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Diagnosis and Management of Rheumatoid Arthritis
A Review

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IMPORTANCE Rheumatoid arthritis (RA) occurs in about 5 per 1000 people and can lead to severe joint damage and disability. Significant progress has been made over the past 2 decades regarding understanding of disease pathophysiology, optimal outcome measures, and effective treatment strategies, including the recognition of the importance of diagnosing and treating RA early.

OBSERVATIONS Early diagnosis and treatment of RA can avert or substantially slow progression of joint damage in up to 90% of patients, thereby preventing irreversible disability. The development of novel instruments to measure disease activity and identify the presence or absence of remission have facilitated new treatment strategies to arrest RA before joints are damaged irreversibly. Outcomes have been improved by recognizing the benefits of early diagnosis and early therapy with disease-modifying antirheumatic drugs (DMARDs). The treatment target is remission or a state of at least low disease activity, which should be attained within 6 months. Methotrexate is first-line therapy and should be prescribed at an optimal dose of 25 mg weekly and in combination with glucocorticoids; 40% to 50% of patients reach remission or at least low disease activity with this regimen. If this treatment fails, sequential application of targeted therapies, such as biologic agents (eg, tumor necrosis factor [TNF] inhibitors) or Janus kinase inhibitors in combination with methotrexate, have allowed up to 75% of these patients to reach the treatment target over time. New therapies have been developed in response to new pathogenetic findings. The costs of some therapies are considerable, but these costs are decreasing with the advent of biosimilar drugs (drugs essentially identical to the original biologic drugs but usually available at lower cost).

CONCLUSIONS AND RELEVANCE Scientific advances have improved therapies that prevent progression of irreversible joint damage in up to 90% of patients with RA. Early treatment with methotrexate plus glucocorticoids and subsequently with other DMARDs, such as inhibitors of TNF, IL-6, or Janus kinases, improves outcomes and prevents RA-related disability. A treat-to-target strategy aimed at reducing disease activity by at least 50% within 3 months and achieving remission or low disease activity within 6 months, with sequential drug treatment if needed, can prevent RA-related disability.

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Supplemental content

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Rheumatoid arthritis (RA) is a chronic, inflammatory joint disease with a worldwide prevalence of about 5 per 1000 adults. The disease affects women 2 to 3 times more often than men and occurs at any age. The peak incidence is in the sixth decade.[1] Previously, RA led to disability, inability to work, and increased mortality. Recent improvement in outcomes has been achieved through a better understanding of RA pathophysiology and development of better outcome measures and therapies.

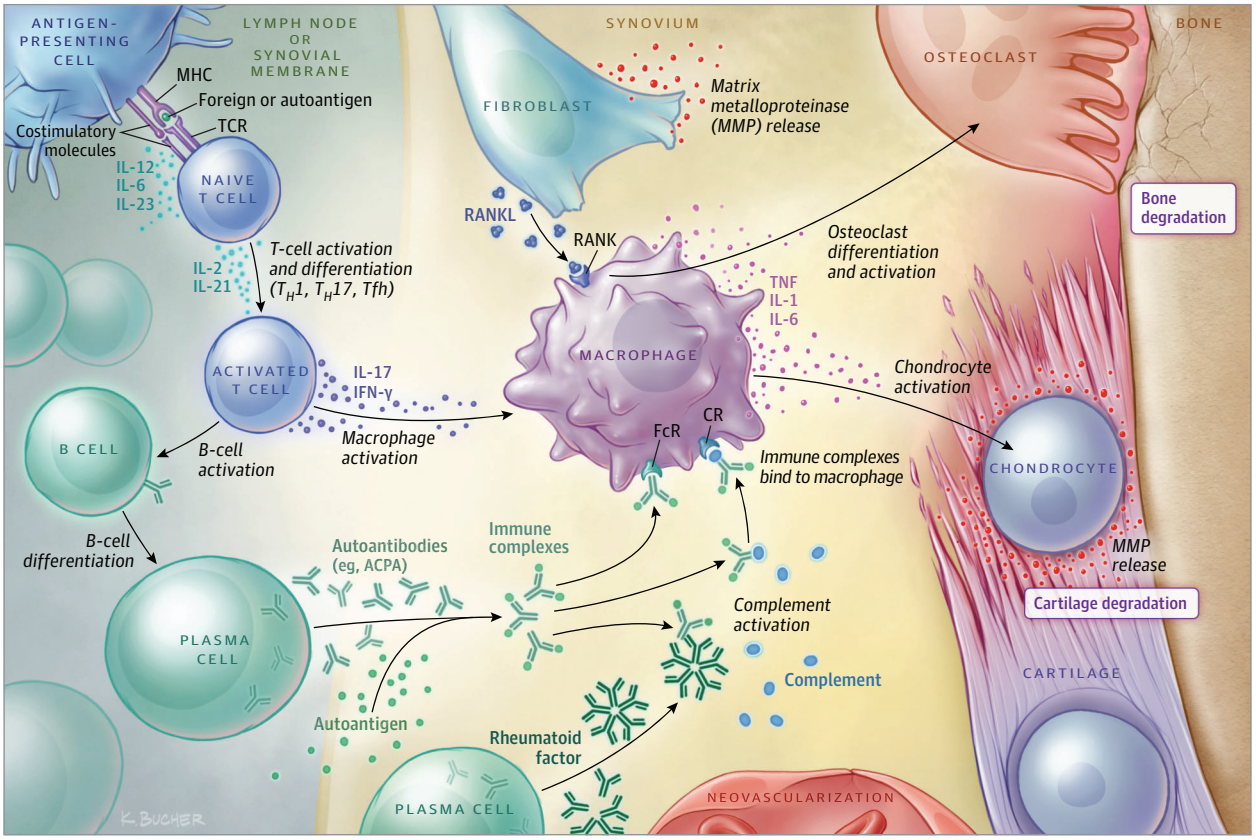
The pathophysiology of RA involves chronic inflammation of the synovial membrane, which can destroy articular cartilage and juxtaarticular bone.[2] Recent discoveries regarding biologic pathways have improved understanding of the phenomena associated with rheumatoid inflammation and their consequences. New molecules and cells in the biologic pathway have been identified and are targets for therapeutic intervention.

