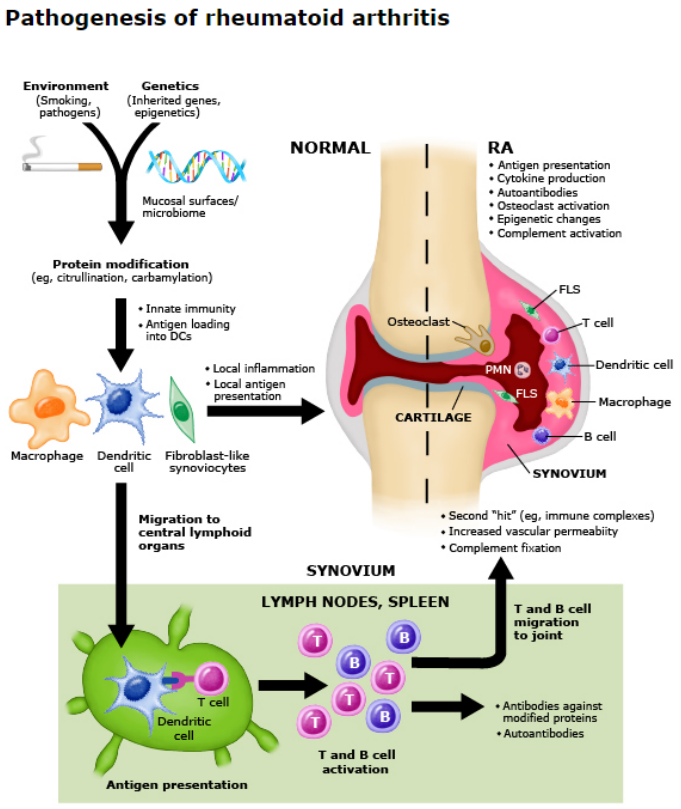
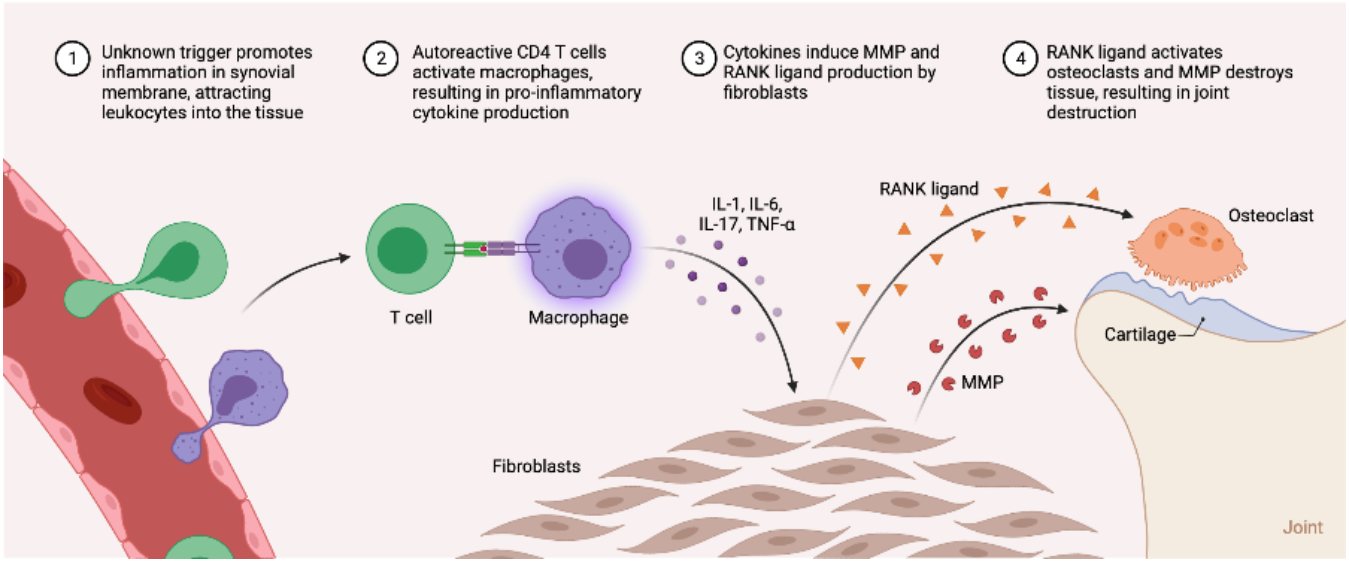
Rheumatoid Arthritis

- The exact etiology of RA is unknown, but like many autoimmune diseases it involves interplay among multiple factors including genetic and environmental influences.
- The onset of RA likely starts years before clinical symptoms develop with the activation of specific genes, resulting in innate immunity activity, leading to synovial hypertrophy, chronic joint inflammation, and extra-articular manifestations.
- The onset of RA and its progression follows the following phases:
  - Phase I: interaction of generic and environmental risk factors of RA (e.g., cigarette smoking, infection, or trauma)
  - Phase II: production of RA autoantibodies, such as RF (rheumatoid factor) and ACCP (anti-cyclic citrullinated peptide)
  - Phase III: development of arthralgia or joint stiffness
  - Phase IV: development of arthritis in 1 or 2 joints (i.e., early undifferentiated arthritis)
  - Phase V: established RA

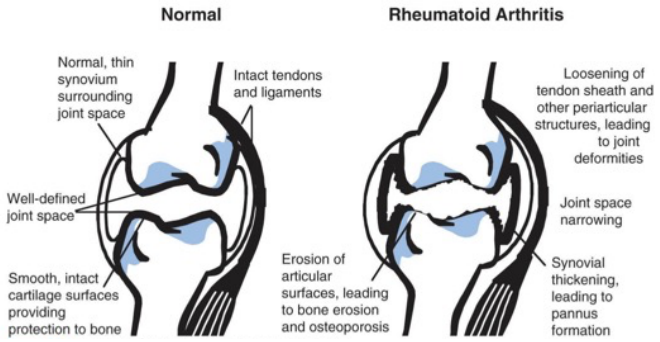


DCs: dendritic cells; RA: rheumatoid arthritis; FLS: fibroblast-like synoviocytes.

