Annals of Internal Medicine®

In the Clinic®

Rheumatoid Arthritis

Risk Factors

Diagnosis

Treatment

Rheumatoid arthritis (RA) is a common systemic inflammatory autoimmune disease characterized by painful, swollen joints that can severely impair physical function and quality of life. The presenting symptoms of musculoskeletal pain, swelling, and stiffness are common in clinical practice, so familiarity with diagnosing and managing RA is crucial. Patients with RA are at greater risk for serious infection, respiratory disease, osteoporosis, cardiovascular disease, cancer, and mortality than the general population. In recent years, early diagnosis, aggressive treatment, and expanded therapeutic options of disease-modifying antirheumatic drugs have markedly improved both the management and long-term prognosis of RA.

CME/MOC activity available at Annals.org.

Physician Writer
Jeffrey A. Sparks, MD, MMSc
From Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

doi:10.7326/AITC201901010

CME Objective: To review current evidence for risk factors, diagnosis, and treatment of rheumatoid arthritis.

Funding Source: American College of Physicians.

Acknowledgment: The author thanks Tom W.J. Huizinga, MD, PhD, and Theodore Pincus, MD, authors of the previous version of this In the Clinic.

Disclosures: Dr. Sparks, ACP Contributing Author, has nothing to disclose. The form can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M18-2488.

With the assistance of additional physician writers, the editors of ***Annals of Internal Medicine*** develop **In the Clinic** using **MKSAP** and other resources of the American College of Physicians.

In the Clinic does not necessarily represent official ACP clinical policy. For ACP clinical guidelines, please go to https://www.acponline.org/clinical_information/guidelines/.

ACP American College of Physicians® Leading Internal Medicine, Improving Lives

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease that affects 0.5%–1% of U.S. adults—an estimated 1.5 million people (1). It is more common in women and may occur at any age; peak incidence is between ages 50 to 60 years. The most prominent feature is symmetrical pain and swelling of the hands, wrists, feet, and knees (polyarthritis), although other joints may be affected. Patients may also present with monoarthritis or oligoarthritis. Some patients with RA may present or later develop disease manifestations in other organs (sometimes without obvious articular involvement), such as interstitial lung disease (ILD), pericarditis, pleural effusion, or bronchiectasis. Given this clinical heterogeneity, RA is probably a clinical syndrome that encompasses several disease subsets, each characterized by immune dysregulation that, if left untreated, can lead to chronic inflammation and irreversible joint or organ damage.

Although laboratory tests for the RA-related autoantibodies rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA) are abnormal (seropositive) in many patients with RA, values are normal (seronegative) in about one third of patients with RA. There is no single pathognomonic laboratory finding or imaging modality that definitively diagnoses RA. Therefore, RA is a clinical diagnosis based on the pattern of symptoms, physical examination, serologic testing results, and imaging findings.

Historically, progressive disability and a shortened lifespan were nearly universal for patients with RA, but the long-term prognosis has improved over the past 2 decades (2–4). These improvements likely result from earlier diagnosis, aggressive treatment before onset of irreversible joint or organ damage, and control of chronic inflammation by widespread use and expanded options of conventional and biologic disease-modifying antirheumatic drugs (DMARDs) (5).

Risk Factors

Although the cause of RA remains unknown, significant progress has been made in identifying risk factors. *HLA-DRB1* (the "shared epitope") is the strongest of many known genetic risk factors (6, 7). Cigarette smoking is the best-established lifestyle risk factor for seropositive RA (8). Elevated body mass index, low alcohol consumption, unhealthy dietary intake, poor dental health, and low socioeconomic status may also affect RA susceptibility (9–12). Because women are at higher risk than men, reproductive and menopausal factors may play a role (13, 14).

Having an affected family member increases personal risk 3-fold; however, most patients with RA have no family history (15). RF and ACPA may be detectable in serum several years before onset, and their presence markedly increases subsequent risk for RA (16). Early disease manifestations, such as palindromic rheumatism (intermittent self-limited episodes of inflammatory arthritis with extended periods of remission), greatly increase risk for progression to RA (17).

1. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955-2007. Arthritis Rheum. 2010;62:1576-82. [PMID: 20191579]
2. Zhang Y, Lu N, Peloquin C, Dubreuil M, Neogi T, Avi a-Zubieta JA, et al. Improved survival in rheumatoid arthritis: a general population-based cohort study. Ann Rheum Dis. 2017;76:408-413. [PMID: 27338777]
3. Markusse IM, Akdemir G, Dirven L, Goekoop-Ruiterman YP, van Groenendael JH, Han KH, et al. Long-Term Outcomes of Patients With Recent-Onset Rheumatoid Arthritis After 10 Years of Tight Controlled Treatment: A Randomized Trial. Ann Intern Med. 2016; 164:523-31. [PMID: 27089068]
4. Lacaille D, Avina-Zubieta JA, Sayre EC, Abrahamowicz M. Improvement in 5-year mortality in incident rheumatoid arthritis compared with the general population-closing the mortality gap. Ann Rheum Dis. 2017;76:1057-1063. [PMID: 28031164]
5. Carpenter L, Norton S, Nikiphorou E, Jayakumar K, McWilliams DF, Rennie KL, et al; Early Rheumatoid Arthritis Study and the Early Rheumatoid Arthritis Network. Reductions in Radiographic Progression in Early Rheumatoid Arthritis Over Twenty-Five Years: Changing Contribution From Rheumatoid Factor in Two Multicenter UK Inception Cohorts. Arthritis Care Res (Hoboken). 2017;69: 1809-1817. [PMID: 28217885]
6. Raychaudhuri S, Sandor C, Stahl EA, Freudenberg J, Lee HS, Jia X, et al. Five amino acids in three HLA proteins explain most of the association between MHC and seropositive rheumatoid arthritis. Nat Genet. 2012;44:291-6. [PMID: 22286218]
7. Okada Y, Wu D, Trynka G, Raj T, Terao C, Ikari K, et al; RACI consortium. Genetics of rheumatoid arthritis contributes to biology and drug discovery. Nature. 2014;506: 376-81. [PMID: 24390342]
8. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis. 2010;69:70-81. [PMID: 19174392]

What are the characteristic articular symptoms and physical examination findings that suggest RA?

RA should be considered in any patient with joint stiffness, pain, or swelling that persists for more than a few weeks. Joint pain in RA is typically symmetrical and polyarticular, but may be asymmetrical, oligoarticular (involving 2 to 4 joints), or monoarticular at onset. Although not specific for RA, new-onset symmetrical joint swelling with morning stiffness lasting longer than an hour that improves with use throughout the day is characteristic. Synovitis is important to recognize for RA diagnosis and determining treatment response. Synovitis is defined as an inflamed joint capsule characterized by erythema, warmth, tenderness to palpation, and swelling; it is typically detected by physical examination, but advanced imaging may be useful in patients with equivocal signs. Arthralgia is generally related to patient symptoms of pain and stiffness and may not necessarily be due to inflammatory arthritis. Patients with synovitis and symptoms lasting more than 6 weeks are more likely to develop a progressive disease versus a self-limited process. Hand, wrist, and foot involvement is most common in RA, but atypical presentations may only involve large joints, such as the knee. The distal interphalangeal joints of the hand are not typically involved, and dactylitis is uncommon. The axial skeleton, including the hips, also is not typically involved, although severe and longstanding RA may involve these joints, particularly the cervical spine.

Physical examination may detect articular and soft-tissue swelling with tenderness to palpation due to synovitis. Medium or large joints may have obvious effusions amenable to arthrocentesis. Mild joint swelling can be subtle and difficult to recognize, particularly in the small joints of patients with obesity or concurrent fibromyalgia. Laboratory testing and imaging, particularly bedside point-of-care musculoskeletal ultrasonography, can be helpful to detect and quantify presence and severity of synovitis in patients with equivocal history and physical examination findings.

Historically, patients with longstanding, inadequately treated RA developed joint damage and deformities, including characteristic ulnar deviation, swan neck, and boutonniere deformities of the hands (**Figure 1**; **Appendix Figure 1**, available at Annals.org), and flexion contractures of the knees and elbows. However, these "classical" deformities are becoming less common, probably because of aggressive treatment with the goal of low disease activity or remission, as well as more options for modern targeted therapeutics.

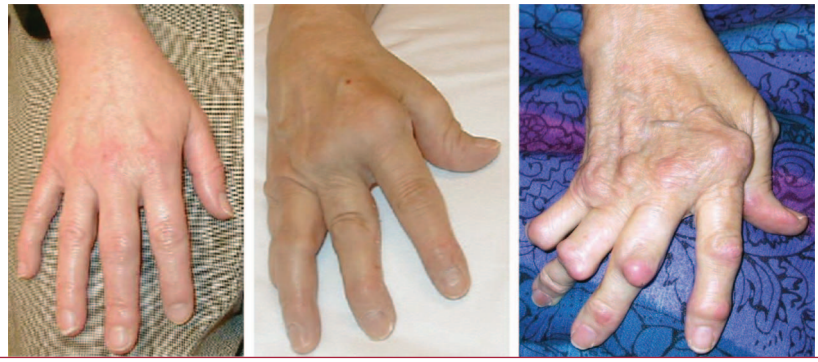
RA is a systemic inflammatory disease and thus may present with or be complicated by extra-articular organ manifestations or treatment side effects (see the **Box:** Selected Extra-articular Manifestations of Rheumatoid Arthritis by Affected Organ System).

What are the American College of Rheumatology and European League Against Rheumatism criteria for classifying RA, and how are they most useful?

