Hashemite University
H · U · M
Medical School Committee

Scientific Team
الفريق العلمي

PHARMACOLOGY

Lecture : 3 & 4

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Treatment of RA & OA

In this lecture we will go deeply through drugs used for treatment of RA & OA and their details.

-First of all, let's talk about inflammation, which is the main cause of RA.

*Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents. Inflammation is the body's effort to inactivate or destroy invading organisms, remove irritants, and set the stage for tissue repair, so it plays an important role in homeostasis. When healing is complete, the inflammatory process usually subsides.

However, inappropriate activation of the immune system can result in inflammation and immune-mediated diseases such as rheumatoid arthritis (RA).

**Normally, the immune system can differentiate between self and non-self. In RA, white blood cells (WBCs) view the synovium as non-self and initiate an inflammatory attack. WBC activation leads to stimulation of T lymphocytes, which recruit and activate monocytes and macrophages.

These cells secrete pro-inflammatory cytokines, including tumor necrosis factor (TNF)-a, interleukin (IL)-1, IL-6, IL-8, Transforming growth factor beta (TGF-ß), Fibroblast growth factor (FGF) and Platelet-derived growth factor (PDGF) into the synovial cavity, ultimately **leading to joint destruction and other systemic abnormalities characteristic of RA. In addition to T lymphocyte activation, B lymphocytes are also involved and produce rheumatoid factor and other autoantibodies to maintain inflammation.

- The release of cytokines then causes:

1) Increased cellular infiltration into the endothelium due to release of histamines, kinins, and vasodilatory prostaglandins;
2) Increased production of C-reactive protein by hepatocytes (a marker for inflammation); which can be tested in patients with chronic inflammatory disorders to monitor the progression of their disease.
3) Increased production and release of proteolytic enzymes by chondrocytes (cells that maintain cartilage), leading to degradation of cartilage and joint space narrowing;
4) Increased osteoclast activity (osteoclasts regulate bone breakdown), resulting in focal bone erosions and bone demineralization around joints; and
5) Systemic manifestations in certain organs such as the heart.

-These defensive reactions cause progressive tissue injury, resulting in joint damage and erosions, functional disability, pain, extra-articular manifestations (which indicates that RA is not a localized disease, but it is a systemic disorder) and reduced quality of life.

**It is very important to note that OA greatly differs from RA. OA isn't an inflammatory disease, it is a localized degenerative disorder, and thus you won't see a patient with OA coming with systemic manifestations.

-So, we have a wide variety of drugs used for treatment of RA, some of which are non-specific, such NSAIDs that can be used for other disorders. And others are highly specific for RA. We will discuss both.

Note: Pharmacotherapy for RA includes anti-inflammatory and/or immunosuppressive agents that modulate/reduce the inflammatory process, with the goals of reducing inflammation and pain, and halting or slowing disease progression.

❖ Prostaglandins:

Prostaglandins are unsaturated fatty acid derivatives containing 20 carbons that include a cyclic ring structure.

**Prostaglandins and related compounds are produced in minute quantities by virtually all tissues. They generally act locally on the tissues in which they are synthesized and are rapidly metabolized to inactive products at their sites of action. Therefore, prostaglandins do not circulate in the blood in significant concentrations.

Note: Thromboxanes and leukotrienes are related compounds that are synthesized from the same precursors as the prostaglandins.

Synthesis of PG:

Arachidonic acid is the primary precursor of the prostaglandins and related compounds, and it is present as a component of the phospholipids of cell membranes. Free arachidonic acid is released from tissue phospholipids by the action of phospholipase A2 via a process controlled by hormones and other stimuli.

-There are two major pathways in the synthesis of eicosanoids from arachidonic acid, the cyclooxygenase (for synthesis of PGs and thromboxanes) and the lipoxygenase pathways (for synthesis of Leukotrienes).

- **Cyclooxygenase pathway:** Two related isoforms of the cyclooxygenase enzymes exist. Cyclooxygenase 1 (COX-1) is responsible for the physiologic production of prostanoids, whereas cyclooxygenase-2 (COX-2) causes the elevated production of prostanoids that occurs in sites of chronic disease and inflammation.

- COX-1 is a constitutive enzyme that regulates normal cellular processes, such as **gastric cytoprotection**, **vascular homeostasis**, **platelet aggregation**, and **reproductive and kidney functions.**

- COX-2 is constitutively expressed in tissues such as the brain, kidney, and bone. **Its expression at other sites is increased during states of chronic inflammation.**

**Differences in binding site shape have permitted the development of selective COX-2 inhibitors (COX-2 has a larger binding site for inhibitors). Additionally, expression of COX-2 is induced by inflammatory mediators like TNF-a and IL-1 but can also be pharmacologically inhibited by glucocorticoids, which may contribute to the significant anti-inflammatory effects of these drugs.

➢ **Lipoxygenase pathway:** Antileukotriene drugs, such as *zileuton, zafirlukast,* and *montelukast,* are treatment options for asthma.

Actions of prostaglandins

Actions of prostaglandins are mediated by their binding to a variety of distinct G-coupled protein receptors in cell membranes. Prostaglandins and their metabolites act as local signals that fine-tune the response of a specific cell type.

