Rheumatoid Arthritis

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EPIDEMIOLOGY

- Arthritis refers to more than 100 different joint diseases causing swelling, pain and damage to joints and connective tissue.

- RA is the most common chronic inflammatory arthritis and is characterized by potentially deforming polyarthritis and a wide spectrum of extra-articular manifestations resulting from abnormal systemic immune response.

- Prevalence: 0.5-1%
- Women > men (2-3 times)
- Prevalence increases with age

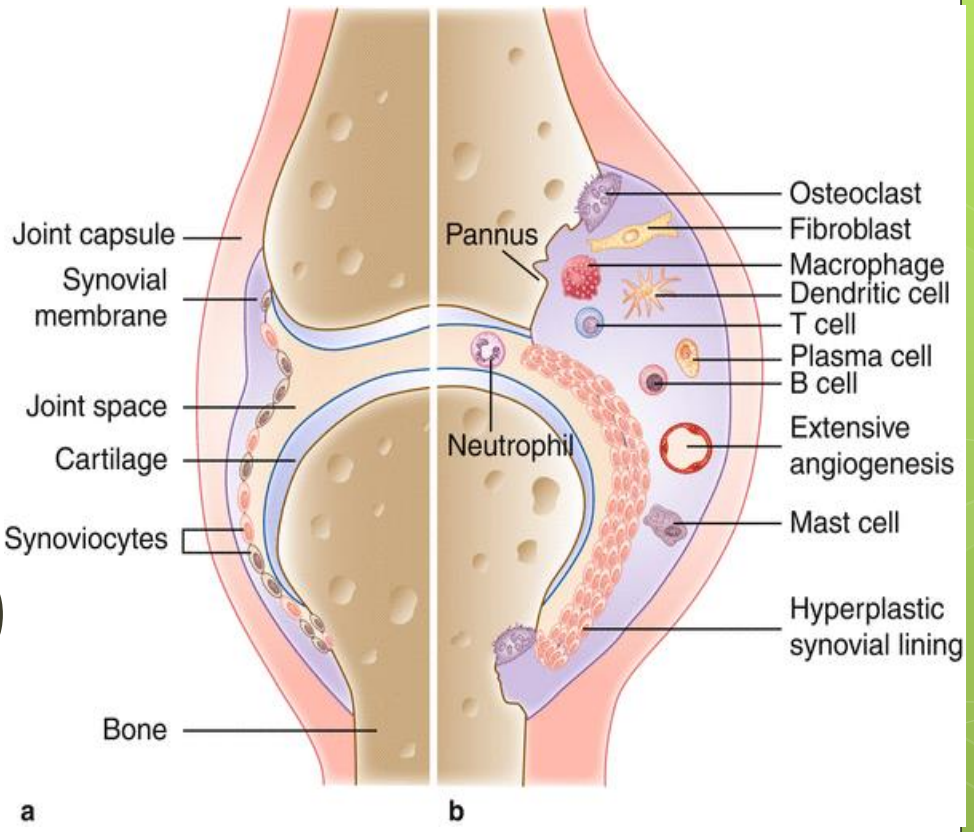
ETIOLOGY

- Exact etiology is unknown.
- ✓ Autoimmune diseases,
- ✓ Genetic susceptibility (50-60%),
- ✓ Environmental influences,
- ✓ Effects of advancing age on somatic changes in the musculoskeletal and immune system

- Cigarette smoking ➲ ↑ RF and anti-CCP
- Female sex hormones
- ✓ Peak incidence occurs at the 5th decade, Estrogen is known to stimulate the immune system
- Diets (fish, olive oil ➲ ↓ RA)

PATHOPHYSIOLOGY

- Persistent inflammation of the synovial lining ➲ joint destruction
- This normally thin membrane proliferates and transforms into the synovial pannus.
- The pannus, a highly erosive enzyme-laden inflammatory exudate, invades articular cartilage (leading to narrowing of joint spaces) erodes bone (resulting in osteoporosis), and destroys periarticular structures (ligaments, tendons), resulting in joint deformities



Clinical Presentation

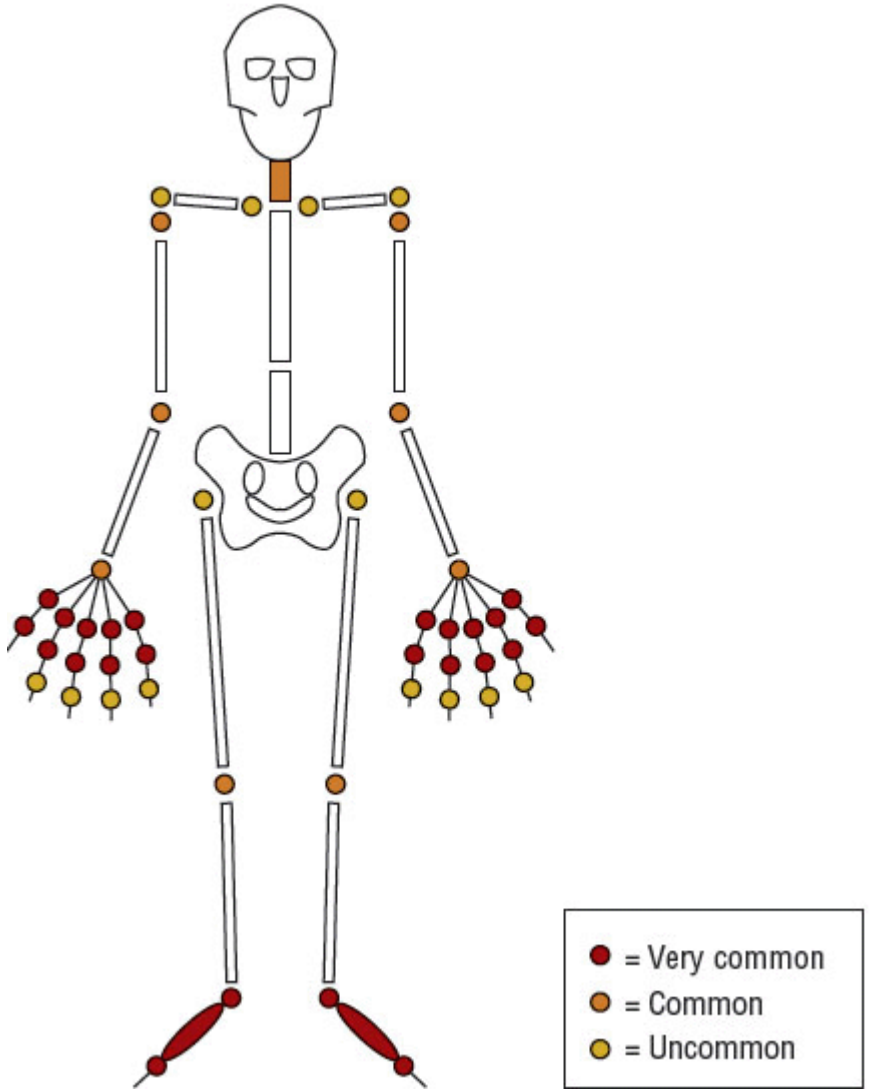
- More than 50% of RA cases have slow onset of symptoms (weeks-months),
- Up to 15% have acute onset (several days)

- Onset of symptoms may be either articular or systemic, including nonspecific complaints such as fatigue, weakness, muscle pains, weight loss, and low-grade fever.