The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) developed classification criteria for RA to

9. Qin B, Yang M, Fu H, Ma N, Wei T, Tang Q, et al. Body mass index and the risk of rheumatoid arthritis: a systematic review and dose-response meta-analysis. Arthritis Res Ther. 2015;17:86. [PMID: 25890172]
10. Sparks JA, Barbhaiya M, Tedeschi SK, Leatherwood CL, Tabung FK, Speyer CB, et al. Inflammatory dietary pattern and risk of developing rheumatoid arthritis in women. Clin Rheumatol. 2018. [PMID: 30109509]
11. Gan RW, Demoruelle MK, Deane KD, Weisman MH, Buckner JH, Gregersen PK, et al. Omega-3 fatty acids are associated with a lower prevalence of autoantibodies in shared epitope-positive subjects at risk for rheumatoid arthritis. Ann Rheum Dis. 2017;76:147-152. [PMID: 27190099]
12. Lu B, Solomon DH, Costenbader KH, Karlson EW. Alcohol consumption and risk of incident rheumatoid arthritis in women: a prospective study. Arthritis Rheumatol. 2014;66:1998-2005. [PMID: 24729427]
13. Orellana C, Saevarsdottir S, Klareskog L, Karlson EW, Alfredsson L, Bengtsson C. Oral contraceptives, breastfeeding and the risk of developing rheumatoid arthritis: results from the Swedish EIRA study. Ann Rheum Dis. 2017;76:1845-1852. [PMID: 28818831]
14. Bengtsson C, Malspeis S, Orellana C, Sparks JA, Costenbader KH, Karlson EW. Association Between Menopausal Factors and the Risk of Seronegative and Seropositive Rheumatoid Arthritis: Results From the Nurses' Health Studies. Arthritis Care Res (Hoboken). 2017;69:1676-1684. [PMID: 28085997]
15. Sparks JA, Chen CY, Hiraki LT, Malspeis S, Costenbader KH, Karlson EW. Contributions of familial rheumatoid arthritis or lupus and environmental factors to risk of rheumatoid arthritis in women: a prospective cohort study. Arthritis Care Res (Hoboken). 2014;66:1438-46. [PMID: 25103278]
16. Rantap -Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum. 2003;48:2741-9. [PMID: 14558078]

Figure 1. **Involvement of the hands in rheumatoid arthritis.**



Early rheumatoid arthritis with mild fusiform soft tissue swelling of the proximal interphalangeal joints (*left*). Moderate to severe rheumatoid arthritis with synovitis of the metacarpophalangeal joints and swan neck deformities of the second and third digits (*center*). Severe deforming rheumatoid arthritis with ulnar deviation, multiple rheumatoid nodules, and proximal interphalangeal joint subluxations (*right*). Reproduced with permission from Medical Knowledge Self-Assessment Program 17. Rheumatology. Philadelphia: American College of Physicians; 2015.

identify patients with early disease, before irreversible joint damage occurs (18) (see the **Box:** ACR/EULAR 2010 Classification Criteria for Rheumatoid Arthritis). However, these criteria were developed to classify patients for research studies, not as diagnostic criteria to be used for clinical purposes.

According to this classification system, RA requires synovitis in at least 1 joint and absence of a more likely clinical explanation. Three key factors indicate probable RA rather than a self-limited polyarthritis: symmetrical arthritis of small joints, presence of ACPA or RF (particularly at titers more than 3 times the upper limit of normal), and symptoms lasting longer than 6 weeks.

The 2010 ACR/EULAR criteria have been successful in enrolling patients in research studies for RA prevention or early RA diagnosed before onset of longstanding complications. However, clinical care patients who have RA may require treatment despite not meeting these criteria. For example, a patient with chronic knee monoarthritis, high-titer RF and ACPA, and elevated levels of acute phase reactants may be treated for RA even if he or she does not meet the criteria. They were developed for classifying patients with articular manifestations of the disease and may not apply to patients who present with predominant extra-articular manifestations, such as ILD without obvious articular involvement (19). Therefore, clinicians should use their best judgment when deciding whether to diagnose and treat RA and consider expert consultation for ambiguous cases.

What differential diagnosis should clinicians consider when evaluating a patient with possible RA?

Patients with the classical longstanding joint deformities are easily recognized, but the current paradigm is to prevent these manifestations by early RA diagnosis and prompt treatment. Among patients with early polyarthritis (< 4 weeks), the major differential diagnosis is a self-limited viral infection that typically resolves spontaneously. Other diseases to consider when evaluating a patient with articular symptoms compatible with RA are listed in **Appendix Table 1** (available at Annals.org). Osteo-

17. Chen HH, Chao WC, Liao TL, Lin CH, Chen DY. Risk of autoimmune rheumatic diseases in patients with palindromic rheumatism: A nationwide, population-based, cohort study. PLoS One. 2018;13:e0201340. [PMID: 30048527]
18. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569-81. [PMID: 20872595]
19. Fischer A, Solomon JJ, du Bois RM, Deane KD, Olson AL, Fernandez-Perez ER, et al. Lung disease with anti-CCP antibodies but not rheumatoid arthritis or connective tissue disease. Respir Med. 2012;106:1040-7. [PMID: 22503074]
20. Lee YC, Lu B, Boire G, Haraoui BP, Hitchon CA, Pope JE, et al. Incidence and predictors of secondary fibromyalgia in an early arthritis cohort. Ann Rheum Dis. 2013;72:949-54. [PMID: 22791744]
21. Sokka T, Pincus T. Erythrocyte sedimentation rate, C-reactive protein, or rheumatoid factor are normal at presentation in 35%-45% of patients with rheumatoid arthritis seen between 1980 and 2004: analyses from Finland and the United States. J Rheumatol. 2009;36:1387-90. [PMID: 19411389]
22. Katchamart W, Koolvisoot A, Aromdee E, Chiowchanwesawakit P, Muengchan C. Associations of rheumatoid factor and anti-citrullinated peptide antibody with disease progression and treatment outcomes in patients with rheumatoid arthritis. Rheumatol Int. 2015;35:1693-9. [PMID: 25903353]
23. Whiting PF, Smidt N, Sterne JA, Harbord R, Burton A, Burke M, et al. Systematic review: accuracy of anti-citrullinated Peptide antibodies for diagnosing rheumatoid arthritis. Ann Intern Med. 2010;152:456-64; W155-66. [PMID: 20368651]
24. Kelly S, Davidson B, Keidel S, Gadola S, Gorman C, Meenagh G, et al. The impact of rheumatologist-performed ultrasound on diagnosis and management of inflammatory arthritis in routine clinical practice. BMC Musculoskelet Disord. 2017;18:487. [PMID: 29166885]

Selected Extra-articular Manifestations of Rheumatoid Arthritis, by Organ System

Dermatologic
Rheumatoid nodules
Vasculitis
Ulcers
Neutrophilic dermatoses
Treatment-related rashes
Lymphedema

Ophthalmologic
Keratoconjunctivitis sicca (secondary Sjögren syndrome)
Episcleritis
Scleritis
Scleromalacia perforans

Pulmonary
Pulmonary fibrosis
Interstitial lung disease (nonspecific interstitial pneumonia, usual interstitial pneumonia, organizing pneumonia)
Nodules
Pleural effusion
Pleuritis
Bronchiectasis
Cryptogenic organizing pneumonia

Cardiovascular
Premature atherosclerosis, coronary and peripheral vascular disease
Pericarditis
Pericardial effusion
Valvular defects
Arrhythmia, conduction defects
Myocarditis
Heart failure (particularly with preserved ejection fraction)
Cardiac nodules

Gastrointestinal
Xerostomia
Gastritis or peptic ulcer disease (e.g., from nonsteroidal anti-inflammatory drugs or glucocorticoids)
Stomatitis, mucositis (e.g., from methotrexate)

Renal
Glomerulonephritis (usually mesangioproliferative)
Proteinuria (rarely due to secondary amyloidosis)
Treatment-related kidney injury
Hepatic
Nodular regenerative hyperplasia
Portal fibrosis
Treatment-related hepatitis/cirrhosis

Neurologic
Cervical spine subluxation/atlantoaxial instability
Peripheral nerve entrapment (e.g., carpal tunnel syndrome)
Mononeuritis multiplex (in rheumatoid vasculitis)
Brain nodules

Hematologic
Lymphadenopathy
Splenomegaly (as part of Felty syndrome)
Leukopenia (as part of Felty syndrome)
Lymphoma
Amyloidosis
Cryoglobulinemia
Large granular lymphocyte syndrome

25. van der Linden MP, le Cessie S, Raza K, van der Woude D, Knevel R, Huizinga TW, et al. Long-term impact of delay in assessment of patients with early arthritis. Arthritis Rheum. 2010;62:3537-46. [PMID: 20722031]
26. van der Heide A, Jacobs JW, Bijlsma JW, Heurkens AH, van Booma-Frankfort C, van der Veen MJ, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. Ann Intern Med. 1996;124:699-707. [PMID: 8633829]
27. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017;76:960-977. [PMID: 28264816]
28. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016;68:1-26. [PMID: 26545940]
29. Lau CS, Chia F, Harrison A, Hsieh TY, Jain R, Jung SM, et al; Asia Pacific League of Associations for Rheumatology. APLAR rheumatoid arthritis treatment recommendations. Int J Rheum Dis. 2015;18:685-713. [PMID: 26334449]
30. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38:44-8. [PMID: 7818570]
31. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford). 2003;42:244-57. [PMID: 12595618]
32. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther. 2005;7:R796-806. [PMID: 15987481]

ACR/EULAR 2010 Classification Criteria for Rheumatoid Arthritis*

These criteria should be restricted to persons with ≥1 swollen joints in the absence of a more likely diagnosis.

A score of ≥6 points is classified as definite RA. In each domain, consider only the category with most points.

A. Joint involvement and distribution (0-5 points)

Any swollen or tender joint on physical examination

Large joints: Shoulders, elbows, hips, knees, and ankles

Small joints: Metacarpophalangeal, proximal interphalangeal, second through fifth metatarsophalangeal, thumb interphalangeal, and wrists

- 1 large joint: 0 points
- 2–10 large joints: 1 point
- 1–3 small joints: 2 points
- 4–10 small joints: 3 points
- > 10 joints (and at least 1 small joint): 5 points

B. Serology (0-3 points)

Low-positive results are > 1 to 3 times the upper limit of normal of the assay used. High-positive results are > 3 times the upper limit of normal of the assay used

- Negative RF and negative ACPA: 0 points
- Low-positive RF or low-positive ACPA: 2 points
- High-positive RF or high-positive ACPA: 3 points

C. Acute-phase reactants (0-1 point)

- Normal CRP and normal ESR: 0 points
- Abnormal CRP or abnormal ESR: 1 point

D. Duration of symptoms (0-1 point)

Patient's self-report on the maximum duration of symptoms of any joint clinically involved at the time of assessment

- < 6 wk: 0 points
- ≥6 wk: 1 point

ACPA = anticitrullinated protein antibodies; ACR/EULAR = American College of Rheumatology/European League Against Rheumatism; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RA = rheumatoid arthritis; RF = rheumatoid factor.

*Data from reference 8.

arthritis is the most common form of arthritis and often causes deformities and pain in the hands of older patients; however, it is characterized by an insidious course, usually without signs or symptoms of systemic inflammation or autoimmunity. Fibromyalgia should also be strongly considered in patients presenting with widespread pain because it is more common than RA (5% vs. 0.5%–1%), particularly in women aged 40–60 years—the same group that has the highest incidence of RA. Further, some patients have fibromyalgia along with RA, or develop it soon after diagnosis (20). Fibromyalgia is characterized by widespread pain in articular and nonarticular sites (particularly the forearms, arms, posterior neck, trapezius, and legs), but distinguishing between these disorders can be difficult, particularly early in the course. Other causes of inflammatory arthritis should also be considered. Expert diagnosis may be required for atypical presentations.

