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College of Medicine

DRUGS FOR RHEUMATOLOGY

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DISCLOSURE

None

Use Statement

OBJECTIVES

1. Identify the appropriate medications for managing gout and rheumatoid arthritis.
2. Explain mechanisms of action for medications used to manage gout (anti-gout and uric-acid lowering drugs) and rheumatoid arthritis (including traditional disease modifying antirheumatic drugs or DMARDs, biological DMARDs, and JAK inhibitors) and correlate with underlying pathophysiology
3. Describe adverse effects and contraindications to medications for managing gout (anti-gout and uric-acid lowering drugs) and rheumatoid arthritis (including traditional disease modifying antirheumatic drugs or DMARDs, biological DMARDs, and JAK inhibitors)
4. Describe the clinically important drug interactions of medications used to manage gout (anti-gout and uric-acid lowering drugs) and rheumatoid arthritis (including traditional disease modifying antirheumatic drugs or DMARDs, biological DMARDs, and JAK inhibitors).

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GOUT

ACTIVE LEARNING

In 60 seconds, write down what you remember about the pathophysiology of gout.

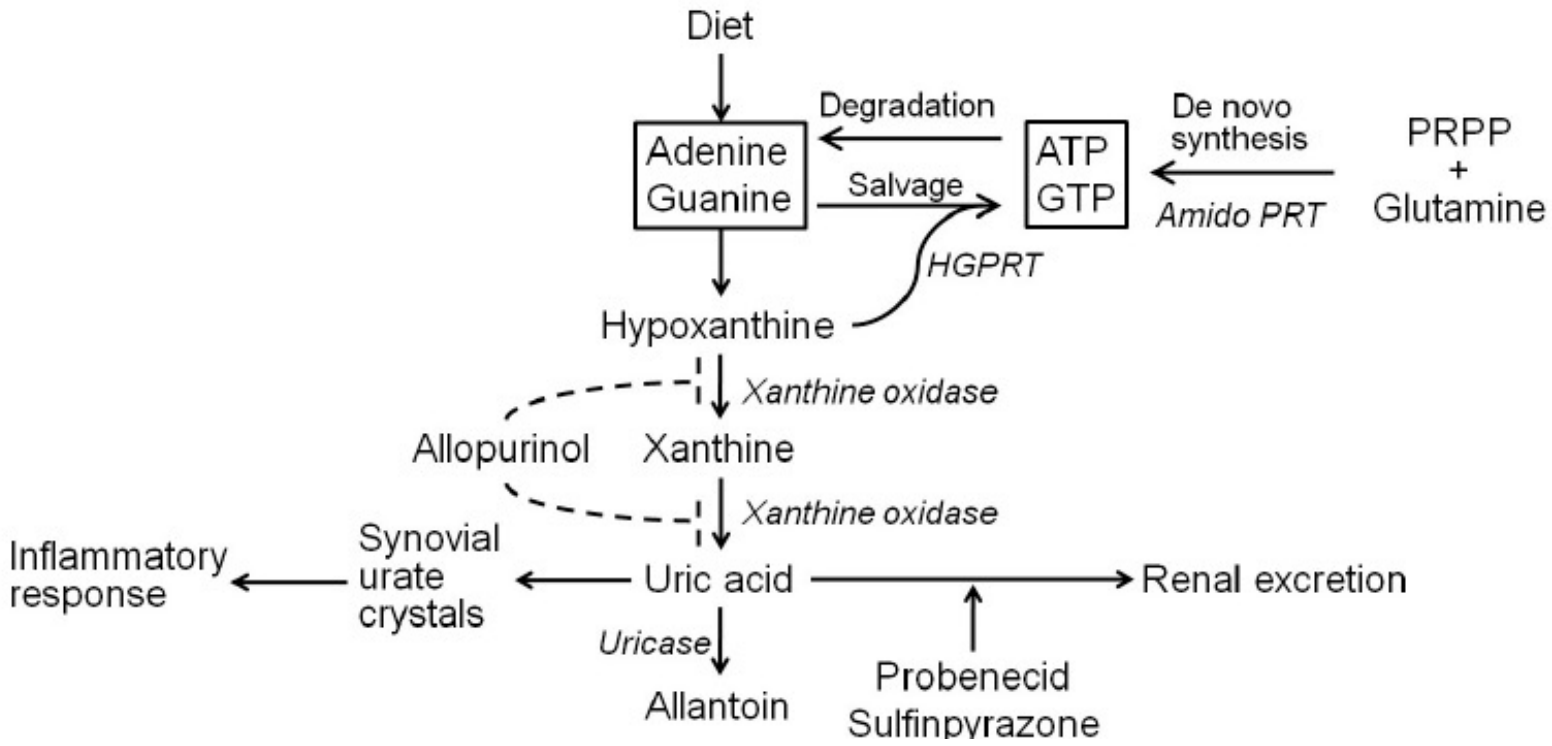
Share what you remember about the pathophysiology of gout.