- Joint involvement is characterized by soft tissue swelling and warmth, decreased range-of motion (ROM), and sometimes muscle atrophy around affected joints.

Clinical Presentation

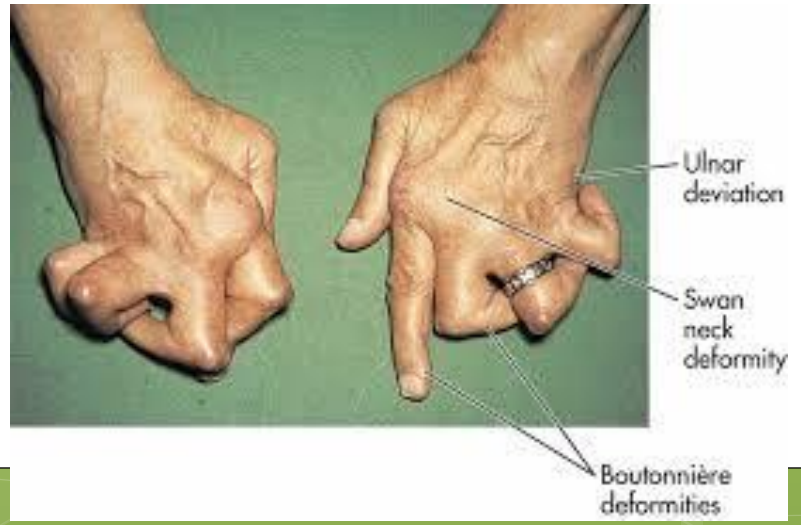
- Pain and stiffness in multiple joints
- Symmetrical involving wrists, proximal interphalangeal joints, and metacarpophalangeal joints
- The peripheral joints of the **hands**, **wrists**, and **feet** are usually involved first.
- Prolonged morning stiffness on awakening lasting **at least 30-45 minutes**, but it can be present all day with decreasing intensity after arising.



Clinical Presentation

- Progressive disease is characterized by irreversible joint deformities, such as ulnar deviation of the fingers.

- Patients with more aggressive disease (multiple joint involvement, positive RF) have a greater than 70% probability of developing joint damage or erosions within 2 years of disease onset.



Diagnosis

- Because no single chemical or laboratory finding is specific for the disease, the diagnosis of RA is based on **multiple clinical criteria.**
- RA criteria in the new classification system include quantifying joint involvement and symptom duration as well as detecting presence of autoantibodies and acute-phase reactants.

Criteria for Diagnosis of Rheumatoid Arthritis

Criteria	Score[a]
Joint Involvement	
1 large joint[b]	0
2–10 large joints	1
1–3 small joints[c]	2
4–10 small joints	3
>10 small joints	5
Serology[d] (≥1 result needed)	
Negative RF and negative anti-CCP	0
Low-positive RF or low-positive anti-CCP	2
High-positive RF or high-positive anti-CCP	3
Acute-Phase Reactants	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of symptoms	
<6 weeks	0
≥6 weeks	1

score of ≥6/10 needed to classify patient as having definite RA.

Diagnosis

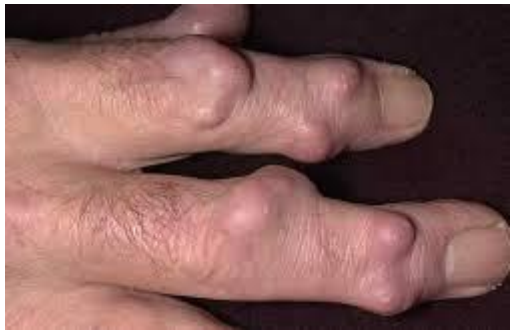
- **RF**, an IgM or IgG autoantibody, is found in 75-80% of patients with RA.
- It may also present in up to 5% of healthy individuals and in patients with diseases other than RA (immune complex formation or with hypergammaglobulinemia (e.g., chronic infections, lymphoproliferative and hepatic diseases, SLE, and Sjogren's syndrome).
- Citrullinated proteins and **anti-CCP antibodies** are abundant in inflamed RA synovium.
- Anti-CCP antibodies can be detected in 50-60% of early RA patients, and the specificity of anti-CCP is very high at 90-95%.

A positive anti- CCP antibody test is highly specific for RA, predictive of the development of RA, is a marker for an erosive disease course, and in combination with positive RF also correlates with 99.5% specificity for RA.

EXTRA-ARTICULAR MANIFESTATIONS

- Rheumatoid nodules (15-20%)
- Pleuropulmonary manifestations : pulmonary nodules, fibrosis, and pleuritis; interstitial pneumonitis and arteritis of the pulmonary vasculature

- Vasculitis (infrequent)
- Skin ulceration, peripheral neuropathy, and arteritis of organs
- Sjögren syndrome



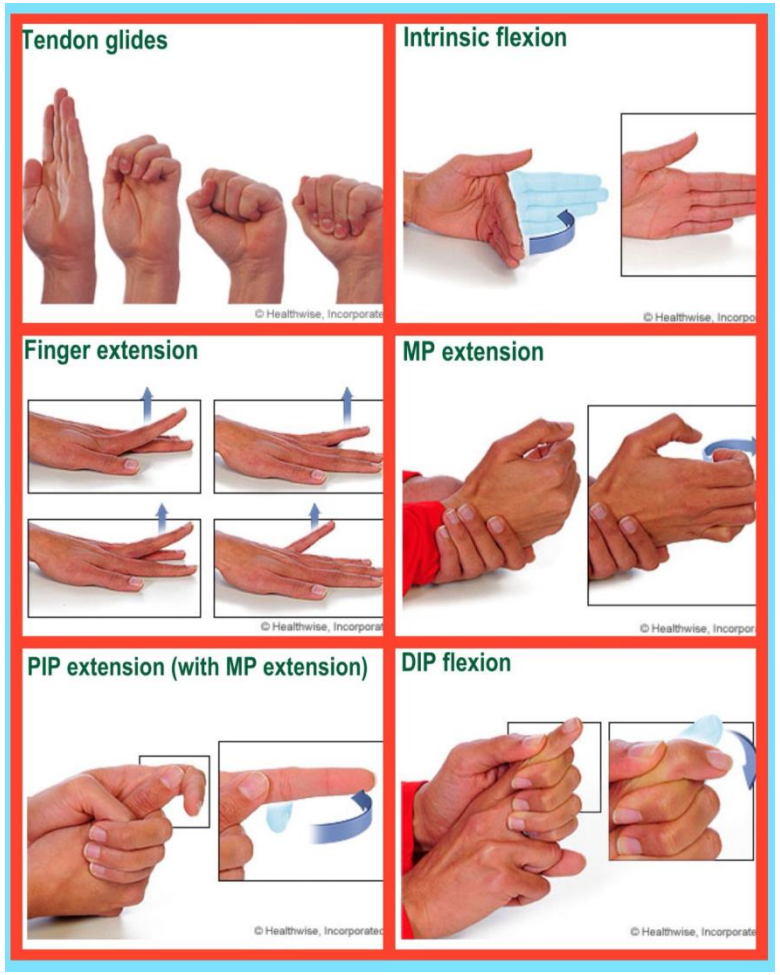
Treatment

- **Goals:**
- ✓ maintenance or improvement of symptoms (e.g., joint pain and swelling),
- ✓ preserve joint function,
- ✓ prevent deformity,
- ✓ improve quality of life,
- ✓ delay disability