What is the role of laboratory studies?

Many patients with RA have an increased erythrocyte sedimentation rate (ESR) or elevated levels of C-reactive protein (CRP); RF; or ACPA, particularly anticyclic citrullinated peptide (anti-

CCP) antibodies. However, none of these tests is sufficiently sensitive for exclusion, because results are normal in about 30% of patients with RA (21). Patients with seropositive RA may have a more severe course than those with seronegative disease (22). Laboratory studies are frequently normal in patients with RA.

In an observational study of more than 2500 patients with newly diagnosed RA in Finland and the United States, ESR was less than 28 mm/h in 44% of patients and CRP levels were normal in 48% (21). A review of 151 studies of patients with early symptoms of RA found that second-generation anti-CCP antibodies and RF had similar sensitivity (67% vs. 70%), but that second-generation anti-CCP antibodies had greater specificity (96% vs. 86%) (23). The relatively low sensitivity of both anti-CCP and RF means that negative results do not rule out RA.

Appendix Table 2 (available at Annals.org) lists laboratory and imaging tests to consider for patients presenting with signs and symptoms suggestive of RA.

What is the role of imaging studies?

Radiographic changes (juxta-articular osteopenia, joint space narrowing, or bone erosions) in joints with signs or symptoms on plain films (**Figure 2**; **Appendix Figure 2**, available at Annals.org) are not required for a definitive diagnosis of RA or to initiate therapy. Indeed, a major goal of treatment is to prevent these radiographic changes, which generally do not develop until patients have had symptoms for months or years. RA is often diagnosed in patients whose radiographs are normal or show only subtle juxta-articular osteopenia in the hands or feet, and in early inflammatory arthritis, these changes may occur in the feet before the hands. It may be reasonable to obtain baseline plain radiographs of the feet and hands, regardless of symptoms, to screen for occult involvement, establish a baseline, and evaluate for alternative causes.

Ultrasonography and magnetic resonance imaging (MRI) are more sensitive than plain radiographs for detecting soft tissue inflammation and synovitis (particularly tenosynovitis) before development of joint damage, but these tests are less specific. Rheumatologists are increasingly being trained in point-of-care musculoskeletal ultrasonography to aid in diagnosis and early treatment of patients with RA (24). Similarly, MRI or other advanced imaging techniques, such as dual-energy computed tomography, may be considered when physical examination findings are equivocal in detecting synovitis and when alternate diagnoses are being considered. Referral to a rheumatologist trained in musculoskeletal ultrasonography to determine whether advanced imaging would be useful if RA is in the differential diagnosis should be considered.

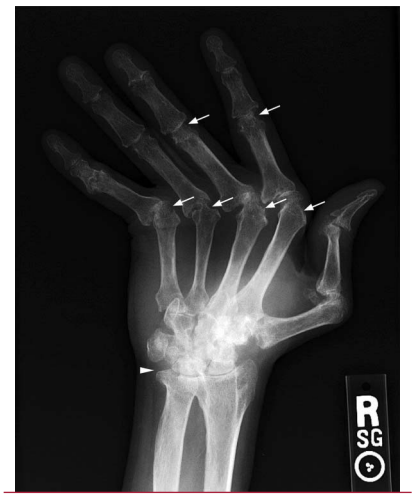
When should synovial fluid be obtained to help in diagnosis?

Obtaining synovial fluid is generally not required to diagnose RA, particularly in patients who present with polyarthritis. However, it should be obtained, usually from medium or large joints (such as knees, shoulders, ankles, or elbows) when septic arthritis, gout, or other diagnoses requiring synovial fluid assessment are being considered. Septic arthritis is more common in patients with RA and should be suspected in a patient with monoarthritis that is warm or erythematous with large effusions and systemic signs, such as fever or hypotension. If suspicion for septic arthritis is high, clinicians should consider referring to specialists for image-guided arthrocentesis to evaluate

33. Pincus T, Swearingen CJ, Bergman M, Yazici Y. RAPID3 (Routine Assessment of Patient Index Data 3), a rheumatoid arthritis index without formal joint counts for routine care: proposed severity categories compared to disease activity score and clinical disease activity index categories. J Rheumatol. 2008;35:2136-47. [PMID: 18793006]
34. Centola M, Cavet G, Shen Y, Ramanujan S, Knowlton N, Swan KA, et al. Development of a multi-biomarker disease activity test for rheumatoid arthritis. PLoS One. 2013;8:e60635. [PMID: 23585841]
35. Haavardsholm EA, Aga AB, Olsen IC, Lillegraven S, Hammer HB, Uhlig T, et al. Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial. BMJ. 2016;354:i4205. [PMID: 27530741]
36. Aletaha D, Alasti F, Smolen JS. Optimisation of a treat-to-target approach in rheumatoid arthritis: strategies for the 3-month time point. Ann Rheum Dis. 2016;75:1479-85. [PMID: 26420577]
37. Visser K, Katchamart W, Loza E, Martinez-Lopez JA, Salliot C, Trudeau J, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis. 2009;68:1086-93. [PMID: 19033291]
38. van der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, et al; TEMPO Study Investigators. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum. 2006;54:1063-74. [PMID: 16572441]
39. Yazici Y, Sokka T, Kautiainen H, Swearingen C, Kulman I, Pincus T. Long term safety of methotrexate in routine clinical care: discontinuation is unusual and rarely the result of laboratory abnormalities. Ann Rheum Dis. 2005;64:207-11. [PMID: 15208176]

40. O'Dell JR, Curtis JR, Mikuls TR, Cofield SS, Bridges SL Jr, Ranganath VK, et al; TEAR Trial Investigators. Validation of the methotrexate-first strategy in patients with early, poor-prognosis rheumatoid arthritis: results from a two-year randomized, double-blind trial. Arthritis Rheum. 2013;65:1985-94. [PMID: 23686414]
41. Humphreys JH, Warner A, Costello R, Lunt M, Verstappen SMM, Dixon WG. Quantifying the hepatotoxic risk of alcohol consumption in patients with rheumatoid arthritis taking methotrexate. Ann Rheum Dis. 2017;76:1509-1514. [PMID: 28341765]
42. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol. 2014;132:1453-60. [PMID: 25275721]
43. Haagsma CJ, van Riel PL, de Jong AJ, van de Putte LB. Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. Br J Rheumatol. 1997;36:1082-8. [PMID: 9374925]
44. Maillefert JF, Combe B, Goupille P, Cantagrel A, Dougados M. Long term structural effects of combination therapy in patients with early rheumatoid arthritis: five year follow up of a prospective double blind controlled study. Ann Rheum Dis. 2003;62:764-6. [PMID: 12860733]
45. Bansback N, Phibbs CS, Sun H, O'Dell JR, Brophy M, Keystone EC, et al; CSP 551 RACAT Investigators. Triple Therapy Versus Biologic Therapy for Active Rheumatoid Arthritis: A Cost-Effectiveness Analysis. Ann Intern Med. 2017;167:8-16. [PMID: 28554192]
46. Sparks JA, Krumme AA, Shrank WH, Matlin OS, Brill G, Pezalla EJ, et al. Brief Report: Intensification to Triple Therapy After Treatment With Nonbiologic Disease-Modifying Antirheumatic Drugs for Rheumatoid Arthritis in the United States From 2009 to 2014. Arthritis Rheumatol. 2016;68:1588-95. [PMID: 26866506]
47. O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, et al; CSP 551 RACAT Investigators. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med. 2013;369:307-18. [PMID: 23755969]

Figure 2. **Radiograph showing advanced rheumatoid arthritis of the hand.**



Ulnar deviation occurs at the metacarpophalangeal joints; marginal erosions most prominently at the second through fourth metacarpophalangeal joints and the second and third proximal interphalangeal joints (*arrows*); and joint-space narrowing at the wrist, metacarpophalangeal, and proximal interphalangeal joints, which also represents erosive disease. Note the loss of the ulnar styloid (*arrowhead*), another common sign of bony erosion in rheumatoid arthritis. Reproduced with permission from Medical Knowledge Self-Assessment Program 18. Rheumatology. Philadelphia: American College of Physicians; 2018.

for small joint involvement or for effusions that are difficult to aspirate at bedside. If obtained, synovial fluid should be evaluated for cell count with differential, crystals using polarized microscopy, and Gram stain with culture.

In patients without suspected septic arthritis who have effusion of a large joint (such as in the knee), aspiration of synovial fluid combined with intra-articular glucocorticoids may reduce symptoms while limiting systemic exposure to glucocorticoids.

When should clinicians consider consulting a rheumatologist?

Delay of RA diagnosis and effective treatment has been associated with poor outcomes (25). Patients with suspected inflammatory arthritis or new-onset joint pain, stiffness, and swelling (without history of overuse or trauma) that persists for several weeks should be referred to a rheumatologist. Inflammatory arthritis may also be the presenting symptom of a multisystem disease. Generally, patients suspected to have RA should have ESR, CRP, anti-CCP, and RF measured by their primary care clinician before being referred to a rheumatologist.

Diagnosis... Rheumatoid arthritis should be considered in patients with joint pain, stiffness, or swelling lasting more than a few weeks. However, in many patients these symptoms may resolve spontaneously. Diagnosis requires a detailed history as well as joint swelling found on physical examination that is unexplained by another diagnosis. Neither radiologic nor laboratory abnormalities are required for diagnosis. While some patients diagnosed with RA have normal values for ESR, CRP, anti-CCP, and RF, abnormalities in these tests can aid in diagnosis. When the diagnosis is uncertain or treatment may be needed, evaluation by a rheumatologist should be strongly considered.

CLINICAL BOTTOM LINE

Treatment

What is the overall approach to drug therapy for RA?

Pharmacologic treatment of RA should tightly control inflammation with the goal of low disease activity or remission (**Appendix Table 3**, available at Annals.org). Methotrexate is considered the

"backbone" of RA treatment because of its known efficacy and safety as initial monotherapy or combination treatment, For patients with moderate or severe disease, methotrexate should be initiated, typically as monotherapy. If treatment response is inadequate, other DMARDs may be added to (rather than replacing) methotrexate to enhance efficacy and reduce the potential for formation of antidrug antibodies. Patients with mild RA can sometimes be treated with hydroxychloroquine as initial monotherapy; if response is inadequate, other DMARDs, such as methotrexate, should be initiated. Clinicians and patients should agree on a treatment plan using a shared decision-making approach, weighing the risks and benefits of methotrexate with those of alternative strategies.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally used on an as-needed basis for pain because of their quick onset of action. Glucocorticoids may be used as "bridge therapy" during episodes of high disease activity given quick onset of action and efficacy in relieving pain and stiffness. However, because they have many long-term negative consequences, patients should be weaned completely or given the lowest possible dose, with DMARDs used as steroid-sparing therapy. Notably, data show that the "step-up" pyramid approach used in the past for RA treatment, in which NSAIDs and glucocorticoids were used first and DMARDs were used later only if the response was inadequate, is inferior to early initiation of DMARD therapy.