-The release of thromboxane A2 (TXA2) from platelets during tissue injury triggers the recruitment of new platelets for aggregation and local vasoconstriction. However, prostacyclin (PGI2), produced by endothelial cells, has opposite effects, inhibiting platelet aggregation and producing vasodilation. The net effect on platelets and blood vessels depends on the balance of these two prostanoids.

*PGI2, PGE2 and PGD2 decrease vasodilation, cAMP, platelet aggregation, leukocytic aggregation, T-cell proliferation, IL-1 and IL-2 and lymphocytic migration.

*PG2Fa increases vasoconstriction, bronchoconstriction and smooth muscle contraction.

*TXA2 increases platelet aggregation, vasoconstriction, lymphocytic proliferation and bronchoconstriction.

-All these mediators act in balance in order to maintain homeostasis.

✓ Prostaglandins have a major role in **modulating pain**, **inflammation**, and **fever.** They also control many physiological functions, such as **acid secretion** and **mucus production in the gastrointestinal (GI) tract**, **uterine contractions**, and **renal blood flow**.

Some Therapeutic Uses of Prostaglandins

- Alprostadil:

Alprostadil is a PGE1 analog that is naturally produced in tissues such as seminal vesicles and cavernous tissues, in the placenta, and in the ductus arteriosus of the fetus. PGE1 maintains the patency of the ductus arteriosus during pregnancy. In neonates with congenital heart conditions, infusion of *alprostadil* keeps the ductus open, allowing time until surgical correction is possible. *Alprostadil* is also used for erectile dysfunction. (CVS action)

- Lubiprostone:

Lubiprostone is a PGE1 derivative indicated for the treatment of chronic idiopathic constipation, opioid-induced constipation, and irritable bowel syndrome with constipation. (GI action)

- Misoprostol:

Misoprostol, a PGE1 analog, is used *to* protect the mucosal lining of the stomach during chronic NSAID treatment. *Misoprostol* interacts with prostaglandin receptors on parietal cells within the stomach, reducing gastric acid secretion. *Misoprostol* is also used off-label in obstetric settings for labor induction, since it increases uterine contractions by interacting with prostaglandin receptors in the uterus. *Misoprostol* has the potential to induce abortion. (GI action)

- Prostaglandin F2a analogs:

Bimatoprost, latanoprost, tafluprost and *travoprost* are PGF2a analogs that are indicated for the treatment of open-angle glaucoma. (Ophthalmology)

- Prostacyclin (PGI2) analogs:

Epoprostenol the pharmaceutical form of naturally occurring prostacyclin, and the synthetic analogs of prostacyclin *(iloprost* and *treprostinil*) are potent pulmonary vasodilators that are used for the treatment of pulmonary arterial hypertension.

**Note: There is a combination product containing the NSAID diclofenac and misoprostol. As we said above, NSAIDs are associated with multiple harmful gastric effects, misoprostol (PGE1) would reverse those effects. (The drug's name is "arthrotec")

Non-Steroidal Anti-Inflammatory Drugs

-There is a wide variety of NSAIDs that are widely used clinically, including aspirin, Indomethacin, Ibuprofen, Naproxen, Ibuprofen, Piroxicam, diclofenac and the selective COX-2 inhibitor *celecoxib.*

**They act primarily by inhibiting the cyclooxygenase enzymes that catalyze the first step in prostanoid biosynthesis. This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects.

-Note: Differences in safety and efficacy of the NSAIDs may be explained by relative selectivity for the COX-1 or COX-2 enzyme. **Inhibition of COX-2 is thought to lead to the anti-inflammatory and analgesic actions of NSAIDs, whereas inhibition of COX-1 is responsible for prevention of cardiovascular events and most adverse events.**

➢ Aspirin/NSAIDs:

Aspirin is a weak organic acid that irreversibly acetylates and, thus, inactivates cyclooxygenase. The other NSAIDs are reversible inhibitors of cyclooxygenase. Aspirin is considered as the traditional NSAID that is used in RA.

-Main actions: *All these actions depend on the dosage of aspirin, since the action of aspirin is concentration (dose) dependent.

- ✓ Anti-inflammatory: Inhibition of cyclooxygenase diminishes the formation of prostaglandins and, thus, modulates aspects of inflammation mediated by prostaglandins. NSAIDs inhibit inflammation in arthritis, **but they neither arrest the progression of the disease nor induce remission (they only inhibit inflammatory reactions)**

- ✓ Antipyretic: Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated. This can be caused by PGE2 synthesis, which is stimulated when endogenous fever-producing agents (pyrogens), such as cytokines, are released from WBCs that are activated by infection, hypersensitivity, malignancy, or inflammation.

