Anti-inflammatory Drugs

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Learning Objectives

- Identify the different classes of drugs and prototype used for the management of inflammation
- Describe the pharmacokinetic and pharmacodynamic properties of the drugs
- Summarize the uses, most common adverse effects and drug interactions of the anti-inflammatory drugs

INFLAMMATION

Inflammation - common nonspecific manifestation of injury, infection, and many diseases

- occurs in acute or chronic forms usually characterized by typical timeframes
- distinguished by the presence and activity of particular cell types and mediators
- Acute and chronic inflammation - occur independently or overlap

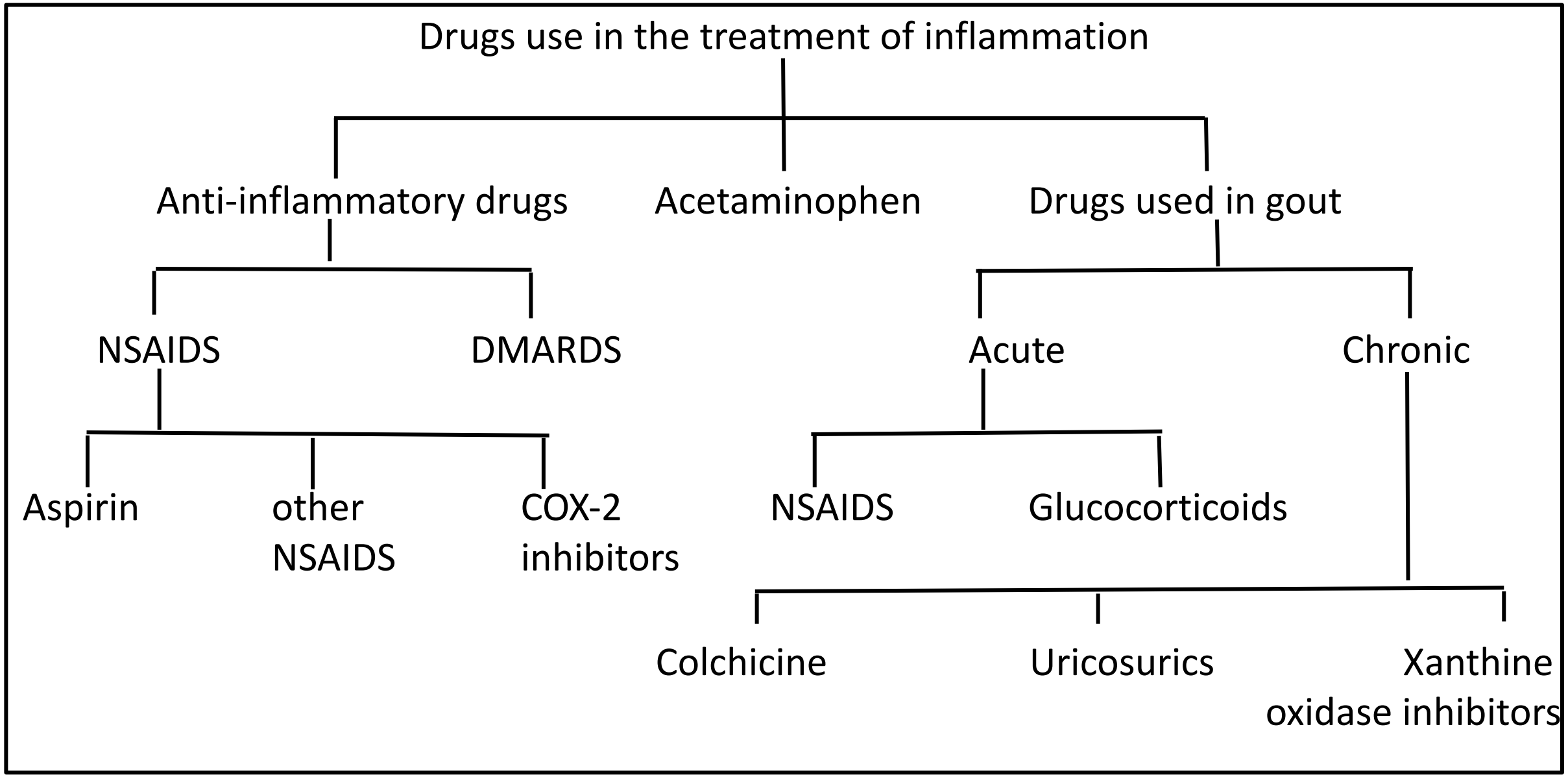
INFLAMMATION

Arthritis - any type of inflammation and damage to a joint

Rheumatic disease - a disease process associated with joints, bones, connective tissues, muscles, bursae, and ligaments

Arthritis and musculoskeletal disorders - classified into three broad categories

- associated with immune complex disorders, ex rheumatoid arthritis (RA)
- associated with degeneration of the joints, ex osteoarthritis (OA)
- associated with metabolic disorders and crystal deposition in joints



https://www.cambridge.org/core/books/essential-clinical-anesthesia/cox-inhibitors-and-2adrenoceptor-agonists/48C9DB1BA6F88041BD209E123A431DAA

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

aspirin-like drugs or antipyretic analgesics

provide symptomatic relief from fever, pain and swelling

- chronic joint disease (osteo- and rheumatoid arthritis)
- acute inflammatory conditions (fractures, sprains, sports, other soft tissue injuries)

different formulations (tablets, injections and gels)

All NSAIDs, sp. traditional NSAIDs, can have significant unwanted effects, especially in older persons

