

Immunosuppressant Medications

Brian C. Keller, MD, PhD
Assistant Professor of Medicine
Division of Pulmonary, Critical Care & Sleep Medicine
The Ohio State University Wexner Medical Center

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

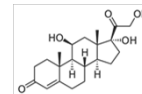


Rheumatologist

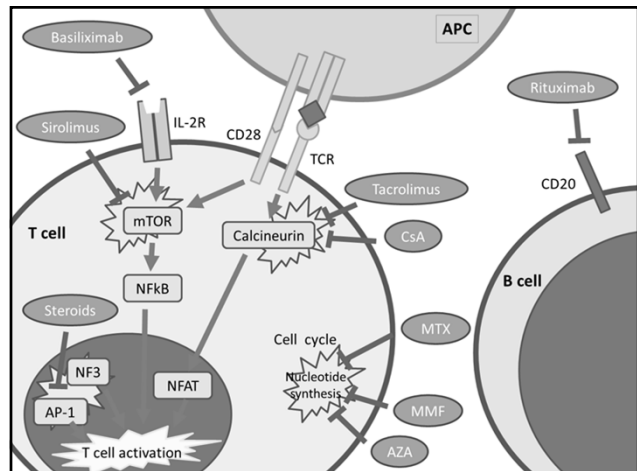
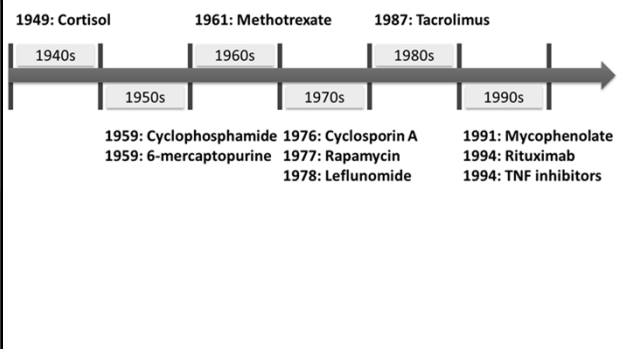
Tadeusz Reichstein



Chemist



History of Immunosuppression



Immunosuppressant Medications

Pamela Burcham, RPh
Specialty Practice Pharmacist
Department of Anesthesiology
The Ohio State University Wexner Medical Center

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/2011/016324s034s035ibl.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/2011/016324s034s035ibl.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/2015/050715s035,050716s038ibl.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
 - Nephrotoxicity (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 t_{1/2} 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

Brian C. Keller, MD, PhD
Assistant Professor of Medicine
Division of Pulmonary, Critical Care & Sleep Medicine
The Ohio State University Wexner Medical Center

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 <i>C. albicans</i> Select non- <i>albicans</i>	100-400 mg daily
Itraconazole	Inhibits sterol synthesis	Most <i>C. albicans</i> Select non- <i>albicans</i> <i>Aspergillus</i> spp.	200 mg BID
Voriconazole	Inhibits sterol synthesis	<i>Candida</i> spp. <i>Aspergillus</i> spp.	200-400 mg BID
Posaconazole	Inhibits sterol synthesis	<i>Candida</i> spp. <i>Aspergillus</i> spp. <i>Mucormycoses</i> spp.	300 mg daily
Nystatin	Disrupts fungal cell wall	Most <i>C. albicans</i>	500,000 units QID
Echinocandins - Caspofungin - Anidulafungin - Micafungin	Inhibit fungal cell wall synthesis	<i>Candida</i> spp. <i>Aspergillus</i> 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

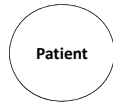


<http://blogs.oregonstate.edu/linuspaulinginstitute/2015/02/24/whats-supplement-bottle/>

Immunosuppressants

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

Primary care physician



Prescribing team (e.g. Transplant)

Specialist