In a randomized trial of 238 patients with recently diagnosed RA, initial therapy with a DMARD was superior to therapy with NSAIDs followed by DMARDs in patients with inadequate responses (26). By 1 year, 29% of patients treated initially with NSAIDs alone had discontinued therapy, compared with 8% of patients whose initial therapy included a DMARD. Patients in the early-DMARD group had less pain and disability and better joint scores than the NSAID-only group.

What is the target of treatment?

Treatment guidelines recommend a treat-to-target of low disease activity or remission according to a validated disease activity measure (27–29). Several measures have been developed and validated for use in clinical care to assess RA activity and aid in treatment decisions. The components of the 4 most commonly used measures are presented in **Table 1**. A widely used measure is the Disease Activity Score 28 (DAS28) (30), which involves tender and swollen joints counted at 28 sites (in the upper extremities and knees), the patient's self-assessment of global status, and measurement of acute-phase reactants (ESR or CRP). These raw values can be entered into an online calculator to obtain an overall DAS28 score (www.das-score.nl/dasculators.html). The Simplified Disease Activity Index is similar to the DAS28 but is easier to calculate and thus may be more amenable to real-time use if laboratory results are available (31). The Clinical Disease Activity Index uses the tender/swollen joints and patient/physician global assessments, and does not require laboratory testing or a calculator (32). As a result, it may be easier to use and interpret in real-time with patients during clinic visits while treatment decisions are being made. Other versions of these measures use expanded joint counts to include other sites,

48. Raaschou P, Söderling J, Turesson C, Askling J; ARTIS Study Group. Tumor Necrosis Factor Inhibitors and Cancer Recurrence in Swedish Patients With Rheumatoid Arthritis: A Nationwide Population-Based Cohort Study. Ann Intern Med. 2018;169:291-299. [PMID: 30105374]
49. Bridges SL Jr, White DW, Worthing AB, Gravallese EM, O'Dell JR, Nola K, et al; American College of Rheumatology. The Science Behind Biosimilars: Entering a New Era of Biologic Therapy. Arthritis Rheumatol. 2018;70:334-344. [PMID: 29411547]
50. Chingcuanco F, Segal JB, Kim SC, Alexander GC. Bioequivalence of Biosimilar Tumor Necrosis Factor-a Inhibitors Compared With Their Reference Biologics: A Systematic Review. Ann Intern Med. 2016;165:565-574. [PMID: 27479870]
51. Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2013;159:253-61. [PMID: 24026258]
52. Nissen SE, Yeomans ND, Solomon DH, Lücher TF, Libby P, Husni ME, et al; PRECISION Trial Investigators. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med. 2016;375:2519-29. [PMID: 27959716]
53. Bakker MF, Jacobs JW, Welsing PM, Verstappen SM, Tekstra J, Ton E, et al; Utrecht Rheumatoid Arthritis Cohort Study Group. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. Ann Intern Med. 2012;156:329-39. [PMID: 22393128]
54. van Vliet-Daskalopoulou E, Jentjens T, Scheffer RT. Intra-articular rimexolone in the rheumatoid knee: a placebo-controlled, double-blind, multicentre trial of three doses. Br J Rheumatol. 1987;26:450-3. [PMID: 3318993]
55. H kkinen A, Sokka T, Kautiainen H, Kotaniemi A, Hannonen P. Sustained maintenance of exercise induced muscle strength gains and normal bone mineral density in patients with early rheumatoid arthritis: a 5 year follow up. Ann Rheum Dis. 2004;63:910-6. [PMID: 15249317]

56. Solomon DH, Fraenkel L, Lu B, Brown E, Tsao P, Losina E, et al. Comparison of Care Provided in Practices With Nurse Practitioners and Physician Assistants Versus Subspecialist Physicians Only: A Cohort Study of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2015;67:1664-70. [PMID: 26096922]
57. Lorig K, Ritter PL, Plant K. A disease-specific self-help program compared with a generalized chronic disease self-help program for arthritis patients. Arthritis Rheum. 2005;53:950-7. [PMID: 16342084]
58. Nikiphorou E, Norton S, Young A, Dixey J, Walsh D, Helliwell H, et al; Early Rheumatoid Arthritis Study and the Early Rheumatoid Arthritis Network. The association of obesity with disease activity, functional ability and quality of life in early rheumatoid arthritis: data from the Early Rheumatoid Arthritis Study/Early Rheumatoid Arthritis Network UK prospective cohorts. Rheumatology (Oxford). 2018. [PMID: 29590474]
59. Tedeschi SK, Frits M, Cui J, Zhang ZZ, Mahmoud T, Iannaccone C, et al. Diet and Rheumatoid Arthritis Symptoms: Survey Results From a Rheumatoid Arthritis Registry. Arthritis Care Res (Hoboken). 2017; 69:1920-1925. [PMID: 28217907]
60. Proudman SM, James MJ, Spargo LD, Metcalf RG, Sullivan TR, Rischmueller M, et al. Fish oil in recent onset rheumatoid arthritis: a randomised, double-blind controlled trial within algorithm-based drug use. Ann Rheum Dis. 2015;74:89-95. [PMID: 24081439]
61. Kreps DJ, Halperin F, Desai SP, Zhang ZZ, Losina E, Olson AT, et al. Association of weight loss with improved disease activity in patients with rheumatoid arthritis: A retrospective analysis using electronic medical record data. Int J Clin Rheumtol. 2018;13:1-10. [PMID: 29606976]
62. Matcham F, Scott IC, Rayner L, Hotopf M, Kingsley GH, Norton S, et al. The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and meta-analysis. Semin Arthritis Rheum. 2014;44:123-30. [PMID: 24973898]

Table 1. **Disease Activity Measures for Clinical Use in Patients With Rheumatoid Arthritis**

Component	*DAS28*	*CDAI*	*SDAI*	*RAPID3*
Number of tender joints*	X	X	X	–
Number of swollen joints*	X	X	X	–
Physician global assessment (0–10)	–	X	X	–
ESR or CRP laboratory results	X	–	X	–
Patient global assessment (0–10)	X	X	X	X
Patient function	–	–	–	X
Patient pain	–	–	–	X

CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; DAS28 = Disease Activity Score with 28 joints; ESR = erythrocyte sedimentation rate; RAPID3 = Routine Assessment of Patient Index Data 3; SDAI = Simplified Disease Activity Index.
**The 28 joints assessed = hands, wrists, elbows, shoulders, and knees.*

such as the feet and ankles. The RAPID3 (Routine Assessment of Patient Index Data 3) uses only patient-reported measures; thus, remote administration can be done easily, with the results readily available to clinicians to monitor and aid in treatment decisions (33). Although some clinicians use commercial multibiomarker disease activity scores that measure several serum inflammatory markers, clinical measures are generally preferred (34). Research is ongoing on whether advanced imaging, such as ultrasonography or MRI, should be incorporated serially to monitor RA disease activity (35).

All of the measures provide a score that can categorize disease activity into remission or low, moderate, or high activity (**Table 2**). Treatment should be tailored so that patients are in either remission or a low category, unless clinically contraindicated (36).

In a randomized trial in the Netherlands, 508 patients with early RA were assigned to 1 of 4 treatment strategies, all aimed at achieving low disease activity (3). At 10 years, all participants had similar functional ability and low rates of radiographic progression. Compared with the general population, there was no evidence of excess mortality. This study provides evidence of favorable outcomes for a treat-to-target of low disease activity, regardless of the drugs used.

Although measures of disease activity provide objective data and have improved long-term RA outcomes, some patients may be misclassified as having active disease based on subjective reports of pain or joint tenderness unrelated to active RA (e.g., mechanical pain or tenderness from joint damage, fibromyalgia, coexistent osteoarthritis, back pain, depression, stress, or poor sleep). Conversely, the tools may misclassify patients with active RA as having low activity or being in remission despite the need for treatment intensification (e.g., foot-predominant inflammatory arthritis, refractory monoarthritis). These tools are helpful in guiding management; however, decisions should be informed by the clinical scenario.

Which traditional DMARDs are used? What are their risks and benefits?

Methotrexate

Methotrexate is the appropriate first-line agent for most patients diagnosed with RA, along with folic acid (typically started at 1 mg daily) (37). Low doses (≤25 mg/week) usually do not reduce leukocyte or platelet counts. About half of all patients treated with methotrexate have little or no radiographic progression, although 30% will require addi-

Table 2. **Rheumatoid Arthritis Disease Activity Categories in the SDAI, DAS28, CDAI, and RAPID3**

Disease Activity Category	*DAS28*	*CDAI*	*SDAI*	*RAPID3*
High: Intensification of therapy very likely needed	>5.1	>22	>26	>12
Moderate: Strongly consider intensifying therapy	3.2–5.1	10.1–22	11.1–26	6.1–12
Low: Consider intensifying therapy	2.7–3.2	2.9–10	3.4–11	3.1–6
Remission	≤2.6	≤2.8	≤3.3	≤3

CDAI = Clinical Disease Activity Index; DAS28 = Disease Activity Score 28; RAPID3 = Routine Assessment of Patient Index Data 3; SDAI = Simplified Disease Activity Index.

tional DMARDs (38). Typical doses for RA range between 10 mg and up to 25 mg per week . Side effects of nausea, stomatitis, diarrhea, alopecia, and post-dosing fatigue may be managed using higher doses of daily folic acid supplementation (or switched to leucovorin given 8–12 hours after methotrexate), split dosing of methotrexate on the day it is administered, switching to subcutaneous administration, or weaning down to the maximum tolerated dose. Long-term treatment with methotrexate is safe and well tolerated for most patients with RA (39).

In a randomized controlled trial of 755 patients with early RA, participants were randomly assigned to methotrexate monotherapy or combination therapy consisting of either methotrexate with etanercept or methotrexate with sulfasalazine and hydroxychloroquine (40). At week 102, patients assigned to methotrexate monotherapy had disease activity and rates of radiographic progression similar to those assigned to combination therapy. These results validate the strategy of initiating methotrexate as monotherapy in patients presenting with RA.