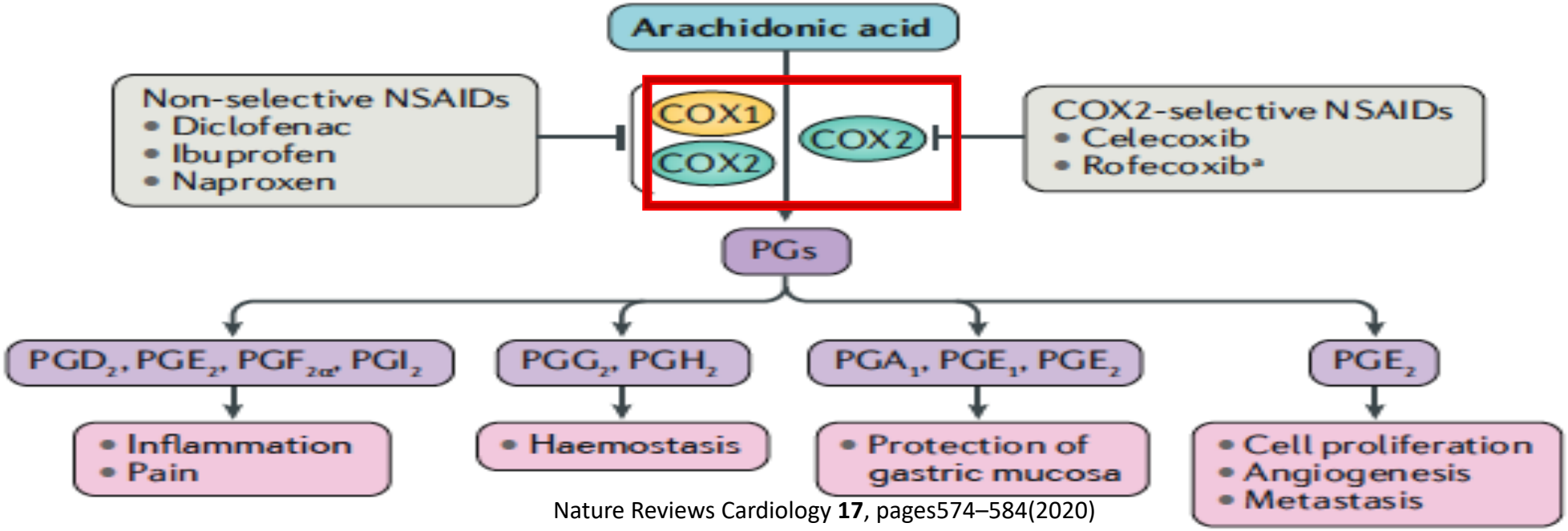
Newer agents have fewer adverse actions

NSAID Classification and Selectivity

Non-selective			**Selective**
More COX-1 selective	Non-selective	More COX-2 selective	COX-2 selective
Ketorolac	Ibuprofen	Sulindac	Celecoxib
Flurbiprofen	Fenoprofen	Diclofenac	Etoricoxib
Ketoprofen	Sodium salicylate	Meloxicam	Lumiracoxib
Indomethacin	Diflunisal	Etodolac	
Aspirin			
Naproxen			
Tolmetin			
Piroxicam			
Meclofenamate			
Increased gastrointestinal effects			Increased cardiovascular effects

https://www.practicalpainmanagement.com/treatments/pharmacological/non-opioids/ask-expert-which-nsaids-are-most-selective-cox-1-cox-2

NSAIDs Mechanism of action



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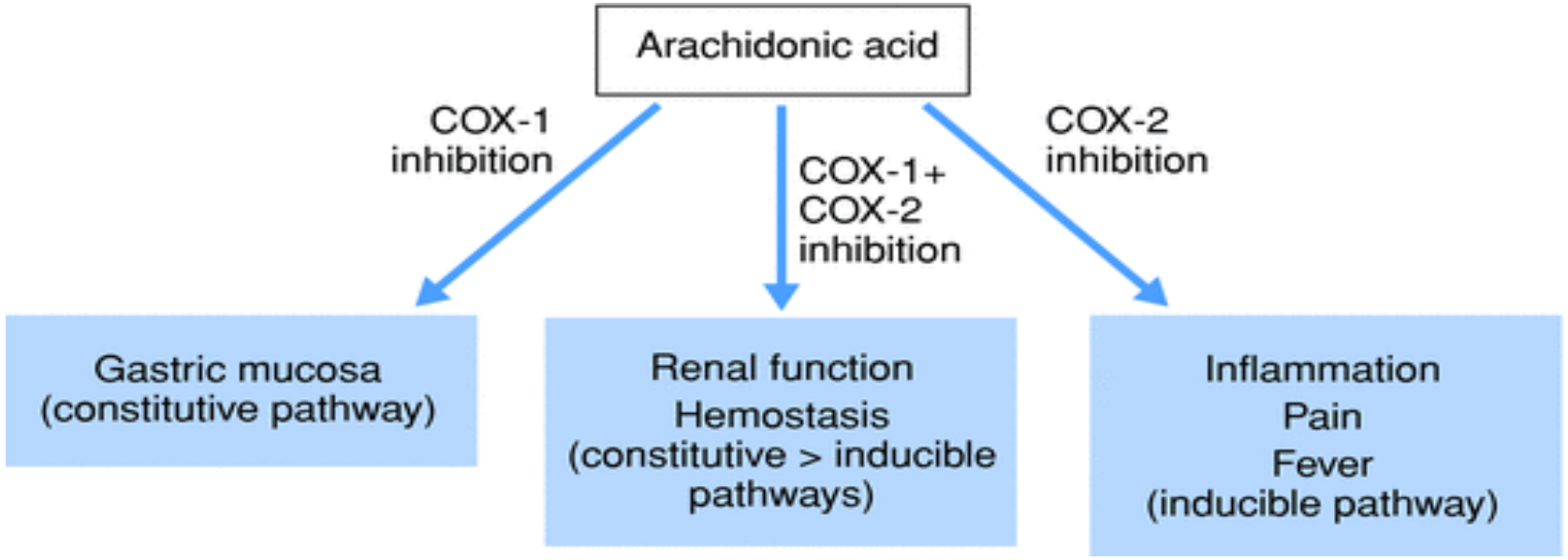

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NSAIDs: Pharmacokinetics

Lipid soluble weak acids

Rapid absorption in stomach and duodenum

Onset 15-30 min; rapid onset – rapid offset

Highly protein bound

- May displace weakly protein-bound drugs (warfarin, sulfonylurea, methotrexate)

Widely distributed

Metabolized in the liver by cytochrome P450

Eliminated by the kidneys

Therapeutic uses

Anti-inflammatory

- Decreased vasodilatation
- Oxygen radical scavenging (parti., sulindac)
- Inhibits expression of transcription factor NKκB – expression of genes for inflammatory mediators (aspirin)

Antipyretic

- Resets thermostat disturbance in the hypothalamus by inhibiting production of prostaglandin

Analgesic

- mild or moderate pain arising from inflammation or tissue damage
  - Peripheral - NSAIDs decrease production of prostaglandins that sensitize nociceptors to inflammatory mediators (ex, bradykinin)
  - central action in the spinal cord and CNS

