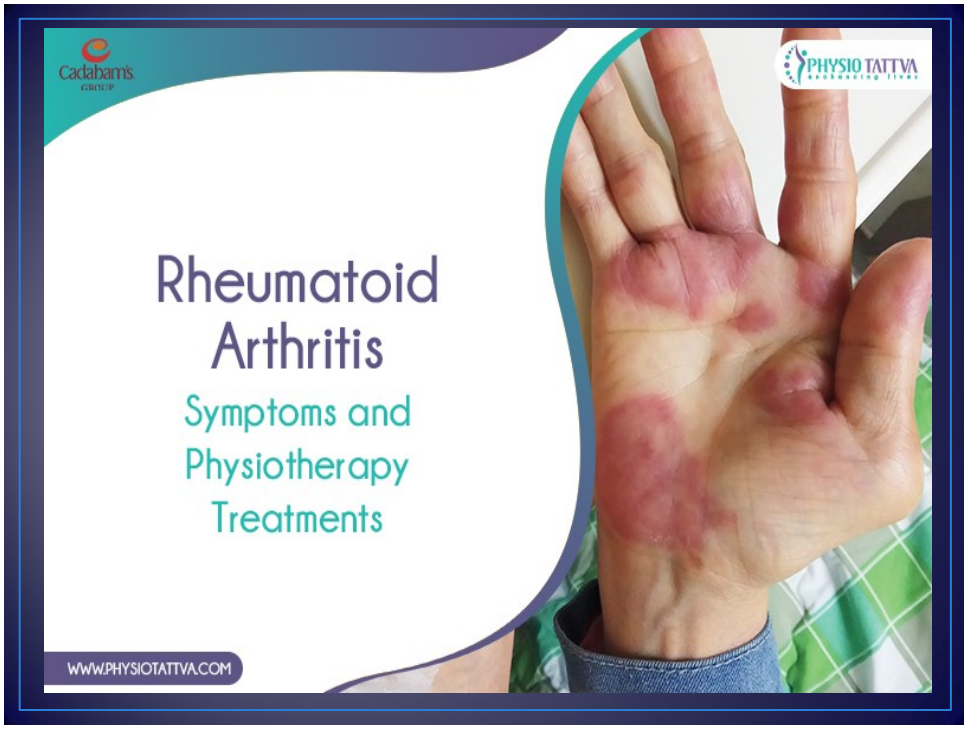
Pharmacology III

- Anti- inflammatory drugs.
- Traditional Disease-Modifying Antirheumatic Drugs
- Biologic Disease-Modifying Antirheumatic Drugs
- Drugs Used for the Treatment of Gout
- Drugs affecting bone metabolism
- Drugs For Diabetes
- Pitutary and thyroid hormones
- The adrenal hormones
- Estrogens and Androgens
- Cancer Chemotherapy