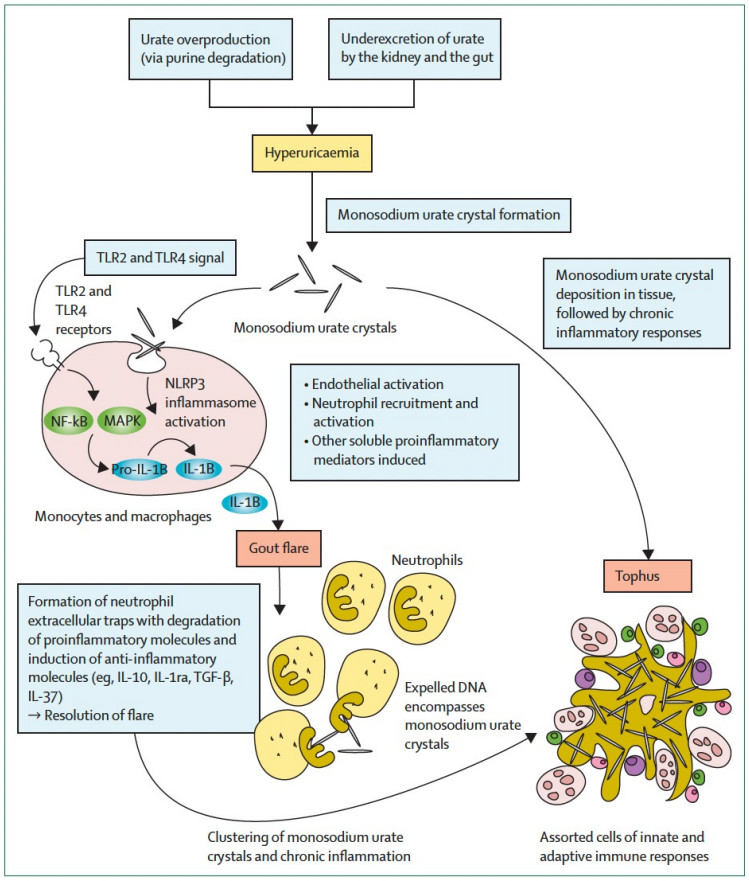
PATHOPHYSIOLOGY RELEVANT TO PHARMACOLOGY

In acute gout

- Urate crystals in the synovial fluid and synovial tissue activate complement
- Complement activation leads to phagocytosis of opsonized crystals by monocyte/macrophages
- Monocyte-secreted factors and other chemotactic factors stimulate neutrophil recruitment
- **Inflammatory response**
  - Intense joint pain, erythema, warmth, and swelling