Mild elevations of liver enzymes are a relatively common side effect of methotrexate, particularly in patients with metabolic syndrome. Baseline liver function should be tested before methotrexate is started, and caution should be used if enzymes are elevated. Methotrexate may be cautiously continued even with mild elevations (< 3-fold above normal) as long as monitoring is done frequently and the dose is reduced if elevations persist. Liver function often returns to normal after dose reduction. It may also normalize in some patients without a change in dose, suggesting comorbid infection or effects of other medications or alcohol intake. Moderate alcohol consumption (≤2 drinks/day) is permissible if there are no other contraindications (41). Persistent elevation of liver enzymes should prompt discontinuation of the medication and further work-up, including imaging and referral to a hepatologist for possible liver biopsy. Methotrexate is a known teratogen; thus, women of childbearing potential should use effective contraception or be referred to a gynecologist. Other rare serious side effects of methotrexate include pneumonitis and pulmonary fibrosis.

Hydroxychloroquine

Hydroxychloroquine is used in some patients with RA, particularly those presenting with mild severity and in patients with overlapping features of other diseases, such as systemic lupus erythematosus. Hydroxychloroquine monotherapy is unlikely to control moderate or severe disease; however, it may be helpful as add-on therapy for patients with a partial response to other DMARDs. Although hydroxychloroquine has only mild anti-

63. Au K, Reed G, Curtis JR, Kremer JM, Greenberg JD, Strand V, et al; CORRONA Investigators. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Ann Rheum Dis. 2011;70:785-91. [PMID: 21288960]
64. Jin S, Hsieh E, Peng L, Yu C, Wang Y, Wu C, et al. Incidence of fractures among patients with rheumatoid arthritis: a systematic review and meta-analysis. Osteoporos Int. 2018;29:1263-1275. [PMID: 29546507]
65. England BR, Thiele GM, Anderson DR, Mikuls TR. Increased cardiovascular risk in rheumatoid arthritis: mechanisms and implications. BMJ. 2018;361:k1036. [PMID: 29685876]
66. Chatzidionisyou A, Catrina AI. The lung in rheumatoid arthritis, cause or consequence? Curr Opin Rheumatol. 2016;28:76-82. [PMID: 26599384]
67. Askling J. Malignancy and rheumatoid arthritis. Curr Rheumatol Rep. 2007;9:421-6. [PMID: 17915099]
68. Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum. 2010;62:1583-91. [PMID: 20155830]
69. Sparks JA, Chang SC, Liao KP, Lu B, Fine AR, Solomon DH, et al. Rheumatoid Arthritis and Mortality Among Women During 36 Years of Prospective Follow-Up: Results From the Nurses' Health Study. Arthritis Care Res (Hoboken). 2016;68:753-62. [PMID: 26473946]

inflammatory effects, it is unlikely to increase infection risk and is well tolerated. The most serious side effect is retinopathy leading to blindness, but this is relatively uncommon and typically only occurs in patients who have used hydroxychloroquine for 5 or more years (42). All patients receiving hydroxychloroquine should be screened annually for retinopathy by an ophthalmologist, particularly after 5 years on the medication. Other rare side effects include hyperpigmentation and severe rash. Hydroxychloroquine may be safe to use during pregnancy.

Sulfasalazine

Sulfasalazine is another traditional DMARD that can be considered in patients who cannot tolerate or who have contraindications to methotrexate. In clinical trials, efficacy of the drugs was similar after 1 year (43), but sulfasalazine may have less efficacy in the long term (44). Side effects may include nausea, diarrhea, and liver function test abnormalities, and these may be dose-related.

Leflunomide

Leflunomide is another traditional DMARD that could be considered as an alternative to methotrexate either as monotherapy or in combination with other traditional or biologic DMARDs. Side effects include nausea, diarrhea, and elevated liver enzymes. Leflunomide is probably teratogenic and has a relatively long half-life (detectable in some patients for up to 2 years after reaching steady state), so its use should generally be avoided in women of childbearing potential who may desire to become pregnant in the future.

Triple therapy

Triple therapy consists of combination therapy with methotrexate, hydroxychloroquine, and sulfasalazine. Sometimes other traditional DMARDs, such as leflunomide or azathioprine, are used instead of sulfasalazine or methotrexate. Triple therapy may be considered in patients with RA who respond inadequately to methotrexate monotherapy and therefore require combination therapy. Triple therapy is more cost-effective than combination biologic DMARDs and methotrexate (45) and may have similar efficacy. However, it is used infrequently compared with biologic DMARDs (46).

In a randomized controlled trial, 353 patients were randomly assigned to triple therapy or combination etanercept and methotrexate (47). After 24 weeks, improvements in disease activity, rates of radiographic progression, and measures of health-related quality of life were similar in both groups.

When should biologic DMARDs be considered, and what are their risk and benefits?

About 30%–50% of patients respond inadequately to traditional DMARDs. Biologic DMARDs should be considered when the response to 2–6 months of methotrexate, as monotherapy or combined with other traditional DMARDs, is inadequate (27, 28). All current biologic DMARDs consist of antibodies that target important inflammatory or immune pathways that are administered either by infusion or subcutaneous injection. Development and use of biologic DMARDs have helped to revolutionize the treatment of RA over the past 2 decades.

The U.S. Food and Drug Administration has approved 10 biologic DMARDs for RA treatment (**Appendix Table 3**), and they have 5 separate mechanisms of action. Infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol are monoclonal antibody- or receptor-antagonist therapies that inhibit tumor necrosis factor (TNF)-α. Additional inflammatory or immune pathways targeted by biological agents that are effective in RA include the T-cell receptor CTLA4 (abatacept), the B-cell marker CD20 (rituximab), interleukin-6 receptor (tocilizumab and sarilumab), and interleukin-1 receptor (anakinra). There may be subtle differences in efficacy between the classes of biologic DMARDs, and individual responses vary considerably. Currently, patients with RA often will initiate a TNF-α inhibitor as the initial biologic DMARD after inadequate response to methotrexate, unless contraindicated (e.g., heart failure). Biologic DMARDs should not be combined but are often paired with traditional DMARDs, particularly methotrexate, because they may enhance efficacy and reduce the rate of development of antidrug antibodies.

The choice of specific biologic DMARD should be made together with the patient, with consideration of personal preferences regarding the route of administration (intravenous infusion vs. self-injection at home), frequency of administration, and financial and other individual factors (such as adherence, other organ dysfunction, previous cancer, and family history). Predicting which patients will respond to a biologic DMARD with a specific mechanism of action is an active area of investigation for personalized medicine in RA.

All biologic DMARDs affect immune function and increase risk for infection, both common (such as pneumonia, cellulitis, and urinary tract infection) and uncommon (such as tuberculosis and fungal infection). Biologic DMARDs should be used with caution in patients with strong risk factors for, or a history of, serious infection. They should be

withheld in the presence of active, serious infection. Screening for tuberculosis and viral hepatitis is mandatory for all patients before drug initiation. Patients should be vaccinated for influenza and pneumococcus, and herpes zoster unless contraindicated. Vaccination against herpes zoster should be considered, but the live attenuated herpes zoster vaccine should not be given after biologic DMARD initiation. Injection or infusion reactions are the most common side effects but are usually mild. Efficacy of biologic DMARDs may be reduced if antidrug antibodies develop. Rarely, drug-induced lupus or other immune side effects can occur in patients receiving these drugs.

In a nationwide observational study in Sweden, 467 patients with RA who initiated a TNF-α inhibitor after a cancer diagnosis were matched to 2164 control patients with similar cancer history (48). Overall, there was no difference in cancer recurrence in patients treated with the TNF-α inhibitor. These results provide further evidence of the favorable long-term safety profile of biologic DMARDs, even in patients with a history of cancer.

What are biosimilars, and what is their role in treatment?

Biosimilars are molecules that have a tight structural relation to another biologic DMARD with an approved indication, termed the "originator molecule." Because biologic DMARDs are complex proteins, it is nearly impossible to completely replicate the originator molecule in the same way that generic drugs are molecular replicates of branded drugs. Before approval, it must be proven that a biosimilar has no clinically meaningful difference in safety or efficacy compared with the originator molecule (49). Biosimilars have a 4-letter suffix appended to the originator molecule name (e.g., etanercept-szzs). Six biosimilars are currently approved for use for RA in the United States, all to TNF-α inhibitors (50). Research is ongoing regarding safety, efficacy, and immunogenicity of biosimilars. The role of these drugs for treatment of RA in the United States is rapidly evolving.

What are small molecule–targeted DMARDs, and what is their role in treatment?

Small molecule–targeted DMARDs are oral drugs that have effects similar to those of biologic DMARDs. In the United States, 2 of these drugs (tofacitinib and baracitinib) are currently approved for use in RA. Both drugs are inhibitors of janus kinase (JAK), which are intracellular molecules involved in signal transduction of JAK/STAT pathways. Inhibition of JAK therefore has targeted downstream biologic consequences to modulate immune cells and inflammation. These JAK inhibitors are generally well tolerated, but side effects may include serious infection, kidney injury, anemia, liver function abnormalities, and thrombosis. Small molecule–targeted DMARDs are typically used for patients in whom other biologic DMARDs have failed or those who cannot receive infusions or injections but research is ongoing on whether to consider treating RA patients with small molecule–targeted DMARDs earlier in the disease course. They can be used as monotherapy or combined with traditional DMARDs (51) but cannot be combined with biologic DMARDs.

What is the role of NSAIDs?

In patients with RA, NSAIDs are used primarily for controlling pain and stiffness. They are not believed to have disease-modifying properties, but are used by nearly half of patients with RA, sometimes regularly but more often on an as-needed basis given their ability to provide quick relief. They are particularly helpful in patients with mechanical pain due to joint damage without active inflammation. These agents have well-known long-term cardiovascular, renal, and gastrointestinal risks, but they remain useful for symptom control (52).

When should clinicians consider using low-dose oral or intra-articular glucocorticoids?

Glucocorticoids are generally believed to be most useful in controlling the pain, stiffness, and swelling of RA but are less useful in halting disease progression. They have many well-documented adverse effects, including infection, hyperglycemia, hypertension, osteoporosis, weight gain, mood instability, and sleep disturbance. Glucocorticoids are most often used in RA for "bridging" therapy at diagnosis or episodes of high disease activity (typically 15 mg or less of prednisone per day) while DMARDs are being initiated. In some patients, glucocorticoids are the only agents that can control the inflammation of RA; in such cases, DMARDs are used as steroid-sparing therapy. The goal should be to wean completely off glucocorticoids or use the lowest dose possible. However, low doses of prednisone (≤5 mg/day) may offer efficacy and likely have a reduced risk for side effects (53).

Intra-articular glucocorticoid injections may be a valuable adjunct in patients with persistent or recurrent joint arthritis despite DMARD treatment. Injections may lead to rapid symptom relief, are well tolerated, and are considered generally safe if no more than 3–4 injections per joint are administered annually (54). Intra-articular glucocorticoids are used primarily when 1 or more medium or large joints are swollen or excessively tender compared with most other

joints. Ultrasonography, fluoroscopy, or computed tomography imaging may be helpful in guiding needle placement for some joints.

