Basic science Rheumatology

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14th March 2024

Nonbiologics Therapeutics in Pediatric Rheumatology

Nonbiologics Therapy

01 Nonsteriodal Antiinflammatory Drugs (NSAIDs)

02 Salicylates

03 Other Disease-Modifying

- Colchicine
- Glucocorticoid Drugs

Nonbiologics Therapy

03 Disease-Modifying Antirheumatic Drugs (DMARDs)

- Methotrexate
- Hydroxychloroquine (HCQ)
- Sulfasalazine
- Leflunomide

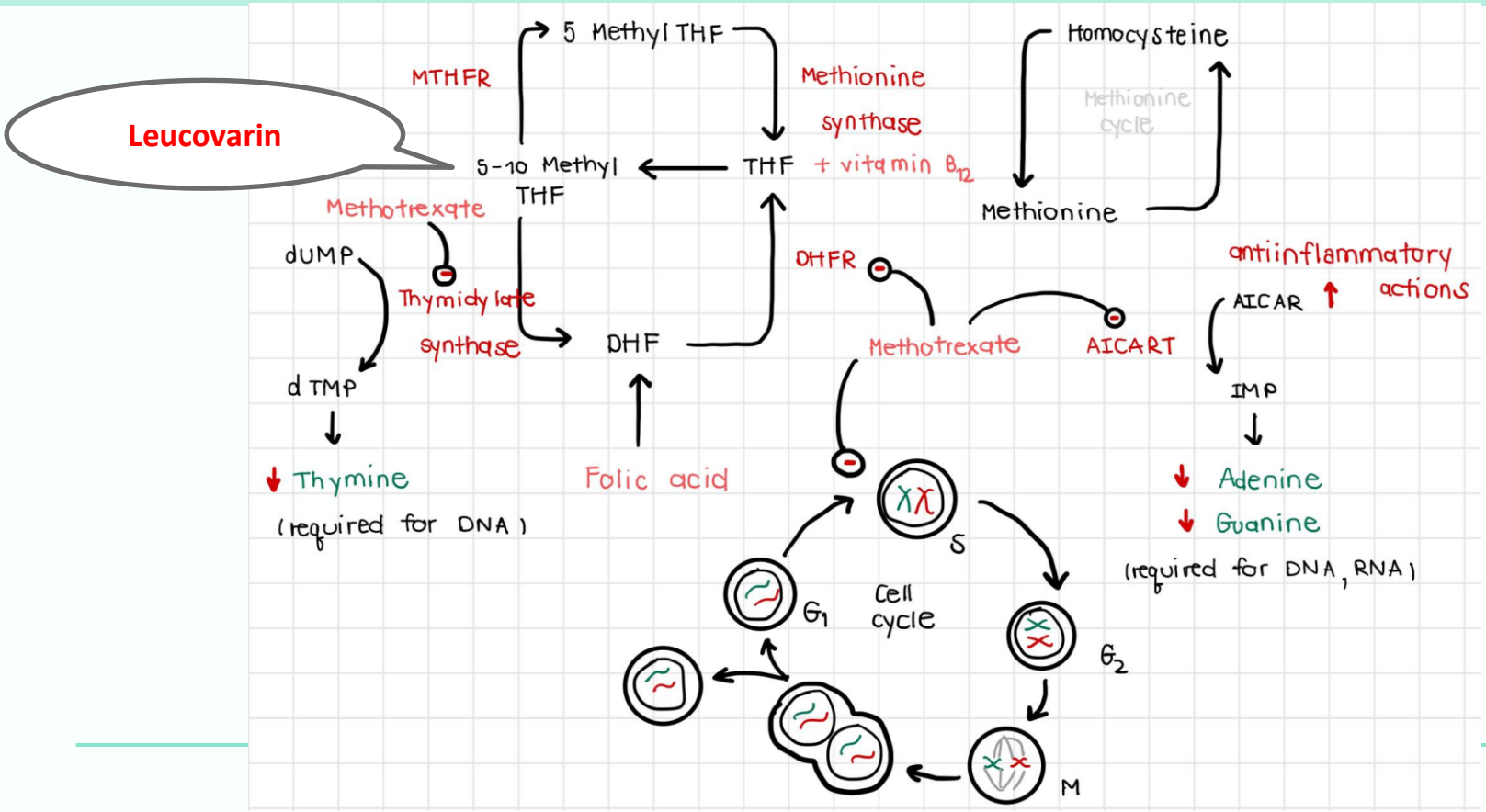
04 Cytotoxic, Antimetabolic, and Immunomodulatory Agents

- Azathioprine
- Mycophenolate Mofetil
- Cyclophosphamide
- Cyclosporine, Tacrolimus
- Sirolimus

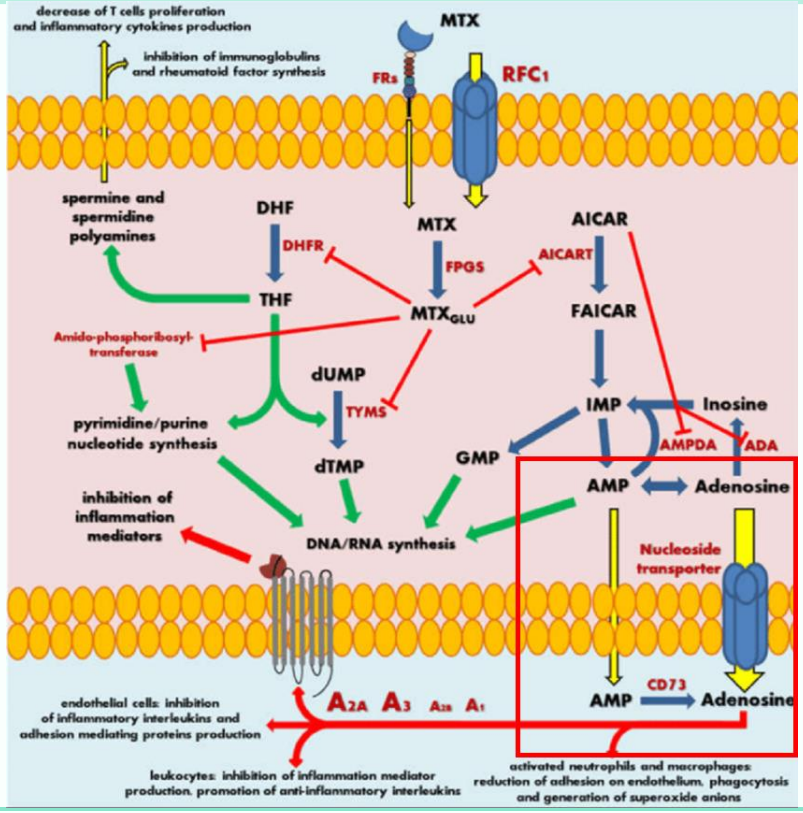
01

Methotrexate

Methotrexate



Methotrexate



www.researchgate.net/figure/Scheme-of-mechanism-of-methotrexate-action

Methotrexate

- Low-dose weekly MTX is the most useful agents in the treatment of rheumatic diseases in children, including many other chronic inflammatory disorders.

- MTX is a folic acid analogue and a potent competitive inhibitor of several enzymes in the folate pathway.

- Intracellular membrane, MTX is converted in methotrexate polyglutamates.

- MTX directly inhibited dihydrofolate reductase (DHFR), thymidylate synthetase (TYMS), and aminoimidazole carboxamide ribonucleotide transformylase (AICART).

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Methotrexate

- Outcome of mechanism of action : Inhibits de novo purine and pyrimidine synthesis.

- Furthermore, MTX promotes the accumulation of extracellular adenosine.

- Adenosine accumulation is an anti-inflammatory effects.

- MTX also modulates the function of many cells involved in inflammation and production of various cytokines.

- Oral absorption is greater in the fasting state (oral bioavailability 15%).

- Route of elimination is renal, and other significant route is biliary tract.

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Methotrexate

- Combination of MTX and trimethoprim-sulfamethoxazole should be avoided.

- Suggestion for parenteral MTX administration :
  -> Have a poor clinical response to orally administered MTX.
  -> Need dosages greater than about 10 to 15 mg/m2/week.

- Teratogenicity effects (spontaneous abortions and congenital anomaly).