*NSAIDs lower body temperature in patients with fever by impeding PGE2 synthesis and release, resetting the "thermostat" back toward normal. This rapidly lowers the body temperature of febrile patients by increasing heat dissipation through peripheral vasodilation and sweating. **NSAIDs have no effect on normal body temperature.**

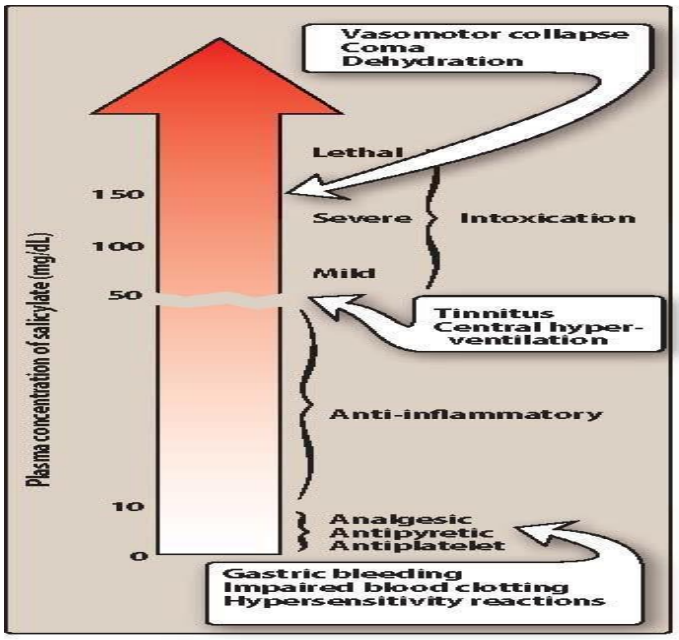
- ✓ Analgesic: PGE2 is thought to sensitize nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process. Thus, by decreasing PGE2 synthesis, the sensation of pain can be decreased.

*No single NSAID has demonstrated superior efficacy over another, and they are generally considered to have equivalent analgesic efficacy. They differ in their pharmacokinetics only.

*The NSAIDs are used mainly for the management of mild to moderate pain arising from musculoskeletal disorders. One exception is ***ketorolac***, which can be used for more severe pain, but for only a short duration.

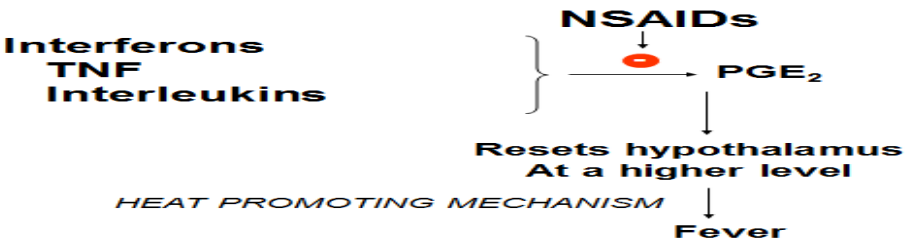
-Therapeutic uses:

a. Anti-inflammatory and analgesic uses: NSAIDs are used in the treatment of osteoarthritis, gout, RA, and common conditions requiring analgesia (for example, headache, arthralgia, myalgia, and dysmenorrhea). Combinations of opioids and NSAIDs may be effective in treating pain caused by malignancy. The salicylates exhibit analgesic activity at lower doses. Only at higher doses do these drugs show anti-inflammatory activity. For example, two 325-mg *aspirin* tablets administered four times daily produce analgesia, whereas 12 to 20 tablets per day produce both analgesic and anti-inflammatory activity.



*This picture indicates that aspirin's action is dose dependent. However, to a certain limit. For example, one the patient develops tinnitus, we know that we've reached the maximum level of the drug, and any increase would cause toxicity.

b. Antipyretic uses: *Aspirin, ibuprofen,* and *naproxen* may be used to treat fever. **Note: ***Aspirin* **should be avoided in patients less than 19 years old with viral infections**, such as varicella (chickenpox) or influenza, to prevent Reye syndrome, a syndrome that can cause fulminating hepatitis with cerebral edema, often leading to death.



COX-2 constitutive in brain responsible for thermoregulation

c. Cardiovascular applications: *Aspirin* irreversibly inhibits COX-1-mediated production of TXA2, thereby reducing TXA2- mediated vasoconstriction and platelet aggregation and the subsequent risk of cardiovascular events. Low doses of *aspirin* (75 to 162 mg-commonly 81 mg) are used prophylactically to reduce the risk of recurrent cardiovascular events, transient ischemic attacks (TIAs), stroke, and death in patients with a history of previous MI, TIA, or stroke. (This point is only for reading, since we've covered this in HLS)

d. External applications: *Salicylic acid* is used topically to treat acne, corns, calluses, and warts. *Diclofenac* is available in topical formulations (gel or solution) for treatment of osteoarthritis in the knees or hands. *Methyl salicylate* ("oil of wintergreen") is used externally as a cutaneous counterirritant in liniments, such as arthritis creams and sports rubs. (as aspirin is a strong exfoliative agent)

Pharmacokinetics

a. **Aspirin:** After oral administration, *aspirin* is rapidly deacetylated by esterases in the body to produce salicylate.

Absorption: Unionized salicylates are passively absorbed mainly from the upper small intestine. Salicylates cross both the bloodbrain barrier and the placenta and are absorbed through intact skin.

Metabolism & elimination: Salicylate is converted by the liver to water-soluble conjugates that are rapidly cleared by the kidney, resulting in first-order elimination and a serum half-life of 3.5 hours. At anti-inflammatory dosages of *aspirin* (more than 4 g/day), the hepatic metabolic pathway becomes saturated, and zero-order kinetics are observed, leading to a half-life of 15 hours or more.

b. **Other NSAIDs**: Most NSAIDs are well absorbed after oral administration and circulate highly bound to plasma proteins. The majority are metabolized by the liver, mostly to inactivate metabolites. Excretion of active drug and metabolites is primarily via the urine.