NSAIDs

Aspirin

- Main use: antithrombotic
  - Prophylaxis of myocardial infarction (MI) in patients with unstable angina and prior MI
  - Prophylaxis of transient ischemic attacks (TIA) or stroke in patients with TIA
  - prevention of thromboembolism after hip replacement surgery
- Anti-inflammatory

NSAIDs

- Osteoarthritis, rheumatoid arthritis
- Arthropathies (ankylosing spondylitis, psoriatic arthritis
- menstrual pain, headaches and migraine
- Postoperative dental surgery pain

NSAIDs: Drug Interactions, Cautions

antihypertensive and uricosuric agents (probenecid, sulfinpyrazone)

Low dose aspirin - reduce urate excretion = should not be used in gout

Warfarin, NSAIDs – increased risk of bleeding

Calcium – dec ASA activity

Metoprolol – dec activity

Side effects

GI - dyspepsia, nausea, vomiting

- Chronic use – GI damage, risk of hemorrhage, ulceration and perforation

CV - edema, hypertension – dose- and time-dependent – in HPN persons not taking antihypertensives

Skin – rashes - mechanism unknown – mefenamic acid, sulindac

- Erythema, urticaria, photosensitivity reactions, Stevens Johnsons syndrome, toxic epidermal necrolysis

Renal - reversible renal insufficiency - mainly in individuals with compromised renal function

- 'Analgesic-associated nephropathy'- long-term high-dose regimes of NSAIDs, often irreversible

Bronchospasm - in 'aspirin-sensitive' asthmatics, uncommon with coxibs

Platelet aggregation – except coxibs

Uncommon - liver disorders, bone marrow suppression

Identification of High-Risk Patients

High risk population / condition	Adverse effect
Age; >85y; women	Slowed metabolism and elevated tissue levels of more lipid soluble drugs
History of peptic ulcer	Repeat ulceration and GI hemorrhage
Low serum albumin	Elevated NSAID serum levels
Concomitant use of multiple antithrombotic agents	Hemorrhage
Concomitant use of other NSAIDs or steroid agents; increase NSAID dose; new NSAID user	GI injury; GI hemorrhage; initiation of GI ulceration
Hypovolemic states; Renal impairment due to age; atherosclerosis; hypertensive renal disease; other intrinsic renal disease	Renal failure, impairment of glomerular filtration; acute renal failure; edema, interstitial nephritis; papillary necrosis; chronic failure; hyperkalemia

Paracetamol

N-acetyl-p-aminophenol

most commonly used analgesic–antipyretic

component of many over-the-counter preparations

Slight anti-inflammatory action

free of the gastric and platelet side effects of the other NSAIDs

sometimes not classified as an NSAID

MA:

- Central: activate descending serotonin inhibitory pain pathway
- Peripheral: incompletely inhibits COX-1 and COX-2 enzymes
  - does not inhibit prostaglandin synthesis in peripheral tissues - lacks anti-inflammatory properties
- Antipyretic: direct action on the hypothalamus - dilation of peripheral blood vessels causing sweating and dissipation of heat

Paracetamol

Rapid and almost complete absorption

Peak concentration: 30-60m

Bioavailability: Oral – 63-89%; rectal – 24-98%

25% protein binding; T1.2: 2-4h

Metabolism:

- glucuronidation (45-55%) and sulfation (30-35%)

- small percentage - CYP2E1 to form N-acetyl-p-benzo-quinone imine (NAPQI): toxic metabolite - conjugated to glutathione

Excretion: 80% in urine; 3% unchanged

Paracetamol

Use

- Antipyretic
- Analgesic - mild to moderate pain
  - combined with other drugs - over the counter (OTC) allergy medications, cold medications, sleep medications, pain relievers

SE:

- Therapeutic doses: uncommon, skin reaction, reversible increase in hepatic enzymes
- Larger doses: dizziness, excitement, disorientation
- Toxic dose (10-15g) hepatotoxicity and nephrotoxicity – death due to severe hepatotoxicity
  - Exacerbated by chronic alcohol consumption

Disease-Modifying Antirheumatic Drugs (DMARDs)

immunosuppressive and immunomodulatory agents

Use: treatment of inflammatory arthritides

- rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS)
- other disorders - connective tissue diseases - systemic sclerosis (SSc), systemic lupus erythematosus (SLE), Sjogren syndrome (SS)
- inflammatory myositis, vasculitis, uveitis, inflammatory bowel disease, and some types of cancers

slow or even reverse damage to cartilage and bone in autoimmune rheumatic diseases

slow-acting - may take 2 weeks to 6 months for their benefit to become apparent

second-line drugs - only resorted to when other therapies (ex. NSAIDs) failed but DMARD therapy may be initiated as soon as a definite diagnosis has been reached

DMARDs

- Heterologous group of agents with different chemical structures and mechanisms of action:
  - Conventional synthetic – small molecules
    - interfere with critical pathways in the inflammatory cascade
  - Biologic – large molecules, usually proteins
    - produced by recombinant DNA technology
    - very selective in their mechanism of action; target a specific pathway of the immune system
    - prescribed after the failure of conventional DMARD therapy
    - functions
      - interfere with cytokine function or production Janus kinase inhibition
      - inhibit the “second signal” required for T-cell activation
      - deplete B-cells or inhibiting factors that activate B-cells
  - Given orally and parenterally (SQ and IV)

Inflammatory Cascade: *Pathogenesis and clinical findings*

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Note: *The Inflammatory Cascade is a non-specific response to all foreign pathogens and trauma.*

Abbreviations:
ILs: Interleukins
WBC's: White Blood Cells

Physical barrier and cell disruption (e.g. skin puncture)

Activation of the immune response at site of injury

Mast cells at injured site release **histamine**

Disrupted endothelial cells release **pro-inflammatory cytokines** (e.g IL's, TNFα) and chemokines

Disrupted endothelial cells release **leukocytosis-inducing factors**

↑ vessel permeability: extravasation of immune cells/mediators (e.g. WBC's, complement proteins, platelets)

Vasodilation: ↑ blood flow to injured site

Chemotaxis: immune cells migrate to injury site

↑ circulating WBC's

Cardinal signs of the inflammatory response
Redness (*rubor*) **Heat** (*calor*) **Pain** (*dolor*) **Swelling** (*tumor*)