- Breast-feeding is a contraindication.

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Toxicity of Methotrexate

- **Gastrointestinal** :
  - abdominal discomfort, nausea, and stomatitis or oral ulcers.

- **Hepatic** :
  - hepatic fibrosis, cirrhosis more common with chronic low dose oral therapy.
  - transient increases in transaminases.
  - requires dosing adjustment in hepatic insufficiency.

- **Myelosuppression** :
  - nadir is 5-10 days and recovery usually within 14-21 days (High dose MTX).
  - macrocytic anemia, leukopenia, thrombocytopenia or pancytopenia.

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Toxicity of Methotrexate

- **Renal** :
  - direct cytotoxicity on tubular cells or precipitation.
  - pKa of MTX is 5.4 (insoluble in acidic urine).
  - alkalinize urine (pH > 7).

- **Pulmonary** :
  - interstitial pneumonitis (less common).

- **Neurotoxicity** (IT therapy) :
  - arachnoiditis (common acute onset) : headache, nuchal rigidity.
  - MTX-induced leukoencephalopathy (irreversible chronic demyelinating encephalopathy).

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Leucovarin

- Concurrent use of MTX with leucovarin (folinic acid) supplement can reduction MTX toxicities.

- Selective for rescuing normal cells more than malignant cells.

- Rescuing all normal cells, except hepatocellular cell.

- Started 24-48 hours after MTX.

- Intravenous or oral route administration are 100% bioavailability.

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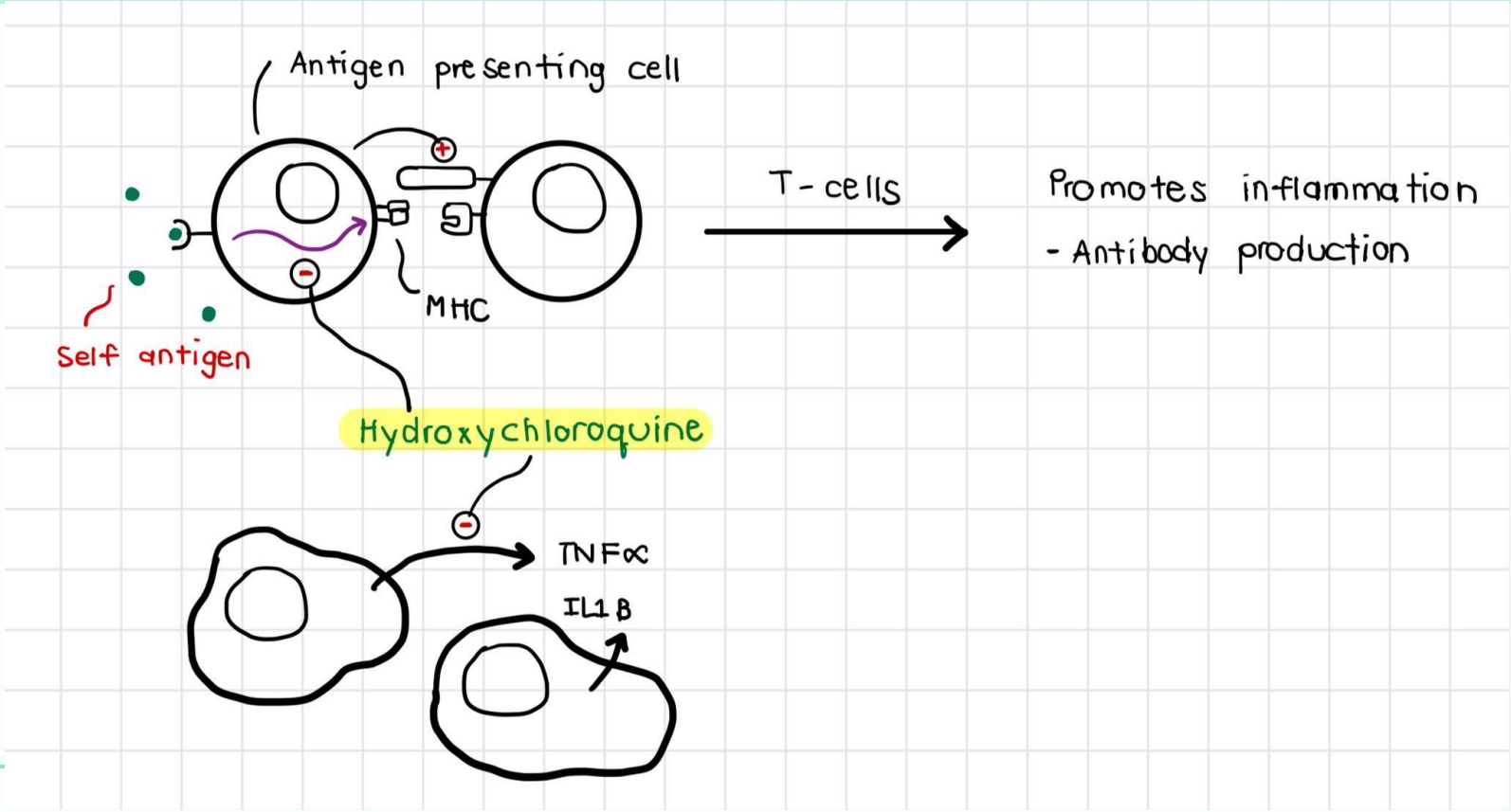
02

Hydroxychloroquine

Hydroxychloroquine



Hydroxychloroquine

- First-line antimalarial used to treat pediatric rheumatic disease.

- HCQ inhibit self-antigen binding and presentation via Toll-like receptor.

- Inhibit of neutrophil chemotaxis, nitric oxide production, and phagocytosis.

- HCQ may also antagonize of inflammation and various cytokines.

- Also has antiplatelet and antihyperlipidemia.

- Absorption from the upper GI tract (unaffected by food).

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Hydroxychloroquine

- HCQ metabolized by multiple CYP enzymes (CYP2C8, CYP3A4, and CYP2D6).

- Route of elimination is renal, others route are sequestered in tissues, via stool, or shedding of epithelial skin cells.

- Safe to use in pregnancy and breast-feeding.

Safety and toxicity

- Gastrointestinal : 10% GI intolerance

- Skin : Skin pigmentation

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Hydroxychloroquine

Safety and toxicity

- CNS :
  - myasthenia, muscle weakness, headache, light-headedness, tinnitus, insomnia, and anxiety.

- Retinal toxicity : irreversible
  - early finding : mottling of the retinal pigmented epithelium (RPE) and blunt foveal reflex.
  - if retinopathy progress : bull's-eye maculopathy development.
  - paracentral scotoma on visual field test.
  - recommendation : baseline exam for screening, then annual examination.

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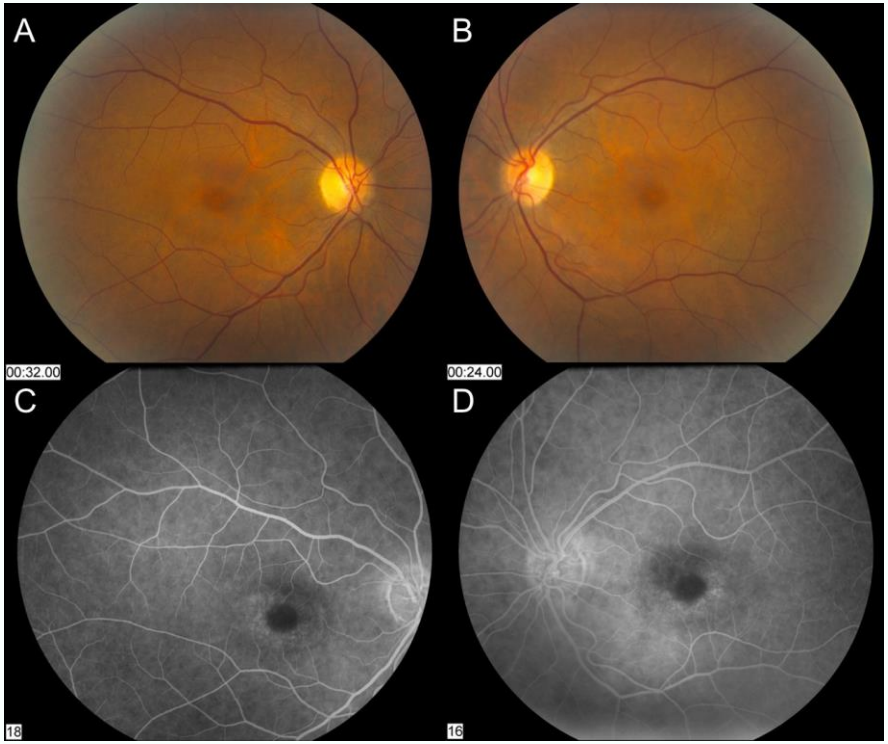

