
بسم الله الرحمن الرحيم

NSAIDs & DMARDS

(NONSTEROIDAL ANTI-INFLAMMATORY DRUGS, DISEASE-MODIFYING ANTIRHEUMATIC DRUGS, NONOPIOID ANALGESICS, & DRUGS USED IN GOUT

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2016

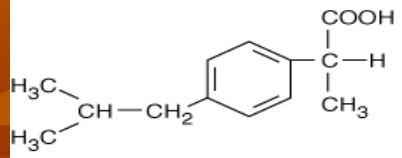
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS(NSAIDs)

- Salicylates and other similar agents used to treat rheumatic disease share the capacity to suppress the signs and symptoms of inflammation.
- These drugs also exert antipyretic and analgesic effects
- Their anti-inflammatory properties that make them most useful in the management of disorders in which pain is related to the intensity of the inflammatory process.
- Since aspirin, the original NSAID, has a number of adverse effects, many other NSAIDs have been developed in attempts to improve upon aspirin's efficacy and decrease its toxicity.

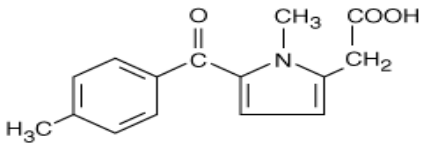
Chemistry & Pharmacokinetics

Propionic acid derivative



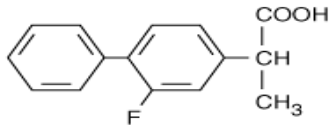
Ibuprofen

Pyrrolealkanoic acid derivative



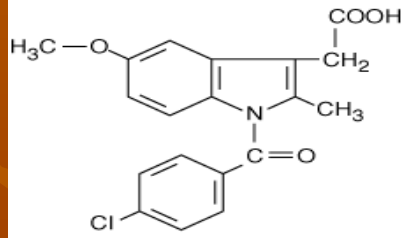
Tolmetin

Phenylalkanoic acid derivative



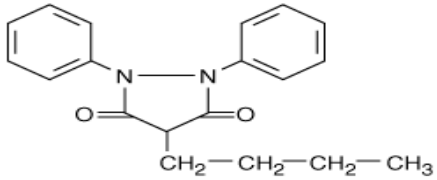
Flurbiprofen

Indole derivative



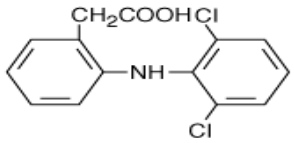
Indomethacin

Pyrazolone derivative



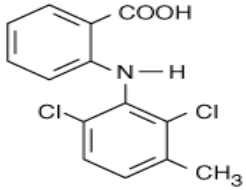
Phenylbutazone

Phenylacetic acid derivative



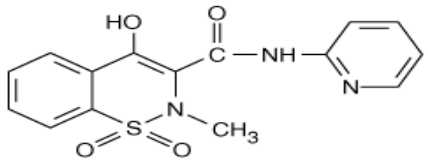
Diclofenac

Fenamate



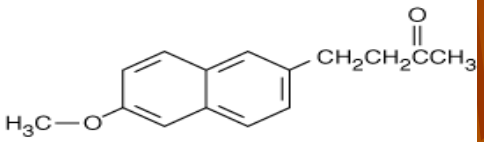
Meclofenamic acid

Oxicam



Piroxicam

Naphthylacetic acid prodrug



Nabumetone

Chemistry & Pharmacokinetics

Drug	Half-Life (hours)	Urinary Excretion of Unchanged Drug	Recommended Anti-inflammatory Dosage
Salicylate[1]	2–19	2–30%	See footnote 2
Celecoxib	11	27%[3]	100–200 mg bid
Diclofenac	1.1	< 1%	50–75 mg qid
Diflunisal	13	3–9%	500 mg bid
Etodolac	6.5	< 1%	200–300 mg qid
Fenoprofen	2.5	30%	600 mg qid
Flurbiprofen	3.8	< 1%	300 mg tid
Ibuprofen	2	< 1%	600 mg qid
Indomethacin	4–5	16%	50–70 mg tid
Ketoprofen	1.8	< 1%	70 mg tid
Ketorolac	4–10	58%	10 mg qid[4]
Meloxicam	20	Data not found	7.5–15 mg qd
Nabumetone[5]	26	1%	1000–2000 mg qd[6]
Naproxen	14	< 1%	375 mg bid
Oxaprozin	58	1–4%	1200–1800 mg qd[6]
Piroxicam	57	4–10%	20 mg qd[6]
Sulindac	8	7%	200 mg bid
Tolmetin	1	7%	400 mg qid

[1]Major anti-inflammatory metabolite of aspirin.

[2]Salicylate is usually given in the form of aspirin.

[3]Total urinary excretion including metabolites.

[4]Recommended for treatment of acute (eg, surgical) pain only.

[5]Nabumetone is a prodrug; the half-life and urinary excretion are for its active metabolite.

Pharmacokinetics

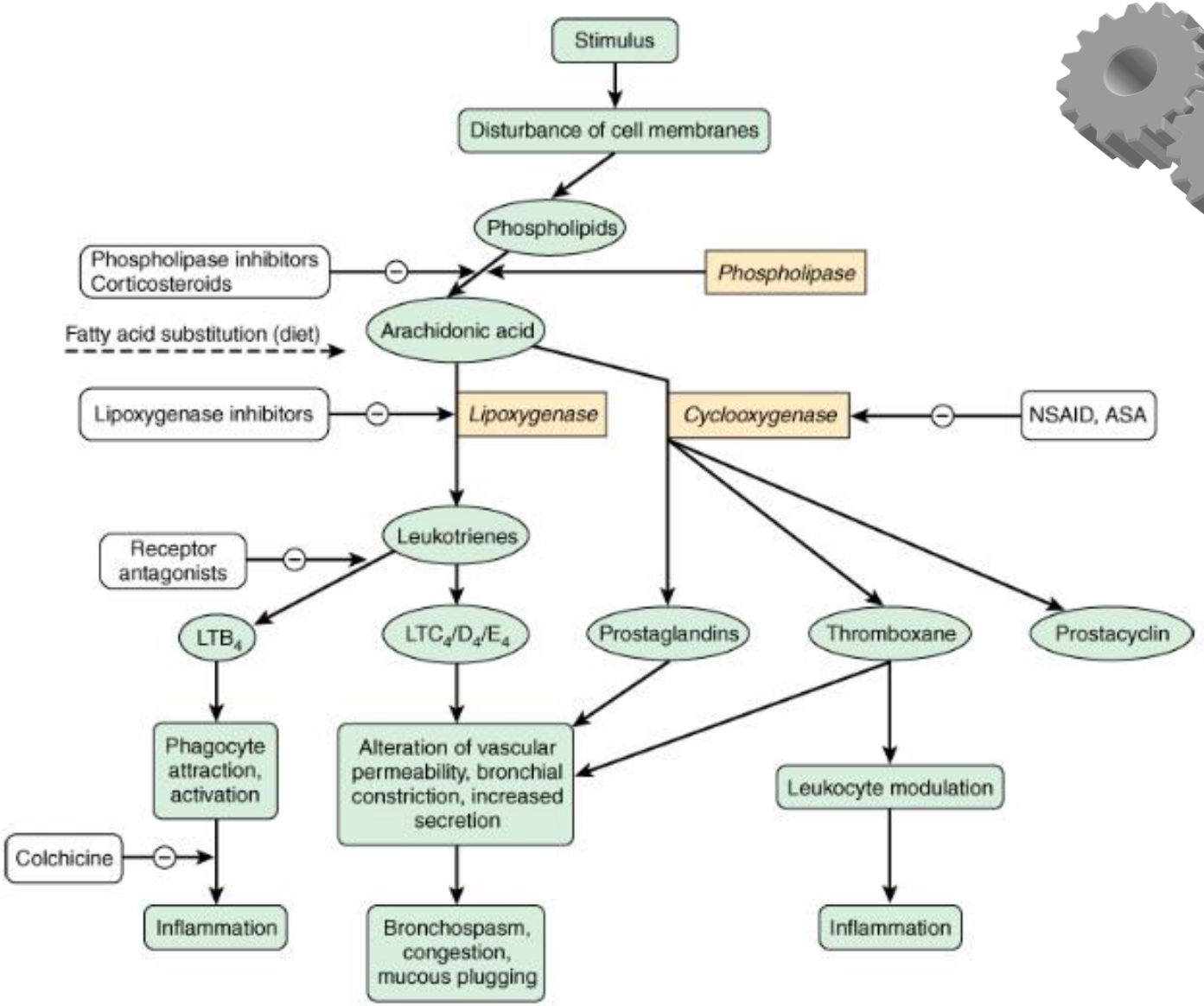
- Most of these drugs are well absorbed, and food does not substantially change their bioavailability.
- Most of the NSAIDs are highly metabolized, some by phase I followed by phase II mechanisms and others by direct glucuronidation (phase II) alone.
- NSAID metabolism proceeds, in large part, by way of the CYP3A or CYP2C families of P450 enzymes in the liver. While renal excretion is the most important route for final elimination,
- Nearly all undergo varying degrees of biliary excretion and reabsorption (enterohepatic circulation). In fact, the degree of lower gastrointestinal tract irritation correlates with the amount of enterohepatic circulation.
- Most of the NSAIDs are highly protein-bound (~98%), usually to albumin.
- Most of the NSAIDs (eg, ibuprofen, ketoprofen) are racemic mixtures, while one, naproxen, is provided as a single enantiomer and a few have no chiral center (eg, diclofenac).

Pharmacodynamics

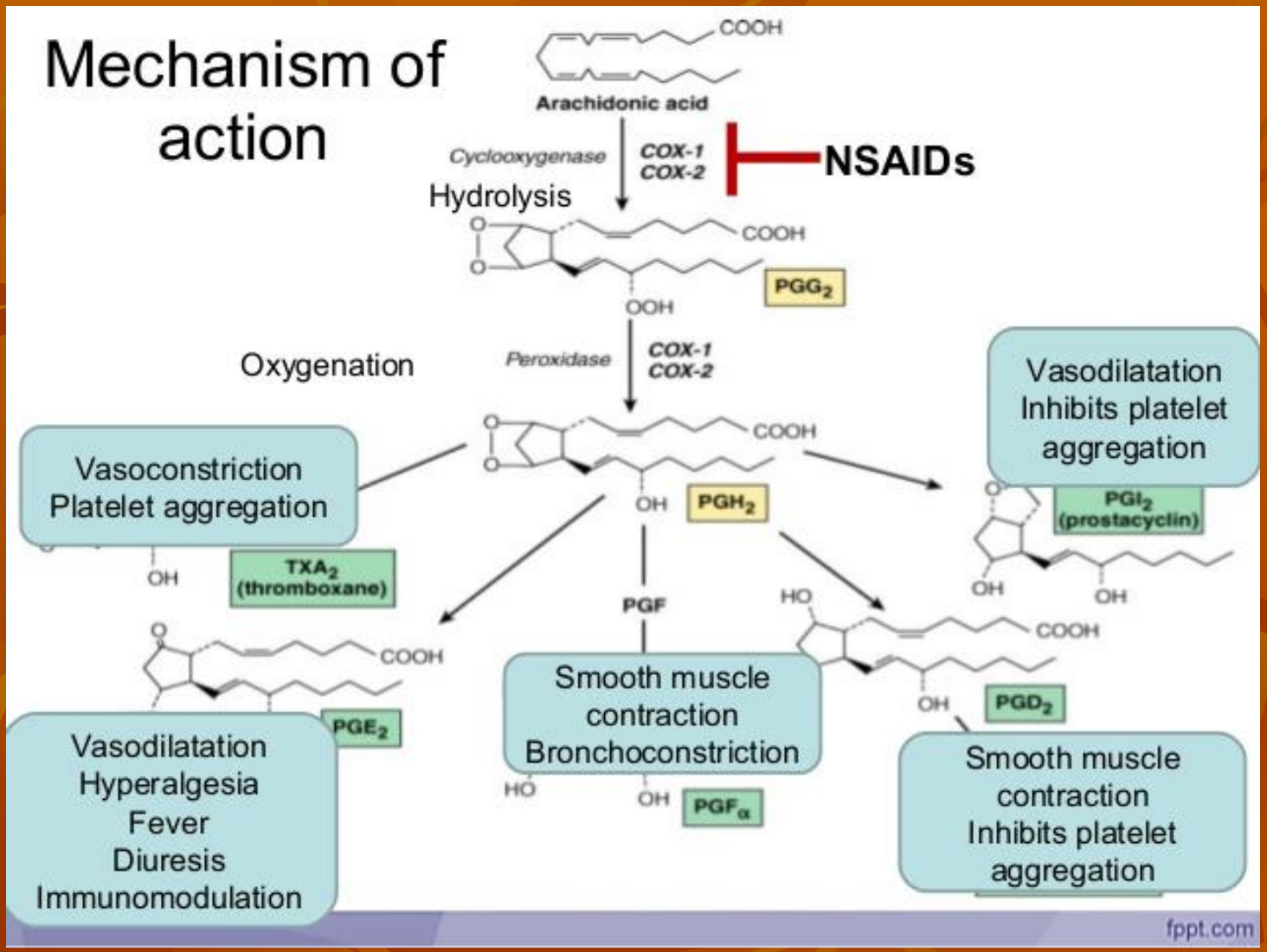
- The anti-inflammatory activity of the NSAIDs is mediated chiefly through inhibition of biosynthesis of prostaglandins

- Various NSAIDs have additional possible mechanisms of action, including inhibition of chemotaxis, down-regulation of interleukin-1 production, decreased production of free radicals and superoxide, and interference with calcium-mediated intracellular events.

