

The Researcher's Ultimate Guide to Rheumatoid Arthritis



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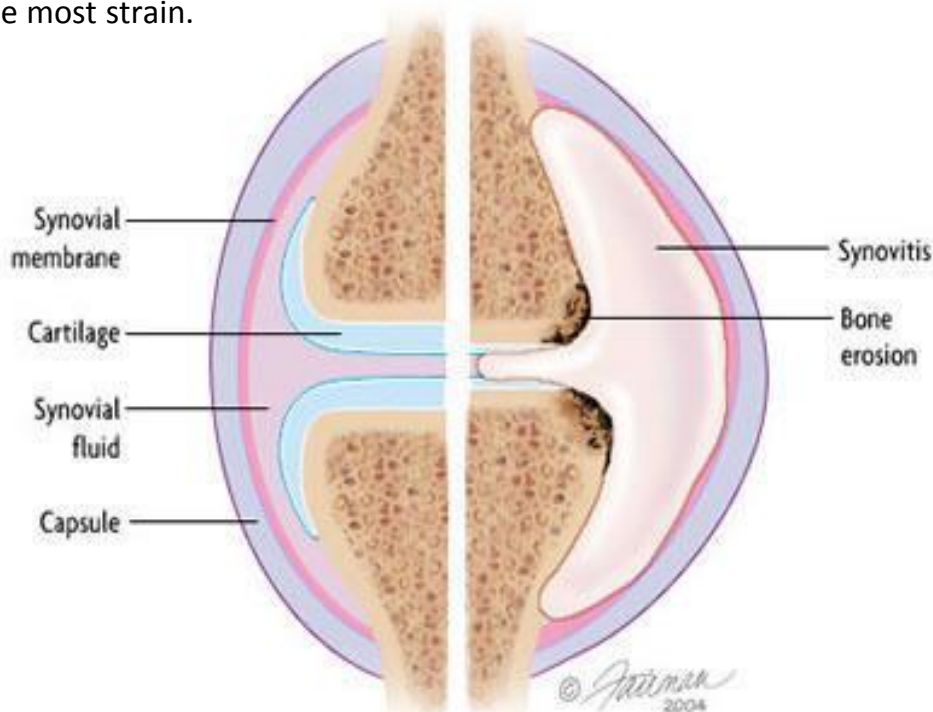
Section 1:

Understanding Rheumatoid Arthritis

What is Rheumatoid Arthritis?

Rheumatoid arthritis is a type of autoimmune disease that causes joint inflammation leading to redness, warmth, swelling, and pain in the joint. As an autoimmune disease, RA develops when the body fails to differentiate the body's own tissues from foreign pathogens. As a result, the immune system launches a response to destroy the body's own healthy tissues. The response causes immune cells to migrate from the blood into the joints and synovium, the joint-lining tissue. There, they produce inflammatory substances that cause irritation, wearing down of cartilage (the cushioning tissue between joint articulations), swelling, and inflammation of the joint lining. The resulting buildup of fluid in the joint can lead to bone damage.

Unlike other forms of arthritis, a distinguishing characteristic of RA is symmetric inflammation, for instance, inflammation in both hands or both knees. On the other hand, osteoarthritis, another common form of arthritis, occurs as a result of physical strain on joint tissues. Consequently, it occurs more prominently on the side of the body incurring the most strain.



Source: http://www.rheumatology.org/Practice/Clinical/Patients/Diseases_And_Conditions/Rheumatoid_Arthritis/

What are the symptoms of RA?

RA affects everyone differently, so the types and severity of symptoms vary greatly depending on the person. For some patients, RA symptoms develop gradually over the course of several years while other experience a sudden onset. The most common symptoms of RA include:

RA Symptoms	
<ul style="list-style-type: none">• Fatigue• Appetite loss• Fever• Muscle & joint aches• Hoarse voice	<ul style="list-style-type: none">• Rheumatoid nodules• Symmetric arthritis• Morning stiffness• Red/swollen joints• Bone deformity

Do RA patients always exhibit symptoms?

No. Patients experience alternating symptomatic and asymptomatic phases. Periods of actively experienced symptoms are called “flares.” During times marked by the absence of symptoms, patients are qualified as “in remission.”

Who is affected by RA?