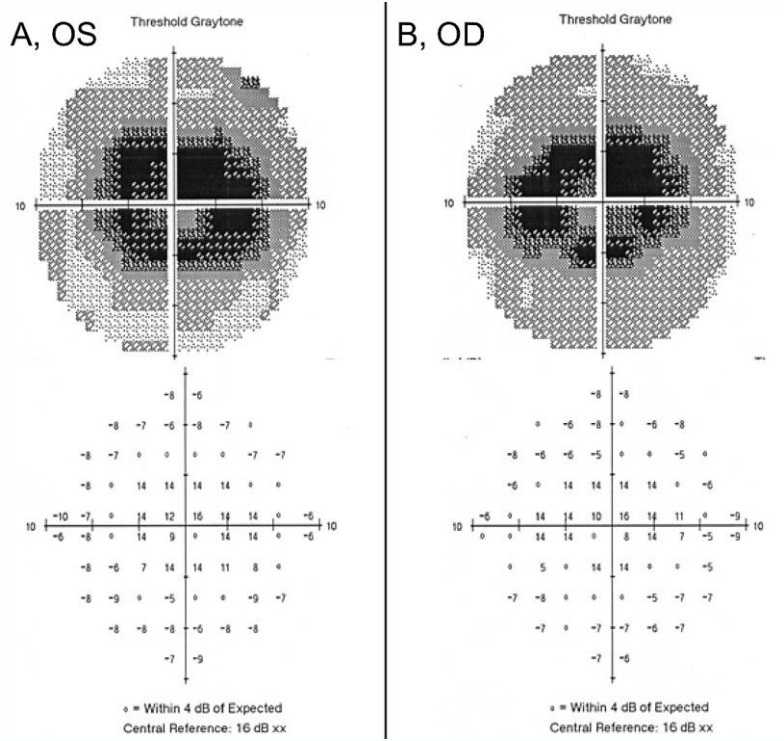

https://webeye.ophth.uiowa.edu/eyeforum/cases/139-plaquenil-toxicity.htm

HCQ treatment SLE

For treatment of SLE

- improve survival of SLE patients.
- prevent SLE flares.
- delay the onset of SLE in those at risk.
- protect against thrombotic events.
- lower serum cholesterol.
- reduce the risk of diabetes mellitus.
- efficacious in cutaneous lupus.
- protection against fetal heart block.

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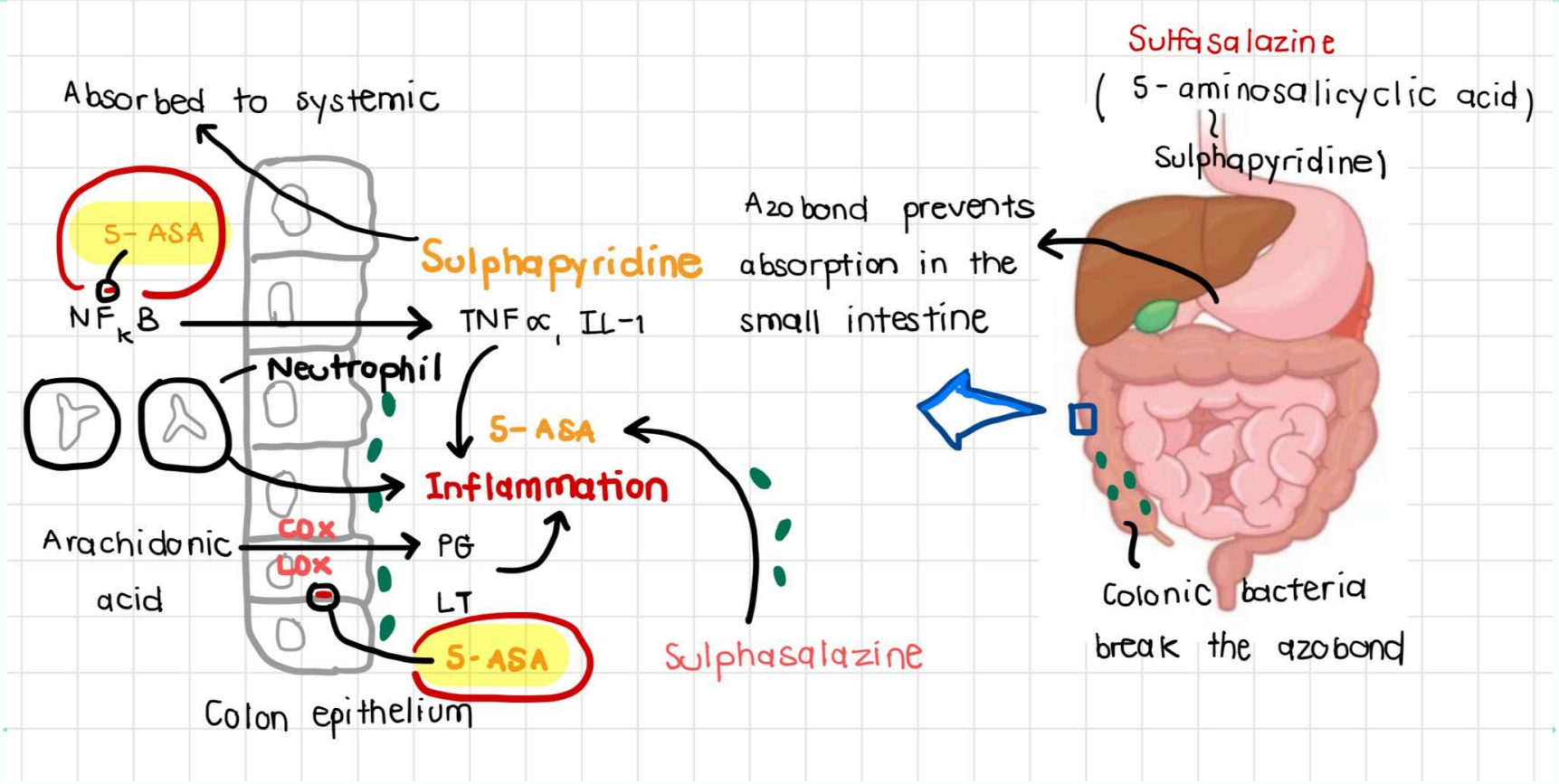
03

Salfasalazine

Salfasalazine



Salfasalazine

- An analog of 5-aminosalicylic acid (5-ASA) linked by an azo bond to sulfapyridine (a sulfonamide).

- Sulfasalazine interferes the formation of leukotrienes and prostaglandins.

- Potent inhibitor of AICAR transformylase.

- Metabolized by intestinal bacteria to sulfapyridine and 5-ASA (active metabolites).

- Route of elimination is renal, the majority of 5-ASA is excreted in the stool.

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Salfasalazine

Recommended treatment

- enthesitis-related arthritis (ERA).
- mild to moderate inflammatory bowel disease.
- childhood arthritis (oligoarthritis, psoriatic arthritis, reactive arthritis).

Safety and toxicity

- maculopapular rash (most common complication) : within 2 days after therapy.
- oral ulcers.
- Stevens-Johnson syndrome.
- rare side effects : cytopenias, drug-induced SLE, Raynaud phenomenon, interstitial pneumonitis, fibrosis, alveolitis, pulmonary syndromes, hepatitis.

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Salfasalazine

Safety and toxicity

- BEWARE : patients with known hypersensitivity to sulfa or salicylics drug.
- avoid in patients with G6PD deficiency.
- avoid in infants due to sulfasalazine displace of bilirubin.

- No absolute contraindication to breast-feeding.

- Safe for pregnancy.

