

Diagnosis and Management of Rheumatoid Arthritis

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Rheumatoid arthritis is the most commonly diagnosed systemic inflammatory arthritis. Women, smokers, and those with a family history of the disease are most often affected. Criteria for diagnosis include having at least one joint with definite swelling that is not explained by another disease. The likelihood of a rheumatoid arthritis diagnosis increases with the number of small joints involved. In a patient with inflammatory arthritis, the presence of a rheumatoid factor or anti-citrullinated protein antibody, or elevated C-reactive protein level or erythrocyte sedimentation rate suggests a diagnosis of rheumatoid arthritis. Initial laboratory evaluation should also include complete blood count with differential and assessment of renal and hepatic function. Patients taking biologic agents should be tested for hepatitis B, hepatitis C, and tuberculosis. Earlier diagnosis of rheumatoid arthritis allows for earlier treatment with disease-modifying antirheumatic agents. Combinations of medications are often used to control the disease. Methotrexate is typically the first-line drug for rheumatoid arthritis. Biologic agents, such as tumor necrosis factor inhibitors, are generally considered second-line agents or can be added for dual therapy. The goals of treatment include minimization of joint pain and swelling, prevention of radiographic damage and visible deformity, and continuation of work and personal activities. Joint replacement is indicated for patients with severe joint damage whose symptoms are poorly controlled by medical management. (*Am Fam Physician*. 2011;84(11):1245-1252. Copyright © 2011 American Academy of Family Physicians.)

► **Patient information:** A handout on this topic is available at <http://familydoctor.org/876>.

Rheumatoid arthritis (RA) is the most common inflammatory arthritis, with a lifetime prevalence of up to 1 percent worldwide.¹ Onset can occur at any age, but peaks between 30 and 50 years.² Disability is common and significant. In a large U.S. cohort, 35 percent of patients with RA had work disability after 10 years.³

Etiology and Pathophysiology

Like many autoimmune diseases, the etiology of RA is multifactorial. Genetic susceptibility is evident in familial clustering and monozygotic twin studies, with 50 percent of RA risk attributable to genetic factors.⁴ Genetic associations for RA include human leukocyte antigen-DR4⁵ and -DRB1, and a variety of alleles called the shared epitope.^{6,7} Genome-wide association studies have identified additional genetic signatures that increase the risk of RA and other autoimmune diseases, including *STAT4* gene and CD40 locus.⁵ Smoking is the major environmental trigger for RA, especially in those with a genetic predisposition.⁸ Although infections may unmask an autoimmune

response, no particular pathogen has been proven to cause RA.⁹

RA is characterized by inflammatory pathways that lead to proliferation of synovial cells in joints. Subsequent pannus formation may lead to underlying cartilage destruction and bony erosions. Overproduction of pro-inflammatory cytokines, including tumor necrosis factor (TNF) and interleukin-6, drives the destructive process.¹⁰

RISK FACTORS

Older age, a family history of the disease, and female sex are associated with increased risk of RA, although the sex differential is less prominent in older patients.¹ Both current and prior cigarette smoking increases the risk of RA (relative risk [RR] = 1.4, up to 2.2 for more than 40-pack-year smokers).¹¹

Pregnancy often causes RA remission, likely because of immunologic tolerance.¹² Parity may have long-lasting impact; RA is less likely to be diagnosed in parous women than in nulliparous women (RR = 0.61).^{13,14} Breastfeeding decreases the risk of RA (RR = 0.5 in women who breastfeed for at least 24 months), whereas early menarche