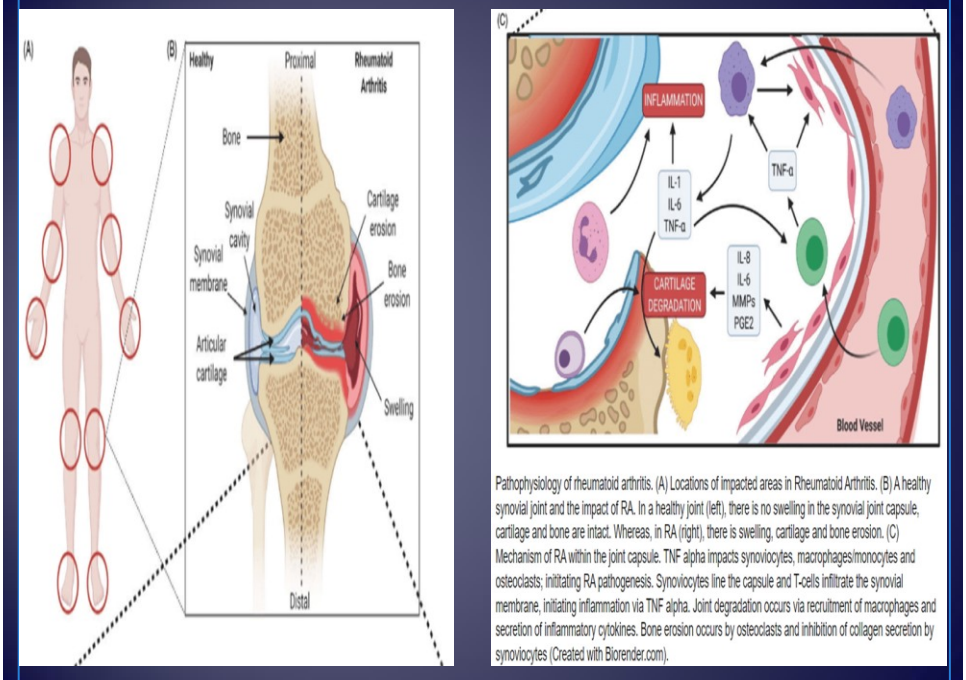
- Rheumatoid arthritis (RA) is an auto immune, chronic, systemic, inflammatory disease predominantly affecting joints, and periarticular (synovial) tissues.
- Autoantibodies to the Fc portion of IgG antibody are produced by B lymphocytes in the blood and synovial tissues in 80% of RA patients. High titers of serum RA factor (RF), typically of the IgM isotype, are associated with more severe joint disease with extra-articular manifestations.
- Other important antibodies are those directed against citrullinated peptide (ACPA) which seems to be more specific and sensitive marker.
- About 50%–80% of RA patients have RF or ACPA or both. Clinical diagnosis is confirmed by estimating ESR, autoantibody and radiographs. Antibodies are detected years before onset of disease.

- Common clinical signs and symptoms of RA are pain and/or joint swelling, morning stiffness at least for 1 h, fatigue, fever and weight loss. Its etiology is unknown, although the main risk factors include genetic factors and smoking. Infection as the initial trigger has been suspected. Current evidence indicates that RA is an autoimmune disease.

Pathophysiology

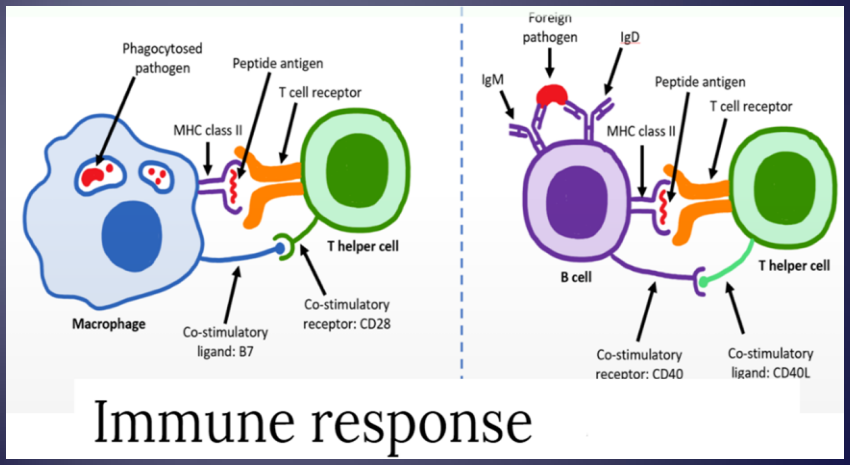
- RA is a clinical syndrome that comprises three basic interrelated pathological processes: inflammation, synovial proliferation, and joint tissue destruction.
- The focus of RA is the synovial lining. RA factor-containing immune complexes found in the joints activate the pathological process. The earliest lesion is vasculitis, an inflammation of small blood vessels. The inflammation causes edema of the synovium and infiltration with mononuclear cells, macrophages, lymphocytes and plasma cells.
- There is intense local production of IgG by the plasma cells. The activated macrophages, lymphocytes and fibroblasts produce a variety of cytokines that promote further synovial proliferation and inflammation.