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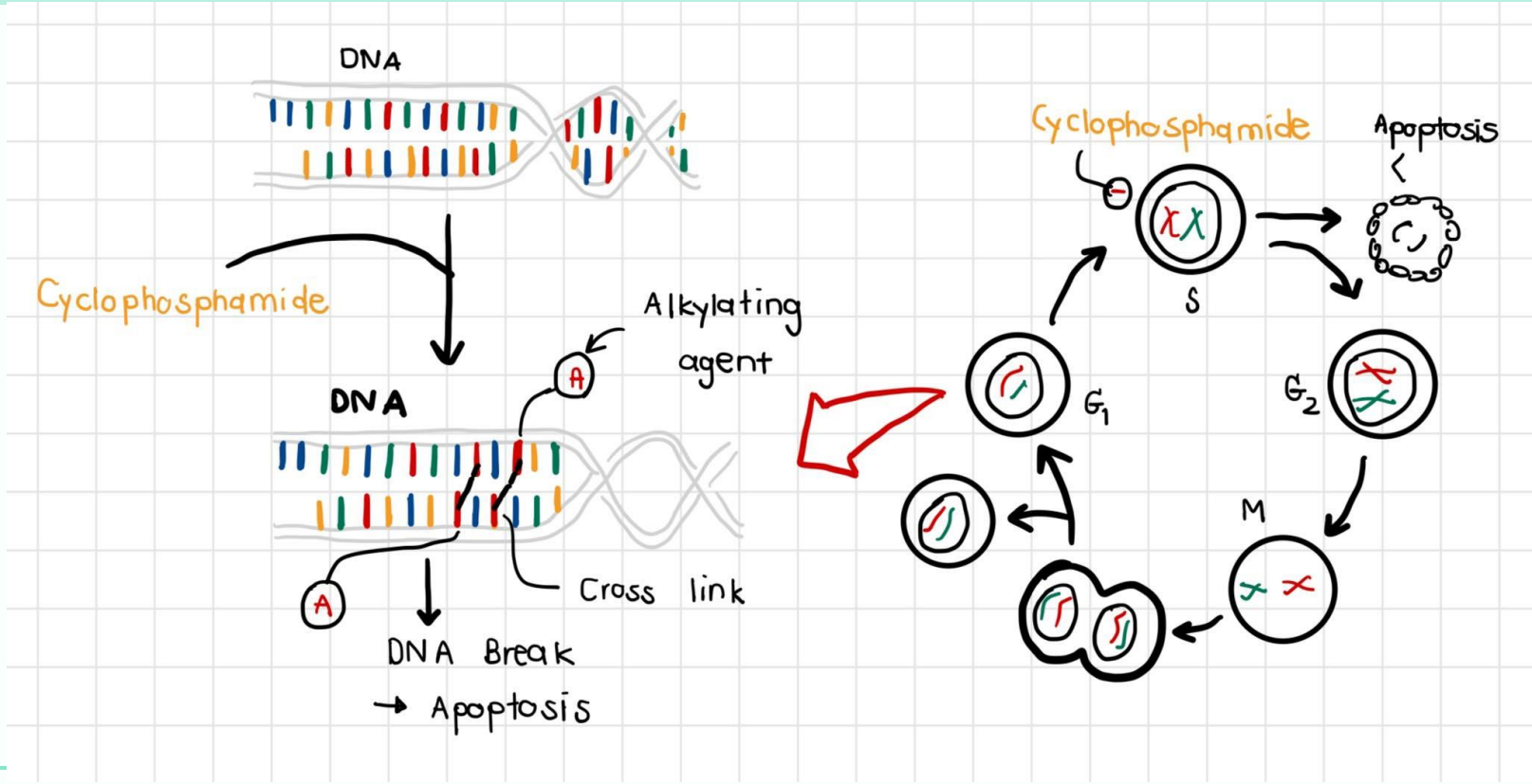
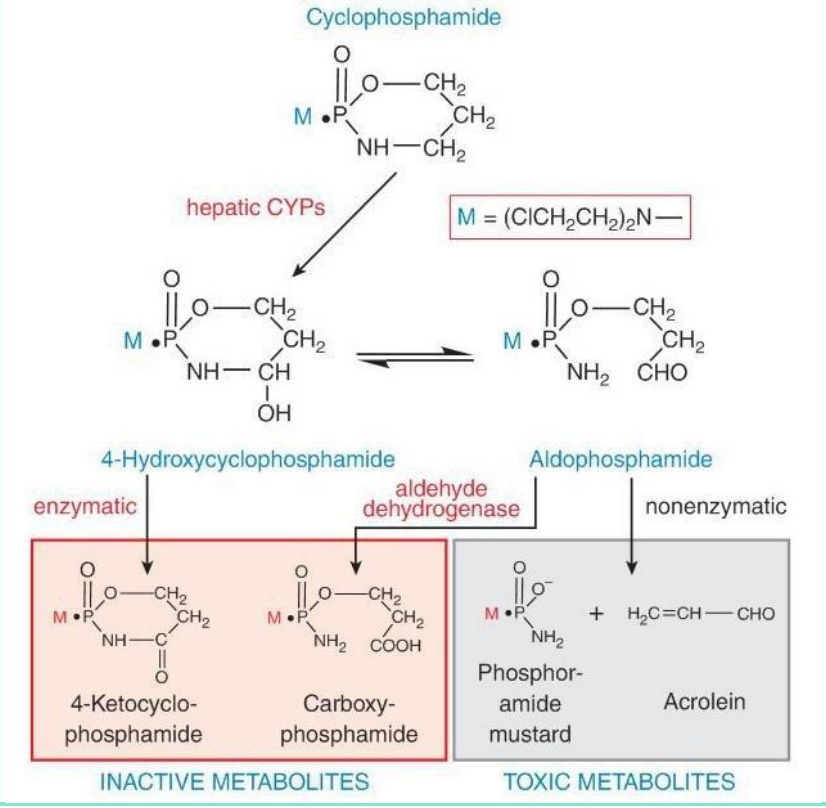
04

Cyclophosphamide

Cyclophosphamide



Cyclophosphamide



www.researchgate.net/figure/8-Metabolism-and-activation-of-cyclophosphamide

Cyclophosphamide

- Cyclophosphamide is an alkylating agent (nitrogen mustard derivative).

- Well absorbed after oral administration, equally with intravenous route.

- Metabolized by liver to inactive and the active metabolite phosphoramide mustard.

- Phosphoramide mustard covalently binds to guanine in DNA.

- Destroyed purine ring and prevent cell replication.

- Route of elimination is renal.

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Cyclophosphamide

Safety and toxicity

- Myelosuppression :
  - primarily leukopenia.

- Bladder toxicity :
  - hemorrhagic cystitis, fibrosis, transitional cell carcinoma.
  - prolonged contact of acrolein metabolite with bladder mucosa.

For prevention

- adequate hydration.
- frequent voiding.
- prophylactic by mesna.

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Cyclophosphamide

Safety and toxicity

- Risk of malignancy :
  - myeloproliferative disorders
  - bladder and skin cancer.

- Infertility

- Teratogenic effects, and contraindication during breast-feeding.