Adverse effects

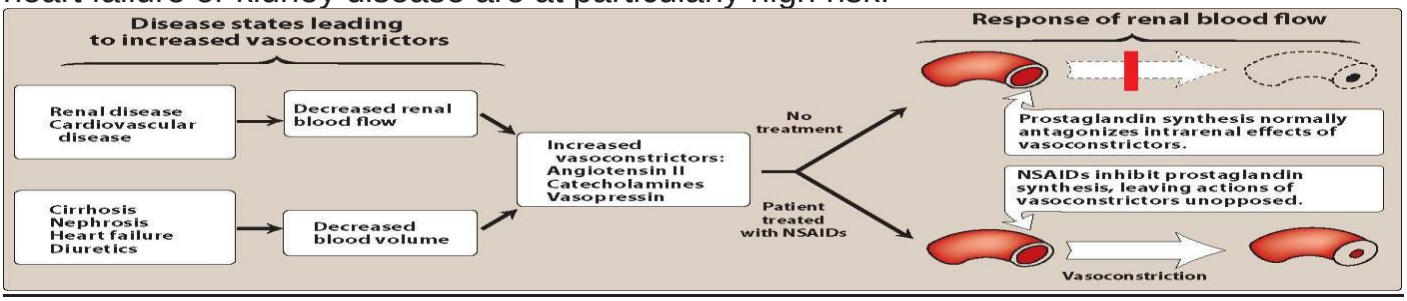
-Gastrointestinal: These are the most common adverse effects of NSAIDs, ranging from dyspepsia to bleeding.

**Normally, production of prostacyclin (PGI 2) inhibits gastric acid secretion, and PGE2 and PGF211 stimulate synthesis of protective mucus in both the stomach and small intestine. Agents that inhibit COX-1 reduce beneficial levels of these prostaglandins, resulting in increased gastric acid secretion, diminished mucus protection, and increased risk for GI bleeding and ulceration.

**Note: Agents with a higher relative selectivity for COX-1 may have a higher risk for GI events compared to those with a lower relative selectivity for COX-1 (that is, higher COX-2 selectivity).

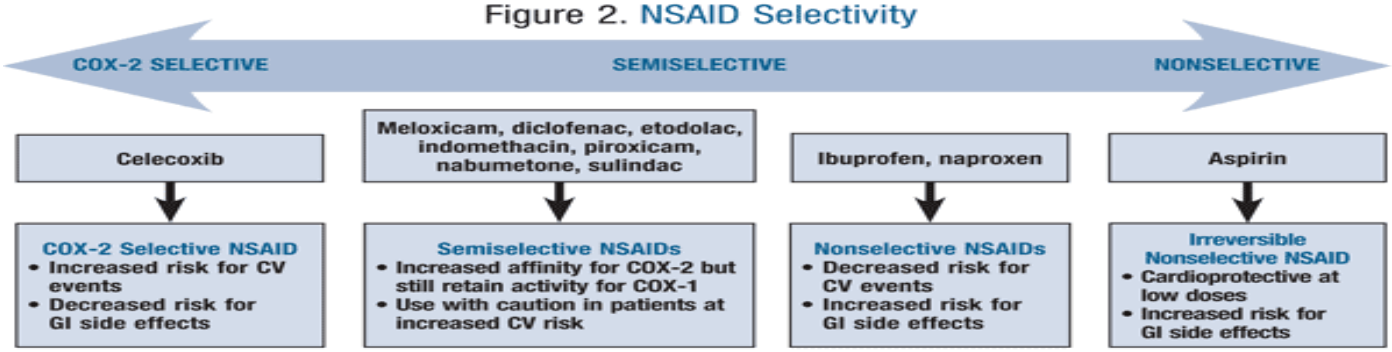
-Increased risk of bleeding (anti platelet effect): As described above, aspirin inhibits COX-1-mediated formation of TXA2 and reduces platelet aggregation for the lifetime of the platelet (3 to 7 days). Platelet aggregation is the first step in thrombus formation, and the antiplatelet effect of aspirin results in a prolonged bleeding time. For this reason, aspirin is often withheld for at least 1 week prior to surgery.

-Renal effects: NSAIDs prevent the synthesis of PGE2 and PGI2, prostaglandins that are responsible for maintaining renal blood flow. Decreased synthesis of prostaglandins can result in retention of sodium and water and may cause edema. Patients with a history of heart failure or kidney disease are at particularly high risk.



-Cardiac effects: Agents such as ***aspirin,*** with a very high degree of COX-1 selectivity at low doses, have a **cardiovascular protective** effect thought to be due to a reduction in the production of TXA2. **Agents with higher relative COX-2** selectivity have been associated with an **increased risk for cardiovascular events**, possibly by decreasing PGI2 production mediated by COX-2. All NSAIDs (EXCEPT aspirin) carry a boxed warning regarding the increased risk for cardiovascular events.