This review summarizes current evidence regarding the pathophysiology, diagnosis, and treatment of RA.

Methods

PubMed was searched on June 18, 2018, for the terms *rheumatoid arthritis* and *pathogenesis* or *diagnosis or classification*. Titles and abstracts were screened by the authors and articles selected based on newly described molecules, new pathogenetic insights, or new biomarkers. The search regarding therapy used evidence from

Figure 1. Pathogenic Aspects of Rheumatoid Arthritis



Left to right: An autoantigen (eg, after citrullination) or a foreign peptide, such as a bacterial or viral peptide cross-reactive with an autoantigen, is presented by an antigen-presenting cell via a major histocompatability complex (MHC) class II molecule (carrying the shared epitope) to a naive T cell, with support by costimulatory molecules, breaking tolerance to self. The T cell now becomes activated and differentiates into a T_H1, T_H17, or T follicular helper (Tfh) cell, releasing lymphokines that can activate macrophages and also provide help to B cells. The latter can be induced to produce autoantibodies (eg, against a citrullinated protein). The B cell differentiates into a plasma cell that secretes these autoantibodies. Autoantibodies bind to respective autoantigens, thus forming immune complexes in the synovium, where these autoantigens have accumulated. The immune complexes, via their Fc portion, elicit other B cells to form anti-IgG antibodies (rheumatoid factor) that enlarge the immune complexes and can increase complement activation. The immune complexes can bind to macrophages and other cells via Fc receptors and complement receptors, thus activating them to secrete proinflammatory cytokines and other mediators of inflammation, such as tumor necrosis factor (TNF) and interleukin (IL)-6, in addition to macrophage activation by lymphokines, like interferon (IFN)-γ or IL-17, that derive from the activated T cells. Fibroblasts that express receptor activator of nuclear factor κB (RANK) ligand (RANKL), especially in the presence of proinflammatory cytokines, can activate macrophages to differentiate via preosteoclasts into osteoclasts that resorb bone from the synovial, exostal site; this process starts at the junction between cartilage and bone. These cytokines also activate chondrocytes to secrete enzymes that degrade cartilage. See text for respective references to this current hypothesis. ACPA indicates anticitrullinated peptide antibody; CR, complement receptor; FcR, Fc receptor; TCR, T-cell receptor.

a search conducted in 2016 on therapy for RA.[3-5] This prior search was updated to June 18, 2018, using the terms *rheumatoid arthritis* and *randomised controlled trials*.

Pathophysiology

RA is characterized by infiltration of the synovial membrane in multiple joints with T cells, B cells, and monocytes. This process is preceded by activation of endothelial cells; neovascularization (growth of new blood vessels) is another hallmark of RA synovitis. Expansion of synovial fibroblast-like and macrophage-like cells leads to a hyperplastic synovial lining layer. This expanded synovial membrane, often termed "pannus," invades the periarticular bone at the cartilage-bone junction and leads to bony erosions and cartilage degradation (**Figure 1**).

Molecules such as receptor activator of nuclear factor κB ligand (RANKL), prostaglandins, and matrix metalloproteinases are induced by pro-inflammatory cytokines, including tumor necrosis factor (TNF) and interleukin (IL)-6, and mediate signs and symptoms of the disease, including pain and swelling, and degradation of cartilage and bone.[6] Stimulation by RANKL, TNF, and IL-6 generates osteoclasts within the synovial membrane and promotes bony damage.[7] These molecular and cellular events result in the clinical disease expression. Progression of joint damage is intrinsically associated with joint swelling.[8]

The cause of RA is unknown. However, genetic and environmental factors both contribute to RA. Many gene loci are associated with RA (**Box**).[9] However, certain HLA class II antigens, such as HLA-DRB1*01 and HLA-DRB1*04, contain the "shared" epitope—a stretch of 5 amino acids in the region responsible for antigen presentation to T lymphocytes—and are most closely

Box. Epidemiology of Rheumatoid Arthritis: Major Genetic and Environmental Factors

Prevalence[1]
≈0.5%

Genetic Associations[9,10]

Antigen presentation	Cytokines/receptors/signaling
HLA-DRB1	*TNF*
T-cell function	*OPG*
PTPN22	*TRAF1*
CTLA4	*IL2RA*
CCR6	*IL2RB*
B cells	*IRF4*
CD40	*IRF5*
Other genes	*TNFAIP3*
MMP9	*GATA3*
PADI4	*REL*
CCR5	

Environment[11,12]
Prevotella copri[11,12]
Viruses (EBV)[13]
Tobacco smoking[14]
Silica[15]

Abbreviation: EBV, Epstein-Barr virus.

associated with RA.[16] Genes with weaker associations (Box) may also contribute, especially by gene-gene and gene-environment interactions.[17] Environmental risk factors for RA are smoking, periodontitis, and characteristics of the microbiome of the gut, mouth, and lungs, as well as viral infections.[13,18] Regarding the microbiome, *Prevotella* species, which are expanded in the gastrointestinal tract in early RA, and *Porphyromonas gingivalis,* which is associated with periodontitis, may have a role in pathogenesis.[19] New data suggest that bacteria may translocate from the gut to tissues, causing inflammation and autoimmunity.[20] The relationship between genetics and environment is evident based on recent observations that HLA-DR molecules of patients with RA present peptides of autoantigens having sequence homology with epitopes from proteins of commensal bacterial species present in RA.[21] Similarities between amino acid sequences of autoantigens and bacterial or viral proteins have been described.[22] Epstein-Barr virus infection[13] has also been implicated, further supported by recent observations that transcription factor EB nuclear antigen 2 (EBNA2) binds preferentially to genetic loci associated with RA and other autoimmune diseases.[23]

