Antirheumatic drugs

Rheumatic Arthritis (RA)
Disease Modifying Antirheumatic drugs (DMARDs)

- DMARDs are used in the treatment of rheumatic arthritis RA and have been shown to
  - slow the course of the disease,
  - induce remission
  - prevent further destruction of the joints and involved tissues.
- When a patient is diagnosed with RA, DMARDs should be started within 3 months to help stop the progression of the disease at the earlier stages.
- NSAIDs or corticosteroids may also be used for relief of symptoms if needed.
A. Choice of drug

- No one DMARD is efficacious and safe in every patient, and trials of several different drugs may be necessary.
- **Monotherapy** may be initiated with any of the DMARDs (methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine) for patients with low disease activity.
- combination DMARD therapy (usually *methotrexate based*) or use of anti-TNF drugs (adalimumab, certolizumab, etanercept, golimumab, and infliximab) may be needed for:
  - Patients with moderate to high disease activity or
  - Inadequate response to monotherapy.
- For patients with more established disease, use of other biologic therapies (for example, abatacept, rituximab) can be considered.
- **Most of these agents are contraindicated for use in pregnant women**
Methotrexate

• **Methotrexate** [meth-oh-TREX-ate] used alone or in combination therapy, has become a mainstay of treatment in patients with rheumatoid or psoriatic arthritis.

• *Methotrexate is a folic acid antagonist* that inhibits cytokine production and purine nucleotide biosynthesis, leading to immunosuppressive and anti-inflammatory effects.

• Response to *methotrexate occurs within 3 to 6 weeks of starting treatment; it* can also slow the appearance of new erosions within involved joints.

• The other DMARDs can be added to *methotrexate therapy if there is* partial or no response to maximum doses of methotrexate.

• *Doses of methotrexate required for RA treatment are much lower than those* needed in cancer chemotherapy and are given once a week, thereby minimizing adverse effects.
• The most common side effects observed after methotrexate treatment of RA are mucosal ulceration and nausea.

• Cytopenias (particularly depression of the WBC count), cirrhosis of the liver, and an acute pneumonia-like syndrome may occur with chronic administration.

• Taking leucovorin (folinic acid) once daily after methotrexate reduces the severity of adverse effects. Folic acid taken on off-days is widely used.

• Periodic liver enzyme tests, complete blood
Hydroxychloroquine

- *Hydroxychloroquine [hye-drox-ee-KLOR-oh-kwin] is used for early, mild RA, often combined with methotrexate.*
- *This agent is also used in* the treatment of lupus and malaria.
- Its mechanism of action in autoimmune disorders is unknown.
- Onset of effects takes 6 weeks to 6 months.
- *Hydroxychloroquine has less effects on the liver and immune system than other DMARDs; however, it may cause ocular toxicity, including irreversible retinal damage and corneal deposits.*
- It may also cause CNS disturbances, GI upset, and skin discoloration and eruptions.
Leflunomide

- **Leflunomide** [le-FLOO-no-mide] is an immunomodulatory agent that preferentially causes cell arrest of the autoimmune lymphocytes through its action on dihydroorotate dehydrogenase (DHODH).
- Activated proliferating lymphocytes require constant DNA synthesis to proliferate.
- Pyrimidines and purines are the building blocks of DNA, and DHODH is necessary for pyrimidine synthesis.
- After biotransformation, *leflunomide becomes a reversible inhibitor of DHODH*
- **Leflunomide is approved for the treatment of RA.**
- *It can* be used as monotherapy or in combination with *methotrexate.*
- *The* most common adverse effects are headache, diarrhea, and nausea.
- Other untoward effects are weight loss, allergic reactions, including a flu-like syndrome, skin rash, alopecia, and hypokalemia.
- It is not recommended in patients with liver disease, because of a risk of hepatotoxicity.
- Monitoring parameters include signs of infection, complete blood counts, and liver enzymes.
Site of action of leflunomide
BIOLOGIC THERAPIES IN RHEUMATOID ARTHRITIS

• IL-1 and TNF-α are proinflammatory cytokines involved in the pathogenesis of RA.

• When secreted by synovial macrophages, IL-1 and TNF-α stimulate synovial cells to proliferate and synthesize collagenase, thereby degrading cartilage, stimulating bone resorption, and inhibiting proteoglycan synthesis.

• The TNF-α inhibitors (adalimumab, certolizumab, etanercept, golimumab, and infliximab) have been shown to decrease signs and symptoms of RA, reduce progression of structural damage, and improve physical function.

• Clinical response can be seen within 2 weeks of therapy.

• As with DMARDs, the decision to continue or stop a biological agent can often be made within 3 months after initiation of therapy.
• If a patient has failed therapy with one TNF-α inhibitor, a trial with a different TNF-α inhibitor or a non-TNF biologic therapy (abatacept, rituximab, tocilizumab, tofacitinib) is appropriate.

• TNF-α inhibitors can be administered with any of the other drugs for RA, except for the non-TNF biologic therapies (due to increased risk of infection).

• Patients receiving TNF-α inhibitors are at increased risk for infections (tuberculosis and sepsis), fungal opportunistic infections, and pancytopenia.