Figure 2. NSAID Selectivity



-As we see above, aspirin is non selective, which means it inhibits both COX-1 and COX-2 however, it has the least COX-2 selectivity, which makes it very useful as cardioprotective. In the other hand, all other NSAIDs have a higher degree of action against COX-2, thus they have harmful effects on the heart. (Naproxen has the least adverse actions on the heart from all those NSAIDs (not including aspirin), therefore it may be used as a substitute for aspirin if the patient developed adverse effects of aspirin.

-Therefore, any patient who is on aspirin treatment and develops GI disorders, it is recommended to co-administer it with proton pump inhibitors or misoprostol. Or we can simply switch into COX-2 selective inhibitors (more preferred choice).

-Other adverse effects: NSAIDs should be used with caution in patients with asthma. As inhibition of prostaglandin synthesis can cause a shift toward leukotriene production and increase the risk of asthma exacerbations. Central nervous system (CNS) adverse events headache, tinnitus, and dizziness, may occur. Approximately 15% of patients taking *aspirin* experience hypersensitivity reactions.

Drug interactions

Salicylate is roughly 80% to 90% plasma protein bound (albumin) and can be displaced from protein binding sites, resulting in increased concentration of free salicylate. Alternatively, *aspirin* can displace other highly protein-bound drugs, such as warfarin, phenytoin, or valproic acid, bilirubin, resulting in higher free concentrations of these agents. **Note: we've discussed in the previous lecture that aspirin causes displacement of probenecid, thus inhibiting their action, increasing serum uric acid concentration and exacerbating gouty attacks.

Toxicity

-Mild salicylate toxicity is called salicylism and is characterized by nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears).

-When large doses of salicylate are administered, severe salicylate intoxication may result Restlessness, delirium, hallucinations, convulsions, coma, respiratory and metabolic acidosis, and death from respiratory failure may occur. Children are particularly prone to salicylate intoxication; **ingestion of as little as 10 g of *aspirin* can be fatal**.

Pregnancy

NSAIDs should be used in pregnancy only if benefits outweigh risks to the developing fetus (in first 2 trimesters). ***Acetaminophen* is preferred if analgesic or antipyretic effects are needed during pregnancy**. In the **third** trimester, NSAIDs should generally be avoided due to the risk of premature closure of the ductus arteriosus.

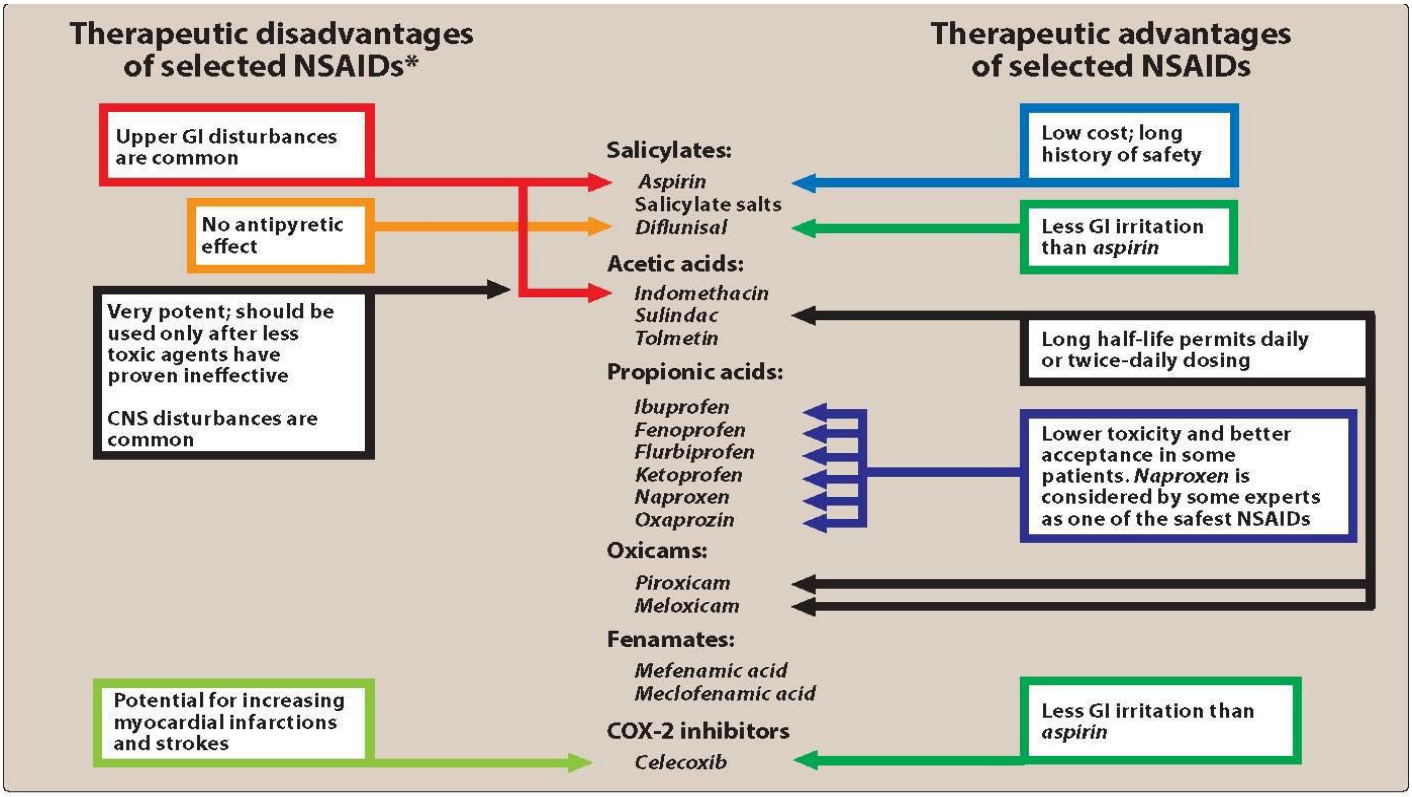
➢ Celecoxib:

-*Celecoxib*, a selective COX-2 inhibitor, is significantly more selective for inhibition of COX-2 than COX-1. Unlike the inhibition of COX-1 by *aspirin* (which is irreversible), the inhibition of COX-2 is reversible.

Therapeutic uses: *Celecoxib* is approved for the treatment of RA, osteoarthritis, and acute pain. *Celecoxib* has similar efficacy to NSAIDs in the treatment of pain.

Pharmacokinetics: *Celecoxib* is readily absorbed after oral administration. It is extensively metabolized in the liver by cytochrome P450 (CYP2C9), and the metabolites are excreted in feces and urine. The half-life is about 11 hours, and the drug may be dosed once or twice daily.

Adverse effects: Headache, dyspepsia, diarrhea, and abdominal pain are the most common adverse effects (these adverse effects are not due to inhibition of COX-2). *Celecoxib* is associated with less GI bleeding and dyspepsia than other NSAIDs. However, this benefit is lost when *aspirin* is added to *celecoxib* therapy.
*Patients who are at high risk of ulcers and require *aspirin* for cardiovascular prevention should avoid the use of *celecoxib.*



Traditional Disease-Modifying Antirheumatic Drugs (DMARDs)

-Traditional DMARDs *(methotrexate, hydroxychloroquine, leflunomide,* or *sulfasalazine)* are used in the treatment of RA and have been shown to slow the course of the disease, induce remission, and prevent further destruction of the joints and involved tissues. Following diagnosis of RA, these agents should be started as soon as possible to delay progression of the disease.

-Monotherapy may be initiated with any of the traditional DMARDs, although *methotrexate* is generally preferred. For patients with inadequate response to monotherapy, a combination of traditional DMARDs, or use of a TNF inhibitor or non-TNF biologic agent may be needed.

❖ Methotrexate:

-Methotrexate is a **folic acid antagonist** that inhibits cytokine production and purine nucleotide biosynthesis, leading to immunosuppressive and anti-inflammatory effects. It has become a mainstay of treatment in patients with RA.

-Response to methotrexate usually occurs within 3 to 6 weeks of starting treatment. Other traditional DMARDs, TNF inhibitors, or non-TNF biologic agents can be added to *methotrexate* if there is inadequate response to monotherapy with this agent.

**Doses of *methotrexate* required for RA treatment are much lower than those needed in cancer chemotherapy and are generally administered once weekly, thereby minimizing adverse effects.

-Common adverse effects of *methotrexate* when used for RA are mucosal ulceration and nausea. Cytopenias (particularly leukopenia), cirrhosis of the liver, and an acute pneumonia-like syndrome may occur with **chronic administration.**

****Supplementation with *folic acid* may improve tolerability of *methotrexate* and reduce GI and hepatic adverse effects.

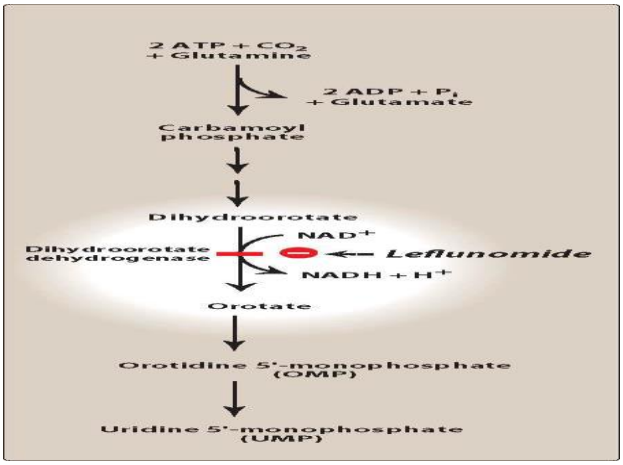
❖ Hydroxychloroquine:

-Hydroxychloroquine is used for early, mild RA, and may be combined with *methotrexate.* Its mechanism of action in autoimmune disorders is unknown, and onset of effects takes 6 weeks to 6 months.

-Hydroxychloroquine has less adverse effects on the liver and immune system than other DMARDs. However, it may cause ocular toxicity, including irreversible retinal damage and corneal deposits, CNS disturbances, GI upset, and skin discoloration and eruptions.