- Aspirin irreversibly acetylates and blocks platele cyclooxygenase, while most non-COX-selective NSAIDs are reversible inhibitors



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com


Mechanism of action
COOH
Arachidonic acid
Cyclooxygenase
COX-1
COX-2
NSAIDs
Hydrolysis
COOH
PGG2
OOH
Oxygenation
Peroxidase
COX-1
COX-2
COOH
Vasoconstriction
Platelet aggregation
PGH2
OH
Vasodilatation
Inhibits platelet
aggregation
PGI2
(prostacyclin)
OH
OH
TXA2
(thromboxane)
PGF
HO
COOH
COOH
Smooth muscle
contraction
Bronchoconstriction
PGE2
PGD2
OH
Vasodilatation
Hyperalgesia
Fever
Diuresis
Immunomodulation
HO
OH
PGFα
Smooth muscle
contraction
Inhibits platelet
aggregation
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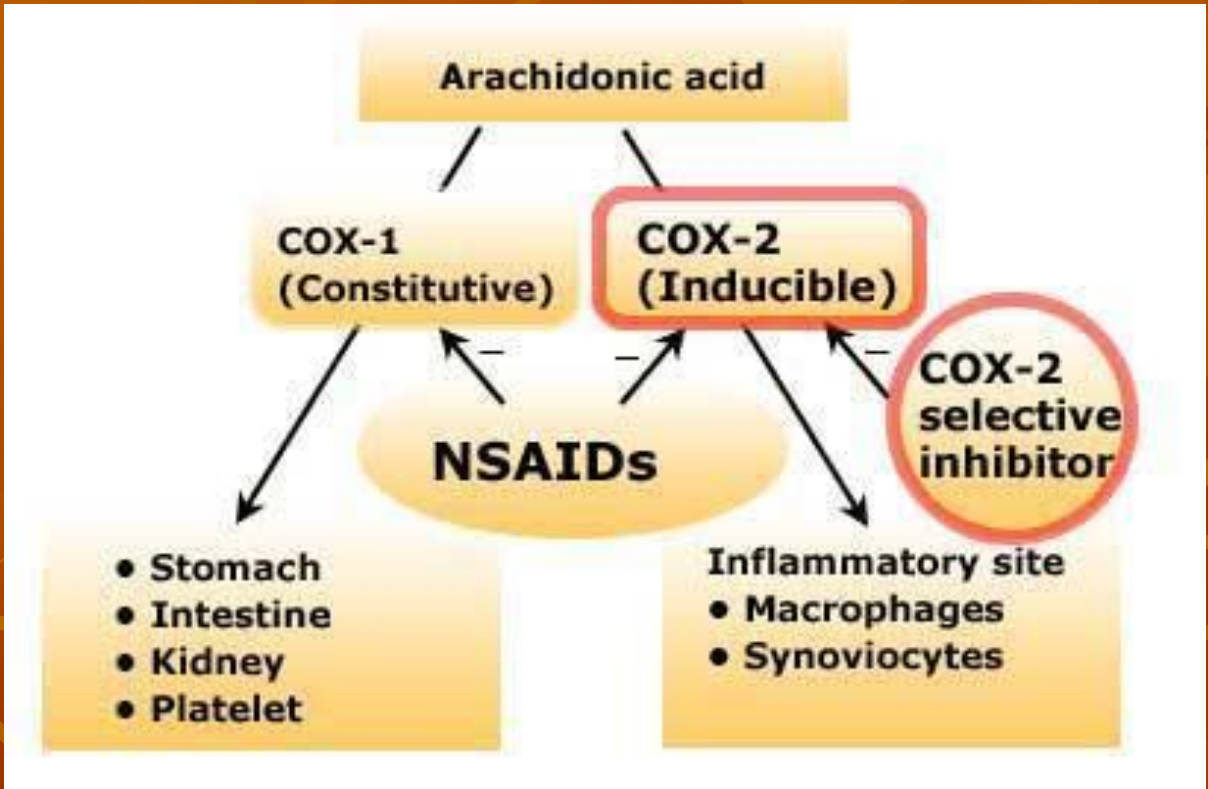

Arachidonic acid
COX-1
(Constitutive)
COX-2
(Inducible)
COX-2
selective
inhibitor
NSAIDs
• Stomach
• Intestine
• Kidney
• Platelet
Inflammatory site
• Macrophages
• Synoviocytes

NSAIDs & CVS : Mechanism

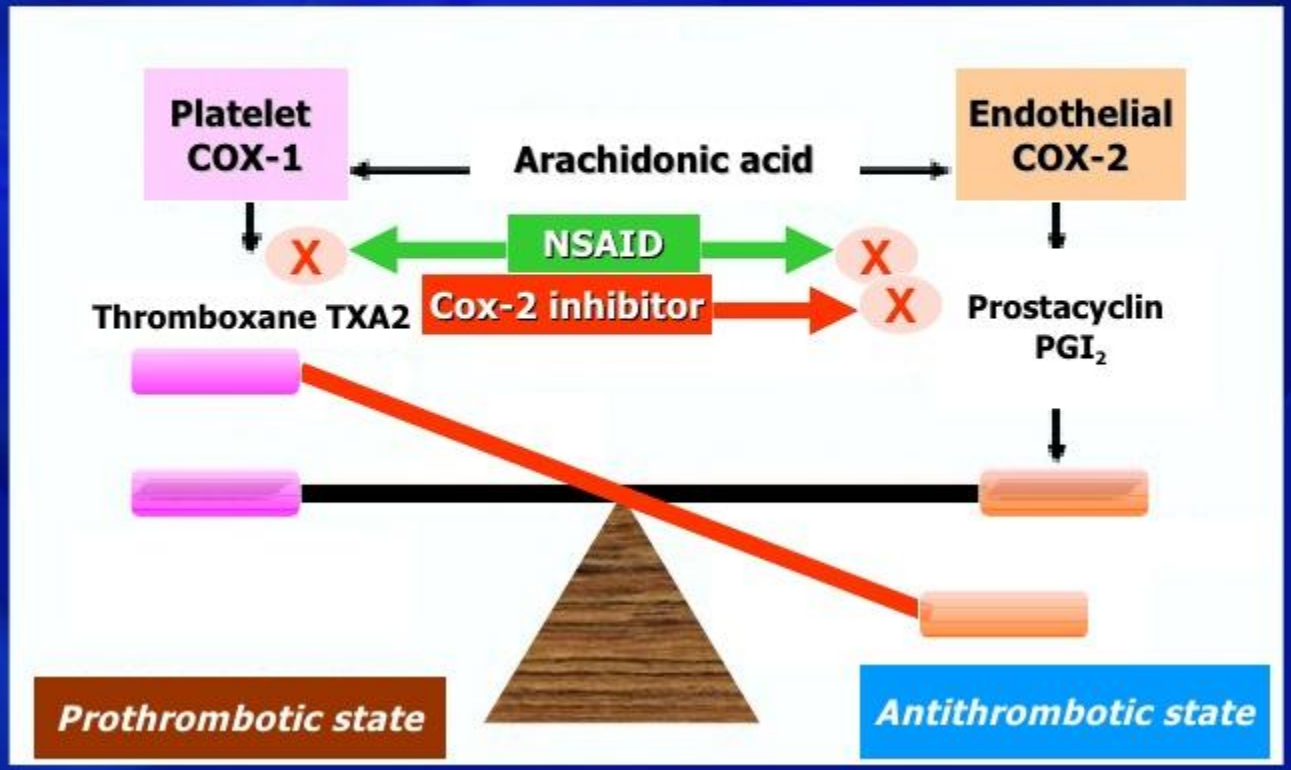
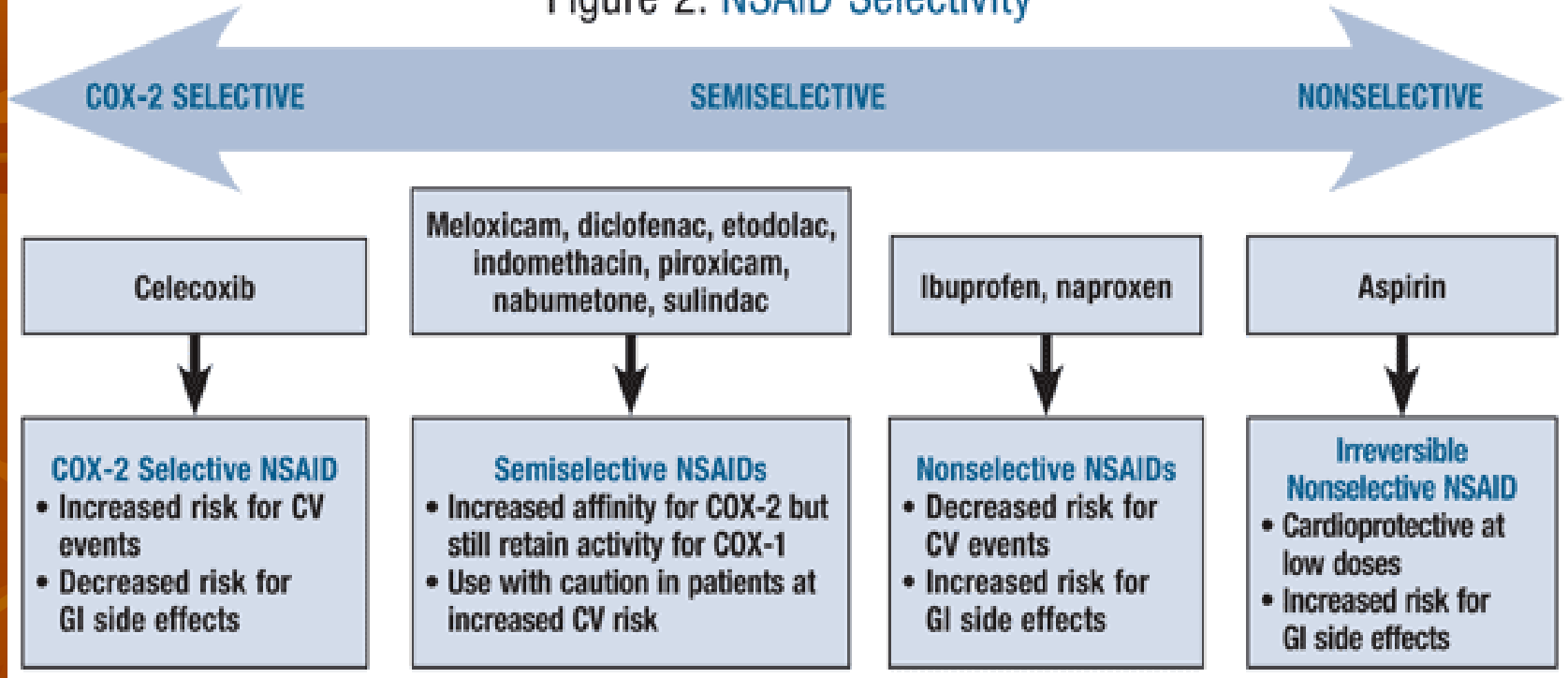
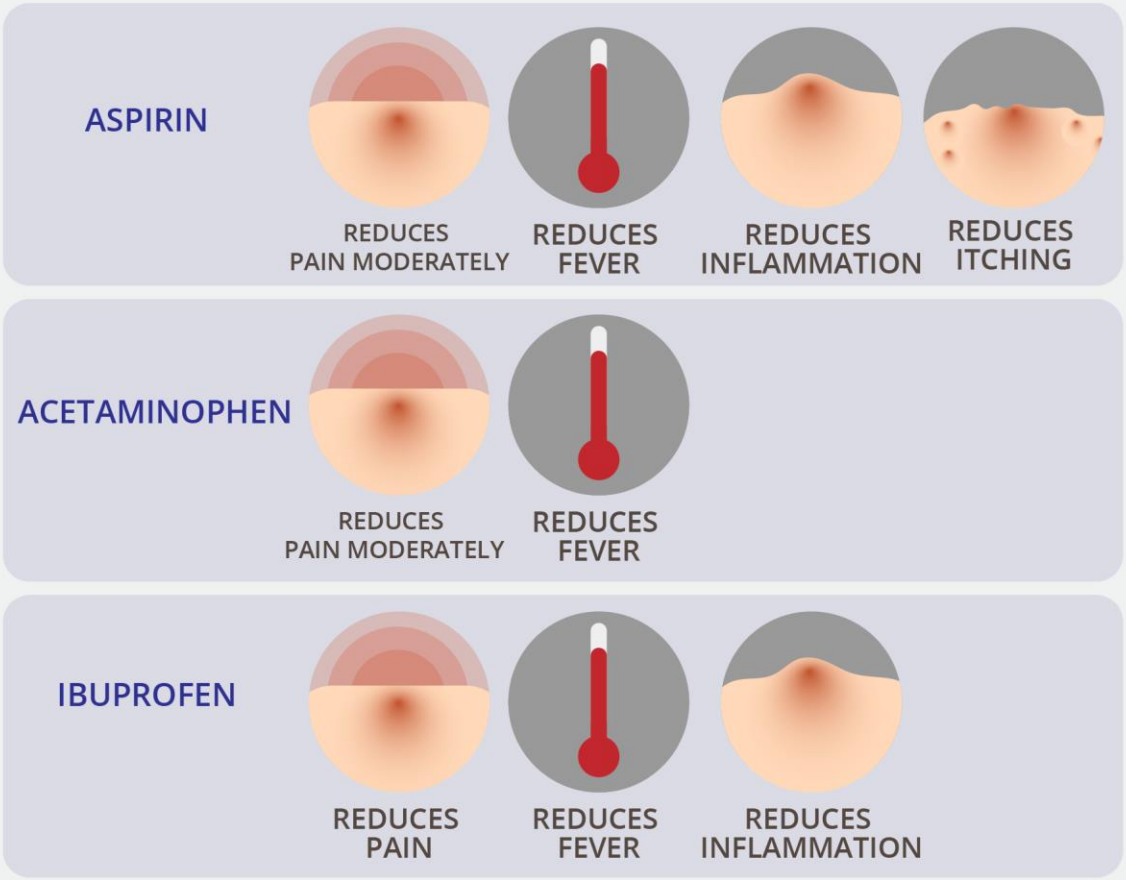


Figure 2. NSAID Selectivity



COX: cyclooxygenase; CV: cardiovascular; GI: gastrointestinal; NSAID: nonsteroidal anti-inflammatory drug. Source: References 3, 17.

Types of NSAIDs

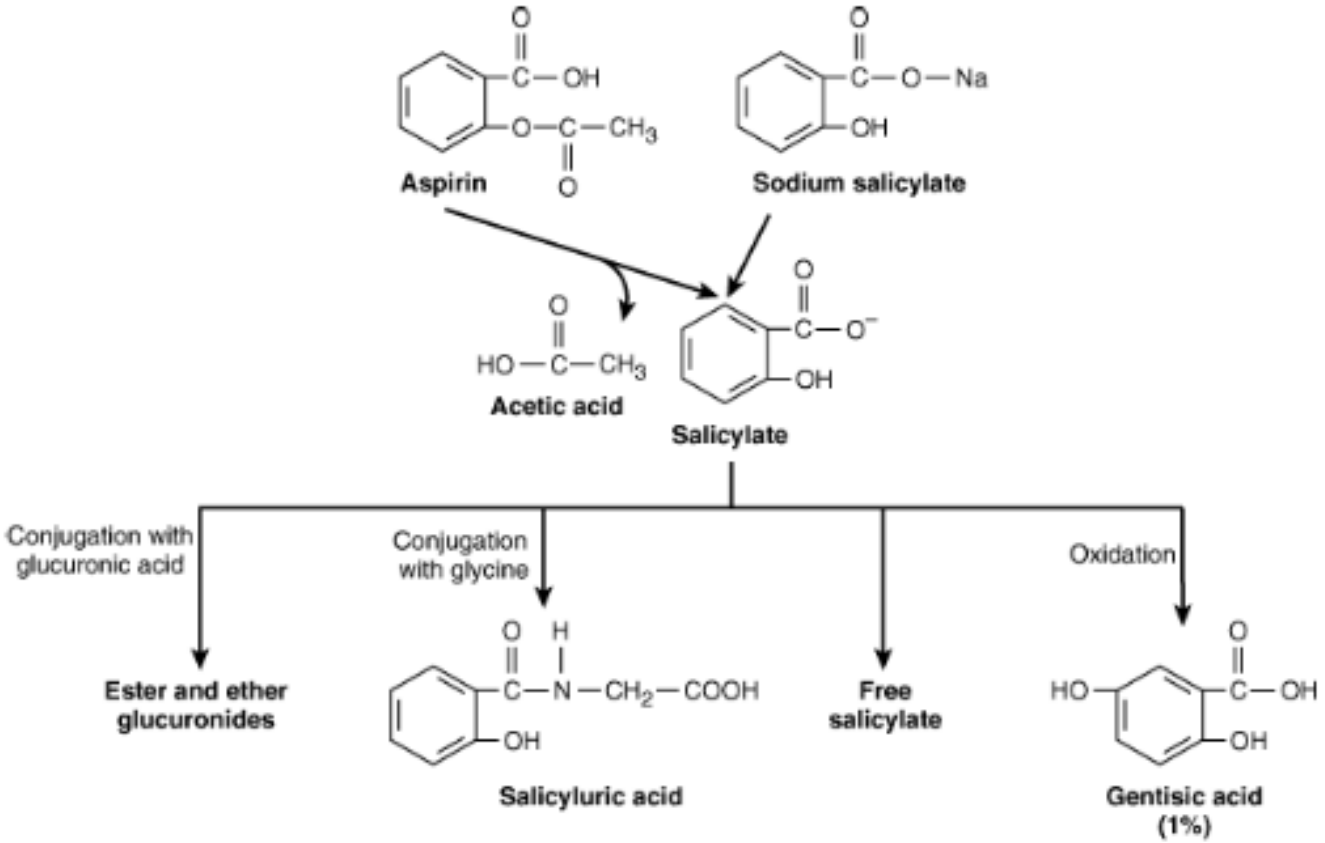


Salicylates	• Aspirin Diflunisal • Na.salicylate salicylamide
Para-aminophenol	• Acetaminophen
Phenyl Acetic acid	• Diclofenac • Ketorolac
Oxicams	• Piroxicam
Pyrazolone derivatives	• Phenylbutazone Oxyphenbutazone • Analgin Azapropazone
Propionic acid derivatives	• Ibuprofen Ketoprofen Flurbiprofen • Naproxen
Fenamates	• Mafenamic acid • Flufenamic acid
Preferential COX-2 inhibitors	• Nimesulide • Meloxicam Nebumatone
Selective COX-2 inhibitors	• Celecoxib Rofecoxib • Paracoxib Lumiracoxib Valdecoxib

ASPIRIN

- Aspirin's long use and availability without prescription diminishes its glamour compared with that of the newer NSAIDs.
- Aspirin is now rarely used as an anti inflammatory medication and will be reviewed only in terms of its anti-platelet effects (ie, doses of 81–325 mg once daily).