PATHOPHYSIOLOGY RELEVANT TO PHARMACOLOGY




Urate overproduction (via purine degradation)
Underexcretion of urate by the kidney and the gut
Hyperuricaemia
Monosodium urate crystal formation
TLR2 and TLR4 signal
TLR2 and TLR4 receptors
Monosodium urate crystals
Monosodium urate crystal deposition in tissue, followed by chronic inflammatory responses
NLRP3 inflammasome activation
NF-kB
MAPK
Pro-IL-1B
IL-1B
• Endothelial activation
• Neutrophil recruitment and activation
• Other soluble proinflammatory mediators induced
IL-1B
Monocytes and macrophages
Gout flare
Neutrophils
Tophus
Formation of neutrophil extracellular traps with degradation of proinflammatory molecules and induction of anti-inflammatory molecules (eg, IL-10, IL-1ra, TGF-β, IL-37)
→ Resolution of flare
Expelled DNA encompasses monosodium urate crystals
Clustering of monosodium urate crystals and chronic inflammation
Assorted cells of innate and adaptive immune responses

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NSAIDs

ACTIVE LEARNING

You learned about NSAIDs in the fall.

- What is their mechanism of action?
- List two examples of generic NSAID drug names.
- State three notable adverse effects of NSAIDs.

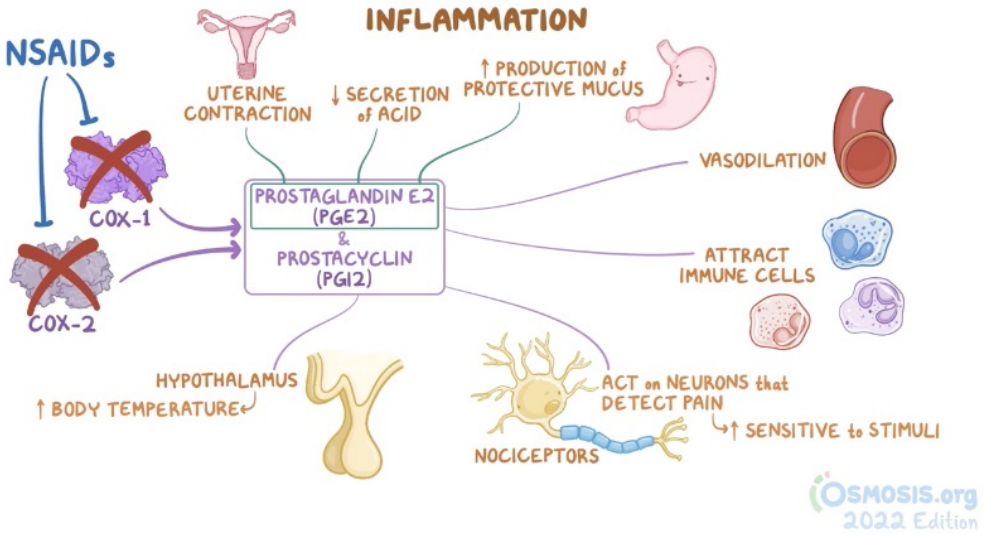
List one notable adverse effect associated with NSAIDs.

MECHANISM OF ACTION

COX inhibitors

- Inhibit prostaglandin, thromboxane, and prostacyclin synthesis

Also: decrease sensitivity of vessels to bradykinin and histamine; decrease lymphocyte production from T lymphocytes; reverse vasodilation and inflammation



NSAIDs

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Diclofenac (Cambia, Zorvolex, Zipsor, Dyloject, Cataflam) 💉 Ibuprofen (Motrin, Advil) 💉 Indomethacin (Indocin, Tivorbex) Ketorolac (Toradol) 💉 Naproxen (Aleve, Naprosyn)	Hypersensitivity **Cardiovascular thrombotic events** May increase potassium Avoid use in pregnancy (esp 3rd trimester)	Interstitial nephritis **Gastric ulcer (prostaglandins protect gastric mucosa)** **Acute kidney injury/Renal ischemia (prostaglandins vasodilate afferent arteriole)** Aplastic anemia	May increase bleeding risk of anticoagulants Increased risk of GI bleeding when used with corticosteroids May decrease efficacy of diuretics

