JAMA | Review

Rheumatoid Arthritis in Adults
A Review

Josef S. Smolen, MD; Andreas Kerschbaumer, MD, PhD; Daniel Aletaha, MD; William H. Robinson, MD, PhD

IMPORTANCE Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes inflammation and destruction of cartilage and adjacent bone and can lead to irreversible disability. Rheumatoid arthritis affects 0.53% of adults worldwide and 0.74% of US adults.

OBSERVATIONS Rheumatoid arthritis is more common among females than males (2:1) and has a peak incidence at ages 55 to 75 years. Rheumatoid arthritis can affect all synovial joints, and extra-articular involvement may include rheumatoid nodules, vasculitis, and rheumatoid lung disease. At diagnosis, approximately 40% to 60% of patients have autoantibodies (eg, rheumatoid factor and/or anticitrullinated peptide antibodies). There are no formal diagnostic criteria for RA, so the diagnosis is based on clinical history, characteristic joint swelling in proximal interphalangeal, metacarpophalangeal, and/or wrist joints and often presence of autoantibodies and elevated C-reactive protein levels. Early diagnosis, ideally within 6 weeks of symptom onset, allows rapid initiation of therapy with disease-modifying antirheumatic drugs (DMARDs), which inhibit inflammation and decrease the risk of joint destruction. The goal of treatment is to achieve at least 50% improvement in disease activity by 3 months and remission or low disease activity at 6 months, measured by validated indexes such as the Clinical Disease Activity Index (CDAI). The European Alliance of Associations for Rheumatology recommends starting treatment with methotrexate, 7.5 mg to 10 mg orally weekly, increasing to 20 mg to 25 mg weekly within 4 to 8 weeks, and considering addition of short-term glucocorticoids (eg, prednisone, 5-7.5 mg/d), tapered and discontinued within 3 months, or 1 intramuscular injection of 80 mg to 160 mg depot methylprednisolone. For patients with contraindications to methotrexate, sulfasalazine (2-4 g/d) or leflunomide (20 mg/d) is recommended. With treatment, about 40% of patients with newly diagnosed RA achieve CDAI remission within 6 months. Patients who do not achieve remission with first-line DMARDs should be prescribed biological DMARDs (eg, tumor necrosis factor α inhibitors, costimulation inhibitors, interleukin 6 receptor inhibitors, anti-CD20–targeting B cells), or Janus kinase (JAK) inhibitors (in patients not at high risk of thromboembolism, cardiovascular disease, or malignancy). With addition of biological DMARDs or JAK inhibitors to first-line DMARDs, overall remission or low disease activity rates increase to approximately 80%.

CONCLUSIONS AND RELEVANCE Rheumatoid arthritis is a chronic autoimmune disease that causes joint destruction. First-line initial therapy is methotrexate, with consideration of glucocorticoids as additive therapy. For patients who do not achieve remission with this initial treatment, adding biological DMARDs or JAK inhibitors increases overall remission or low disease activity rates to 80%.

Multimedia

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Author Affiliations: Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria (Smolen, Kerschbaumer, Aletaha); Division of Immunology and Rheumatology, Stanford University, Stanford, California (Kerschbaumer, Robinson).

Corresponding Author: Josef S. Smolen, MD, Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Spitalgasse 23, 1090 Vienna, Austria (josef.smolen@meduniwien.ac.at).

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Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by symmetric synovial inflammation, autoantibody formation, and progressive joint destruction. Rheumatoid arthritis is the most common autoimmune disease in the US,[1] with an estimated incidence rate of 18.3 per 100 000 and a global incidence rate of 11.8 per 100 000.[2,3]

If not treated early and intensively to decrease synovial inflammation, RA can cause extra-articular manifestations such as rheumatoid nodules, vasculitis, and pulmonary fibrosis.[4,5] Although RA is a chronic disease, highly effective therapies such as methotrexate plus glucocorticoids, biological disease-modifying antirheumatic drugs (DMARDs), and Janus kinase (JAK) inhibitors administered to achieve remission or low disease activity within 6 months from initiation of treatment often lead to sustained remission.[6] This Review discusses the pathogenesis, epidemiology, risk factors, clinical presentation, diagnosis, treatment, and prognosis of RA (**Box**).

Box. Common Questions About Adult Rheumatoid Arthritis (RA)

How is RA diagnosed?

Rheumatoid arthritis is typically diagnosed based on clinical history and characteristic joint swelling in wrist joints, metacarpophalangeal, and/or proximal interphalangeal joints of both hands, with sparing of the distal interphalangeal joints. About 75% of patients with RA experience morning joint stiffness of more than 30 minutes. Most patients with RA have autoantibodies (rheumatoid factor and/or anticitrullinated peptide antibodies) and elevated levels of C-reactive protein.

How should RA be clinically assessed?

Patients with active RA should have disease activity evaluated every 1 to 3 months using the Clinical Disease Activity Index (CDAI), which includes the number of swollen and tender joints, and patient and physician global assessments. High disease activity is defined by a CDAI score greater than 22. Patients with low disease activity have a CDAI score of 10 or less, and remission is defined as a CDAI score of 2.8 or less. Improvements in CDAI score of 50%, 75%, and 85% define minimal, moderate, and major response to treatment, respectively.

How should RA be treated?

Patients should initiate treatment with a disease-modifying antirheumatic drug (DMARD) on diagnosis with RA. First-line treatment is oral methotrexate (20-25 mg/wk), with consideration of the addition of low-dose glucocorticoids (prednisone, 5-7.5 mg/d, for up to 3 months, with subsequent tapering off). For patients not achieving a reduction in disease activity by at least 50% within 3 months and remission within 6 months, a biological DMARD (such as a tumor necrosis factor inhibitor, interleukin 6 receptor inhibitor, abatacept, or rituximab) should be added. A Janus kinase inhibitor may be considered for patients at low risk of cardiovascular disease, thromboembolism, or malignancy.

Methods

A systematic literature search was conducted in PubMed/MEDLINE from database inception to July 6, 2026, to identify peer-reviewed publications related to treatment, pathogenesis, genetics, epidemiology, outcomes, and disease management. The search strategy is available in the eTable in the Supplement.

We screened 15 886 articles and prioritized inclusion of randomized clinical trials (RCTs), systematic reviews and meta-analyses, and large cohort studies, focusing on studies published after the *JAMA* 2018 narrative review on diagnosis and management of RA.[7] Of 620 articles assessed in detail, this Review includes 123 articles, comprising 46 RCTs, 28 cohort studies, 11 systematic reviews and meta-analyses, 15 society guidelines/management recommendations, 9 basic/translational science articles, 6 outcomes research analyses, and 8 narrative reviews.

Pathophysiology

Synovial inflammation due to RA involves cells of the innate and adaptive immune system, fibroblasts, and increased vascularization, which form a hyperplastic and destructive synovial membrane (pannus) that causes joint destruction, mediated by macrophage-derived, bone-eroding osteoclasts[8] and activated fibroblasts that damage cartilage[9] (**Figure 1**).

