College of Pharmacy
Fourth year. Clinical Pharmacy

Rheumatologic Disorders

Rheumatoid Arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic, **progressive autoimmune condition** that primarily affects joints and the synovium but can **also have systemic manifestations**.

Pathophysiology

1-RA results from a combination of **genetic** susceptibility, **nongenetic** factors, and a **triggering event**. An **unknown infectious process is thought to be the primary trigger**.

2-**Antigen-presenting cells** process and present antigens to T cells; **activated T cells stimulate B cells to produce autoantibodies** .

3-**Antibodies to immunoglobulin G (IgG) are known as rheumatoid factor** (RF) and have a strong correlation to the pathogenesis and **poor prognosis of RA.**

4-B cells also produce **proinflammatory cytokines**, including tumor necrosis factor (**TNF**) and the interleukin (**IL**) system, which induce further enhance T-cell proliferation and differentiation, and encouraging cell migration.

5-**Overexpression of tumor suppressor gene p53** increased anticitrullinated protein antibodies (**ACPA**). ACPA positivity is associated with a **worse prognosis** in patients with RA.

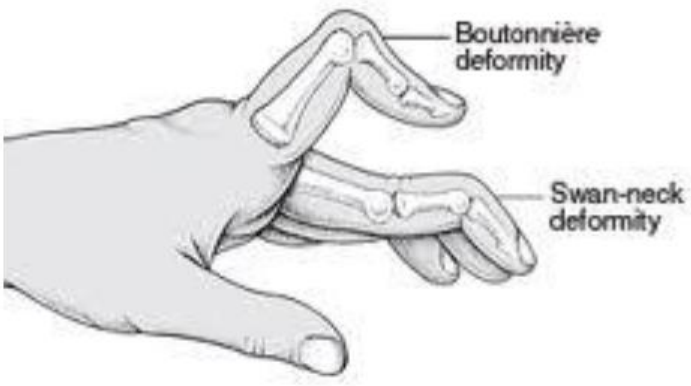
6-The inflamed, fibrotic synovium (**pannus**) **invades cartilage and bone around it**, promoting further destruction and dysregulation.

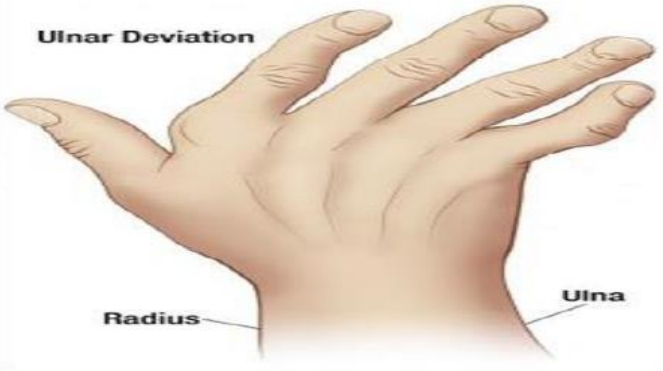
Clinical presentation

1-**Nonspecific prodromal symptoms** developing over weeks to months include fatigue, weakness, low-grade fever, anorexia, and joint pain.

2-**Stiffness and myalgias may precede development of synovitis**. Joint involvement tends to be **symmetric and affects small joints** of the hands, feet, wrists, and ankles; elbows, knees, shoulders, hips, cervical spine, and temporomandibular joints may also be affected.

3-**Joint stiffness is typically worse in the morning, usually exceeds 30 minutes, and may persist all day**. Tissue warm, and may be erythematous.





4-If **left untreated, long-term joint inflammation may lead to** bony erosions and **deformities of** joints (**swan neck deformity, boutonnière deformity, and ulnar deviation**).

5-**Extra-articular involvement may include** rheumatoid nodules, interstitial lung disease, pleural effusions, vasculitis, ocular manifestations, pericarditis, cardiac conduction abnormalities, bone marrow suppression, and lymphadenopathy.

6-RF is detected in 70%–80% of patients; **higher titers generally reflect a more severe disease course**. **ACPA antibodies generally predict a more aggressive disease course**.