ASPIRIN



Structure and metabolism of the salicylates.

(Modified and reproduced, with permission, from Meyers FH, Jawetz E, Goldfien A: *Review of Medical Pharmacology,* 7th ed. McGraw-Hill, 1980.)

Mechanisms of Action

- Aspirin irreversibly inhibits platelet COX so that aspirin's antiplatelet effect lasts 8–10 days (the life of the platelet).

- In other tissues, synthesis of new COX replaces the inactivated enzyme so that ordinary doses have a duration of action of 6–12 hours.

Clinical Uses

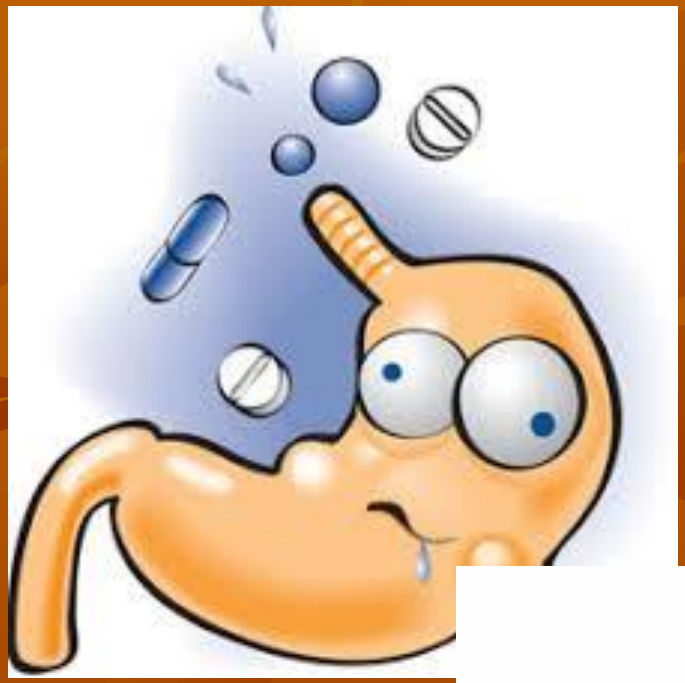
- Aspirin decreases the incidence of transient ischemic attacks, unstable angina, coronary artery thrombosis with myocardial infarction, and thrombosis after coronary artery bypass grafting

- Epidemiologic studies suggest that long-term use of aspirin at low dosage is associated with a lower incidence of colon cancer, possibly related to its COX-inhibiting effects.

Adverse Effects

- Aspirin's main adverse effects at antithrombotic doses are gastric upset (intolerance) and gastric and duodenal ulcers. Hepatotoxicity, asthma, rashes, gastrointestinal bleeding, and renal toxicity rarely if ever occur at antithrombotic doses.

- The antiplatelet action of aspirin contraindicates its use by patients with hemophilia.
- Although previously not recommended during pregnancy,aspirin may be valuable in treating preeclampsia-eclampsia.



NONACETYLATED SALICYLATES

- These drugs include magnesium choline salicylate, sodium salicylate, and salicyl salicylate.

- All nonacetylated salicylates are effective anti-inflammatory drugs, although they may be less effective analgesics than aspirin. Because they are much less effective than aspirin as COX inhibitors and they do not inhibit platelet aggregation, they may be preferable when COX inhibition is undesirable such as in patients with asthma, those with bleeding tendencies, and even (under close supervision) those with renal dysfunction.

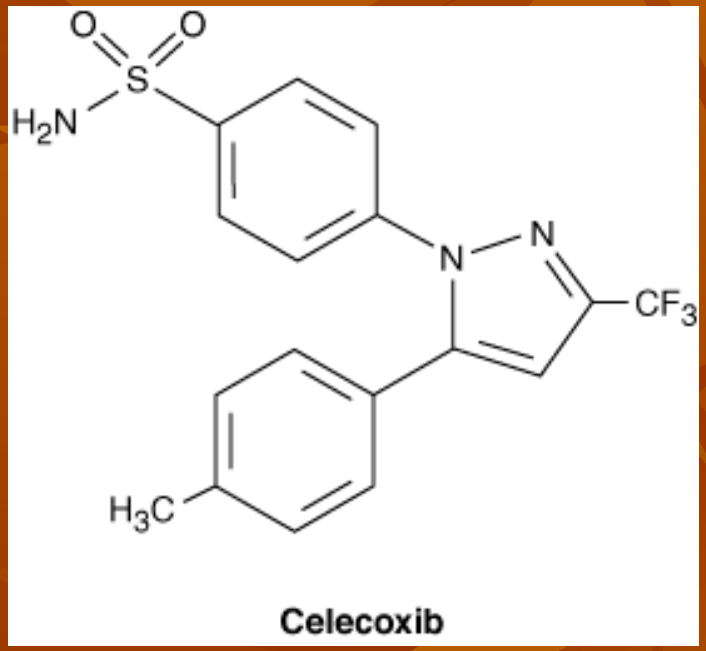
- The nonacetylated salicylates are administered in doses up to 3–4 g of salicylate a day and can be monitored using serum salicylate

COX-2 SELECTIVE INHIBITORS

- COX-2 selective inhibitors, or coxibs, were developed in an attempt to inhibit prostaglandin synthesis by the COX-2 isozyme induced at sites of inflammation without affecting the action of the constitutively active "housekeeping" COX-1 isozyme found in the gastrointestinal tract, kidneys, and platelets.
- Coxibs selectively bind to and block the active site of the COX-2 enzyme much more effectively than that of COX-1.
- COX-2 inhibitors have analgesic, antipyretic, and anti-inflammatory effects similar to those of nonselective NSAIDs but with an approximate halving no gastrointestinal adverse effects.
- Likewise, COX-2 inhibitors at usual doses have been shown to have no impact on platelet aggregation, which is mediated by thromboxane produced by the COX-1 isozyme.
- In contrast, they do inhibit COX-2-mediated prostacyclin synthesis in the vascular endothelium. As a result, COX-2 inhibitors do not offer the cardioprotective effects of traditional nonselective NSAIDs, which has resulted in some patients taking low-dose aspirin in addition to a coxib regimen to maintain this effect.
- Unfortunately, because COX-2 is constitutively active within the kidney, recommended doses of COX-2 inhibitors cause renal toxicities similar to those associated with traditional NSAIDs.
- Clinical data have suggested a higher incidence of cardiovascular thrombotic events associated with COX-2 inhibitors such as rofecoxib and valdecoxib, resulting in their withdrawal from the market.

Celecoxib

- Celecoxib is a selective COX-2 inhibitor—about 10–20 times more selective for COX-2 than for COX-1..
- Celecoxib is associated with fewer endoscopic ulcers than most other NSAIDs.
- Probably because it is a sulfonamide, celecoxib may cause rashes
- It does not affect platelet aggregation at usual doses.
- It interacts occasionally with warfarin—as would be expected of a drug metabolized via CYP2C9.



Celecoxib

NSAIDs

Dr. Karun Kumar

JR-II

Meloxicam

- Meloxicam is an enolcarboxamide related to piroxicam that preferentially inhibits COX-2 over COX-1, particularly at its lowest therapeutic dose of 7.5 mg/d.
- It is not as selective as celecoxib and may be considered "preferentially" selective rather than "highly" selective.
- The drug is popular in Europe and many other countries for the treatment of most rheumatic diseases and approved for treatment of osteoarthritis in the USA.
- It is associated with fewer clinical gastrointestinal symptoms and complications than piroxicam, diclofenac, and naproxen.
- Similarly, while meloxicam is known to inhibit synthesis of thromboxane A 2, even at supratherapeutic doses its blockade of thromboxane A does not reach levels that result in decreased in vivo platelet function (see common adverse effects above).

NONSELECTIVE COX INHIBITORS

Diclofenac

- Diclofenac is a phenylacetic acid derivative that is relatively nonselective as a COX inhibitor.
- Gastrointestinal ulceration may occur less frequently than with some other NSAIDs.
- A preparation combining diclofenac and misoprostol decreases upper gastrointestinal ulceration but may result in diarrhea. Another combination of diclofenac and omeprazole was also effective with respect to the prevention of recurrent bleeding,
- but renal adverse effects were common in high-risk patients. Diclofenac, 150 mg/d, appears to impair renal blood flow and glomerular filtration rate.
- Elevation of serum aminotransferases occurs more commonly with this drug than with other NSAIDs.
- A 0.1% ophthalmic preparation is recommended for prevention of postoperative ophthalmic inflammation and can be used after intraocular lens mplantation and strabismus surgery.
- A topical gel containing 3% diclofenac is effective for solar keratoses.
- Diclofenac in rectal suppository form can be considered for preemptive analgesia and postoperative nausea.
- In Europe, diclofenac is also available as an oral mouthwash and for intramuscular administration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Diclofenac Sodium Gel
3%


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NOVARTIS
Voltaren
12.5mg


0.74 mg/ml
Diclofenac
0.74mg/ml Mouthwash
Diclofenac acid

Diflunisal

- Although diflunisal is derived from salicylic acid, it is not metabolized to salicylic acid or salicylate. It undergoes an enterohepatic cycle with reabsorption of its glucuronide metabolite followed by cleavage of the glucuronide to again release the active moiety.

- Diflunisal is subject to capacity-limited metabolism, with serum half-lives at various dosages approximating that of salicylates .

- In rheumatoid arthritis the recommended dose is 500–1000 mg daily in two divided doses.

- It is claimed to be particularly effective for cancer pain with bone metastases and for pain control in dental (third molar) surgery.

- A 2% diflunisal oral ointment is a clinically useful analgesic for painful oral lesions.
- Because its clearance depends on renal function as well as hepatic metabolism, diflunisal's dosage should be limited in patients with significant renal impairment.

Etodolac

- Etodolac is a racemic acetic acid derivative with an intermediate half-life (Table 36–1).
- Etodolac does not undergo chiral inversion in the body.
- The dosage of etodolac is 200–400 mg three to four times daily.

Flurbiprofen

- Flurbiprofen is a propionic acid derivative with a possibly more complex mechanism of action than other NSAIDs.
- Its *(S)(–) enantiomer inhibits* COX nonselectively, but it has been shown in rat tissue to also affect tumor necrosis factor- (TNF-) and nitric oxide synthesis.
- Hepatic metabolism is extensive; its *(R)(+) and (S)(–) enantiomers are metabolized differently, and it does not undergo chiral conversion.*
- *It does* demonstrate enterohepatic circulation.
- Flurbiprofen is also available in a topical ophthalmic formulation for inhibition of intraoperative miosis. Flurbiprofen intravenously is effective for perioperative analgesia in minor ear, neck, and nose surgery and in lozenge form for sore throat.
- Although its adverse effect profile is similar to that of other NSAIDs in most ways, flurbiprofen is also associated rarely with cogwheel rigidity, ataxia, tremor, and myoclonus.

Ibuprofen

- Ibuprofen is a simple derivative of phenylpropionic acid (Figure 36–1). In doses of about 2400 mg daily, ibuprofen is equivalent to 4 g of aspirin in anti-inflammatory effect.
- Oral ibuprofen is often prescribed in lower doses (< 2400 mg/d), at which it has analgesic but not anti-inflammatory efficacy.
- It is available over the counter in low-dose forms under several trade names.

- Ibuprofen is effective in closing patent ductus arteriosus in preterm infants, with much the same efficacy and safety as indomethacin. The oral and intravenous routes are equally effective for this indication.

- A topical cream preparation appears to be absorbed into fascia and muscle; an *(S)(–) formulation has been tested. Ibuprofen cream was more effective than placebo cream in the treatment of primary knee osteoarthritis.*
- *A* liquid gel preparation of ibuprofen, 400 mg, provides prompt relief and good overall efficacy in postsurgical dental pain.

- In comparison with indomethacin, ibuprofen decreases urine output less and also causes less fluid retention.

- The drug is relatively contraindicated in individuals with nasal polyps, angioedema, and bronchospastic reactivity to aspirin. Aseptic meningitis (particularly in patients with systemic lupus erythematosus), and fluid retention have been reported.
- Interaction with anticoagulants is uncommon.
- The concomitant administration of ibuprofen and aspirin antagonizes the irreversible platelet inhibition induced by aspirin. Thus, treatment with ibuprofen in patients with increased cardiovascular risk may limit the cardioprotective effects of aspirin. Furthermore, the use of ibuprofen concomitantly with aspirin may *decrease* rare hematologic effects include agranulocytosis and aplastic anemia.