Continued Innate Immunity

Phagocytosis: *(*main mechanism)* neutrophils and macrophages engulf foreign pathogens and dead tissue

Pus

Complement System: opsonize pathogen (tag for destruction), promote inflammation

Natural Killer Cells: perforin-mediated wall breakdown (puncture holes), enzyme-mediated destruction

Acquired Immunity Recruitment

Humoral: *(B cell response)* production of antibodies, activation of complement system

Cell-mediated: *(T cell response)* ↑ helper cell and cytotoxic cell activity

Note: *Dendritic cells at injury site aid in phagocytosis and antigen presentation to T cells.*

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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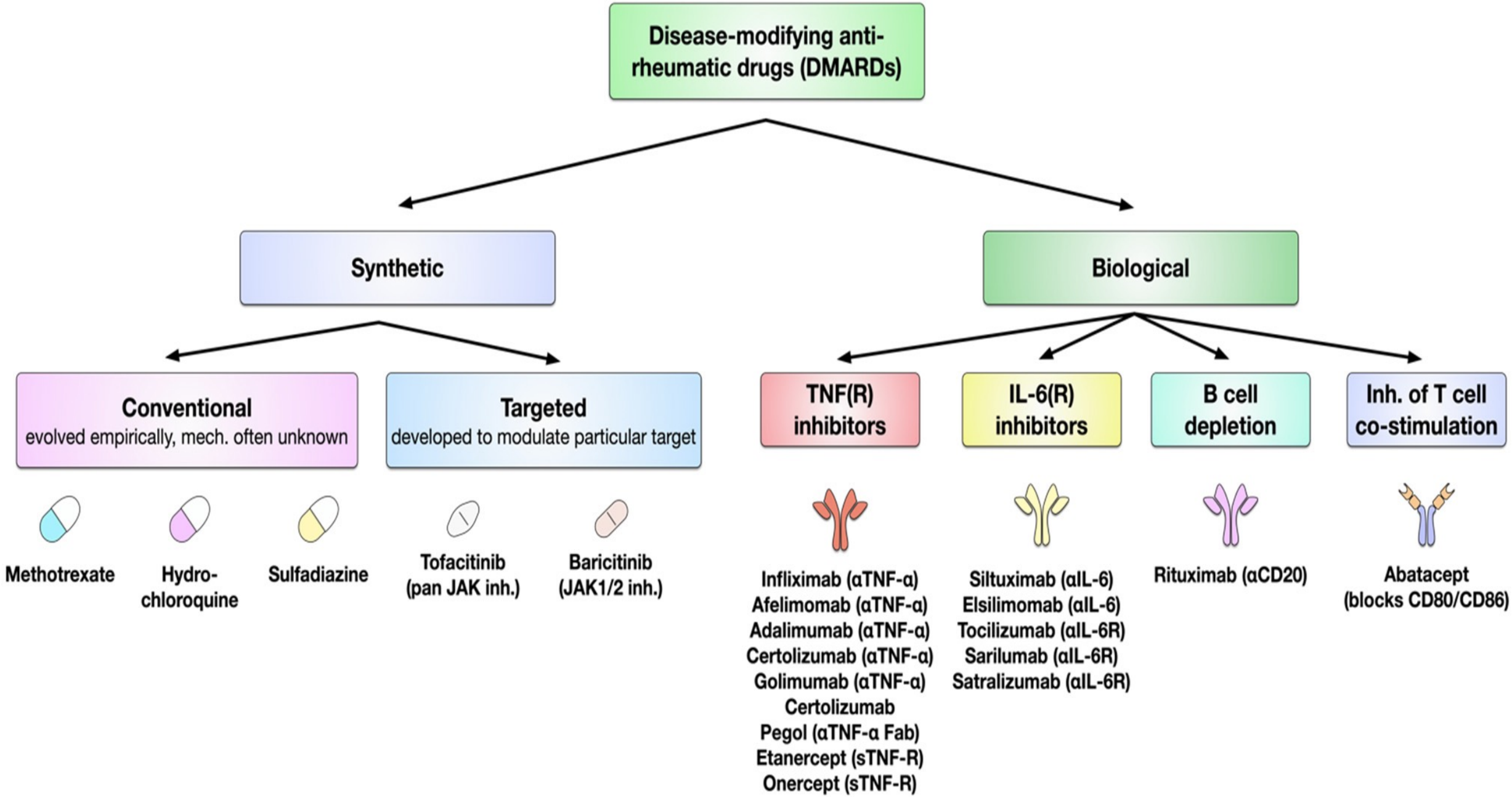


Jobst % Panus, 2020

csDMARDS

- Methotrexate
- Azathiopine
- Antimalarials: chloroquine, hydroxychloroquine
- Cyclophosphamide
- Cyclosporine
- Leflunomide
- Mycophenolate mofetil
- Sulfasalazine

Methotrexate

first-line csDMARD for treatment of RA

MA: inhibition of amino-imidazolecarboxamide ribonucleotide (AICAR) transformylase and thymidylate synthetase AICAR = accumulation of AMP and converted to adenosine = potent inhibitor of inflammation

- Inhibit inflammatory functions of neutrophils, macrophages, dendritic cells, and lymphocytes

70% absorbed after oral administration; rapid onset of action

Both methotrexate and metabolite are polyglutamated within cells - stay for prolonged periods

serum half-life - 6–9 hours

Excreted in urine, 30% excreted in bile

Use: treatment of RA, also psoriasis, psoriatic arthritis, ankylosing spondylitis, polymyositis, dermatomyositis, Wegener's granulomatosis, giant cell arteritis, SLE, vasculitis

AE: nausea, mucosal ulcers - most common; leukopenia, anemia, stomatitis, GI ulcerations, alopecia; progressive dose-related hepatotoxicity = enzyme elevation

Azathioprine

MA: acts through its major metabolite, 6-thioguanine to suppresses purine nucleotide synthesis, B-cell and T-cell function, immunoglobulin production, and IL-2 secretion

Metabolism in liver (bimodal)

- converted to mercaptopurine – inhibits DNA synthesis

Use: management of RA, prevent kidney transplant rejection

Adverse effects: bone marrow depression, nausea, vomiting, skin eruption, mild hepatotoxicity