Women are 3 times more likely to develop RA than men; however, men typically experience more severe symptoms. RA most commonly occurs between the ages of 40-60 years old. Women who have never been pregnant and those who have recently given birth have an increased risk. Individuals with first-degree relatives (mother, father, brother, or sister) with RA have a 2-to 3-fold increased risk for the disease. Estimates indicate that about 1% of Americans have rheumatoid arthritis.

What causes RA?

Researchers are not sure exactly what causes RA, but most concur that it probably results from a combination of genetic and environmental triggers. Genetic factors account for 50% of the risk of developing RA.¹ People with specific human leukocyte antigen (HLA) genes have an increased risk of developing RA; however, having these genes does not guarantee that an individual will develop RA.



Exposure to cigarette smoking and certain infectious bacteria and viruses may also increase one's risk for developing the disease. Evidence indicates that exposure to *Mycoplasma* organisms, Epstein-Barr virus, periodontopathic (gum disease-causing) bacteria, and rubella virus increases the risk of developing RA.

What is the prognosis for RA patients?

Most RA patients face a life of slowly worsening RA symptoms, eventually leading to joint damage. Only about 10% of patients experience an abrupt onset of symptoms.

Prolonged Remission	10-20% of RA patients
Intermittent	25% of RA patients
Chronic	60-70% of RA patients

¹Barton A, Worthington J. Genetic susceptibility to rheumatoid arthritis: an emerging picture. *Arthritis Rheum.* Oct 15 2009;61(10):1441-6. [\[Medline\]](#).

Did You Know?

- Approximately 1.3 million Americans suffer from RA.
- Approximately 40% of patients with this disease become disabled after 10 years.
- The typical work experience of people with RA differs substantially from that of someone without arthritis. Compared with people without arthritis, people with RA were more likely to do the following: change occupation (3.3% vs. 0%), reduce work hours (12.2% vs. 1.7%), lose their job (3.3% vs. 0%), retire early (26.3% vs. 5.2%), and be unable to find a job (15.3% vs. 5.2%).
- In 2009, there were 15,600 hospitalizations with RA listed as the principal diagnosis with total hospital charges of \$545 million—a mean charge of \$35,000 per person.



Statistics obtained from <http://www.cdc.gov/arthritis/basics/rheumatoid.htm>

Section 2:

From the Real World to the Lab

How is RA diagnosed?

Diagnosing RA can be especially challenging because it shares symptoms with several other prevalent diseases such as gout, fibromyalgia, systemic lupus erythematosus, and synovitis. A combination of the following laboratory tests and imaging studies are used in conjunction with a thorough physical examination and medical history to establish a diagnosis of RA.

Laboratory Tests



- Erythrocyte sedimentation rate (ESR)
- C-reactive protein level (CRP level)
- Complete blood count (CBC)
- Rheumatoid factor assay (RF assay)
- Antinuclear antibody assay (ANA assay)
- Anti-cyclic citrullinated peptide and anti-mutated citrullinated vimentin assays (anti-CCP and anti-MCV assays)
- Synovial fluid Gram stain, cell count, culture, and visual assessment

Imaging Tests



- Radiography (primary choice): hands, wrists, knees, feet, elbows, shoulders, hips, cervical spine, and other joints as indicated
- MRI: primarily for cervical spine
- Ultrasonography of joints

What is the diagnostic criteria for RA?

Diagnosing RA requires 4 or more of the following 7 criteria be expressed for at least 6 months:

1. **Morning stiffness for at least 1 hour**
2. **Swelling of 3+ joints simultaneously**
3. **1+ swollen area in wrist, hand, or finger**
4. **Symmetric arthritis**
5. **Rheumatoid nodules**
6. **High rheumatoid factor blood level**
7. **X-ray indication of involved joint damage**

What is RF?

RF, rheumatoid factor, is an antibody directed against the body's own tissues. It plays a role in many inflammatory reactions, including those of RA. Seventy to eighty percent of RA patients have high RF levels. A high RF level is anything above 20 IU/ml. RF can exist in any antibody form: IgA, IgG, IgE, IgM and/or IgD. The amount of RF generally correlates to the severity of the disease.

What are the stages of RA?

Early Stage

- Patient has evidence of inflammation for no more than 6 months.
- Treatment is aimed to protect joints and control inflammation.

Persistently Active

- Patient has evidence of inflammation for 6 to 12 months and may have irreversible joint damage.
- Treatment goals are the same as early stage RA.

End Stage

- Patient has little or no inflammation but severe joint damage & loss of function.
- Treatment aims to reduce pain and additional joint damage.