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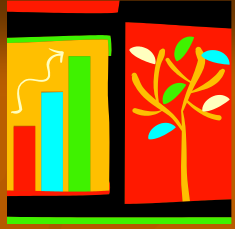
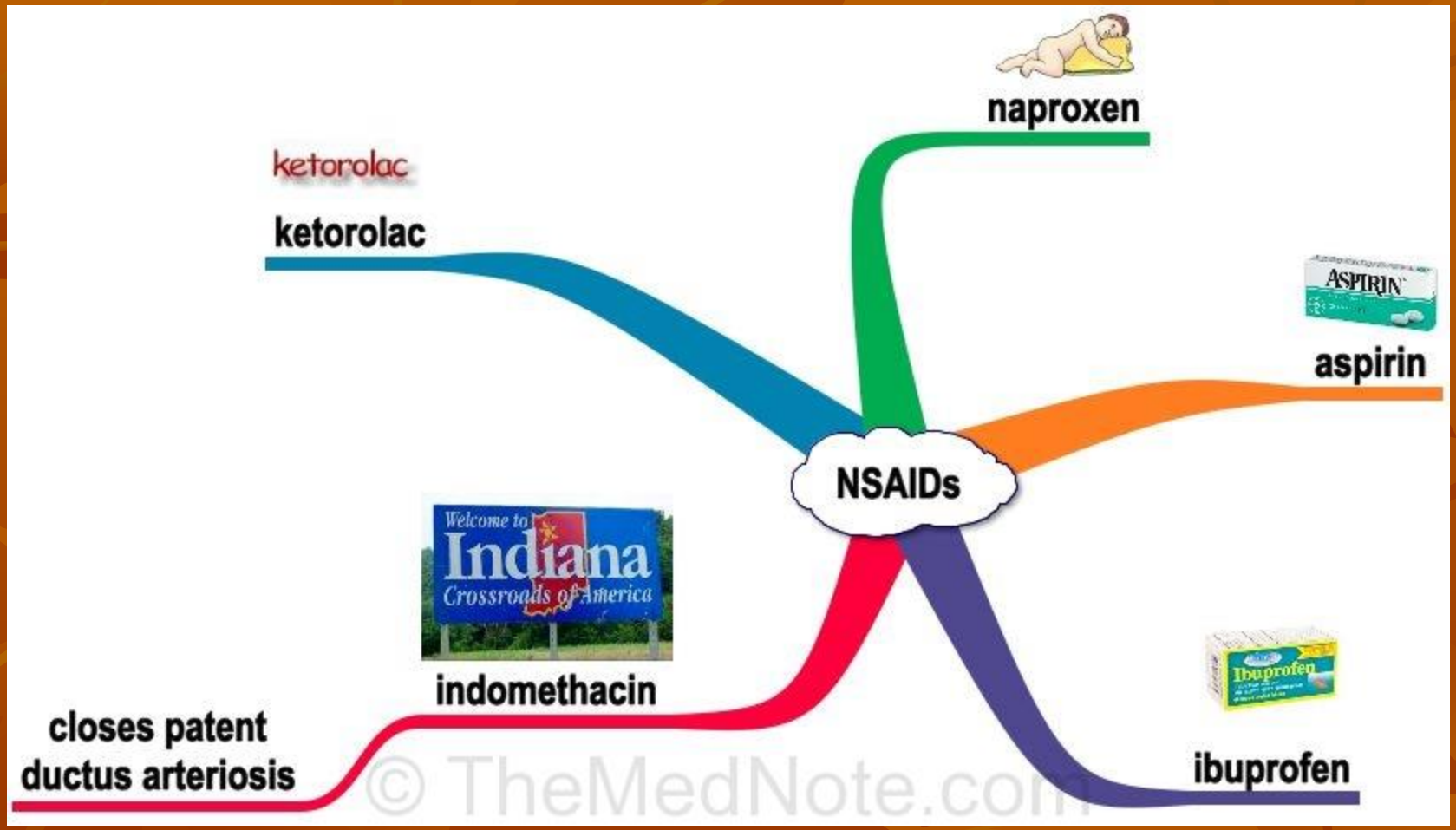
Indomethacin



- Indomethacin, introduced in 1963, is an indole derivative (Figure 36–1). It is a potent nonselective COX inhibitor and may also inhibit phospholipase A and C, reduce neutrophil migration, and decrease T-cell and B-cell proliferation.
- It differs somewhat from other NSAIDs in its indications and toxicities.
- Indomethacin was particularly popular for gout and ankylosing spondylitis.

- In addition, it has been used to accelerate closure of patent ductus arteriosus.
- Indomethacin has been tried in numerous small or uncontrolled trials for many other conditions, including Sweet's syndrome, juvenile rheumatoid arthritis, pleurisy, nephrotic syndrome, diabetes insipidus, urticarial vasculitis, postepisiotomy pain, and prophylaxis of heterotopic ossification in arthroplasty.

- An ophthalmic preparation seems to be efficacious for conjunctival inflammation and to reduce pain after traumatic corneal abrasion. Gingival inflammation is reduced after administration of indomethacin oral rinse.
- Epidural injections produce a degree of pain relief similar to that achieved with methylprednisolone in postlaminectomy syndrome.
- . The gastrointestinal effects may include pancreatitis.
- **Headache is experienced by 15–25% of patients and may be associated with dizziness, confusion, and depression**
- . Rarely, psychosis with hallucinations has been reported. Serious hematologic reactions have been noted, including thrombocytopenia and aplastic anemia.
- Renal papillary necrosis has also been observed. A number ofinteractions with other drugs have been reported **Probenecid** prolongs indomethacin's half-life by inhibiting both renal and biliary clearance.


naproxen
ketorolac
ketorolac
aspirin
NSAIDs
Welcome to
Indiana
Crossroads of America
indomethacin
ibuprofen
closes patent
ductus arteriosis
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Ketoprofen

- Ketoprofen is a propionic acid derivative that inhibits both COX (nonselectively) and lipoxygenase.
- Concurrent administration of probenecid elevates ketoprofen levels and prolongs its plasma half-life.
- The effectiveness of ketoprofen at dosages of 100–300 mg/d is equivalent to that of other NSAIDs.
- In spite of its dual effect on prostaglandins and leukotrienes, ketoprofen is not superior to other NSAIDs in clinical efficacy.
- Its major adverse effects are on the gastrointestinal tract and the central nervous system (see common adverse effects above).


#NSAID
non-steroidal anti-inflammatory drugs
Many cold, allergy, and sinus medications contain NSAIDs
SOME NSAIDS ARE:
aspirin
Motrin
Advil
Ibuprofen
Aleve
For an extensive list of NSAIDs visit

Ketorolac

- Ketorolac is an NSAID promoted for systemic use mainly as an analgesic, not as an anti-inflammatory drug (although it has typical NSAID properties).
- The drug is an effective analgesic and has been used successfully to replace morphine in some situations involving mild to moderate postsurgical pain.
- It is most often given intramuscularly or intravenously, but an oral dose formulation is available. When used with an opioid, it may decrease the opioid requirement by 25–50%.
- An ophthalmic preparation is available for ocular inflammatory conditions.
- Toxicities are similar to those of other NSAIDs, although renal toxicity may be more common with chronic
- use.

Naproxen

Naproxen is a naphthylpropionic acid derivative. It is the only NSAID presently marketed as a single enantiomer. Naproxen's free fraction is significantly higher in women than in men, but half-life is similar in both sexes (Table 36–1). Naproxen is effective for the usual rheumatologic indications and is available in a slow-release formulation, as an oral suspension, and over the counter. A topical preparation and an ophthalmic solution are also available.

The incidence of upper gastrointestinal bleeding in over-the-counter use is low but still double that of over-the-counter ibuprofen (perhaps due to a dose effect). Rare cases of allergic pneumonitis, leukocytoclastic vasculitis, and pseudoporphyria as well as the common NSAID-associated adverse effects have been noted.

Oxaprozin

Oxaprozin is another propionic acid derivative NSAID. As noted in Table 36–1, its major difference from the other members of this subgroup is a very long half-life (50–60 hours), although oxaprozin does not undergo enterohepatic circulation. It is mildly uricosuric, making it potentially more useful in gout than some other NSAIDs. The drug has the same benefits and risks that are associated with other NSAIDs.

Piroxicam

Piroxicam, an oxicam (Figure 36–1), is a nonselective COX inhibitor that at high concentrations also inhibits polymorphonuclear leukocyte migration, decreases oxygen radical production, and inhibits lymphocyte function. Its long half-life (Table 36–1) permits once-daily dosing.

Piroxicam can be used for the usual rheumatic indications. When piroxicam is used in dosages higher than 20 mg/d, an increased incidence of peptic ulcer and bleeding is encountered. Epidemiologic studies suggest that this risk is as much as 9.5 times higher with piroxicam than with other NSAIDs (see common adverse effects above).

Sulindac

Sulindac is a sulfoxide prodrug. It is reversibly metabolized to the active sulfide metabolite, which is excreted in bile and then reabsorbed from the intestine. The enterohepatic cycling prolongs the duration of action to 12–16 hours.

In addition to its rheumatic disease indications, sulindac suppresses familial intestinal polyposis and it may inhibit the development of colon, breast, and prostate cancer in humans. It appears to inhibit the occurrence of gastrointestinal cancer in rats. The latter effect may be caused by the sulfone rather than the sulfide.

Among the more severe adverse reactions, Stevens-Johnson epidermal necrolysis syndrome, thrombocytopenia, agranulocytosis, and nephrotic syndrome have all been observed. Like diclofenac, sulindac may have some propensity to cause elevation of serum aminotransferases; it is also sometimes associated with cholestatic liver damage, which disappears when the drug is stopped.

Tolmetin

Tolmetin is a nonselective COX inhibitor with a short half-life (1–2 hours)and is not often used. Its efficacy and toxicity profiles are similar to
those of other NSAIDs with the following exceptions: it is ineffective (for unknown reasons) in the treatment of gout, and it may cause (rarely)
thrombocytopenic purpura.

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDS)

Approach to Inflammatory Arthritis

- Paradigm shift in the treatment of inflammatory arthritis
- Rationale for Treatment
  - Large body of evidence which shows joint damage is an early phenomenon of rheumatoid arthritis
  - Joint erosions occur in up to 93% of patients with less than 2 years of disease activity
  - The rate of radiographic progression is greatest in the first two years
  - Disability occurs early – 50% of patients with RA will be work disabled at 10 years
  - Severe disease is associated with increased mortality!

It’s like an Iceberg

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDS)

- Careful clinical and epidemiologic studies have shown that rheumatoid arthritis is an immunologic disease that causes significant systemic effect which shorten life in addition to the joint disease that reduces mobility and quality of life.
- NSAIDs offer mainly symptomatic relief; they reduce inflammation and the pain it causes and often preserve function, but they have little effect on the progression of bone and cartilage destruction.
- Interest has therefore centered on finding treatments that might arrest—or at least slow—this progression by modifying the disease itself.
- The effects of disease-modifying therapies may take 6 weeks to 6 months to become evident although some biologics are effective within 2 weeks;
- they are slow-acting compared with NSAIDs.
- These therapies include methotrexate, a T-cell-modulating biologic (abatacept), azathioprine, chloroquine and hydroxychloroquine,
- cyclophosphamide, cyclosporine, leflunomide, mycophenolate mofetil, a B-cell cytotoxic agent (rituximab), sulfasalazine, and the TNF- -blocking agents.
- These drugs comprise both biologically derived and nonbiologic agents and will be listed alphabetically, independent of origin. Gold salts, which were once extensively used, are no longer recommended because of their significant toxicities and questionable efficacy.

Overview

- DMARDS
  - Traditional
    - Methotrexate
    - Sulfasalazine
    - Plaquenil
    - Leflunomide
  - TNF Inhibitors (infliximab, adalimumab, etancercept)
  - Newer biologics (abatacept, rituximab)

Approach to Inflammatory Arthritis

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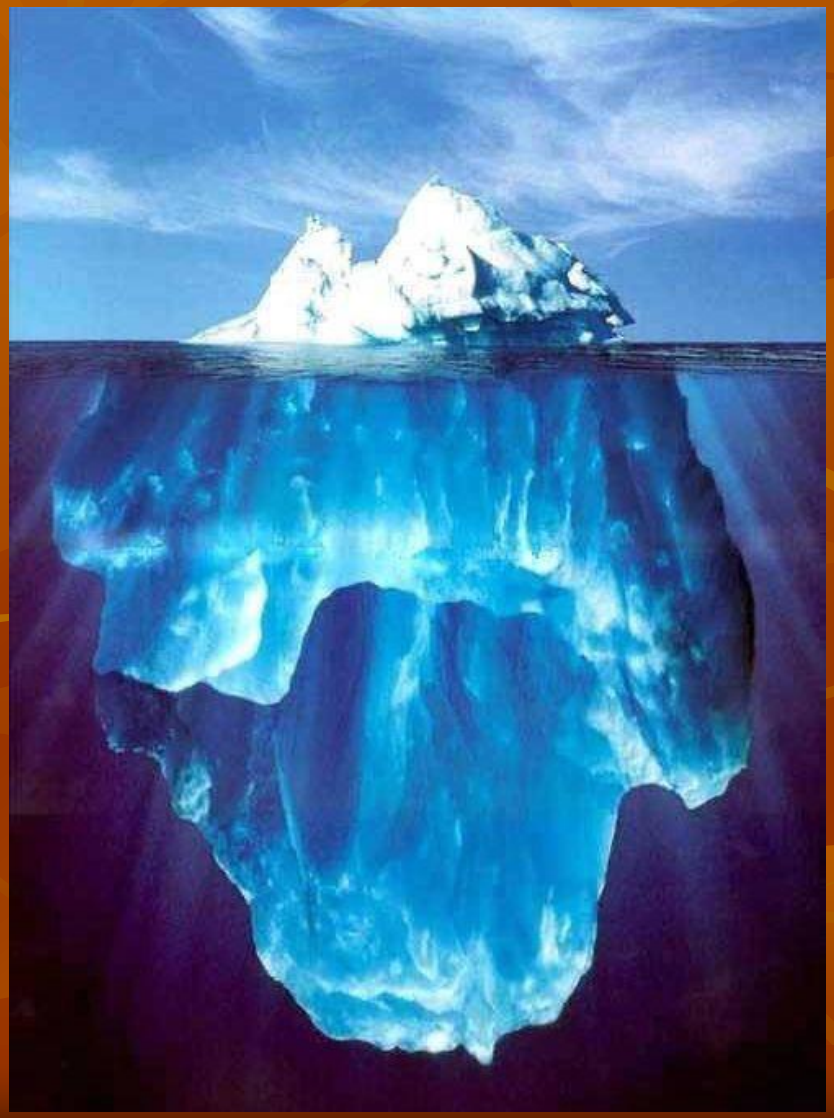
  - Disability occurs early – 50% of patients with RA will be work disabled at 10 years
  - Severe disease is associated with increased mortality!

It’s what you don’t see!



Approach to Inflammatory Arthritis

- "Window of Opportunity"
  - Early and aggressive treatment may have long-term benefits
- Principles of Treatment
  - Treat Early
  - Treat Appropriately

Therapeutic Strategies

- Use of early DMARDs
- Combinations of Conventional DMARDs
  - Three studies have confirmed the use of "triple therapy" in early RA is more effective than a single agent. (Clin Exp Rheumatol 17:699-704, 1999, Arthritis Rheum 50:2072-81, 2004, Arthritis Rheum 46:1164-70, 2002).
- Combinations of Methotrexate plus Biologic agents

What are DMARDs?