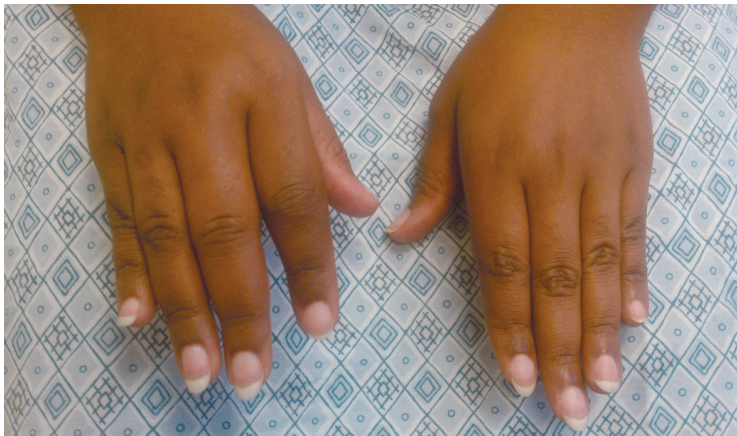


Figure 1. Boggy swelling in proximal interphalangeal and metacarpophalangeal joints (more prominent on patient's right hand) in a patient with new-onset rheumatoid arthritis. Note that with joint swelling, the skin creases over the proximal interphalangeal joints become less apparent.

(RR = 1.3 for those with menarche at 10 years of age or younger) and very irregular menstrual periods (RR = 1.5) increase risk.¹⁴ Use of oral contraceptive pills or vitamin E does not affect RA risk.¹⁵

Diagnosis

TYPICAL PRESENTATION

Patients with RA typically present with pain and stiffness in multiple joints. The wrists, proximal interphalangeal joints, and metacarpophalangeal joints are most commonly involved. Morning stiffness lasting more than one hour suggests an inflammatory etiology. Boggy swelling due to synovitis may be visible (*Figure 1*), or subtle synovial thickening may be palpable on joint examination. Patients may also present with more indolent arthralgias before the onset of clinically apparent joint swelling. Systemic symptoms of fatigue, weight loss, and low-grade fever may occur with active disease.

DIAGNOSTIC CRITERIA

In 2010, the American College of Rheumatology and European League Against Rheumatism collaborated to create new classification criteria for RA (*Table 1*).¹⁶ The new criteria are an effort to diagnose RA earlier in patients who may not meet the 1987 American College of Rheumatology classification criteria. The 2010 criteria do not include presence of rheumatoid nodules or radiographic erosive changes, both of which are less likely in early RA. Symmetric arthritis is also not required in the 2010 criteria, allowing for early asymmetric presentation.

In addition, Dutch researchers have developed and validated a clinical prediction rule for RA (*Table 2*).^{17,18} The purpose of this rule is to help identify patients with undifferentiated arthritis that is most likely to progress to RA, and to guide follow-up and referral.

DIAGNOSTIC TESTS

Autoimmune diseases such as RA are often characterized by the presence of autoantibodies. Rheumatoid factor is not specific for RA and may be present in patients with other diseases, such as hepatitis C, and in healthy older persons. Anti-citrullinated protein antibody is more specific for RA and may play a role in disease pathogenesis.⁶ Approximately 50 to 80 percent of persons with RA have rheumatoid factor, anti-citrullinated protein antibody, or both.¹⁰ Patients with RA may have a positive antinuclear antibody test result, and the test is of prognostic importance in juvenile forms of this disease.¹⁹ C-reactive protein levels and erythrocyte sedimentation rate are often increased with active RA, and these acute phase reactants are part of the new RA classification criteria.¹⁶ C-reactive protein levels and erythrocyte sedimentation rate may also be used to follow disease activity and response to medication.

Baseline complete blood count with differential and assessment of renal and hepatic function are helpful because the results may influence treatment options (e.g., a patient with renal insufficiency or significant thrombocytopenia likely would not be prescribed a nonsteroidal anti-inflammatory drug [NSAID]). Mild anemia of chronic disease occurs in 33 to 60 percent of all patients with RA,²⁰ although gastrointestinal blood loss should also be considered in patients taking corticosteroids or NSAIDs. Methotrexate is contraindicated in patients with hepatic disease, such as hepatitis C, and in patients with significant renal impairment.²¹ Biologic therapy, such as a TNF inhibitor, requires a negative tuberculin test or treatment for latent tuberculosis. Hepatitis B reactivation can also occur with TNF inhibitor use.²² Radiography of hands and feet should be performed to evaluate for characteristic periarticular erosive changes,