Chronic inflammation due to RA may be preceded by mucosal barrier disruption, causing chronic inflammation in the mouth (periodontitis), lungs (induced by environmental factors like smoking), and intestinal surfaces (increased permeability), allowing bacteria such as *Porphyromonas gingivalis* in the mouth or *Prevotella* in the gut to interact with the immune system. Citrullinated microbial antigens exposed at mucosal surfaces can trigger and sustain systemic (auto)antibody production, which may potentially initiate RA.[10]

T cells play an important role in initiating RA given the specific autoantibody response and genetic association of RA with the major histocompatibility complex.[11,12] Progressive synovial inflammation and joint damage is propagated by innate immune cells such as macrophages, fibroblasts, continuously activated B cells, and plasma cells that produce autoantibodies with subsequent immune complex formation (Figure 1).[13] The first autoantibody described in RA was rheumatoid factor, which is directed against the Fc portion of immunoglobulin G.[14] Anticitrullinated peptide antibodies (ACPAs) are also common among patients with RA. On binding to their antigens, ACPAs can form immune complexes in the joint, and rheumatoid factor can increase and further promote formation of immune complexes and complement activation, which may lead to activation of tumor necrosis factor (TNF) and interleukin 6 (IL-6) by macrophages (Figure 1). In RA, autoantibodies can also form against other modified proteins.[15] These pathogenetic inflammatory pathways lead to degradation of cartilage and bone, resulting in joint destruction and deformity (Figure 1).

Epidemiology and Risk Factors

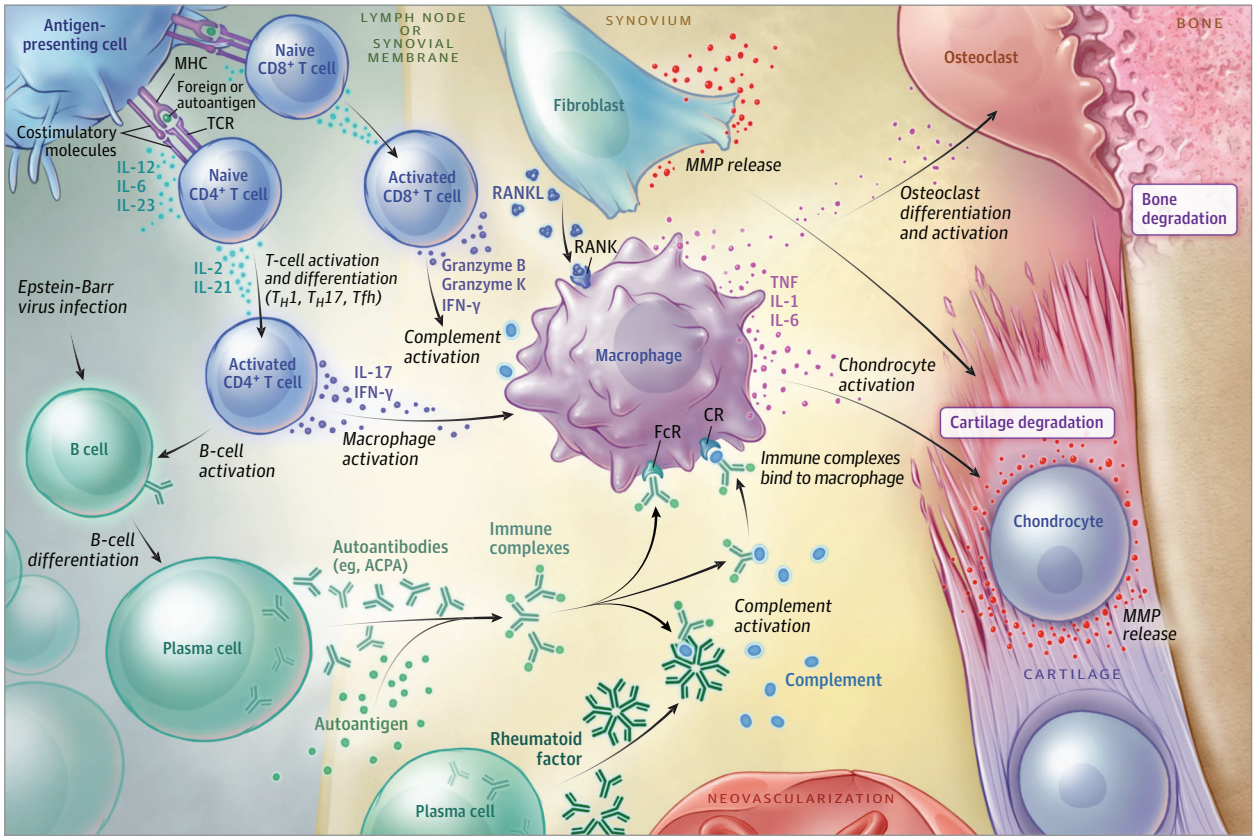
Rheumatoid arthritis affects females more commonly than males (ratio of 2:1 to 3:1), and peak incidence occurs at ages 55 to 75 years.[16,17] Genetic susceptibility accounts for 60% of RA risk, with monozygotic twins having 15% concordance compared with 3.5% concordance in dizygotic twins.[18] Among the many associated genes, the *HLA-DRB1* shared epitope family, a set of immune-response genes carried by 70% to 80% of patients with RA, is the most important.[11]

Certain environmental factors are associated with increased risk of RA (Figure 1). In a case-control study in the US, 644 patients with

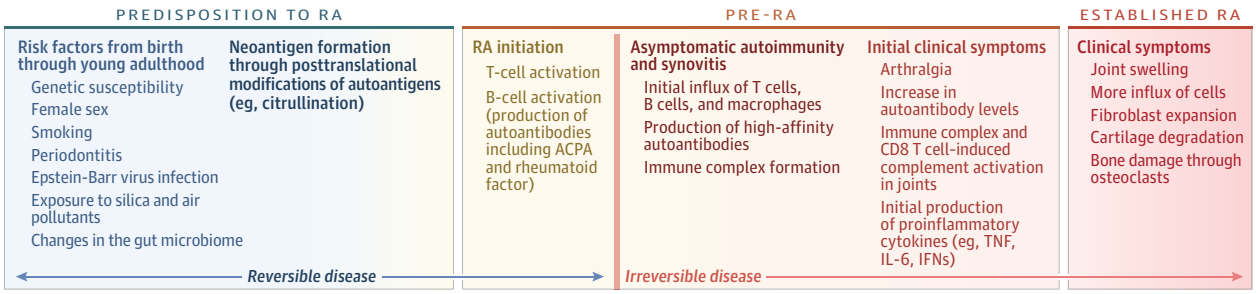
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Figure 1. Illustration of the Pathophysiology and Evolution of RA