- Synovial cell hyperplasia and endothelial cell activation are early events in the pathologic process that progresses to uncontrolled inflammation, leading to cartilage and bone destruction.
- CD4 T-cells, macrophages, neutrophils, fibroblasts, and osteoclasts play major cellular roles in the pathophysiology of RA; whereas, B-cells produce autoantibodies.
  - Abnormal production of numerous cytokines, chemokines, and other inflammatory mediators include tumor necrosis factor (TNF-alpha), interleukin-1 (IL-1), IL-6, IL-8; MMP, etc…

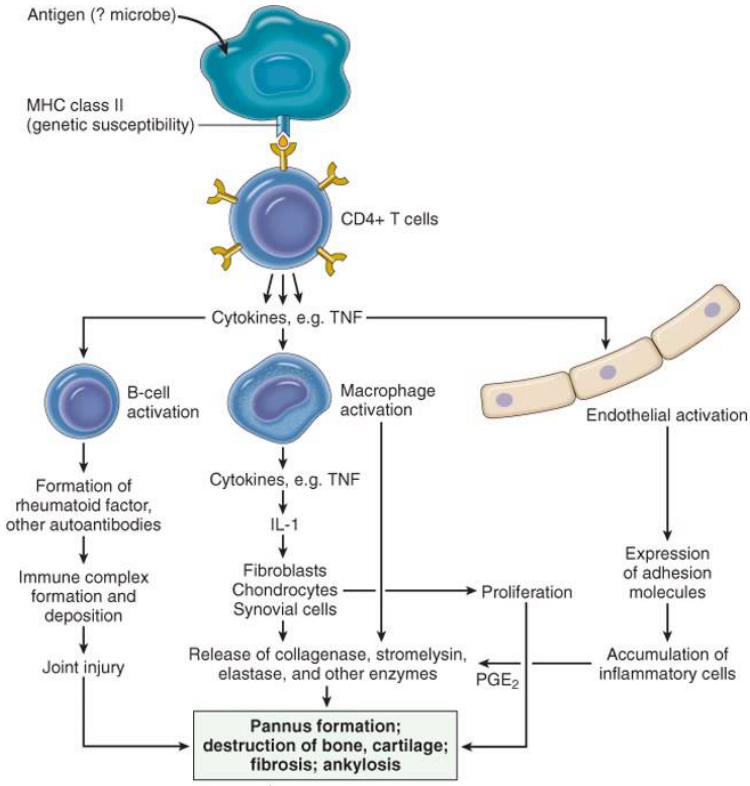


- Pharmacologic therapy for RA targets the components of the inflammatory cascade which lead to persistent inflammation of the synovial lining and ultimately cause joint destruction.
    - The synovial lining is a normally thin membrane; but in RA it proliferates and transforms into the synovial pannus.
    - The pannus is a highly erosive inflammatory exudate --> invades articular cartilage (leading to narrowing of joint spaces), erodes bone (resulting in osteoporosis), and destroys periarticular structure (ligaments, tendons) resulting in joint deformities.



Pathophysiology

- The initiating interaction for an autoimmune response takes place between antigen-presenting cells (APC) or dendritic cells and CD4 T-cells
    - T-cell activation leads to activation of macrophages and secretion of cytokines (IL-1, TNF-alpha); polypeptides that serve as important mediators of inflammation; and cytotoxins which directly destroy cells and tissues.
    - Cytokines (IL-1 and TNF-alpha) stimulate both synovial fibroblasts and chondrocytes in neighboring articular cartilage to secrete enzymes that cause degradation of proteoglycan and collagen tissues.
- B-cells can also become activated leading to antibody formation (RF and anti-CCP), proinflammatory cytokine production, and accumulation of polymorphonuclear leukocytes that release cytotoxins and other substances destructive to the synovium and joint structures.



Diagnostic Criteria

- The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) uses a scoring system to diagnose RA, based on multiple clinical criteria since no single chemical or laboratory finding is specific for the disease.
- The intent of this scoring system is to identify patients early in the disease development so that therapeutic intervention can be initiated as soon as possible to decrease disease progression and improve clinical outcomes.
- RA criteria quantifies joint involvement and symptom duration (e.g., synovitis or joint swelling) as well as detecting the presence of autoantibodies and acute-phase reactants.