Table 1. The 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for RA

	Score
Target population (who should be tested?): patients who	
1) have at least one joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A through D; a score of ≥ 6 out of 10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
One large joint	0
Two to 10 large joints	1
One to three small joints (with or without involvement of large joints)¶	2
Four to 10 small joints (with or without involvement of large joints)	3
> 10 joints (at least one small joint)**	5
B. Serology (at least one test result is needed for classification)††	
Negative RF and negative ACPA	0
Low positive RF or low positive ACPA	2
High positive RF or high positive ACPA	3
C. Acute phase reactants (at least one test result is needed for classification)‡‡	
Normal CRP and normal ESR	0
Abnormal CRP or normal ESR	1
D. Duration of symptoms§§	
< six weeks	0
\geq six weeks	1

ACPA = anti-citrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RA = rheumatoid arthritis.

*—The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of RA with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with long-standing disease, including those whose disease is inactive (with or without treatment), who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

†—Differential diagnoses differ in patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

‡—Although patients with a score of less than 6 out of 10 are not classifiable as having RA, their status can be reassessed, and the criteria might be fulfilled cumulatively over time.

§—Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

||—“Large joints” refers to shoulders, elbows, hips, knees, and ankles.

¶—“Small joints” refers to the metacarpophalangeal joints, proximal interphalangeal joints, second to fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

**—In this category, at least one of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular).

††—Negative refers to international unit values that are less than or equal to the upper limit of normal for the laboratory and assay; low positive refers to international unit values that are higher than the upper limit of normal but three or less times the upper limit of normal for the laboratory and assay; high positive refers to international unit values that are more than three times the upper limit of normal for the laboratory and assay. When rheumatoid factor information is only available as positive or negative, a positive result should be scored as low positive for rheumatoid factor.

‡‡—Normal/abnormal is determined by local laboratory standards.

§§—Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

Adapted with permission from Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative [published correction appears in *Ann Rheum Dis*. 2010;69(10):1892]. *Ann Rheum Dis*. 2010;69(9):1583.

Table 2. Clinical Rule for Predicting the Risk of RA in Patients with Undifferentiated Arthritis

Patient characteristics	Points			
Age	Years × 0.02			
Female sex	1.0			
Distribution of affected joints (patients may receive points for more than one item)				
Small joints of hands or feet	0.5			
Symmetric	0.5			
Upper extremities	1.0			
Upper and lower extremities	1.5			
Score for morning stiffness on a 100-mm visual analog scale				
26 to 90 mm	1.0			
> 90 mm	2.0			
Number of tender joints				
Four to 10	0.5			
≥ 11	1.0			
Number of swollen joints				
Four to 10	0.5			
≥ 11	1.0			
C-reactive protein level				
5 to 50 mg per L (47.62 to 476.20 nmol per L)	0.5			
≥ 51 mg per L (485.72 nmol per L)	1.5			
Positive for rheumatoid factor	1.0			
Positive for anti-citrullinated protein antibody	2.0			
Total: _____				
Score*	Number with RA	Number without RA	Likelihood ratio	Percentage with RA at one year
0 to 3.5	0	109	0	0
3.51 to 6.5	41	214	0.42	16
6.51 to 8.5	71	53	3.0	57
≥ 8.51	63	11	12.7	85

RA = rheumatoid arthritis.

*—Score rounded to the nearest number ending in 0 or 0.5.

Adapted with permission from van der Helm-van Mil AH, le Cessie S, van Dongen H, et al. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis. *Arthritis Rheum.* 2007;56(2):436, with scoring information from reference 18.

which may be indicative of a more aggressive RA subtype.¹⁰

DIFFERENTIAL DIAGNOSIS

Skin findings suggest systemic lupus erythematosus, systemic sclerosis, or psoriatic arthritis. Polymyalgia rheumatica should be considered in an older patient with symptoms primarily in the shoulder and hip, and the patient should be asked questions related to associated temporal arteritis.

Chest radiography is helpful to evaluate for sarcoidosis as an etiology of arthritis.