When should clinicians consider consultation with a rheumatologist or orthopedist for management?

Optimal management of RA requires sufficient experience in assessment of disease activity, and the choice of DMARDs usually requires ongoing management by a rheumatologist, particularly with the growing list of options. However, patients in underserved areas who do not have access to a rheumatologist will require care from primary care providers. Some patients with early inflammatory arthritis of the knee or shoulder may be evaluated by an orthopedic surgeon for possible synovectomy or osteotomy to aid in symptom relief and rule out other diagnoses, although these procedures are being performed less frequently. Patients with extensive joint damage or comorbid osteoarthritis should be referred to an experienced orthopedic surgeon for consideration of a total joint replacement procedure after a sufficient DMARD trial.

What is the role of physical and occupational therapy?

Although some health professionals cautioned against exercise for patients with RA in the past, an appropriately designed program is now generally considered beneficial. Physical and occupational therapists may optimize functional capacity in patients whose RA limits performance of activities of daily living. Physical therapists may help implement a long-term exercise program, focused on both aerobic capacity and muscle strength. Occupational therapists can also assist patients with work-related activities, using a computer, such as homemaking activities as cooking and cleaning and many other domains. Splints may be helpful to certain patients.

In a randomized trial of patients with early RA, an exercise program directed at aerobic fitness and muscle strength increased strength and improved overall disease activity assessment at 2 years, and these benefits were maintained over the next 3 years (55). There was no evidence of joint or bone damage because of the moderately intense exercise regimen, indicating its safety in patients with RA.

What is the role of other health professionals?

Nurses, pharmacists, nutritionists, physical and occupational therapists, podiatrists, social workers, and psychologists can each help to address the needs of patients with RA. Nurse practitioners and physician assistants are increasingly being used in rheumatology practices (56). Nurse-educators can increase patients' knowledge about their disease and its treatments, which improves outcomes (57). Pharmacists may help patients understand complex medication regimens, particularly biologic DMARDs, which invoke anxiety for some patients and their families. Patients with RA frequently face difficult vocational and interpersonal issues, for which social workers may be invaluable. Nutritionists are useful in providing advice on dietary intake since obesity can affect RA outcomes (58).

Does evidence support specific dietary recommendations, vitamin supplements, or complementary–alternative therapies?

Although some patients report diet as an important factor in improving or worsening their clinical status, there is no strong evidence indicating that vitamin supplements or complementary–alternative therapies benefit all patients with RA (59). A randomized clinical trial suggested some benefit of fish oil in patients with early disease (60). Patients should be encouraged to lose weight if necessary and to maintain or enhance physical fitness only as adjuncts to treatment with DMARDs (61).

What are the long-term clinical consequences and common comorbid conditions?

In most patients, RA is a chronic, progressive disease characterized by episodes of disease flares or long-term chronic inflammation. Only a few patients achieve long-term remission without the need for long-term medications. Patients with RA may be more likely to develop depression, anxiety, and social deprivation, perhaps related to chronic pain, poor sleep, and absenteeism from work or school. Therefore, patients with RA have diminished health-related quality of life compared with the general population and this is most pronounced in patients with low socioeconomic status (62).

Patients with RA are at increased risk for serious comorbid conditions, particularly severe infection, osteoporosis, cardiovascular and respiratory disease, and cancer (63–67). This excess risk is complex and probably related to autoimmunity, immunosuppression, chronic inflammation, smoking, obesity, and poor functional status. For example, risk for coronary artery disease and stroke is increased for patients with RA compared with healthy controls in the general population. This elevated risk is not explained by traditional cardiovascular risk factors, suggesting that RA-specific factors, such as systemic inflammation, autoantibodies, and medications, are important contributors to the excess risk. Patients with RA may also have excess cancer risk related to dysfunctional immune surveillance

or from medication side effects. Serious infections related to DMARD side effects, as well as disease-induced anatomical damage (bronchiectasis increasing risk for pneumonia and bone erosions increasing risk for septic arthritis), are a major contributor to excess RA morbidity, accelerated aging, and frailty. Osteoporosis and increased fracture risk in RA may be related to glucocorticoid use, systemic inflammation, frailty, and impaired bone quality. Patients with seropositive RA are particularly at increased risk for these comorbidities—especially excess respiratory mortality, which is likely related to ILD as an RA-related disease manifestation and accumulation of other types of lung damage related to inflammation and deconditioning (68). Patients with seropositive RA who develop ILD have median survival of only 2.6 years (69). All-cause mortality is 50% higher in patients with RA than in the general population (69). However, this mortality gap seems to be closing (2, 4), perhaps because of early aggressive treatment, expanded therapeutic options, and long-term control of chronic inflammation.

Treatment... The goal of RA treatment is to achieve remission as assessed by a disease activity measure. Treatment with DMARDs should start early, because a delay results in worsened outcomes. Weekly low-dose methotrexate (10-25 mg/week) should be initiated in most patients at the time of diagnosis. If the response is inadequate after 3–4 months, hydroxychloroquine, sulfasalazine, or a biologic DMARD should be substituted or added. Low-dose corticosteroids (≤5 mg prednisone/day) may also be appropriate, although long-term side effects make higher doses undesirable. Nonsteroidal anti-inflammatory drugs are used as needed to control pain and other symptoms. Regular exercise is usually safe and may improve disease and overall health status.

CLINICAL BOTTOM LINE

In the Clinic
Tool Kit

Rheumatoid Arthritis

Patient Information

www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Rheumatoid-Arthritis
www.rheumatology.org/I-Am-A/Patient-Caregiver/Enfermedades-y-Condiciones/Artritis-Reumatoide
Information for patients and caregivers on rheumatoid arthritis in English and Spanish from the American College of Rheumatology.

www.niams.nih.gov/health-topics/rheumatoid-arthritis
www.niams.nih.gov/es/informacion-de-salud/artritis-reumatoide
Patient handout on rheumatoid arthritis and questions and answers on arthritis and rheumatic diseases in English and Spanish from the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Clinical Guidelines

www.rheumatology.org/Portals/0/Files/ACR%202015%20RA%20Guideline.pdf
2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis.

www.nice.org.uk/guidance/ng100
Guidelines from the National Institute for Health and Clinical Excellence on management of rheumatoid arthritis in adults.

In the Clinic

WHAT YOU SHOULD KNOW ABOUT RHEUMATOID ARTHRITIS

What is Rheumatoid Arthritis?

Rheumatoid arthritis (RA) happens when your body's defense system—the immune system—attacks your joints and causes them to become painful and swollen. Joints are where 2 or more bones join together, such as at your hands, wrists, feet, or knees. RA usually causes inflamed joints on both sides of your body.

Am I at Risk?

RA is more common in women than in men. It may occur at any age, but is most common in older adults. Other risk factors include:

- Having a family member with RA
- Cigarette smoking
- Being overweight
- Unhealthy diet
- Poor dental health

What Are the Symptoms?

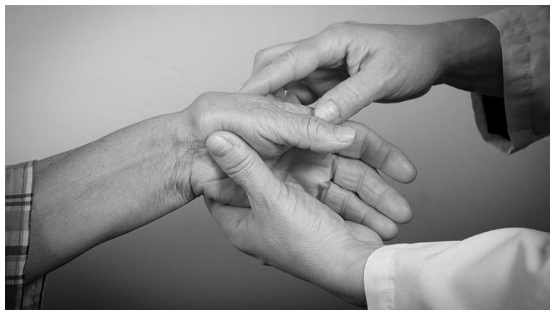
- Joint pain or stiffness on both sides of your body, especially in the hands, wrists, feet, or knees
- Joint pain or stiffness lasting more than a few weeks
- Stiffness or pain that is worse in the morning, lasts for more than 1 hour, and improves during the day
- Feeling tired and unwell

How Is It Diagnosed?

- Your health care provider will ask you questions about your symptoms and medical history.
- You will have a physical examination.
- You will have simple blood tests.
- You might also get an imaging test, like an X-ray or ultrasound.
- You might be referred to a rheumatologist. This is a doctor who specializes in diseases of the joints, muscles, and bones.

How Is It treated?

Early diagnosis and treatment are important to stopping joint pain and preventing long-term damage to your joints.



- There are several medicines available that can keep your RA from getting worse and help you with your symptoms. Talk to your health care provider about which one is best for you.
- Your provider might also talk to you about physical or occupational therapy. Occupational therapy may help you work and do daily activities.
- Exercise is safe and may help you feel better.
- If you smoke, ask your health care provider to help you quit.

Questions for My Doctor

- If I have swollen joints, does that mean that I have RA?
- How will my symptoms change over time?
- What medicines are best for me?
- What are the side effects of the medicines?
- Will other medicines interact with my RA medicines?
- What exercise is safe for me to do?
- Should I see a physical or occupational therapist?
- Do I need to see any other doctors?

For More Information

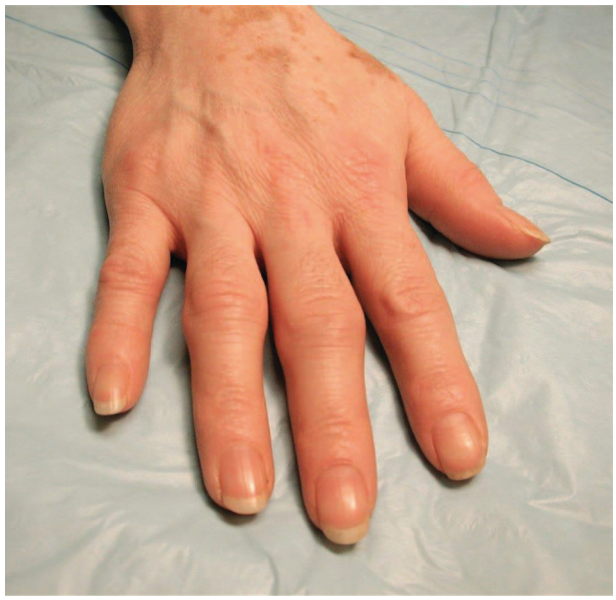
ACP℠
American College of Physicians
Leading Internal Medicine, Improving Lives

Medline Plus
https://medlineplus.gov/rheumatoidarthritis.html

National Institute of Arthritis and Musculoskeletal and Skin Diseases
www.niams.nih.gov/health-topics/rheumatoid-arthritis

Patient Information

Appendix Figure 1. **Early rheumatoid arthritis of the hands, with swelling in the third and fourth proximal interphalangeal joints.**



Reproduced with permission from Medical Knowledge Self-Assessment Program 18. Rheumatology. Philadelphia: American College of Physicians; 2018.