- Tumor necrosis factor (TNF-alpha), produced by activated macrophage like synoviocytes, exerts powerful effects on the immune system, including induction of proinflammatory mediators.
- Synovial fluid in RA contains PGs (mainly PGE2), leukotriene B4 , TNF-alpha, interleukins and other cytokines. It is now believed that the monokines IL-1 and IL-6, and TNF-α are the central mediators of active rheumatoid process.
- Joint damage occurs early in the course of RA. Fibroblasts like synoviocytes invade the cartilage. Osteoclasts activation is considered to be a key event in bone destruction.



Pathophysiology of rheumatoid arthritis. (A) Locations of impacted areas in Rheumatoid Arthritis. (B) A healthy synovial joint and the impact of RA. In a healthy joint (left), there is no swelling in the synovial joint capsule, cartilage and bone are intact. Whereas, in RA (right), there is swelling, cartilage and bone erosion. (C) Mechanism of RA within the joint capsule. TNF alpha impacts synoviocytes, macrophages/monocytes and osteoclasts; initiating RA pathogenesis. Synoviocytes line the capsule and T-cells infiltrate the synovial membrane, initiating inflammation via TNF alpha. Joint degradation occurs via recruitment of macrophages and secretion of inflammatory cytokines. Bone erosion occurs by osteoclasts and inhibition of collagen secretion by synoviocytes (Created with Biorender.com).

The Normal Immune Response



Immune response

Traditional Disease-Modifying Antirheumatic Drugs (DMARDs)

- These include: (methotrexate, hydroxychloroquine, leflunomide, or sulfasalazine).
- They are used in the treatment of RA (rheumatoid arthritis), 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.
- **Choice of drug:** Mono-therapy 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.
- Combination therapies are both safe and efficacious, NSAIDs or glucocorticoids can also be used for their anti-inflammatory actions.

Methotrexate

- Methotrexate is a folic acid antagonist that inhibits cytokine production and purine nucleotide biosynthesis, leading to immunosuppressive and anti-inflammatory effects.
- Other traditional DMARDs, TNF inhibitors, or non-TNF biologic agents can be added to methotrexate if there is inadequate response to mono-therapy with this agent.
- Mainstay of treatment in patients with rheumatoid or psoriatic arthritis.
- Response to methotrexate occurs within 3 to 6 weeks of starting treatment. Doses of methotrexate required for this treatment are much lower than those needed in cancer chemotherapy and are given once a week, thereby minimizing adverse effects.

Methotrexate

- adverse effects: mucosal ulceration and nausea , Cytopenias (particularly depression of the WBC count), cirrhosis of the liver, and an acute pneumonia-like syndrome. Taking leucovorin once daily after methotrexate reduces the severity of the adverse effects.
- [Note: Supplementation with folic acid may improve tolerability of methotrexate and reduce GI and hepatic adverse effects.]
- Periodic liver function tests, complete blood counts, and monitoring for signs of infection are recommended. Methotrexate is contraindicated in pregnancy.

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

- Leflunomide is an immune-modulatory agent, 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.
- It not only reduces pain and inflammation associated with the disease but also appears to slow the progression of structural damage.
- 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.

- Common adverse effects include Headache, diarrhea, and nausea.
- Other effects are weight loss, allergic reactions, including a flu-like syndrome, skin rash, alopecia, and hypokalemia. The drug is not recommended in patients with liver disease as it can be hepatotoxic. Leflunomide is contraindicated in pregnancy. Monitoring parameters include signs of infection, complete blood count, electrolytes, and liver enzymes.

Sulfasalazine

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

Glucocorticoids

- Glucocorticoids are potent anti-inflammatory drugs that are commonly used in patients with RA to provide symptomatic relief and bridge the time until other DMARDs become effective.
- Glucocorticoids should always be used at the lowest dose and for the shortest duration possible to avoid adverse effects associated with long-term use.