Cyclophosphamide

MA: converted to metabolite phosphoramide mustard - cross-links DNA to prevent cell replication, suppresses T-cell and B-cell function

Use: treatment of SLE, vasculitis, Wegener's granulomatosis, and other severe rheumatic diseases

AE: Leukopenia, thrombocytopenia, anemia

- High doses – cardiotoxic and neurotoxic

Antimalarials

- chloroquine, hydroxychloroquine
  - MA: suppression of T-lymphocyte responses to mitogens, inhibition of leukocyte chemotaxis, stabilization of lysosomal enzymes, inhibition of DNA and RNA synthesis, and trapping of free radicals
  - rapidly absorbed
  - 50% protein-bound in the plasma
  - extensively tissue-bound, sp in melanin-containing tissues (ex eyes)
  - Metabolized in the liver
  - elimination half-lives = up to 45 days
  - Use: not considered very effective DMARD; takes 3–6 months for a response
    - used in SLE - decrease mortality; Sjögren's syndrome
  - AE: skin manifestations, serositis, joint pains of this disease.

Cyclosporine

peptide antibiotic

MA: regulation of gene transcription - inhibits IL-1 and IL-2 receptor production

- inhibits macrophage–T-cell interaction and T-cell responsiveness and function

Incomplete and erratic absorption

- microemulsion formulation - improves its consistency and provides 20–30% bioavailability
- Bioavailability improved by grapefruit juice by as much as 62%

metabolized by CYP3A- subject to a large number of drug interactions

Use: RA and retards the appearance of new bony erosions

AE: Leukopenia, thrombocytopenia, anemia

- High doses: cardiotoxic and neurotoxic

Leflunomide

MA: converted to its active metabolite, teriflunomide - interfere with ribonucleotide synthesis and the arrest of stimulated cells in the G1 phase of cell growth

- Inhibits T-cell proliferation and reduces production of autoantibodies by B cells

completely absorbed from the GIT

mean plasma half-life = 19 days

Metabolism: enterohepatic circulation

Use: as effective as methotrexate in RA, inhibition of bony damage

AE: diarrhea; mild alopecia, weight gain, increased blood pressure

Contraindicated in pregnancy

Mycophenolate mofetil

MA: converted to mycophenolic acid (active form)

- suppression of T- and B-lymphocyte proliferation

Use: treatment of renal disease due to SLE,

- vasculitis and Wegener’s granulomatosis

AE: nausea, vomiting, diarrhea, abdominal pain, headache, hypertension, reversible myelosuppression (mainly neutropenia), hepatotoxicity

Sulfasalazine

complex of sulfinamide (sulfapyridine) and salicylate

MA: inhibits COX and lipoxygenase pathways

- suppress T-cell responses, inhibit B-cell proliferation, and decreased release of inflammatory cytokines (IL-1, IL-6, IL-12, and tumor necrosis factor-alpha [TNF-a]) produced by monocytes or macrophages

Poorly absorbed after oral administration (10%)

Undergo enterohepatic circulation then metabolized in colon to sulfapyridine (absorbed) and 5-aminosalycylic acid (unabsorbed)

Sulfapyridine excreted in urine; salicylate metabolized in liver

use: treatment of RA; chronic inflammatory bowel disease (sulfapyridine)

tsDMARDs

- Tofacitinib
  - Janus kinase (JAK3) inhibitor – enzyme associated with cytokine receptors on cells surfaces for inflammatory and immune response
  - 74% oral bioavailability
  - Metaboized in liver by CYP3A4
  - 30% excreted unchanged in kidneys
  - Use: moderate–severe RA in patients who failed treatment or intolerant to methotrexate
    - IBD, psoriasis, spondyloarthritis
  - AE: increase risk of infection, sp URT and urinary tract; pneumonia, cellulitis, esophageal candidiasis
    - Patients should be screened for TB before treatment

bDMARDs

Use: reserved for patients with persistent moderate or high disease activity and indicators of poor prognosis

Therapy is tailored to the individual patient

use must be weighed against their potentially serious adverse effects

Often given in combination with methotrexate

TNF α-inhibitors	**T-cell modulators**	**B-cell modulators**	**Interleukin-1 inhibitors**
Adalimumab Cetolizumab Etanercept Golimumab Infliximab	Abatacept	Belimumab Rituximab	Anakinra Canakinumab Rilonacept

TNF α-inhibitors

- Tumor necrosis factor (TNF) - central role in the pathogenesis of several inflammatory conditions, including RA
  - two types:
    - TNF-alpha and TNF-beta - present on almost all cell types (except erythrocytes)
  - Activates signaling pathway and leads to activation of the target cell leading to the inflammatory and immune response by releasing several cytokines and apoptotic pathway initiation
    - activation of macrophages, T-cells, B-cells
    - production of proinflammatory cytokine production (IL-1, IL-6), chemokine (IL-8, RANTES)

TNF α-inhibitors

SQ –etarnecept (E), adalimumab (A), certolizumab (C)

IV infusion - Infliximab (I)

SQ or IV – golimumab (G)

Use: monotherapy or in combination with csDMARDs (methotrexate)

- ACEGI – RA, ankylosing spondylitis, psoriatic arthritis
- ACI - Crohn disease
- AEI - , plaque psoriasis
- AGI – ulcerative colitis
- A - hidradenitis suppurativa, juvenile idiopathic arthritis, uveitis
- E - polyarticular juvenile idiopathic arthritis

AE: generally well-tolerated

- headache, injection site reaction, rashes, anemia, transaminitis (mild)
- Upper respiratory tract infections, sinusitis, cough, pharyngitis, diarrhea, nausea, abdominal pain

Contraindications:

- History of hypersensitivity, CHF class III, IV

T-cell Modulators

Abatacept

MA: Inhibits T-cell activation

Administered by SQ and IV infusion (3 infusions)

Half-life 13-16 days

Response of patients – within 12-16 weeks

Use: monotherapy or in combination with csDMARDs

- moderate to severe RA
- Severe PJIA (polyarticular juvenile idiopathic arthritis)

AE: increased risk of infection (upper respiratory, urinary tract); Increase in lymphoma