Patients with inflammatory back symptoms, a history of inflammatory bowel disease, or inflammatory eye disease may have spondyloarthropathy. Persons with less than six weeks of symptoms may have a viral process, such as parvovirus. Recurrent self-limited episodes of acute joint swelling suggest crystal arthropathy, and arthrocentesis should be performed to evaluate for monosodium urate monohydrate or calcium pyrophosphate dihydrate crystals. The presence of numerous myofascial trigger points and somatic symptoms may suggest fibromyalgia, which can coexist with RA. To help guide diagnosis and determine treatment strategy, patients with inflammatory arthritis should be promptly referred to a rheumatology subspecialist.^{16,17}

Treatment

After RA has been diagnosed and an initial evaluation performed, treatment should begin. Recent guidelines have addressed the management of RA,^{21,22} but patient preference also plays an important role. There are special considerations for women of childbearing age because many medications have deleterious effects on pregnancy. Goals of therapy include minimizing joint pain and swelling, preventing deformity (such as ulnar deviation) and radiographic damage (such as erosions), maintaining quality of life (personal and work), and controlling extra-articular manifestations. Disease-modifying antirheumatic drugs (DMARDs) are the mainstay of RA therapy.

DMARDs

DMARDs can be biologic or nonbiologic (Table 3).²³ Biologic agents include monoclonal antibodies and recombinant receptors to block cytokines that promote the inflammatory cascade responsible for RA symptoms. Methotrexate is recommended as the first-line treatment in patients with active RA, unless contraindicated or not tolerated.²¹ Leflunomide (Arava) may be used as an alternative to methotrexate, although gastrointestinal adverse effects are more common. Sulfasalazine (Azulfidine) or hydroxychloroquine (Plaquenil) is recommended as monotherapy in patients with low disease

Table 3. Biologic and Nonbiologic Disease-Modifying Antirheumatic Drugs

Drug*	Mechanism for rheumatoid arthritis	Adverse effects	Monthly cost†
Nonbiologic			
More commonly used			
Methotrexate	Inhibits dihydrofolate reductase	Liver effects, teratogenesis, hair loss, oral ulcers	\$
Leflunomide (Arava)	Inhibits pyrimidine synthesis	Liver effects, gastrointestinal effects, teratogenesis	\$
Hydroxychloroquine (Plaquenil)	Antimalarial, blocks toll-like receptors	Rare ocular toxicity	\$\$
Sulfasalazine (Azulfidine)	Folate depletion, other mechanisms unknown	Anemia in G6PD deficiency, gastrointestinal effects	\$
Minocycline (Minocin)	Antimicrobial, other mechanisms unknown	Drug-induced lupus erythematosus, <i>Clostridium difficile</i> colitis	\$
Less commonly used			
Gold sodium thiomalate	Inhibits antigen processing, decreases cytokines (TNF, interleukin-6)	Skin, heme, renal effects	\$\$
Penicillamine (Cuprimine)	Chelates metal, other mechanisms unknown	Heme, renal effects	\$\$
Cyclophosphamide	Nitrogen mustard alkylating agent, cross-links DNA	Infertility, cancer, hemorrhagic cystitis	\$\$
Cyclosporine (Sandimmune)	Calcineurin inhibitor, decreases interleukin-2	Hypertension, renal effects, hirsutism	\$\$
Biologic			
Anti-TNF agents			
Adalimumab (Humira)	Anti-TNF- α	TB, opportunistic infection	\$\$\$
Certolizumab pegol (Cimzia)	Anti-TNF- α , pegylated	TB, opportunistic infection	\$\$\$
Etanercept (Enbrel)	Anti-TNF- α , receptor	TB, opportunistic infection	\$\$\$
Golimumab (Simponi)	Anti-TNF- α	TB, opportunistic infection	\$\$\$
Infliximab (Remicade)	Anti-TNF- α	TB, opportunistic infection, infusion reaction	\$\$\$
Other biologic agents			
Abatacept (Orencia)	Costimulator blocker, cytotoxic T lymphocyte antigen 4	Opportunistic infection	\$\$\$
Anakinra (Kineret)	Anti-interleukin-1 receptor blocker	Opportunistic infection, injection site pain	\$\$\$
Rituximab (Rituxan)	Anti-CD20, eliminates B cells	Infusion reaction, opportunistic infection, progressive multifocal leukoencephalopathy	\$\$\$\$
Tocilizumab (Actemra)	Anti-interleukin-6 receptor blocker	Opportunistic infection	\$\$\$

G6PD = glucose-6-phosphate dehydrogenase; TB = tuberculosis; TNF = tumor necrosis factor.

