# Rheumatology High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 19 in several important ways. MKSAP 19 includes HVC-identified key points in the text, HVC-focused multiple-choice questions, and, in MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

**High Value Care Recommendation:** A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Rheumatology section of MKSAP 19.

- An accurate history and a thorough musculoskeletal physical examination are essential to diagnose and differentiate inflammatory and noninflammatory symptoms and can help to avoid unnecessary testing.
- Antinuclear antibody testing should not be performed in a patient with nonspecific symptoms and normal findings on clinical examination because it does not establish the diagnosis of a connective tissue disease.
- Antinuclear antibody (ANA) subserology testing should not be performed routinely, even in the setting of a positive ANA result, without strong clinical suspicion of an underlying connective tissue disease.
- Radiography is usually the first imaging test ordered in the evaluation of rheumatologic diseases because it is readily available, is inexpensive, exposes patients to only a low level of ionizing radiation, and is useful in monitoring arthritis progression.
- Ultrasonography is an inexpensive means to assess soft-tissue abnormalities, assess disease activity, and assist with tendon or joint injections.
- All tumor necrosis factor inhibitors provide similar benefit in patients with rheumatoid arthritis (see Item 36).
- Laboratory testing is usually not necessary to diagnose osteoarthritis but is helpful if other causes of arthritis are being considered or to help define the safety of potential therapies.
- Topical NSAIDs are safe and effective for treatment of knee and hand osteoarthritis and should be considered before oral NSAIDs (see Item 24).
- The use of chondroitin sulfate (with or without glucosamine), biologics, intra-articular hyaluronic acid, platelet-rich plasma, stem cells, or botulinum toxin is not recommended in the treatment of knee osteoarthritis (see Item 50).
- Acetaminophen provides no benefit for hip or knee osteoarthritis; it may be considered as add-on therapy for short-term and episodic use but not as initial therapy (see Item 54).
- Tai chi is as beneficial as physical therapy for knee and hip osteoarthritis pain (see Item 34).
- Exercise is beneficial in hip, knee, and hand osteoarthritis; no one exercise program is superior (see Item 82).
- Arthroscopic surgery is not indicated in patients with osteoarthritis unless there is joint buckling, instability, or locking, or a concomitant and symptomatic mechanical disorder.
- Patients with fibromyalgia should not be treated with anti-inflammatory drugs, including NSAIDs and glucocorticoids, and do not respond to opioids, with the exception of tramadol (see Item 7).
- *Borrelia burgdorferi* DNA can be detected by polymerase chain reaction in synovial fluid, but this test offers no advantage to serologic testing (see Item 12).
- A muscle biopsy is not necessary to diagnose dermatomyositis in patients with characteristic clinical and laboratory findings (see Item 38).
- A muscle biopsy can help to confirm the diagnosis of inclusion body myositis but is not needed when clinical features are characteristic (see Item 45).
- In the absence of additional suggestive symptoms, physical findings, and supporting laboratory data, oral dryness should not be attributed to a rheumatologic condition (see Item 47).
- If a patient has many features of spondyloarthritis, a positive HLA-B27 result adds little to the posttest probability (see Item 5).
- Antibiotics generally are not indicated in reactive arthritis because they do not affect illness outcomes (see Item 67).

# Rheumatology

## Approach to the Patient With Rheumatologic Disease

### Inflammatory Versus Noninflammatory Pain

The differentiation between inflammatory and noninflammatory signs and symptoms is central to the evaluation of patients with musculoskeletal pain. Autoimmune conditions typically present with inflammation, whereas mechanical or degenerative disorders are characteristically noninflammatory. The cardinal signs of inflammation are pain, erythema, swelling, and warmth; noninflammatory conditions usually lack these features, except for pain. Patients may simultaneously experience more than one type of pain. **Table 1** compares the features of inflammatory and noninflammatory arthritis.

### The Musculoskeletal Examination

An accurate history and a thorough musculoskeletal physical examination are essential to diagnose and differentiate inflammatory and noninflammatory symptoms and can help to avoid unnecessary testing. Musculoskeletal pain may be articular, periarticular, or referred. Pain with passive range of motion suggests an articular condition, whereas pain only with active range of motion suggests a periarticular condition.

See MKSAP 19 General Internal Medicine 1 for more information.

**KEY POINTS**

- Inflammatory symptoms include pain, erythema, swelling, and warmth; noninflammatory conditions usually lack these features, except for pain.
- An accurate history and a thorough musculoskeletal physical examination are essential to diagnose and differentiate inflammatory and noninflammatory symptoms and can help to avoid unnecessary testing.

HVC

### Arthritis

#### Monoarthritis

Monoarthritis involves a single joint and is classified as acute or chronic.

Acute monoarthritis can be noninflammatory (e.g., caused by trauma, hemarthrosis, or internal derangement) or inflammatory (e.g., crystal-induced or infectious). Evaluation for infectious arthritis should be guided by the clinical presentation and examination, but suspicion should always be high. Joint aspiration is usually the most effective means of diagnosing the underlying cause.

Chronic inflammatory monoarthritis (≥26 weeks) can be caused by chronic infection (e.g., mycobacterial, fungal, or *Borrelia burgdorferi*) or by autoimmune rheumatologic disease. Synovial fluid cell count analysis can help determine the presence of inflammation but may be inadequate for diagnosis; assessment for systemic disease (complete history; examination; and laboratory studies, including serologic testing) may be indicated. Rarely, synovial biopsy may be required to rule out chronic infection, deposition diseases, or malignancy.

Chronic noninflammatory monoarthritis is usually caused by osteoarthritis.

**TABLE 1. Features of Inflammatory Versus Noninflammatory Arthritis**

| Feature | Inflammatory Arthritis | Noninflammatory Arthritis |
|---|---|---|
| Morning stiffness | >60 min; worsens with immobility | <30 min |
| Constitutional symptoms | Fever; fatigue; malaise | Generally absent |
| Physical examination findings | Erythema; warmth; soft-tissue swelling; joint effusions; reduced ROM is frequent | Minimal or no warmth; no soft-tissue swelling; bony enlargement and joint effusions may occur in osteoarthritis; reduced ROM may occur |
| Synovial fluid | Leukocyte count >2000/μL ($2.0 \times 10^9$/L), predominantly neutrophils in acute inflammation and monocytes in chronic inflammation | Leukocyte count of 200-2000/μL ($0.2\text{-}2.0 \times 10^9$/L), predominantly monocytes |
| Other laboratory findings | Elevated inflammatory markers (ESR, CRP); anemia of inflammation | Inflammatory markers usually normal or minimally elevated |

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ROM = range of motion.

### Oligoarthritis

Oligoarthritis involves two to four joints, typically in an asymmetric pattern.

Acute inflammatory oligoarthritis may be caused by gonorrhea or rheumatic fever. Chronic inflammatory oligoarthritis can be caused by autoimmune conditions, such as seronegative spondyloarthritis (e.g., psoriatic arthritis, reactive arthritis, arthritis related to inflammatory bowel disease, or ankylosing spondylitis).

Chronic noninflammatory oligoarthritis is usually caused by osteoarthritis.

### Polyarthritis

Polyarthritis involves five or more joints. In many cases, it involves the small joints of the hands and/or feet.

Acute polyarthritis (<6 weeks in duration) can be caused by viral infections (e.g., with parvovirus B19, HIV, hepatitis viruses, rubella, or chikungunya virus) or may be an early manifestation of chronic (≥6 weeks in duration) inflammatory polyarthritis, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or psoriatic arthritis.

## Soft-Tissue Abnormalities

Common nonarticular sources of musculoskeletal symptoms are the soft tissues (tendons, ligaments, and bursae) around or away from the joints. Isolated tendon and/or ligament involvement usually suggests noninflammatory disorders, such as mechanical injury/irritation, overuse, or degeneration (e.g., rotator cuff disorders or tennis elbow). Disorders of widespread musculoskeletal pain (e.g., fibromyalgia) also cause symptoms localizing to these structures.

The enthesis is a complex structure at the site of the insertion of a tendon or ligament onto the bone. Severe persistent inflammation of the enthesis (enthesitis) strongly suggests spondyloarthritis, especially when it affects multiple sites. The inflammation may extend along the associated tendon and local ligaments; it results in dactylitis ("sausage digits"), which is typically a feature of spondyloarthritis, particularly psoriatic arthritis.

See MKSAP 19 General Internal Medicine 1 for more information.

**KEY POINTS**

HVC

- Joint aspiration is usually the most effective means of diagnosing the underlying cause of acute monoarthritis.
- Chronic noninflammatory arthritis is usually caused by osteoarthritis.
- Isolated tendon and/or ligament involvement usually suggests noninflammatory disorders, such as mechanical injury/irritation, overuse, or degeneration.
- Persistent inflammation of the enthesis (enthesitis) strongly suggests spondyloarthritis.

## Extra-Articular Manifestations of Rheumatologic Disease

### Constitutional Symptoms

Fever, morning stiffness, and fatigue occur in numerous rheumatologic conditions. Fever is usually low grade but may be high-grade and spiking in some conditions (e.g., adult-onset Still disease and autoinflammatory diseases). Morning stiffness lasting more than 60 minutes is most commonly described in RA but also occurs with other forms of inflammatory arthritis. Significant and even disabling fatigue is a prominent feature of fibromyalgia.

### Skin Involvement

Skin involvement is common in rheumatologic conditions and may go unnoticed by the patient (**Table 2**). It may also be an adverse effect of medications used to treat rheumatologic conditions, including skin infections secondary to immunosuppressive therapy.

### Eye Involvement

Eye involvement in different rheumatologic diseases usually follows fairly distinct patterns, and the location and type of involvement can help narrow the differential diagnosis (**Table 3**). If not quickly recognized and treated, certain forms of eye involvement can have devastating consequences, including permanent loss of vision. See MKSAP 19 General Internal Medicine 2 for additional information on ocular manifestations of rheumatologic disease.

### Internal Organ Involvement

Rheumatologic diseases frequently affect internal organs, with different diseases tending to follow characteristic patterns (**Table 4**).