RA Biomarkers

In order to optimize treatment outcomes, it is essential to identify RA in the very early phases of development, ideally even before some of the aforementioned diagnostic criteria and other clinical symptoms are apparent. Research on RA biomarkers has revealed several potential indicators of RA that can be used for diagnosis and/or observation of disease progression and treatment efficacy. The following biomarkers are frequently employed for these tasks:

Name	Normal Levels	Significance
Rheumatoid Factor (RF)	20-30 IU/mL	Levels over normal indicate autoimmunity, specifically RA
C-reactive protein (CRP)	5-6 mg/mL	Levels over normal indicate RA
Anti-cyclic citrullinated peptide (anti-CCP)	<20 IU/mL	Levels over normal indicate RA
Erythrocyte Sedimentation Rate (ESR)	20mm/hr	Levels over normal indicate inflammatory disorder
Anti-nuclear antibodies (ANA)	0	Levels over normal indicate autoimmunity, specifically SLE
Alpha-1-antitrypsin (AAT)	170-230 mg/dL	Levels over normal indicate RA
Immunoglobulin M (IgM)	50-220 mg/dL	Levels over normal indicate RA

Note: The acute phase of RA is indicated by high levels of the inflammatory biomarkers CRP and ESR.

Treating RA

What are the lines of treatment for RA?

The answer depends on the severity of an individual patient's RA. If diagnosed early and at a relatively juvenile stage, the first line of treatment will be anti-inflammation via NSAIDs and steroids. If the RA progresses to a more advanced stage—or was already advanced at the time of diagnosis—the first line of treatment would be DMARDs and/or biologics (which include anti-TNFs).

NSAIDs

Nonsteroidal anti-inflammatory drugs

Biologics

Drugs engineered to target specific components of the immune system in order to suppress them and control the overactive immune functions responsible for RA

Anti-TNFs

Biologic drugs designed to inhibit RA specific inflammation by blocking Tumor Necrosis Factor (TNF), a mediator of the inflammatory response implicated in RA

DMARDs

Disease-Modifying Antirheumatic Drugs suppress the immune system non-selectively to inhibit joint damage

What are the most common drugs given for RA?

Besides analgesics and NSAIDs, which vary greatly from patient-to-patient, the most common drug currently prescribed to treat RA is methotrexate. Of the biologics, Humira, Enbrel, and Simponi compete for the title of most commonly used.

Medication Type	Drugs	Dosages	Side Effects
Analgesics <i>Standard</i>	Acetaminophen	500-1000 mg/day	<ul style="list-style-type: none"> itching rash jaundice
NSAIDs* <i>Primary</i>	Ibuprofen Naproxene Celebrex	Higher dosages (amount varies by drug)	<ul style="list-style-type: none"> internal bleeding kidney damage liver damage
Steroids <i>Primary</i>	Prednisone	Most patients: 10 mg/day	<ul style="list-style-type: none"> anxiety insomnia abdominal pain
DMARDs <i>Secondary</i>	Methotrexate Sulfasalazine hydroxychloroquine	Methotrexate: 15-30 mg/week Sulfasalazine: 2-3g/day Hydroxychloroquine: 400-600 mg/day	<ul style="list-style-type: none"> kidney damage heart attack stroke brain damage
Biologics <i>Secondary</i>	Actemra (IL-6) Cimzia(TNF) Enbrel(TNF) Kineret (IL-1) Orencia (T-cell) Remicade (TNF) Rituxan (B-cell) Simponi(TNF)	Humira: 40 mg Every 2 weeks Kineret : 100 mg/day Enbrel: 50 mg/week Remicade: 3-10 mg Every 4-8 weeks	<ul style="list-style-type: none"> pain at site of injection infections cough headache

Note: Only 10% of RA patients are on NSAID treatment alone.

What is TNF?

Tumor necrosis factor, TNF, is a type of protein known as a “cytokine” that is involved in the inflammatory reactions of RA. Anti-TNFs are biologic drugs designed to bind to TNF and thereby inhibit it from instigating inflammation.

Anti-TNFs	
Generic	Trade
Etanercept	Enbrel
Infliximab	Remicade
Adalimumab	Humira
Golimumab	Simponi
Abatacept	Orencia
Certolizumab pergol	Cimzia
Tocilizumab	Actemra

What is the typical washout period between RA medications?

Biologics: No washout period

Methotrexate: 3 to 6 months, but in many cases doctors will switch medications immediately



What surgical treatment options are available?