Appendix Table 1. **Differential Diagnosis of Rheumatoid Arthritis**

Disease	*History*	*Physical Examination*	*Comments*
Self-limited polyarthritis	Symmetrical polyarthritis, pain, morning stiffness, fatigue	Symmetrical joint swelling and tenderness	40%–60% of patients with acute polyarthritis have a self-limited process (such as a postviral syndrome); usually resolves within 8 weeks
Fibromyalgia	Widespread musculoskeletal pain, fatigue, poor sleep	Tenderness of articular and nonarticular anatomic sites; no swelling	Much more common than RA (5% of women aged 40–60 years); 20%–30% of patients with RA may also have fibromyalgia
Erosive hand osteoarthritis	Oligoarthritis, often symmetric	Bony enlargement and tenderness of distal interphalangeal (Heberden's nodes) and/or proximal interphalangeal joints (Bouchard's nodes). Metacarpophalangeal joints typically spared	Hands may have severe deformities, but function relatively preserved compared to RA; distal interphalangeal joints prominently involved unlike RA; metacarpophalangeal joints typically spared unlike RA; first carpometacarpal joint often affected
Ankylosing spondylitis	Primarily axial skeleton involvement, back and neck pain	Limited motion of cervical and lumbar spine, hips, shoulders, knees, limited chest expansion	Involves primarily axial skeleton and large rather than small joints
Psoriatic arthritis	Usually history of psoriasis, but arthritis may precede psoriasis	May be mono-, oligo-, or polyarthritis involving the peripheral or axial joints. Psoriatic patches on skin including scalp or gluteal fold	May mimic RA or ankylosing spondylitis; more likely to have distal interphalangeal joint involvement and dactylitis than RA
Reactive arthritis	Axial or peripheral inflammatory arthritis, typically after viral or bacterial gastrointestinal or urinary tract infection	May be mono-, oligo-, or polyarthritis involving the peripheral or axial joints	May mimic RA or ankylosing spondylitis
Polymyalgia rheumatica	Acute or subacute onset of pain and stiffness in the neck, shoulders, and hip in patient >50 years of age	Impaired rotation of the neck, shoulders, and hips. Sometimes with	Rarely has distal joint involvement in the remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome
Other systemic rheumatic diseases (systemic lupus erythematosus, adult-onset Still's disease, juvenile idiopathic arthritis, scleroderma, polymyositis, acute rheumatic fever, systemic vasculitis-related, Lyme disease, inflammatory bowel disease-related, other rare syndromes)	May include symmetrical polyarthritis, pain, morning stiffness, fatigue	May include symmetrical joint swelling and tenderness of the axial or peripheral joints	Seek rheumatology consultation for accurate diagnosis if unclear cause
Septic arthritis	History of trauma or known infection or gonococcal exposure may be seen	Usually monoarticular, rarely involves >1 joints. Swollen red and warm joint, fever	Emergent joint aspiration to confirm diagnosis if suspect to prevent septicemia and joint destruction. More common in patients with RA than in general population
Gout	Usually acute attacks, but may be insidious and chronic	Tophi. Swollen, red joints. Mono- or oligoarticular	Should document crystals for accurate diagnosis
Calcium pyrophosphate deposition, pseudogout, and hydroxyapatite crystal arthritis	Usually acute attacks, but may be insidious and chronic	Swollen, red joints. Mono- or oligoarticular	Should document crystals for accurate diagnosis
Cancer-related	Variable presentation	Swollen joints	Some cancers may have paraneoplastic phenomenon causing inflammatory arthritis; immune-related adverse events from immunotherapy such as checkpoint inhibitors may cause inflammatory arthritis

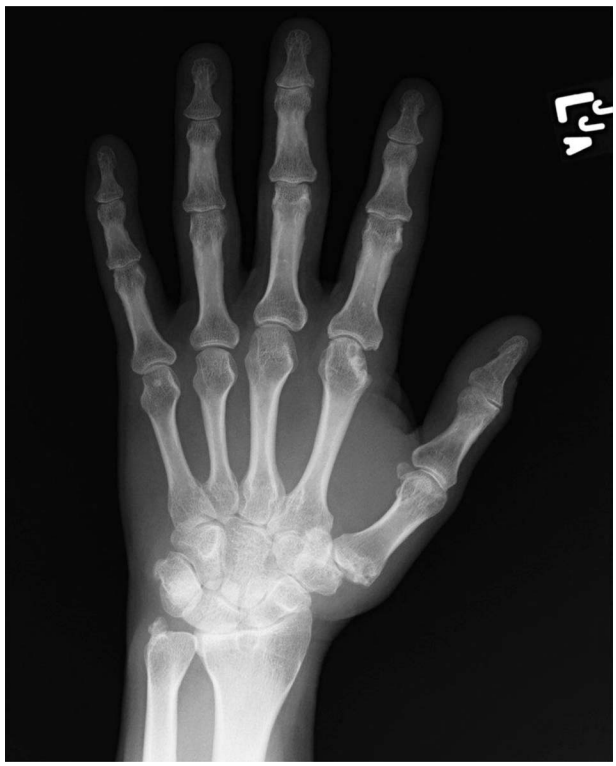
RA = rheumatoid arthritis.

Appendix Table 2. **Tests for Patients With Signs and Symptoms Suggestive of Rheumatoid Arthritis**

Test	*Comments*
Laboratory	
Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)	Useful to detect systemic inflammation and establish a baseline, but nonspecific and may be normal in patients with RA; component of 2010 ACR/EULAR criteria for RA
Rheumatoid factor (RF)	Present in 50%–65% of patients with RA; may be present in other conditions (primary or secondary Sjögren's syndrome, systemic lupus erythematosus, aging, infections); component of 1987 ACR and 2010 ACR/EULAR criteria for RA
Anticyclic citrullinated protein (anti-CCP) or anticitrullinated protein antibodies (ACPA)	Present in about 60%–70% of patients with RA, specific for RA but sometimes present without disease, in other systemic rheumatic diseases, in autoimmune lung diseases or in individuals at-risk for future RA; component of 2010 ACR/EULAR criteria for RA
Antinuclear antibody (ANA)	Nonspecific finding and may be negative in patients with RA
Extractable nuclear antibodies (ENAs) and anti–double-stranded DNA (anti-dsDNA)	Useful in making alternate or overlap diagnoses such as systemic lupus erythematosus or primary Sjögren's syndrome; may aide in diagnosis of secondary Sjögren's syndrome in patients with RA
Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb), and Hepatitis core antibody (HBcAb)	Screen for hepatitis B infection which may prompt treatment and affect DMARD choice for RA; consider vaccination for patients without immunity
Hepatitis C antibody	Screen for hepatitis C infection which may prompt treatment and affect DMARD choice for RA
Basic metabolic panel including creatinine	Evaluate electrolytes and renal function to establish a baseline and may affect DMARD choice for RA
Liver function testing including AST (aspartate transaminase) and ALT (alanine transaminase)	Evaluate liver function to establish a baseline and may affect DMARD choice for RA
Complete blood count (CBC) with differential	Establish a baseline and screen for hematologic disease manifestations or disease mimickers
Creatine kinase (CK)	Screen for myositis and establish a baseline
Thyroid stimulating hormone (TSH)	Screen for autoimmune thyroid disease as a disease mimicker and as a common comorbidity in patients with RA
Screening for tuberculosis with interferon-γ release assays (IGRAs) or purified protein derivative (PPD) placement	Screen for latent tuberculosis which may prompt treatment and affect DMARD choice for RA
Commercial multi-biomarker disease activity assay	Consider if using to monitor RA disease activity to establish a baseline; controversial utility in both diagnosis and monitoring disease activity
Lipid panel and hemoglobin A1c (HbA_{1c})	Consider screening for dyslipidemia and diabetes mellitus in patients with RA
14-3-3 η (14-3-3 eta)	May aide in diagnosing RA in patients with negative RF and CCP; controversial utility
Synovial fluid studies (cell count/differential, crystals, Gram stain, culture)	Consider as clinically indicated for patients with atypical presentation such as monoarthritis or oligoarthritis involving medium/large joints with moderate/large effusions
Other laboratory testing (interleukin-6, serum protein electrophoresis and immunofixation, angiotensin converting enzyme, 25(OH)vitamin D, other vitamins, ionized calcium, uric acid, parathyroid hormone, other hormones, *HLA-B27*, other genetics, HIV antibody, parvovirus B19 antibody, Lyme antibody, other infection screens, other autoantibodies, etc.)	Consider as clinically indicated for some patients and atypical presentations
Imaging	
Musculoskeletal plain film imaging (hands, wrists, feet, other affected joints)	Evaluate for RA-related damage, establish a baseline, and disease mimickers; consider imaging hands, wrists, and feet even without signs or symptoms
Musculoskeletal ultrasound of affected or unaffected joints	Detect and quantify subclinical or clinical synovitis, establish baseline, and detect alternate diagnosis; may aide in joint aspirations/injections; many rheumatologists are now trained in point-of-care ultrasound and may be used to monitor disease activity
Magnetic resonance imaging of affected joint	Detect and quantify subclinical or clinical synovitis, establish baseline, and detect alternate diagnosis; useful for detecting subtle synovitis and soft tissue involvement
Computed tomography scan of affected joint	Detect and quantify bone erosions, establish baseline, and detect alternate diagnosis; useful for detecting bone erosions
Chest plain film	Establish a baseline prior to DMARD treatment; screen for pulmonary manifestations such as interstitial lung disease, pleural effusions, nodules, or bronchiectasis; screen for other diseases such as cancer and pulmonary infections such as tuberculosis
Other imaging (positron emission tomography, bone scan, dual-energy X-ray absorptiometry, musculoskeletal dual-energy computed tomography scan, chest/abdomen/cervical spine computed tomography scan, abdominal ultrasound, transthoracic echocardiogram, etc.)	Consider as clinically indicated for some patients and atypical presentations

DMARD = disease-modifying antirheumatic drug; RA = rheumatoid arthritis.

Appendix Figure 2. **Radiograph of rheumatoid arthritis of the hands.**



Periarticular osteopenia is present at the metacarpophalangeal joints. Marginal erosions are present at the second proximal interphalangeal and metacarpophalangeal joints, as well as the ulnar styloid. Both are characteristic of rheumatoid arthritis and findings that can aid in diagnosis. Joint-space narrowing (a nonspecific finding) is seen at the second and fifth proximal interphalangeal joints. Reproduced with permission from Medical Knowledge Self-Assessment Program 17. Rheumatology. Philadelphia: American College of Physicians; 2015.