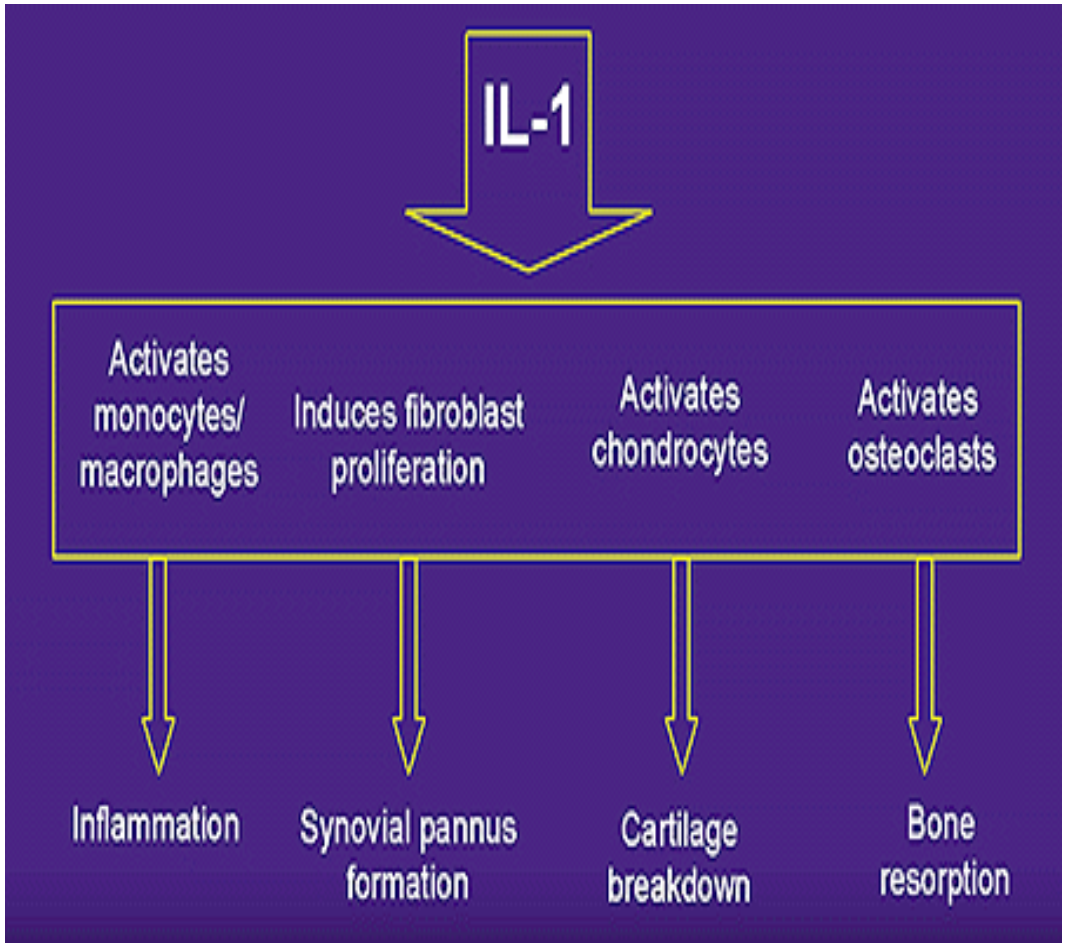
B-cell Modulators

- Rituximab - chimeric monoclonal antibody that targets the CD20 B-cell antigen
  - CD20 - found on surface of B cells = development and differentiation
    - Result in cell-mediated and complement-dependent cytotoxicity and cell apoptosis
  - IV infusion
  - T ½ ~22 days
  - Use:
    - moderate to severe RA – in combination with methotrexate for patients with inadequate response to TNF α-inhibitors
    - adult patients with granulomatosis with polyangiitis (Wegener's granulomatosis), microscopic polyangiitis, other forms of vasculitis as – in combination with glucocorticoids
  - AE: Rash – first IV infusion treatment then diminishes with second infusion
    - Reactivation of hepatitis B infection

B-cell Modulators

- Belimumab
  - MA: inhibits B lymphocyte stimulator (BLyS) – important for B-cell differentiation, homeostasis, and selection
  - administered as an IV infusion
  - Distribution half-life of 1.75 days
  - Terminal half-life of 19.4 days.
  - Use: only for the treatment of adults with active SLE – not to be given in patients with active renal or neurological manifestations of SLE
  - AE:
    - Nausea, diarrhea
    - Risk for infections (respiratory)

Interleukin-1 Inhibitors



- Interleukin-1 (IL-1) - promotes sterile inflammatory disease pathogenesis at multiple levels
  - directly cause tissue destruction, altered fibroblast proliferation, and collagen deposition
  - induces the production of secondary inflammatory cytokines and chemokines such as IL-6, TNFα, KC, and G-CSF
  - contributes to the perpetuation of inflammatory disease by promoting the induction of pathogenic cytokines (IFN-γ, IL-17, and GM-CSF) by T cells and innate effector cells
  - promotes the activation and recruitment of inflammatory immune cells including macrophages, neutrophils, natural killer (NK) cells, and T cells

https://www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis/ra-treatment/interleukin-1-inhibition/

Interleukin-1 Inhibitors

Anakinra

Rilonacept

Canakinumab

MA:

- Bind directly to IL-1 receptor (anakinra)
- Bind to IL-1 (rilonacept, canakinumab)

Proteins, not classified as slow-acting anti-RA drugs

Potent, more specific and rapidly developing actions

Not absorbed orally

Administered by SQ

cleared by the mononuclear phagocytes in the reticuloendothelial system

Interleukin-1 Inhibitors

- Anakinra
  - Recombinant DNA technology in cultured E coli
  - 95% bioavailability
  - limited distribution
  - Short T1/2: 5h
  - Dose reduced for patients with renal failure by 75%
  - Use:
    - drug of choice for CAPS (cryopyrin-associated periodic syndrome) neonatal-onset multisystem inflammatory disease (NOMID) subtype
    - Gout, Behçet’s disease and adult-onset JIA