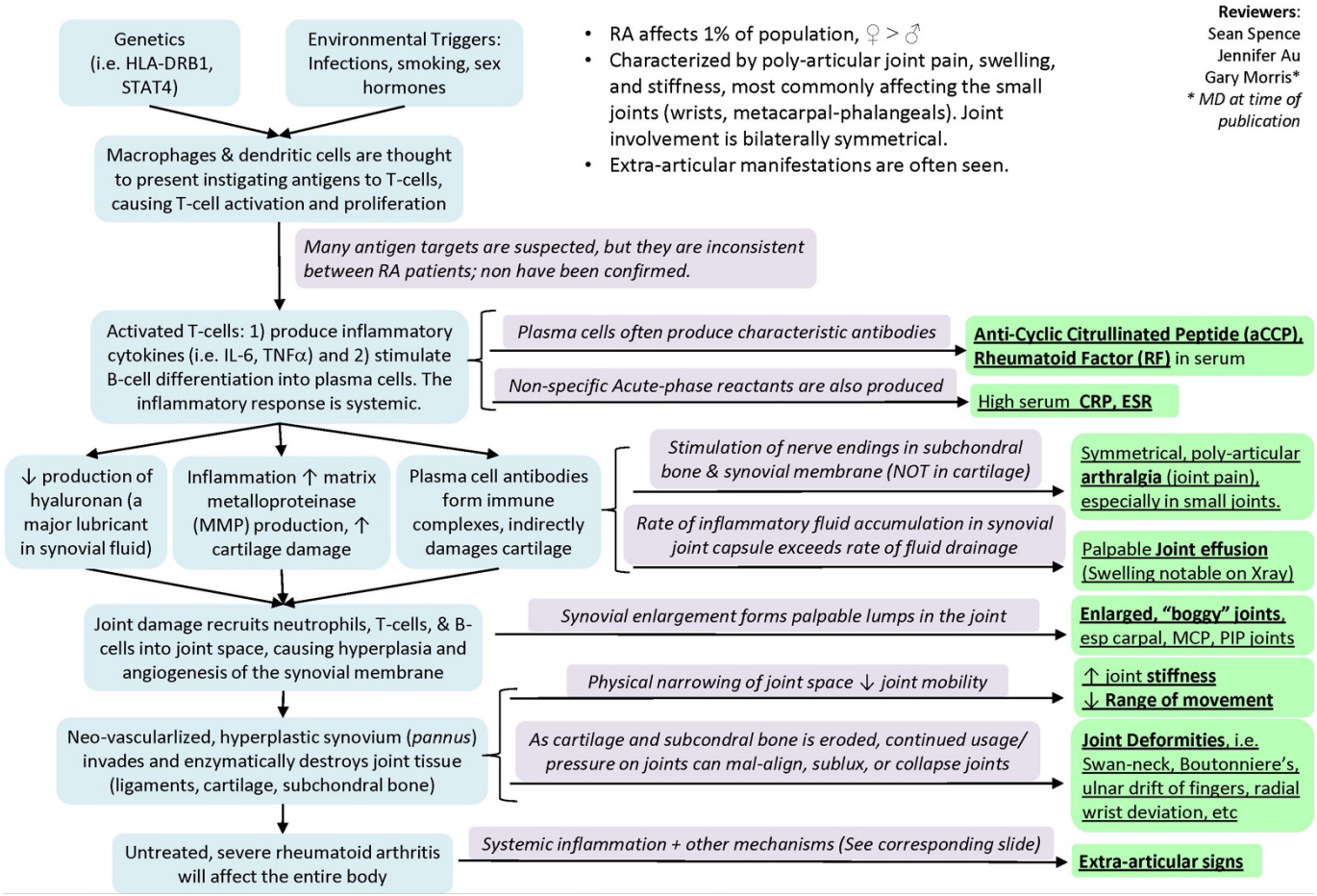
Diagnostic Criteria

Criteria	Score
Low-positive RF or ACPA	2
High-positive RF or ACPA	3
High ESR or CRP	1
Duration of symptoms ≥6 weeks	1
Joint Involvement (at least one joint not explained by another disease)	
2-10 large joints	1
1-3 small joints (± large joint)	2
4-10 small joints (± large joint)	3
>10 joints (at least one small joint)	5

ACR/EULAR, American College of Rheumatology/European League Against Rheumatism; ACPA, anti-citrullinated protein antibodies; CRP, C-reactive protein; ESR, eosinophil sedimentation rate; RF, rheumatoid factor.

- Using a score-based algorithm based on 4 categories, a score of 6 or more out of a total possible score of 10 suggest RA.
- ACPA (anti-citrullinated peptide antibody or anti-CCP) and rheumatoid factor (RF) are more definitive and specific for RA than erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).
  - Autoimmune diseases are frequently characterized by autoantibodies, with 50-80% of RA patients having RF, ACPA, or both.
    - RF level of 1:160 is considered a positive test and most patients with RA have titers of at least 1:320.
      - A higher RF titer in early disease correlates with increased disease severity and progression.
    - ACPA is the most specific blood test for RA than RF, with a specificity of approx. 95%.
  - A positive ACPA test and a positive RF test correlates with 99.5% specificity for RA.
- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are nonspecific markers for inflammation and are typically elevated in proportion to disease activity.

Summary: Pathogenesis and Clinical Findings of Rheumatoid Arthritis

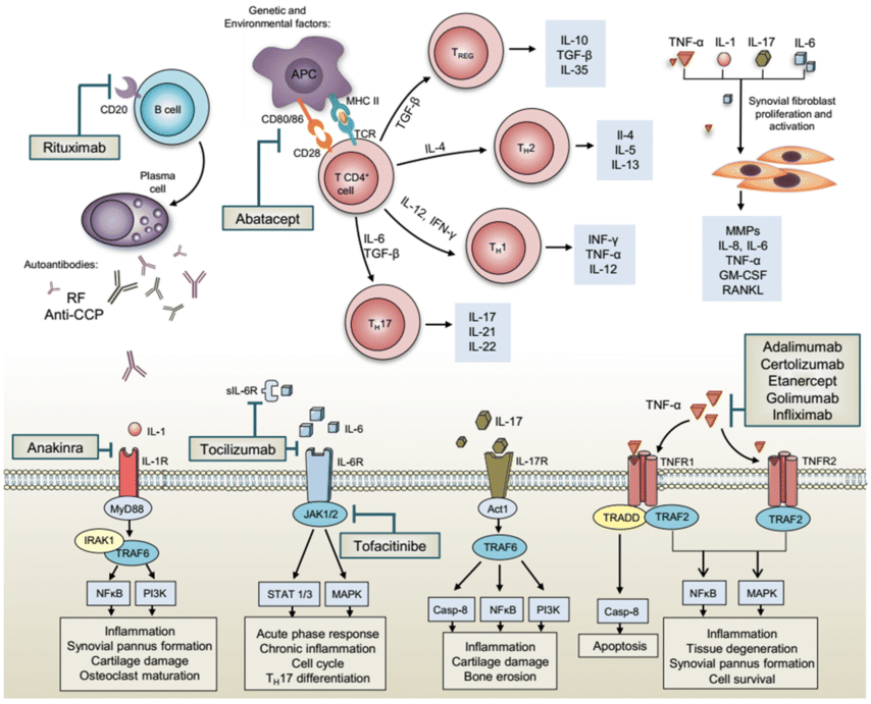


Treatment of Rheumatoid Arthritis

- The treatment goals of RA are to maximize functional status through improvement of symptoms (e.g., joint pain and swelling), preserve joint function, and prevent deformity --> improve quality of life and delay disability.
- Initiation of pharmacologic therapy at the point of diagnosis is critical to achieve remission or lowest possible disease activity.
- Other supportive interventions include rest, exercise, physical/occupational therapy, and emotional support.
- While symptoms of RA may be controlled with NSAIDs and short-term corticosteroids, more aggressive therapy is needed to prevent disease progression/disability.
    - NSAIDs and corticosteroids are often used to provide rapid anti-inflammatory and analgesic effects; however, they do not prevent or slow joint destruction compared to DMARDs and should be reserved for rapid symptomatic relief while awaiting DMARD onset of action.
    - DMARDs are the mainstay of pharmacologic care for RA and should be initiated in all patients as soon as they are diagnosed with RA.
- DMARDs: Choice of treatment is individualized based on joint function, degree of disease activity, patient age, sex, occupation, drug costs, and results of previous therapy.
- The 2 classes of DMARDs are synthetic DMARDs ("*s*DMARDs") and biologic DMARDs ("*b*DMARDs")
    - *s*DMARDs are subdivided into "conventional" *s*DMARDs ("*cs*DMARDs") and "targeted" *s*DMARDs ("*ts*DMARDs").
        - *cs*DMARDs include: hydroxychloroquine (Plaquenil), sulfasalazine (Azulfidine), methotrexate (MTX), and leflunomide (Arava).
        - *cs*DMARDs, alone or in combination, are considered initial therapy for most patients and, in the absence of contraindications, MTX is the treatment of choice because of its strong efficacy and favorable safety profile
    - *ts*DMARD: The 1st and only is tofacitinib (Xeljanz), a Janus kinase inhibitor used in moderate-to-severe disease who have failed treatment with or are intolerant to *cs*DMARDs.
- The *b*DMARDs target the physiologic proinflammatory and joint-damaging effects of inflammatory mediators (i.e., TNF-alpha, IL-1, IL-6, T-cell, and B-cell).
    - TNF-alpha inhibitors include: Etanercept (Enbrel), Infliximab (Remicade), Adalimumab (Humira)
    - IL-1 inhibitor: Anakinra (Kineret)
    - IL-6 inhibitor: Tocilizumab (Actemra)
    - B-cell inhibitor (CD20+): Rituximab (Rituxan)
    - T-cell activation inhibitor (co-stimulator modulator): Abatacept (Orencia)