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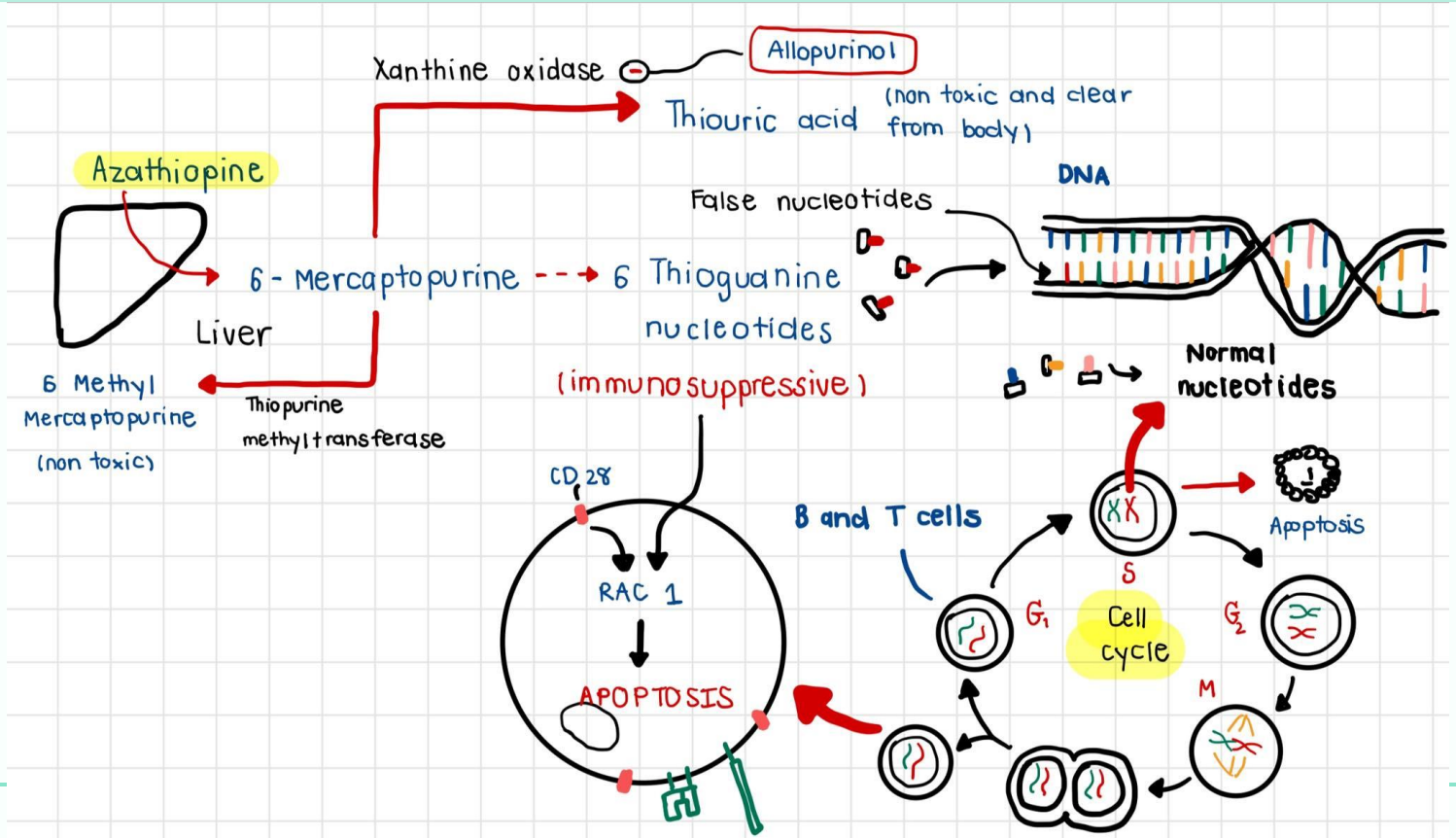
05

Azathioprine

Azathioprine



Azathioprine

- Purine analog, is metabolized to 6-mercaptopurine (6MP – active form).

- Intracellular activation of 6MP is formation of thioguanine monophosphate.

- Thioguanine monophosphate inhibits de novo purine synthesis.

- Inhibit of T-cell growth (in S phase), and decrease in antibody synthesis in long-term administration.

- Route of elimination is renal.

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Azathioprine

Safety and toxicity

- Myelosuppression : especially in 6-MP
  - maximal toxic begins 14-21 days after administration.
  - targets : granulopoiesis (agranulocytosis) and platelet production.
  - CD4+ T-cell depletion (6-MP).
  - avoid concomitant use of trimethoprim.

- common toxicity :
  - GI tract (oral ulcers, nausea, vomiting, diarrhea, epigastrium pain)

- uncommon toxicity :
  - liver, lung (interstitial pneumonitis), pancreas, or skin (maculopapular rash)

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Azathioprine

- Bone marrow toxicity associated with genetic variation of Thiopurine methyltransferase (TPMT).

- Teratogenic effects.

- Breast-feeding is contraindication.

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06

Mycophenolate Mofetil (MMF)

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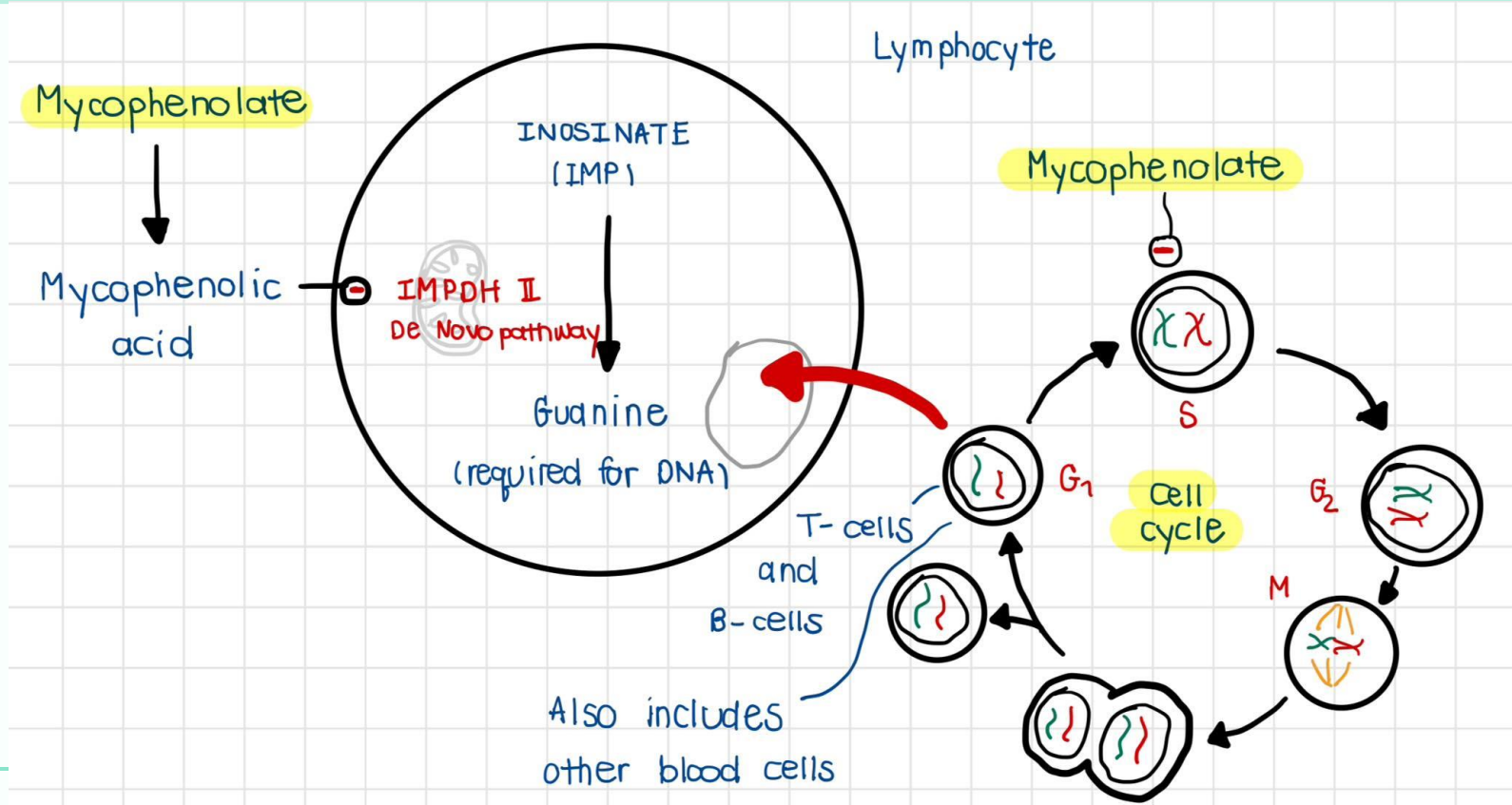

Mycophenolate Mofetil (MMF)

- Ester prodrug form of mycophenolic acid (MPA)

- Inhibitor of inosine monophosphate dehydrogenase (IMPDH), in de novo of guanine nucleotide synthesis.

- Bioavailability of oral administration is 94%, it was hydrolyzed in the acidic environment.
  BEWARE : coadministration of PPIs and antacids.

- Route of elimination are liver and intestine.