Interleukin-1 Inhibitors

Canakinumab

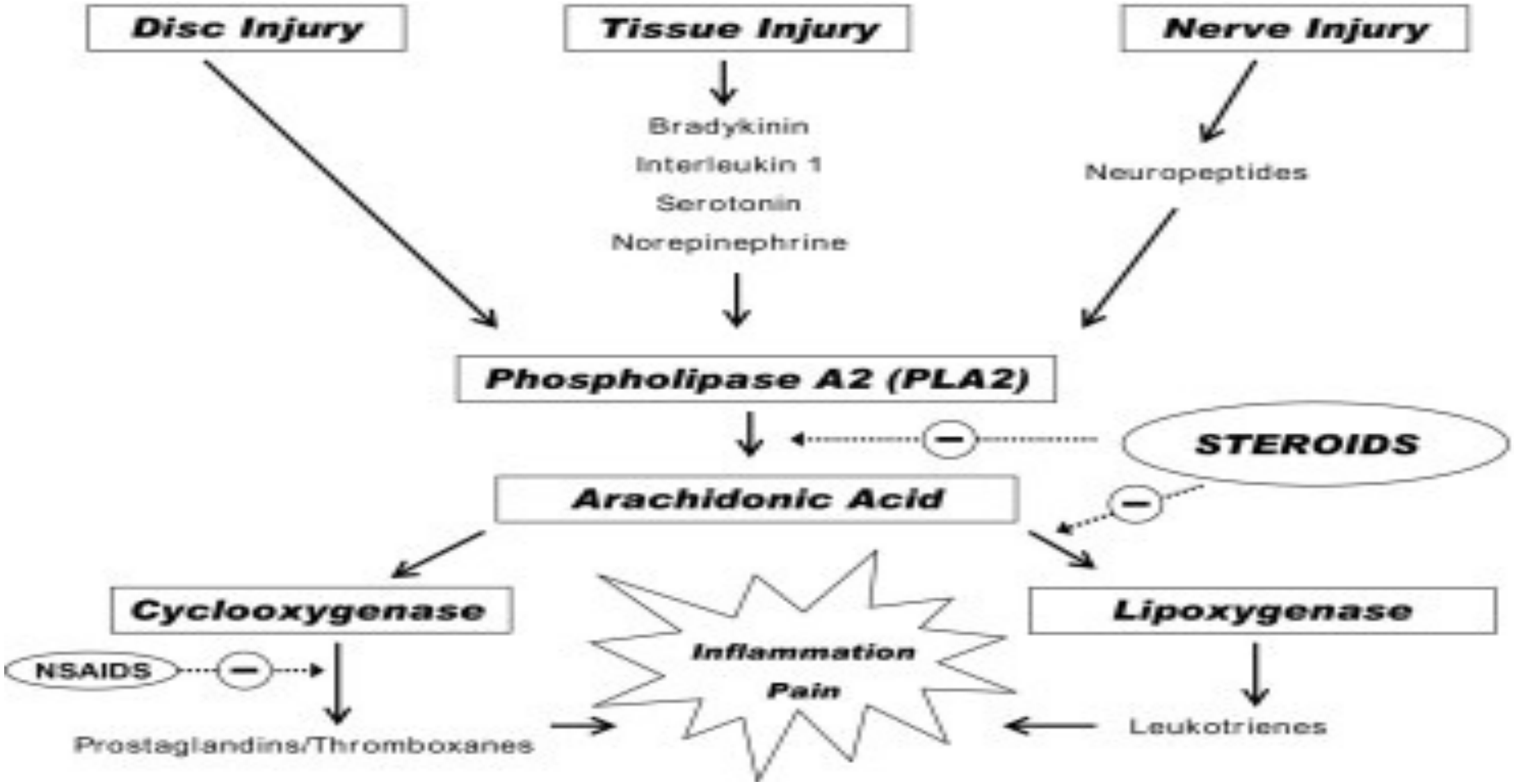
- Human IgG monoclonal Ab
- Bioavailability 66%
- Peak serum concentration 7 days
- T1/2 – 21-27 days
- use:
  - active sJIA (systemic Juvenile Idiopathic arthritis) in children 2 years and older
  - Treatment of gout

Rilonacept

- Recombinant DNA technology in Chinese hamsters
- Peak plasma after 3 days
- T1/2 - 7.5 days
- Use
  - treat CAPS subtypes: familial cold autoinflammatory syndrome and Muckle-Wells syndrome in patients 12 years or older
  - treatment of gout

Glucocorticoids

MA: inhibits phospholipase A2 to inhibit production of arachidonic acid



Baqai & Bal, 2009

Glucocorticoids

used in 60–70% of RA patients

effects are prompt and dramatic, capable of slowing the appearance of new bone erosions

Use: severe extra-articular manifestations of RA (ex. pericarditis or eye involvement) or during periods of exacerbation

- delayed-release prednisone - early morning stiffness and pain in RA
- Require gradual reduction of the dose
- Other rheumatic diseases - vasculitis, SLE, Wegener's granulomatosis, PA, giant cell arteritis, sarcoidosis, and gout
- Intra-articular corticosteroids - alleviate painful symptoms

Prednisone – most commonly used,

- oral dose - 30–50 mg/d for 1–2 days, tapered over 7–10 days

Triamcinolone acetonide - Intra-articular injection (small joints, wrist, ankle, elbow, knee - if patient is unable to take oral medications

Drugs used in Gout

Gout - characterized by extremely painful intermittent attacks of acute arthritis produced by the deposition of the crystals in the synovial tissue of distal joints (ex. big toe, external ear)

- the precipitation of urate crystals in the tissues and the subsequent inflammatory response
- Acute gout - painful distal monoarthritis and can cause joint destruction, subcutaneous deposits (tophi), and renal calculi and damage.

aims of treatment:

- Decrease the symptoms of an acute attack
- Decrease the risk of recurrent attacks
- Lower serum urate levels

Drug and its properties

- relieve inflammation and pain (NSAIDs, colchicine, glucocorticoids)
- prevent inflammatory responses to crystals (colchicine and NSAIDs)
- inhibit urate formation (allopurinol, febuxostat)
- augment urate excretion (probenecid)

Management of Gout

Acute gout

- NSAIDs
- Colchicine
- Glucocorticoids

Chronic gout

- Colchicine
- Uricosuric
  - Probenecid
  - Sulfinpyrazone
  - Lesinurad
- Xanthine oxidase inhibitors
  - Allopurinol
  - Febuxostat

Colchicine

one of the oldest available therapies for acute gout

alkaloid isolated from the autumn crocus, Colchicum autumnale

narrow therapeutic window

high rate of side effects (at higher doses)

MA:

- prevents migration of neutrophils to the joints by
  - binding to tubulin, resulting in the depolymerization of the microtubules and reduced cell motility
  - colchicine-treated neutrophils exhibit erratic locomotion = likened to a ‘drunken walk’
- prevent the production, by neutrophils that have phagocytosed urate crystals, of a putative inflammatory glycoprotein
- Higher doses - inhibits mitosis = risk of serious bone marrow depression

Colchicine

Pharmacokinetics

- absorbed readily after oral administration
- peak plasma levels within 2 hours,
- serum half-life of 9 hours
- excreted in the intestinal tract and urine

Use:

- Prevention of acute gout (low doses)
- Treatment of acute gouty flares

AE:

- Diarrhea, nausea, vomiting, and abdominal pain.
- Hepatic necrosis, acute renal failure, disseminated intravascular coagulation, and seizures
- Rare - hair loss, bone marrow depression, peripheral neuritis, myopathy, death (IV)

Caution in patients with renal or hepatic disease, older patients

Uricosurics

Decrease urates in patients with frequent gouty attack and tophaceous gout

Given to patients with

- decreased uric acid excretion
- Contraindication to allopurinol or febuxostat
- Presence of tophi

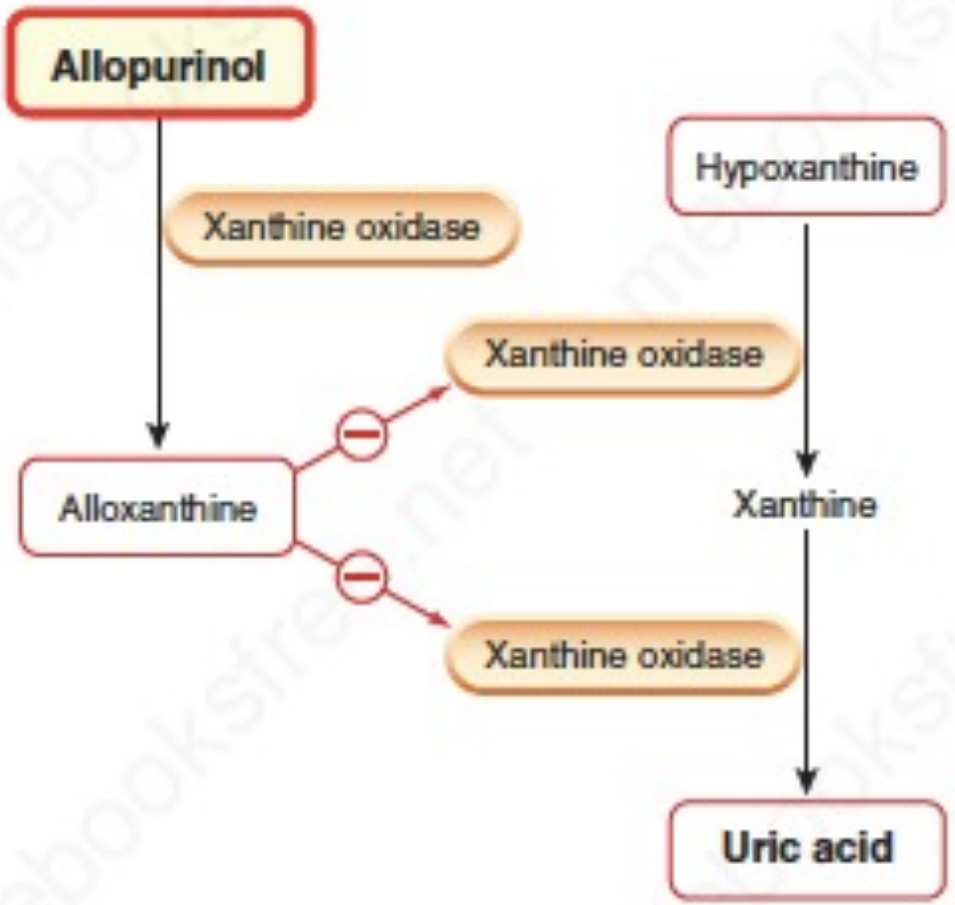
MA: inhibit active transport sites for reabsorption and secretion of uric acid in the proximal tubules (inhibited by salicylates)

- Decreases the total amount of uric acid in the body but plasma concentration may not be greatly reduced

Uricosurics

- Probenecid
  - Complete oral absorption
  - Peak plasma concentration – 2-4h
  - 85-95% plasma protein binding
  - 5-15% of free drug and metabolites excreted in urine
  - Use: Treatment of gout; requires increased fluid intake to prevent renal stones
    - Combined with colchicine or NSAIDs early in the course of therapy to avoid precipitating an attack of gout = occurs in <20% of gouty patients treated with probenecid alone
  - AE: mild GI irritation (2%) sulfinpyrazone > probenecid
    - Avoided in patients with nephrolithiasis or overproduction of uric acid

Xanthine oxidase inhibitors



Rang and Dale Pharmacology

allopurinol

febuxostat

MA: reduces the synthesis of uric acid by competitive inhibition of xanthine oxidase

- Reverses the deposition of urate crystals in tissues
- Inhibits formation of urate stones in the kidneys

80% oral absorption

Allopurinol metabolized to alloxanthine – also inhibit xanthine oxidase, longer duration of action

febuxostat – metabolized and excreted in urine

Xanthine oxidase inhibitors

Use

- Allopurinol - first-line agent for the treatment of chronic gout in the period between attacks, therapy for years or for life
  - Should not be given during an attack
  - When initiating allopurinol, colchicine or NSAID should be used until steady-state serum uric acid is normalized or decreased to less than 6 mg/dL and continued for 6 months or longer. Then colchicine or the NSAID can be cautiously stopped while continuing allopurinol therapy
- Febuxostat – more effective in lowering urates

AE:

- Allopurinol and febuxostat- precipitate gout (given with colchicine or NSAID), GI intolerance (nausea, vomiting, diarrhea),
- Allopurinol
  - rare: peripheral neuritis and necrotizing vasculitis, bone marrow suppression, aplastic anemia
  - Hepatic toxicity, interstitial nephritis; allergic skin reaction (pruritic maculopapular lesions)
- Febuxostat – well tolerated, given to patients intolerant to allopurinol
  - Liver function abnormalities, nausea, diarrhea, headache

References

- Katzung Basic and Clinical Pharmacology, 14th ed
- Rang and Dale's Pharmacology, 9th ed
- Good and Gilman's Manual of Pharmacology and Therapeutics, 2nd ed