TABLE 248-1 EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS

Skin	Nodules, fragility, vasculitis, pyoderma gangrenosum
Heart	Pericarditis, premature atherosclerosis, vasculitis, valve disease, and valve ring nodules
Lung	Pleural effusions, interstitial lung disease, bronchiolitis obliterans, rheumatoid nodules, vasculitis
Eye	Keratoconjunctivitis sicca, episcleritis, scleritis, scleromalacia perforans, peripheral ulcerative keratopathy
Neurologic	Entrapment neuropathy, cervical myelopathy, mononeuritis multiplex (vasculitis), peripheral neuropathy
Hematopoietic	Anemia, thrombocytosis, lymphadenopathy, Felty syndrome, large granular lymphocyte syndrome
Kidney	Amyloidosis, vasculitis
Bone	Osteopenia

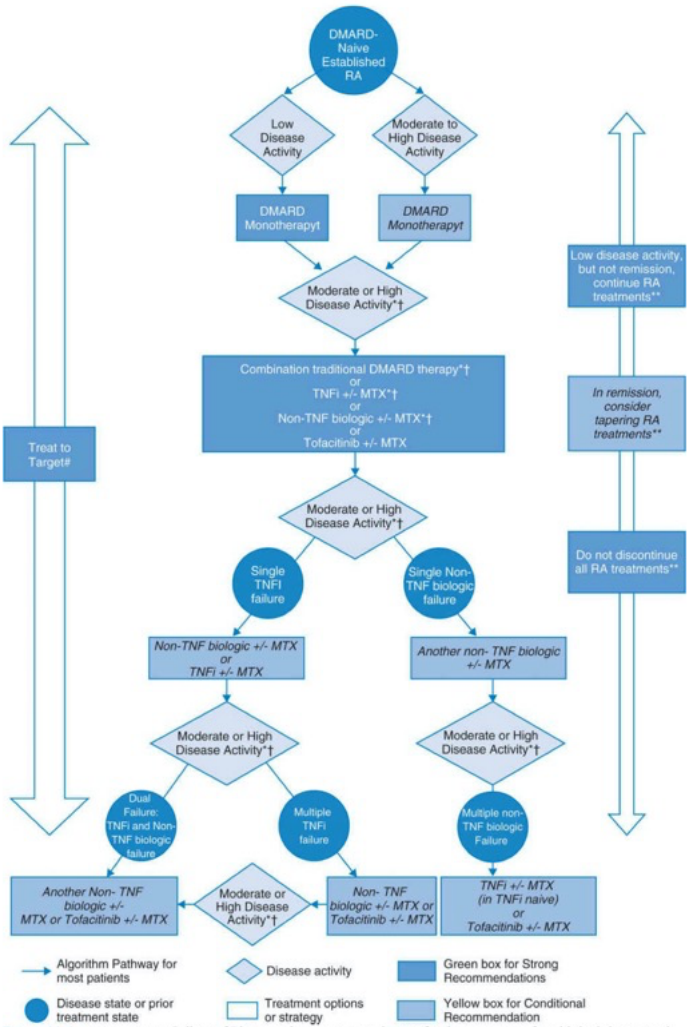


NSAIDs / Corticosteroids

- NSAIDs and corticosteroids are effective for providing short-term pain and inflammation control, but do not alter disease course.
  - SEs: GI intolerance, nephrotoxicity, and increased risk of bleeding and cardiovascular events.
  - The cardiovascular risk associated with some agents is particularly concerning since RA patients are at higher cardiovascular mortality risk; therefore, NSAIDs use should be judicious and reserved only as adjuncts to DMARD therapy.
- Low dose corticosteroids are often prescribed in RA on an as-needed basis for brief periods of severe disease activity or while awaiting the onset of DMARD action.
- During periods of disease remission in RA, NSAIDs and corticosteroids should be discontinued.

Conventional Synthetic DMARDs (*cs*DMARD)

- Hydroxychloroquine (Plaquenil), Sulfasalazine (Azulfidine), Methotrexate (MTX), and Leflunomide (Arava)
- Every RA patient should receive *cs*DMARD therapy soon after diagnosis to minimize loss of joint integrity, function, and risk of cardiovascular related to RA.
- Onset of action of most csDMARDs is low (3-6 months); however, sulfasalazine, MTX, leflunomide can produce beneficial effects within 1-2 months.
- MTX, a folate anti-metabolite with immunosuppressive and anti-inflammatory properties, remains the mainstay 1st line DMARD because of its relatively rapid onset of action (1-2 months), excellent history of efficacy & safety.
- Leflunomide and sulfasalazine are recommended if a contraindication to MTX is present, or if intolerance to MTX occurs.
- Hydroxychloroquine as monotherapy may be used in mild cases of RA; however, 37% of patients discontinue HCQ within a year and 54% within 2 years, primarily due to lack of efficacy.



Methotrexate (MTX)

- MTX is recommended as initial DMARD therapy for all patients with RA because it has a rapid onset (1-2 months), a high efficacy rate at management symptoms and slowing disease progression, low toxicity, and a long history of successful use.
- Patients who experience loss of efficacy or intolerable adverse effects from MTX can add 1 or 2 *cs*DMARDs (MTX + SSZ + HCQ), or add or substitute a *b*DMARD (e.g., MTX + infliximab) or tofacitnib (e.g., MTX + tofacitnib).
- MTX dose: 7.5 mg PO once a week, as a single dose.
  - Dose may be increased to 15 mg/week, then to 25 mg/week in 1-2 month intervals if therapeutic response is not achieved.

Methotrexate (cont.)

- MTX SEs: gastric irritation, stomatitis, leukopenia, thrombocytopenia (rarely, pancytopenia due to bone marrow suppression); and hepatoxicity (hepatic fibrosis, cirrhosis).
    - Hepatoxicity is uncommon with liver enzyme testing and monitoring.
        - Risk of hepatotoxicity increases with heavy alcohol consumption and patients with diabetes mellitus / kidney disease.
        - MTX should be discontinued if liver enzymes increase to 3 times baseline value.
        - Patients taking MTX should avoid alcohol and be instructed to report symptoms of jaundice or dark urine.
- Contraindications: pregnancy, renal impairment (CrCl < 30 ml/min); and patients with pre-existing liver disease.
- "Folate 1 mg PO daily" or "leucovorin calcium (folinic acid) 2.5 - 5 mg PO weekly 24 hours after the dose of MTX" is recommended to reduce gastric irritation, stomatitis, cytopenia (bone-marrow suppression), and hepatoxicity.