**KEY POINT**

- Rheumatologic disease can cause constitutional symptoms and extra-articular manifestations affecting the skin, eyes, and internal organs.

## Laboratory Studies

Laboratory studies are useful for diagnosing rheumatologic diseases, identifying the extent/severity of involvement, evaluating disease activity, and monitoring therapeutic responses. Because of limited specificity, results of these tests should always be interpreted in the context of the clinical history and physical examination and should be applied with great caution, if at all, in the setting of low pretest probability (see MKSAP 19 General Internal Medicine 1 for discussion of pretest probabilities).

### Tests That Measure Inflammation

#### Erythrocyte Sedimentation Rate

The erythrocyte sedimentation rate (ESR) measures the fall of erythrocytes (in millimeters per hour) through anticoagulated

**TABLE 2. Dermatologic Manifestations of Rheumatologic Disease**

| Rheumatologic Disease | Dermatologic Manifestations |
|---|---|
| Systemic lupus erythematosus | Acute cutaneous lupus erythematosus (commonly a malar rash); subacute cutaneous lupus erythematosus; photosensitive rash; chronic cutaneous lupus erythematosus (most commonly discoid lupus); oral ulcerations (on the tongue/hard palate; usually painless); alopecia; lupus panniculitis (painful, indurated subcutaneous swelling with overlying erythema of the skin) |
| Dermatomyositis | Gottron papules (erythematous plaques on extensor surfaces of MCP and PIP joints); photodistributed poikiloderma, including shawl sign (over the back and shoulders) and V sign (over the posterior neck/back or neck/upper chest); heliotrope rash (violaceous rash on the upper eyelids); mechanic's hands (hyperkeratotic, fissured skin on the palmar and lateral aspects of fingers); nailfold capillary abnormalities; holster sign (poikiloderma along lateral thigh); can occur in the absence of myositis (amyopathic dermatomyositis) |
| Systemic sclerosis | Skin tightening, thickening, and hardening; nailfold capillary changes; calcinosis; telangiectasias; decreased oral aperture; bi- or tri-color Raynaud phenomenon |
| Vasculitis | Palpable purpura; nodules; ulcers; necrosis; Raynaud phenomenon if cryoglobulins present |
| Behçet syndrome | Painful oral and genital ulcers; erythema nodosum; acne/folliculitis; pathergy (skin inflammation/ulceration from minor trauma) |
| Sarcoidosis | Erythema nodosum; infiltrated plaques; maculopapular and papular lesions; nodules; soft infiltrates of the nose (lupus pernio); on blanching with a glass slide, sarcoid skin lesions reveal "apple jelly" discoloration |
| Psoriatic arthritis | Plaque psoriasis typically on extensor surfaces, umbilicus, gluteal fold, scalp, and behind ears; pustular psoriasis on palms and soles; nail pitting; onychodystrophy |
| Reactive arthritis | Keratoderma blennorrhagicum (psoriasiform rash on soles, toes, palms); circinate balanitis (psoriasiform rash on penis) |
| Adult-onset Still disease | Evanescent, salmon-colored rash on trunk and proximal extremities |
| Rheumatic fever (secondary to streptococcal infection) | Erythema marginatum (annular pink to red nonpruritic rash with central clearing) |
| Lyme disease | Erythema chronicum migrans (slowly expanding, often annual lesion with central clearing) |

MCP = metacarpophalangeal; PIP = proximal interphalangeal.

**TABLE 3. Ocular Manifestations of Systemic Inflammatory Disease**

| Systemic Inflammatory Disease | Ocular Manifestations |
|---|---|
| Ankylosing spondylitis, reactive arthritis, and inflammatory bowel disease (anterior chamber); sarcoidosis and Behçet syndrome (anterior and/or posterior chamber); granulomatosis with polyangiitis (posterior chamber) | Uveitis (inflammation of anterior and/or posterior chamber and/or retina); anterior uveitis symptoms include pain, redness, visual change; posterior uveitis symptoms include painless visual change or floaters |
| Rheumatoid arthritis; spondyloarthritis; systemic vasculitis; rarely, SLE | Episcleritis; symptoms include redness, watering, and irritation but no vision loss |
| Rheumatoid arthritis; relapsing polychondritis; systemic vasculitis; inflammatory bowel disease; rarely, SLE | Scleritis; symptoms include severe eye pain that is worse at night and with eye movements; redness; photophobia |
| Systemic vasculitis; antiphospholipid syndrome; SLE | Retinal ischemia; symptoms include painless vision loss or change |
| Sjögren syndrome | Keratoconjunctivitis sicca; symptoms include dry eyes |
| Giant cell arteritis | Anterior/posterior ischemic optic neuropathy; central retinal artery occlusion; symptoms include loss of vision |
| Sarcoidosis; granulomatosis with polyangiitis; IgG4-related diseases | Proptosis/retrobulbar inflammatory infiltrate |
| Reactive arthritis | Conjunctivitis; symptoms include red eye |

SLE = systemic lupus erythematosus.

plasma. Erythrocytes tend to be negatively charged on their surfaces, leading to repulsion and a prolonged ESR. Fibrinogen and other acute phase reactants, as well as hypergammaglobulinemia (polyclonal or monoclonal), neutralize the erythrocytes' surface charges, promoting their ability to settle at a faster rate. Elevated fibrinogen levels and high ESRs are seen in many rheumatologic diseases, as well as in nonrheumatologic inflammatory conditions, such as chronic infections and malignancies. The normal ESR increases with age and is usually higher in women. A well-accepted rule of thumb is to adjust the upper limit of normal as (age in years)/2 for men and (age in years + 10)/2 for women.

**TABLE 4. Internal Organ Involvement in Rheumatologic Disease**

| Disease | Type of Involvement |
|---|---|
| **Heart** | |
| Kawasaki disease | Coronary artery vasculitis |
| Systemic sclerosis | Arrhythmia; myocardial fibrosis |
| SLE | Pericarditis; valvular disease; myocarditis |
| RA | Pericarditis; myocarditis |
| Rheumatic fever; antiphospholipid syndrome | Valvular disease |
| Giant cell arteritis | Aortic aneurysm/dissection; aortitis; large-vessel obstruction |
| Sarcoidosis | Atrioventricular block; arrhythmia; cardiomyopathy |
| **Lung** | |
| RA | Serositis; ILD; rheumatoid nodules |
| SLE; CTDs; myositis; Henoch-Schönlein purpura | Serositis; pneumonitis; pulmonary hemorrhage from vasculitis |
| AAV | Pulmonary hemorrhage; cavitary nodules |
| Diffuse cutaneous systemic sclerosis | ILD; pulmonary hypertension |
| Limited cutaneous systemic sclerosis | Pulmonary hypertension |
| Antiphospholipid syndrome | Pulmonary embolism; pulmonary hemorrhage in catastrophic antiphospholipid syndrome |
| Sarcoidosis | Hilar lymphadenopathy; ILD |
| Goodpasture syndrome | Pulmonary hemorrhage |
| **Kidney** | |
| SLE; CTDs; AAV; systemic vasculitis (except PAN) | Glomerulonephritis |
| PAN | Renal artery vasculitis; pseudoaneurysms |
| Antiphospholipid syndrome | Renal infarct; renal vein thrombosis |
| Sjögren syndrome | Acute interstitial nephritis/renal tubular acidosis |
| Goodpasture syndrome | Glomerulonephritis |
| **Gastrointestinal System** | |
| PAN | Mesenteric vasculitis |
| Henoch-Schönlein purpura | Intestinal vasculitis and ulcerations |
| Diffuse and limited cutaneous systemic sclerosis | Esophageal and small-bowel hypomotility |
| Behçet syndrome | Mucosal ulcerations |
| Familial Mediterranean fever | Peritonitis |
| **Nervous System** | |
| SLE; CTDs; AAV; systemic vasculitis | CNS involvement may include mental status changes, stroke, seizures; peripheral involvement may include mononeuritis multiplex and peripheral neuropathy |
| PACNS | CNS vasculitis |

AAV = ANCA-associated vasculitis; CNS = central nervous system; CTD = connective tissue disease; ILD = interstitial lung disease; PACNS = primary angiitis of the central nervous system; PAN = polyarteritis nodosa; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

In addition to inflammatory conditions, ESRs can be elevated in pregnancy, diabetes mellitus, obesity, and end-stage kidney disease. Because of rheostatic properties, anemia and macrocytosis are also associated with an increased ESR. ESR can be excessively low in low-fibrinogen states, such as liver or heart failure, and in conditions promoting rouleaux formation (e.g., polycythemia vera). Sickle cell disease and microcytosis (including spherocytosis) may also decrease ESR.

A markedly elevated ESR (>100 mm/h) should alert physicians to conditions such as giant cell arteritis, multiple myeloma, metastatic cancer, or other overwhelming inflammatory states (infection or autoimmune disease).

### C-Reactive Protein

C-reactive protein (CRP) is produced by the liver mainly in response to interleukin-6 generated by leukocytes during the inflammatory state. CRP levels and ESR usually follow a

common pattern, but CRP is often more rapidly responsive to changes in inflammation. In rheumatologic conditions, CRP is typically elevated 2 to 10 times the normal level; a higher level (especially >10 mg/dL [100 mg/L]) should prompt consideration of an alternative diagnosis, such as infection. CRP is thought to be a better marker than ESR for measuring inflammation in spondyloarthritis. In contrast, in some patients with SLE, ESR is a better marker of disease activity and the CRP level may remain normal despite active disease. An elevated CRP level in a patient with SLE is often related to infection. CRP can be elevated in obesity and low with the use of certain antibiotics and interleukin-6 blockers.

### Complement

The complement system is an essential part of the immune response, promoting vasodilation, attracting leukocytes, and assisting in the lysis of opsonized bacteria during humoral immunity.

Complement components are acute phase reactants that are synthesized in the liver and rise in many inflammatory states. However, in response to diseases that lead to immune complex formation (SLE; cryoglobulinemic and urticarial vasculitis) and other states, such as infections (subacute bacterial endocarditis, sepsis, viremia) and glomerulonephritis, complement cascades are activated, and complement levels fall because of excessive consumption. Paradoxically, genetic deficiency of early complement components may increase the risk for lupus-like autoimmune diseases.