7-Antinuclear antibodies (ANAs) are detected in 25% of patients with RA. **Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) indicate the presence of a nonspecific inflammatory process.**

8-**Normocytic anemia, thrombocytosis or thrombocytopenia, and leukopenia may also be present**.

Diagnosis

1-The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revised criteria for diagnosis of RA in 2010.

2-The criteria use a scoring system with a combined **score of 6 or more out of 10 indicating that the patient has definite RA.**

Treatment

Goals of Treatment: The ultimate goal is **to induce complete remission or low disease activity**. Additional goals are to reduce inflammation and symptoms, maintain ability to function in daily activities, slow destructive joint changes, and delay disability.

Nonpharmacologic Therapy

1-**Patient education** about the disease and medications (e.g., potential adverse effects, self-administration of injectable agents) is important.

2-**Physical therapy** can reduce pain and inflammation while preserving joint function. Exercise and physical activity (including **aerobic activity** and **muscle-strengthening exercises)** can improve disease outcomes.

3-**Assistive devices and orthoses** such as braces and supports are useful to improve pain and function. **Occupational therapy** can provide benefits such as appropriate footwear and splinting.

4-**Weight loss** can help decrease stress on joints. **Surgical options** (e.g., joint replacements) are reserved for patients with more severe disease with significant cartilage loss.

Pharmacologic Therapy

General Approach

1-Therapies to **treat RA and slow disease progression** include conventional and biologic disease-modifying antirheumatic drugs (DMARDs) and the small-molecule oral Janus-kinase (JAK) inhibitors.

- **Conventional DMARDs** include methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine.
- **Biologic DMARDs** include **TNF inhibitors** (adalimumab, certolizumab, etanercept, golimumab, and infliximab) and **non-TNF biologics** (abatacept, sarilumab, tocilizumab, rituximab, and anakinra).
- **JAK inhibitors** include baricitinib, tofacitinib, and upadacitinib.

2-Current RA treatment guidelines recommend **initiating conventional DMARDs irrespective of disease activity once a diagnosis is established**.

3-**The preferred conventional DMARD is methotrexate unless a contraindication exists**.

4-For patients with early RA (<6 months duration) and **low disease activity, DMARD monotherapy is recommended**. **Double or triple DMARD therapy is recommended for moderate or high disease activity.**

5-**A biologic agent can be used as monotherapy or with conventional DMARD(s) in patients with moderate or high disease activity**.

6-**A JAK inhibitor is an alternate** option if disease activity remains moderate or high with combination conventional DMARDs.

7-**If disease activity remains moderate or high** despite conventional DMARDs or biologics, **a low-dose glucocorticoid** (prednisone ≤10 mg/day or equivalent) can be added for the shortest duration necessary.

8-**If patients achieve remission, DMARDs and biologic agents can be tapered**, but patients should remain on DMARD therapy at some dosage level.

9-Dual biologic therapy should be avoided due to the risk of infection associated with immunosuppression.

10-**Because DMARDs can take weeks to months to take effect**, NSAIDs, **glucocorticoids**, and other **analgesics** (eg, acetaminophen) can be used to provide more rapid symptomatic relief ("**bridge therapy**").

11-**NSAIDs do not slow disease progression**, and g**lucocorticoids can have serious side effects**, making **both drug classes less desirable for long-term use**.

Conventional DMARDs

1-Methotrexate inhibits dihydrofolate reductase. Injectable (subcutaneous [**SC**], intramuscular [**IM**]) methotrexate **has higher bioavailability than oral methotrexate** and thus provides superior clinical efficacy; it is typically **better tolerated** with **less potential to cause gastrointestinal (GI) side effects as well.**

2-Oral methotrexate doses >15 mg weekly may not have significant added clinical benefit; **changing to SC methotrexate may increase bioavailability and clinical benefit in this situation.**

3-Clinical benefit can be seen 3–6 weeks after starting therapy. Methotrexate has numerous adverse effects; **concomitant folic acid 1–5 mg/day may reduce some adverse effects without loss of efficacy.**

4-**Methotrexate is teratogenic**, and patients should use contraception and discontinue the drug if conception is planned.

5-**Leflunomide ***** efficacy for RA is similar to that of methotrexate.

6-Sulfasalazine ***** use is limited by GI adverse effects**.