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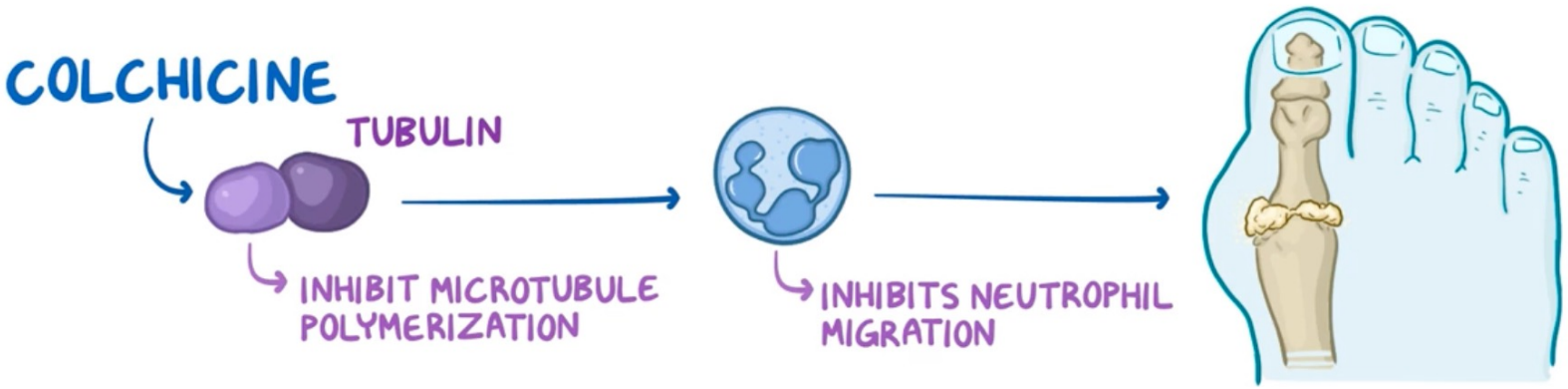
COLCHICINE

Gout

COLCHICINE MOA

Binds to the intracellular tubulin

- Inhibits microtubule polymerization → prevention of microtubule formation → inhibition of mitosis
- This leads to inhibition of several leukocytes and macrophages
  - Inhibits release of inflammatory mediators



COLCHICINE

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Colchicine	**Concomitant use of a P-glycoprotein (P-gp) inhibitor or strong CYP3A4 inhibitor in presence of renal or hepatic impairment** Caution: Narrow therapeutic window	**Nausea and vomiting, abdominal pain** **Bloody diarrhea (due to inhibition of mitosis in the intestinal mucosa)** Myelosuppression leading to leukopenia, thrombocytopenia, agranulocytosis (after chronic administration)	Inhibition of P-gp within the intestinal lumen increases colchicine oral bioavailability CYP3A4 inhibitors may increase colchicine levels

P-GP INHIBITORS

Abrocitinib

Adagrasib

Amiodarone

Azithromycin (systemic)

Cannabidiol and cannabidiol-containing coformulations

Capmatinib

Carvedilol

Clarithromycin

Cobicistat and cobicistat-containing coformulations

Cyclosporine (systemic)

Daclatasvir

Diosmin (a plant flavonoid sold as dietary supplement)

Dronedarone

Elagolix

Elagolix-estradiol-norethindrone

Eliglustat

Elexacaftor-tezacaftor-ivacaftor

Enzalutamide

Erythromycin (systemic)

Flibanserin

Fostamatinib

Glecaprevir-pibrentasvir

Isavuconazole

Itraconazole

Ivacaftor

Ketoconazole (systemic)