C3 and C4 are the commonly measured complement components. The CH50 assay should not be performed routinely because of cost and limited utility.

## Autoantibody Tests

Rheumatologic diseases are commonly associated with autoantibodies, but their presence does not equate with the diagnosis of an underlying condition because they lack specificity and may be seen in patients with other conditions and in healthy persons. In commercial laboratories, autoantibody testing has been automated with enzyme-linked immunosorbent assays in a sequential algorithm, which may simplify physician assessment but tend to have reduced sensitivity and specificity.

Rheumatoid factor is an IgM antibody directed against the Fc portion of IgG. Although characteristically associated with RA, rheumatoid factor is present in less than 70% of patients with RA and is common in several other diseases, such as bacterial endocarditis and hepatitis C virus infection. Anti–cyclic citrullinated peptide antibodies are more specific (95%) for RA but less sensitive (67%). The presence of both autoantibodies together increases the likelihood of RA. Patients with RA who have anti–cyclic citrullinated peptide antibodies are more likely to experience rapid joint damage from erosive disease. Patients with hepatitis C virus infection alone are typically positive for rheumatoid factor but negative for anti–cyclic citrullinated peptide antibodies.

Antinuclear antibodies (ANAs) are directed against nuclear antigens and are traditionally associated with SLE. Up to one third of the healthy population has a low titer (1:40) for ANA, and up to 5% have a titer of 1:160 or more. ANA can also be seen in other autoimmune conditions, infection, and malignancy and may be drug-induced. ANA testing should not be performed in a patient with nonspecific symptoms and normal findings on clinical examination because it does not establish the diagnosis of a connective tissue disease.

A higher ANA titer is more often associated with an underlying rheumatologic disease, although not always SLE. However, almost all patients with SLE (>95%) are positive for ANA. ANA titer does not correlate with SLE disease activity and should not be used for activity assessment.

ANA specificity or subserology testing (i.e., testing for antibodies to specific nuclear components, such as DNA or centromeres) should be reserved for patients positive for ANA and a clinical syndrome suggesting an underlying connective tissue disease. ANA subserology testing should not be routinely performed, even in the setting of a positive ANA result, without a strong clinical suspicion of an underlying connective tissue disease.

**Table 5** provides details on these and other autoantibodies and their associations with specific conditions.

**KEY POINTS**

- Erythrocyte sedimentation rate and C-reactive protein (CRP) levels usually follow a common pattern, but CRP is often more rapidly responsive to changes in inflammation.
- Antinuclear antibody testing should not be performed in a patient with nonspecific symptoms and normal findings on clinical examination because it does not establish the diagnosis of a connective tissue disease. **HVC**
- Antinuclear antibody (ANA) subserology testing should not be routinely performed, even in the setting of a positive ANA result, without strong clinical suspicion of an underlying connective tissue disease. **HVC**

# Imaging Studies

## Radiography

Radiography is essential in the evaluation of many rheumatologic diseases and can assess and differentiate inflammatory arthritis, osteoarthritis, and crystal arthropathies (**Table 6**). Radiography has limitations because it gives a two-dimensional picture of three-dimensional structures, is limited in its ability to visualize soft tissues, and may not detect early or small erosive changes. Despite these limitations, radiography is usually the first imaging test ordered in the evaluation of rheumatologic diseases because it is readily available, is inexpensive, exposes patients to only a low level of ionizing radiation, and is useful in monitoring arthritis progression.

**TABLE 5. Autoantibodies in Rheumatologic Disease**

| Autoantibody | Rheumatologic Disease | Sensitivity/Specificity | Comments |
|---|---|---|---|
| ANA | SLE; also SSc, Sjögren syndrome, MCTD | SLE: >95% sensitivity, poor specificity; indirect IFA is the most appropriate method | Does not correlate with disease activity |
| Anti–double-stranded DNA | SLE | 50%-60% sensitivity, >95% specificity; *Crithidia* IFA or Farr assays more specific than ELISA | Found in more severe disease, especially kidney disease; antibody levels commonly follow disease activity and are useful to monitor |
| Anti-Smith | SLE | 30% sensitivity, 99% specificity | Most specific test for SLE; does not correlate with disease activity |
| Anti–U1-RNP | MCTD; SLE | High sensitivity for MCTD | High titer seen in MCTD (>1:10,000); does not correlate with disease activity |
| Anti-Ro/SSA; anti-La/SSB | Sjögren syndrome; SLE; RA; SSc | Sjögren syndrome: 70% sensitivity; SLE: 20% sensitivity | Sicca symptoms; in SLE, associated with photosensitive rash; offspring of mothers who are positive for anti-Ro/SSA or anti-La/SSB are at increased risk for neonatal lupus erythematosus (rash and congenital heart block) |
| Antiribosomal P | SLE | 15% sensitivity | Associated with CNS lupus and lupus hepatitis |
| Anti–Scl-70 (antitopoisomerase-1) | DcSSc | 10%-30% sensitivity | Seen more often in patients with DcSSc who have ILD leading to pulmonary fibrosis |
| Anticentromere | LcSSc (CREST) | 10%-30% sensitivity | Patients with LcSSc with this antibody are more likely to develop pulmonary arterial hypertension |
| c-ANCA (antiproteinase-3) | GPA | 90% sensitivity when disease is active; high specificity in classic presentations | Correlation with disease activity is unclear |
| p-ANCA (antimyeloperoxidase) | MPA; EGPA | MPA: 80% sensitivity; EGPA: 60% sensitivity; less specific than c-ANCA | Atypical p-ANCA (antimyeloperoxidase negative) can be seen in inflammatory bowel disease and with positivity for ANA; may be seen in drug-induced vasculitis |
| Anti–Jo-1 | Polymyositis | 20%-30% sensitivity | Associated with antisynthetase syndrome, which may include mechanic's hands, Raynaud phenomenon, and lung inflammation |
| Anti-SRP | Polymyositis | Found in 5% of patients with myositis | Associated with immune-mediated necrotizing myopathy with muscle fiber necrosis and minimal inflammation on biopsy |
| Anti–Mi-2 | Dermatomyositis | Rare | Acute onset of skin rash in shawl distribution, usually responsive to treatment |
| Anti–TIF-1-γ | Dermatomyositis | Approximately 70% sensitivity and 90% specificity | Increased risk for malignancy; also seen in juvenile dermatomyositis |
| Anti–MDA-5 | Dermatomyositis | Rare | Associated with rapid ILD, cutaneous ulcerations, Gottron papules; poorer prognosis |
| Rheumatoid factor | RA; Sjögren syndrome; cryoglobulinemia | RA: 70% sensitivity; limited specificity, especially in patients without a classic disease presentation | RF is common in multiple other diseases (e.g., hepatitis C virus infection, endocarditis, SLE); 30% of patients with RA are RF negative but may become positive later in RA course |
| Anti–cyclic citrullinated peptide | RA | 70% sensitivity; 95% specificity | Can be positive in RF-negative patients with RA; often present before RF becomes positive; associated with erosions; predicts disease progression in undifferentiated arthritis |
| Antihistone | DILE | 95% sensitivity; poor specificity | Also seen in primary SLE |
| Cryoglobulins | Vasculitis; hepatitis C virus infection; myeloma; SLE; RA | Type II or III cryoglobulins seen in cryoglobulinemic vasculitis | May be present in connective tissue diseases in the absence of vasculitis |

ANA = antinuclear antibody; CNS = central nervous system; CREST = calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; DcSSc = diffuse cutaneous systemic sclerosis; DILE = drug-induced lupus erythematosus; EGPA = eosinophilic granulomatosis with polyangiitis; ELISA = enzyme-linked immunosorbent assay; GPA = granulomatosis with polyangiitis; IFA = immunofluorescence assay; ILD = interstitial lung disease; LcSSc = limited cutaneous systemic sclerosis; MCTD = mixed connective tissue disease; MDA = melanoma differentiation–associated; MPA = microscopic polyangiitis; RA = rheumatoid arthritis; RF = rheumatoid factor; RNP = ribonucleoprotein; SLE = systemic lupus erythematosus; SRP = signal recognition particle; SSc = systemic sclerosis; TIF = transcription intermediary factor.

**TABLE 6. Standard Radiographic Findings of Common Rheumatologic Diseases**

| Rheumatologic Disease | Radiographic Findings |
|---|---|
| Rheumatoid arthritis | Soft-tissue swelling and periarticular osteopenia early; bony marginal erosions and uniform joint-space narrowing later |
| | Swan neck deformity and ulnar deviation if unresponsive or untreated; MCP, PIP, wrist, and MTP involvement; noncalcified soft-tissue nodules |
| Osteoarthritis | Asymmetric joint-space narrowing; osteophytes; subchondral sclerosis and cystic changes; degenerative disk disease with collapse of disks; degenerative joint disease with facet joint osteophytes; spondylolisthesis (anterior/posterior misalignment of the spine); kyphosis |
| Diffuse idiopathic skeletal hyperostosis | Calcification (ossification) of anterior longitudinal ligament (bone spurs); bridging horizontal syndesmophytes; usually seen in thoracic spine and more prominent on right side of spine |
| Ankylosing spondylitis | Sacroiliitis best seen on modified anteroposterior Ferguson view of sacrum on radiograph, usually bilateral; squaring of the vertebral bodies in early disease; bridging vertical syndesmophytes (ossification of annulus fibrosus) in later disease; shiny corners; ankylosis does not skip vertebrae |
| Psoriatic arthritis | Destructive arthritis with erosions and osteophytes; DIP involvement is common; pencil-in-cup deformity on hand radiograph; arthritis mutilans; syndesmophytes |
| Gout | Soft-tissue swelling; punched-out erosions with sclerotic borders and overhanging edges; periarticular tophi appear as high-density radiopaque deposits |
| Calcium pyrophosphate deposition | Chondrocalcinosis, most commonly of knees, shoulders, wrists, pubic symphysis; osteoarthritis, including in locations atypical for primary osteoarthritis (MCPs, wrists, shoulders); hooked osteophytes of second and third MCP joints |

DIP = distal interphalangeal; MCP = metacarpophalangeal; MTP = metatarsophalangeal; PIP = proximal interphalangeal.