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Mycophenolate Mofetil (MMF)

Safety and toxicity

- Gastrointestinal : diarrhea (most common side effect)

- Hematologic :
  - cytopenias, pure red cell aplasia

- Opportunistic infections

- Induced the metabolism of contraceptive drugs.

- Teratogenic effects (1st trimester) : pregnancy loss and structural malformation, and breast-feeding is contraindication.

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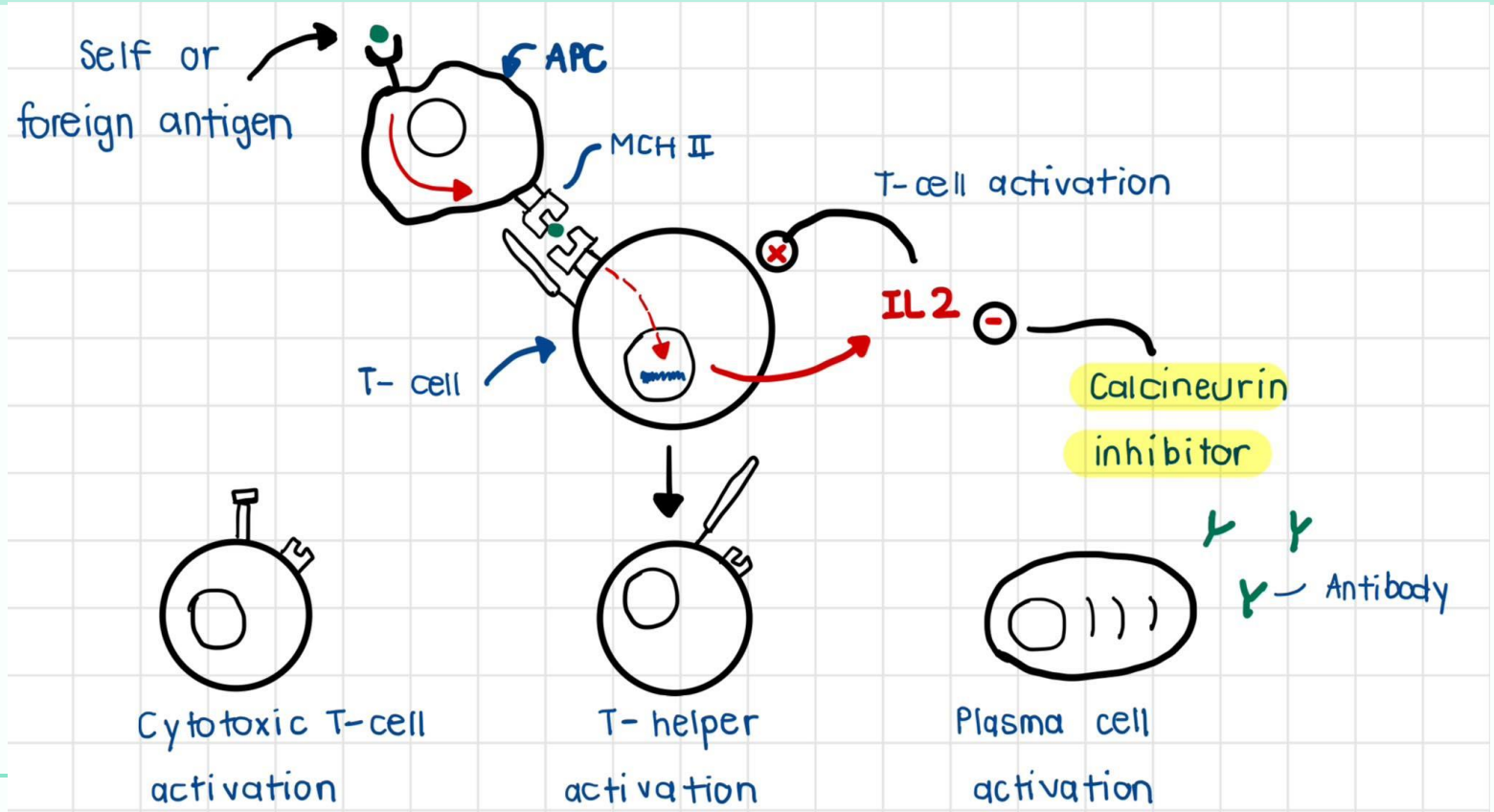
07

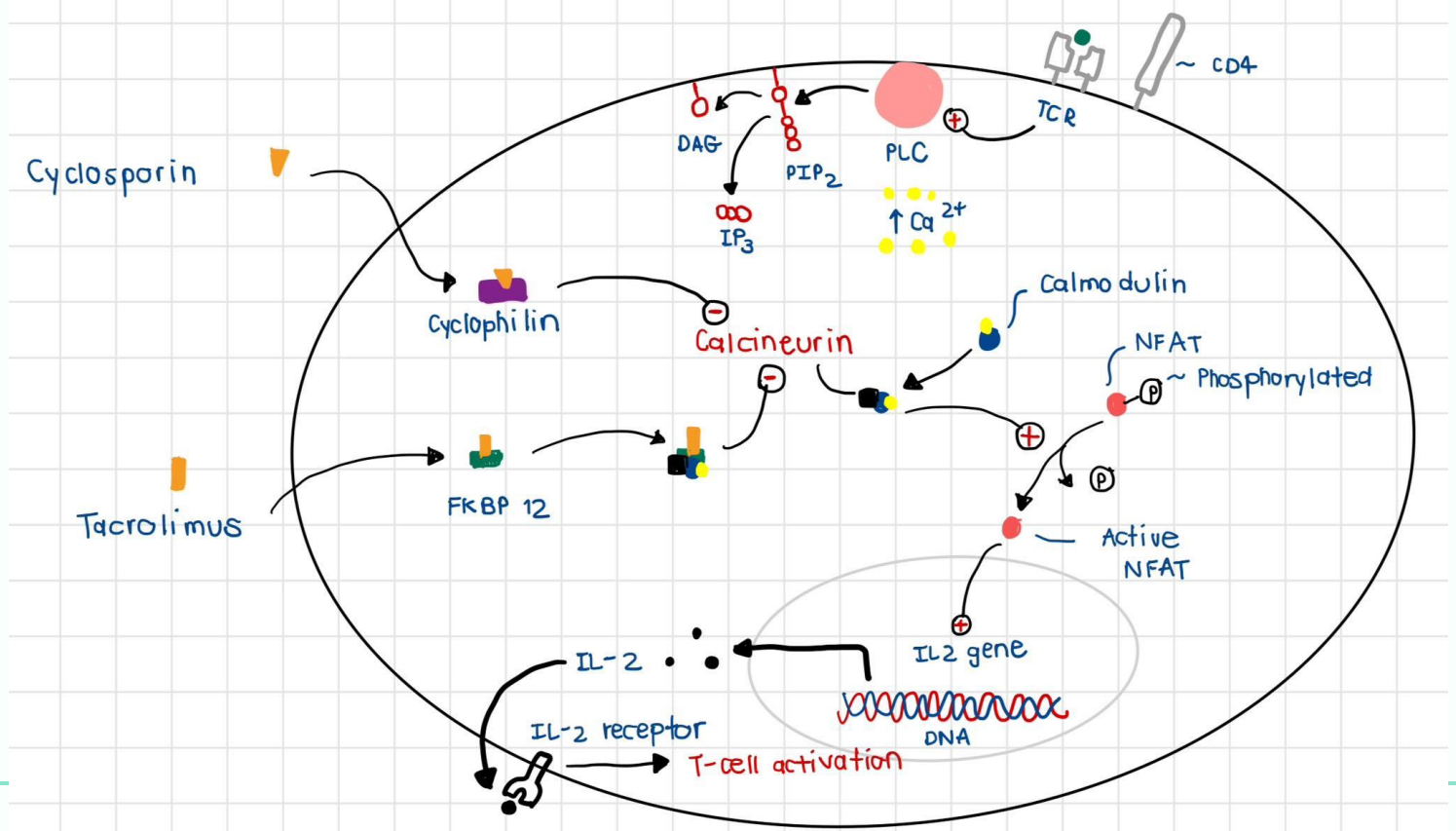
Calcineurin inhibitors (CNI)

Cyclosporine, Tacrolimus (TAC)

Cyclosporine and Tacrolimus



Cyclosporine and Tacrolimus



Cyclosporine and Tacrolimus

- Cyclosporine (a cyclic peptide of fungal origin), Tacrolimus (a macrolide).