Lapatinib

Ledipasvir

Levoketoconazole

Neratinib

Nirmatrelvir-ritonavir

Ombitasvir-paritaprevir-ritonavir

Osimertinib

Pirtobrutinib

Posaconazole

Propafenone

Quinidine

Quinine

Ranolazine

Ritonavir and ritonavir-containing coformulations

Rolapitant

Selpercatinib

Simeprevir

Tamoxifen

Tepotinib

Tezacaftor-ivacaftor

Ticagrelor

Tucatinib

Velpatasvir

Vemurafenib

Verapamil

Voclosporin

STRONG CYP3A4 INHIBITORS

Adagrasib

Atazanavir

Ceritinib

Clarithromycin

Cobicistat and cobicistat-containing coformulations

Darunavir

Idelalisib

Indinavir

Itraconazole

Ketoconazole

Levoketoconazole

Lonafarnib

Lopinavir

Mifepristone

Nefazodone

Nelfinavir

Nirmatrelvir-ritonavir

Ombitasvir-paritaprevir-ritonavir

Ombitasvir-paritaprevir-ritonavir plus dasabuvir

Posaconazole

Ritonavir and ritonavir-containing coformulations

Saquinavir

Telithromycin

Tucatinib

Voriconazole

CLINICAL USE & ADME

Gout

Familial Mediterranean fever

Stable ischemic heart disease
(prevention of atherosclerotic CV events)

Narrow therapeutic window

Metabolized via CYP3A4 and glucuronidation

Excreted in urine (40-65% unchanged drug)

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XANTHINE OXIDASE INHIBITORS

Gout

ACTIVE LEARNING

Describe the role of xanthine oxidase in uric acid metabolism.

How might inhibition of xanthine oxidase be useful in the management of gout?

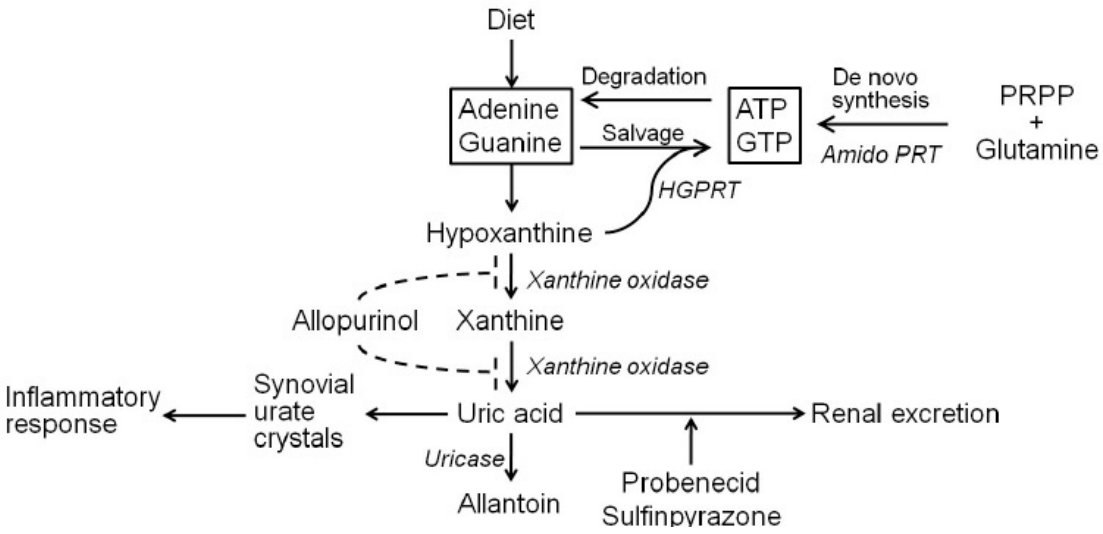
XANTHINE OXIDASE INHIBITORS MOA

Irreversible inhibition of xanthine oxidase

Inhibition of conversion to hypoxanthine and xanthine to uric acid

Decreased hyperuricemia

Decreases risk of precipitation of uric acid crystals in joints, tissues



ALLOPURINOL VS FEBUXOSTAT

Allopurinol

Purine analog

Allopurinol is competitive inhibitor of xanthine oxidase

Allopurinol metabolite, oxypurinol, is a non-competitive inhibitor of xanthine oxidase

Febuxostat

Non-purine inhibitor

Individuals that cannot tolerate allopurinol

XANTHINE OXIDASE INHIBITORS

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Allopurinol	HLA-B*5801-positive patients should avoid allopurinol HLA-B*5801 screening recommended in patients at elevated risk of SCAR, including patients of Asian descent (eg, Korean, Han Chinese, Thai) and African American patients	Cutaneous reactions (including Stevens-Johnson syndrome; Patients may be screened for HLA-B*5801 allele) Increased liver enzymes Increased risk of gout attack during the early phase of treatment (can be prevented by colchicine/NSAID)	Inhibits metabolism of mercaptopurine and azathioprine, drugs that are metabolized by xanthine oxidase → decrease dose of these drugs