### CT

CT provides multiple views and orientations from a single study but is more useful for bony abnormalities than for soft-tissue inflammation or fluid collections. CT is more sensitive for detecting bone erosions than is radiography or MRI. However, CT is more expensive than radiography and exposes the patient to more radiation. It is mainly used in acute trauma or when a patient cannot undergo MRI. Dual-energy CT may be used to detect tissue urate deposits but is not indicated in routine testing.

### MRI

MRI is the most sensitive routine radiologic technique for detecting soft-tissue abnormalities, inflammation, and fluid collections but is less effective than CT in demonstrating bony abnormalities or erosions. MRI is sensitive for detecting early spine and sacroiliac joint inflammation and may be indicated for the evaluation of suspected spondyloarthritis if radiographs are negative. MRI is also indicated in the evaluation of osteonecrosis if the findings on plain imaging are normal and suspicion is high. MRI does not expose patients to radiation but is associated with high cost, limited availability, and possible patient intolerance due to claustrophobia or body habitus. The American College of Rheumatology Choosing Wisely list recommends against routine MRI of the peripheral joints to monitor RA because of inadequate data supporting its use.

### Ultrasonography

The use of ultrasonography to evaluate patients with rheumatologic diseases has expanded dramatically. Ultrasonography is relatively inexpensive, can scan across three-dimensional structures, and can provide real-time data in the clinic without exposure to ionizing radiation. It can assess soft-tissue abnormalities, including synovitis, tendonitis, bursitis, crystal deposition, and effusions; assess disease activity using Doppler technology; and assist with tendon or joint injections. However, it is operator dependent, and training and practice are needed to achieve competence.

**KEY POINTS**

- Radiography is usually the first imaging test ordered in the evaluation of rheumatologic diseases because it is readily available, is inexpensive, exposes patients to only a low level of ionizing radiation, and is useful in monitoring arthritis progression. **HVC**
- CT is more sensitive for detecting bony abnormalities or erosions than is radiography or MRI, whereas MRI is the most sensitive routine radiologic technique for detecting soft-tissue abnormalities, inflammation, and fluid collections. **HVC**
- Ultrasonography is an inexpensive means to assess soft-tissue abnormalities, assess disease activity, and assist with tendon or joint injections, but it is operator dependent. **HVC**

## Joint Aspiration

Joint aspiration and synovial fluid analysis are essential for discriminating between inflammatory and noninflammatory effusions and for distinguishing between infectious arthritis and acute crystal arthropathies. In the evaluation of any monoarthritis or when infection is being considered, joint

**TABLE 7. Synovial Fluid Analysis**

| | Normal | Noninflammatory | Inflammatory | Crystal-Induced | Infectious | Hemorrhagic |
|---|---|---|---|---|---|---|
| Appearance | Clear/yellow/ transparent | Clear/yellow/ transparent | Yellow/white/ translucent/ opaque | Yellow/white/ translucent/ opaque | Yellow/white/ opaque | Red/opaque |
| Leukocyte count | <200/μL ($0.2 \times 10^9$/L) | 200-2000/μL ($0.2\text{-}2.0 \times 10^9$/L) | 2000-20,000/μL ($2.0\text{-}20 \times 10^9$/L) (may be higher) | 10,000-50,000/μL ($10\text{-}50 \times 10^9$/L) (may be higher) | >50,000/μL ($50 \times 10^9$/L) (may be lower) | — |
| Other studies | Negative Gram stain; negative culture | Negative Gram stain; negative culture | Negative Gram stain; negative culture | Negative Gram stain; positive crystals[a] | Positive Gram stain[b]; positive culture[c] | Negative Gram stain; negative culture |

[a]Crystal description: Urate crystals are needle-shaped and bright. Viewed under polarized light, they are negatively birefringent; they appear yellow when parallel to the axis of the polarized field and blue when perpendicular to the axis. Calcium pyrophosphate crystals are rhomboid, pale, and weakly (not as vividly) positively birefringent; they appear blue when parallel to the axis and yellow when perpendicular.

[b]Gram stain sensitivity for infection is approximately 30% to 50%.

[c]Nearly all cultures are positive except for infection caused by *Neisseria gonorrhoeae*, which may be positive in 50% or fewer cases.

aspiration should be performed to diagnose the underlying cause. Aspirated synovial fluid should be sent for leukocyte count, Gram stain, and cultures, as well as evaluation for crystals under polarized light. See **Table 7** for more information.

There is no absolute cutoff of synovial fluid leukocyte counts for ruling out infectious arthritis; however, counts greater than 50,000/μL ($50 \times 10^9$/L) with polymorphonuclear cell predominance have a high likelihood of infection. Counts less than 2000/μL ($2.0 \times 10^9$/L) are usually associated with noninflammatory causes. Notably, crystals can coexist with infection, and their presence does not rule out infection if suspicion is high.

## Tissue Biopsy

When appropriate, tissue biopsy of involved organs can be helpful in diagnosing numerous rheumatologic conditions, such as vasculitis (lung, kidney, or temporal artery biopsy) and SLE or dermatomyositis (skin biopsy). Tissue biopsy may also help assess disease activity (e.g., kidney biopsy in SLE). The benefits should be appropriately balanced with possible risks of the procedure.

## Mental Health Screening

Practitioners should be aware that patients with arthritis experience mental distress and have a history of depression at higher rates than the general population. Concurrent depression in chronic conditions, such as arthritis, is associated with reduced adherence to medical treatment recommendations. Among patients with rheumatoid arthritis, anxiety and depression are associated with reduced response to treatment and poorer quality of life. Active screening for depression, recommended for all adults, is therefore of still greater importance in individuals with arthritis and may improve outcomes. Actively engaging adults with arthritis in evidence-based self-management programs is helpful not only for arthritis but also for reducing depression and improving self-efficacy.

**KEY POINTS**

- Synovial fluid leukocyte counts greater than 50,000/μL ($50 \times 10^9$/L) with polymorphonuclear cell predominance have a high likelihood of infection; counts less than 2000/μL ($2.0 \times 10^9$/L) are usually associated with noninflammatory causes.
- Tissue biopsy of involved organs can be helpful in diagnosing numerous rheumatologic conditions and in assessing disease activity in some conditions.

# Principles of Therapeutics

## Overview

This section reviews the indications for use, mechanisms of action, major toxicities, and monitoring requirements of medications used in rheumatologic disease. Drug applications in specific disease states are elaborated on in their respective sections.

## Anti-Inflammatory Agents

### Glucocorticoids

Glucocorticoids are effective in many rheumatologic diseases, including rheumatoid arthritis (RA), acute crystal arthropathy, systemic vasculitis, polymyalgia rheumatica, systemic lupus erythematosus, inflammatory myopathies, and autoinflammatory diseases. Advantages include rapid onset, ease of use, low cost, and universal availability; they are often disease modifying and sometimes lifesaving.

Adverse effects include osteoporosis, immunosuppression, skin fragility, glaucoma, cataracts, weight gain, diabetes mellitus, hypertension, psychomotor agitation, osteonecrosis, and suppression of the hypothalamic-pituitary-adrenal axis. These effects are more likely with higher doses and longer treatment.

The immunosuppressive adverse effects of glucocorticoids are apparent at moderate (prednisone at ≥20 mg/d) and high

doses but can also occur at lower doses (e.g., 7.5 mg/d for more than a few weeks). The American College of Rheumatology (ACR) recommends that patients who are anticipated to be receiving long-term glucocorticoid treatment (prednisone at ≥2.5 mg/d for ≥3 months) should have a baseline clinical risk assessment for osteoporosis within 3 to 6 months of initiation of therapy. Those with risk factors and those older than age 40 years should also undergo periodic bone mineral density testing. Furthermore, those at moderate or high risk for osteoporotic fractures who are prescribed long-term glucocorticoid therapy should be treated prophylactically with an antiresorptive agent, preferably an oral bisphosphonate.

### NSAIDs

NSAIDs prevent prostaglandin production by inhibiting the two isoforms of cyclooxygenase (COX): COX-1 and COX-2. COX-2 is an inducible enzyme typically expressed in inflammatory milieus, whereas COX-1 is constitutively expressed and helps maintain organismal homeostasis. Nearly all available COX inhibitors are nonselective (i.e., they inhibit both COX isoforms), down-regulating prostaglandin production in inflammatory states, and interfering with functions of prostanoids (e.g., renal blood flow and gut mucosal integrity maintenance) (**Table 8**). Nonselective COX inhibitors also inhibit thromboxane $A_2$, thereby inhibiting platelet function.

Although they alleviate symptoms, COX inhibitors are not disease modifying, with the possible exception of ankylosing spondylitis. Major concerns surrounding all COX inhibitors include increased risk for gastrointestinal bleeding and adverse cardiovascular events; therefore, they should be prescribed at the lowest dose for the shortest time possible. COX inhibitors should generally be avoided in patients receiving concomitant anticoagulation.

NSAIDs vary with regard to kinetics, COX-1/2 selectivity, and other features, and they carry somewhat different degrees of cardiovascular and other risks; having experience with several different NSAIDs is beneficial in clinical practice.

A topical preparation of the NSAID diclofenac is available both by prescription and over the counter for arthritis. It poses a lower risk for systemic adverse effects compared with oral NSAIDs. Topical NSAIDs are strongly recommended for patients with knee osteoarthritis and conditionally recommended for patients with hand osteoarthritis. Topical diclofenac may also be preferred for patients at high risk for toxicity from oral NSAIDs or those 75 years of age or older.

### Colchicine

Colchicine inhibits microtubules, impairs neutrophil function, and inhibits inflammasome-mediated interleukin-1 activation. Inflammasome is a central signaling system that regulates the inflammatory response. It is most commonly used for gout and acute calcium pyrophosphate crystal arthritis (pseudogout). It is also a treatment for hypersensitivity vasculitis and familial Mediterranean fever.