- Early initiation of pharmacologic therapy starting at the point of diagnosis is critical to quality RA care.
- Other supportive interventions include rest, exercise and physical therapy, occupational therapy, and emotional support.

Nonpharmacologic therapy

- Systemic and articular rest (achieved by splinting the affected joints)
- Restful and adequate sleep
- ✓ daytime rest periods should be limited to 30-60 minutes each as prolonged rest can also induce rapid losses in strength and endurance.
- Passive ROM exercises
- Regular aerobic exercises (cycling, swimming, or walking)



Pharmacologic therapy

- **NSAIDs** ➲ rapid anti-inflammatory & analgesic effects
- **DMARDs** ➲ prevent or slow joint destruction & alter long-term disease course
- **Corticosteroids**

- DMARDs ➲ should be initiated in all patients as soon as they are diagnosed

- **Specific choice of treatment is individualized based on:**

⊙ joint function,
⊙ patient age,
⊙ occupation,
⊙ responsibilities,
⊙ results of previous therapy
⊙ degree of disease activity,
⊙ sex,
⊙ family,
⊙ drug costs,

DMARDs

- Synthetic chemical compounds (sDMARDs)
  - ✓ **conventional sDMARDs (csDMARDs):** HCQ, sulfasalazine, MTX, leflunomide
  - ✓ **targeted sDMARDs (tsDMARD):** tofacitinib
- Biologic agents (bDMARDs)

csDMARDs alone or in combination, are considered as initial therapy for most patients and in the absence of contraindication, **MTX is the treatment of choice** because of its strong efficacy and favorable safety profile.

DMARDs

- **csDMARDs**: AZA, gold, and D-penicillamine are rarely used because of **slow onset of action** and **toxicity profile**.
- **Tofacitinib** ➲ moderate-to-severe disease who have failed treatment with or are intolerant to MTX.
- **bDMARDs** target the physiologic proinflammatory and joint damaging effects of inflammatory mediators, including TNF-a, IL-1, IL-6, T cell, and B cells.

bDMARDs

- **TNF-a inhibitors** (adalimumab, certolizumab pegol, etanercept, infliximab)
- **IL-1 receptor antagonist** (anakinra),
- **Anti-B cell therapy** (rituximab),
- **IL-6 receptor antagonist** (tocilizumab),
- **T cell modulator** (abatacept)

The bDMARDs are typically reserved for patients who fail to achieve an adequate response with csDMARD monotherapy.

Corticosteroids

- Potent anti-inflammatory agents that slow the progression of joint damage.
- **Short-term oral therapy** may be reserved as bridge therapy in early RA with **moderate-to-high disease** activity while awaiting onset of DMARD activity, brief periods of active disease, or with therapy failure.
- Local intra-articular injections may be used for isolated joints experiencing disease flares.

Corticosteroids

- Oral corticosteroids seem to slow the rate of disease progression and have been shown to reduce radiographic changes for 1-2 years.

- Use of corticosteroids in combination with DMARD therapy appears to improve clinical outcomes (signs and symptoms, functionality, radiologic damage) for patients with RA above the benefit of a DMARD used alone.

Corticosteroids

- Long-term use of corticosteroids, however, is associated with many serious adverse effects (e.g., osteoporosis, weight gain, diabetes, cataract formation, adrenal suppression, HTN, infections, and impaired wound healing).
- As a result, oral corticosteroid dosing should be limited to daily doses of ≤10 mg of prednisone (or equivalent) and should be administered for as short a time as possible.
- Frequent corticosteroid injections for an extended period have the potential to accelerate bone and cartilage deterioration; therefore, **the same joint should not be injected more than once every 3 months**.

Intra-Articular Corticosteroids

- Intra-articular corticosteroid injections are safe and effective for pain relief in patients with RA.
- This strategy is most sensible when flaring occurs in one or a few joints.
- Systemic side effects are minimal when compared with oral corticosteroid therapy. Although onset of action is virtually immediate, effects are often short-lived.

NSAIDs

- Short-term pain and inflammation control but do not alter disease course.
- Side effects: GI intolerance, nephrotoxicity, and increased risk of bleeding and cardiovascular events.

NSAID use should be judicious and reserved only as an adjunct to DMARD therapy

NSAIDs

- Although NSAIDs differ in chemical structure, they generally have similar:

- ✓ **pharmacologic properties** (e.g., antipyresis, analgesia, anti-inflammatory activity, and inhibition of PG synthesis),
- ✓ **mechanisms of action** (i.e., inhibition of COX activity),
- ✓ **pharmacokinetic properties** (e.g., ↑ PB and extensively metabolized to renally cleared inactive metabolites),
- ✓ **side effect profile**

Choice of particular NSAID has traditionally been based on **cost**, **duration of action**, and **patient preference** because of interpatient variability in response.

NSAIDs

- **There is no NSAID of choice for treatment of RA.**
- There is no significant difference among the NSAIDs in efficacy, and it is difficult to predict a given patient's response to a particular agent.
- A 1-2-week trial of any NSAID at a moderate-to-high dose on a scheduled basis (i.e., not as needed) is the best method of determining anti-inflammatory efficacy.
- The analgesic and antipyretic effects are relatively prompt in onset and can be achieved with single and low doses.

CV risks with NSAIDs

- Although aspirin at high doses is just as effective as other NSAIDs, it is seldom used today because of well-documented GI toxicity and the availability of other safer and more convenient NSAIDs.
- Several NSAIDs increase the risk of MI, with diclofenac, meloxicam, and indomethacin showing the highest risk of thrombosis, although **celecoxib** and **ibuprofen** at **high doses** also carry **relatively high cardiovascular risk**.
- **Naproxen appears to have the best cardiovascular safety profile.**

CNS risks with NSAIDs

- Indomethacin penetrates the BBB better than any other NSAID, achieving levels in the CSF of up to 50% of serum levels.
- As a result, the incidence of CNS side effects of indomethacin such as dizziness often precludes the use of optimal anti-inflammatory doses, particularly in the elderly.
- If the first agent chosen is ineffective or not well tolerated ➲ other NSAIDs can be tried

GI risks with NSAIDs

- **Longer-acting NSAIDs** such as piroxicam and ketorolac ➲ ↑ peptic ulcer disease and GI bleeding
- Other NSAIDs, depending on their **COX-2 selectivity**, have varying **GI toxicity** profiles with naproxen conferring moderate risk and ibuprofen lower risk.
- The selective COX-2 inhibitor celecoxib, at least with short-term use, is associated with a 20% lower risk of GI bleeding than traditional NSAIDs.