A Immunopathogenetic cascade in RA



B Evolution of RA

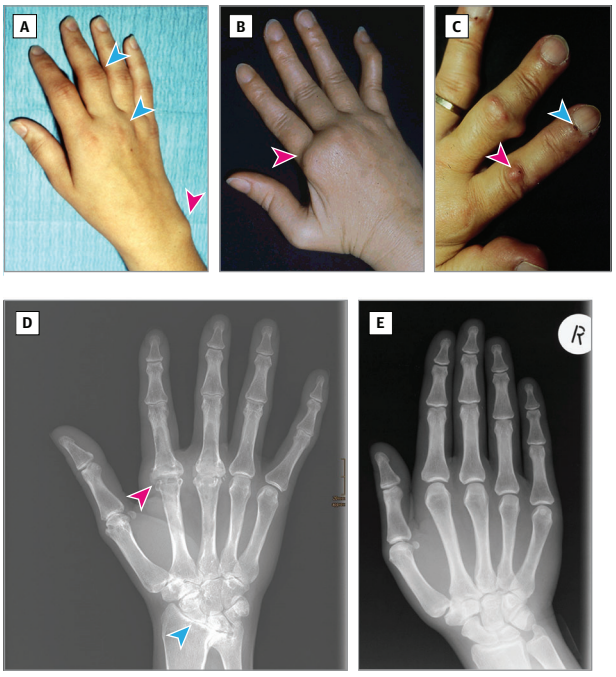


ACPA indicates anticitrullinated peptide antibody; CR, complement receptor; FcR, Fc receptor; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; RANK, receptor activator of nuclear factor κB; RA, rheumatoid arthritis; RANKL, RANK ligand; TCR, T-cell receptor, Tfh, follicular helper T cell; T_H1, T helper cell; TNF, tumor necrosis factor. Panel A is a schematic of the proposed immunopathogenetic cascade in RA. Left to right, top to bottom: modified autoantigens (eg, citrullinated proteins) or foreign peptides (eg, bacterial or viral, potentially cross-reactive) are presented by an antigen-presenting cell via MHC class II molecule (shared epitope) with costimulation (CD80/CD86) to naive CD4 T cells, breaking tolerance. Activated T cells differentiate into T_H1 or Tfh cells and secrete IL-2 and IFN-γ, activating macrophages and providing B-cell help. B cells differentiate into plasma cells that produce autoantibodies (eg, ACPA, rheumatoid factor). Immune complexes engage FcRs and complement receptors on B cells and macrophages, amplifying inflammation and complement activation. Activated macrophages produce proinflammatory cytokines, including TNF and IL-6. Antigens presented via MHC class I activate CD8 T cells, which secrete IFN-γ and TNF and release granzyme K, further enhancing complement activation and joint inflammation. B cells may also be activated independently by Epstein-Barr virus, expanding autoreactive responses. Proinflammatory cytokines induce RANKL expression by synovial fibroblasts, driving macrophage differentiation from within the synovial compartment into osteoclasts that mediate bone erosion at the cartilage-bone junction. Activated fibroblasts and chondrocytes secrete MMPs, degrading cartilage and causing joint space narrowing. Neovascularization by activated endothelial cells sustains inflammatory cell influx. Panel B shows evolution of RA from genetic predisposition to disease.

RA were more likely to have ever smoked (57%) than geographically matched controls (49%) (odds ratio, 1.34; 95% CI, 1.0-1.81; $P = .05$).[19] Smoking promotes chronic airway inflammation and leads to peptidyl arginine deiminase–mediated citrullination (the process by which the amino acid arginine is changed to citrulline) and presentation of citrullinated antigens to the immune system, which

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Figure 2. Photographs and Imaging Depicting Clinical Aspects of RA



A, Early arthritis. Blue arrowheads point toward swelling at proximal interphalangeal and metacarpophalangeal joints, red arrowhead points toward tenosynovitis. B, Patient with long-standing rheumatoid arthritis (RA) with subluxation at the metacarpophalangeal joints (arrowhead) and a so-called swan-neck deformity of the fifth digit. C, Patient with rheumatoid nodules and rheumatoid vasculitis. Red arrowhead points toward a nodule, blue arrowhead toward a vasculitic lesion (black dot). D, Radiograph of the right hand of a patient with severe joint damage at the metacarpophalangeal (red arrowhead) and wrist joints (blue arrowhead), revealing erosions and joint space narrowing. Compare this image with the same patient's radiograph at the time of early disease 6 years prior with near normal joints by radiography (E).

treats these altered proteins as foreign targets.[20,21] Smoking is also linked to periodontitis, which is associated with RA. In a nationwide cohort study in Taiwan, the incidence of RA in people with periodontal disease (n = 628 828) was 23.4 per 10 000 person-years vs 8.3 per 10 000 person-years in those without periodontal disease (n = 168 842) (adjusted hazard ratio, 1.90; 95% CI, 1.57-2.3; $P < .001$).[22] In the UK, the incidence of RA was 13.9 per 10 000 person-years for individuals with periodontitis vs 12.4 per 10 000 person-years in those without periodontitis ($P < .001$).[23] Another potential risk factor for RA is Epstein-Barr virus, the reactivation of which has been associated with RA, although the causal relationship between RA and Epstein-Barr virus infection is currently unclear.[24,25] Other environmental risk factors for RA include exposure to silica and air pollutants (Figure 1B).[26,27]

Clinical Presentation

Patients with RA typically present with symmetric synovial swelling and pain in multiple joints (polyarthritis); the synovial swelling is soft, with a fluctuant quality with palpation, in contrast to the hard swelling associated with osteoarthritis caused by bony changes (**Figure 2**A). However, some patients with RA have joint pain and tenderness without clinically evident swelling.[29] Among patients with RA, the most commonly affected joints are the wrist (about 75% of patients), metacarpophalangeal and proximal interphalangeal joints (about 65%), knee (about 50%), and metatarsophalangeal joints (about 45%) (Figure 2A and B).[29] Unlike in osteoarthritis and psoriatic arthritis, the distal interphalangeal joints are not affected in RA. Morning joint stiffness for more than 30 minutes and sometimes many hours occurs in about 75% of patients with RA,[30] and tenosynovitis, especially in the extensor carpi ulnaris tendon with swelling on the ulnar side of the wrist, is clinically evident in about 20% of patients (Figure 2A).[31]

Extra-articular manifestations such as rheumatoid nodules (eg, at the forearm near the elbow or the dorsal side of the fingers; see Figure 2C), rheumatoid vasculitis (Figure 2C), or interstitial lung disease are uncommon in early RA but may occur in patients who have had RA for at least 3 years without remission or low disease activity.[4] Among 1226 Swedish patients with early RA followed up for a mean of 9.3 years while taking DMARDs, 238 (19.4%) exhibited extra-articular manifestations, of which 45% had rheumatoid nodules, 22% had pulmonary fibrosis, and 3% had vasculitis.[32]