Epigenetic modifications such as DNA methylation and histone acetylation also promote inflammatory responses. Posttranslational protein modifications such as citrullination of arginine by peptidylarginine deiminase or carbamylation of lysine contribute to breaking immunological tolerance by creating neoepitopes of various autologous proteins (eg, collagen, vimentin, fibrinogen),[24] resulting in formation of autoantibodies against autoantigens (eg, anticitrullinated peptide antibodies [ACPAs]), antibodies to IgG (rheumatoid factor [RF]), nuclear antigens, or autoantigens that cross-react with bacterial or viral antigens, such as *Prevotella* or Epstein-Barr virus.[13,21] These autoantibodies can form immune complexes that may activate complement, further increasing inflammatory responses.[13] RF and ACPAs together can promote a substantial inflammatory response, whereas ACPAs alone cause little inflammation. RFs enlarge the immune complexes formed by ACPAs and amplify the inflammatory response elicited by immune complexes and complement activation.[13,25,26]

Autoantibodies develop before signs and symptoms occur.[27] This stage is termed "pre-RA" and can last between less than 1 and more than 10 years. The length of time before appearance of RA symptoms is related to the autoantibody profile. Individuals who only express ACPAs develop symptoms 5 to 10 years after the autoantibody appearance, whereas people who develop ACPAs and RF and also increased C-reactive protein (CRP) levels develop symptoms within a few months after the third of these factors appears.[27] Subtle inflammatory changes in the synovium have been noted in some patients with pre-RA. Even in established RA, overt inflammatory changes identified by histology are not always accompanied by clinical signs and symptoms.[28] Early manifestations of RA range from mild arthritis with few involved joints to severe polyarticular disease and from a state of negative autoantibodies to multiple positive autoantibodies. Very early disease does not yet exhibit structural damage, whereas later stages are characterized by erosive disease or joint space narrowing as an indicator of cartilage degradation. If not adequately treated, RA progresses into a more homogeneous, destructive disease (**Figure 2**).

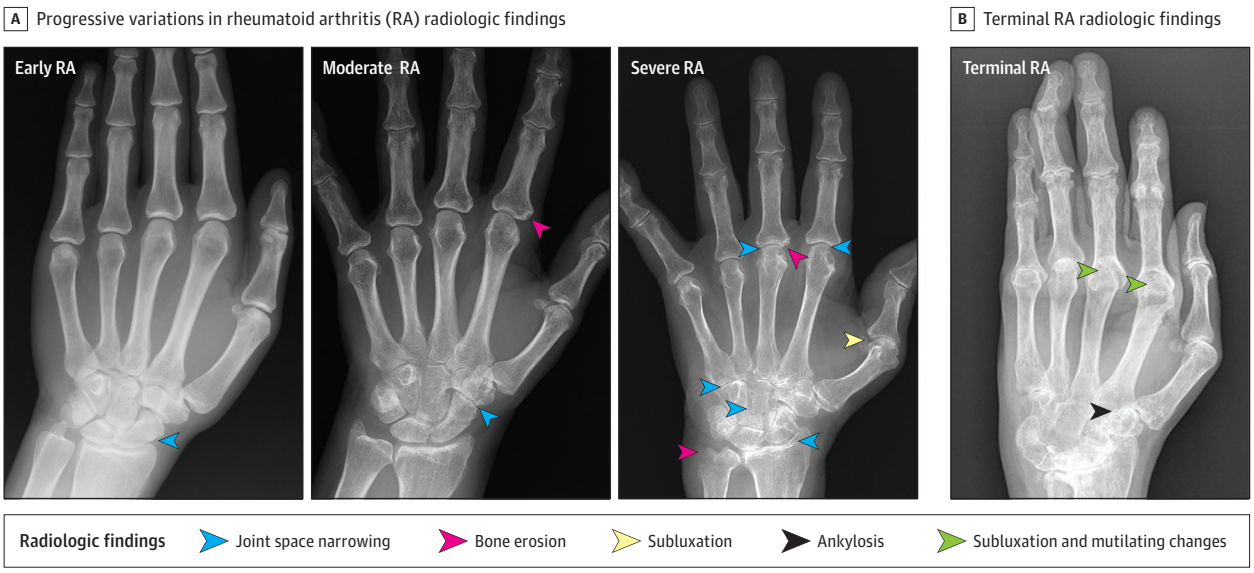
Clinical Presentation

RA is a polyarticular symmetric disease that involves multiple joints bilaterally. A patient with RA typically presents with pain and swelling in the joints of the hands and feet. The swelling is primarily in the wrists and metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal joints. This is accompanied by morning joint stiffness lasting more than 30 minutes and usually up to several hours. The swelling is typically "soft" because of synovitis and effusion, in contrast to the "hard" (bony) swellings of osteoarthritis. When the fingers are involved, swelling centers around the joint (fusiform) rather than involving the whole digit ("sausage digit"), as seen in psoriatic arthritis. Both small and large joints can be involved, although the distal interphalangeal joints are rarely affected. Small joints include the metacarpophalangeal, metatarsophalangeal, proximal interphalangeal, and wrist joints. Large joints include the ankle, knee, elbow, and shoulder joints.

If RA is insufficiently treated, extra-articular manifestations may develop. The most frequent are rheumatoid nodules (firm subcutaneous lumps near bony prominences such as the elbow). A more serious manifestation is rheumatoid vasculitis, a necrotizing inflammation of small or medium-sized arteries, mostly involving the skin, vasa nervorum, and occasionally arteries in other organs.