❖ Leflunomide: *unique action*

Leflunomide is an **immunomodulatory agent** that preferentially causes cell arrest of the autoimmune lymphocytes through its action on dihydroorotate dehydrogenase (DHODH). After biotransformation, ***leflunomide* becomes a reversible inhibitor of DHODH, an enzyme necessary for pyrimidine synthesis. (inhibiting DNA and RNA synthesis)**



**This action affects rapidly growing cells, causing cell cycle arrest in these cells, mainly lymphocyte.

-Leflunomide may be used as monotherapy in patients who have intolerance or contraindications to use of methotrexate in RA, or it may be used in combination with methotrexate for patients with suboptimal response to methotrexate alone.

**The drug is not recommended in patients with liver disease as it can be hepatotoxic.

❖ Sulfasalazine:

Sulfasalazine has recommendations for use similar to *leflunomide* in the treatment of RA. Its mechanism of action in treating RA is unclear. The onset of activity is 1 to 3 months, and it is associated with GI adverse effects (nausea, vomiting, anorexia) and leukopenia.

Biologic Disease-Modifying Antirheumatic Drugs (B-DMARDs)

-IL-1 and TNF-a are proinflammatory cytokines involved in the pathogenesis of RA. When secreted by synovial macrophages, IL-1 and TNF-a stimulate synovial cells to proliferate and synthesize collagenase, thereby degrading cartilage, stimulating bone resorption, and inhibiting proteoglycan synthesis.

-The TNF-a inhibitors *(adalimumab, certo/izumab, etanercept, golimumab,* and *infliximab)* are biologic DMARDs which have been shown to decrease signs and symptoms of RA, reduce progression of structural damage, and improve physical function.

-TNF-a inhibitors are usually employed in RA after a patient has an inadequate response to traditional DMARDs.

-If a patient has **failed** monotherapy with one TNF-a inhibitor, a traditional DMARD may be added, or therapy with a non-TNF biologic agent or a different TNF-a inhibitor may be tried.

**Like TNF-a inhibitors, non-TNF biologics are generally used in RA after a patient has an inadequate response to traditional DMARDs, and they may be used alone or in combination with traditional DMARDs. If a patient has failed monotherapy with one non-TNF biologic, a trial of another non-TNF biologic with or without *methotrexate* is warranted.

-Biologic DMARDs should be used **cautiously** in those:

- With heart failure, as they can cause and/or worsen preexisting heart failure.
- An increased risk of lymphoma and other cancers has been observed with the use of TNF-a inhibitors.
- Increased risk for infections, such as tuberculosis, fungal opportunistic infections, and sepsis.
- Reactivation of hepatitis B may occur with the use of these agents.
- Live vaccinations should not be administered to patients taking any of the biologic DMARDs
- Pancytopenia.

Imp: Note: TNF-a inhibitors and non-TNF biologic agents **should not be used together due to the risk of severe infections.

❖ Adalimumab:

-Adalimumab is a recombinant monoclonal antibody that binds to TNF-a and interferes with its activity by blocking interaction of TNF-a with cell surface receptors.

-This agent is indicated for treatment of moderate to severe RA, either as monotherapy or in combination with *methotrexate*.

-It is also indicated for psoriatic arthritis, ankylosing spondylitis, and Crohn disease.

-*Adalimumab* is administered **subcutaneously** weekly or every other week. It may cause headache, nausea, agranulocytosis, rash, reaction at the injection site, and increased risk of infections.

❖ Certolizumab:

-*Certolizumab* is a humanized antibody that neutralizes biological actions of TN F-a potently.

-Similar uses, administration and adverse effects to other TNF-α inhibitors.

❖ Etanercept:

-*Etanercept* is a genetically engineered fusion protein that binds to TNF-a, thereby blocking its interaction with cell surface TNF-a receptors. This agent is approved for use in patients with moderate to severe RA, either alone or in combination with *methotrexate.*

-The combination of *etanercept* and *methotrexate* is more effective than *methotrexate* or *etanercept* alone in hindering the RA disease process, improving function, and achieving remission.

-It is also approved for use in ankylosing spondylitis and psoriasis.

-*Etanercept* is given subcutaneously twice a week. The drug is generally well tolerated. (Same adverse effects)

❖ Golimumab:

-*Golimumab* neutralizes the biological activity of TNF-a by binding to it and blocking its interaction with cell surface receptors.

-This compound is administered subcutaneously once a month in combination with *methotrexate* or other non-biologic DMARDs.

-*Golimumab* may increase hepatic enzymes. **Reactivation of hepatitis B may occur in chronic carriers.**

❖ Infliximab:

-*Infliximab* is a **chimeric** monoclonal antibody composed of human and murine regions. The antibody binds specifically to human TNF-α and inhibits binding with its receptors.

-*Infliximab* is approved for use in combination with *methotrexate* in patients with RA who have had inadequate response to *methotrexate* monotherapy.

Note: This agent is **not** indicated for monotherapy, as this leads to the development of *anti-infliximab* antibodies and reduced efficacy. *Infliximab* should be administered with *methotrexate.*

-Additional indications include plaque psoriasis, psoriatic arthritis, ulcerative colitis, ankylosing spondylitis, and Crohn disease.
**Similar adverse effects of previous drugs.