Laboratory Assessment

Patients being evaluated for RA should undergo autoantibody testing; those with rheumatoid factor and/or ACPAs are considered seropositive and those without these antibodies are considered seronegative. At diagnosis, rheumatoid factor and/or ACPAs are detected in about 40% to 60% of patients, and the prevalence of these autoantibodies increases to about 80% in those who have had RA for 3 years or longer.[33-35] In an inception cohort of 242 patients with RA who were seronegative for rheumatoid factor and ACPAs, 28 (12%) became seropositive over the following 3 years.[36] Elevation of acute-phase reactants (C-reactive protein, erythrocyte sedimentation rate) and anemia of chronic disease with normocytic, normochromic anemia (hemoglobin <12 g/dL) occur in 25% of patients with RA during the first year after symptom onset.[37]

Classification, Diagnosis, and Assessment

Formal diagnostic criteria for RA do not exist because the diagnosis may be made in patients who do not fulfill the full set of classification criteria of patients included in clinical trials (**Table 1**).[38,39] However, the clinical diagnosis of RA can be supported by the American College of Rheumatology (ACR)–European Alliance of Associations for Rheumatology (EULAR) classification criteria, which include the number of involved joints, serologic test results (rheumatoid factor and ACPAs), symptom duration, and presence of acute-phase reactants (C-reactive protein and erythrocyte sedimentation rate) (Table 1).[39] The presence of typical erosions, as identified on radiography and defined as cortical breaks or cavities in the surface of the bone near joints, in at least 3 joints of the hands or feet is strongly associated with the diagnosis of RA.[40] Individuals without joint swelling who are seropositive for RA or ACPAs are considered to have pre-RA, which is associated with increased risk of developing RA (Figure 1B). In some patients, the ACPAs can be detected approximately 14 years before the onset of signs and symptoms of RA, and

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rheumatoid factor may be present approximately 10 years before clinical manifestations of RA.[41] The ACR and EULAR have created criteria for the stratification of these at-risk persons to predict the likelihood of developing RA.[42]

Among patients being evaluated for or diagnosed with RA, conventional radiography of affected joints should be performed to identify joint space narrowing (reflecting cartilage damage) and erosions, most prominently seen in the joints of hands and feet (Figure 2D). When diagnosis is made early, joint radiographs are usually normal (Figure 2E). Annual radiographs of affected joint regions should be obtained in patients with active RA, defined as those having joint swelling, pain, and inflammatory markers.[43] Joint space narrowing has a stronger association with functional impairment than erosions.[44] Ultrasound or magnetic resonance imaging may identify inflammation in the joint (synovitis) or in tendon sheath in proximity to joints (tenosynovitis) that was not visualized on radiography, but these imaging modalities provide no additional benefit beyond clinical assessment or plain radiographs as follow-up or outcomes tools.[45]

Several reliable variables that are sensitive to change with therapy are used to assess RA treatment response (**Table 2**), including the swollen and tender joint count (for which the 28-joint count is easy to perform), global disease activity and pain assessments, acute-phase reactant levels, and physical function such as by the Health Assessment Questionnaire disability index[46,47] (Table 2). Rheumatologists assess these core components and integrate them into composite scores. The Clinical Disease Activity Index (CDAI) includes 4 components, and the Simplified Disease Activity Index (SDAI), adds C-reactive protein to the CDAI formula. The ACR and EULAR define clinical remission based on a CDAI score of 2.8 or lower or an SDAI score of 3.3 or lower (Table 2).[48]

Table 1. ACR-EULAR 2010 Classification Criteria for Rheumatoid Arthritis[a]

Criteria	No. of points
Joints (0-5)	
1 Large joint	0
2-10 Large joints	1
1-3 Small joints (large joints not counted)	2
4-10 Small joints (large joints not counted)	3
>10 Joints (≥1small joint)	5
Serology (0-3)	
Negative for rheumatoid factor and negative for anticitrullinated peptide antibodies	0
Low positive for rheumatoid factor or low positive for anticitrullinated peptide antibodies	2
High positive for rheumatoid factor or high positive for anticitrullinated peptide antibodies	3
Symptom duration (0-1)	
<6 wk	0
≥6 wk	1
Acute-phase reactants (0-1)	
Normal C-reactive protein and normal erythrocyte sedimentation rate	0
Abnormal C-reactive protein or abnormal erythrocyte sedimentation rate	1

Abbreviations: ACR, American College of Rheumatology; EULAR, European Alliance of Associations for Rheumatology.

[a] Adapted from Aletaha et al.[39] A patient with 6 or more points can be classified as having rheumatoid arthritis. There are no explicit diagnostic criteria for rheumatoid arthritis. A diagnosis must be established by an individual physician in an individual patient based on that patient's features, which may occasionally differ from those represented in classification criteria. Classification criteria are meant to identify patients for consideration of participation in clinical studies to provide a homogeneous study population. Nevertheless, classification criteria can aid in diagnosis and are often used so in teaching.

Treatment

The treatment goal for previously untreated patients with an RA disease duration of 3 years or less is remission within 6 months after starting DMARDs (**Table 3**).[6,49,82] For patients with an RA disease duration of more than 3 years, remission may not be easily achievable, so low disease activity can be an alternative treatment goal.[82] To support decision-making, the ACR and EULAR have developed management recommendations, most recently updated in 2021 (ACR)[49] and 2025 (EULAR).[6]

DMARDs

All patients with RA should be treated with DMARDs, which are disease modifying because they prevent irreversible joint damage, unlike medications such as nonsteroidal anti-inflammatory drugs or analgesics that reduce pain and swelling but do not modify RA progression. Types of DMARDs include conventional synthetic DMARDs, biological DMARDs, and targeted synthetic DMARDs (Table 3). All DMARDs reduce or inhibit joint swelling, pain, and joint damage and can reverse physical disability (Table 3). Pain medications such as nonsteroidal antirheumatic drugs, acetaminophen (paracetamol), or tramadol should be used only as adjunctive pain control therapy until the therapeutic target of remission or low disease activity is reached or for persistent pain after this therapeutic target has been attained. Of note, targeted therapies, such as biological DMARDs or JAK inhibitors, halt progression of joint damage even among patients who continue to have RA symptoms while taking these drugs,[83,84] thus reducing the risk of irreversible physical disability.