GI risks with NSAIDs

- **H2 receptor antagonists** ➲ significantly reduce dyspepsia
- Also, routine use of H2-receptor antagonists is associated with tachyphylaxis ➲ not recommended for routine use in asymptomatic patients receiving NSAIDs
- **PPIs** ➲ relieve dyspepsia better than H2-receptor antagonists and prevent the development of NSAID-induced gastroduodenal ulcers.

GI risks with NSAIDs

- Routine concomitant antiulcer prophylactic therapy is not warranted for all patients taking NSAIDs; rather the risk for GI ulcer development must be assessed to determine the need for preventive measures.

- **Established risk factors for NSAID-induced GI bleeding:**

❶ advanced age (>65 years),

❷ history of ulcers (a history of complicated ulcers, particularly recent)

❸ concurrent use of other drugs (e.g., corticosteroids, aspirin and anticoagulants),

❹ high-dose NSAID therapy

High risk
Moderate risk
low risk

GI risks with NSAIDs

- Helicobacter pylori infection increases the risk of peptic ulcers in individuals taking NSAIDs.

- Therefore, H. pylori testing, and treatment if positive, should be considered for all patients prior to starting chronic NSAID therapy.

NSAIDs & Kidney

- Mild fluid retention 5% of NSAID users
- NSAID induced kidney disease < 1% of patients

- NSAID therapy should be avoided, if possible, in patients with preexisting HF, kidney disease, or cirrhosis.

- Inhibition of COX by NSAIDs within the kidney reduces PG concentrations and unopposed vasoconstriction ➲ ↓urine output, ↑ BUN /Cr, and fluid is retained

NSAIDs & Kidney

- Patients at high risk for NSAID-induced renal disease, should have their serum creatinine levels checked regularly (e.g., weekly) for several weeks after initiation of NSAID therapy because renal insufficiency more commonly occurs early in the course of therapy rather than later.

- NSAID-induced nephrotic syndrome and allergic interstitial nephritis occur, on average, about 6.6 months and 15 days after NSAID initiation, respectively.

Medical

DMARDs

means

disease-modifying antirheumatic drugs

by acronymsandslang.com

csDMARDs

- With rare exception, every patient should receive csDMARD therapy soon after diagnosis to minimize loss of joint integrity, function, and risk of CVD related to RA.
- csDMARDs➲ 🡻 joint inflammation, reduce or prevent joint damage, maintain joint function and integrity, and ultimately reduce health care costs and allow patients to remain productive.
- The onset of action of most csDMARDs is slow over 3-6 months; however, SSZ, MTX, and LEF can be beneficial within 1-2 months.

csDMARDs

- Several factors must be considered when selecting a csDMARD including:
- ✓ convenience of administration,
- ✓ monitoring requirements,
- ✓ medication and monitoring costs,
- ✓ time to therapeutic onset,
- ✓ frequency and severity of adverse reactions

- MTX, a folate antimetabolite with immunosuppressive and anti-inflammatory properties, remains the mainstay first-line DMARD because of its **relatively rapid onset of action** and **excellent history of efficacy and safety**.

MTX

- Gold standard ➲ high response rate, mild side effect profile, low cost, and long sustained efficacy ± glucocorticoids, other csDMARDs, and bDMARDs.
- MTX ➲ 🡻 in CV morbidity and mortality in patients with RA.
- Optimization of MTX therapy also involves **appropriate dose titration**, **adequate trial duration**, and **folate supplementation**.
- Regardless of disease duration, ACR recommends that in the setting of low, moderate, or high disease activity, a trial of MTX as monotherapy may be started initially, with success predicted in 25-50% of individuals within 1 year.

csDMARDs

- LEF and SSZ are recommended if a contraindication to MTX is present, or if intolerance to MTX occurs.
- The primary metabolite of **LEF**, M1, is responsible for nearly all of its pharmacologic activity.
- Although the exact mechanism of M1 is not completely understood, it is known that M1 inhibits dihydro-orotate dehydrogenase, an enzyme in cell mitochondria responsible for catalyzing an important step in de novo pyrimidine synthesis; this is believed to be its main mechanism of action.

csDMARDs

- **SSZ** appears to induce **anti-inflammatory** effects through one of its active metabolites, **mesalamine**, which is believed to inhibit both COX and lipooxygenase.
- **HCQ** as **monotherapy** or in **combination** may be used for **relatively mild** cases of RA.
- HCQ ➲ inhibition of migration of neutrophils and eosinophils, histamine and serotonin blockade, or inhibition of PG synthesis.

Older csDMARDs such as AZA, CSA, minocycline, and gold are no longer recommended because of the superior risk–benefit ratio of other csDMARDs, bDMARDs, and tofacitinib.

DMARDs

- Moderate or high disease activity unresponsive to csDMARD monotherapy, ➲ csDMARD **combination** therapy/ **addition of a bDMARD** (either TNF inhibitor or non-TNF bDMARD)

- The addition of tofacitinib may also be considered for patients with established RA and moderate-to-high disease activity.

- csDMARD + MTX (MTX, SSZ, and HCQ) ➲ moderate or high disease activity with poor prognostic features (i.e., functional limitation, extra-articular disease, positive RF or anti-CCP, and bony erosions).

Methotrexate

- MTX is recommended as initial DMARD therapy for all patients with RA.

- MTX is ideal because it has a rapid onset (usually 1–2 months before a plateau of effectiveness), a high efficacy rate at managing symptoms and slowing disease progression, low toxicity, and a long history of successful use.

- Tab 2.5 mg
- Inj 5, 50, 500, 1000 mg

Dosing

- Initial dose of **7.5 mg/week**, usually in a single weekly dose or 2.5 mg BD for 3 doses for patients who are unable to tolerate adverse effects, particularly hepatotoxicity.
- No response in 1-2 months ➲ ↑ to **15 mg/week** (or 5 mg every 12 hours for 3 doses) for at least 12 additional weeks.
- No response ➲ ↑ to **the maximum of 25 mg/week**
- (b) the dose can be administered as a SC or IM injection to address BA concerns,
- (c) the same dose can be continued for a longer time,
- (d) another DMARD can be added to MTX or MTX can be substituted.

SC MTX seems to be more effective than oral MTX and not associated with a higher incidence of adverse effects.