Gastrointestinal adverse effects (particularly diarrhea) are common but reversible with dose adjustment or discontinuation. With overdose, severe (even fatal) myelosuppression can occur. Dosing must be adjusted for kidney disease. When given over the long term, colchicine can rarely cause neuromuscular toxicity, particularly if coadministered with strong CYP3A4 inhibitors (e.g., clarithromycin) that reduce the hepatic catabolism of colchicine. Such coadministration should be avoided.

**KEY POINTS**

- Patients anticipated to be receiving long-term glucocorticoid treatment (prednisone at ≥2.5 mg/d for ≥3 months) should have a baseline clinical risk assessment for osteoporosis within 3 to 6 months of initiation of therapy.
- Because of the increased risk for gastrointestinal bleeding and adverse cardiovascular and renal events, cyclooxygenase inhibitors should be prescribed at the lowest dose for the shortest time possible.

## Analgesics and Pain Pathway Modulators

Pain is a central symptom for patients with inflammatory arthritis and osteoarthritis. It is important to use a patient-centered approach while managing pain in these patients. In addition to pharmacologic interventions, treatment should include patient education, guidance on physical activity and exercise, orthotics, psychological and social interventions, sleep hygiene education, and, if indicated, sleep interventions.

**TABLE 8. Potential Toxicities of NSAID Use**

| Category | Toxicity |
|---|---|
| Cardiovascular | Myocardial infarction; exacerbation of heart failure |
| Hemostatic | Platelet dysfunction |
| Gastrointestinal | Dyspepsia; reflux; peptic ulcer disease; gastrointestinal bleeding |
| Obstetric/Gynecologic | Bleeding; delayed labor; premature ductus arteriosus closure |
| Pulmonary | Asthma exacerbation |
| Renal | Hypertension; decreased glomerular filtration; increased salt and water retention; increased renin production; uncommonly, allergic interstitial nephritis or acute tubular necrosis |

### Acetaminophen

The efficacy of acetaminophen for osteoarthritis and lower back pain has been questioned. Controlled trials and meta-analyses have shown no benefit from the drug, even at high doses. However, because of its favorable safety profile, it may be empirically tried for short-term or add-on therapy. The daily dosage should not exceed 3000 mg/d. ACR guidelines conditionally recommend acetaminophen for patients with knee, hip, or hand osteoarthritis and limited pharmacologic options.

### Tramadol

Tramadol is a mixed opioid analgesic and weak serotonin-norepinephrine reuptake inhibitor (SNRI) with a lower potential for addiction than traditional opioids. It may be considered in a limited number of patients for whom other methods of analgesia were ineffective or not tolerated. Adverse effects may include nausea, vomiting, constipation, lightheadedness, and sedation. Traditional opioids should generally be avoided in rheumatologic treatment because of limited efficacy, high toxicity, and high potential for dependence. See MKSAP 19 General Internal Medicine 1 for discussion of risk assessment and monitoring of long-term opioid therapy.

### Serotonin-Norepinephrine Reuptake Inhibitors

Duloxetine is an SNRI approved by the FDA for the management of chronic musculoskeletal pain and fibromyalgia. Duloxetine provides modest pain relief for knee osteoarthritis, chronic lower back pain, and fibromyalgia. Milnacipran is another SNRI approved for fibromyalgia. To avoid withdrawal symptoms, patients must be slowly weaned off SNRIs when the drug is discontinued.

### Gabapentinoids

Gabapentinoids (gabapentin and pregabalin) inhibit voltage-gated calcium channels, thereby reducing pain signaling from the periphery to the central nervous system. Pregabalin is FDA approved for fibromyalgia. Common adverse effects (dizziness, disequilibrium, somnolence, weight gain, peripheral edema, and cognitive difficulties) may limit its utility. The FDA has issued a safety alert stating that serious breathing difficulties may occur in patients using gabapentin or pregabalin who have respiratory risk factors (e.g., older persons, patients with COPD, and patients receiving opioids and other drugs that depress the central nervous system).

KEY POINTS

- The American College of Rheumatology conditionally recommends acetaminophen for knee, hip, and hand osteoarthritis.
- Traditional opioids should generally be avoided in rheumatologic treatment because of limited efficacy, high toxicity, and high potential for dependence.

# Disease-Modifying Antirheumatic Drugs

## Nonbiologic Disease-Modifying Antirheumatic Drugs

**Table 9** summarizes the mechanisms of action, indicatio common monitoring parameters of various nonbiologic d modifying antirheumatic drugs (DMARDs). See Medicati Pregnancy for information on these drugs in pregnancy.

### Methotrexate

Methotrexate is a first-line medication for RA and other immune diseases. Once-weekly dosing is generally 25 mg; the drug can be given orally or subcutaneously. At above 15 mg, parenteral administration is more reliabl much more expensive.

Potential adverse effects include headaches, fatigue nausea (particularly around the time of weekly dos Hepatotoxicity and cytopenia can occur (especially ma cytic anemia), and dose adjustment is required with kid disease. Methotrexate should be avoided in patients with nificant hepatic or kidney disease and is absolutely contr dicated around pregnancy. Folic acid supplements minim toxicity while preserving efficacy. Limiting alcohol inta recommended.

### Hydroxychloroquine

Hydroxychloroquine is an immunomodulator widely used systemic lupus erythematosus, in which it decreases morta and the likelihood of nephritis. It is rarely sufficient as sin drug therapy for RA but is useful as an adjunctive therapy

### Sulfasalazine

Sulfasalazine is used to treat RA and nonaxial psoriatic arth tis. It is now most frequently used as part of combina DMARD therapy for RA. Serious adverse effects include bl dyscrasias, hepatitis, and hypersensitivity reactions. Beca of the benefit of its salicylate moiety for inflammatory bo disease, it may be a useful strategy for patients with inflam tory bowel disease–associated arthritis.

### Leflunomide

Leflunomide is FDA approved for RA and psoriatic arthr with efficacy similar to that of methotrexate. Patients must monitored for hepatotoxicity and myelosuppression. Co common adverse effects include nausea, headaches, rash, d rhea, and elevation of serum aminotransferase levels. Peripher neuropathy is an uncommon adverse effect that is usually s limited if the drug is discontinued. Leflunomide is highly te togenic and absolutely contraindicated around pregnancy.

### Azathioprine

Azathioprine is an immunosuppressant used in various inf matory diseases. Its primary toxicity is myelosuppressi especially in individuals with a decreased or absent thiopur

**TABLE 9. Nonbiologic Disease-Modifying Antirheumatic Drugs**

| Agent | Mechanisms of Action | Indications | Common Monitoring Parameters |
|---|---|---|---|
| Methotrexate | Low dose: anti-inflammatory agent via up-regulation of adenosine $A_{2A}$ signaling<br>High dose: antimetabolite/folate antagonist used in neoplastic disease | RA; psoriasis; psoriatic arthritis; IBD; SLE (arthritis only); reactive arthritis; DM; PM; vasculitis | Baseline: chest radiography, hepatitis screening, CBC, LCTs, serum creatinine<br>Thereafter: CBC, LCTs, serum creatinine after first month, then approximately every 2-3 months[a] |
| Hydroxychloroquine | Uncertain; appears to involve stabilization of lysosomal vacuoles, leading to inhibition of antigen processing and/or inhibition of Toll-like receptor activation | SLE; RA | Baseline: CBC, LCTs, serum creatinine<br>Retinal examinations at baseline and annual examination after 5 years of therapy to evaluate for retinopathy |
| Sulfasalazine | Unknown; the prodrug is broken down into 5-amino salicylic acid (active metabolite in gastrointestinal tract) and sulfapyridine (exerts systemic action) | RA; SpA; IBD | Baseline: CBC, LCTs, serum creatinine<br>Thereafter: CBC, LCTs, serum creatinine every 3-6 months |
| Leflunomide | Inhibits mitochondrial enzyme dihydroorotate dehydrogenase to block pyrimidine synthesis (decreasing lymphocyte production); antiproliferative | RA; psoriatic arthritis | Baseline: hepatitis screening, CBC, LCTs, serum creatinine<br>Thereafter: CBC, LCTs, serum creatinine after 4 weeks, then every 3 months |
| Azathioprine | Prodrug of 6-mercaptopurine; purine analogue; inhibits DNA synthesis essential for proliferating T and B lymphocytes | SLE; DM; PM; vasculitis; IBD | Baseline: CBC, LCTs, serum creatinine<br>Thereafter: CBC, LCTs, serum creatinine every 3 months[a] |
| Cyclophosphamide | Alkylating agent; blocks DNA synthesis and causes cell death, especially of T cells | Severe and life-threatening complications in SLE, DM, PM, and vasculitis; may be used when other agents fail | Close monitoring clinically and measuring CBC, chemistries, LCTs, urinalysis every 4-8 weeks |
| Mycophenolate mofetil | Active metabolite (mycophenolic acid) inhibits purine synthesis; preferentially inhibits T and B lymphocytes | SLE (especially lupus nephritis); vasculitis (maintenance therapy); DM; PM; SSc | Baseline: CBC, LCTs, serum creatinine<br>Thereafter: CBC, LCTs, serum creatinine after 4 weeks and then every 3 months[a] |
| Cyclosporine, voclosporin | Inhibit calcineurin (transcription activating factor); preferentially target T cells | SLE; psoriasis; RA (cyclosporine)<br>Lupus nephritis (voclosporin) | Baseline: CBC, LCTs, serum creatinine<br>Thereafter: CBC, LCTs, serum creatinine every 2-3 months[a] |
| Tofacitinib, baricitinib, upadacitinib | Janus kinase inhibitors | RA (tofacitinib, baricitinib, upadacitinib)<br>Psoriatic arthritis (tofacitinib) | Baseline: CBC, LCTs, serum creatinine, lipid panel<br>Thereafter: CBC, LCTs, serum creatinine every 8 weeks, lipids after 8 weeks and then every 6 months |
| Apremilast | Phosphodiesterase-4 inhibitor | Psoriasis; psoriatic arthritis; oral ulcers associated with Behçet syndrome | Baseline: weight<br>Thereafter: weight, neuropsychiatric effects |

CBC = complete blood count; DM = dermatomyositis; IBD = inflammatory bowel disease; LCT = liver chemistry test; PM = polymyositis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SpA = spondyloarthritis; SSc = systemic sclerosis.

