

Rheumatoid Arthritis

BY

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Rheumatoid arthritis

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

Pathophysiology

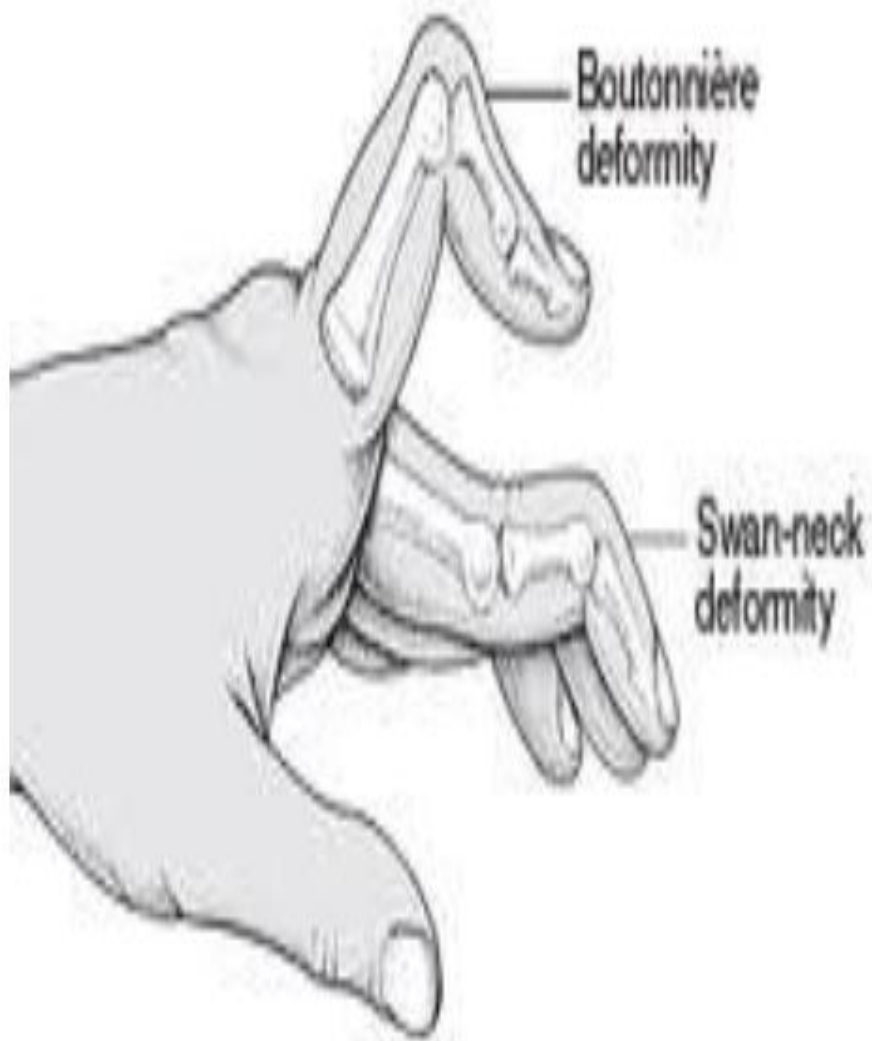
- RA results from a combination of **genetic** susceptibility, **nongenetic** factors, and a **triggering event**. An **unknown infectious process** is thought to be the **primary trigger**.
- **Antigen-presenting cells** process and present antigens to T cells; **activated T cells stimulate B cells to produce autoantibodies** that form **large complexes** that deposit throughout the body.
- **Antibodies to immunoglobulin G (IgG)** are known as **rheumatoid factor (RF)** and have a strong correlation to the pathogenesis and **poor prognosis of RA**.

- 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.
- **Overexpression of tumor suppressor gene p53** increased anticitrullinated protein antibodies (**ACPA**). ACPA positivity is associated with a **worse prognosis** in patients with RA.
- **Migration** of lymphocytes, macrophages, and mononuclear cells into the synovium and synovial cavity **increases synovial mass, causing hypertrophy and angiogenesis**. As the vessels develop, cytokines stimulate further migration of cells into the synovium, causing inflammation.

- The inflamed, fibrotic synovium (**pannus**) **invades cartilage and bone around it**, promoting further destruction and dysregulation.
- **Chronic inflammation** in vascular endothelial and visceral, cutaneous, and pleural tissues leads to complications including **vasculitis, fibrosis, and anemia**.

Clinical presentation

- **Nonspecific prodromal symptoms** include fatigue, weakness, low-grade fever, anorexia, and joint pain.
- **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.
- **Joint stiffness is typically worse in the morning, usually exceeds 30 minutes, and may persist all day.** Tissue warm, and may be erythematous.
- **If left untreated, long-term joint inflammation may lead to bony erosions and deformities of joints**



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

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

Diagnosis

- The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revised criteria for diagnosis of RA in 2010.
- The criteria use a scoring system with a combined **score of 6 or more out of 10** indicating that the patient has definite RA.