7-**Hydroxychloroquine *****: Its main advantage is that **it does not require frequent, routine laboratory monitoring because it is not generally associated with infection risk or hepatic, renal, or blood cell abnormalities.** GI side effects can sometimes be mitigated by taking the **medication with food or splitting the dose** into two doses. **Periodic ophthalmologic examinations are necessary** for early detection of **irreversible retinal toxicity**.

*****: Can be used alone or in combination with DMARDs**

Biologic DMARDs (given i.v or s.c)

1-Biologic agents are **genetically engineered** . They are categorized as **either TNF inhibitors or non-TNF biologics**. They may be effective **when conventional DMARDs fail** to achieve adequate disease control but are considerably **more expensive**.

2-**Biologic DMARDs are associated with an increased risk of infection** due to immunosuppressive effects. A **tuberculin skin test** or interferon gamma release assay (IGRA) blood test should be obtained before starting a biologic **to detect and treat latent or active tuberculosis.**

3-Patients should also be **screened for hepatitis B** before starting biologic therapy because of the risk for reactivation.

4-Biologics can be used in **combination with conventional DMARDs**, but **multiple biologics should not be used** concomitantly due to additive immunosuppressive effects.

5-In general, if **patients are switched from one biologic to another, the new agent should be initiated when the patient is due for a dose of the previous biologic**.

6-Because of immunosuppressive effects, **patients taking biologics should notify their providers if they are being treated for an infection or plan to undergo major surgery**. Treatment may need to be held u**ntil appropriate postsurgical healing and/or resolution of infection** can be confirmed. **Live vaccines should not be given** to patients taking biologic agents.

7-**Biosimilars are biologic products that have been verified to have no clinically meaningful differences compared to an FDA-approved reference biologic product**. These agents can increase access to RA treatment because **their costs are lower** than the originator products. However, concerns that limit their use include **lack of regulatory guidelines about switching** from the original biologic product to the biosimilar and **uncertainty about extrapolation of indications** for biosimilars from the original biologic product.

A-TNF-α Inhibitors (Adalimumab, Certolizumab, Etanercept, Golimumab, Infliximab)

1-TNF inhibitors block the proinflammatory cytokine TNF-α. **It may take several weeks for clinical benefit to be noted and up to 3 months to achieve full clinical benefit**. These agents are typically used when disease activity remains moderate or high despite conventional DMARD therapy.

2-TNF inhibitors are **more expensive** than conventional DMARDs.

3-They **should not be used in patients with moderate-to-severe heart failure** (New York Heart Association [NYHA] class III/IV) because new-onset and worsening heart failure have been reported.

4-These agents increase **the risk of serious infection and malignancies** (eg, lymphoma, skin cancers), and new-onset or exacerbation of demyelinating disorders such as multiple sclerosis has been observed.

5-**To prevent formation of an antibody response to Infliximab, methotrexate must be given orally** in doses used to treat RA for as long as the patient continues infliximab. **Premedication with an antihistamine**, **acetaminophen**, and/or a **glucocorticoid** can decrease development of **infusion-related reactions**.

B-Costimulation Modulator

Abatacept *** inhibits the activation of T cells. Abatacept is indicated for moderate-to-severe RA .

C-IL-6 Receptor Antagonists

1-**Sarilumab ***** is indicated for treatment of patients with moderate-to-severe RA who have had an incomplete response or intolerance to one or more DMARDs.

2-**Tocilizumab ***** can be used for patients with moderate-to-severe RA who have had an incomplete response to one or more DMARDs.

D-Anti-CD20 Monoclonal Antibody

1-**Rituximab** is a monoclonal antibody that binds the CD20 antigen on the surface of B cells. Binding of rituximab to B cells results in nearly complete depletion of peripheral B cells, with a gradual recovery over several months.

2-Rituximab can be initiated in patients **with moderate to-severe RA who have had an incomplete response to one or more TNF inhibitors**. **Methotrexate should be given concurrently** in the usual doses for RA to achieve optimal outcomes.

3-**Methylprednisolone** 100 mg IV is recommended 30 minutes before each infusion as well as **acetaminophen** and an **antihistamine** to reduce the incidence and severity of **infusion reactions.**

E-IL-1 Receptor Antagonist

1-**Anakinra***** is an IL-1 receptor antagonist; **it is less effective than other biologics**, is used **infrequently**, and is not included in the current ACR treatment recommendations.