[a]Recommended monitoring interval is for a stable dose but may be shorter after initiation or in the case of abnormal results; must be individualized to the patient's risk for toxicity.

methyltransferase enzyme. Because azathioprine is metabolized by xanthine oxidase, concomitant use with xanthine oxidase inhibitors (allopurinol, febuxostat) is contraindicated.

### Cyclophosphamide

Cyclophosphamide has a rapid onset of action (days to weeks). It is used to treat vasculitis, life-threatening complications of systemic lupus erythematosus, and interstitial lung disease. Cyclophosphamide has largely been displaced by safer drugs for first-line treatment of ANCA-associated vasculitis and lupus nephritis (rituximab and mycophenolate mofetil, respectively) but is still used in severe cases or when these agents fail. Serious potential adverse effects include severe immunosuppression, leukopenia, hemorrhagic cystitis, and ovarian failure, as well as long-term risk for bladder cancer, leukemia, and lymphoma.

### Mycophenolate Mofetil

Mycophenolate mofetil is the first-line agent for lupus nephritis and may be effective for systemic sclerosis with associated interstitial lung disease. Gastrointestinal adverse effects, including diarrhea, are common. Myelosuppression may occur.

### Calcineurin Inhibitors

Calcineurin inhibitors include cyclosporine, tacrolimus, and voclosporin. Cyclosporine is now rarely used for rheumatologic conditions because of renal adverse effects, hypertension, hyperuricemia (often presenting as gout), and need for frequent drug level monitoring. Tacrolimus may be considered as alternative therapy for some patients with lupus nephritis. Voclosporin, a next-generation calcineurin inhibitor with higher potency and improved side-effect profile, is FDA approved for lupus nephritis.

### Janus Kinase Inhibitors

Tofacitinib is an oral agent that inhibits Janus kinase (JAK) 1/3 signaling. Tofacitinib is FDA approved for RA and psoriatic arthritis, with efficacy equal to that of biologic DMARDs. Risks include hyperlipidemia, hepatotoxicity, leukopenia, reactivation of zoster (at a rate higher than seen with biologic therapies), and thrombotic events when used at higher doses. Newer JAK inhibitors approved for rheumatologic diseases include baricitinib (JAK1/2) and upadacitinib (JAK1).

### Apremilast

Apremilast is modestly effective for psoriasis and psoriatic arthritis. It does not cause immunosuppression or myelosuppression. However, apremilast is less efficacious than biologic DMARDs and has a slow onset of action, and its effect on progression of erosive damage is unknown. Risks include gastrointestinal adverse effects (mainly nausea and diarrhea) and weight loss. It should be used with caution in patients with a history of depression. Apremilast is also FDA approved for treatment of oral ulcers in Behçet syndrome.

**KEY POINTS**

- Methotrexate is a first-line medication for rheumatoid arthritis and other autoimmune diseases.
- Hydroxychloroquine decreases mortality and the likelihood of developing nephritis in patients with systemic lupus erythematosus.
- Cyclophosphamide is used in severe cases of vasculitis and lupus nephritis or when other agents fail.
- The oral Janus kinase inhibitor tofacitinib is FDA approved for rheumatoid arthritis and psoriatic arthritis and has efficacy equal to that of biologic agents.

## Biologic Disease-Modifying Antirheumatic Drugs

Biologic DMARDs are highly specific, parenterally administered, protein-based agents with extracellular targets (cytokines, cytokine receptors, or cell surface molecules on immune cells) (**Figure 1**). The end of the generic name of a biologic agent

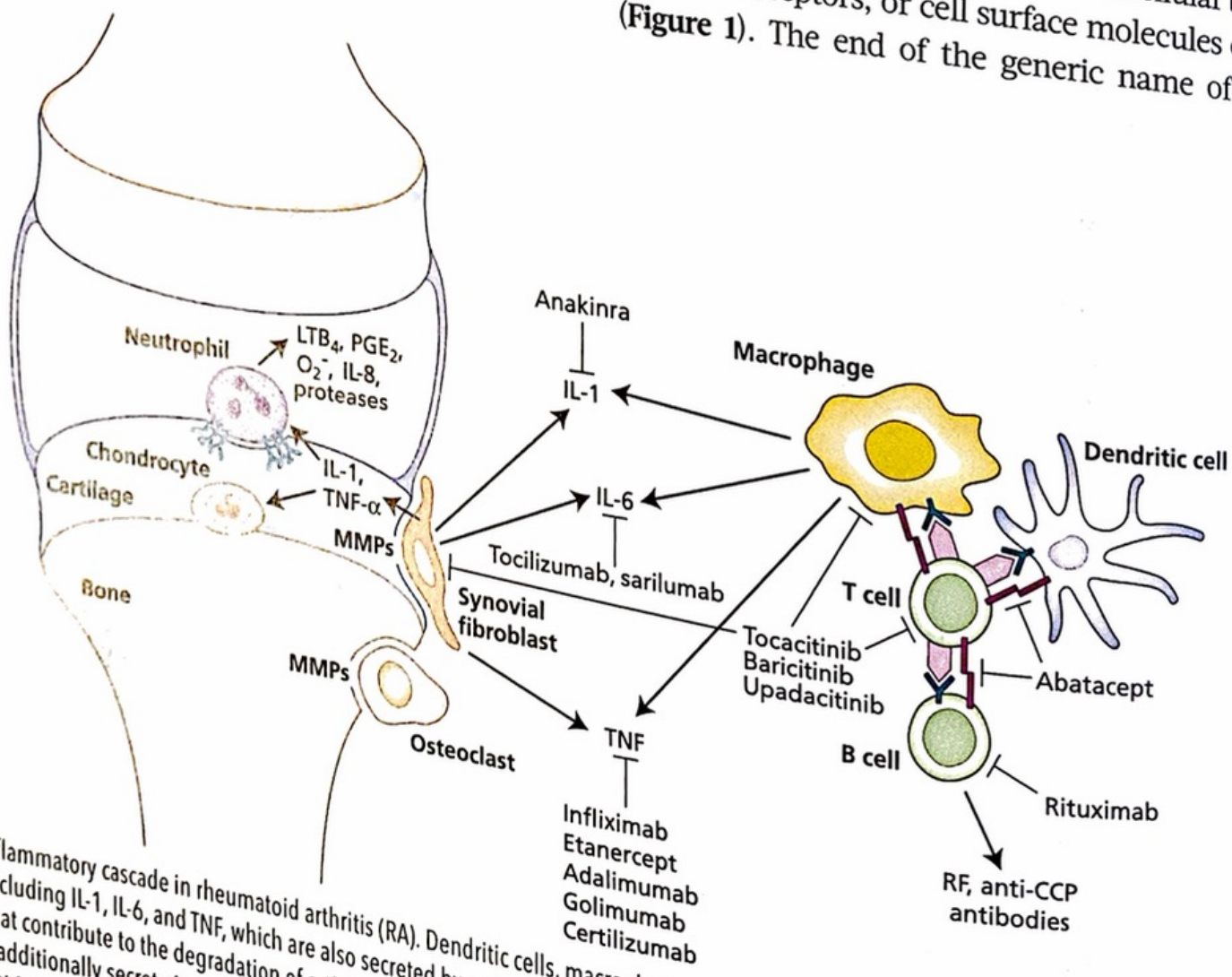


**FIGURE 1.** The inflammatory cascade in rheumatoid arthritis (RA). Dendritic cells, macrophages, and B cells present inciting antigens to T cells. Macrophages secrete multiple cytokines, including IL-1, IL-6, and TNF, which are also secreted by activated synovial fibroblasts. The activated fibroblasts secrete matrix metalloproteinases (MMPs) and other enzymes that contribute to the degradation of articular cartilage and activate neutrophils, which mediate joint damage through proteases and other enzymes. Activated osteoclasts additionally secrete MMPs that contribute to marginal erosions of bone. ILs, TNF, T cells, and B cells may all be targeted for inhibition by the various disease-modifying antirheumatic drugs useful in RA. CCP = cyclic citrullinated peptide; IL = interleukin; $LTB_4$ = leukotriene $B_4$; MMP = matrix metalloproteinase; $O_2$ = oxygen; $PGE_2$ = prostaglandin $E_2$; RF = rheumatoid factor; TNF = tumor necrosis factor.

**TABLE 10. Tumor Necrosis Factor Inhibitors[a]**

| Agent | Agent Structure | Indications |
|---|---|---|
| Infliximab | Chimeric (mouse-human) monoclonal antibody | RA; psoriatic arthritis; ankylosing spondylitis; IBD |
| Adalimumab | Humanized monoclonal antibody | RA; psoriatic arthritis; ankylosing spondylitis; IBD |
| Etanercept | Fusion protein made of two p75 TNF receptors linked to IgG Fc segment | RA; psoriatic arthritis; ankylosing spondylitis |
| Certolizumab pegol | Fab' segment of humanized monoclonal antibody attached to polyethylene glycol strands | RA; psoriatic arthritis; ankylosing spondylitis |
| Golimumab | Humanized monoclonal antibody | RA; psoriatic arthritis; ankylosing spondylitis |

IBD = inflammatory bowel disease; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

[a]Common monitoring parameters for TNF inhibitors include tuberculosis, fungal, and other infections as well as complete blood count, serum creatinine, and liver chemistry tests at baseline and every 3 to 6 months thereafter.

indicates what type of molecule it is: *-mab* indicates a monoclonal antibody, *-kin* indicates an interleukin-type substance, *-ra* is for a receptor antagonist, and *-cept* is for receptor-based molecule. All biologics require parenteral administration.

**Table 10** and **Table 11** summarize the structures, targets, indications, and common monitoring parameters of various biologic DMARDs. See Medications and Pregnancy for information on these drugs in pregnancy. Biologic DMARDs increase the risk for infection to varying degrees. Targeted screening is therefore necessary before initiation (see Vaccination and Screening in Immunosuppression).

