Nephroxicity (less than CSA)
    - Hyperkalemia, hypomagnesemia
    - Hyperglycemia, hypertension (more common in CSA)
    - Alopecia
      - Try Rogaine or biotin supplementation

J Heart Lung Transplant. 2001;20:734-738.

Calcineurin Inhibitors

- TAC
  - Monitoring
    - Chem-7 every 2 weeks for the first 3 months then monthly
    - Troughs are routinely utilized
    - Clarify trough goals

J Heart Lung Transplant. 2001;20:734-738.

mTOR

- Sirolimus and everolimus
  - Inhibit T-cell proliferation
  - Used in transplant immunosuppression
  - Everolimus has better bioavailability and a short t1/2 compared to sirolimus (30 vs. 60 hours)
  - Available PO (tablet, suspension)
  - Dosing
    - Sirolimus: 0.5-5mg daily
    - Everolimus: 0.25-1mg q12H

Drugs. 2007;67:369-391.
Transplantation. 2012;94:659-668.

mTOR

- Sirolimus and everolimus
  - Drug interactions (substrate of CYP3A4 and P-glycoprotein)
    - CYP3A4
      - Inhibitors: atorvastatin, amlodipine, amiodarone, fluconazole, etc.
      - Inducers: carbamazepine, phenytoin, rifampin, phenobarbital
    - Grapefruit and grapefruit juice (↑ levels)

Drugs. 2007;67:369-391.
Transplantation. 2012;94:659-668.

mTOR

- Sirolimus and everolimus
  - Adverse effects
    - Leukopenia and thrombocytopenia (dose dependent)
    - Hyperlipidemia
    - Proteinuria
    - Increased LFTs (dose dependent and reversible)
    - Abnormal wound healing (reported more with sirolimus)

Drugs. 2007;67:369-391.
Transplantation. 2012;94:659-668.

mTOR

- Sirolimus and everolimus
  - Monitoring
    - CBC, lipid profile, quantitative monitoring of urinary protein excretion routinely
    - Troughs are routinely utilized
    - Clarify trough goals

Drugs. 2007;67:369-391.
Transplantation. 2012;94:659-668.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021083s062,021110s081lbl.pdf

Immunosuppressant Medications

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Infection ppx: *Pneumocystis jiroveci*

- **Risk factors:**

Corticosteroids > 15 mg/day	High-intensity immunosuppression	Age > 65 years
Coexisting lung disease	Treatment of rejection	CMV infection
Lymphopenia	Low albumin level	Hypogammaglobulinemia

- **Drugs:**

	Mechanism of Action	**Spectrum of Activity**	**Prophylaxis Dose**
SMX-TMP	Inhibits fungal replication	PCP	400mg/80 mg daily or 800mg/160 mg TIW
Dapsone	Inhibits fungal replication	PCP	100 mg daily
Atovaquone	Inhibits fungal cell energy production	PCP	1500 mg daily
Pentamidine	Inhibits fungal replication	PCP	300 mg monthly

***Best Pract Res Clin Rheum* 2015;29:306**
***Crit Care Nurs Q* 2017;40:383**

Infection ppx: Other fungal infections

	Mechanism of Action	**Spectrum of Activity**	**Prophylaxis Dose**
Fluconazole	Inhibits sterol synthesis	Most *C. albicans* Select non-*albicans*	100-400 mg daily
Itraconazole	Inhibits sterol synthesis	Most *C. albicans* Select non-*albicans* *Aspergillus* spp.	200 mg BID
Voriconazole	Inhibits sterol synthesis	*Candida* spp. *Aspergillus* spp.	200-400 mg BID
Posaconazole	Inhibits sterol synthesis	*Candida* spp. *Aspergillus* spp. *Mucormycoses* spp.	300 mg daily
Nystatin	Disrupts fungal cell wall	Most *C. albicans*	500,000 units QID
Echinocandins - Caspofungin - Anidulafungin - Micafungin	Inhibit fungal cell wall synthesis	*Candida* spp. *Aspergillus* spp.	 50 mg daily 100 mg daily 50-100 mg daily

***Crit Care Nurs Q* 2017;40:383**

Infection ppx: Viral infections

- **Cytomegalovirus (CMV)**
- **Herpes simplex virus (HSV)**
- **Varicella zoster virus (VZV)**

	Mechanism of Action	Spectrum of Activity	Prophylaxis Dose
Acyclovir	Prevents viral replication by disrupting DNA	HSV VZV	400 mg BID
Valacyclovir	Same as acyclovir; better pharmacokinetics	HSV VZV	500 mg BID
Valganciclovir	Inhibits viral replication (blocks DNA synthesis)	CMV HSV VZV	900 mg daily or 450 mg BID

***Crit Care Nurs Q* 2017;40:383**

Immunization considerations

- **Recommend vaccination at time of diagnosis or prior to transplant**
- **Variable vaccination response with immunosuppression**
  - **Affected by depth and duration of immunosuppression**

***Expert Rev Clin Immunol* 2017;13:939**
***J Infect* 2017;74:433**

Inactive vaccines

- **No increased risk of vaccine reaction**
- **No worsening or reactivation of underlying disease or development of allograft rejection**
- **Include recombinant, subunit, toxoid, polysaccharide, conjugated polysaccharide, inactivated or heat-killed vaccines**

Influenza	Td/Tdap	HPV	PCV13	PPSV23
HepA	HepB	MenB	Hib	

- **Follow routine vaccine schedule (per CDC)**
- **Household contacts should also be vaccinated**

***Best Pract Res Clin Rheum* 2015;29:306**

Live attenuated vaccines, the jury is still out

- **Relatively few studies of live vaccines in setting of immunosuppressive therapy**
- **Most studies suggest live vaccines are safe, but…**
- **Per CDC, live vaccines (MMR, VAR, HZV) contraindicated**
- **Serious vaccine-related adverse outcomes do occur, including death**
- **While live vaccines are generally discouraged in setting of immunosuppressive therapy, risks and benefits must be weighed on an individual basis.**

***Vaccine* 2017;35:1216**

Pregnancy and immunosuppression

- **Category C: adverse fetal effects in animals; insufficient human data**

Corticosteroids	Cyclosporine A	Tacrolimus
Sirolimus	Everolimus	Hydroxychloroquine

- **Category D: evidence of human fetal risk; benefit of drugs may outweigh risk**

Azathioprine	Mycophenolate

- **Category X: contraindicated**

Methotrexate	Leflunomide

Clinical Pearls

- **Balance effectiveness with risk of infection and malignancy**
  - **Sun protection, regular screening**
- **Typically advocate against the use of herbals and homeopathic medications**
  - **Drug interactions**
  - **Inability to verify Good Manufacturing Practices**

http://blogs.oregonstate.edu/linuspaulinginstitute/2015/02/24/whats-supplement-bottle/

Immunosupressants

- You may see your patients on a combination of therapies
- Regularly communicate with the primary prescriber of the immunosupressants
  - Ongoing labs
  - Status of patient