After initiating DMARDs, disease activity should be formally assessed by rheumatologists using standardized disease activity indexes at least monthly; if at least 50% CDAI improvement is not achieved by 3 months or remission by 6 months, therapy should be adjusted by changing DMARDs.[6,82] This treat-to-target strategy has been shown to improve outcomes compared with routine care.[85,86] The TICORA study[85] randomized 55 patients with RA to an intervention of monthly monitoring with disease activity scoring and protocol-driven treatment escalation (injecting swollen joints with glucocorticoids, increasing medication dose, or changing to another drug regimen) and randomized 55 patients to routine care with quarterly visits without formal disease activity measurement or predefined treatment escalations. At 18 months, 70% improvement of disease activity according to the ACR response criteria (defined in Table 2) was observed in 71% of patients in the intervention group vs 18% in the routine care group (odds ratio, 11; 95% CI, 4.5-27).[85] The treat-to-target approach includes shared decision-making to optimize the choice of treatment target and medication and to increase adherence,[82] which improves outcomes.[87]

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Table 2. Common Disease Activity Measures and Clinical Response Criteria[a]

Measure	Components or definition	Remission thresholds or response criteria	Comments
Clinical Disease Activity Index (CDAI)	Sum of SJC-28, TJC-28, patient global assessment, and evaluator global assessment[b]	• Remission: score ≤2.8; low disease activity: score >2.8 to 10; moderate disease activity: score >10 to 22; high disease activity: score >22[c] • Flare: score increase of 4.5	Useful in routine clinical practice, does not require laboratory values, simple to calculate
Simplified Disease Activity Index (SDAI)	Sum of SJC-28, TJC-28, patient global assessment, evaluator global assessment, and CRP, measured in milligrams per deciliter (capped at 10 mg/dL)[b]	• Remission: score ≤3.3; low disease activity: score >3.3 to 11; moderate disease activity: score >11 to 26; high disease activity: score >26[c] • Flare: score increase of ≥4.7	Similar to CDAI but requires CRP
Disease Activity Score in 28 joints using CRP (DAS28-CRP)[d]	Composite index including SJC-28, TJC-28, patient global assessment, and CRP (in milligrams per liter)	Remission: score <2.6; low disease activity: score 2.6 to 3.2; moderate disease activity: score >3.2 to 5.1; high disease activity: score >5.1	Often used in clinical trials and registry studies, more complicated to calculate than CDAI or SDAI, CRP highly weighted
Revised ACR-EULAR remission definition	CDAI ≤2.8 or SDAI ≤3.3 or simultaneous presence of SJC-28 ≤1, TJC-28 ≤1, CRP ≤1 mg/dL, and patient global assessment ≤2, or when CRP not used, SJC-28 ≤1, TJC-28 ≤1, and patient global assessment ≤2	Defines remission	Current international consensus definition of remission using stringent criteria
ACR20/ACR50/ACR70 response criteria	Percentage reduction in TJC-28 and SJC-28 plus percentage reduction in 3 of the following variables: patient global assessment, patient pain assessment, physician global assessment, functional assessment (Health Assessment Questionnaire), and acute-phase reactants (CRP or erythrocyte sedimentation rate)[b]	ACR20, ACR50, and ACR70 correspond to ≥20%, ≥50%, and ≥70% improvement of these variables	• Used in clinical trials to establish efficacy. Starts with baseline activity and requires follow-up assessment of percentage change from baseline • Not an activity instrument but a response measure • ACR70 aligns with low disease activity
28-Joint count	Assessment of 28 joints including shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, and knees	Not applicable	Component of all composite measures but excludes feet and ankles, allows quick bedside assessment

Abbreviations: ACR, American College of Rheumatology; CRP, C-reactive protein; EULAR, European Alliance of Associations for Rheumatology; SJC-28, 28 swollen joint count; TJC-28, 28 tender joint count.

SI conversion: To convert CRP to milligrams per liter, multiply by 10.

[a] The measures used for rheumatoid arthritis are described in further detail in Aletaha and Smolen.[28]

[b] Patient global assessment and evaluator global assessment are scored as 0-10 on a visual analog or numeric rating scale. Patients are prompted with "Considering all the ways your arthritis has affected you, how do you feel your arthritis is today?"

[c] Minor, moderate, and major responses are defined as 50%, 70%, and 85% improvement, respectively.

[d] Calculated as $(0.56 \times \sqrt{\text{TJC-28}}) + (0.28 \times \sqrt{\text{SJC-28}}) + (0.36 \times \ln[\text{CRP} + 1]) + (0.014 \times \text{patient global assessment score}) + 0.96$.

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Table 3. Currently Approved DMARDs in the US, Europe, and Asia and Their Use in Accordance With EULAR[6] and ACR[49] Recommendations

			Efficacy, ACR70 response rate, %				
	Maintenance dosage	Target	DMARD-naive patients[a]	Patients with insufficient methotrexate response[a,b]	Patients with insufficient TNF inhibitor response[a,c]	Comment	Adverse events
Synthetic DMARDs							
Conventional synthetic							
Methotrexate	15-25 mg/wk (0.3 mg/kg), orally or subcutaneously	Unknown	21-40 (without added glucocorticoids)[50,51]	Not applicable	Not applicable	Clinical Disease Activity Index remission: 43% at 6 mo (combined with glucocorticoids)[52]; inhibits progression of joint damage	Nausea (10%), stomatitis (3%-10%), liver enzyme increase (15%), bone marrow suppression (3%-10%), all reduced by use of folate supplementation; pneumonitis (1%); teratogenicity
Sulfasalazine	2-4 g/d (ideally enteric coated), orally	Unknown	8 (2 g/d)[53]	Not applicable	Not applicable	Using 3 g/d had significantly better clinical effects than 1.5 g/d[54]; up to 4 g/d used in a clinical trial with no difference from methotrexate at up to 25 mg/wk[55]; inhibits progression of joint damage[56]; contraindicated in people with sulfonamide allergy	Rash (13%), leukopenia (3%), thrombopenia (1%), nausea (19%), dyspepsia/abdominal pain/vomiting/diarrhea (8%-13%), drug-induced lupus, Stevens-Johnson syndrome (<1%), reversible oligospermia
Leflunomide	20 mg/d, orally	Dihydro-orotate dehydrogenase	10[53]	Not applicable	Not applicable	Inhibits progression of joint damage	Diarrhea (27%), hypertension (9%), hypersensitivity reactions (5%), liver enzyme increases (10%), alopecia (9%), teratogenicity
Targeted synthetic[d]							
Tofacitinib	5 mg twice daily; 11 mg once daily (slow release); orally	JAK1, JAK2, JAK3	Not applicable	20[57]	14[58]	When combined with methotrexate, noninferior to adalimumab plus methotrexate; as a monotherapy, not noninferior to combination with methotrexate[59]	Infections, reactivation of tuberculosis, herpes zoster, cytopenias including anemia, hyperlipidemia, creatine phosphokinase increases, nonmelanoma skin cancer[60]; venous thromboembolic events[e]
Baricitinib	4 mg once daily (US: 2 mg once daily), orally	JAK1, JAK2	Not applicable	24[61]	17[62]	Combination with methotrexate superior to adalimumab plus methotrexate, but difference not clinically relevant according to EULAR[63]	
Filgotinib	100 mg once daily, orally	JAK1	Not applicable	30[64]	Approximately 21[65]	Combination with methotrexate noninferior to adalimumab plus methotrexate; filgotinib not licensed in the US[64]	
Upadacitinib	15 mg once daily, orally	JAK1 (JAK2)	Not applicable	21[66]	12[67]	Combination with methotrexate superior to adalimumab plus methotrexate, but difference not clinically relevant according to EULAR[68]	
Peficitinib	100-150 mg once daily, orally	JAK1, JAK2, JAK3	Not applicable	24[69]	Not applicable	Peficitinib approved in Asia (eg, Japan)	