The cost of biologic agents is significant and may be a barrier to access.

### Tumor Necrosis Factor Inhibitors

Tumor necrosis factor (TNF) inhibitors (see Table 10) are widely used for treating RA, psoriasis, psoriatic arthritis, and ankylosing spondylitis, as well as several nonrheumatologic diseases.

TNF inhibitors are generally well tolerated; increased risk for infection is the primary safety concern. Because TNF inhibitors pose a particularly high risk for reactivation of tuberculosis, all patients being considered for treatment must be screened for latent infection and, if needed, receive treatment. Except for nonmelanoma skin cancer and possibly melanoma, TNF inhibitors do not appear to increase the risk for new cancers; the risk for malignant recurrence remains unclear. TNF inhibitors may exacerbate heart failure and rarely provoke a demyelinating condition. Over time, individual TNF inhibitors may lose efficacy owing to formation of antidrug antibodies.

### Other Biologic Disease-Modifying Antirheumatic Drugs

Multiple biologic DMARDs with non-TNF extracellular and cell-surface targets have been approved by the FDA. Most of these agents are started after one or two TNF inhibitors have failed. See Table 11 for more information.

### Biosimilars

Biosimilar agents are "copycat" versions of brand-name biologic medications. The drugs are not exact replicas (hence the term "biosimilar"); therefore, they must undergo phase III testing to prove equivalent efficacy to the parent biologic. In the United States, biosimilars are distinguished from their originator molecules by the presence of a four-character alphabetic suffix. Biosimilars hold promise for decreasing cost and improving access, but those benefits have rarely been realized because of regulatory and market factors.

**KEY POINTS**

- All biologic agents increase the risk for infection; therefore, targeted screening is necessary before initiation.
- Tumor necrosis factor inhibitors pose a particularly high risk for reactivation of tuberculosis, and patients must be screened for latent infection before initiation of therapy.
- Biologic agents that are not directed at tumor necrosis factor (TNF) are usually started after one or two TNF inhibitors have failed. **HVC**

## Urate-Lowering Therapy

### Allopurinol

Allopurinol is the recommended first-line urate-lowering agent. It competitively inhibits the enzyme xanthine oxidase, blocking the conversion of hypoxanthine (a breakdown product of purines) to uric acid. Allopurinol is metabolized to oxypurinol, which also inhibits xanthine oxidase. Allopurinol is FDA approved for dosages up to 800 mg/d. Allopurinol should be initiated at 100 mg/d and titrated in 100-mg increments until the therapeutic target is achieved. For patients with stage 4 or 5 chronic kidney disease, allopurinol should be initiated at 50 mg/d and titrated in 50- to 100-mg increments as needed.

Allopurinol use is rarely associated with a hypersensitivity syndrome, most severely as DRESS (drug reaction with eosinophilia and systemic symptoms), a potentially fatal reaction. DRESS is also increasingly being referred to as *drug-induced hypersensitivity syndrome* (DIHS) to emphasize the fact that eosinophilia is not always present. Risk factors include chronic kidney disease and diuretic use; allopurinol dosage titration appears to substantially reduce the risk. Another DRESS risk

**TABLE 11. Other Biologic Disease-Modifying Antirheumatic Drugs[a]**

| Agent | Agent Structure | Target | Indications | Comments |
|---|---|---|---|---|
| Abatacept | Soluble CTLA4 receptor/IgG Fc segment chimera | CD80/CD86; blocks T-cell costimulation | RA | Preferred for patients with history of severe infection; relatively contraindicated in COPD |
| Rituximab | Chimeric (mouse-human) monoclonal antibody | $CD20^+$ B cells | RA; ANCA-associated vasculitis; occasionally for SLE (off-label); IgG4-related disease | Given as intravenous infusion over several hours; has higher risk for infusion reactions than other biologic DMARDs; can cause hypogammaglobulinemia |
| Tocilizumab | Humanized monoclonal antibody | IL-6 receptor | RA; JIA; Castleman disease; GCA | Can cause elevated aminotransferase levels, hyperlipidemia, leukopenia, thrombocytopenia; avoid in patients with history of diverticulitis because of attendant risk for bowel perforation |
| Sarilumab | Human monoclonal antibody | IL-6 receptor | RA | Can cause elevated aminotransferase levels, hyperlipidemia, leukopenia, thrombocytopenia |
| Belimumab | Human monoclonal antibody | BLyS/BAFF | SLE; lupus nephritis | Phase III trials showed small but statistically significant improvement versus standard therapy alone, with glucocorticoid-sparing effect |
| Ustekinumab | Human monoclonal antibody | IL-12/IL-23 | Psoriasis; psoriatic arthritis | Injectable; less robust effect than other biologic DMARDs |
| Secukinumab | Human monoclonal antibody | IL-17a | Psoriatic arthritis; ankylosing spondylitis | Phase III trials suggest efficacy equal to that of TNF inhibitors; can cause IBD flares |
| Ixekizumab | Humanized monoclonal antibody | IL-17a | Psoriatic arthritis; ankylosing spondylitis | Phase III trials suggest efficacy equal to that of TNF inhibitors; can cause IBD flares |
| Guselkumab | Human monoclonal antibody | IL-23 | Psoriasis; psoriatic arthritis | Selective IL-23 inhibitor |
| Anakinra | Recombinant receptor antagonist | IL-1β receptor | RA; CAPS[b]; AOSD (off-label); acute gouty arthritis (off-label) | Rarely used in RA because efficacy is inferior to that of other biologic DMARDs; reversible neutropenia can develop |
| Canakinumab | Human monoclonal antibody | IL-1β | CAPS[b] | More expensive IL-1β inhibitor |
| Rilonacept | Dual IL-1β receptors chimerically attached to IgG Fc segment | IL-1 | CAPS[b]; refractory gout | More expensive IL-1 inhibitor |
| Mepolizumab | Humanized monoclonal antibody | IL-5 | EGPA; eosinophilic asthma | Only biologic approved for treatment of EGPA |

AOSD = adult-onset Still disease; BAFF = B-cell–activating factor; BLyS = B-lymphocyte stimulator; CAPS = cryopyrin-associated periodic syndromes; DMARD = disease-modifying antirheumatic drug; EGPA = eosinophilic granulomatosis with polyangiitis; GCA = giant cell arteritis; IBD = inflammatory bowel disease; IL = interleukin; JIA = juvenile idiopathic arthritis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; TNF = tumor necrosis factor.

[a]Before initiation of any biologic, tuberculosis screening must be performed. Complete blood counts should be performed every 3 to 6 months for all biologics, and aspartate aminotransferase/alanine aminotransferase and a lipid panel should be checked every 2 to 3 months for tocilizumab.

[b]The cryopyrin-associated periodic syndromes (CAPS) include familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (chronic infantile neurologic, cutaneous, articular syndrome).

factor is the HLA-B*58:01 allele, which is more common in Black persons and persons of Han Chinese, Thai, and Korean descent and increases the risk for hypersensitivity by several hundred-fold. Screening for HLA-B*58:01 in these populations is conditionally recommended before initiation of allopurinol. Xanthine oxidase inhibitors should not be coadministered with purine analogues (such as azathioprine). See MKSAP 19 General Internal Medicine 2 for more information on DRESS.

### Febuxostat

Febuxostat is a noncompetitive xanthine oxidase inhibitor. Elevated aminotransferase levels can rarely occur, and liver enzymes should be monitored. Concomitant use with purine analogues is contraindicated. Incidence of hypersensitivity is rarer and usually less severe than with allopurinol. In a 2018 safety study, febuxostat users had an increased risk for cardiovascular death and all-cause mortality compared with patients receiving allopurinol. These data do not define febuxostat as raising risk compared with no treatment, and other studies have failed to support this observation; however, the results prompted the FDA to mandate a boxed warning for febuxostat regarding increased risk compared with allopurinol. The FDA has also limited the approved use of febuxostat to patients who are unresponsive to or cannot tolerate allopurinol.

### Uricosuric Agents

Probenecid is an organic acid transport inhibitor that decreases renal reuptake of uric acid. It is uncommonly used because of limited efficacy, inconvenience, and limitations on use (e.g., drug interactions and adverse effects).

### Pegloticase

Unlike most other mammals, humans lack a functioning uricase to break down uric acid. Pegloticase is a recombinant, nonhuman, infusible pegylated uricase that is highly effective at lowering serum urate. Pegloticase is reserved for severe and/or refractory gout. Because of its extreme potency, mobilization flares of gout are common, and prophylaxis against acute gouty attacks is required. Pegloticase is administered intravenously every 2 weeks; if the preinfusion serum urate increases to more than 6.0 mg/dL (0.35 mmol/L) on two occasions, antibodies have probably formed, and the drug should be discontinued to prevent infusion reactions.

**KEY POINTS**

- Allopurinol is the first-line urate-lowering agent; the biggest risk the drug poses is DRESS (drug reaction with eosinophilia and systemic symptoms).
- Concomitant use of xanthine oxidase inhibitors (allopurinol or febuxostat) with purine analogues is contraindicated.

## Medications and Pregnancy

Some rheumatologic medications can have adverse effects on pregnancy. **Table 12** lists these agents and their relative risks.

**KEY POINTS**

- Methotrexate is highly teratogenic and abortifacient; it must be discontinued at least 3 months before pregnancy.
- Hydroxychloroquine is relatively safe in pregnancy and should not be discontinued if it is needed.
- Leflunomide is extremely teratogenic and must not be used before or during pregnancy; upon discontinuation, cholestyramine is required to remove the drug from the body in all women of childbearing potential and specifically in those wishing to become pregnant.