Sulfasalazine (Azulfidine)

- Sulfasalazine is a 2nd line agent for RA.
- Dose: 500 mg – 1500 mg PO BID.
- SEs: neutropenia and thrombocytopenia occur in 10-25% of patients --> CBC should be monitored every 2-4 weeks for the first 3 months, then every 3 months thereafter.

Leflunomide (Arava)

- Leflunomide is a pyrimidine synthesis inhibitor.
- SEs: diarrhea (20-30%), rash (10%), alopecia (10-17%) and hepatoxicity (reversible liver enzyme elevations more than 3 times upper normal limit occurs in 2-4%) --> monitor liver enzymes and CBC.
- Leflunomide is teratogenic and due to its long half-life ($t_{1/2}$ = 2 weeks), traces of active metabolites can be detected in plasma for up to 2 years --> therefore, leflunomide should not be used in premenopausal women who plan to become pregnant.
    - Cholestyramine (Questran) 8 gm PO TID for 11 days may reduce plasma levels of leflunomide metabolites by 40-65% in 24-48 hours and undetectable at the end of therapy.

Hydroxychloroquine (Plaquenil)

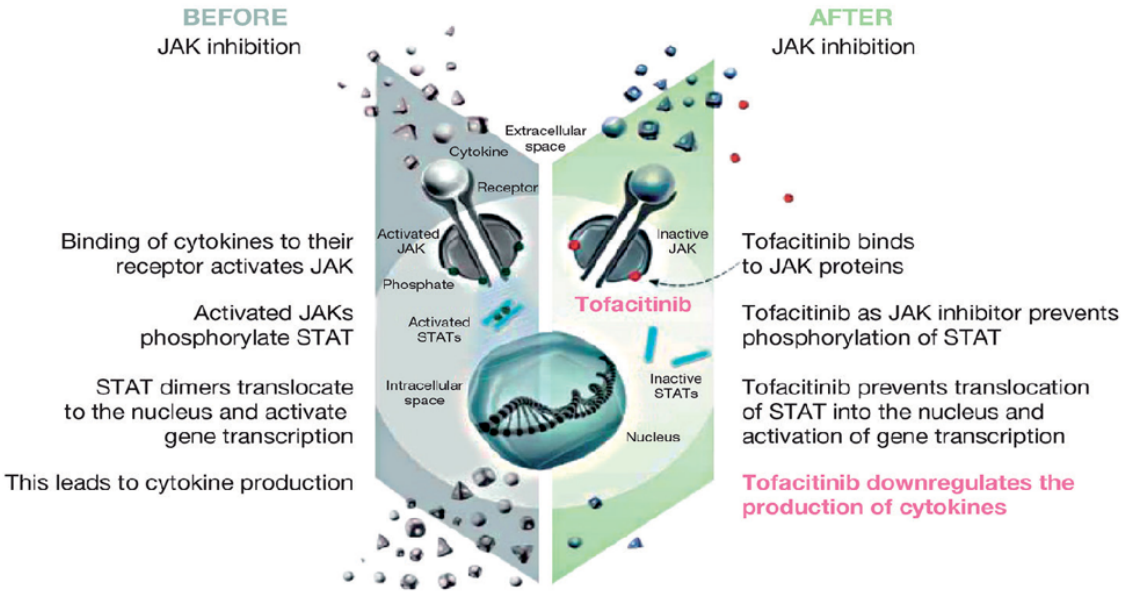
- Hydroxychloroquine (HCQ) as monotherapy may be used in mild cases of RA.
- Approx. 2/3^{rds} of patients who tolerate HCQ respond favorably within 2-3 months; however, 37% of patients discontinue HCQ within a year and 54% within 2 years, primarily due to lack of efficacy.
- HCQ is often used in combination with other cDMARDs --> "triple therapy" (MTX+sulfasalazine+HCQ)
- MOA: inhibition of migration of neutrophils and eosinophils, histamine, and serotonin blockade, and/or inhibition of prostaglandin synthesis.
- HCQ maintenance dose: 200-400 mg PO daily.
- HCQ most serious SE: retinopathy.
    - Risk of retinopathy is increased with high cumulative doses (> 5 years), increased age (> 60 years), liver disease, and retinal disease.
    - A baseline eye exam is recommended prior to starting HCQ, then annually after 5 years of treatment.

Monitoring Strategies for NSAIDs, Glucocorticoids, and *c*DMARDs

Drugs	Ongoing monitoring via system review and physical examination*	Ongoing laboratory monitoring and other testing ¶Δ
Salicylates, NSAIDs	Dyspepsia, nausea/vomiting, abdominal pain, edema, blood pressure	CBC and complete metabolic panel (electrolytes, creatinine, albumin, transaminases) every 6 months.
Glucocorticoids	Mood, weight gain, visual changes, weakness, polyuria, polydipsia, edema, infection, blood pressure	Diabetes screening, lipids, bone mineral density testing.
Hydroxychloroquine	Visual change, skin color change, paresthesia ◊	Ophthalmologic evaluation for retinal toxicity. ◊
Sulfasalazine	Headache, nausea, diarrhea, photosensitivity, symptoms of myelosuppression, hepatotoxicity, rash	CBC, aminotransferases and creatinine every 2 to 4 weeks for the first 3 months or after increasing the dose, every 8 to 12 weeks for months 3 to 6, then every 12 weeks.
Methotrexate §	Stomatitis, alopecia, diarrhea, nausea/vomiting, flu-like symptoms, shortness of breath, symptoms of myelosuppression, hepatotoxicity, infection, lymph node swelling, pregnancy	CBC, aminotransferases, and creatinine every 2 to 4 weeks for the first 3 months or after increasing the dose, every 8 to 12 weeks for months 3 to 6, then every 12 weeks.
Leflunomide §	Nausea/vomiting, diarrhea, shortness of breath, paresthesia, hepatotoxicity, weight loss, blood pressure, pregnancy	CBC, aminotransferases, and creatinine every 2 to 4 weeks for the first 3 months or after increasing the dose, every 8 to 12 weeks for months 3 to 6, then every 12 weeks.