Biologic Disease-Modifying Antirheumatic Drugs

- 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.
- Biologic DMARDs include the TNF-α inhibitors, as well as the non-TNF biologic agents (abatacept, rituximab, tocilizumab).

- The TNF-α inhibitors (adalimumab, certolizumab, 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.
- Clinical response can be seen within 2 weeks of therapy. TNF-α inhibitors 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-α inhibitors. Like TNF-α inhibitors, non-TNF biologics are generally used in RA after a patient has an inadequate response to traditional DMARDs.

- Patients receiving biologic DMARDs are at increased risk for infections, such as tuberculosis, fungal opportunistic infections, and sepsis.
- [Note: TNF-α inhibitors and non-TNF biologic agents should not be used together due to the risk of severe infections.]
- 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.

- **Adalimumab :**
- Adalimumab is a recombinant monoclonal antibody that binds to TNF-α and interferes with its activity by blocking interaction of TNF-α with cell surface receptors. **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 TNF-α. **It is combined with polyethylene glycol (pegylated) and is administered every 2 weeks via Sc injection.** Adverse effects are similar to other TNF-α inhibitors.

- **Etanercept :**
- Etanercept is a genetically engineered fusion protein that binds to TNF-α, thereby blocking its interaction with cell surface TNF-α receptors.
- **Etanercept is given subcutaneously once weekly and is generally well tolerated.**
- **Golimumab:**
- Golimumab neutralizes the biological activity of TNF-α by binding to it and blocking its interaction with cell surface receptors.
- **It is administered subcutaneously once a month in combination with methotrexate. Golimumab may increase hepatic enzymes.**

- **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.
- **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. Infliximab is administered as an IV infusion every 8 weeks. Infusion-related reactions, such as fever, chills, pruritus, and urticaria, may occur.

- **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.
- 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 co- stimulation modulator that competes with CD28 for binding on CD80/CD86 protein, thereby preventing full T cell activation and reducing the inflammatory response.**
- Abatacept is administered as an IV infusion every 4 weeks. Common adverse effects include infusion-related reactions, headache, upper respiratory infections, and nausea.

- **Rituximab:**

- In RA, B lymphocytes can perpetuate the inflammatory process in the syovium by 1) Activating T lymphocytes, 2) producing autoantibodies and rheumatoid factor, and 3) Producing proinflammatory cytokines, such as TNF-α 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 B-cell depletion. Rituximab is administered as an intravenous infusion every 16 to 24 weeks. To reduce infusion reactions, methylprednisolone, acetaminophen, and an antihistamine are administered prior to each infusion. Infusion reactions (urticaria, hypotension, and angioedema) are the most common complaints and typically occur during the first infusion.

- **Tocilizumab and sarilumab**

- Tocilizumab and sarilumab are recombinant monoclonal antibodies that bind to IL- 6 receptors and inhibit activity of the proinflammatory cytokine IL-6.
- Both tocilizumab and sarilumab are administered as a subcutaneous injection every 2 weeks.
- Tocilizumab may also be administered as an intravenous infusion every 4 weeks.
- Adverse reactions include • elevated liver function tests, • hyperlipidemia, • neutropenia, • hypertension, and • infusion-related and injection site reactions.

Other Drugs for Rheumatoid Arthritis

- Janus kinases are intracellular enzymes that modulate immune cell activity in response to the binding of inflammatory mediators to the cellular membrane.
- Tofacitinib is a synthetic small molecule that is an oral inhibitor of Janus kinases. It is indicated for the treatment of moderate to severe established RA in patients who have had an inadequate response or intolerance to methotrexate.
- 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 new primary malignancy and opportunistic infections.
- Due to long-term safety concerns, Tofacitinib is usually reserved for patients who have inadequate response or intolerance to other agents.
- [Note: Anakinra, azathioprine, cyclosporine, gold, and minocycline are other agents used infrequently in the treatment of RA due to their adverse effect profile or the availability of other agents with more proven efficacy.]


THANK
YOU