Appendix Table 3. **Drugs for Treatment of Rheumatoid Arthritis**

Agent	*Mechanism of Action*	*Dose*	*Notes and Side Effects*
Commonly used traditional DMARDs			
Methotrexate	Anti-inflammatory in weekly low doses	PO 5–25 mg/week SC injection 5–25 mg/week	Initial therapy and backbone for moderate/severe RA, used by >80% of patients. Highest effectiveness, fewest adverse events, best tolerated over 5 years. Combination use with biologic DMARDs enhances efficacy and lowers risk for anti-drug antibody formation. Always administer with either folic acid (1 mg/day or higher doses) or leucovorin (8–12 hours after. Caution in liver disease, contraindicated in pregnancy. Rarely may cause pneumonitis or pulmonary fibrosis (consider CXR before starting). Monitor CBC, BMP, LFTs monthly for first 2–3 months, then every 8–24 weeks.
Hydroxychloroquine	Antimalarial, immunomodulator	PO 200–400 mg/day (maximum dose of 5 mg/kg/day)	Consider as initial therapy for mild RA. May be useful in combination with methotrexate and other DMARDs. Consider testing for G6PD deficiency. May be safe in pregnancy. Ophthalmologic examination yearly to screen for rare retinal toxicity (risk occurs after 5 years on drug). Minimal need for blood test monitoring.
Sulfasalazine	Anti-inflammatory salicylate and sulfa moieties	PO 2–3 g/day in divided doses	Alternative to methotrexate. May be used in combination with methotrexate and hydroxychloroquine as "triple therapy". GI intolerance common at doses >2 g/d. Monitor CBC, BMP, and LFTs every 3 months.
Leflunomide	Pyrimidine-synthesis inhibitor	PO 100 mg/day PO for 3 days, then 20 mg/day	Alternative to methotrexate. May be used as part of triple therapy. Very long half-life, caution use in women of childbearing potential. Contraindicated in pregnancy. GI intolerance, headache. Monitor CBC, BMP, and LFTs monthly for 3 months, then every 8–12 weeks.
Unusual or rarely used traditional DMARDs			
Azathioprine	Purine analog inhibiting purine synthesis	PO 50–250 mg/day with food (typically 2 mg/kg/day)	Alternative to methotrexate. May be used as part of triple therapy. Check thiopurine methyltransferase (TPMT) prior to initiation. May cause GI side effects and bone marrow suppression. Caution in pregnancy, liver disease, or kidney disease and with concomitant use of allopurinol. Monitor CBC, BMP, and LFTs at 1 and 2 weeks after dose change, then every 1–3 months.
Mycophenolate mofetil	Inhibits guanosine nucleotide synthesis	PO 0.5–3 g/day divided in 1–2 doses	Not FDA approved for RA. Side effects include colitis, diarrhea, nausea, and vomiting. Consider use in interstitial lung disease. Monitor CBC every 8–12 weeks.
Cyclosporine	Inhibition of T-cell activation by IL-2	PO 2.5–5 mg/kg/day	Limited by nephrotoxicity, may be useful for flares and recalcitrant cases. Avoid long-term use. Monitor serum creatinine and blood pressure 2–4 weeks until stable dose, then monthly. Monitor CBC, BMP, LFTs, and blood pressure monthly.
Minocycline	Matrix metalloproteinase inhibitor	PO 100 mg twice daily	Not FDA approved for RA. Slow onset. Side effects include rash, hepatitis, hyperpigmentation, dizziness, headache, GI distress, vaginal candida infections, photosensitivity.
Penicillamine	Chelator of sulfhydryl groups inhibiting T-cells	PO 250–1000 mg/day in 3 doses	Not FDA approved for RA. Slow onset. Side effects include bone marrow suppression, anorexia, diarrhea, rash fever, stomatitis, dysgeusia, proteinuria. Monitor CBC, chemistry, urinalysis every 2–4 weeks until stable, then every 1–3 months.
Cyclophosphamide	Alkylating agent disrupting cell cycle	PO 2 mg/kg daily IV infusion 1000 mg monthly	Not FDA approved for RA. Use only in life-threatening rheumatoid vasculitis or in other serious manifestations such as interstitial lung disease. Side effects include bone marrow and gonadal suppression, alopecia, hemorrhagic cystitis, infection, long-term risk for bladder and hematologic cancer. Generally contraindicated in pregnancy. Monitor CBC every 1–2 weeks until stable, then every 1–3 month. Monitor chemistry and urinalysis every 6–12 weeks.
Gold thiomalate, aurothioglucose, auranofin	Decreases cellular proliferation, reduce cytokine release, and inhibit collagenase	IM injection 10 mg week 0, then increase to 25–50 mg/week PO 3–9 mg/day	Slow onset. Infrequently used because of other options and bone marrow suppression, stomatitis, photosensitivity, proteinuria. Monitor CBC, platelet count, and urinalysis for protein every 1–2 week for 20 weeks, then monthly or at time of injection.
Biologic anti-TNF DMARDs			
Infliximab (Remicade) Biosimilars*: Infliximab-dyyb (Inflectra) Infliximab-qbtx (Ixifi) Infliximab-abda (Renflexis)	Chimeric mouse-monoclonal antibody to TNF-α	IV infusion 3–10 mg/kg at week 0, 2, and 6, then every 4–8 weeks	Side effects include upper respiratory tract infection, urinary tract infections. Increased risk for opportunistic infections. Lymphoproliferative diseases, worsening or new-onset heart failure, anaphylaxis or serious allergic reactions, demyelinating disease, local injection-site reactions. Perform permanent partial disability before starting. Use caution in infection. Efficacy increased when used with concomitant methotrexate. Live vaccines are contraindicated. Caution in heart failure.

Continued on following page

Appendix Table 3–Continued

Agent	*Mechanism of Action*	*Dose*	*Notes and Side Effects*
Etanercept (Enbrel) Biosimilar: Etanercept-szzs (Erelzi)	Anti-TNF-α-receptor protein	SC injection 50 mg every week or 25 mg twice per week	
Adalimumab (Humira) Biosimilars: Adalimumab-atto (Amjevita) Adalimumab-adbm (Cyltezo)	Humanized monoclonal antibody to TNF-α	SC injection 40 mg every other week	
Golimumab (Simponi, Simponi Aria)	Humanized monoclonal antibody to TNF-α	SC injection 50 mg every month IV infusion 2 mg/kg at week 0, 4 and every 8 weeks	
Certolizumab pegol (Cimzia)	F_{ab} portion of monoclonal antibody to TNF-α	SC injection 400 mg; 400 mg at weeks 0, 2, and 4, then 200 mg every other week or 400 mg every 4 weeks	Similar to anti-TNF biologics. May not cross the placental barrier so this drug is the preferred anti-TNF to use if use needed during pregnancy, but use with caution.
Other biologic DMARDs			
Abatacept (Orencia)	Inhibits T-cells by recombinant CTLA4	IV infusion 10 mg/kg weeks 0, 2, and 4, then every 4 weeks SC injection 125 mg weekly	Similar to anti-TNF biologics. Infection, infusion reaction, headache, dizziness.
Rituximab (Rituxan)	Monoclonal antibody to CD20 on B-cells	IV infusion 1000 mg on week 0 and 2. Follow-up infusions may be given every 6 months	Similar to anti-TNF biologics. Infusion reaction, rash, renal failure, serum sickness, arrhythmia, serious infection. Infusion reactions more common than other biologic DMARDs. Premedication with IV glucocorticoids decreases rate and severity of infusion reactions. Rarely causes progressive multifocal leukoencephalopathy, a fatal brain infection.
Tocilizumab (Actemra)	Humanized monoclonal antibody to IL-6 receptor	IV infusion 4 mg/kg every 4 weeks (maximum 8 mg/kg, maximum 800 mg per infusion) SC injection 162 mg/week or every other week	Similar to anti-TNF biologics. Elevated alanine aminotransferase/aspartate aminotransferase levels, hyperlipidemia, hypertension, monitor lipid levels. Consider statins. Increased risk for GI perforation, caution in diverticulosis/diverticulitis.
Sarilumab (Kevzara)	Humanized monoclonal antibody to IL-6 receptor	SC injection 200 mg every other week	Similar to anti-TNF biologics. Elevated alanine aminotransferase/aspartate aminotransferase levels, hyperlipidemia, hypertension, monitor lipid levels. Consider statins.
Anakinra (Kineret)	IL-1 receptor antagonist	SC injection 100 mg daily	Similar to anti-TNF biologics. Immunomodulating agent. Injection-site reactions. Decreased leukocyte (neutrophil) and platelet counts. Infrequently used for RA, more often used in adult-onset Still's disease.
Targeted small molecule DMARDs			
Tofacitinib (Xeljanz)	Janus kinase (JAK3) inhibitor	PO 5 mg twice daily or 11 mg once daily (extended release form)	Similar to anti-TNF biologics. Can use as monotherapy or in combination with methotrexate. Side effects include GI intolerance, kidney injury, anemia, and serious infections.
Baricitinib (Olumiant)	Janus kinase (JAK1/2) inhibitor	PO 2 mg daily	Similar to anti-TNF biologics. Can use as monotherapy or in combination with methotrexate. Side effects include GI intolerance, kidney injury, anemia, serious infections, and thrombosis.
Selected NSAIDs			
Ibuprofen Naproxen Diclofenac Indomethacin Nabumetone Ketoprofen Flurbiprofen Etodolac Meloxicam Piroxicam Oxaproxin Celecoxib	COX inhibitors. Some selectively inhibit COX-2, some suppress lipooxygenase	PO as instructed for each drug, use as needed for pain relief	Abdominal pain, diarrhea, edema, dizziness, peptic ulcers and bleeding, gastroesophageal reflux disease, bruising, nausea, nightmares, rash, tinnitus, renal insufficiency, confusion, depression, aseptic meningitis. Use with caution in preexisting heart, liver, or kidney disease. Use with caution in elderly persons, those with previous history of peptic ulcer disease (may add misoprostol as prophylaxis), or sensitive to aspirin or other NSAIDs; BMP weekly for 3 weeks in high-risk patients, then CBC, BMP, LFTs every year. Follow blood pressure regularly. Decrease dose when glomerular filtration rate <20 mL/min per 1.73 m^2 or in chronic liver disease.

ACR/EULAR = American College of Rheumatology/European League Against Rheumatism; BMP = basic metabolic panel; CBC = complete blood count; COX = cyclooxygenase; DMARD = disease-modifying antirheumatic drug; FDA = U.S. Food and Drug Administration; G6PD = glucose-6-phosphate dehydrogenase; GI = gastrointestinal; IM = intramuscular; IV = intravenous; LFT = liver function test; NSAID = nonsteroidal anti-inflammatory drug; PO = oral; SC = subcutaneous; TNF = tumor necrosis factor.
**Only biosimilars approved by the U.S. Food and Drug Administration as of 1 September 2018 are included.*