Patients with RA may be affected by multiple comorbidities. Cardiovascular disease is a common consequence of chronic inflammation and the primary cause of death in people with RA. In patients with RA, cardiovascular disease is more closely associated with disease activity than with traditional cardiovascular risk factors.[29] Treatment with targeted biologic agents reduces

Figure 2. Structural Phenotypes of Rheumatoid Arthritis



RA is a dynamic disease causing increasing damage to increasing numbers of joints over time, as depicted by the increasing radiographic abnormalities seen from left to right. In early disease (left 2 images), there is no or at most minimal bony or cartilage damage (as can be seen in these radiographs, which are almost normal). In severe, established RA (second image from the right), joint damage progresses in affected joints and spreads to additional joints—in this image, damage has accrued, both in terms of cartilage (joint space narrowing) and bone damage (erosions); malalignment can also be seen, especially at the fifth digit. In late, terminal RA (right), joint damage has severely involved most joints typically affected by RA, with coalescence of carpal joints (black arrowhead). The stages of joint damage in RA are exemplified by the evolution of these structural changes in insufficiently treated patients. Colored arrowheads refer to specific abnormalities exemplified here, and many more changes exist in the right 2 radiographs.

cardiovascular risk.[30] Interstitial lung disease may be a manifestation of RA or may be a complication of RA therapies, such as methotrexate and leflunomide.[31]

RA interferes with physical functioning, work productivity, and quality of life.[32] If insufficiently treated, 80% of patients will have malaligned joints and 40% will be unable to work within 10 years from disease onset.[32,33] Quality of life, as assessed by the 36-Item Short Form Health Survey, is similar to or worse than that associated with cardiovascular disease and diabetes.[34] RA affects all activities of daily life.[35] In long-standing, insufficiently treated disease, accumulation of joint damage, which is irreversible in RA, leads to disability; patients who sustain irreversible joint damage will never recover normal physical function, even if clinical remission (ie, absence of signs of inflammation such as joint swelling and elevated CRP levels) is subsequently attained. Even the most effective therapies will not reverse joint damage.[36] The evolution of radiographic findings ranges from joints with minimal abnormalities to severe destructive changes seen as bony erosions and joint space narrowing, reflecting cartilage changes (since cartilage is radiotranslucent, changes can only be seen indirectly) (Figure 2). Cartilage damage contributes more to irreversible disability than bony damage.[2]

Diagnosis and Assessment

In early disease, RA may involve just 1 or a few joints. Simultaneously or even earlier, tendon inflammation (tenosynovitis) develops. The presence of tenosynovitis, eg, at the flexor carpi ulnaris tendon, and subclinical synovial inflammation can be detected by imaging with color Doppler sonography or gadolinium-enhanced magnetic resonance imaging, which demonstrate expansion of intra-articular soft tissue or hypervascularization of the synovial membrane.

No diagnostic criteria exist for RA. However, the 2010 classification criteria, although primarily developed for identification of homogenous patient populations in clinical studies of RA, may help physicians establish a diagnosis[37,38]; differences between classification and diagnosis have been summarized in a recent report.[39] The classification of RA requires presence of at least 1 clinically swollen joint and at least 6 of 10 points from a scoring system (**Table 1**).[37] Joint involvement based on physical examination or imaging by ultrasound or magnetic resonance imaging contributes up to 5 points; elevated levels of RF, ACPAs, or both provides 2 additional points (or 3 points with levels >3 times the upper limit of normal); and elevated acute phase reactant (APR) response, such as increased CRP level or erythrocyte sedimentation rate, and duration of symptoms (≥6 weeks) provide 1 additional point each. These 2010 criteria have a sensitivity of 82% and specificity of 61%. Sensitivity of the new classification criteria was 11% greater and specificity 4% lower compared with the 1987 criteria.[38]

Since early diagnosis and treatment prevents progression of joint damage in 90% of patients with early RA,[40] it is important to identify patients with RA as soon as possible. Specific symptoms that may indicate possible RA include articular pain and swelling in metacarpophalangeal joints, metatarsophalangeal joints, or both, morning stiffness of finger joints lasting 30 minutes or longer, and autoantibody positivity.[41]

Table 1. Rheumatoid Arthritis Classification and Follow-up[a]

Classification	Points
Joint Distribution (0-5 points)	
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 (≥1 small joint)	5
Serology (0-3 points)	
Negative RF and negative ACPA	0
Low positive RF or low positive ACPA	2
High positive RF or high positive ACPA	3
Symptom Duration (0-1 point), weeks	
<6	0
≥6	1
Acute Phase Reactants (0-1 point)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1

Abbreviations: ACPA, anticitrullinated peptide antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.

[a] American College of Rheumatology–European League Against Rheumatism classification criteria (adapted from Aletaha et al[37]); a patient with 6 or more points can be classified as having rheumatoid arthritis (RA). There are no diagnostic criteria for RA. A diagnosis has to 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 homogenous study population. Nevertheless, classification criteria can aid in diagnosis and are often used so in teaching.[39]

Initial assessment requires examination of the joints as well as serologic testing for autoantibodies and APRs. For follow-up, joint assessment, evaluation of APRs, and evaluation of patient-reported outcomes such as patient global assessment of disease activity and evaluation of physical function are important. Composite measures that include joint counts, ie, number of tender and swollen joints, constitute the best way to evaluate RA disease activity in practice (and in trials), since they capture the most important disease aspects in a single score. These scores, namely the clinical disease activity index (CDAI), the disease activity score using 28 joint counts (DAS28), or the simplified disease activity index (SDAI), correlate with outcomes such as damage progression and functional impairment.[42,43] These measures allow quantification of disease activity, and disease activity states based on specific cutpoints of these indices have been defined to help guide treatment. Treatment goals include remission, defined as no disease activity, and low disease activity, corresponding to mild residual activity with low risk of damage progression; these 2 states thus contrast with moderate and high disease activity states, which signify uncontrolled disease associated with progression over time.[44] Among all available indices, the CDAI is most easy to perform. It is a simple numerical summation of 4 variables: swollen and tender joints (using 28 joint counts), patient global assessment, and evaluator global assessment, both on a 10-cm visual analogue scale (eTable in the Supplement). The CDAI ranges from 0 to 76 (higher scores worse).[42] The formula of the CDAI and other indices, including the respective cutpoints defining disease activity states, are depicted in the eTable in the Supplement.