2-However, it can be used in patients with moderate-to-severe RA who have failed one or more DMARDs.

Janus-Kinase Inhibitors

1-Baricitinib, tofacitinib, and upadacitinib are **oral**, small-molecule, **nonbiologic** JAK inhibitors.

2-**Baricitinib ***** is FDA approved for adults with moderately to severely active RA who have had an inadequate response to one or more TNF inhibitors.

3-**Tofacitinib*** and upadacitinib ***** have FDA approval for treatment of adults with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate.

4-**JAK inhibitors should not be given concomitantly with biologic**. Labeling for all JAK inhibitors includes black-box warnings about serious infections, lymphomas, and other malignancies. **Live vaccinations should not be given during treatment**.

5-Patients should be **tested and treated for latent tuberculosis** before starting therapy.

Nonsteroidal Anti-inflammatory Drugs

1-NSAIDs possess both analgesic and anti-inflammatory properties and reduce stiffness, but **they do not slow disease progression or prevent bony erosions or joint deformity** and should not be used as monotherapy for RA treatment.

2-They have a more rapid onset of action than DMARDs and may be beneficial to "**bridge**" **patients while DMARDs take effect**.

*****: Can be used alone or in combination with DMARDs**

Glucocorticoids

1-Glucocorticoids have anti-inflammatory and immunosuppressive properties; although they have been shown to slow RA progression, **glucocorticoids should not be used as monotherapy for RA due to the potential for serious, long-term adverse effects**.

2-They should be used at the **lowest effective dose for the shortest period of time**. According to the ACR, short-term glucocorticoid therapy is **defined as <3 months**, and low-dose glucocorticoid is defined as **prednisone ≤10 mg/day (or equivalent).**

3-Similar to NSAIDs, oral glucocorticoids (eg, prednisone, methylprednisolone) can be used to **"bridge" patients while DMARDs take effect**. They can also be used **as adjuncts** to DMARDs at the lowest dose possible in patients with refractory disease.

4-**High-dose, short-term bursts can** be used as needed **for acute flares of RA symptoms**, **followed by tapering** to the lowest effective dose to control symptoms or until discontinued over several days.

5-**The IM route may be useful in nonadherent patients**. **Depot forms** (triamcinolone and methylprednisolone) **provide 2–6 weeks of symptom control**. **Onset of effect may be delayed for several days**.

6-The **depot effect provides a physiologic taper**, avoiding hypothalamic–pituitary axis suppression.

7-**Intra-articular injections may be useful when only a few joints are involved**. Injections should **not be repeated more often than every 3 months** because of the potential for accelerated loss of joint cartilage.

Evaluation of therapeutic outcomes

1-**Assess disease activity at baseline and at each follow-up visit to evaluate therapeutic response**.

2-**Perform a physical examination at each visit** to objectively evaluate the number of swollen and tender joints, joint mobility, and presence of deformity.

3-Several assessment tools are available to measure RA disease activity, such as the Clinical Disease Activity Index (**CDAI**), Disease Activity Score (**DAS28**), Patient Activity Scale (**PAS**), Routine Assessment of Patient Index Data 3 (**RAPID**-3), and Simplified Disease Activity Index (**SDAI**).

4-**Laboratory monitoring** of acute phase reactants such as **CRP** and **ESR** can be useful in assessing inflammation.

5-**Obtain plain radiographs** of the hands, wrists, and forefeet **at baseline and every 2 years** in patients with low disease activity or in remission. Imaging may be needed **more frequently in patients with moderate or high disease activity**. **Drug therapy should be modified** if patients have radiographic changes suggestive of disease progression.

6-It is important to monitor and assess for **clinical and laboratory adverse effects** of the medications used to treat RA which may include [**complete blood count** (CBC) with differential to detect hematological toxicity, **SCr** to detect renal toxicity, liver function tests (**LFTs**): (**ALT**, **AST**) to detect hepatic toxicity]and **ophthalmologic examination** (for patient taking hydroxychloroquine) to detect ocular toxicity.

Reference

Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 11th Edition. 2021.