• Live vaccinations should not be administered while on TNF-α inhibitor therapy.

• These agents should be used very 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-α inhibitors.
Mechanisms of infliximab
(1) Soluble TNF is neutralized. (2) Production of TNF is blocked. (3) TNF producing cells are eliminated.

Mechanism of tocilizumab
(1) Intracellular signal is blocked from the receptor on the cell surface. (2) Function of soluble IL-6 receptor/IL-6 complex is suppressed.
Adalimumab

- **Adalimumab** \[a-dal-AYE-mu-mab\] is a recombinant monoclonal antibody that binds to TNF-\(\alpha\), thereby interfering with endogenous TNF-\(\alpha\) activity by blocking its interaction 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, or increased risk of infections, such as urinary tract infections, upper respiratory tract infections, and sinusitis.
Certolizumab pegol

- **Certolizumab** [ser-toe-LIZ-oo-mab] is a unique TNF-α blocker that contains a Fab fragment of a humanized antibody and is a potent neutralizer of TNF-α biological actions.
- It is combined with polyethylene glycol (pegylated) and is administered every 2 weeks via subcutaneous injection.
- It has similar indications to adalimumab.
- *Adverse effects* are similar to other TNF-α inhibitors.
**Etanercept**

- **Etanercept** [ee-TAN-er-cept] is a genetically engineered, soluble, recombinant, fully human receptor fusion protein that binds to TNF-α, thereby blocking its interaction with cell surface TNF-α receptors.

- This agent is approved for use in patients with moderate to severe RA, either alone or in combination with methotrexate.

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

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

- **Etanercept is given** subcutaneously twice a week.

- The drug is generally well tolerated. As with all TNF-α inhibitors, it can increase the risk for infections, malignancy, and new or worsening heart failure.
Golimumab

- **Golimumab** [goe-LIM-ue-mab] neutralizes the biological activity of TNF-α 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 nonbiologic DMARDs.

- Golimumab may increase hepatic enzymes.

- Reactivation of hepatitis B may occur in chronic carriers.

- As with other TNF-α inhibitors, this drug may increase the risk of malignancies and serious infections.
Infliximab

- **Infliximab** [in-FLIX-i-mab] 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.**
- This agent is not indicated for monotherapy, as this leads to the development of anti-infliximab antibodies, resulting in reduced efficacy.
- Additional indications include plaque psoriasis, psoriatic arthritis, ulcerative colitis, ankylosing spondylitis, and Crohn disease.
- **Infliximab is administered as an IV infusion every 8 weeks. Infusion site reactions, such as fever, chills, pruritus, and urticaria, may occur.**
- Infections (for example, pneumonia, cellulitis, and activation of latent tuberculosis), leukopenia, and neutropenia have also been reported.
• **Abatacept (ORENCIA®)**

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

- **Abatacept** [a-BAT-ah-cept] *is a soluble recombinant fusion* protein that competes with CD28 for binding on CD80/CD86 protein, thereby preventing full T-cell activation.
Abatacept

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

• *Abatacept is administered* as an IV infusion every 4 weeks.

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

- **B lymphocytes** are derived from the bone marrow and are necessary for efficient immune response.
- In RA, however, B cells can perpetuate the inflammatory process in the synovium by:
  - 1) activating T lymphocytes.
  - 2) producing autoantibodies and rheumatoid factor
  - 3) producing proinflammatory cytokines, such as TNF-α and IL-1.

  **Rituximab** [ri-TUK-si-mab] is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes, resulting in B-cell depletion.
**Rituximab**

• 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.

• *Rituximab is administered as* an intravenous infusion every 16 to 24 weeks.

• To reduce the severity of infusion reactions, *methylprednisolone is administered 30 minutes* prior to each infusion.

• Infusion reactions (urticaria, hypotension, and angioedema) are the most common complaints with this agent and typically occur during the first infusion.
Anti-CD20: Mechanism of Action

- Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)
- Complement-dependent Cytotoxicity
- Apoptosis

Anti-CD20 antibody binds to CD20 on B cells, triggering FcγRIIIA and FcγRIII to activate complement (MAC) and trigger apoptosis.
Tocilizumab

- Tocilizumab [toe-si-LIZ-ue-mab] is a monoclonal antibody that inhibits the actions of IL-6 by blocking the IL-6 receptor.
- 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 [toe-fa-SYE-ti-nib]* is an oral inhibitor of Janus kinases indicated for the treatment of moderate to severe RA in patients who have had an inadequate response or intolerance to methotrexate.
Tofacitinib

- **Metabolism of tofacitinib** is mediated primarily by CYP3A4, and dosage adjustments may be required if the drug is taken with potent inhibitors or inducers of this isoenzyme.

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

- Likewise, lymphocyte and neutrophil counts should be checked prior to initiation of therapy and monitored during treatment.

- **Tofacitinib** treatment may also increase the risk for secondary malignancy, opportunistic infections, renal, or hepatic dysfunction.
Anakinra

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

• *Anakinra [an-a-KIN-ra] is an IL-1 receptor antagonist.*

• *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.