- Disease Modifying Anti-Rheumatic Drugs (DMARDs).
  - Symptom Control
    - Control current inflammatory features
  - Modify the course of disease
    - Reduce joint damage and deformity
    - Reduce radiographic progression
    - Reduce long-term disability

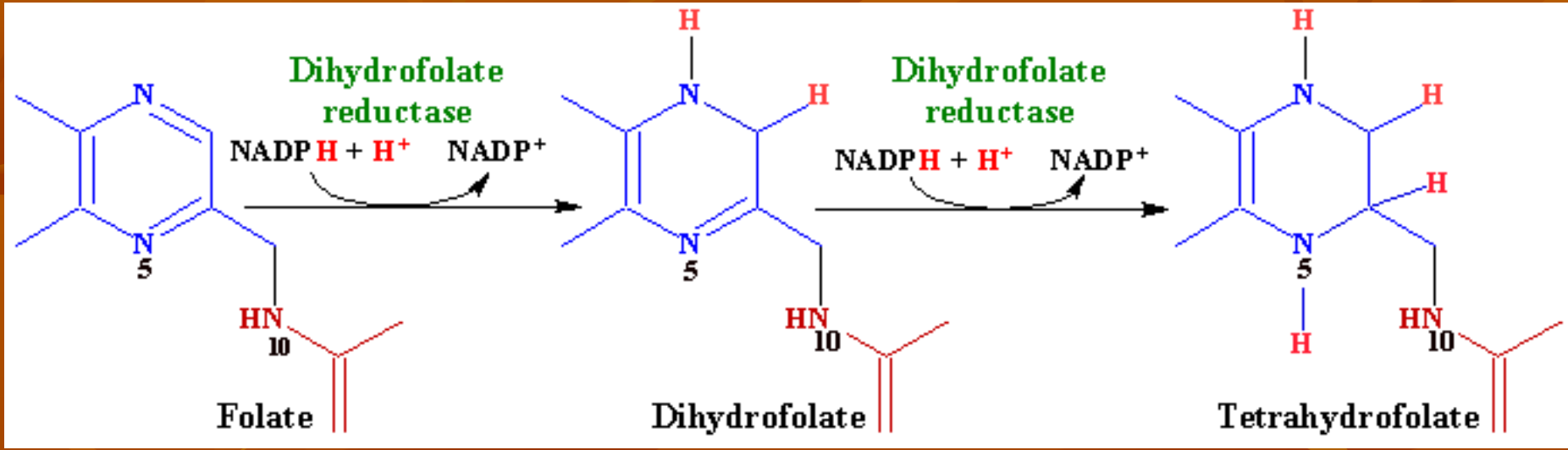
Available DMARDs

- Methotrexate
- Sulfasalazine (Salazopyrin®)
- Hydroxychloroquine (Plaquenil®)
- Leflunomide (Arava®)
- Gold (Myochrisine®)
- Others
  - Cyclosporine
  - Azathioprine
  - Cyclophosphamide

Common DMARD Combinations

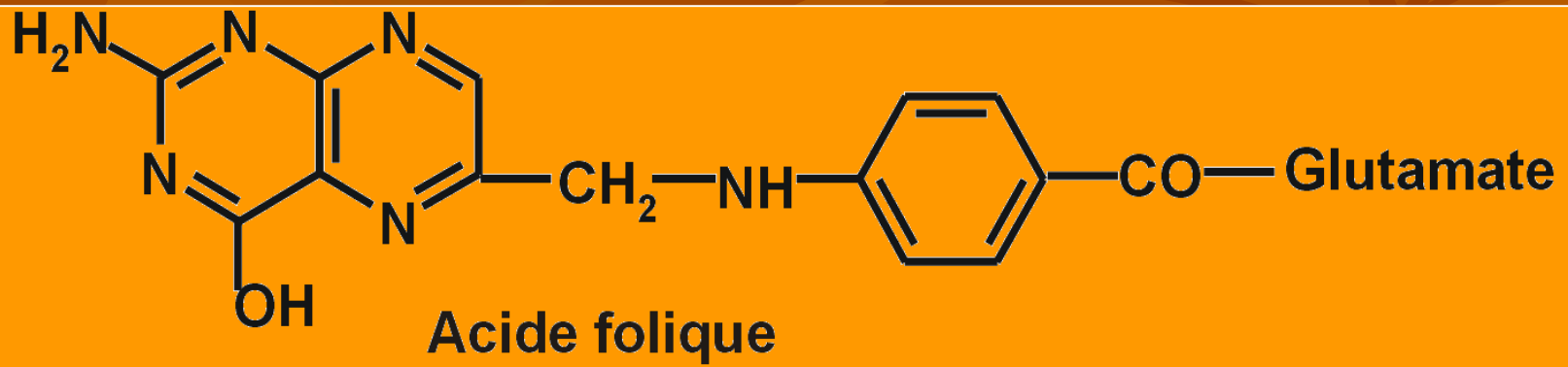
- **Triple Therapy**
  - Methotrexate, Sulfasalazine, Hydroxychloroquine
- ***Double Therapy***
  - Methotrexate & Leflunomide
  - Methotrexate & Sulfasalazine
  - Methotrexate & Hydroxychloroquine
  - Methotrexate & Gold
  - Sulfasalazine & Plaquenil
- ***Monotherapy***

Methotrexate

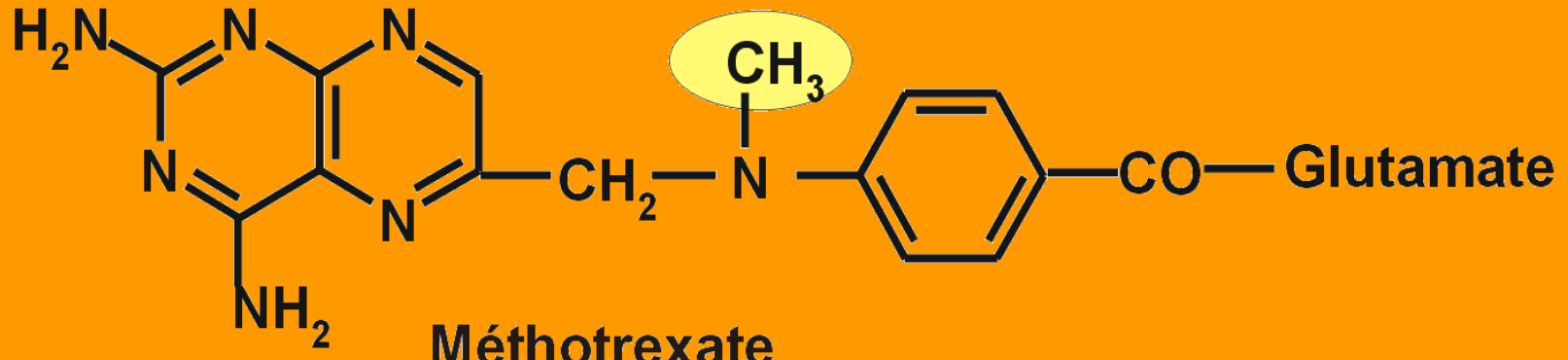


Tetrahydrofolate is an important cofactor in the production of purines transferring a carbon atom.

Methotrexate



Acide folique



Méthotrexate

Methotrexate

- Substitutes as Folic Acid
  - Interferes with the production of Tetrahydrofolate
  - Interferes with the de novo synthesis of purines
  - Affects cells that rapidly turn over
    - Immune cells
    - Mucosal cells
    - Hair follicles

Methotrexate – What to tell Patients

- **Dose and Administration**
  - Dose ranges from 7.5 to 25 mg
  - ONLY GIVEN ONCE A WEEK
  - 2.5 mg Tablets or Subcutaneous Injection 25 mg/mL
- **Onset of Action**
  - 6-8 weeks
- **Avoid**
  - Pregnancy – Teratogenic
  - Alcohol
  - Sulfa Antibiotics (Sulfasalazine is ok)

Methotrexate – What to Tell Patients

- Common S/E
  - Malaise, Nausea
  - Rise in Liver Enzymes
- Dose/Sensitivity
  - Oral ulcers, alopecia, liver and bone marrow toxicity
- Rare S/E
  - Pulmonary: Fever, cough, SOB (early, old, lung disease)
  - Bone Marrow: Follow bloodwork – dose/sensitivity related
  - Infection
  - Pregnancy
  - Malignancy

Methotrexate – What to give Patients

- Information Sheet – www.RheumInfo.com
- Folic Acid supplementation may help with nuisance side effects (nausea, mouth sores)
- Lab Monitoring (monthly initially)
  - CBC, ESR, CRP
  - AST, ALT, ALP, Albumin
  - Cr

Hydroxychloroquine (Plaquenil®)

- Anti-malarial medication found useful for the treatment of inflammatory arthritis
- Highly concentrated within cells
- Increases intracellular pH
- Interferes with cell's ability to degrade and process proteins

Hydroxychloroquine (Plaquenil®)

- **Dose & Administration**
  - 200 mg tablets
  - Dose ranges from 200 – 400 mg per day
- **Onset**
  - 6-12 weeks
- **Avoid**
  - May increase sensitivity to the sun

Hydroxychloroquine (Plaquenil®)

- Common S/E
  - Rash, nausea, diarrhea
  - Difficult with reading (affects accomodation)
- Rare S/E
  - Ocular, Skeletal muscle, heart

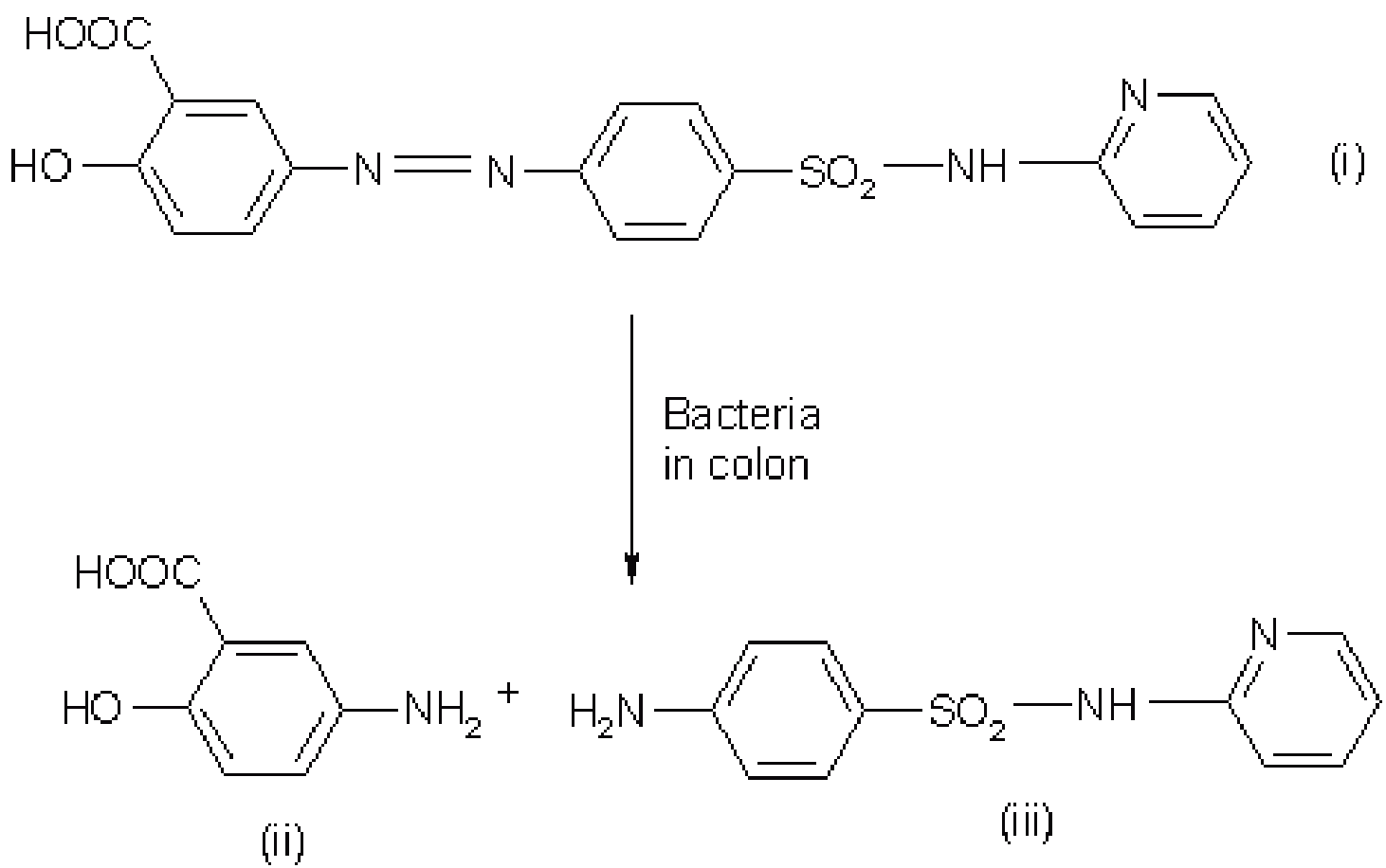
Hydroxychloroquine – What to give Patients

- Information Sheet – www.RheumInfo.com
- Dose is based on lean body weight (6.5 mg/kg/day)
- Average Dose 300 (2 alt with 1 per day)– 400 (2 per day) mg per day
- No laboratory monitoring
- Ophthalmologic screen for visual acuity, colour vision, and visual fields qyearly

Sulfasalazine

- Developed in the late 1930s by Dr. Nana Svartz (Swedish Rheumatologist) for the treatment of "infective polyarthritis"
- Anti-inflammatory: Salicylic Acid
- Antibiotic: Sulfapyridine
- Sulfasalazine consists of salicylic acid and sulfapyridine joined by an azo bond.
- Sulfinpyradone is thought to be the active ingredient although, in RA, the mechanism of action is not understood

Sulfasalazine

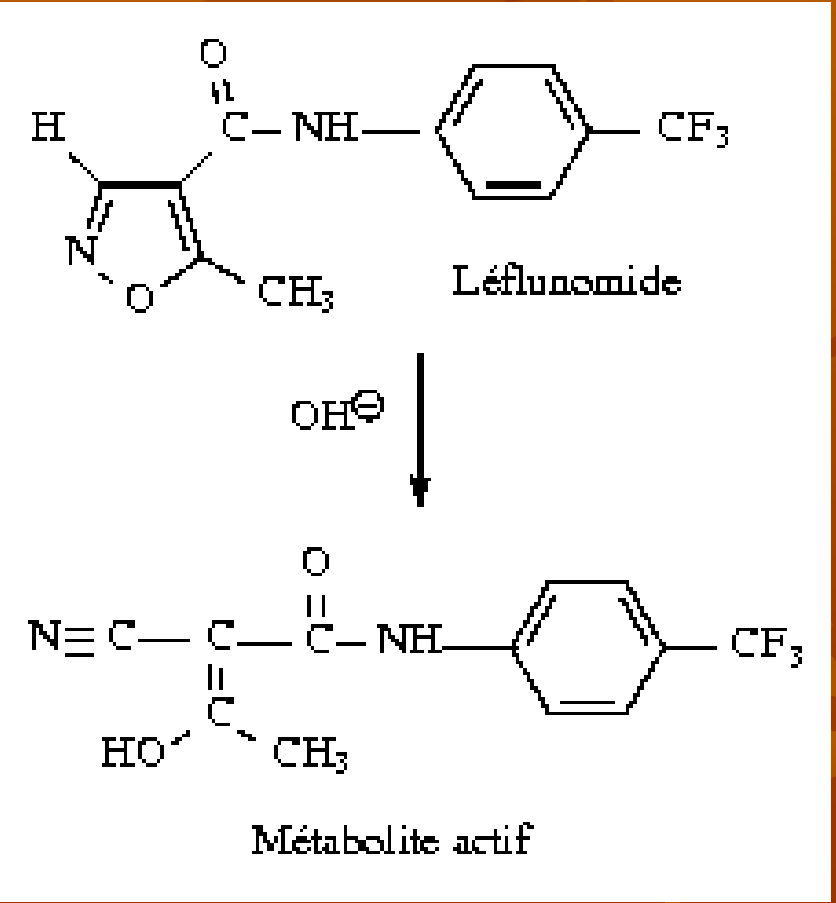


Sulfasalazine

- Pills taken twice daily (CPS and some pharmacists – QID!)
- Start at a low dose 1 per day and gradually work up to 4 per day
- Takes 6-8 weeks to work
- Common S/E: Malaise, Nausea, Abd pain, Rash, headaches, dizziness
- Rare S/E:
  - Hypersensitivity reaction
  - Liver: Follow enzymes – not usually a problem
  - Bone Marrow: Follow bloodwork – dose/sensitivity related
  - Renal: Very Rare