❖ Abatacept:

T lymphocytes need two interactions to become activated:
1) The antigen-presenting cell (macrophages or B cells) must interact with the receptor on the T cell and
2) The CD80/CD86 protein on the antigen- presenting cell must interact with the CD28 protein on the T cell.

-Abatacept is a recombinant fusion protein and costimulation modulator that **competes with CD28 for binding on CD80/ CD86 protein, thereby preventing full T-cell activation and reducing the inflammatory response.**

-This agent is indicated for patients with moderate to severe RA who have had an inadequate response to DMARDs or TNF-α inhibitors.

-Common adverse effects include headache, upper respiratory infections, nasopharyngitis, and nausea. Concurrent use with TNF-α inhibitors is not recommended due to increased risk of serious infections.

❖ Rituximab:

In RA, **B lymphocytes** can perpetuate the inflammatory process in the synovium by
1) Activating T lymphocytes,
2) Producing autoantibodies and rheumatoid factor, and
3) Producing proinflammatory cytokines, such as TNF-a and IL-1.

-*Rituximab* is a chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. **Administration of *rituximab* results in 8-cell depletion**. (This is the first drug that doesn't act on TNF-a)

-This agent is indicated for use in combination with *methotrexate* for patients with moderate to severe RA who have had an inadequate response to TNF-α inhibitors.

*The following drugs the doctor didn't discuss them, but take an idea about them.

❖ Tocilizumab:

-Tocilizumab is a recombinant monoclonal antibody that binds to IL-6 receptors and inhibits activity of the proinflammatory cytokine IL-6.

-*Tocilizumab* is administered as an intravenous infusion every 4 weeks. The drug can be used as monotherapy or in combination with *methotrexate* or other nonbiologic DMARDs for patients with moderate to severe RA.

❖ Tofacitinib:

-Janus kinases are intracellular enzymes that modulate immune cell activity in response to the binding of inflammatory mediators to the cellular membrane. Cytokines, growth factors, interferons, ILs, and erythropoietin can lead to an increase in Janus kinase activity and activation of the immune system.

-*Tofacitinib* is an oral inhibitor of Janus kinases indicated for the treatment of moderate to severe RA in patients who have had an inadequate response.

-Hemoglobin concentrations must be greater than **9 g/dL** to start *tofacitinib* and must be monitored during therapy due to the risk for anemia.

❖ Anakinra: *discussed before*

-IL-1 is induced by inflammatory stimuli and mediates a variety of immunologic responses, including degradation of cartilage and stimulation of bone resorption.

-*Anakinra* treatment leads to a modest reduction in the signs and symptoms of moderate to severe RA in patients who have failed one or more DMARDs. This agent is associated with neutropenia and is **infrequently** used in the treatment of RA.

Study questions

-A patient with RA is being treated with ibuprofen, but joint pain and stiffness are increasing. His physician prescribes another drug to be used with ibuprofen that may slow progression of the disease. Unfortunately, side effects develop, including dizziness, tinnitus, blurred vision, and pruritus. Ocular examination reveals corneal deposits and slight retinal pigmentation. What is the drug?
A. Gold salts
B. Etanercept
C. Hydroxychloroquine
D. Methotrexate
E. Thioridazine

Answer: C. Ocular toxicity is characteristic of chloroquine and hydroxychloroquine. Corneal deposits are reversible, but retinal pigmentation can ultimately lead to blindness. Patients will complain about gastrointestinal distress, visual dysfunction, ringing in the ears (note that tinnitus also occurs in salicylism), and “itchy skin.” Hydroxychloroquine also promotes oxidative stress that can lead to hemolysis in G6PD deficiency. DMARDs include gold salts (e.g., auranofin), methotrexate, and etanercept, but thioridazine is a phenothiazine used as an antipsychotic; it lacks an antiinflammatory effect, but does cause retinal pigmentation.

-Which one of the following antiinflammatory drugs used in rheumatoid arthritis can bind directly tumor necrosis factor?
A. Etanercept
B. Sulfasalazine
C. Prednisone
D. Celecoxib
E. Penicillamine

Answer: A. Etanercept binds directly to tumor necrosis factor (TNF), resulting in the inactivation of this cytokine, which plays a major role in a number of inflammatory disorders, including Crohn disease and rheumatoid arthritis. In the synovium, TNF recruits inflammatory cells and leads to angiogenesis and joint destruction. Infliximab, a monoclonal antibody, also inactivates TNF.

-Which statement below is accurate regarding aspirin overdose?
A. N-acetylcysteine should be given immediately
B. The metabolism rate of aspirin is first-order
C. Elimination rate is directly proportional to plasma concentration.
D. Increasing urinary pH would be beneficial
E. Plasma concentrations decrease exponentially with time.

Answer: D. Back to basic principles. Zero-order elimination means that plasma levels of a drug decrease linearly with time. This occurs with ASA at toxic doses, with phenytoin at high therapeutic doses, and with ethanol at all doses. Enzymes that metabolize ASA are saturated at high plasma levels → constant rate of metabolism = zero-order kinetics. Remember that application of the Henderson-Hasselbalch principle can be important in drug overdose situations. In the case of aspirin, a weak acid, urinary alkalinization favors ionization of the drug →↓ tubular reabsorption → renal elimination. N-acetylcysteine is the antidote for acetaminophen.