- Prevention of solid organ transplant rejection and treatment of T-cell mediated autoimmune disease (MAS, HLH).

- Inhibit the early phase of T-cell activation and IL-2 production.

- Absorption from the GI tract (both drugs), and metabolized by liver.

- Absorption of cyclosporine depends on bile salts.

- Cyclosporine and Tacrolimus are CYP P-450 3A4/5 substrates.

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Cyclosporine and Tacrolimus

- Route of elimination is excreted in the bile.

Safety and toxicity

- hypertension, hepatic toxicity, tremor, mucous membrane lesions, nausea and vomiting, hirsutism, and gum hypertrophy.

- Renal :
  - impaired renal function.
  - interstitial fibrosis or tubular atrophy.

  BEWARE : coadministration with nephrotoxic drugs

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Cyclosporine and Tacrolimus

- Monitor drug level must be done in both drugs.

- Both drugs cross placenta, but no contraindication for pregnancy.

- Not to breast-feeding while using these drugs.

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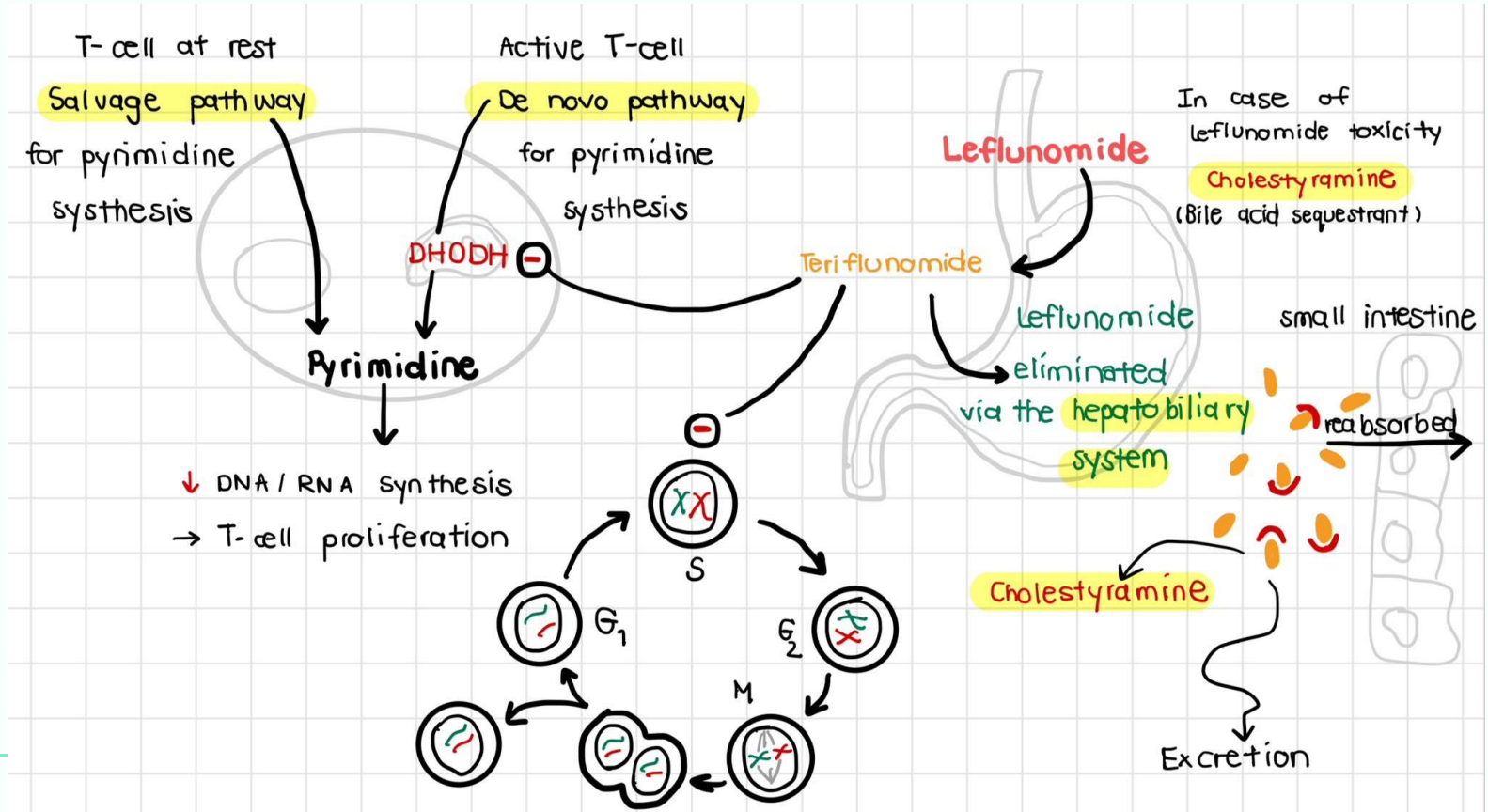
08

Leflunomide

Leflunomide



Leflunomide

- Immunomodulatory agent, its active plasma metabolite teriflunomide.

- Inhibits de novo pyrimidines synthesis by inhibiting dihydroorotate dehydrogenase.

- Initiates cellular arrest in the G1 phase of the cell cycle.

- Substrate for CYP2C8, CYP1A2.

- Route of elimination (teriflunomide) are urine and stool.

- Teratogenic effects, and contraindication during breast-feeding.

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Leflunomide

Safety and toxicity

- Gastrointestinal :
  - abdominal pain, dyspepsia, anorexia, diarrhea, gastritis.
  - elevated hepatic transaminases.

- Myelosuppession :
  - pancytopenia, neutropenia, thrombocytopenia.

- Allergic rash, reversible alopecia

- Decreased toxicity of drug : removed the drug via cholestyramine.

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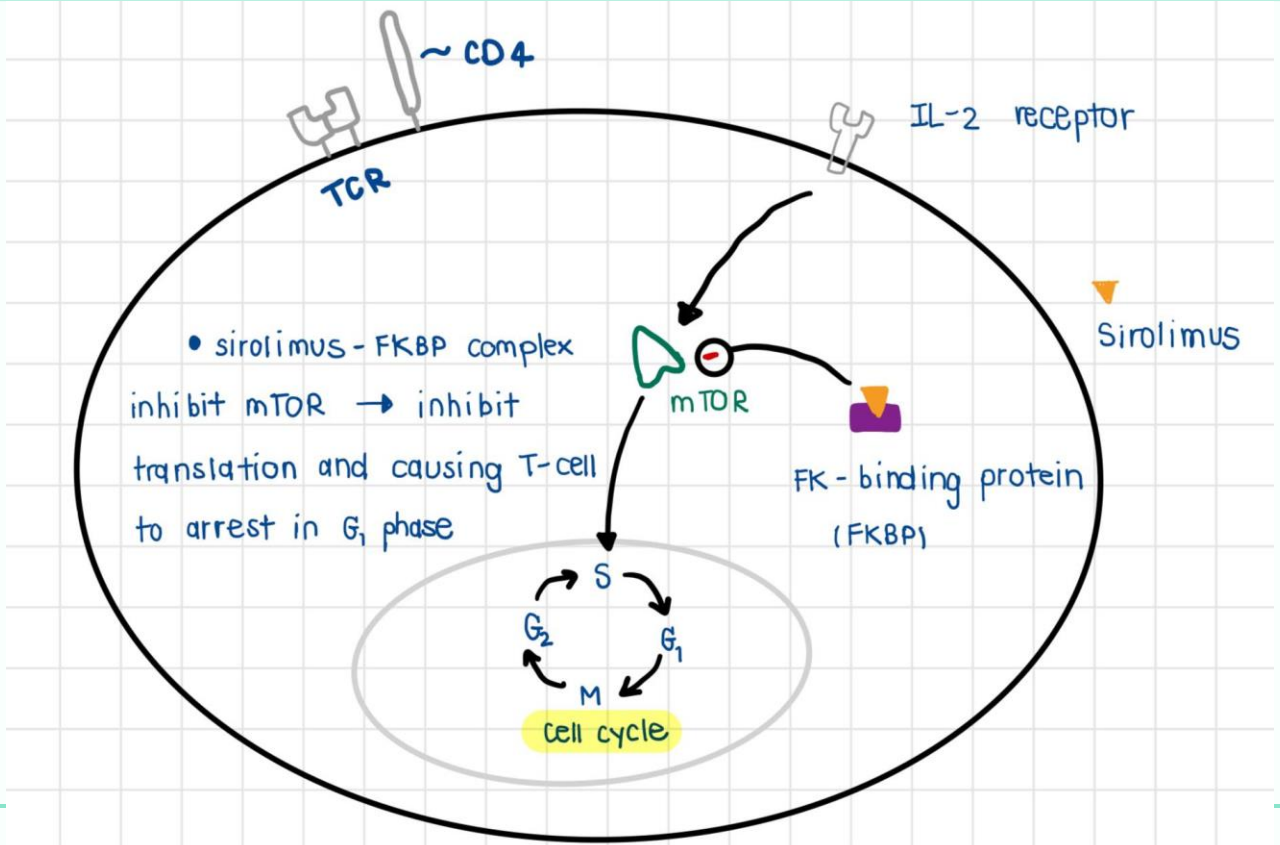
09