Assessment instruments, primarily the CDAI, should be used to follow therapy using the "treat-to-target" approach.[45] This strategy consists of treating, and adapting therapy as needed, to obtain an improvement in a disease activity index of at least 50% within 3 months and thus to have more than a 50% probability to reach low disease activity or remission at 6 months. The therapeutic goal is to reach clinical remission (especially in early RA) or low disease activity (in established RA if remission is not achievable).[46] Clinical remission as indicated by CDAI or SDAI is a state in which physical function is maximally improved and progression of joint damage is halted.[8] The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have recently defined remission criteria based on a Boolean approach or based on indices, namely the SDAI and CDAI.[47] Therapy should be titrated to achieve clinical remission according to the definition by these indices (eTable in the Supplement) and not according to improvement in subclinical inflammation as measured by ultrasound, for example. There is no evidence that treatment beyond clinical remission, as defined by ACR and EULAR index or Boolean criteria, improves outcomes; therefore, it should not be pursued.[48]

Treatment

Disease-Modifying Antirheumatic Drugs

Although RA is incurable, modern therapeutic approaches allow achievement of excellent disease control. Patients with RA must be treated with disease-modifying antirheumatic drugs (DMARDs). A DMARD is defined as a medicine that interferes with signs and symptoms of RA, improves physical function, and inhibits progression of joint damage. Therapies that only improve symptoms, such as nonsteroidal anti-inflammatory drugs or pain medications, do not prevent damage progression and irreversible disability. These drugs are not DMARDs and should only be used as adjunctive, symptomatic therapy or during the short phase until a diagnosis is established.

DMARDs are categorized into synthetic (small chemical molecules given orally) and biologic (proteins administered parenterally) agents (**Table 2**).[64] The former consist of conventional synthetic and targeted synthetic DMARDs. Conventional synthetic DMARDs came into clinical practice based on empiric observations, have been used for more than 50 years, and have molecular targets that have not been identified. The molecule acted on by leflunomide was detected after the recognition of its efficacy as RA therapy. In contrast, targeted synthetic DMARDs were developed to interfere with a specific molecule, based on advances in molecular and structural biology. They interfere with enzymes such as Janus kinases (JAKs)— intracellular signal transduction molecules that translate the effects of some cytokines to cellular responses.

Among the empirically developed conventional DMARDs, methotrexate is the most important. Although methotrexate has been used in treatment of RA for more than 50 years,[65] the optimal dose of 25 mg weekly was more recently identified.[66] Patients who cannot tolerate this dose because of adverse effects

Table 2. Currently Approved Disease-Modifying Antirheumatic Drugs (United States, Europe, or Both)

Subgroup and Type[a]	Molecular Target	Structure	Selected Adverse Events[b]	Efficacy (ACR70 Response Rates)[c]
Synthetic DMARDs				
Conventional[d]				
Methotrexate (10-25 mg/wk)	Unknown	Small chemical molecules (oral)	Nausea, stomatitis, liver enzyme level increase, bone marrow suppression, pneumonitis, teratogenicity	20-40%[49,50]
Sulfasalazine (2-4 g/d)	Unknown		Hypersensitivity reactions (mainly cutaneous), nausea, diarrhea, agranulocytosis, drug-induced lupus, azoospermia	No RCT data for 3 g daily; little modern data at all 8% at 2 g[51]
Leflunomide (20 mg/d)	Dihydroorotate dehydrogenase		Diarrhea, hypertension, hypersensitivity reactions, liver enzyme level increase, leukocytopenia, teratogenicity	10%[51]
(Hydroxy-) chloroquine (Hydroxychloroquine: 400 mg/d; chloroquine: 250 mg/d)	Unknown		Retinopathy	Unavailable
Targeted[d]				
Tofacitinib (10 mg/d)	JAK 1,2,3	Small chemical molecules (oral)	Infections, reactivation of tuberculosis, herpes zoster, cytopenias (including anemia), hyperlipidemia, CPK level increases	20% (methotrexate insufficient responders)[52] 14% (TNF inhibitor insufficient responders)[53]
Baricitinib (2-4 mg/d)	JAK 1,2			24% (methotrexate insufficient responders)[54] 17% (TNF inhibitor insufficient responders)[55]
Biologic DMARDs				
Originator biologic[e]				
Etanercept (50 mg/wk)	TNF	Receptor construct	Infections, reactivation of tuberculosis, psoriasiform skin changes, exacerbation of demyelinating diseases, drug-induced lupus, nonmelanoma skin cancer, injection site or infusion reactions	20% (methotrexate insufficient responders) 12% (TNF inhibitor insufficient responders)[56]
Infliximab (3-10 mg/kg every 8 wk)	TNF	Chimeric monoclonal antibody		
Adalimumab (40 mg every 2 wk)	TNF	Human monoclonal antibodies		
Golimumab (50 mg/mo)	TNF	Human monoclonal antibodies		
Certolizumab (200 mg every 2 wk)	TNF	Fab' fragment of humanized monoclonal antibody		
Tocilizumab (162 mg/wk)	IL-6 receptor	Humanized monoclonal antibody	Infections, reactivation of tuberculosis, bowel perforation, hypersensitivity reactions, neutropenia, injection site reactions, hyperlipidemia	22% (methotrexate insufficient responders)[57] 12% (TNF inhibitor insufficient responders)[58]
Sarilumab (150 mg-200 mg every 2 wk)		Human monoclonal antibody		
Rituximab 1000 mg every 6 mo	CD20 (B-cell)	Chimeric monoclonal antibody	Hypersensitivity reactions, reactivation of hepatitis B, leukocytopenia	22% (methotrexate insufficient responders)[59] 12% (TNF inhibitor insufficient responders)[60]
Abatacept (125 mg/wk)	CD80/86 (costimulation)	Receptor construct	Infections, reactivation of tuberculosis, leukocytopenia, injection site reactions	22% (methotrexate insufficient responders)[61] 10% (TNF inhibitor insufficient responders)[62]
Biosimilar[e]				
Etanercept	TNF	Receptor construct	See above	Similar to originator data[63]
Infliximab	TNF	Chimeric monoclonal antibody		
Adalimumab	TNF	Human monoclonal antibody		
Rituximab	CD-20 (B cell)	Chimeric monoclonal antibody		

Abbreviations: ACR, American College of Rheumatology; CPK, creatine phosphokinase; DMARD, disease-modifying antirheumatic drug; IL, interleukin; JAK, Janus kinase; RCT, randomized clinical trial; TNF, tumor necrosis factor.

[a] The DMARD subsets are grouped according to the new nomenclature[64] (see footnotes d and e).

[b] The frequency of adverse events differs between regions/ethnicities, and the reader is referred to respective regional package inserts for these details.