XANTHINE OXIDASE INHIBITORS

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Febuxostat	CV disease (increased risk of death from cardiovascular causes)	Increased liver enzymes	Inhibits metabolism of mercaptopurine and azathioprine, drugs that are metabolized by xanthine oxidase → decrease dose of these drugs

Boxed Warning: Higher risk of death from cardiovascular causes with febuxostat than with allopurinol

CLINICAL USE

Allopurinol

Gout

Nephrolithiasis, prevention

Tumor lysis syndrome, prevention

Febuxostat

Hyperuricemia

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URICOSURICS

Gout

URICOSURICS (PROBENECID) MOA

Normally > 90% uric acid filtered by kidneys is reabsorbed in proximal tubules

Uricosurics are weak acids and compete with uric acid for reabsorption by weak acid transport mechanism in proximal tubules

- ↑ uric acid excretion
- Low doses may compete with uric acid for secretion; can occasionally elevate serum uric acid concertation
  - Elevation of uric acid levels by this mechanism occurs with aspirin

PROBENECID

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Probenecid	Acute nephrolithiasis	Hypersensitivity reactions (sulfonamide) Increased risk of uric acid stones (due to increased urate excretion; can be prevented by maintaining fluid intake) Increased risk of gout attack during the early phase of treatment (can be prevented by colchicine or an NSAID)	Inhibition of tubular secretion of many weak acids including, penicillins, cephalosporins, methotrexate, sulfonylureas, indomethacin. The dose of these other drugs should be reduced. Aspirin in low doses can antagonize completely the uricosuric effect of probenecid (mechanism likely involves competition for renal tubular transport)

ACTIVE LEARNING

Probenecid inhibits tubular secretion of many weak acids including, penicillins, and cephalosporins. How might this inhibition be used to therapeutic advantage?

CLINICAL USE

Hyperuricemia, gout prevention

Sexually transmitted infections, as a pharmacokinetic enhancer to prolong beta-lactam serum levels

ACTIVE LEARNING

Based on mechanism of action, onset of action, and adverse effects, which drugs would you expect to be used for acute gout versus prophylaxis of gout? Defend your answers.

COMMON DRUGS FOR GOUT

Acute Attack

- NSAIDs
- Glucocorticoids
- Colchicine

Prophylaxis

- Xanthine oxidase inhibitors
  - Allopurinol
  - Febuxostat
- Uricosurics
  - Probenecid
  - Sulfinpyrazone
- Recombinant urate oxidases
  - Rasburicase
  - Pegloticase
- NSAIDs/colchicine

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RHEUMATOID ARTHRITIS

PATHOPHYSIOLOGY RELEVANT TO PHARMACOLOGY

The initiating interaction for an autoimmune response takes place between antigen-presenting cells (APC), which display complexes of class II MHC molecules, and CD4-lineage T-cell lymphocytes.

B cells can become activated, which leads to antibody formation, proinflammatory cytokine production, and accumulation of polymorphonuclear (PMN) leukocytes that release cytotoxins and other substances destructive to the synovium and joint structures.

T-cell activation leads to activation of macrophages and secretion of cytotoxins and cytokines. Cytotoxins can directly destroy cells and tissues.

Proinflammatory cytokines such as interleukin (IL)-1 and TNF-α stimulate both synovial fibroblasts and chondrocytes in neighboring articular cartilage to secrete enzymes that lead to tissue destruction.