Adverse Effects

- low-dose MTX ➲ Nausea and other GI distress, malaise, dizziness, **mucositis**, and **mild alopecia**
- **More serious**, but less common➲ myelosuppression, pneumonitis, and hepatic fibrosis and cirrhosis.
- **A CBC, LFTs, and a Scr** ➲ baseline, monthly for the first 6 months of therapy, and then every 4-8 weeks during MTX therapy.

Renal dysfunction can result in accumulation of MTX and higher risk of myelosuppression.

Adverse Effects

- Interstitial pneumonitis, occurring in <1% of patients, has no known risk factors for development, although it may be more common in patients with a history of lung disease.
- Interstitial pneumonitis can occur at any time during therapy and at any MTX dosage.
- **A baseline CXR is recommended within the year before MTX initiation.**
- If the patient is found to have preexisting lung disease, MTX treatment should be reconsidered because further pulmonary damage could be devastating to the patient.

Adverse Effects

- MTX-induced liver disease is rare:

⊙↑ age,
⊙ obesity,
⊙ ethanol consumption
⊙ long duration of therapy,
⊙ DM
⊙ history of HBV, HCV

↑ the risk of hepatotoxicity

- If LFT > to 3 times the baseline value or if the liver enzyme serum concentrations remain elevated for sustained periods during therapy ➲ MTX should be withheld

☑ Avoid alcohol and be instructed to report symptoms of jaundice or dark urine to their primary care provider.

MTX and Folate or Folinic Acid

- Folate supplementation ➲ ↓ **GI disturbances**, **mucositis** (mouth or GI ulcerations), and **LFT elevations**.

- The current consensus and evidence-based recommendation is >5 mg folic acid daily.
- Although daily doses of folic acid as low as 1 mg are associated with protection against liver toxicity, GI disturbances are best prevented at doses above 5 mg daily.

- **Folinic acid ➲ ↓ GI and hepatotoxicity**,
- doses >5 mg/week ➲ worsening of arthritis symptoms, consistent with the fact that MTX is a folate antagonist, and folic acid supplementation could adversely impact efficacy.

MTX-Related Pulmonary Disorders

- Pneumonitis, a rare, is characterized by a **nonproductive cough**, **malaise**, and **fever**, **progressing to severe dyspnea**.

- **Risk factors:**

⊙ older age (over 60 years),
⊙ low albumin,
⊙ previous use of DMARDs,
⊙ diabetes

- After discontinuation of MTX, pulmonary function improves.

- Corticosteroids can accelerate improvement in pulmonary symptoms associated with pneumonitis.

MTX Interactions

- NSAIDs ➲ ↑ MTX serum concentrations & toxicity
- **Trimethoprim** ➲ ↑ MTX-induced BMS
- MTX + LEF ➲ ↑ major liver damage, including fatalities ➲ this combination should be avoided.
- **Inorganic acids** in cola drinks ➲ delay MTX elimination ➲ ↑ risk of toxicity (renal) ➲ cola drinks should be avoided with MTX therapy.
- Salicylates, probenecid, penicillin, and ciprofloxacin ➲interact with MTX (Because MTX is protein bound and renally excreted)

Leflunomide: Place in Therapy

- LEF, an oral csDMARD, seems to be similar in efficacy to MTX.
- The onset of benefit (as early as 4 weeks)
- LEF is a reasonable consideration as a replacement for MTX-intolerant patients, along with bDMARDs.

Dosing and Monitoring

- Tab 10, 20, 100 mg
- The active metabolite of LEF, M1, is responsible for virtually all the pharmacologic activity of LEF.
- T ½ M1 metabolite ≈ 2 weeks

- LD: 100 mg orally once daily for 3 days to reduce time to steady state.
- MD: 20 mg once daily ➲ If not tolerated, ⬇ dose to 10 mg once daily

Monitoring for Adverse Effects

- Diarrhea (20%–30%), rash (10%), alopecia (10%–17%), and reversible liver enzyme elevations >3 times the ULN (2%–4%)
- Routine laboratory testing includes a **baseline ALT** followed by **monthly** ALT testing for several months.
- Because of the risk of liver toxicity and the need for activation by the liver to the M1 active metabolite, LEF is not recommended in patients with preexisting liver disease, including HBV & HCV.

Monitoring for Adverse Effects

- Guidelines for managing potential hepatotoxicity include:
- ✓ **dosage reduction** from 20 to 10 mg/day if ALT increases >2 times the ULN.

- If ALT elevations remain steady between 2 and 3 times the ULN and treatment continuation is desired, a liver biopsy is recommended.

- If ALT elevations are persistently > 3 times the ULN despite dosage reduction and cholestyramine administration to enhance elimination ➲ drug should be discontinued and another course of cholestyramine elimination therapy should be given.

Enhancement of Elimination with Cholestyramine

- LEF (pregnancy category X) has not been tested in pregnant women, but it greatly increases the risk of fetal death or teratogenicity in animals receiving as little as 1% of human equivalent doses.

- After discontinuation of therapy, however, up to 2 years may be needed to elapse before plasma M1 metabolite levels of LEF are undetectable.

- **Cholestyramine is recommended for all women who discontinue LEF and who are hoping to become pregnant**.

Sulfasalazine

- The onset of SSZ effect is generally more rapid than that of HCQ, usually providing benefits within 2-3 months.
- Overall, SSZ adverse effects are relatively mild, although SSZ is considered to be slightly more toxic than HCQ.
- Adverse effects include nausea, abdominal discomfort, heartburn, dizziness, headaches, skin rashes, and, rarely, hematologic effects such as leukopenia (1%–3%) or thrombocytopenia.

A CBC is recommended every 2-4 weeks for the first 3 months of therapy, then every 3 months thereafter.

Sulfasalazine

- Leukopenia, agranulocytosis, or hepatitis are rare, but serious side effects of SSZ usually manifest within the first 2-3 months of therapy.

- To **minimize GI-related adverse effects**, SSZ is initiated at 500 mg/day or 1 g/day, and the dosage is increased at **weekly** intervals by 500 mg until 1,000 mg 2 or 3 times daily is reached.

- Tab 500 mg

Antimalarial Drug Dosing

- HCQ adult dose of 400-600 mg/day (310–465 mg of base), dosages for HCQ generally range from 2-6.5 mg/kg/day.
- If the patient responds well, the **maintenance dose** can be reduced by 50% and the medication continued at a dose of **200-400 mg/day** (155–310 mg of base).
- About two-thirds of patients who tolerate HCQ respond favorably.
- Benefits usually are apparent within 2-4 months of therapy, but it can vary between 1-6 months.

Risk of Retinopathy

- The **most serious toxicity**, retinal damage and subsequent visual impairment, is rare.
- Risk of retinopathy is increased with **high cumulative doses** (>800 g), **increased age** (>60 years), **liver disease**, and **retinal disease**.
- Daily HCQ doses <5 mg/kg for the first 5 years are very rarely associated with increased risk of retinal damage, particularly in patients without renal or hepatic dysfunction.
- HCQ should not be used for patients with significant renal impairment.