Targeted Conventional DMARDs (tcDMARDs) or Janus Kinase Inhibitors

- Tofacitnib (Xeljanz) is an oral Janus kinase (JAK) inhibitor that is indicated for the treatment of moderate-to-severe RA refractory to MTX or other DMARDs.
- Tofacitinib can be used as monotherapy or in combination with MTX, but should NOT be used with biologic DMARDs (*b*DMARDs).
- Dose: 5 mg PO BID or 11 mg (extended-release tablet) PO daily.
- SEs: upper respiratory tract infection (URIs), cardiovascular effects, GI perforation, serious infections, malignancy, diarrhea, bone marrow suppression.

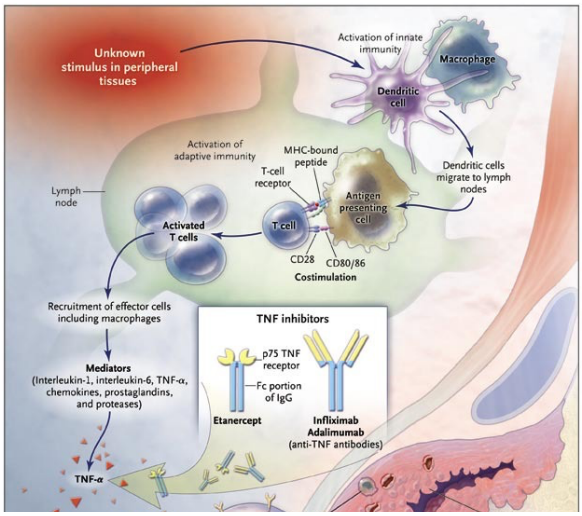


(STAT=signal transducer and activator of transcription in CD4 T-cells)

Biologic DMARDs (*b*DMARDs)

- *b*DMARDs should be considered for patients with: (1) moderate-to-high disease activity with poor prognostic factors, who do not reach treatment targets with the first csDMARD strategy (MTX alone or in combination with another csDMARD) within 6 months, OR
  (2) without poor prognostic factors who fail a 2nd csDMARD strategy
- *b*DMARDs include:
  - TNF-alpha inhibitors include: Etanercept (Enbrel), Infliximab (Remicade), Adalimumab (Humira)
  - IL-1 inhibitor: Anakinra (Kineret)
  - IL-6 inhibitor: Tocilizumab (Actemra)
  - B-cell inhibitor (CD20+ receptor blocker): Rituximab (Rituxan)
  - T-cell activation inhibitor: Abatacept (Orencia)

TNF-alpha Inhibitors: Etanercept, Infeximab, Adalimumab



- Indication: TNF inhibitors are indicated for reducing the signs and symptoms of moderate-severe RA, either alone or in combination with MTX.
- MOA: TNF inhibitors block the pro-inflammatory cytokine TNF-alpha.
- TNF inhibitors can take up to 3 months to achieve full clinical benefit.
- A major limitation of TNF inhibitors is cost, as they are more expensive than *c*DMARDs.
- Although TNF inhibitors have similar side effect profiles and contraindications, they all have differing structures, pharmacokinetics, and dosing regimens.
  - The selection of a TNF inhibitor depends on cost and patient preference for route (SC versus IV) and frequency of administration.
    - Etanercept is a soluble TNF receptor inhibitor that is self-administered: 50 mg SC weekly.
    - Adalimumab is a human monoclonal antibody that is self-administered: 40 mg SC every other week.
    - Infliximab is a chimeric (mouse-human) monoclonal antibody that is administered as an IV infusion (3 mg/kg) at weeks 0, 2, and 6, then every 8 weeks thereafter.

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

- SEs and monitoring of TNF inhibitors:
  - Risk of immunosuppression and infections (including sepsis, TB, fungal infections) are greatest concerns of TNF inhibitors, since TNF is a key mediator of inflammation and plays a major role in immune system regulation.
    - Patients should receive a TB skin test prior to initiating TNF inhibitors.

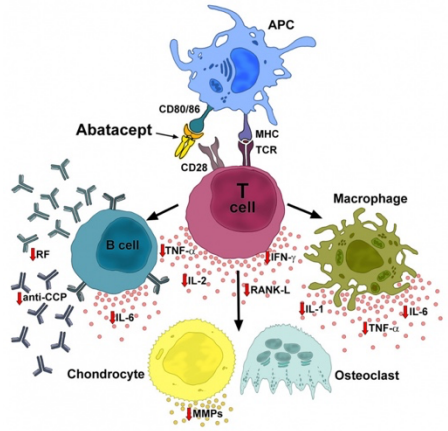
SEs and monitoring of TNF inhibitors (cont.)

- TNF inhibitors should not be used in patients with moderate-to-severe heart failure, as new onset and worsening heart failure has been reported with TNF inhibitors.
  - Proposed mechanisms include: left ventricular remodeling and negative inotropic effects.
  - Patients with mild heart failure should be monitored closely for cardiac decompensation.
- FDA has issued a warning of increased risk of lymphomas with TNF inhibitors, although causation has not been established because both RA and MTX are associated with an increased risk of lymphoma.
- New-onset or exacerbation of demyelinated disorders, such as multiple sclerosis, have been observed rarely with TNF inhibitors.
- Other SEs include: headache, URIs (rhinitis, pharyngitis, cough), dizziness, abdominal pain, and rash.

Non-TNF Biologic DMARDs: Rituximab, Abatacept, Tocilizumab, Anakinra

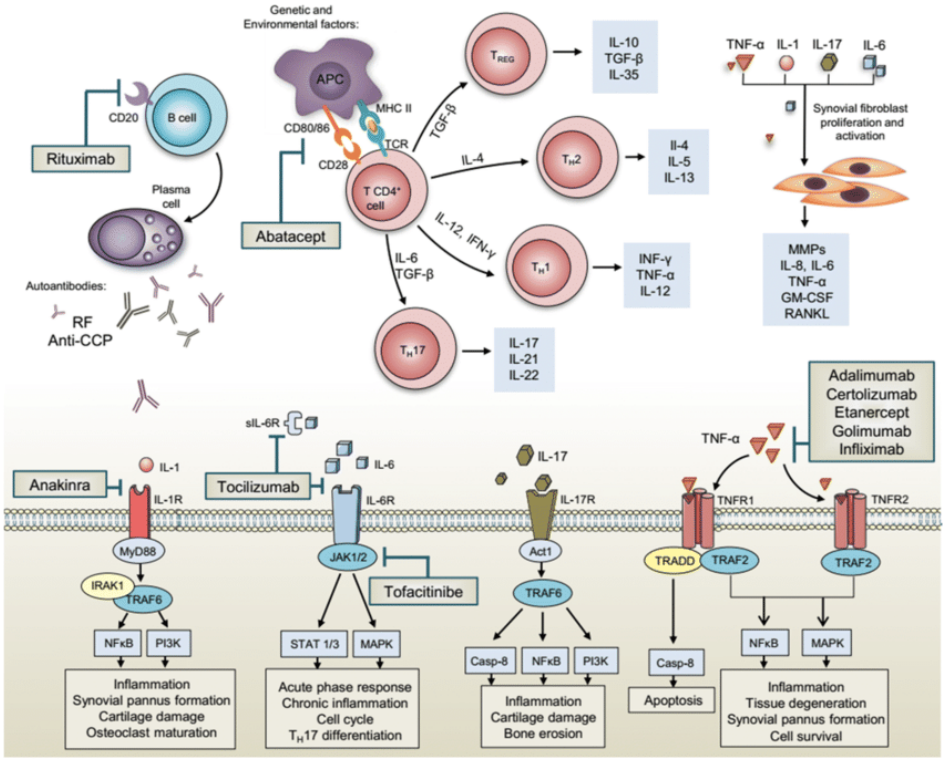
Abatacept (Orencia)