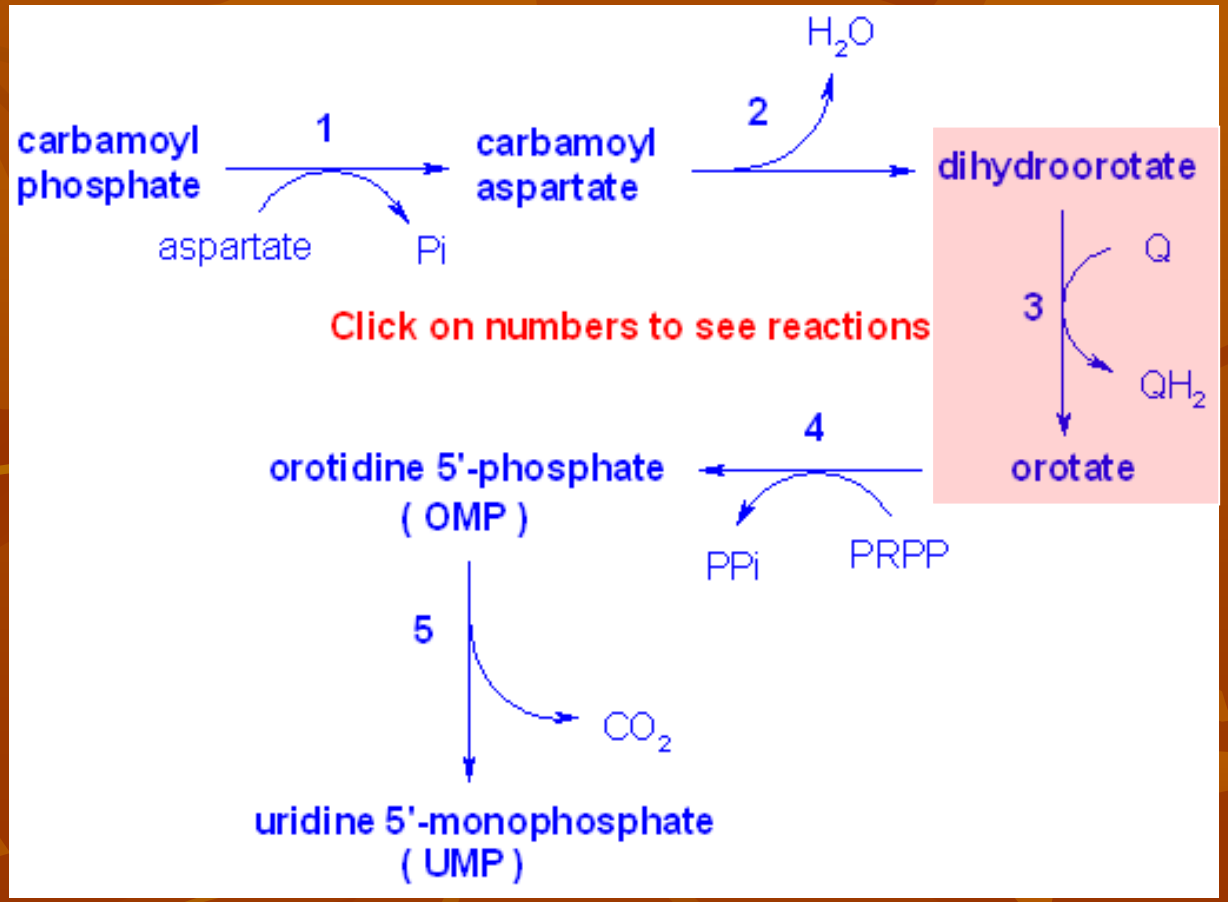
Leflunomide (Arava®)

- Newer DMARD
- Inactive and converted to A177-1726 in the GI tract and liver



Leflunomide (Arava®)

- A77-1726 inhibits the activity of dihydro-orotate dehydrogenase, an important enzyme in the de novo synthesis of pyrimidines.



Leflunomide (Arava®)

- Dose and Administration
  - 10 & 20 mg Tablets
  - Given daily – ranges from 10-20 mg per day
- Onset of Action
  - 6-8 weeks
- Avoid
  - Pregnancy – Teratogenic
  - Alcohol

Leflunomide (Arava®)

- Common S/E
  - Diarrhea, nausea, malaise, hypertension, alopecia, rash
- Rare S/E
  - Liver: Follow enzymes – not usually a problem
  - Bone Marrow: Follow bloodwork – dose/sensitivity related
  - Infection
  - Pregnancy
  - Malignancy

Common Strategies

- Triple therapy for 3-6 months
  - Optimize dose and route of medications
- Incomplete Response
  - Changing to sc methotrexate
  - Adding Leflunomide
  - Adding a Biologic Agent

Biologics

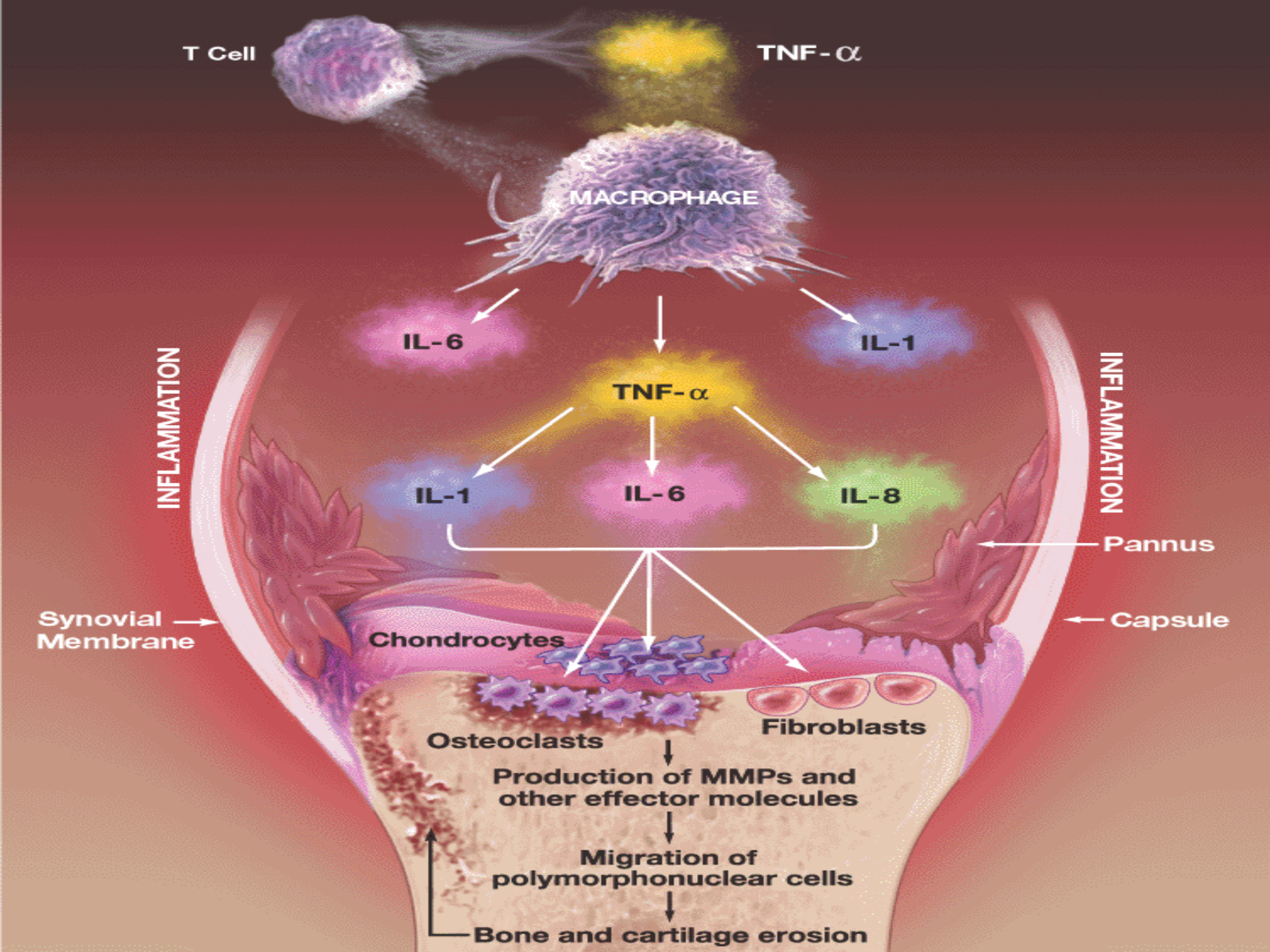
- Specially designed to treat inflammatory types of arthritis such as rheumatoid and psoriatic arthritis.
- Six biologics currently available (and more coming)
- Work by different mechanisms.
- Like DMARDs, biologics are used to suppress inflammation and help prevent damage to the joint.

Current Available Biologics

- **TNF Inhibitors**
  - Adalimumab
  - Etanercept
  - Infliximab (Remicade)
- **IL-1 Inhibitors**
  - Anakinra (Kineret)
- **T-Cell Co-Stimulatory Blockade**
  - Abatacept (Orencia)
- **B-Cell Depletion**
  - Rituximab (Rituxan)

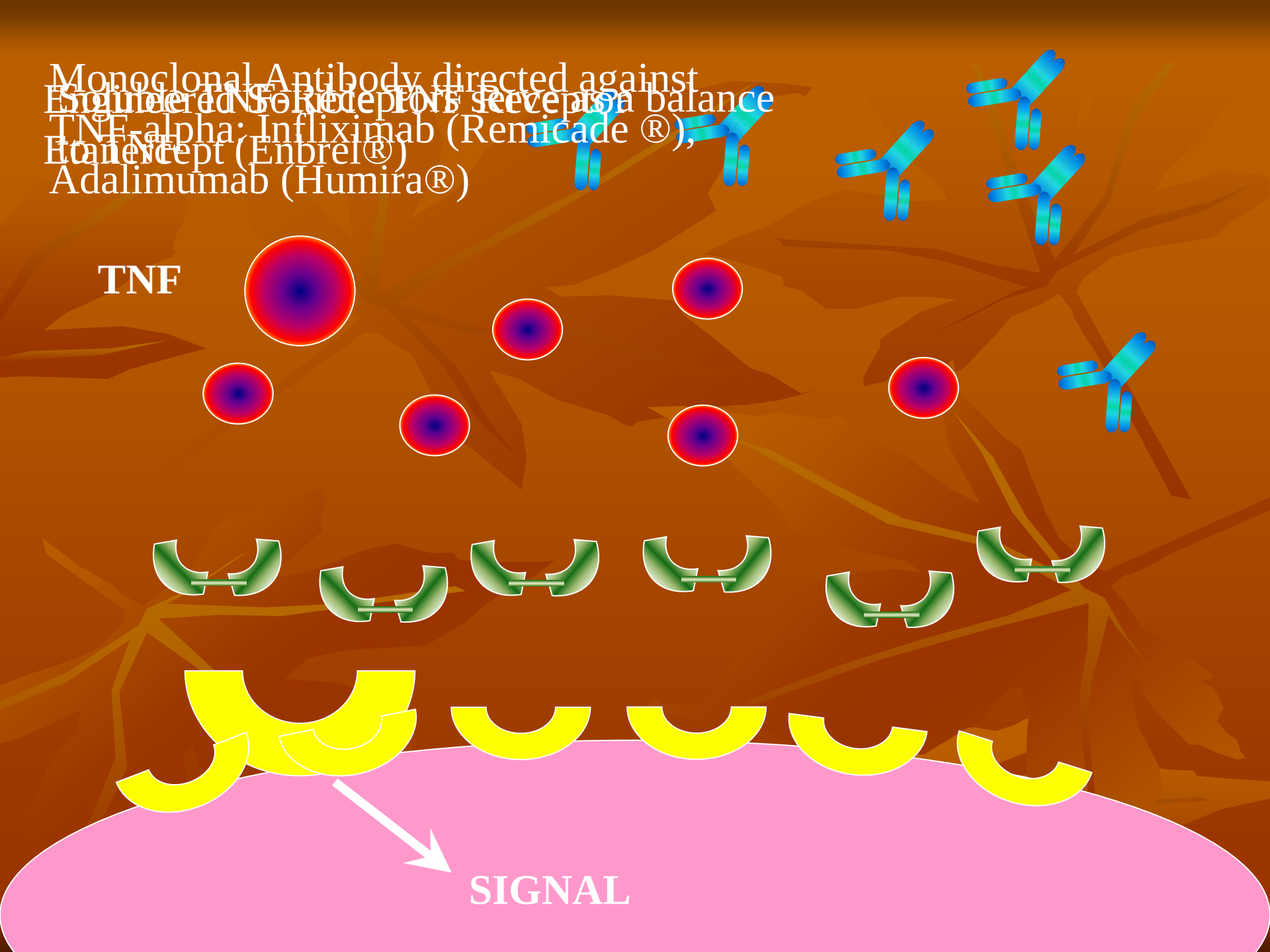
Available Biologics

COMMONLY PRESCRIBED BIOLOGICS		
Brand Names	**Product**	**Common Dose**
Enbrel	Etanercept	50 mg injection once weekly or 25 mg injection twice weekly
Humira	Adalimumab	40 mg injection every other week
Kineret	Anakinra	100 mg injection every other week
Orencia	Abatacept	500 to 1000 mg intravenous infusion every 4 weeks
Remicade	Infliximab	200 – 1000 mg intravenous infusion every 6 to 8 weeks
Rituxan	Rituximab	1000 mg intravenous infusion given twice two weeks apart


T Cell
TNF-α
MACROPHAGE
IL-6
IL-1
TNF-α
IL-1
IL-6
IL-8
INFLAMMATION
INFLAMMATION
Pannus
Synovial Membrane
Capsule
Chondrocytes
Fibroblasts
Osteoclasts
Production of MMPs and other effector molecules
Migration of polymorphonuclear cells
Bone and cartilage erosion

Monoclonal Antibody directed against TNF-alpha: Infliximab (Remicade ®), Adalimumab (Humira®)

Engineered soluble TNF receptor: Etanercept (Enbrel®)



TNF-Inhibitors

- Mechanism of Action
  - Infliximab and Adalimumab are antibodies directed against TNF
  - Etanercept is a soluble receptor decoy
- Administration
  - Infliximab is given intravenously
  - Etanercept and Adalimumab are given by subcutaneous injection