HCQ

- Symptoms of antimalarial associated retinopathy ➲ stop therapy immediately and undergo an ophthalmologic evaluation

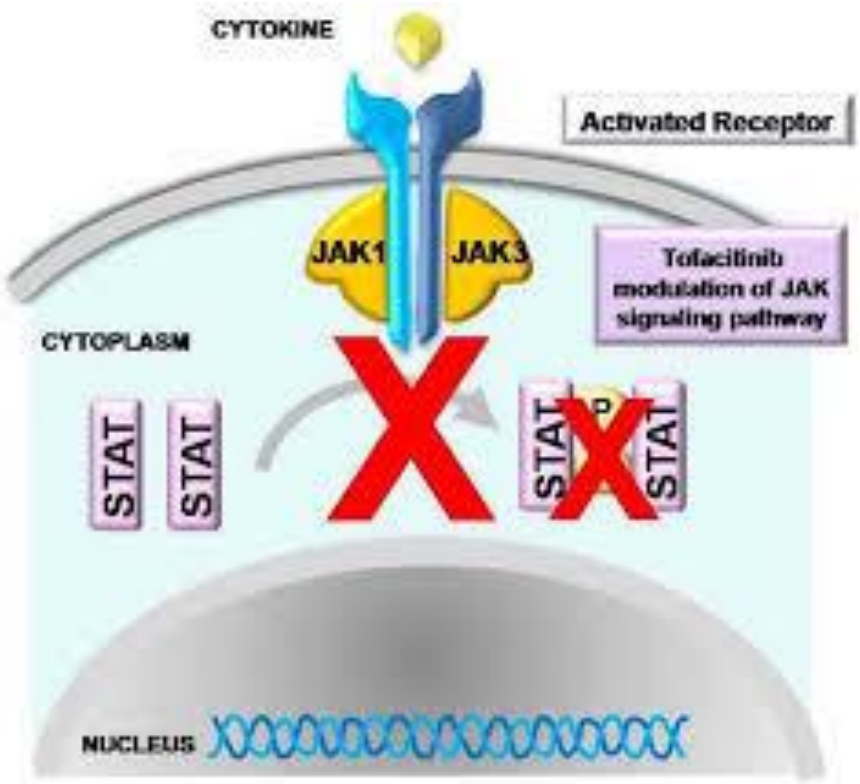
- The retinopathy can be progressive even after discontinuation of the drug.

- A **baseline eye examination** is recommended prior to starting HCQ therapy, then **annually after 5 years of treatment**. More frequent testing is recommended for patients:

⊙ > 6.5 mg/kg daily
⊙ renal dysfunction
⊙ elderly
⊙ cumulative dose of >200 g
⊙ existing poor visual acuity

tsDMARD

- Janus kinase (JAK) inhibitor, a targeted molecule involved with inhibition of signal transduction pathways
- Tofacitinib inhibits JAKs, enzymes that stimulate inflammatory cytokines; therefore, inhibition modulates leukocyte function and immune response.
- It is indicated for individuals with moderate-to-high disease activity who have failed csDMARD monotherapy.



Tofacitinib (Xeljanz)

- Tab IR 5, 10 mg
- Tab ER 11 mg
- Dose: 5 mg BD or 11 mg daily

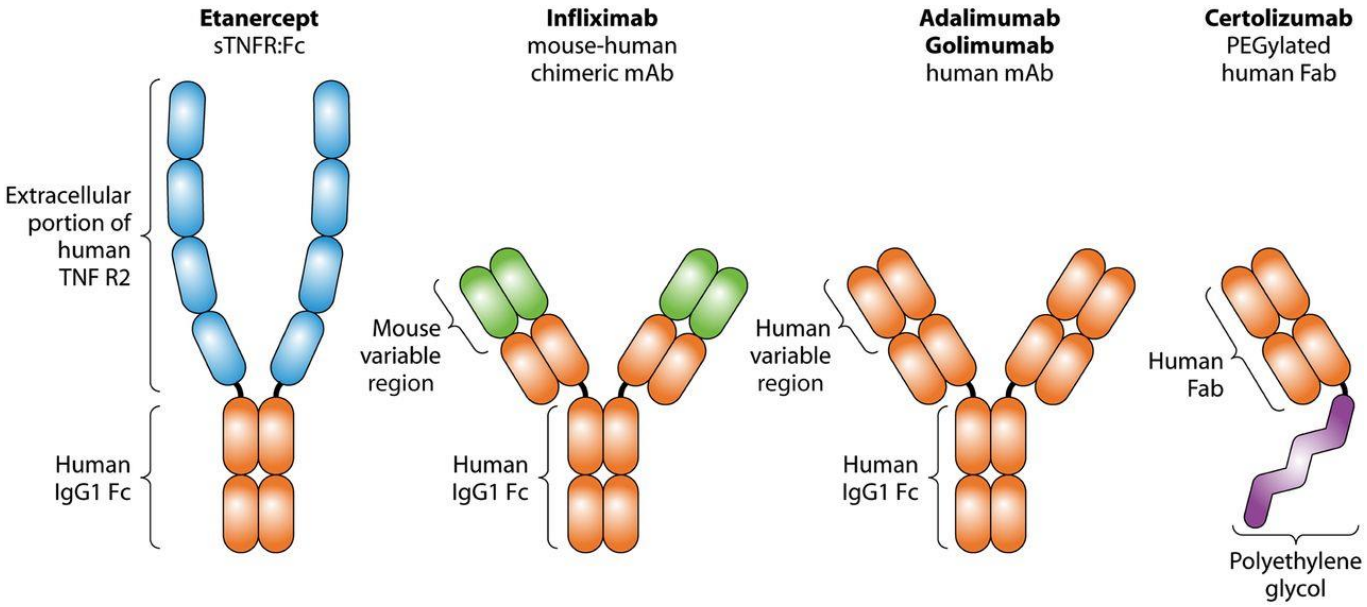
- Monotherapy or combination with non-biologic DMARD

bDMARDs

- Reserved for patients who have **failed to respond to one or more csDMARDs alone or in combination**.
- The ACR and EULAR guidelines recommend the use of bDMARDs in patients with established RA who experience moderate or high disease activity despite csDMARD monotherapy.
- Excessive macrophage-produced cytokines (e.g., TNF-a, IL-1, IL-6, and IL-8) correlate closely with RA disease activity and severity.
- RA improves when the physiologic action of TNF-a or several different ILs are suppressed.

TNF-a inhibitors

- Etanercept is a recombinant TNF-receptor Fc fusion protein with the extracellular portion of two p75 receptors fused to the Fc portion of human IgG1
- Infliximab is a chimeric IgG monoclonal antibody
- Adalimumab is a genetically engineered human IgG1 monoclonal antibody
- Certolizumab pegol is a PEG Fab fragment of a humanized anti-TNF monoclonal antibody



TNF-a inhibitors

- There is no conclusive evidence from well-controlled comparative trials that any one TNF-a inhibitor is superior to another with regard to efficacy and safety.