[c] ACR70 percent response rates correspond well with a state of low disease activity (including remission) and are used as surrogates of low disease activity states. The maximum efficacy for ACR70 is seen at 6 months.

[d] Conventional synthetic DMARDs are approved DMARDs identified as treatment for rheumatoid arthritis based on empiric testing, and their target is unknown; they are distinguished from targeted synthetic DMARDs developed to interfere with a specific molecular target.

[e] Originator biologic DMARDs are original biologic agents developed to target a specific extracellular or cell membrane molecule; the first such compound is defined as the "originator" drug and is distinguished from biosimilar DMARDs (copies of the originator molecule corresponding to batch variability of the originator, ie, DMARDs essentially identical to the original biologic DMARDs but usually available at lower cost).

Table 3. Similarities and Differences Among American College of Rheumatology and European League Against Rheumatism Management Recommendations for Rheumatoid Arthritis

Item	ACR	EULAR
Methodology	GRADE (comprising strong or conditional recommendations)	EULAR standard operating procedures and Oxford evidence-based medicine approach (comprising levels of evidence and strength of recommendation for each recommendation)
Composition of guidelines panel	Rheumatologists, patients	Rheumatologists, patients, non-MD health professionals
Panel location	United States	International (Europe, North America, Latin America, Asia, Australia)
General structure of recommendations	Distinction between early (≤6 mo) and established RA with separate algorithm for each	Single algorithm with 3 treatment phases irrespective of disease duration: Phase 1: DMARD-naive Phase 2: Failure of conventional synthetic DMARD Phase 3: Failure of a biologic DMARD or targeted synthetic DMARD Overarching, ie, general principles separated from actual recommendations
Treat-to-target strategy	Yes (aim at reducing disease activity by ≥50% within 3 mo and achieving remission or low disease activity within 6 mo, with sequential drug treatment if needed)	Yes (>50% improvement by 3 mo, target to be reached by 6 mo, with sequential drug treatment if needed)
Treatment target	Remission or low disease activity	Remission (ACR-EULAR definition) or low disease activity
Initial therapy	Methotrexate monotherapy with or without addition of glucocorticoids	Methotrexate monotherapy with addition of glucocorticoids
Glucocorticoids dosing	Low-dose oral (≤10 mg daily, maximum 3 mo)	Short term application (up to 30 mg/d oral, tapered to 0 over 3-4 mo; or single intravenous [up to 250 mg] or intramuscular [up to 160 mg])
Stratification of patients if there is failure of initial therapy	None	By risk factors for rapid progression
Approach after failure of initial therapy	Combination of conventional synthetic DMARDs or use of biologic DMARD or JAK inhibitors	No risk factors: add or switch to another conventional synthetic DMARD; poor risk factors (presence of autoantibodies, early joint damage, high disease activity, failure of 2 conventional synthetic DMARDs): add biologic DMARD (preferred) or JAK inhibitor
Combination of conventional synthetic DMARD	Recommended	Not recommended, but not opposed in phase 2
Use of biologic DMARDs or JAK inhibitors	Monotherapy or combination with methotrexate	Combination with methotrexate strongly recommended
Monotherapy with biologic DMARDs or JAK inhibitors	No specific preference	If monotherapy needed because of contraindications to conventional synthetic DMARDs, then IL-6R inhibitors or JAK inhibitors preferred
Failure of a first TNF inhibitor	Use another mode of action such as IL-6 receptor inhibitor, anti-CD20, or inhibitor of T-cell costimulation	Use another TNF inhibitor or another mode of action
Stopping all DMARDs in sustained remission	Not recommended	Not recommended
Dose reduction or interval increase in sustained remission	Recommended	Recommended

Abbreviations: ACR, American College of Rheumatology; DMARD, disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IL, interleukin; JAK, Janus kinase; RA, rheumatoid arthritis; TNF, tumor necrosis factor.

(<10%) may improve with a lower dose. Fewer than 5% of patients have to stop methotrexate because of adverse events.

Methotrexate is important for several reasons. First, a large proportion of patients (≈25%-40%) significantly improve with methotrexate monotherapy, and in combination with glucocorticoids almost half of patients can attain low disease activity or remission in early RA, a rate similar to that achieved with biologic DMARDs.[49,67] Second, its adverse events are well known and many, such as nausea, hair loss, stomatitis, and hepatotoxicity, can be prevented by prophylactic use of folates (folic acid at 1 mg/d or 10 mg/wk).[66] Third, targeted DMARDs, biologic and synthetic, have less efficacy as monotherapies than when combined with methotrexate.[3]

Other conventional synthetic DMARDs include sulfasalazine (3-4 g/d) and leflunomide (20 mg/d with or without a loading dose of 100 mg/d for the first 3 days). In some patients, lower doses (1.5-2 g of sulfasalazine or 10 mg of leflunomide daily) are used because of intolerability of higher doses. Hydroxychloroquine (400 mg/d) is another conventional synthetic DMARD, but its efficacy is lower than that of other agents.[68] EULAR recommends treating every newly diagnosed patient as soon as possible, using methotrexate combined with short-term glucocorticoids and a treat-to-target approach (**Table 3** and **Figure 3**)[69]; the ACR guidelines are similar.[70] Glucocorticoids should be prescribed for short-term (up to 3-4 months) use only, because prolonged use is associated with adverse events.[4] There are no advantages of prescribing combinations of conventional synthetic DMARDs over methotrexate monotherapy. These combinations are associated with more adverse events and drug discontinuation.[69]

If the treatment target is not reached with methotrexate and glucocorticoids, patients should be categorized using prognostic markers. Poor prognostic markers such as the presence of

Figure 3. Proposed Algorithm to Reach and Sustain the Treatment Target in Rheumatoid Arthritis