INFLAMMATORY PROCESS REGULATION

Proinflammatory cytokines

- *IL-1, TNF-α*

Anti-inflammatory cytokines

- *IL-1 receptor antagonist (IL-1Ra)*

PRINCIPLES OF DRUG THERAPY

NSAIDs and aspirin provide rapid anti-inflammatory and analgesic effects

- Do NOT prevent or slow joint destruction

Disease modifying anti-rheumatic drugs (DMARDs) reduce joint inflammation

- Reduce/prevent joint destruction
- Maintain joint function/integrity
- Slow acting (weeks to months)

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TRADITIONAL DMARDs

Rheumatoid Arthritis

METHOTREXATE MOA

Reduces the number of immune cells available to maintain the inflammatory response

Cytotoxic to rapidly dividing immune cells due to inhibition of dihydrofolate reductase

ACTIVE LEARNING

Based on methotrexate's mechanism of action, what adverse effects would you expect?

METHOTREXATE

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Methotrexate	Pregnancy (teratogen) Renal disease (excreted in urine) Pulmonary disease (pneumonitis) Liver disease (hepatotoxicity)	Myelosuppression (reversible with leucovorin "rescue") Hepatotoxicity Mucositis Pulmonary fibrosis Folate deficiency (teratogen) Nephrotoxicity	Trimethoprim-sulfamethoxazole and high-dose aspirin can exacerbate toxicity of MTX

METHOTREXATE ADVERSE EFFECTS

GI, hematologic, renal and hepatic adverse effects may be prevented or managed with leucovorin or folic acid

Folic acid can displace methotrexate from the active site of DHFR

- Restores nucleotide synthesis
- Takes time

Folinic acid (leucovorin) may be used to reverse bone marrow suppression

- Folinic acid (leucovorin) is pre-reduced form of folic acid
- Does NOT require DHFR for activation
- After entering cell, folinic acid (leucovorin) readily converted into 5, 10-methyl-THF which is used for nucleotide synthesis

CLINICAL USE

Cancers: leukemias, lymphomas, choriocarcinoma, sarcomas

Ectopic pregnancy

Medical abortion (with misoprostol)

Rheumatoid arthritis

Psoriasis

Inflammatory bowed disease

Vasculitis

HYDROXYCHLOROQUINE MOA

Exact MOA unknown

Thought to inhibit release of TNF-α and IL-1 by macrophages

- May prevent synovial cell proliferation and pannus formation, slowing down joint destruction

HYDROXYCHLOROQUINE

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Hydroxychloroquine	Cautions: Renal disease Myasthenia gravis Liver disease Porphyria Psoriasis	Nausea Epigastric pain Skin hyperpigmentation Retinal damage Rash Myopathy Neuropathy QT interval prolongation Lowers seizure threshold	Increase serum digoxin and cyclosporine levels Avoid use with drugs that prolong QT interval

CLINICAL USE

Methotrexate

Cancers: leukemias, lymphomas, choriocarcinoma, sarcomas

Ectopic pregnancy

Medical abortion (with misoprostol)

Rheumatoid arthritis

Psoriasis

Inflammatory bowel disease

Vasculitis

Hydroxychloroquine

Lupus

Malaria

Rheumatoid arthritis

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BIOLOGIC DMARDs

Rheumatoid Arthritis

TNF-α INHIBITORS

Bind to TNF-α such that it cannot bind to its receptor

Adalimumab and infliximab are monoclonal antibodies to TNF-α

Etanercept is a TNF inhibitor and binds to TNF-α and TNF-β

TNF-α INHIBITORS

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Adalimumab Infliximab Etanercept	Active infection, history of recurring infections, or medical conditions predisposing them to infection Severe heart failure (↑ mortality)	Increased risk of infection Latent tuberculosis can become active Injection reactions • Etanercept and adalimumab are injected subcutaneously and can cause erythema, pain, and pruritus at the injection site • Infliximab administered intravenously and can cause an infusion reaction manifested as fever and chills	Combination of TNF-α inhibitors is contraindicated because of a significantly increased risk of serious infections

CLINICAL USE

Adalimumab, infliximab

Inflammatory bowel disease

Rheumatoid arthritis

Psoriasis

Ankylosing spondylitis

Etanercept

Rheumatoid arthritis

Psoriasis

Ankylosing spondylitis

ACTIVE LEARNING

Biologic products are created with biotechnology and encompass blood components, somatic cells, gene therapy, tissues, recombinant proteins, and vaccines. They are derived from microorganisms, plant, animal, or human cells.