(continued)

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Table 3. Currently Approved DMARDs in the US, Europe, and Asia and Their Use in Accordance With EULAR[6] and ACR[49] Recommendations (continued)

	Maintenance dosage	Target	Efficacy, ACR70 response rate, %			Comment	Adverse events
			DMARD-naive patients[a]	Patients with insufficient methotrexate response[a,b]	Patients with insufficient TNF inhibitor response[a,c]		
Biological DMARDs							
Biological originators							
Etanercept	50 mg once weekly, subcutaneously	TNF	Not applicable	20[70]	Not studied directly in RCT	No difference between various TNF inhibitor compounds in clinical or radiographic responses	Infections, reactivation of tuberculosis, psoriasiform skin changes, exacerbation of demyelinating diseases, drug-induced lupus, nonmelanoma skin cancer, injection site or infusion reactions
Infliximab	3-5 mg/kg every 6 wk, intravenously	TNF	Not applicable	20[70]	Not studied directly in RCT		
Adalimumab	40 mg every 2 weeks, subcutaneously	TNF	Not applicable	20[70]	Not studied directly in RCT		
Golimumab	50 mg every month, subcutaneously	TNF	Not applicable	20[70]	12[71]		
Certolizumab pegol	200 mg every 2 wk, subcutaneously	TNF	Not applicable	20[70]	9 (at wk 12)[72]		
Tocilizumab	162 mg once weekly, subcutaneously	IL-6 receptor	Not applicable	22[73]	12[74]		Infections, reactivation of tuberculosis, bowel perforation, hypersensitivity reactions, neutropenia, injection site reactions, hyperlipidemia
Sarilumab	200 mg every 2 wk, subcutaneously	IL-6 receptor	Not applicable	25[75]	20[76]		
Rituximab	500-1000 mg as 2 infusions 2 wk apart, repeated every 6 mo, intravenously	CD20 (B cell)	Not applicable	22[77]	12[78]	Head-to-head trials show similar response rates as seen with TNF inhibitors[79]	Infections, hypersensitivity reactions, reactivation of hepatitis B, leukocytopenia, hypogammaglobulinemia
Abatacept	125 mg once weekly, subcutaneously	CD80/CD86 (costimulation)	Not applicable	22[80]	12[81]		Infections, reactivation of tuberculosis, leukocytopenia, injection site reactions
Biosimilars			Not applicable	Similar to originator data	Similar to originator data		See originator agents
Etanercept	50 mg once weekly, subcutaneously	TNF					
Infliximab	3-5 mg/kg every 6 wk, intravenously	TNF					
Adalimumab	40 mg every 2 weeks, subcutaneously	TNF					
Rituximab	500-1000 mg as 2 infusions 2 wk apart, repeated every 6 mo, intravenously	CD20 (B cell)					
Tocilizumab	162 mg once weekly, subcutaneously	IL-6 receptor					

Abbreviations: ACR, American College of Rheumatology; DMARD, disease-modifying antirheumatic drug; EULAR, European Alliance of Associations for Rheumatology; IL, interleukin; JAK, Janus kinase; RCT, randomized clinial trial; TNF, tumor necrosis factor.

[a] ACR70 response: at least 70% improvement according to the ACR response criteria, ie, at least 70% reduction in swollen and tender joint counts and 70% reduction in at least 3 of the following variables: patient global assessment, patient pain assessment, physician global assessment (all using a visual analog scale), C-reactive protein or erythrocyte sedimentation rate, and physical function (for further details, see Table 2).

[b] Response among patients with an insufficient response after 3 to 6 months of methotrexate therapy, as evidenced by moderate to high disease activity.

[c] Response among patients with an insufficient response after 3 to 6 months to at least 1 previously administered TNF inhibitor as well as prior methotrexate therapy before that; in some trials, especially those investigating JAK inhibitors, other biological DMARDs may have been used before without adequate response.

[d] Currently, only JAK inhibitors are approved as targeted synthetic DMARDs for rheumatoid arthritis.

[e] For frequencies of adverse events with individual biological DMARDs and JAK inhibitors, refer to product labels.

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Conventional Synthetic DMARDs

EULAR recommends methotrexate as the first-line DMARD, which should be prescribed for all patients with RA without contraindications (eg, kidney failure, liver disease, heavy alcohol use, pregnancy). Based on EULAR recommendations, methotrexate should be started at 7.5 mg to 10 mg orally weekly and increased to 20 mg to 25 mg weekly (0.3 mg/kg) within 4 to 8 weeks.[88] To reduce adverse events due to methotrexate (eg, nausea, vomiting, abdominal discomfort, elevated transaminases), folic acid should be added (1 mg/d to 15 mg/wk).[89] Use of oral methotrexate is noninferior to subcutaneous methotrexate. In a meta-analysis of 3 RCTs (557 patients), among those treated with an oral methotrexate regimen, 26.2% had a response of at least 70% improvement according to the ACR response criteria (ACR70; defined in Table 2); 31.9% treated with parenteral methotrexate regimens achieved an ACR70 response (odds ratio, 0.75; 95% CI, 0.51-1.09).[90] However, for patients who cannot tolerate oral methotrexate despite folic acid supplementation, subcutaneous methotrexate may be considered.

Among patients initiating methotrexate for RA, EULAR also recommends consideration of adding glucocorticoids (5-7.5 mg/d of oral prednisone for 6 to 12 weeks, tapered and discontinued within 3 months, or a single dose of 80 mg to 160 mg intramuscular methylprednisolone).[6] With methotrexate plus glucocorticoids, more than 40% of patients with newly diagnosed RA achieve remission.[6,52] If this goal is not reached or a if glucocorticoid taper or discontinuation of glucocorticoids results in an RA flare, defined as loss of low disease activity response and transition into a moderate or high disease activity state (Table 2), a biological agent (or JAK inhibitor) should be added.[6] In contrast to EULAR, the 2021 ACR management guidelines for RA "conditionally recommended" conventional synthetic DMARD initiation without use of short-term glucocorticoids, albeit with "very low certainty of evidence."[49]

Combining conventional synthetic DMARDs (such as methotrexate with sulfasalazine and hydroxychloroquine or with leflunomide) is not recommended as first-line therapy due to higher risk of adverse effects such as anemia and liver toxicity without conveying better efficacy.[91] In a prespecified secondary analysis of the NORD-STAR RCT (217 patients with newly diagnosed RA), CDAI remission rates at 24 weeks were not higher with use of combined conventional synthetic DMARDs (41%; 95% CI, 29%-54%) vs methotrexate monotherapy (47%; 95% CI, 39%-56%) (*P* value not reported).[92]

For patients with intolerance or contraindications to methotrexate, EULAR recommends alternatives of sulfasalazine at 2 to 4 g/d, ideally in an enteric-coated application, or leflunomide at 20 mg/d,[6] as both have similar efficacy to methotrexate in comparative trials.[53,93] In a meta-analysis comparing methotrexate and leflunomide (6 RCTs; 1984 patients with RA), clinical response occurred in 56% of patients taking leflunomide vs 58% taking methotrexate.[94] Nevertheless, methotrexate is the first-line recommended DMARD because its clinical trial evidence is substantially larger than any other conventional synthetic DMARD. Additionally, its once-weekly administration is easier to use than 6 daily tablets of sulfasalazine or daily leflunomide.