Phase	Standard strategy	Alternate strategy	Results and subsequent actions[a]		
			Target reached	Target sustained	Target failure
First-line treatment	Start initial csDMARD (methotrexate) plus short-term glucocorticoids	If methotrexate is contraindicated, use an alternate csDMARD (leflunomide or sulfasalazine)	Continue first-line treatment	Move to remission phase	Move to second-line treatment
Second-line treatment	Continue csDMARD and add a bDMARD (combination csDMARD + bDMARD) or continue csDMARD and add a tsDMARD (combination csDMARD + tsDMARD)	If no poor prognostic factor[b] is present, switch to another csDMARD monotherapy or add another csDMARD	Continue second-line treatment	Move to remission phase	Move to third-line treatment
Third-line treatment	Use any other bDMARD or tsDMARD, in combination with continued csDMARD	Not applicable	Continue third-line treatment	Move to remission phase	Repeat third-line treatment with other drugs until target is reached[c]
Remission phase	Consider tapering existing therapy by reducing doses or by extending intervals between treatment	Continue therapy based on patient or physician preference	Not applicable; patients already at target	Continue tapering and revisit remission phase standard and alternative strategies	Retry previously effective strategy

[a] *Target* is defined as remission or low disease activity based on disease activity indices that include results of joint examination (eg, the Clinical Disease Activity Index [CDAI]). *Target sustained* indicates that remission or low disease activity was maintained for at least 6 months. *Target failure* is defined as either failure to achieve the treatment target (primary failure) or failing to sustain the target after it has been reached (secondary failure). csDMARD indicates conventional synthetic disease-modifying antirheumatic drug; bDMARD, biologic disease-modifying antirheumatic drug; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

[b] Poor prognostic factors include continuing high disease activity by composite measures (ie, scores that combine multiple assessments, including joint counts, into a single index, such as the CDAI), high number of residual swollen joints, or acute phase reactant levels; presence of autoantibodies (rheumatoid factor, anticitrullinated peptide antibodies); erosive bony disease.

[c] Additional changes in drugs used during this phase would correlate to the fourth-line and (if necessary) subsequent lines of treatment.

autoantibodies, early joint damage, and high disease activity are associated with rapid disease progression that can be halted or slowed by adding a biologic DMARD or targeted synthetic DMARD (JAK inhibitor) rather than another conventional synthetic DMARD.[44,71] When patients do not respond to 2 or more conventional synthetic DMARDs, they are unlikely to achieve the treatment target.[72] In the presence of poor prognostic markers, EULAR recommends starting any biologic DMARD or a targeted synthetic DMARD in addition to methotrexate, with a current preference for biologic DMARDs because of long-term experience with efficacy and safety profiles (Table 3 and Figure 3). Evidence for treating patients according to prognostic markers is limited. When the treatment target is not reached using a first biologic DMARD (or targeted synthetic DMARD), then any biologic DMARD or targeted synthetic DMARD except for a previously ineffective DMARD may be used. This includes another biologic DMARD or targeted synthetic DMARD treating the same pathway as the first one, since evidence from randomized trials reveals that administering a TNF inhibitor after another one has failed can be as efficacious as using a drug with another mode of action, such as inhibitors of IL-6 or of other pathways (Table 3 and Figure 3).[3,73] Progression of therapies in a treat-to-target strategy may be limited by comorbidities and patient preferences. A shared decision-making process with the patient should be followed.[45]

All biologic DMARDs and targeted synthetic DMARDs have greater efficacy when combined with methotrexate or other conventional synthetic DMARDs, compared with prescription alone.[74-77] Therefore, EULAR recommends using biologic DMARDs and targeted synthetic DMARDs combined with methotrexate or other conventional synthetic DMARDs. However, compared with anti-TNF monotherapy (eg, adalimumab), monotherapies of IL-6 receptor antibodies (sarilumab, tocilizumab), and perhaps also JAK inhibitors (eg, baricitinib), have better clinical efficacy.[78,79] If all conventional synthetic DMARDs are poorly tolerated or contraindicated, then IL-6R antibodies and JAK inhibitors are more efficacious than other agents.[69]

Management Recommendations

Generally, ACR[70] and EULAR[69] both recommend a strategy targeting an outcome of remission or low disease activity. Therefore, EULAR recommendations favor combining biologic DMARDs and targeted synthetic DMARDs with methotrexate, while ACR recommendations do not recommend against biologic DMARD monotherapy. EULAR recommends stratifying patients by poor prognostic markers and ACR by disease stage. EULAR strongly recommends short-term prescription of glucocorticoids whenever any conventional synthetic DMARD is started. ACR recommends combining conventional synthetic DMARDs with each other more strongly than EULAR (Table 3).

Each drug has limited efficacy and achieves low disease activity in up to 40% and remission in up to 20% of patients with RA (Table 2). If a specific pharmacotherapy does not achieve the treatment goals, therapy must be modified. To maximize treatment effects, glucocorticoids should be added to methotrexate for about 3 months in DMARD-naive patients; for patients who did not respond to initial therapy, biologic DMARDs and targeted synthetic DMARDs should be added to methotrexate or other conventional synthetic DMARDs, rather than switching to biologic DMARD monotherapy. About 50% to 60% of patients will not meet treatment goals after the first DMARD course, and more than 60% of these will require at least a third DMARD course. However, with the correct treatment strategy, low disease

activity or remission is currently a realistic goal for more than 75% to 80% of patients with RA.

Randomized trials and indirect comparisons demonstrated that, when combined with methotrexate, all biologic DMARDs and targeted synthetic DMARDs have similar efficacy.[80] One exception may be JAK inhibitors (eg, tofacitinib and baricitinib). Combined with methotrexate, baricitinib had better efficacy than adalimumab.[81] However, tofacitinib plus methotrexate was noninferior to adalimumab plus methotrexate.[77] More data are needed. A third JAK inhibitor, upadacitinib, which interferes with JAK 1 and perhaps JAK 2, demonstrated significant efficacy in phase 3 trials in methotrexate insufficient responders (ie, patients who did not attain the goal of low disease activity or remission, regardless of whether they had slightly improved with methotrexate), in anti-TNF insufficient responders, and as a monotherapy[82-84] but is still under investigation. A JAK 1 selective inhibitor, filgotinib, is being studied in phase 3 clinical trials.[85]