## Vaccination and Screening in Immunosuppression

Patients with autoimmune diseases should be assessed for immunization status at diagnosis and/or initiation of treatments. Whenever possible, patients should be updated with vaccinations at least 2 to 4 weeks before initiating biologic DMARD regimens. Vaccine response may be diminished during biologic immunosuppressive treatment (particularly with B-cell–depleting therapy), and patients receiving biologic DMARDs and/or JAK inhibitors, such as tofacitinib, should not receive live attenuated vaccines (e.g., for measles, mumps and rubella; varicella herpes zoster; influenza; and yellow fever) because of risk for active infection. Such patients can receive the killed influenza and pneumococcal vaccines, as well as recombinant herpes zoster vaccine as needed. Other non-live vaccines that are indicated should be administered as per standard care (see MKSAP 19 General Internal Medicine 2 for more information). Patients receiving traditional oral DMARDs (e.g., hydroxychloroquine, methotrexate, and sulfasalazine) may receive any vaccines as needed.

Before initiation of immunosuppressive therapy, the following screening is recommended:

- Tuberculosis screening with tuberculin skin testing or interferon-γ release assay, particularly for patients initiating biologic DMARDs
- Hepatitis B and C virus serologic testing (for patients initiating biologic DMARDs and drugs that can cause hepatotoxicity)
- HIV screening

Patients with latent or active tuberculosis, active hepatitis B virus infection, or untreated HIV infection require initiation of appropriate therapy before initiating immunosuppression. Patients with risk factors for ongoing tuberculosis exposure should have annual tuberculosis screening.

**KEY POINTS**

- Whenever possible, vaccinations should be updated before initiating biologic disease-modifying antirheumatic drug regimens.
- Screening (and therapy if needed) for tuberculosis, hepatitis B and C virus, and HIV is appropriate before initiation of immunosuppressive therapy.

## Nonpharmacologic and Nontraditional Management

Because rheumatologic diseases frequently affect the musculoskeletal system, nonpharmacologic measures are often used to address pain not eliminated by medications. These measures include physical therapy, occupational therapy, surgery, weight reduction, psychosocial support, and self-management programs. Many patients turn to complementary and alternative medicine as adjuncts to traditional medical interventions.

### Physical and Occupational Therapy

Physical therapists can help primary care physicians assess aerobic fitness and conditioning as well as ability to carry out activities of daily living. Pain and functional limitation can be addressed through manual therapy, assistive devices, joint protection techniques, and thermal treatments. A targeted exercise program can be initiated, and adapting the program

**TABLE 12. Rheumatologic Medications and Pregnancy**

| Medication/Class | Comments |
|---|---|
| **Anti-Inflammatory Agents** | |
| NSAIDs | May impede implantation and be associated with small increased risk for miscarriage when used before 20 weeks' gestation. NSAID use after 30 weeks' gestation can lead to premature closure of ductus arteriosus. |
| Glucocorticoids | When taken in first trimester, can increase risk for fetal cleft palate and raise risk for maternal gestational diabetes throughout the pregnancy.<br>Useful in managing active autoimmune disease in pregnancy. Nonfluorinated glucocorticoids (e.g., prednisone, prednisolone, methylprednisolone) have limited ability to cross placenta and are preferred, except when treating the fetus (e.g., neonatal lupus erythematosus). |
| Colchicine | Should be used only if potential benefit justifies potential risk to fetus. |
| **Analgesics and Pain Pathway Modulators** | |
| Acetaminophen | Generally considered safe at standard dosing but does cross the placenta. |
| Opiates | Some opiates/opioids cross placenta; may cause fetal opioid withdrawal at birth. |
| Tramadol | Should be used only if potential benefit justifies potential risk to fetus; postmarketing reports suggest possibility of neonatal seizures, withdrawal syndrome, and stillbirth. |
| Topical agents | Topical use may limit serum levels; individual agents should be reviewed for pregnancy impact before use. |
| **Nonbiologic DMARDs** | |
| Methotrexate | Highly teratogenic and abortifacient; must be discontinued at least 3 months before pregnancy. |
| Hydroxychloroquine | Relatively safe in pregnancy and should not be discontinued if it is needed. |
| Sulfasalazine | Relatively safe during pregnancy. |
| Leflunomide | Extremely teratogenic; must not be used before/during pregnancy; upon discontinuation, cholestyramine administration is required to remove drug from the body in all women of childbearing potential and specifically in those wishing to become pregnant; should be followed up with measurement of leflunomide and its metabolite levels to ensure removal of drug. |
| Azathioprine | Routine use in pregnancy is not recommended; however, azathioprine may be safer than some other DMARDs and may be used if immunosuppressive agent is imperative. |
| Cyclophosphamide | Not used in pregnancy unless absolutely necessary. |
| Mycophenolate mofetil | Teratogenic; should not be used in pregnancy; discontinue for 3 months before pregnancy is attempted. |
| Cyclosporine | May be used in pregnancy only if benefits outweigh risks. |
| Tofacitinib; baricitinib; upadacitinib | May be teratogenic at high doses. |
| **Biologic DMARDs** | |
| TNF inhibitors | Accumulating retrospective data suggest low risk in pregnancy, but evidence is limited; can be continued if absolutely needed; different agents may have different considerations regarding crossing placenta. |
| Ustekinumab; anakinra; secukinumab; sarilumab; ixekizumab; guselkumab | Should be used only if potential benefit justifies undefined risk to fetus. |
| Abatacept; belimumab; canakinumab; rilonacept; rituximab; tocilizumab | Should be used only if potential benefit justifies potential risk to fetus. |
| **Urate-Lowering Therapy (rarely needed in premenopausal women)** | |
| Allopurinol | Should be used only if potential benefit justifies potential risk to fetus. |
| Febuxostat | Should be used only if potential benefit justifies potential risk to fetus. |
| Probenecid | No current evidence for adverse impact on pregnancy. |
| Pegloticase | Should be used only if potential benefit justifies potential risk to fetus. |

DMARD = disease-modifying antirheumatic drug; TNF = tumor necrosis factor.

for home use is critical. Physical therapy referral is appropriate for tendinitis; bursitis; many forms of arthritis; and chronic soft-tissue pain due to overuse, injury, and chronic pain syndromes (e.g., fibromyalgia).

Occupational therapists assess upper extremity functioning, including the ability to perform self-care and job-related tasks. Braces and splints may be provided for painful or unstable joints. An ergonomic evaluation of the workstation may

accompany instruction in improved body mechanics and avoidance of repetitive trauma.

### Complementary and Alternative Medicine

Nontraditional options for symptom management are used by about one third of patients overall and up to 90% of patients with chronic pain, including arthritis and rheumatologic diseases. Commonly used over-the-counter supplements include fish oil, vitamins, glucosamine, and chondroitin. Providers should ask about supplement use because patients rarely volunteer this information. Significant drug interactions may occur; for example, some herbal preparations can interact with anticoagulants. See MKSAP 19 General Internal Medicine 1 for discussion of cannabis for pain management.

Mind-body interventions, such as tai chi, meditation, and yoga, can improve psychological well-being, strength, balance, and pain level. Chiropractic and osteopathic manipulation as well as massage remain popular. Randomized controlled trials support the use of tai chi for arthritis; smaller trials suggest benefit from meditation techniques, yoga, massage, acupuncture, and manipulative medicine for various musculoskeletal problems.

### Role of Surgery

Surgical procedures, such as carpal tunnel release or rotator cuff tendon repair, can address conditions that arise from repetitive trauma, injury, and degenerative changes in the soft tissue. Synovectomy of inflammatory pannus is occasionally used when a single or limited number of joints in patients with RA do not respond to medications. Total joint arthroplasty, particularly of the knee or hip, can reduce or eliminate pain and restore function in patients with an inadequate response to medication and physical or occupational therapy.

**KEY POINT**

- Nonpharmacologic measures used in rheumatologic diseases include physical or occupational therapy, surgery, weight reduction, psychosocial support, and self-management programs.

# Rheumatoid Arthritis

## Pathophysiology and Risk Factors

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammatory polyarthritis affecting both large and small joints, with a characteristic predilection for the joints of the hands and feet. RA has a prevalence of 0.5% to 1% in the general population; some specific populations have rates as high as 7%.

### Genetic Factors

Genes are responsible for 60% of the risk for RA. Among some 100 genetic loci recognized as associated with RA risk, the most important is the class II HLA group, especially HLA-D alleles. These risk alleles code for the shared epitope, a five–amino acid sequence that preferentially binds and presents citrullinated peptide antigens important in the pathophysiology of RA. Citrullinated proteins are immunogenic, especially in people who have the shared epitope.

Citrulline is not a native amino acid in humans; instead, it is formed by the action of the enzyme peptidylarginine deiminase (PADI), which deiminates arginine to form citrullinated peptides. PADI expression is typically limited to sites of inflammation and may therefore provide a link between early inflammation and subsequent autoimmunity. Many of the other genes associated with RA modify immune responses to provide a milieu for the development of autoantibodies.

### Environmental Factors

Environmental factors are responsible for the other 40% of the risk for RA. One of the most provocative environmental factors is smoking. Smoking can lead to lung inflammation, which activates enzymes (including PADI), and may promote local protein citrullination. Patients who smoke are at increased risk for RA, particularly those with a family history of RA, and should be counseled about smoking cessation. Exposure to silica dust has also been associated with increased risk.

### Infectious Agents

One potential risk factor for RA is periodontal disease. *Porphyromonas gingivalis*, a bacterium associated with periodontitis, expresses its own PADI enzyme and provides a potential link to formation of citrullinated peptide. Other infectious agents implicated in RA include *Mycoplasma* species, Epstein-Barr virus, and parvovirus B19. However, a direct infectious cause of RA has not been identified. There is also interest in the role of the intestinal microbiome in RA. Gut dysbiosis has been postulated to promote early RA, possibly by activating proinflammatory lymphocytes.

### Hormones

Women are two to three times as likely as men to develop RA. The role of estrogen and other sex-specific factors is incompletely understood, and estrogen and other sex hormones have both stimulatory and inhibitory effects on the immune system. Estrogen receptors are present on synovial fibroblasts and may drive the production of cartilage-damaging metalloproteinases. Stimulation of estrogen receptors on macrophages can increase production of tumor necrosis factor, a key RA inflammatory cytokine.

**KEY POINTS**

- Potential risk factors for rheumatoid arthritis include genetic and environmental factors, infectious agents, and hormones; genes make up 60% of the risk.
- Smoking is an important and modifiable risk factor for rheumatoid arthritis.