Biological DMARDs

Biological DMARDs target specific soluble molecules or surface structures of cells involved in the inflammatory response (Figure 1). Agents targeting TNF-α include adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. Two biological DMARDs bind the IL-6 receptor (sarilumab and tocilizumab); abatacept targets the costimulatory molecule CD80/CD86; and rituximab binds to the B-cell antigen CD20. All biological DMARDs convey similar efficacy across all end points in RA clinical trials.[95] EULAR guidelines recommend use of any biological DMARD for patients treated with methotrexate or other conventional synthetic DMARDs who do not achieve a target of 50% reduction of disease activity at 3 months or achievement of remission or low disease activity at 6 months.

In the NORD-STAR trial, 795 patients with early RA were randomized 1:1:1:1 to conventional treatment with methotrexate plus glucocorticoids vs 1 of 3 different regimens that included methotrexate plus 1 biological DMARD: certolizumab pegol (a TNF inhibitor), abatacept (a costimulation inhibitor), or tocilizumab (an IL-6 receptor inhibitor). The CDAI 6-month remission rate (defined as a CDAI score ≤2.8) in the methotrexate plus glucocorticoid group was 42.7% (95% CI, 36.1%-49.3%), which was similar to that of the 3 biological DMARD strategies (certolizumab pegol: 52.6% [95% CI, 45.6%-59.7%]; abatacept: 56.3% [95% CI, 49.6 %-63.0%]; and tocilizumab: 48.7% [95% CI, 41.2%-56.1%]).[52]

All biological DMARDs have improved efficacy in combination with methotrexate compared with use as monotherapy. In a meta-analysis of 3 RCTs (1601 patients with RA), combination therapy with TNF inhibitors or IL-6 receptor inhibitors plus methotrexate increased the likelihood of an ACR70 response (34%) compared with monotherapy with TNF inhibitors or IL-6 receptor inhibitors (25%) (odds ratio, 1.82; 95% CI, 1.45-2.28).[96] Another RCT (351 patients) reported CDAI remission (CDAI score <2.8) in 42% (95% CI, 33%-50%) of patients treated with abatacept plus methotrexate vs 31% (95% CI, 23%-39%) in those treated with abatacept monotherapy (*P* value not reported).[97] Similarly, in an RCT of 223 patients with RA who had insufficient clinical response to methotrexate, switching from methotrexate to tocilizumab led to 55% remission at 6 months while adding tocilizumab to methotrexate conveyed 70% remission (*P* = .02).[98] The methotrexate dosage can be as low as 10 mg/wk to see this added effect,[99] and other conventional synthetic DMARDs such as sulfasalazine or leflunomide convey a similar benefit with combination therapy.[100] Of note, among patients who do not tolerate any conventional synthetic DMARDs, IL-6 receptor inhibitors may be preferred over other biological DMARDs.[101,102] In the double-blind ADACTA trial, 163 and 162 patients with RA, respectively, were randomized to receive monotherapy (without methotrexate or other conventional synthetic DMARDs) with tocilizumab (an anti–IL-6 receptor antibody) or adalimumab (an anti-TNF antibody); at week 24, CDAI-measured low disease activity was achieved by 50 patients (30.7%) taking tocilizumab vs 32 (19.8%) taking adalimumab (*P* = .02).[101] Similar results were obtained in an RCT of sarilumab, another anti–IL-6 receptor agent, vs adalimumab.[102]

Targeted Synthetic DMARDs

Janus kinase inhibitors, which target signal transduction molecules activated by various cytokines, include baricitinib, filgotinib, peficitinib, tofacitinib, and upadacitinib.[103] Although comparative RCTs are lacking, the EULAR recommendations conclude that JAK inhibitors have similar efficacies in achieving low disease activity when added to methotrexate, with ACR70 responses (Table 2) ranging from 20% to 30%.[6] A network meta-analysis of 39

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placebo-controlled RCTs (16 894 patients) reported that ACR20 rates of clinical response (defined in Table 2) were similar among JAK inhibitors, with relative risks vs placebo ranging from 1.57 (95% CI, 1.25-1.97) for filgotinib to 2.02 (95% CI, 1.67-2.44) for tofacitinib.[104]

Similar to biological DMARDs, patients with RA that is not well controlled with conventional synthetic DMARDs benefit from addition of, rather than switching to, a JAK inhibitor. In a trial of 1146 patients, 384 taking tofacitinib monotherapy, 376 taking tofacitinib plus methotrexate, and 386 taking adalimumab plus methotrexate, ACR50 response rates (defined in Table 2) were 38% (147/384), 46% (173/376), and 44% (169/386), respectively; the difference between tofacitinib plus methotrexate vs adalimumab plus methotrexate was 2.2% (95% CI, −6.4% to 10.9%); between tofacitinib monotherapy and adalimumab plus methotrexate, −5.5% (95% CI, −14.0% to 3.0%); and between tofacitinib monotherapy and tofacitinib plus methotrexate, −7.7% (95% CI, −16.3% to 0.8%)—exceeding the predefined noninferiority margin of −13%.[59] A 2022 meta-analysis of 3 RCTs (n = 2290) showed a higher ACR70 response rate with the combination of a JAK inhibitor and methotrexate vs JAK inhibitor monotherapy (40.4% vs 32.3%; risk difference, 5.6%; 95% CI, 1.2%-10%; *P* = .01).[105]

In a September 2021 regulatory decision based on findings of increased risk of cardiovascular events, thromboembolic events, and malignancy, the US Food and Drug Administration concluded that JAK inhibitors should be reserved for patients not improving with or not able to tolerate 1 or more TNF inhibitor.[106,107] In contrast, the European Medicines Agency, like EULAR, does not recommend against use of JAK inhibitors in patients with insufficient response to methotrexate who are at low risk of cardiovascular events, thromboembolic events, or malignancy.[6,108]