- Abatacept inhibits T-cell activation by binding to CD80 and CD86 --> reduces production and release pro-inflammatory cytokines (TNF, ILs)
- Abatacept is typically used as an alternative to TNF inhibitors with or without MTX and can also be initiated in patients who have failed or have had an inadequate response to TNF inhibitors.
- SEs: headache, URI, nasopharyngitis, COPD exacerbation, malignancy, nausea.
- Administration: Abatacept is available as an autoinjector (125 mg SC weekly) or IV infusion 500-1000 mg IV on weeks 0, 2, then every 4 weeks thereafter.

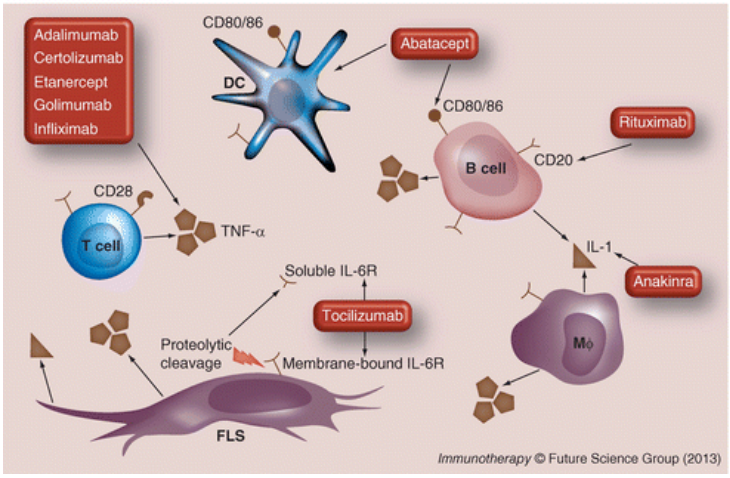


Tocilizumab (Actemra)

- Tocilizumab is a monoclonal antibody that blocks the binding of the pro-inflammatory cytokine IL-6 to its receptor site.
- Tocilizumab can be used in patients with moderate-to-severe RA who have had an incomplete response to one or more *c*DMARD and/or TNF inhibitor.
- SEs: URIs, nasopharyngitis, headache, HTN, increased liver enzymes.
- Administration: Tocilizumab is available as a prefilled syringe for SC injection 162 mg SC every other week, followed by weekly as needed for clinical response; tocilizumab is also available as an IV infusion: 4-8 mg/kg IV every 4 weeks.

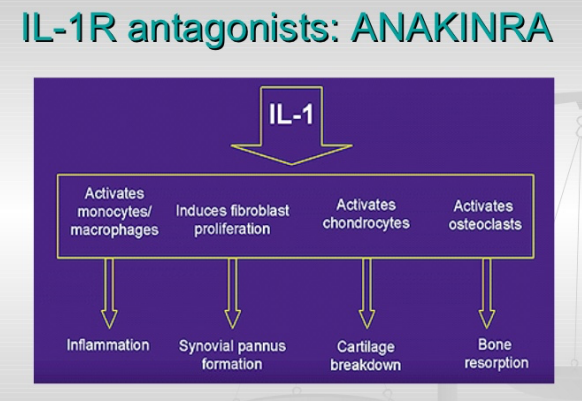


Rituximab (Rituxin)



- Rituximab is a chimeric monoclonal antibody that binds the CD20 antigen found on the surface of B-cells --> depletes B-cells.
- Rituximab can be given as monotherapy or in combination with MTX and can be initiated in patients with moderate-severe RA who have had an incomplete response to one or more TNF inhibitors.
- SEs: URIs, nasopharyngitis, UTIs, bronchitis, and infusion reactions.
- Administration: Rituximab is available as an IV infusion and can be given as two 1,000-mg infusions separated by 2 weeks, then every 24 weeks thereafter since recovery of B-cells can take several months.
- Infusion reactions (sometimes, severe reactions) can be caused by rituximab; therefore careful monitoring is warranted and methylprednisolone (Solu-Medrol) 100 mg is recommended 30 mins prior to each infusion.

Anakinra (Kineret)



- Anakinra inhibits IL-1, which is involved in inflammatory response.
- Anakinra can be used in patients with moderate-to-severe RA who have failed one or more DMARDs; however, the ACR (American College of Rheumatology) did not include this drug in its treatment recommendations due to its infrequent use for the treatment of RA and a lack of new data to support its use.
- Administration: Anakinra is administered as a SC injection: 100 mg SC daily.

Summary: Side Effects and Monitoring Strategies of Drug Treatment for RA

Monitoring strategies for drug treatment of rheumatoid arthritis

Drugs	Ongoing monitoring via system review and physical examination*	Ongoing laboratory monitoring and other testing ¶Δ
TNF inhibitors (eg, etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab)	Infection, malignancy, demyelination, congestive heart failure, autoimmune phenomenon	No routine laboratory monitoring (unless also receiving a concurrent conventional DMARD).
IL-6 inhibitors (eg, tocilizumab and sarilumab)	Infection, symptoms of myelosuppression (PMNs and platelets), demyelination, hepatotoxicity, gastrointestinal perforations	CBC with differential (neutrophils) and LFTs every 4 to 8 weeks until stable, then every 3 months. Lipids 4 to 8 weeks after starting therapy, then every 6 months.
Rituximab	Infection, PML, symptoms of neutropenia	CBC every 2 to 4 months.
Abatacept	Infection, COPD exacerbation, malignancy	No routine laboratory monitoring (unless also receiving a concurrent conventional DMARD).
JAK inhibitors (eg, tofacitinib, baricitinib, and upadacitinib)	Infection, zoster, symptoms of myelosuppression, hepatotoxicity, malignancy, gastrointestinal perforation	CBC with differential, creatinine, LFTs (transaminases, albumin, bilirubin) every month for 3 months, then every 3 months; lipids 6 to 8 weeks after drug start.