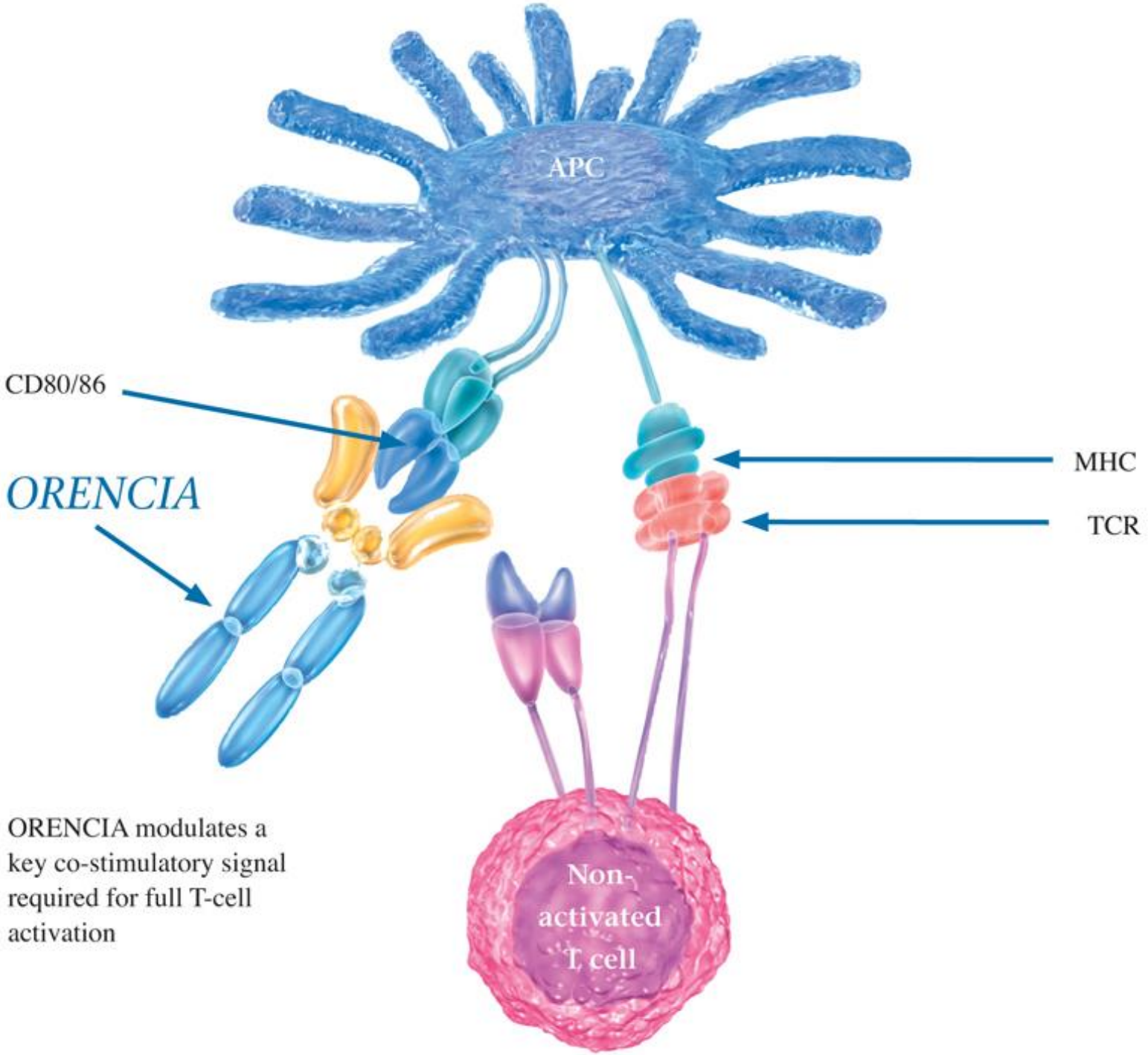
Side Effects of TNF Inhibition

- Infusion Reactions with Infliximab, Injection Site Reactions with Adalimumab and Etanercept
- **Infection**
  - Tuberculosis
  - Serious resulting in death
- Malignancy
  - Increased risk of lymphoma – early data
  - Solid tumors?
- Neurologic
  - Multiple Sclerosis, seizures, inflammation of the ocular nerve
- Autoimmune
  - Antibody formation – SLE like illness
- Worsening of Congestive Heart Failure

When to Stop TNF-Inhibitors

- STOP if develop a fever, have an infection, or have been prescribed antibiotics
- Tell your doctor about any upcoming surgeries

T-Cell Co-Stimulatory Blockade (Abatacept)



ORENCIA modulates a key co-stimulatory signal required for full T-cell activation

Practical Aspects

- Given on week 0, 2, and 4 then every 4 weeks
- Quick infusions over 30 minutes
- Well tolerated
- Home infusion program

Practical Aspects

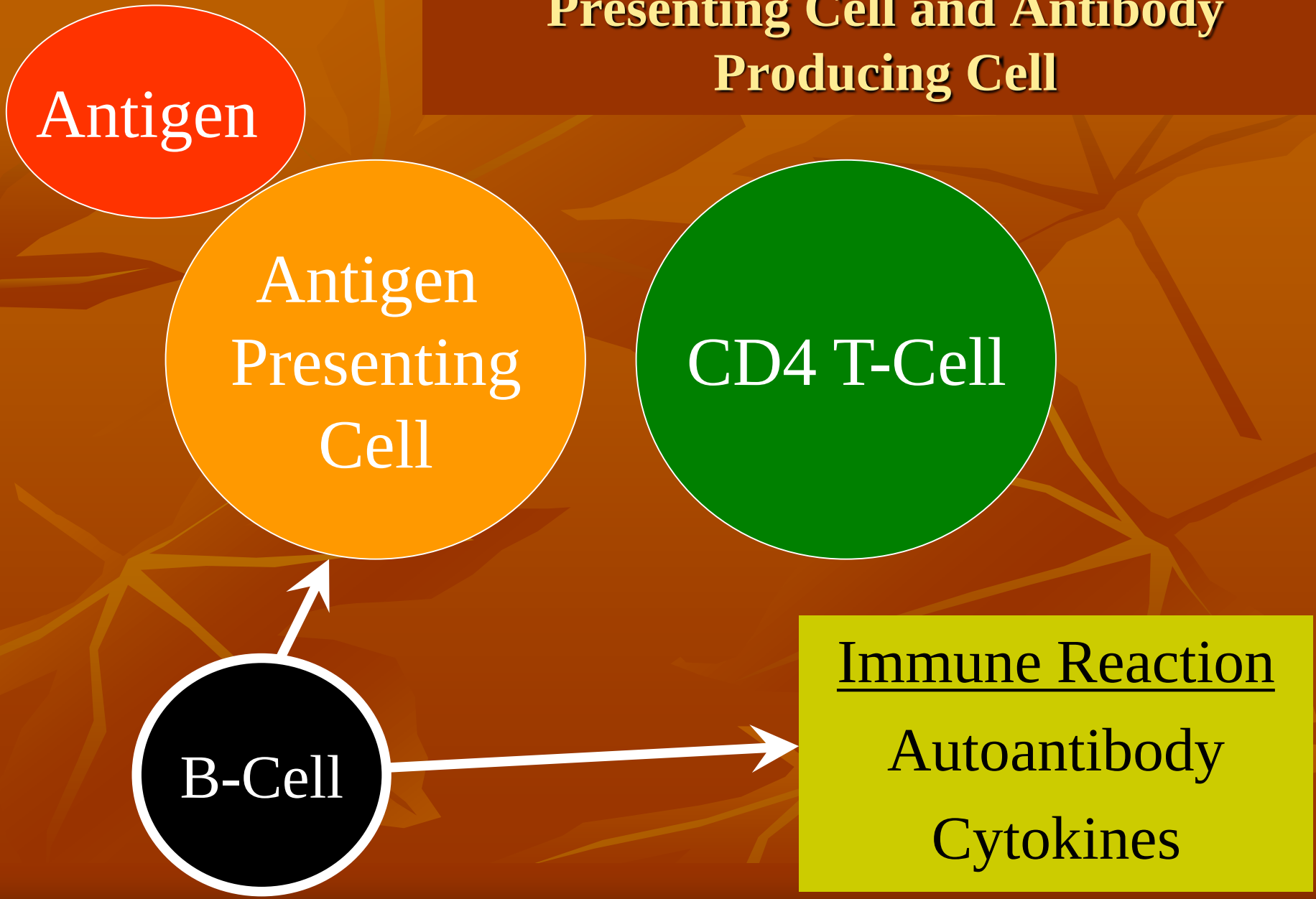
- Side Effects
  - INFECTION
  - COPD Exacerbation
  - MALIGNANCY – Lung Cancer
  - Infusion Reactions – Rare

B-Cell Depletion (Rituximab)

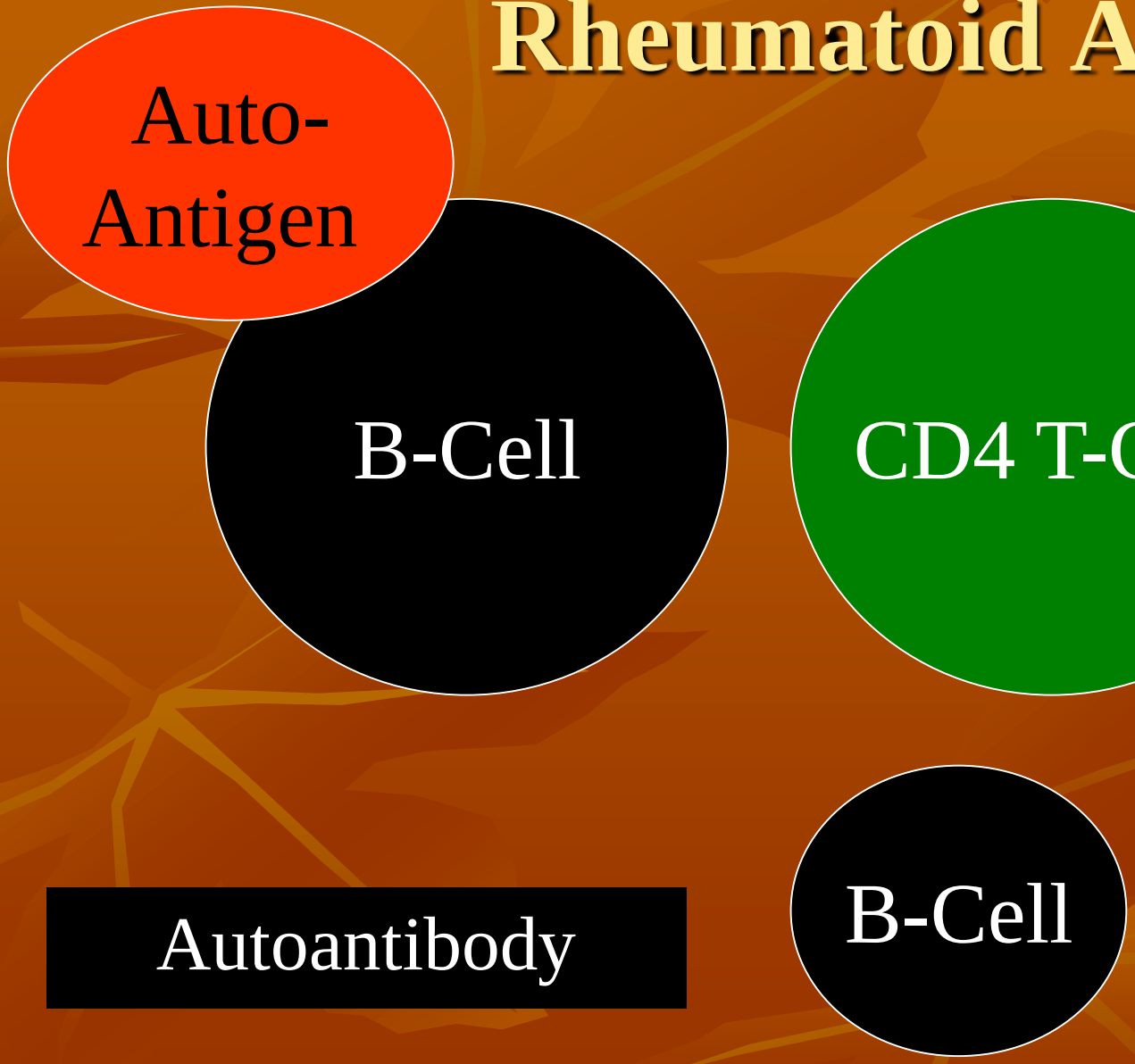
Rheumatoid Arthritis (RA)

- RA was thought to be ***T-Cell*** mediated
- Most widely accepted hypothesis:
  - Professional Antigen Presenting Cell encounters some “unknown” antigen
  - It presents this “unknown” antigen to a CD4 T-helper Cell
  - In a genetically predisposed individual, this starts an immune chain reaction
  - Immune system is confused and targets healthy tissue