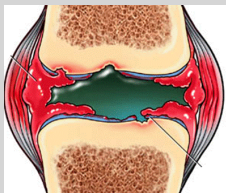
Drugs used to treat RA slow the progression of the disease; however, if joint damage has already occurred, surgery may be a reasonable treatment option to relieve pain and improve mobility. The timing of surgical intervention is critical. Surgery should be used only when necessary to avoid unnecessary risks; however, delaying surgery too long can decrease the chances of success. Rheumatologists, orthopedic surgeons, and patients should consult to determine when surgical options should be pursued. The types of surgeries frequently employed to treat RA patients are described below.

Joint Replacement



Knee and hip joint replacements are the most common replacement surgeries for RA patients. In this surgery, the damaged joints are removed and an artificial joint is inserted.

Synovectomy



The removal of the abnormal joint lining to prevent it from damaging cartilage and bone. Because the joint lining may grow back, the surgery may have to be repeated.

Carpel Tunnel Release



This can relieve the pain of carpal tunnel syndrome which results from compression of a nerve in the hand.

Arthodesis



Bone or joint fusion surgery used to relieve pain in the ankles, wrists, fingers, thumbs, or spine.

Patient Lifestyle

Doctor Visits

The average RA patient goes in for a check-up once every 6 months. The frequency of visits increases with increasing RA severity. At each checkup, physicians ask about the patient's symptoms and order appropriate biomarker blood tests and imaging tests.



Lifestyle

Patients frequently have trouble performing activities of daily living (ADLs) such as standing, eating, dressing, walking, personal hygiene, and use of hands. Consequently, they may require caregivers to assist them with their normal, everyday activities.

Occupational and physical therapy are often a part of RA treatment. When used in conjunction with medication, these supplementary therapies help improve patients' range of motion, strength, and sense of independence.

Section 3:

Research Challenges

The activity level of rheumatoid arthritis is defined in one of the following three ways. There is no clear consensus on exactly what constitutes each specific level, so the severity diagnosis may vary from doctor to doctor.



RA Activity Levels:

Mild

A person with mild RA has *some* of these symptoms: joint pain, inflammation of 3+ joints with no inflammation in other tissues, negative RF test, elevated ESR or CRP levels, no bone and/or cartilage damage.

Moderate

A person with mild RA has *some* of these symptoms: joint pain, inflammation of 3+ joints with no inflammation in other tissues, negative RF test, elevated ESR or CRP levels, no bone and/or cartilage damage.

Severe

A person with severe RA has *one or more* of these symptoms: 20+ persistently inflamed joints with inflammation in other tissues, rapid loss of functional ability, elevated ESR or CRP levels, anemia related to chronic illness, low blood albumin level, positive RF test, bone and/or cartilage damage.

Targeting Capabilities

It is not possible to target patients experiencing symptoms above their normal base-line, but it is possible to target patients who have active RA. Because defining the level of activity is subjective, targeting by activity stage is difficult but not impossible.

Most suspected RA patients are immediately placed on some type of NSAID. As the disease progresses towards joint damage, more potent RA drugs, such as the biologics and anti-TNFs, are prescribed. While it is possible to target patients prior to treatment with anti-TNFs, it is not feasible to target RA patients prior to NSAID treatment.

Targeting a patient based on their CRP score or ESR is possible; however, patients would be targeted based on their prior scores. Their current scores will be known only after collection and analysis when the tests are performed.

A high disease activity (DAS28) score generally indicates a high CRP score. However, a high DAS28 score does not always guarantee a patient will have a high CRP score. Targeting patients with a high DAS28 score is one of the best ways to target a patient that will likely have a high CRP score, but the method is not fail proof.

Section 4:

Case Studies

Case 1: Data, Data, Data



Conversant Bio provided approximately 90 unique samples from rheumatoid arthritis patients for a pharmaceutical company. The inclusion/exclusion criteria involved current treatment, treatment history, and comorbidities. Conversant Bio's access to patient records allowed the targeting of patients meeting these specific criteria. All previous and current clinical lab data (e.g. ESR, CRP, Anti-CCP, RF, CBC, etc.) found was provided to the researcher.

Case 2: Quick Turnaround



A contract research organization contacted Conversant Bio to identify patients with high, medium, low, and absent levels of RF. Conversant Bio was able to obtain patient samples from each level in less than one month with data including the RF level as well as basic clinical data.

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