Monoclonal antibodies are a large subset of biologics.

Adalimumab and infliximab are two monoclonal antibodies used to treat rheumatoid arthritis. Based on their names, what is the target and source species of adalimumab and infliximab?

MONOCLONAL ANTIBODY NOMENCLATURE

Name Component	Meaning
Prefix	Random, should contribute to distinctive name
Substem A	Target class
Substem B	Species
Suffix	-mab (for **m**onoclonal **a**nti**b**ody)

Target Class	Substem A
Bacterial	-b(a), -ba(c)
Serum amyloid protein	-am(i)
Cardiovascular	-c(i), -ci(r)
Fungal	-f(u), -fung
Skeletal muscle related growth factors	-gr(o)
Interleukin	-k(i), -ki(n)
Immunomodulating	-l(i), -li(m)
Neural	-n(e)
Bone	-s(o), -os
Toxin	-tox(a)
Tumor	-t(u)
Viral	-v(i), -vi(r)

Source Species	Substem B
Rat	a
Rat/mouse	axo
Hamster	e
Primate	i
Mouse	o
Human	u
Chimeric	xi
Chimeric/humanized	xizu
Humanized	zu

ADALIMUMAB

Name Component	Meaning	Adalimumab Example	
Prefix	Random, should contribute to distinctive name	Ada	Random
Substem A	Target class	-lim	immunomodulating
Substem B	Species	-u	Human
Suffix	-mab (for **m**onoclonal **a**nti**b**ody)	-mab	Monoclonal antibody

INFLIXIMAB

Name Component	Meaning	Adalimumab Example	
Prefix	Random, should contribute to distinctive name	Inf	Random
Substem A	Target class	-li	immunomodulating
Substem B	Species	xi	Chimeric
Suffix	-mab (for **m**onoclonal **a**nti**b**ody)	-mab	Monoclonal antibody

ACTIVE LEARNING

Ustekinumab (Stelara) is commonly used monoclonal antibody for psoriasis, psoriatic arthritis, and Chron's disease.

Based on its name, what is the target and source species?

USTEKINUMAB

Name Component	Meaning	Adalimumab Example	
Prefix	Random, should contribute to distinctive name	Uste	Random
Substem A	Target class	-kin	interleukin
Substem B	Species	u	Humanized
Suffix	-mab (for **m**onoclonal **a**nti**b**ody)	-mab	Monoclonal antibody

Ustekinumab (Stelara) is a fully human monoclonal antibody that targets interleukin-12 and -23

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JAK INHIBITORS

Rheumatoid Arthritis

JAK INHIBITORS MOA

In response to cytokines, Janus kinase (JAK) enzymes activate STATs (signal tranducers and activators of transcription) which regulate gene expression and intracellular activity

Tofacitinib inhibits JAK enzymes preventing cytokine-mediated gene expression and intracellular activity in immune cells (so technically not a biologic)

JAK INHIBITORS

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Tofacitinib	Cautions: Avoid with active infections Hepatic/renal impairment Lung disease	Increased risk of infection Elevated liver enzymes Neutropenia, thrombocytopenia GI perforation Cholesterol changes (↑ LDL cholesterol and HDL cholesterol) Malignancies (lung, breast, gastric, colorectal, renal cell, prostate, lymphoma, malignant melanoma)	Use with another biological is not recommended Inhibitors of P450 enzymes (CYP3A4 and CYP2C19) can increase serum concentrations of tofacitinib; concurrent use requires a dose reduction of tofacitinib Potent inducers of CYP3A4 (e.g. rifampin) decrease tofacitinib levels Live vaccines should not be given

CLINICAL USE

Ankylosing spondylitis

Polyarticular course juvenile idiopathic arthritis

Psoriatic arthritis

Rheumatoid arthritis

Ulcerative colitis

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ANY QUESTIONS?