Optimization of Efficacy

All drugs exhibit decreasing efficacy with increasing disease duration or drug exposure, even if they target a different biologic pathway than prior therapies. In methotrexate-naive patients with high disease activity, ACR70 response rates for treatment with biologic DMARDs plus methotrexate are approximately 35% to 40%; in methotrexate insufficient responders this rate is about 20%, and in anti-TNF insufficient responders the rate is 10% to 15% (Table 2).[86] Two points should be made. First, although biologic DMARDs or targeted synthetic DMARDs combined with methotrexate appear most effective in patients not previously exposed to methotrexate, they should not be started before methotrexate, because these response rates include patients who would have responded to methotrexate alone. For this reason, biologic DMARDs or targeted synthetic DMARDs are not recommended as initial therapy. Second, when one biologic DMARD or targeted synthetic DMARD does not achieve remission or low activity, there is still a reasonable (10%-15%) chance that another will be beneficial. Treat-to-target therapy entails timely decisions to switch therapies at 3 months if disease improves to less than 50% activity and at 6 months if the treatment target is not reached.[45]

Five classes of targeted therapies are available (Table 2). For some of them, more than 1 drug is licensed. However, there are not genetic, gene expression, and other laboratory markers for predicting which patients will respond to a specific drug or class of drugs.[87] The only "biomarker" available is early response, measured by disease activity.[46] Assessment of this early clinical "biomarker," as well as response in general and achievement of the treatment target, requires careful monitoring and switching therapy when the treatment target is not reached.

The natural history of RA is characterized by a close association between disease activity and progression of joint damage[44]; biologic DMARDs disrupt this association.[88,89] This disruption is based on the finding that the threshold level of proinflammatory cytokines is higher for activation of the processes leading to joint damage than those leading to mere synovial inflammation.[90] Thus, even if a biologic DMARD shows insufficient clinical efficacy, progression of joint damage will be slowed or stopped. However, in these patients physical function and quality of life may remain impaired because of pain and stiffness. Since remission prevents structural damage from progressing and leads to improved physical function, absence of remission (or at least low disease activity) should prompt therapy change after a maximum of 6 months, irrespective of the type of therapy. This approach can prevent joint damage and disability.

Once sustained remission is attained, tapering biologic DMARDs or targeted synthetic DMARDs may be considered. Best results are achieved when patients have been in remission for at least 6 months.[91] Relapses are common after withdrawal of the drug. Therefore, dose reduction or interval increases between doses is preferred to therapy cessation.[92] Relapses after withdrawal of biologic DMARD therapy can be controlled by reinstituting the same biologic DMARD[93] (Figure 3).

Adverse events associated with most of the biologic DMARDs and targeted synthetic DMARDs are similar (Table 2) and include higher risk of infections. Biologic DMARDs and targeted synthetic DMARDs, except for rituximab and perhaps abatacept, can reactivate tuberculosis.[94] Therefore, before starting biologic DMARDs or targeted synthetic DMARDs, screening for tuberculosis must be performed; if results are positive, treatment of the latent infection is required. After patients travel to endemic areas, tuberculosis screening should be reevaluated. TNF inhibitors can activate demyelinating disorders, while JAK inhibitors increase herpes zoster virus reactivation; IL-6 inhibition may interfere with gut endothelial homeostasis and has a higher risk of intestinal perforations in patients with risk factors, such as diverticulitis.

Important lessons regarding pathophysiology have been learned from studies of biologic DMARDs and targeted synthetic DMARDs. In addition to currently approved drugs, many therapies have been evaluated in clinical trials. Therapies such as anti-CD4 (T helper cells), anti-IL-12/23 and anti-IL-23, anti-IL-17 (T_H17 cells), and inhibitors of p38 mitogen-activated protein kinase failed to demonstrate efficacy.[95-98]

Cost of Therapy

Biologic DMARDs and targeted synthetic DMARDs are costly. Prices vary with region and country and range between $10 000 (Europe) to $36 000 (United States) annually. The advent of biosimilar DMARDs has led to a reduction of biologic DMARD prices. In some countries, prices have decreased by more than 50% compared with the original biologic DMARD.[63,99]

Prognosis

With the availability of effective therapies and treatment strategies, remission or low disease activity can be achieved in about 75% to 80% of patients.[100] Patients in remission, but also those with low disease activity, can continue normal participation in social and work activities and have normal life expectancy.[101]

However, about 20% to 25% of the patients in the industrialized world and many more in less affluent countries[102] do not reach low disease activity. For some patients, poor access to optimal care precludes better outcomes. For other patients, causes of refractory disease have not been identified, but delaying prescription of effective therapy and higher disease activity at treatment onset appear to be important factors contributing to resistance. For these

patients, novel therapies are needed and several are currently in development, eg, more selective JAK inhibitors, inhibitors of Bruton tyrosine kinase and the phosphoinositide-3-kinase pathway, antibodies to the granulocyte-monocyte colony-stimulating factor receptor, or dual antibodies targeting more than 1 cytokine at the same time.[103-105] Biomarkers that predict which patients will respond well to which drug are needed,[106] as are therapies that may prevent disease from occurring in patients at risk,[107] because RA remains incurable.[108]

Limitations

This review has several limitations. First, it provides only a general, brief overview of the topic and omits detailed information about genetics or pathogenesis. Second, scientific advances are occurring rapidly. It is possible that new therapies not mentioned in this review will be available in the near future.[20,23,82,83]

Conclusions

Recently acquired knowledge regarding the pathogenesis, optimal management, and optimal outcome measures of RA have significantly improved therapy for RA. Early diagnosis of RA allows clinicians to promptly prescribe methotrexate as the initial DMARD, arresting disease in a large proportion of patients. The 2010 classification criteria facilitate early identification of patients with RA for clinical studies and may inform the clinical diagnosis. Effects of therapy should be closely monitored with disease activity measures, such as the CDAI. Absence of remission or low disease activity requires alteration in therapy, according to treat-to-target recommendations. If methotrexate (in combination with short-term glucocorticoids) does not induce remission, biologic DMARDs or JAK inhibitors should be added, particularly in patients with continuing high disease activity, presence of autoantibodies, or preexisting damage. With these methods, the adverse consequences of RA can be prevented.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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