The Importance of Biomarkers: 2010 ACR/EULAR RA Classification Criteria

40% of the total possible score relies on blood test results

Swollen/Tender Joints (0-5)

- 0 = 1 large joint
- 1 = 2-10 large joints
- 2 = 1-3 small joints
- 3 = 4-10 small joints
- 5 = > 10 joints (≥ small joint)

Serology (0-3)

- 0 = Negative RF and ACPA
- 2 = Low positive RF or ACPA
- 3 = High positive RF or ACPA

Symptom Duration (0-1)

- 0 = < 6 wk
- 1 = ≥ 6 wk

Acute Phase Reactants (0-1)

- 0 = Normal CRP and normal ESR
- 1 = Abnormal CRP or abnormal ESR

Score of ≥ 6 indicates "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
 - 2-Physical therapy
 - 3-Assistive devices and orthoses ,Occupational therapy can provide benefits such as appropriate footwear and splinting.
 - 4- **Weight loss**

Pharmacologic Therapy

- **General Approach**
- Therapies to **treat RA and slow disease progression** can be achieved by
- **1- Conventional DMARDs** include methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine.
- **2- Biologic DMARDs** include **TNF inhibitors** (adalimumab, certolizumab, etanercept, golimumab, and infliximab) and **non-TNF biologics** (abatacept, sarilumab, tocilizumab, rituximab, and anakinra).
- **3-JAK inhibitors** include baricitinib, tofacitinib, and upadacitinib.

Guidelines for RA

- Current RA treatment guidelines recommend **initiating conventional DMARDs irrespective of disease activity once a diagnosis is established.**
- **The preferred conventional DMARD is methotrexate unless a contraindication exists**

For patients with early RA (<6 months duration)

- 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.**
- **A biologic agent can be used as monotherapy or with conventional DMARD(s) in patients with moderate or high disease activity.**
- **A JAK inhibitor is an alternate option if disease activity remains moderate or high with combination conventional DMARDs.**

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

For patients with established RA (**duration ≥ 6 months**)

- For patients with established RA (**duration ≥ 6 months**), **DMARD monotherapy is recommended despite disease activity.**
- **Combination** conventional DMARDs, a biologic DMARD, or a JAK inhibitor can be used **if disease activity remains** moderate or high after an adequate trial with DMARD monotherapy.

- In patients taking **TNF inhibitor monotherapy** with moderate or high disease activity, **one or two conventional DMARDs can be added to the TNF inhibitor**. A non-TNF biologic can be used in place of a TNF inhibitor if disease activity remains moderate or high on a TNF inhibitor and is recommended over a JAK inhibitor.
- Therapy can be **switched to another non-TNF biologic** if the first non-TNF agent cannot adequately control disease activity. **A non-TNF biologic can also be started** if separate courses of two different TNF inhibitors have not adequately controlled disease activity.
- **A JAK inhibitor can be initiated if disease activity persists despite multiple TNF inhibitors in patients for whom non-TNF biologics are not an option. Dual biologic therapy should be avoided** due to the risk of infection associated with immunosuppression.

- A **glucocorticoid** can be added if disease flares occur or disease activity is inadequately controlled despite DMARD, TNF inhibitor, or non-TNF biologic therapy.
- **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”).**
- **NSAIDs do not slow disease progression, and glucocorticoids can have serious side effects, making both drug classes less desirable for long-term use.**

1- Conventional DMARDs

- 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.**
- 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.**

- 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.**
- **Methotrexate is teratogenic**, and patients should use contraception and discontinue the drug if conception is planned. Methotrexate is contraindicated in pregnant and nursing women, chronic liver disease, immunodeficiency, and preexisting hematologic disorders (eg, leukopenia, thrombocytopenia).

- **Leflunomide** efficacy for RA is similar to that of methotrexate.
- Sulfasalazine **use is limited by GI adverse effects.**
- **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**

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

- 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
- **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**.

- Patients should also be **screened for hepatitis B** before starting biologic therapy because of the risk for reactivation.
- Biologics can be used in **combination with conventional DMARDs**, but **multiple biologics should not be used** concomitantly due to additive immunosuppressive effects.
- In general, if **patients are switched from one biologic to another**.

- **. Live vaccines should not be given** to patients taking biologic agents.
- 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)

- 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.
- TNF inhibitors are **more expensive** than conventional DMARDs. Selection of a particular TNF inhibitor depends on cost and patient preference for route and frequency of administration.

- **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.
- 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.
- **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**
- **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.

3-Janus-Kinase Inhibitors

- 1-Baricitinib, tofacitinib, and upadacitinib are **oral**, small-molecule, **nonbiologic** JAK inhibitors.
- **Baricitinib** is FDA approved for adults with moderately to severely active RA who have had an inadequate response to one or more TNF inhibitors.
- **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.
- **AK inhibitors should not be given concomitantly with biologic.**
- Patients should be **tested and treated for latent tuberculosis** before starting therapy

4-Nonsteroidal Anti-inflammatory Drugs

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

5-Glucocorticoids

- 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.**
- 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)**.
- 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.

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

- **Assess disease activity at baseline and at each follow-up visit to evaluate therapeutic response.** Clinical signs of improvement include reduction in joint pain, swelling, and tenderness; less morning stiffness; reduced fatigue; and improved ability to perform activities of daily living.
- **Perform a physical examination at each visit** to objectively evaluate the number of swollen and tender joints, joint mobility, and presence of deformity.

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

- 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