- TNF-a inhibitor selection may be driven by cost, insurance coverage, provider preference, and patient-specific factors.

- There are also three **non-TNF biologic agents** recommended for RA patients who have not responded to at least one csDMARD, which include **abatacept**, **rituximab**, and **tocilizumab**.

bDMARDs

- Abatacept and tocilizumab may be considered as first-line biologic DMARDs along with the TNF-a inhibitors.
- However, rituximab should only be considered as a first-line bDMARD in the presence of certain contraindications (i.e., recent history of lymphoma, latent TB with contraindications to treatment, or history of demyelinating disease) to the other bDMARDs.
- There is also one final bDMARD, **anakinra**, which is seldom used because of lack of comparative efficacy.

bDMARDs

- Anakinra is a recombinant human IL-1 receptor antagonist, which inhibits the binding of cytokines IL-1a and IL-1b to their receptor.
- In addition to proinflammatory properties, IL-1 augments cartilage damage and inhibits bone formation.
- Anakinra has not shown comparable efficacy against other bDMARDs in meta-analyses and is infrequently used, although some individuals may still respond to this agent.

bDMARD

- Triple csDMARD therapy has been shown to be non-inferior to combination MTX and TNF inhibitor therapy.
- It is preferred that the **bDMARDs** be used in combination with either MTX or other csDMARDs rather than as monotherapy.
- Furthermore, even if clinical response is achieved with combination therapy, the **csDMARD(s) should not be discontinued.**
- If a patient truly cannot be treated with csDMARDs, consideration may be given to monotherapy with etanercept, adalimumab, certolizumab pegol, abatacept or tocilizumab.

bDMARD

- Inadequate response to the initial bDMARD ➲ another bDMARD
- There is no preferred step-up bDMARD and choice is dependent on patient-specific factors.
- If a TNF inhibitor was initially chosen, or if a patient has failed successive TNF inhibitor trials, changing to a non-TNF bDMARD is recommended.
- If a non-TNF bDMARD was initially chosen, switching to another non-TNF bDMARD is preferred.

Etanercept

- ETA is the first biologic response modifier to be approved by the FDA for reducing the signs and symptoms of moderate to severe active RA ± MTX.
- ETA is a soluble TNF receptor that competitively binds two TNF molecules, rendering both molecules inactive.
- **Inj 25, 50 mg**
- **50 mg SC once weekly**

Adalimumab

- Genetically engineered, fully humanized IgG1 mab➲ inhibit the structural damage of RA while reducing clinical signs and symptoms.
- **Inj 20, 40 mg**
- **40 mg SC every other week**.
- It is recommended to give ADA in combination with MTX.
- Patients who cannot or choose not to take MTX may benefit from weekly dosing.
- Data also support the long-term efficacy and safety of ADA for **more than 8 years**.

Infliximab

- Chimeric (mouse–human) IgG antibody directed against TNF.
- IFX is approved in combination with MTX for the treatment of moderate to severe active RA.
- **Inj 100 mg**
- **3 mg/kg IV infusion at weeks 0, 2, and 6, then every 8 weeks.** Some patients may benefit from an increase in dose up to 10 mg/kg or a decrease in treatment interval to as often as every 4 weeks.
- IFX should be given with MTX therapy to prevent the formation of antibodies to infliximab.

bDMARDs & infection

- Significant risk factors for infection (e.g., poorly controlled diabetes, concurrent corticosteroid use, or concomitant csDMARD therapy), **biologic agents should not be given to patients with active infection**, **history of recurring infections**, or **medical conditions predisposing them to infection**.

Standard and high-dose biologic DMARDs are associated with an increase in risk of serious infections compared to csDMARDs.

low-dose bDMARDs were not associated with increased risk.

bDMARDs & infection

💣 It is recommended that all patients be screened for latent TBI prior to initiation of a bDMARD or tofacitinib.

- If LTBI is identified, patients should receive at least 1 month of treatment prior to starting a bDMARD or tofacitinib.
- Patients with active TB should complete treatment prior to initiation of a bDMARD or tofacitinib.
- Patients should be monitored for active TB during treatment.

bDMARDs & infection

- It is recommended that patients receive the **following vaccinations prior to the initiation of csDMARD or bDMARD** therapy: pneumococcal, influenza, hepatitis B, HPV, and herpes zoster.

- However, if not completed prior to the initiation of therapy, these vaccinations, with the exception of herpes zoster, may be given following the initiation of csDMARDs or bDMARDs.

Herpes zoster, as well as any other live vaccines, should not be administered in patients receiving bDMARDs

Side Effects

- TNF-a has been implicated in the pathophysiology of **HF**, and increased serum levels of TNF-a seem to be associated with worsening HF.

- Proposed mechanisms: accelerated left ventricular remodeling, negative inotropic effects, and increased apoptosis of myocytes and endothelial cells.

- Anti-TNF therapy is **not recommended** for RA patients with moderate-to-severe (**NYHA III/IV**) HF.
- Anti-TNF therapy can be used with caution in patients with mild (NYHA I/II) HF.

Side Effects

- Included in the labeling for all anti-TNF bDMARDs is a warning for increased risk of **lymphoma**.

- Other adverse effects, in order of decreasing frequency, include **headache**, **rhinitis**, **dizziness**, **pharyngitis**, **cough**, **asthenia**, **abdominal pain**, and **rash**.

Table 44-7

Biologic Disease-Modifying Antirheumatic Drug Dosing Information

Generic (Brand)	Mechanism of Action	Dosage Range	Administration Schedule	Routes of Administration	Can Be Self-Administered?
Infliximab (Remicade)	TNF-α inhibitor	3 mg/kg[a]	Weeks 0, 2, and 6 and then every 8 weeks	IV	No
Etanercept (Enbrel)	TNF-α inhibitor	50 mg	Weekly	SC	Yes
Adalimumab (Humira)	TNF-α inhibitor	40 mg	Every 14 days	SC	Yes
Certolizumab pegol (Cimzia)	TNF-α inhibitor	Initial: 400 mg SC on weeks 0, 2, 4 Subsequent: 200 mg every 2 weeks or 400 mg	Weeks 0, 2, and 4, then every 2 or 4 weeks	SC	Yes

bDMARDs

- Many patients who lose responsiveness to an initial trial of anti-TNF therapy can be successfully treated with an alternative anti-TNF agent.

- **Abatacept** (inhibitor of T-cell activation), **rituximab** (selective depletor of CD20+ B cells), and **tocilizumab** (anti-IL-6 receptor antibody) have demonstrated excellent efficacy in patients with inadequate response to csDMARDs (e.g., MTX) as well as to anti-TNF therapy.

Abatacept

- **Selective costimulation inhibitor** of T-cell activation indicated for the treatment of moderate-severe active RA.
- **ABT ± csDMARDs**
- IV / SC

- ABT IV dosing is based on body weight (500 mg for patients <60 kg, 750 mg for patients 60–100 kg, and 1,000 mg for patients >100 kg) and should be infused over 30 minutes at weeks 2 and 4 after the first dose, then every 4 weeks thereafter.