Mammalian target of rapamycin (mTOR) inhibitors

Sirolimus

Sirolimus


~ CD4
TCR
IL-2 receptor
Sirolimus
• sirolimus - FKBP complex
inhibit mTOR → inhibit
translation and causing T-cell
to arrest in G1 phase
mTOR
FK - binding protein
(FKBP)
S
G2
G1
M
cell cycle

Sirolimus

- A macrolide antibiotic produced by Streptomyces hygroscopicus.

- Treatments in solid organ transplantation and refractory autoimmune cytopenias.

- Metabolized by the liver.

- CYP 3A4 substrate.

- Monitoring of levels is required.

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Sirolimus

Safety and toxicity

- common adverse reactions :
  - hypertension, increased creatinine, peripheral edema.
  - hypercholesterolemia, hypertriglyceridemia.
  - abdominal pain, diarrhea.
  - headache, fever, arthralgia.
  - anemia and thrombocytopenia.

- serious risks :
  - severe infections.
  - increased risk of malignancies.

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Summary

Drug	Dosage and Route	Clinical monitoring	Laboratory monitoring
Hydroxychloroquine	≤ 5 mg/kg/day to a maximum of 400 mg/day, oral	Baseline ophthalmological exam and yearly screening testing	None
Methotrexate	10-15 mg/m2, once weekly, oral (preferably on empty stomach) or subcutaneous Administer with folic acid or folinic acid	Improvement seen in 6-12 weeks Initial evaluation in 2-4 weeks, then monitor every 3-6 months	CBC, AST, ALT, creatinine, albumin, (+/- UPT) baseline and in 4-8 weeks initially and with dose adjustments, then every 12 weeks
Sulfasalazine	Initial : 10-15 mg/kg/day (max 500 mg) in two to three divided doses, oral Increase over course of 4 weeks to 30-50 mg/kg/day in two divided doses (max dose 2 g/day)	Improvement seen 4-8 weeks Initial evaluation in 2-4 weeks, then every 2-4 months Discontinue if rash appears	CBC, AST, ALT, creatinine, UA, G6PD level, baseline and every 1-2 weeks with dose increases, then every 3 months while on maintenance doses F/U immunoglobulin every 6 months

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Summary

Drug	Dosage and Route	Clinical monitoring	Laboratory monitoring
Leflunomide	< 20 kg : 10 mg every other day 20-40 kg : 10 mg daily > 40 kg : 20 mg daily, oral	Improvement seen in 6-12 weeks Initial evaluation in 2-4 weeks then every 3-6 months	CBC, AST, ALT, creatinine, (+/- UPT) baseline and in 2-4 weeks with dose adjustments, then every 3 months while on maintenance doses
Azathioprine	0.5-2.5 mg/kg/day in a single dose, max 150 mg daily, oral	Initial evaluation in 1-2 months and then every 3 months	CBC every 1-2 weeks until stable dose, then every 4-12 weeks AST, ALT, BUN, creatinine every 4 weeks until stable dose achieved, then every 12 weeks Adjust dosing for WBC < 3500/mm3, platelet < 100,000/mm3, or elevated AST, ALT

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Summary

Drug	Dosage and Route	Clinical monitoring	Laboratory monitoring
MMF	Initial : 300 mg/m2/dose given twice daily, oral Increase in 2 weeks to 600 mg/m2/dose twice daily Maximum dose 2-3 g/day depending on indication	Initial evaluation in 1-2 months and then every 3 months	CBC, (+/- UPT), if appropriate, then every 4-12 weeks Adjust dosing for WBC < 3500/mm3, platelet < 100,000/mm3, or falling hemoglobin not related to disease activity
Cyclophosphamide	Daily : 0.5-2 mg/kg/day, oral or IV IV pulse : 0.5-1.0 g/m2 every 2-4 weeks	Evaluation monthly Encourage fluid intake to minimize risk of hemorrhagic cystitis Encourage frequent emptying of bladder	CBC, UA every week until stable dose, then every 4 weeks AST, ALT, BUN, creatinine and UPT screening, if appropriate, every 4 weeks Adjust dosing for WBC < 1500/mm3, platelet < 100,000/mm3, or hematuria

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Summary

Drug	Dosage and Route	Clinical monitoring	Laboratory monitoring
Cyclosporine	3-5 mg/kg/day divided twice a day, oral If using liquid Neoral, use glass dropper ; may be mixed with milk, apple juice, or orange juice	Blood pressure every week for first month, then monthly	CBC, AST, ALT, BUN, creatinine, UA and UPT screening, if appropriate, at baseline and every 4 weeks Reduce dose if creatinine increases by 30%

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Summary

Significant Cytochrome P450 Enzymes and Their Inhibitors, Inducers, and Substrates

Enzyme	*Potent inhibitors**	*Potent inducers†*	*Substrates*
CYP1A2	Amiodarone (Cordarone), cimetidine (Tagamet), ciprofloxacin (Cipro), fluvoxamine (Luvox‡)	Carbamazepine (Tegretol), phenobarbital, rifampin (Rifadin), tobacco	Caffeine, clozapine (Clozaril), theophylline
CYP2C9	Amiodarone, fluconazole (Diflucan), fluoxetine (Prozac), metronidazole (Flagyl), ritonavir (Norvir), trimethoprim/sulfamethoxazole (Bactrim, Septra)	Carbamazepine, phenobarbital, phenytoin (Dilantin), rifampin	Carvedilol (Coreg), celecoxib (Celebrex), glipizide (Glucotrol), ibuprofen (Motrin), irbesartan (Avapro), losartan (Cozaar)
CYP2C19	Fluvoxamine, isoniazid (INH), ritonavir	Carbamazepine, phenytoin, rifampin	Omeprazole (Prilosec), phenobarbital, phenytoin
CYP2D6	Amiodarone, cimetidine, diphenhydramine (Benadryl), fluoxetine, paroxetine (Paxil), quinidine, ritonavir, terbinafine (Lamisil)	No significant inducers	Amitriptyline, carvedilol, codeine, donepezil (Aricept), haloperidol (Haldol), metoprolol (Lopressor), paroxetine, risperidone (Risperdal), tramadol (Ultram)
CYP3A4 and CYP3A5	Clarithromycin (Biaxin), diltiazem (Cardizem), erythromycin, grapefruit juice, itraconazole (Sporanox), ketoconazole (Nizoral), nefazodone (Serzone‡), ritonavir, telithromycin (Ketek), verapamil (Calan)	Carbamazepine,*Hypericum perforatum* (St. John's wort), phenobarbital, phenytoin, rifampin	Alprazolam (Xanax), amlodipine (Norvasc), atorvastatin (Lipitor), cyclosporine (Sandimmune), diazepam (Valium), estradiol (Estrace), simvastatin (Zocor), sildenafil (Viagra), verapamil, zolpidem (Ambien)

CYP=cytochrome P.

https://www.aafp.org/pubs/afp/issues/2007/0801/p391.html

Thank You