Adverse Events

All biological and targeted synthetic DMARDs are associated with increased risk of serious infections. In a matched cohort study from Denmark, the 12-month risk of developing a serious infection among patients with RA starting a biological DMARD was 5.9% (352/5985) vs 1.5% (880/59 848) in the general population matched for age, sex, and postal code.[109] In a systematic review and meta-analysis, the risk of serious infections with TNF inhibitors vs conventional DMARDs such as methotrexate was increased, with a relative risk of 1.48 (95% CI, 1.18-1.85), based on 7 registry studies (total sample size not reported)[110]; similar data were obtained in a more recent analysis that included JAK inhibitors.[111] Because TNF inhibitors and, to a lesser extent, other biological DMARDs and JAK inhibitors can activate tuberculosis, testing for latent tuberculosis is mandatory before starting therapy; prophylactic treatment with isoniazid should be started in those testing positive for latent tuberculosis before initiating biological DMARDs or JAK inhibitors. Herpes zoster occurs in up to 7.5% of patients taking JAK inhibitors for 1 year (possibly with the exception of filgotinib).[112-114] Therefore, all vaccinations, including herpes zoster vaccination, should be updated or newly obtained before treatment initiation; the 2022 ACR guideline on vaccinations for patients with RA recommends pneumococcal, herpes zoster, influenza, COVID-19, all age-appropriate vaccines, human papillomavirus for those aged 26 to 45 years, and hepatitis B for previously unvaccinated persons younger than 60 years.[115] Medications affecting the IL-6 pathway such as tocilizumab, sarilumab, and JAK inhibitors are associated with increased risk of diverticulitis and bowel perforation, especially among those with a history of diverticulitis.[116]

The JAK inhibitor tofacitinib has been associated with a higher risk of major adverse cardiovascular events and malignancies compared with TNF inhibitors,[106] and several JAK inhibitors have also been connected to thromboembolic events.[111,112] A trial of patients with RA aged 50 years or older with at least 1 additional cardiovascular risk factor (1455 patients receiving tofacitinib, 5 mg twice daily; 1456 receiving tofacitinib, 10 mg twice daily; and 1451 receiving a TNF inhibitor) reported major adverse cardiovascular events in 3.4% patients randomized to tofacitinib vs 2.5% randomized to the TNF inhibitor (hazard ratio, 1.33; 95% CI, 0.91-1.94, which exceeded the noninferiority margin of 1.8) and cancers (excluding nonmelanoma skin cancer) in 4.2% receiving tofacitinib vs 2.9% receiving the TNF inhibitor (hazard ratio, 1.48; 95% CI, 1.04-2.09; likewise beyond the 1.8 noninferiority boundary).[106]

A recent RCT of the JAK inhibitor baricitinib at 2 different doses (2433 patients) compared with TNF inhibitors (1207 patients) in those with increased risk of venous thromboembolic events suggested similar major adverse cardiovascular event outcomes (1.8% vs 1.9%, respectively; hazard ratio, 1.06; 95% CI, 0.64-1.76; below the upper margin of noninferiority of 1.8). However, venous events in those randomized to baricitinib did not show noninferiority (0.79 vs 0.51 events per 100 person-years, respectively; hazard ratio, 1.61; 95% CI, 0.97-2.66; *P* = .07), while malignancies excluding nonmelanoma skin cancer did not have statistically different rates (3.6% vs 2.8%; hazard ratio, 1.27; 95% CI, 0.85-1.89; *P* = .24).[117]

Prognosis

In an inception cohort of 521 patients with newly diagnosed RA, approximately 40% achieved sustained CDAI remission at 10 years after start of treatment.[118] Low disease activity, the primary goal in long-standing RA (>3 years), is achieved by an additional 40%. Therefore, RA remission or low disease activity is achieved in about 80% of patients, and about 20% experience insufficient control of symptoms despite use of biological DMARDs and JAK inhibitors.

Seropositivity is associated with a higher risk of damage progression. In a meta-analysis of 10 cohort studies (2727 patients) investigating long-term radiographic progression, the relative risk of damage progression by radiography was 2.07 (95% CI, 1.61-2.65) among those with rheumatoid factor positivity.[119] In a meta-analysis of 5 cohort studies (1100 patients), the relative risk of damage progression by radiography was 2.49 (95% CI, 1.96-3.15) among those with ACPA positivity.[119] In a prospective observational study of 242 seronegative and 375 seropositive patients with early RA, radiographic erosions were identified in 62.7% of seropositive patients vs in 29.3% of seronegative patients over the first 3 years of follow-up despite use of conventional synthetic and biological DMARDs in 80.8% of seropositive patients vs 55.6% of seronegative patients.[36]

A registry study (8908 patients) showed that compared with individuals without RA, RA overall is associated with an increased standardized mortality ratio (females: 1.5 [95% CI, 1.3-1.7]; males: 1.4 [95% CI, 1.2-1.6]).[120] The association is primarily due to those with high disease activity (Disease Activity Score in 28 joints >5.1), as those with low disease activity (Disease Activity Score in 28 joints <3.2)

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had no increase in standardized mortality ratio compared with the general population.[120]

Practical Considerations

If remission or low disease activity is not achieved with a first biological agent or JAK inhibitor, another agent with the same or a different mechanism of action can be prescribed. However, if improvement does not occur with a second drug of the same mode of action, patients should subsequently receive treatment with a biological or targeted synthetic DMARD that has a different mechanism of action.[6]

In addition to DMARDs, nonsteroidal anti-inflammatory drugs and pain medications such as acetaminophen (paracetamol) and tramadol may be useful to treat joint pain in patients with RA. Physiotherapy, occupational therapy (including provision of splints to prevent or improve joint malalignment), and psychological counseling or antidepressive therapy may be appropriate for certain patients with RA. Also, because RA is associated with higher risk of myocardial infarction, congestive heart failure, and cerebrovascular accident, guideline-recommended preventive measures such as use of statins and blood pressure control should be implemented as needed. Clinicians treating patients with RA who smoke should provide smoking cessation therapy because in addition to its cardiovascular and malignancy risk, smoking is associated with higher RA disease activity, and smoking cessation reduces disease activity.[121]

The best predictor of remission is the clinical response after 3 months of therapy. Among 2393 patients with early RA and high disease activity at baseline (SDAI score >26; mean, 40.0 [SD, 12.8]), those with an SDAI score greater than 40 at 3 months after DMARD initiation had an 80% probability of continued active disease at 1 year.[122] In contrast, those whose disease activity had improved to an SDAI score of 12 or less at 3 months (decreasing by >50%) had a 75% probability of remission or low disease activity at 1 year.[122]

Over the last decade, biosimilars for several biological agents (adalimumab, etanercept, infliximab, rituximab, and tocilizumab) have been approved by US, European, and other regulatory agencies (Table 3). These biosimilars have similar efficacy and safety as the originator products but are less expensive.[123]

Limitations

This Review has several limitations. First, this was not a systematic review, and the quality of the selected articles was not formally assessed. Second, only articles published in English were included. Third, some relevant articles may have been missed. Fourth, detailed discussion of certain topics (preclinical RA, difficult-to-treat RA, treatment of RA during pregnancy and lactation, biomarkers of response, and potential future RA therapies, such as chimeric antigen receptor T-cell or bispecific T-cell engager approaches) was beyond the scope of this article.

Conclusions

Rheumatoid arthritis is a chronic autoimmune disease that causes joint destruction. First-line initial therapy is methotrexate, with consideration of glucocorticoids as additive therapy. For patients who do not achieve remission with this initial treatment, adding biological DMARDs or JAK inhibitors increases overall remission or low disease activity rates to 80%.

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