- SC dose is 125 mg weekly.

Side effects

- **Infections** such as pneumonia, cellulitis, UTI, bronchitis, diverticulitis, and acute pyelonephritis.
- Infections are significantly more common when ABT is combined with anti-TNF therapy; thus, this combination is not recommended.
- A few case reports of **malignancy** have been associated with ABT,

Rituximab

- Chimeric monoclonal antibody that binds to the antigen **CD20 on B cells**.
- RTX + MTX ➲ moderate to severe active RA in patients who have had an inadequate response to one or more TNF antagonist medications.

- EULAR: rituximab may be considered as a first-line bDMARD in patients with contraindications to other bDMARDs, such as recent history of lymphoma, latent TB with contraindications to chemoprophylaxis, living in a TB-endemic areas or a previous history of demyelinating disease.

Rituximab

- Vials 100, 500 mg
- Dose: **1000-mg IV infusions separated by 2 weeks**

- RXB must be diluted to a final concentration of 1-4 mg/mL with either 0.9% sodium chloride or 5% dextrose in water.

- To reduce the incidence and severity of infusion-related adverse effects, premedication with IV methylprednisolone 100 mg, or its equivalent, 30 minutes before each infusion is strongly recommended; other premedications (e.g., acetaminophen and antihistamine) may also be beneficial.

Tocilizumab

- Humanized **anti-IL-6 receptor Ab** indicated for the treatment of adult patients with moderate to severe active RA, who have had an inadequate response to one or more csDMARDs.

- IV / SC
- IV dose is 4 mg/kg, infused every 4 weeks with an increase to 8 mg/kg as needed based on clinical response.

- SC dose is 162 mg either weekly or every other week depending on patient weight and response.

Tocilizumab

- TCZ should not be initiated in patients with an **ANC**< 2,000 cells/µL, **platelet** < 100,000, or in patients who have an **ALT or AST** >1.5 times the ULN.
- TCZ treatment should be interrupted if a patient experiences a serious **infection**; therapy may be resumed once the infection is controlled.
- Monotherapy, in combination with csDMARDs, and in patients who are refractory to anti-TNF medications.
- TCZ has also shown decreased radiographic progression of RA compared to csDMARDs.

Side effects

- Severe **infections**, **GI perforation**, and **laboratory abnormalities**
- As with the TNF-a inhibitors, TCZ has a boxed warning for increased risk of developing serious infections, especially those caused by opportunistic pathogens. The risk for infection is increased when TCZ is taken in combination with other immunosuppressant agents (e.g., MTX and corticosteroids).
- As with the anti-TNF agents, a TB skin test result and CXR must be obtained before initiating treatment.

Side effects

- TCZ has also been associated with a number of blood chemistry changes including **neutropenia**, **thrombocytopenia**, **elevated LFTs**, and **lipid changes**.
- Increases in lipids (total cholesterol, LDL, HDL, and TG) have been shown in clinical trials.
- Lipid elevations respond to lipid-lowering agents.

RESPONSE TO DRUG THERAPY

- In active disease, successful implementation of the treat to target approach requires reevaluation of pharmacologic therapy every 1-3 months.
- Therapy adjustment no later than 3 months into the treatment course is warranted because if there is no improvement by this time then it is unlikely that continuing the same course will achieve satisfactory results.
- Once **treatment targets** have been achieved, monitoring may occur less frequently every **6-12 months.**
- In patients with good response, glucocorticoids should be the first medications tapered and withdrawn, and if remission is sustained then tapering and discontinuing DMARD therapy (all types) may be considered.

Table 4. Guidance related to the timing of COVID-19 vaccination in relation to use of immunomodulatory therapies in RMD patients*

Medication(s)	COVID-19 vaccine administration timing considerations	Level of task force consensus
Hydroxychloroquine; sulfasalazine; leflunomide; apremilast; IVIG	Do not delay or adjust vaccine administration timing.	Strong
Methotrexate; mycophenolate mofetil; azathioprine; cyclophosphamide (IV or oral); TNFi; IL-6R; IL-1R; IL-17; IL-12/23; IL-23; belimumab; JAK inhibitors; abatacept (IV or SC); oral calcineurin inhibitors; GCs (prednisone-equivalent dose <20 mg/day)†	Do not delay or adjust vaccine administration timing.	Moderate
Rituximab	Assuming that a patient's COVID-19 risk is low or able to be mitigated by preventive health measures (e.g., self-isolation), schedule vaccination so that the vaccine series is initiated ~4 weeks prior to next scheduled rituximab cycle.	Moderate

Table 5. Guidance related to the use and timing of immunomodulatory therapies in relation to COVID-19 vaccination administration in RMD patients*

Medication(s)	Immunomodulatory therapy timing considerations	Level of task force consensus
Hydroxychloroquine; apremilast; IVIG; GCs (prednisone-equivalent dose <20 mg/day)	No modifications.	Strong
Sulfasalazine; leflunomide; azathioprine; cyclophosphamide (oral); TNFi; IL-6R; IL-1R; IL-17; IL-12/23; IL-23; belimumab; oral calcineurin inhibitors; GCs (prednisone-equivalent dose ≥20 mg/day)†	No modifications.	Moderate
Mycophenolate	Assuming that disease is stable, withhold for 1 week following each vaccine dose.	Moderate
Methotrexate	Hold methotrexate for 1 week after each of the 2 mRNA vaccine doses, for those with well-controlled disease; no modifications to vaccination timing.	Moderate
Methotrexate	Withhold methotrexate 2 weeks after single-dose COVID-19 vaccination, for those with well-controlled disease.	Moderate
JAK inhibitors†	Withhold JAK inhibitors for 1 week after each vaccine dose.	Moderate
Abatacept (SC)	Withhold abatacept both 1 week prior to and 1 week after the first COVID-19 vaccine dose only; no interruption around the second vaccine dose.	Moderate

Abatacept (IV)	Time administration so that the first vaccination will occur 4 weeks after abatacept infusion (i.e., the entire dosing interval), and postpone the subsequent abatacept infusion by 1 week (i.e., a 5-week gap in total); no medication adjustments for the second vaccine dose.	Moderate
Cyclophosphamide (IV)	Time cyclophosphamide administration so that it will occur ~1 week after each vaccine dose, when feasible.	Moderate
Acetaminophen, NSAIDs	Assuming that disease is stable, withhold for 24 hours prior to vaccination (no restrictions on postvaccination use to treat symptoms).	Moderate
Rituximab	Assuming that patient's COVID-19 risk is low or is able to be mitigated by preventive health measures (e.g., self-isolation), schedule vaccination so that the vaccine series is initiated ~4 weeks prior to next scheduled rituximab cycle; after vaccination, delay rituximab 2–4 weeks after final vaccine dose if disease activity allows.	Moderate