*—Nonbiologic drugs listed in approximate order of priority, biologic drugs listed in alphabetical order.

†—\$ = \$30 to \$100; \$\$ = \$100 to \$1,000; \$\$\$ = \$1,000 to \$5,000; \$\$\$\$ = more than \$5,000.

Information from reference 23.

activity or without poor prognostic features (e.g., seronegative, nonerosive RA).^{21,22}

Combination therapy with two or more DMARDs is more effective than monotherapy; however, adverse effects may also be greater.²⁴ If RA is not well controlled with a nonbiologic DMARD, a biologic DMARD should be initiated.^{21,22} TNF inhibitors are the first-line biologic therapy and are the most studied of these agents. If TNF inhibitors are ineffective, additional biologic therapies can be considered. Simultaneous use of more than one biologic therapy (e.g., adalimumab [Humira] with abatacept [Orencia]) is not

recommended because of an unacceptable rate of adverse effects.²¹

NSAIDS AND CORTICOSTEROIDS

Drug therapy for RA may involve NSAIDs and oral, intramuscular, or intra-articular corticosteroids for controlling pain and inflammation. Ideally, NSAIDs and corticosteroids are used only for short-term management. DMARDs are the preferred therapy.^{21,22}

COMPLEMENTARY THERAPIES

Dietary interventions, including vegetarian and Mediterranean diets, have been

Table 4. Extra-Articular Manifestations of RA

<i>Manifestation</i>	<i>Characteristics</i>
Cardiac	
Accelerated atherosclerosis	Leading cause of death in patients with RA
Pericarditis	Present in 30 to 50 percent of persons with RA on autopsy, rarely leads to tamponade
Eye	
Episcleritis/scleritis	Acute, red, painful eye; occurs in less than 1 percent of patients with RA
Keratoconjunctivitis sicca	Secondary Sjögren syndrome, dry mouth may also occur
Peripheral ulcerative keratitis	More severe scleritis, if untreated can perforate anterior chamber
Hematologic	
Amyloidosis	Caused by chronic inflammation
Felty syndrome	Splenomegaly, neutropenia, and thrombocytopenia
Nervous system	
Cervical myelopathy	Caused by C1-C2 subluxation, seen on flexion-extension radiography
Neuropathy	Carpal tunnel, mononeuritis multiplex (foot drop)
Pulmonary	
Caplan syndrome	Nodules and pneumoconiosis (e.g., in coal miners)
Interstitial lung disease	May resemble bronchiolitis obliterans with organizing pneumonia, idiopathic pulmonary fibrosis, patient may also have pulmonary arterial hypertension
Pleural effusion	Exudative effusion with markedly low glucose level
Pulmonary nodules	Can be asymptomatic
Skin	
Rheumatoid nodules	Firm or rubbery, located on pressure areas (e.g., olecranon)
Vasculitis	Poor prognosis, increased mortality, rare but occurs with severe RA (i.e., erosive, deforming, and seropositive disease)

RA = rheumatoid arthritis.

Information from references 1, 2, and 10.

studied in the treatment of RA without convincing evidence of benefit.^{25,26} Despite some favorable outcomes, there is a lack of evidence for the effectiveness of acupuncture in placebo-controlled trials of patients with RA.^{27,28} In addition, thermotherapy and therapeutic ultrasound for RA have not been studied adequately.^{29,30} A Cochrane review of herbal treatments for RA concluded that gamma-linolenic acid (from evening primrose or black currant seed oil) and *Tripterygium wilfordii* (thunder god vine) have potential benefits.³¹ It is important to inform patients that serious adverse effects have been reported with use of herbal therapy.³¹

EXERCISE AND PHYSICAL THERAPY

Results of randomized controlled trials support physical exercise to improve quality of life and muscle strength in patients with RA.^{32,33} Exercise training programs have not been shown to have deleterious effects on RA disease activity, pain scores, or radiographic joint damage.³⁴ Tai chi has been shown to improve ankle range of motion in persons with RA, although randomized trials are limited.³⁵ Randomized controlled trials of Iyengar yoga in young adults with RA are underway.³⁶