B-Cell can serve role as Antigen Presenting Cell and Antibody Producing Cell

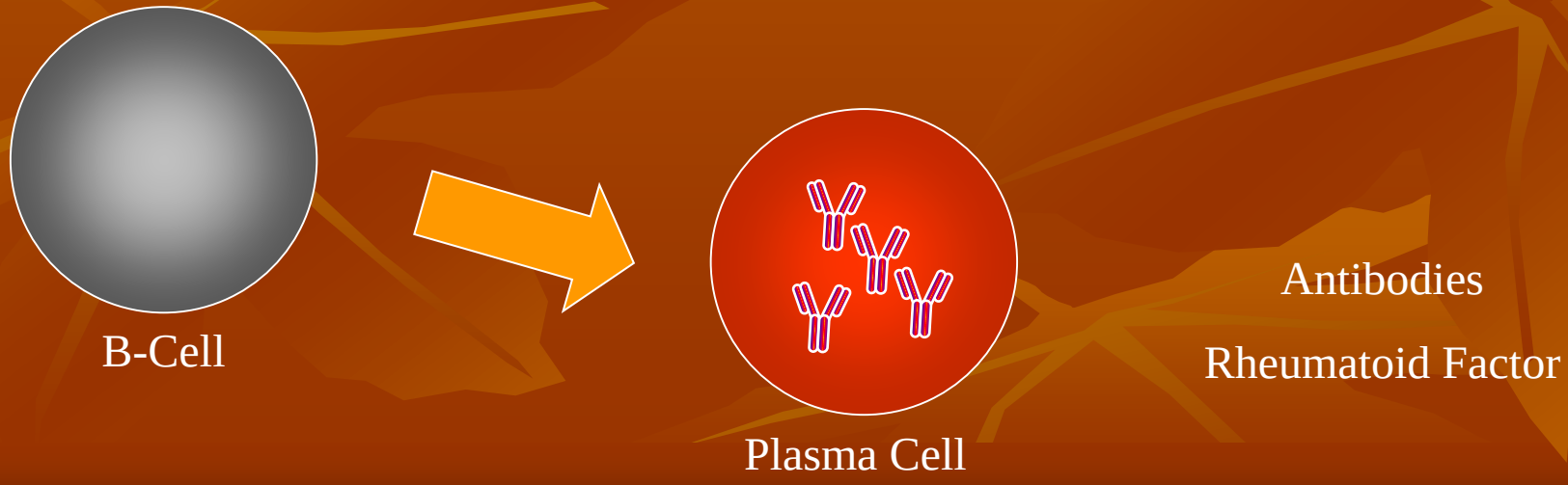


Rheumatoid Arthritis

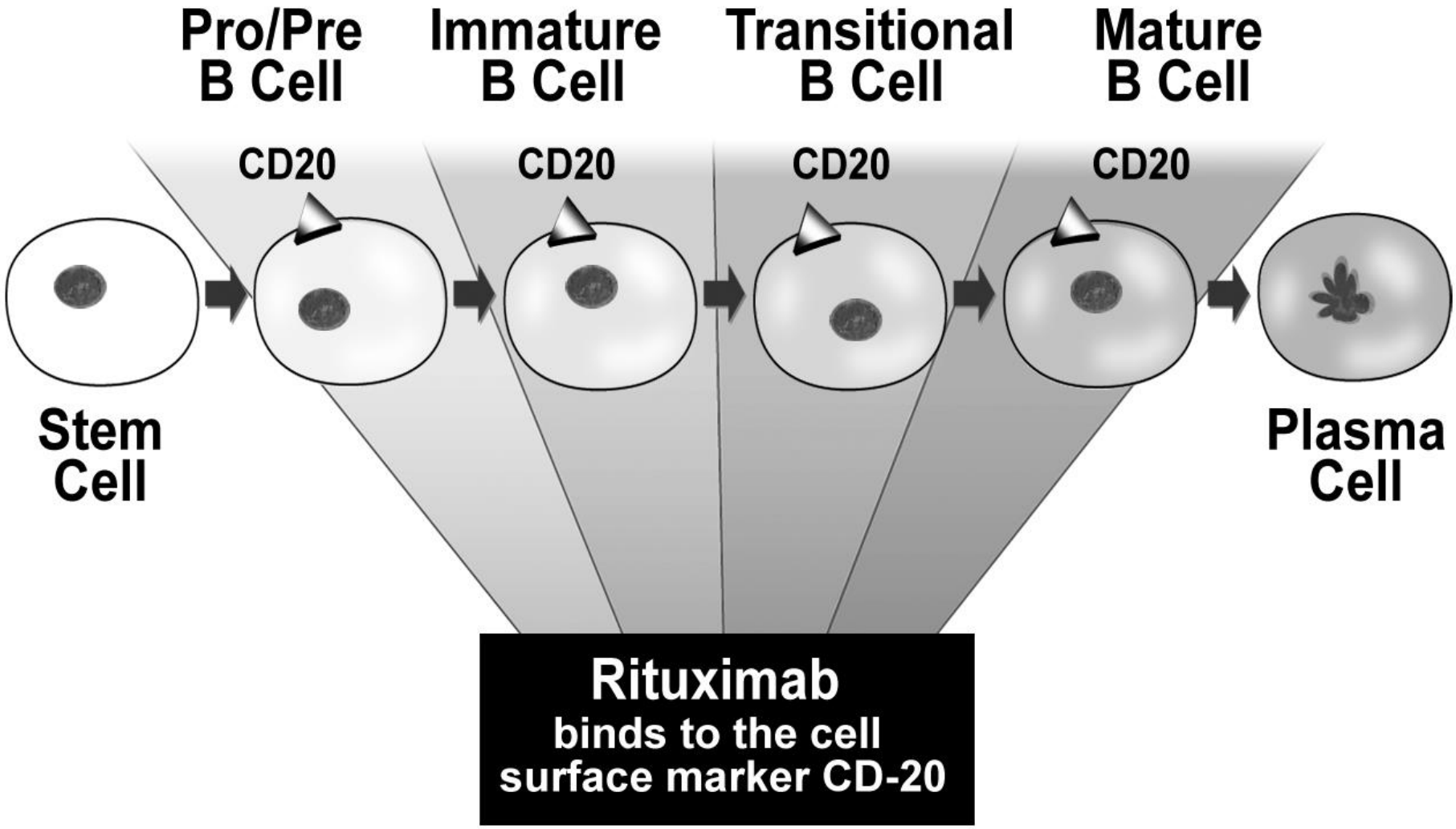


B-Cell Depletion Therapy in RA

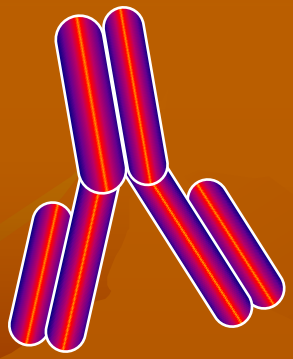
- How does B-Cell Depletion work?
  - B-Cells cannot act as antigen presenting cells to activate T-Cells
  - B-Cells cannot produce Rheumatoid Factor
  - B-Cells cannot release cytokines



Rituximab
Rituximab



Rituximab in RA



Rituximab: anti-CD-20

CD-20

B-Cell

Practical Aspects

- Side Effects
  - INFECTION
  - INFUSION REACTIONS
  - Other rare things – severe skin reactions, arrhythmia, drop in blood counts

ABATACEPT

Mechanism of Action

Abatacept is a costimulation modulator that inhibits the activation of T cells (see also Chapter 55). After a T cell has engaged an antigen-presenting cell (APC), a signal is produced by CD28 on the T cell that interacts with CD80 or CD86 on the APC, leading to T-cell activation. Abatacept (which contains the endogenous ligand CTLA-4) binds to CD80 and 86, thereby inhibiting the binding to CD28 and preventing the activation of T cells.

Pharmacokinetics

Abatacept is given as an intravenous infusion in three initial doses (day 0, week 2, and week 4), followed by monthly infusions. The dose is based on body weight, with patients weighing less than 60 kg receiving 500 mg, those 60–100 kg receiving 750 mg, and those more than 100 kg receiving 1000 mg. Dosing regimens in any adult group can be increased if needed. The terminal serum half-life is 13–16 days. Coadministration with methotrexate, NSAIDs, and corticosteroids does not influence abatacept clearance.

Indications

Abatacept can be used as monotherapy or in combination with other DMARDs in patients with moderate to severe rheumatoid arthritis who have had an inadequate response to other DMARDs. It reduces the clinical signs and symptoms of rheumatoid arthritis, including slowing of radiographic progression. It is also being tested in early rheumatoid arthritis.

Adverse Effects

There is a slightly increased risk of infection (as with other biologic DMARDs), predominantly of the upper respiratory tract. Concomitant use with TNF-α antagonists is not recommended due to the increased incidence of serious infection with this combination. Infusion-related reactions and hypersensitivity reactions, including anaphylaxis, have been reported but are rare. Anti-abatacept antibody formation is infrequent (< 5%) and has no effect on clinical outcomes. The incidence of malignancies is similar to placebo with the exception of a possible increase in lymphomas. The role of abatacept in this increase is unknown.

AZATHIOPRINE

Mechanism of Action

Azathioprine acts through its major metabolite, 6-thioguanine. 6-Thioguanine suppresses inosinic acid synthesis, B-cell and T-cell function, immunoglobulin production, and interleukin-2 secretion (see Chapter 55).

Pharmacokinetics

The metabolism of azathioprine is bimodal in humans, with rapid metabolizers clearing the drug four times faster than slow metabolizers. Production of 6-thioguanine is dependent on thiopurine methyltransferase (TPMT), and patients with low or absent TPMT activity (0.3% of the population) are at particularly high risk of myelosuppression by excess concentrations of the parent drug if dosage is not adjusted.

Indications

Azathioprine is approved for use in rheumatoid arthritis and is used at a dosage of 2 mg/kg/d. Controlled trials show efficacy in psoriatic arthritis, reactive arthritis, polymyositis, systemic lupus erythematosus, and Behçet's disease.

Adverse Effects

Azathioprine's toxicity includes bone marrow suppression, gastrointestinal disturbances, and some increase in infection risk. As noted in Chapter 55, lymphomas may be increased with azathioprine use. Rarely, fever, rash, and hepatotoxicity signal acute allergic reactions.

CHLOROQUINE & HYDROXYCHLOROQUINE

Mechanism of Action

Chloroquine and hydroxychloroquine are used mainly in malaria (see Chapter 52) and in the rheumatic diseases. The mechanism of the anti-inflammatory action of these drugs in rheumatic diseases is unclear. The following mechanisms have been proposed: suppression of T-lymphocyte responses to mitogens, decreased leukocyte chemotaxis, stabilization of lysosomal enzymes, inhibition of DNA and RNA synthesis, and the trapping of free radicals.

Pharmacokinetics

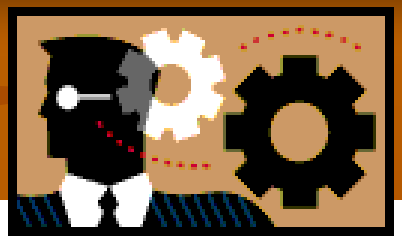
Antimalarials are rapidly absorbed and 50% protein-bound in the plasma. They are very extensively tissue-bound, particularly in melanin-containing tissues such as the eyes. The drugs are deaminated in the liver and have blood elimination half-lives of up to 45 days.

Indications

Antimalarials are approved for rheumatoid arthritis, but they are not considered very effective DMARDs. Dose-response and serum concentration-response relationships have been documented for hydroxychloroquine and dose-loading may increase rate of response. Although antimalarials improve symptoms, there is no evidence that these compounds alter bony damage in rheumatoid arthritis at their usual dosages (up to 6.4 mg/kg/d for hydroxychloroquine or 200 mg/d for chloroquine). It usually takes 3–6 months to obtain a response. Antimalarials are often used in the treatment of the skin manifestations, serositis, and joint pains of systemic lupus erythematosus, and they have been used in Sjögren's syndrome.

Adverse Effects

Although ocular toxicity (see Chapter 52) may occur at dosages greater than 250 mg/d for chloroquine and greater than 6.4 mg/kg/d for hydroxychloroquine, it rarely occurs at lower doses. Nevertheless, ophthalmologic monitoring every 6–12 months is advised. Other toxicities include dyspepsia, nausea, vomiting, abdominal pain, rashes, and nightmares. These drugs appear to be relatively safe in pregnancy.



CYCLOPHOSPHAMIDE

Mechanism of Action

Cyclophosphamide's major active metabolite is phosphoramide mustard, which cross-links DNA to prevent cell replication. It suppresses T-cell and B-cell function by 30–40%; T-cell suppression correlates with clinical response in the rheumatic diseases. Its pharmacokinetics and toxicities are discussed in Chapter 54.

Indications

Cyclophosphamide is active against rheumatoid arthritis when given orally at dosages of 2 mg/kg/d but not when given intravenously. It is used regularly to treat systemic lupus erythematosus, vasculitis, Wegener's granulomatosis, and other severe rheumatic diseases.

CYCLOSPORINE

Mechanism of Action

Through regulation of gene transcription, cyclosporine inhibits interleukin-1 and interleukin-2 receptor production and secondarily inhibits macrophage–T-cell interaction and T-cell responsiveness (see Chapter 55). T-cell-dependent B-cell function is also affected.

Pharmacokinetics

Cyclosporine absorption is incomplete and somewhat erratic, although a microemulsion formulation improves its consistency and provides 20–30% bioavailability. Grapefruit juice increases cyclosporine bioavailability by as much as 62%. Cyclosporine is metabolized by CYP3A and consequently is subject to a large number of drug interactions (see Chapters 55 and 66).

Indications

Cyclosporine is approved for use in rheumatoid arthritis and retards the appearance of new bony erosions. Its usual dosage is 3–5 mg/kg/d divided into two doses. Anecdotal reports suggest that it may be useful in systemic lupus erythematosus, polymyositis and dermatomyositis, Wegener's granulomatosis, and juvenile chronic arthritis.

LEFLUNOMIDE

Mechanism of Action

Leflunomide undergoes rapid conversion, both in the intestine and in the plasma, to its active metabolite, A77-1726. This metabolite inhibits dihydroorotate dehydrogenase, leading to a decrease in ribonucleotide synthesis and the arrest of stimulated cells in the G_1 phase of cell growth. Consequently, leflunomide inhibits T-cell proliferation and production of autoantibodies by B cells. Secondary effects include increases of interleukin-10 receptor mRNA, decreased interleukin-8 receptor type A mRNA, and decreased TNF-α–dependent nuclear factor kappa B (NF-κB) activation.

Pharmacokinetics

Leflunomide is completely absorbed and has a mean plasma half-life of 19 days. A77-1726, the active metabolite of leflunomide, is thought to have approximately the same half-life and is subject to enterohepatic recirculation. Cholestyramine can enhance leflunomide excretion and increases total clearance by approximately 50%.

Indications

Leflunomide is as effective as methotrexate in rheumatoid arthritis, including inhibition of bony damage. In one study, combined treatment with methotrexate and leflunomide resulted in a 46.2% ACR20 response compared with 19.5% in patients receiving methotrexate alone.

Adverse Effects

Diarrhea occurs in approximately 25% of patients given leflunomide, although only about 3–5% discontinue the drug because of this effect. Elevation in liver enzymes also occurs. Both effects can be reduced by decreasing the dose of leflunomide. Other adverse effects associated with leflunomide are mild alopecia, weight gain, and increased blood pressure. Leukopenia and thrombocytopenia occur rarely. This drug is contraindicated in pregnancy.

METHOTREXATE

Methotrexate is now considered the DMARD of first choice to treat rheumatoid arthritis and is used in 50–70% of patients. It is active in this condition at much lower doses than those needed in cancer chemotherapy (see Chapter 54).

Mechanism of Action

Methotrexate's principal mechanism of action at the low doses used in the rheumatic diseases probably relates to inhibition of aminoimidazolecarboxamide ribonucleotide (AICAR) transformylase and thymidylate synthetase, with secondary effects on polymorphonuclear chemotaxis. There is some effect on dihydrofolate reductase and this affects lymphocyte and macrophage function, but this is not its principal mechanism of action. Methotrexate has direct inhibitory effects on proliferation and stimulates apoptosis in immune-inflammatory cells. Additionally, inhibition of proinflammatory cytokines linked to rheumatoid synovitis has been shown, leading to decreased inflammation seen with rheumatoid arthritis.

Pharmacokinetics

The drug is approximately 70% absorbed after oral administration (see Chapter 54). It is metabolized to a less active hydroxylated metabolite, and both the parent compound and the metabolite are polyglutamated within cells, where they stay for prolonged periods. Methotrexate's serum half-life is usually only 6–9 hours, although it may be as long as 24 hours in some individuals. Methotrexate's concentration is increased in the presence of hydroxychloroquine, which can reduce the clearance or increase the tubular reabsorption of methotrexate. This drug is excreted principally in the urine, but up to 30% may be excreted in bile.

SULFASALAZINE

- **Mechanism of Action**
- Sulfasalazine is metabolized to sulfapyridine and 5-aminosalicylic acid, and it is thought that the sulfapyridine is probably the active moiety when treating rheumatoid arthritis (unlike inflammatory bowel disease, see Chapter 62). Some authorities believe that the parent compound,sulfasalazine, also has an effect.
- In treated arthritis patients, IgA and IgM rheumatoid factor production are decreased. Suppression of T-cell responses to concanavalin and inhibition of in vitro B-cell proliferation have also been documented.
- In vitro studies have shown that sulfasalazine or its metabolites inhibit the release of inflammatory cytokines, including those produced by monocytes or macrophages, eg, interleukins-1, -6, and -12, and TNF- . These findings suggest a possible mechanism for the clinical efficacy of sulfasalazine in rheumatoid arthritis.
- **Indications**
- Sulfasalazine is effective in rheumatoid arthritis and reduces radiologic disease progression. It has been used in juvenile chronic arthritis and in ankylosing spondylitis and its associated uveitis. The usual regimen is 2–3 g/d.
- **Adverse Effects**
- Approximately 30% of patients using sulfasalazine discontinue the drug because of toxicity. Common adverse effects include nausea, vomiting, headache, and rash. Hemolytic anemia and methemoglobinemia also occur, but rarely. Neutropenia occurs in 1–5% of patients, while thrombocytopenia is very rare.
- Pulmonary toxicity and positive double-stranded DNA are occasionally seen, but drug-induced lupus is rare. Reversible infertility occurs in men, but sulfasalazine does not affect fertility in women. The drug does not appear to be teratogenic.