Biologic and Nonbiologic Disease-Modifying Antirheumatic Drugs

Drug	Mechanism for rheumatoid arthritis	Adverse effects	Typical dosage	Cost*
Nonbiologic†				
Methotrexate	Inhibits dihydrofolate reductase	Liver effects, teratogenesis, hair loss, oral ulcers	Up to 25 mg orally or subcutaneously every week	$60 for 40 2.5-mg tablets $10 for one 2-mL vial (25 mg per mL)
Leflunomide (Arava)	Inhibits pyrimidine synthesis	Liver effects, gastrointestinal effects, teratogenesis	10 to 20 mg orally every week	$30 ($175)
Hydroxychloroquine (Plaquenil)	Antimalarial, blocks toll-like receptors	Rare ocular toxicity	200 to 400 mg daily	$55 ($210)
Sulfasalazine (Azulfidine)	Folate depletion, other mechanisms unknown	Anemia in glucose-6-phosphate dehydrogenase deficiency, gastrointestinal effects	500 to 1,500 mg twice per day	$15 ($90)
Biologic				
Anti-TNF agents				
Adalimumab (Humira)	Anti-TNF-α	TB, opportunistic infection	40 mg subcutaneously every two weeks	NA ($4,500)
Certolizumab pegol (Cimzia)	Anti-TNF-α, pegylated	TB, opportunistic infection	400 mg subcutaneously every four weeks	NA ($4,000)
Etanercept (Enbrel)	Anti-TNF-α, receptor	TB, opportunistic infection	50 mg subcutaneously every week	NA ($4,500)
Golimumab (Simponi)	Anti-TNF-α	TB, opportunistic infection	100 mg every four weeks	NA ($4,900)
Infliximab (Remicade)	Anti-TNF-α	TB, opportunistic infection, infusion reaction	3 to 5 mg per kg intravenously every six to eight weeks	NA ($2,500) for two 100-mg vials
Other biologic agents				
Abatacept (Orencia)	Costimulator blocker, cytotoxic T lymphocyte antigen 4	Opportunistic infection	125 mg subcutaneously every week, or 500 to 1,000 mg intravenously every four weeks	NA ($4,000)
Anakinra (Kineret)	Anti-interleukin-1 receptor blocker	Opportunistic infection, injection site pain	100 mg subcutaneously daily	NA ($4,000)
Rituximab (Rituxan)	Anti-CD20, eliminates B cells	Infusion reaction, opportunistic infection, progressive multifocal leukoencephalopathy	1,000 mg intravenously every six months	NA (> $5,000‡)
Sarilumab (Kevzara)	Anti-interleukin-6 receptor blocker	Opportunistic infection	150 to 200 mg subcutaneously every two weeks	NA ($2,700)
Tocilizumab (Actemra)	Anti-interleukin-6 receptor blocker	Opportunistic infection, hyperlipidemia	4 to 8 mg per kg intravenously every four weeks, or 162 mg subcutaneously every week or every two weeks	NA ($2,000) for one 20-mL vial (20 mg per mL)
Tofacitinib (Xeljanz)	Janus kinase inhibitor	TB, opportunistic infection	5 mg daily or twice per day, or 11 mg daily extended release	NA ($2,000) NA ($4,000) for extended release

NA = not available; TB = tuberculosis; TNF = tumor necrosis factor.

*—Estimated retail price of one month's treatment (lower dose used for pricing purposes) based on information obtained at http://www.goodrx.com (accessed October 20, 2017). Generic price listed first; brand price listed in parentheses.

†—Nonbiologic drugs listed in approximate order of priority.

‡—Cost of a single dose; typically infused in a hospital setting.

Adapted with permission from Wasserman AM. Diagnosis and management of rheumatoid arthritis. Am Fam Physician. *2011;84(11):1249.*

Summary of Treatment Algorithm for Rheumatoid Arthritis

Treat-to-Target Strategy	1. Start with DMARDs as soon as RA diagnosis is made. 2. Aim treatment for every patient at reaching the target of sustained remission or low disease activity. 3. Frequently monitor patients for active disease (every 1–3 months). For patients who do not improve by 3 months or do not reach their target by 6 months, adjust therapy.
Initial Treatment: Specific Agents	4. MTX should be part of the first treatment strategy. 5. Leflunomide or sulfasalazine should be considered as part of the initial treatment strategy in patients with contraindications or early intolerance to MTX. 6. Consider short-term glucocorticoids when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible.
Second-Line Treatment: Specific Agents & Combinations	*If the treatment target is not reached with the first csDMARD strategy and the patient does not have poor prognostic factors:* 7. Consider other csDMARDs. *If the patient has poor prognostic factors:* 8. Consider adding a bDMARD (current practice) or tsDMARD.
Biologic Agents	9. Combine bDMARDs and tsDMARDs with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared with other bDMARDs. 10. If a bDMARD or tsDMARD has failed, consider using another bDMARD or a tsDMARD; if one TNF inhibitor has failed, patients may receive another TNF inhibitor or an agent with another mode of action.
Tapering Drugs	11. If a patient is in persistent remission after having tapered glucocorticoids, consider tapering bDMARDs, especially if combining with a csDMARD. 12. If a patient is in persistent remission, consider tapering the csDMARD.

Illustration: Detailed Schematic Representation of Events Occurring in Rheumatoid Arthritis (RA)

- T-cells activate monocytes, macrophages, and synovial fibroblasts.
- The latter then overproduce proinflammatory cytokines, mainly TNF-alpha, IL-1, and IL-6, which seems to constitute the pivotal event leading to chronic inflammation.
- Through complex signal transduction cascades, these cytokines activate a variety of genes characteristic of inflammatory responses, including genes coding for various cytokines and matrix metalloproteinases (MMPs) involved in tissue degradation.
- TNF-alpha and IL-1 also induce RANK expression on macrophages, which when interfering with RANKL on stromal cells or T-cells, differentiate into osteoclasts that resorb and destroy bone.
- In addition, chondrocytes also become activated, leading to the release of MMPs.
- Initial events might also involve activation of APCs through Toll-like receptors (TLRs) before T-cell engagement.