DURATION OF TREATMENT

Remission is obtainable in 10 to 50 percent of patients with RA, depending on how remission is defined and the intensity of therapy.¹⁰ Remission is more likely in males, nonsmokers, persons younger than 40 years, and in those with late-onset disease (patients older than 65 years), with shorter duration of disease, with milder disease activity, without elevated acute phase reactants, and without positive rheumatoid factor or anti-citrullinated protein antibody findings.³⁷

After the disease is controlled, medication dosages may be cautiously decreased to the minimum amount necessary. Patients will require frequent monitoring to ensure stable symptoms, and prompt increase in medication is recommended with disease flare-ups.²²

JOINT REPLACEMENT

Joint replacement is indicated when there is severe joint damage and unsatisfactory control of symptoms with medical management. Long-term outcomes are good, with only 4 to 13 percent of large joint replacements requiring revision within 10 years.³⁸ The hip and knee are the most commonly replaced joints.

Long-term Monitoring

Although RA is considered a disease of the joints, it is also a systemic disease capable of involving multiple organ systems. Extra-articular manifestations of RA are included in *Table 4*.^{1,2,10}

Patients with RA have a twofold increased risk of lymphoma, which is thought to be caused by the underlying inflammatory

process, and not a consequence of medical treatment.³⁹ Patients with RA are also at an increased risk of coronary artery disease, and physicians should work with patients to modify risk factors, such as smoking, high blood pressure, and high cholesterol.^{40,41} Class III or IV congestive heart failure (CHF) is a contraindication for using TNF inhibitors, which can worsen CHF outcomes.²¹ In patients with RA and malignancy, caution is needed with continued use of DMARDs, especially TNF inhibitors. Biologic DMARDs, methotrexate, and leflunomide should not be initiated in patients with active herpes zoster, significant fungal infection, or bacterial infection requiring antibiotics.²¹ Complications of RA and its treatments are listed in *Table 5*.^{1,2,10}

Prognosis

Patients with RA live three to 12 years less than the general population.⁴⁰ Increased mortality in these patients is mainly due to accelerated cardiovascular disease, especially in those with high disease activity and chronic inflammation. The relatively new biologic therapies may reverse progression of atherosclerosis and extend life in those with RA.⁴¹

Data Sources: A PubMed search was completed in Clinical Queries using the key terms rheumatoid arthritis, extra-articular manifestations, and disease-modifying antirheumatic agents. The search included meta-analyses, randomized controlled trials, clinical trials, and reviews. Also searched were the Agency for Healthcare Research and Quality evidence reports, Clinical Evidence, the Cochrane database, Essential Evidence, and UpToDate. Search date: September 20, 2010.

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Table 5. Complications of RA and Its Treatments

Complication	Comments
Depression	Affects up to 40 percent of patients with RA, can also be caused by corticosteroid use
Infection	May be caused by RA itself or use of immunosuppressants
Malignancy	
Lymphoma	Risk is double in persons with RA, independent of immunosuppressant use
Lung cancer	Caused by smoking, underlying interstitial lung disease
Skin cancer	Risk may be increased with immunosuppressant use

RA = rheumatoid arthritis.

Information from references 1, 2, and 10.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References
Patients with inflammatory joint disease should be referred to a rheumatology subspecialist, especially if symptoms last more than six weeks.	C	16, 17
In persons with RA, combination therapy with two or more disease-modifying antirheumatic drugs is more effective than monotherapy. However, more than one biologic agent should not be used at one time (e.g., adalimumab [Humira] with abatacept [Orencia]) because of the high risk of adverse effects.	A	21, 22, 24
A guided exercise program can improve quality of life and muscle strength in patients with RA.	B	32, 34, 35
Cardiovascular disease is the main cause of mortality in persons with RA; therefore, risk factors for coronary artery disease should be addressed in these patients.	C	40, 41

RA = rheumatoid arthritis.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort.xml>.

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