



## RHEUMATOID ARTHRITIS

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### ABSTRACT:

Despite all improvements in rheumatoid arthritis, we are still not able to prevent or cure the disease. Diagnostic delays due to lack of access to a specialist and costly therapies are still a major obstacle for many patients. Even in first-world countries, the treat-to-target principle and the goal of disease remission are often missed. Thus, rheumatoid arthritis (RA) is still the reason for disability and reduced quality of life for many patients. So, is it time to move the goalpost even further? Where are we heading next? And will we finally be able to cure the disease? These questions are addressed in our review article.

**Keywords:** P4 medicine, personalized medicine, digital health, Rheumatoid arthritis

### INTRODUCTION: <sup>(1)</sup>

Rheumatoid arthritis is an auto immune disease that is caused by “Chronic Inflammation” of the joints or in the membrane surrounding the joints (Synovial membrane)



**Fig. 1**

It is a chronic inflammatory disorder of unknown etiology that primarily involves synovial joints. It typically starts in small peripheral joints, is often symmetric, and progresses to involve proximal joints if left untreated.

### ETIOLOGY: <sup>(2,3)</sup>

The etiology of RA remains unknown. It is thought to result from the interaction between patients' genotype and environment. In a nationwide study of 91 monozygotic (MZ) and 112 dizygotic (DZ) twin pairs in the United Kingdom, the overall MZ concordance rate was 15% and 5% among dizygotic twins. The heritability of rheumatoid arthritis is approximately 40% to 65% for seropositive rheumatoid arthritis and 20% for seronegative rheumatoid arthritis. The risk of developing rheumatoid arthritis has been associated with HLA-DRB1 alleles: HLA-DRB1\*04, HLA-DRB1\*01, and HLA-DRB1\*10. These HLA-DRB1 alleles

contain a stretch of conserved five amino acid sequences and the shared epitope (SE) in the third hypervariable region of their DRB1 chain, which has been associated with the risk of developing RA.

### **EPIDEMIOLOGY:** (4,5)

The worldwide prevalence of RA is about 0.24. The annual incidence of RA in the United States and other western nations of northern Europe is about 40 per 100,000 persons. According to epidemiologic data, RA is more prevalent in women compared to men, lifetime risk of RA 3.6% in women compared to 1.7% in men. RA risk also increases with age, with a peak incidence between age 65 to 80 years of age.

### **PATHOPHYSIOLOGY:** (6)

Joint swelling in RA is usually synovial-membrane inflammation, with cytokine and chemokine involvement.<sup>7</sup> The most relevant components in the inflamed space include tumor necrosis factor (TNF), interleukin-6 (IL-6), and granulocyte-macrophage colony-stimulating factor.<sup>7</sup> Cytokines and chemokines induce or aggravate the inflammatory response by activating endothelial cells and promoting immune-system cell accumulation within the synovial compartment.<sup>7</sup> Activated fibroblasts, B cells, T cells, monocytes, and macrophages can eventually trigger osteoclast generation via receptor activator of nuclear factor kappa-B ligand (RANKL), which is expressed on B cells, T cells, and fibroblasts.<sup>7</sup> The RANK receptor is present on macrophages, dendritic cells, and preosteoclasts.<sup>7</sup> In addition, the cartilage matrix within joints is eventually degraded by metalloproteinases and other enzymes.

### **Non-specific inflammation:** (7,8)

Factors allowing an abnormal immune response, once initiated, become permanent and chronic. These factors are genetic disorders which change regulation of the adaptive immune response. Genetic factors interact with environmental risk factors for RA, with cigarette smoking as the most clearly defined risk factor.

Other environmental and hormonal factors may explain higher risks for women, including onset after childbirth and hormonal medications. A possibility for increased susceptibility is that negative feedback mechanisms – which normally maintain tolerance – are overtaken by positive feedback mechanisms for certain antigens, such as IgG Fc bound by rheumatoid factor and citrullinated fibrinogen bound by antibodies to citrullinated peptides (ACPA - Anti-citrullinated protein antibody). A debate on the relative roles of B-cell produced immune complexes and T cell products in inflammation in RA has continued for 30 years, but neither cell is necessary at the site of inflammation, only autoantibodies to IgGFc, known as rheumatoid factors and ACPA, with ACPA having an 80% specificity for diagnosing RA. As with other autoimmune diseases, people with RA have abnormally glycosylated antibodies, which are believed to promote joint inflammation.

### **DIAGNOSIS:** (9,10)

Rheumatoid arthritis can be difficult to diagnose in its early stages because the early signs and symptoms mimic those of many other diseases. There is no one blood test or physical finding to confirm the diagnosis.

**BLOOD TESTS:** People with rheumatoid arthritis often have an elevated erythrocyte sedimentation rate (ESR, also known as sed rate) or C-reactive protein (CRP) level, which may indicate the presence of an inflammatory process in the body. Other common blood tests look for rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies.

### **Imaging tests:** (11)

X-rays of the hands and feet are generally performed when many joints affected. In RA, there may be no changes in the early stages of the disease or the x-ray may show osteopenia near the joint, soft tissue swelling, and a smaller than normal joint space. As the disease advances, there may be bony erosions and subluxation. Other medical imaging techniques such as magnetic resonance imaging (MRI) and ultrasound are also used in RA.

Technical advances in ultrasonography like high-frequency transducers (10 MHz or higher) have improved the spatial resolution of ultrasound images depicting 20% more erosions than conventional radiography. Color Doppler and power Doppler ultrasound are useful in assessing the degree of synovial inflammation as they can

show vascular signals of active synovitis. This is important, since in the early stages of RA, the synovium is primarily affected, and synovitis seems to be the best predictive marker of future joint damage.

## **TREATMENT:** <sup>(12)</sup>

The most important goal of treating rheumatoid arthritis is to reduce joint pain and swelling. Doing so should help maintain or improve joint function. The long-term goal of treatment is to slow or stop joint damage. Controlling joint inflammation reduces your pain and improves your quality of life.

**How is rheumatoid arthritis treated?** Joint damage generally occurs within the first two years of diagnosis, so it's important to see your provider if you notice symptoms. Treating rheumatoid arthritis in this "window of opportunity" can help prevent long-term consequences. Treatments for rheumatoid arthritis include lifestyle changes, therapies, medicine and surgery. Your provider considers your age, health, medical history and how bad your symptoms are when deciding on a treatment.

## **DRUGS:**

Early treatment with certain drugs can improve your long-term outcome. Combinations of drugs may be more effective than, and appear to be as safe as, single-drug therapy. There are many medications to decrease joint pain, swelling and inflammation, and to prevent or slow down the disease. Medications that treat rheumatoid arthritis include:

Non-steroidal anti-inflammatory drugs (NSAIDs); Non-steroidal anti-inflammatory drugs decrease pain and inflammation. They include products like:

- Ibuprofen (Advil®, Motrin®).
- Naproxen (Aleve®).
- Aspirin.

## **COX-2 inhibitors:**

COX-2 inhibitors are another kind of NSAID. They include products like celecoxib (Celebrex®). COX-2 inhibitors have fewer bleeding side effects on your stomach than typical NSAIDs.

**Corticosteroids:** Corticosteroids, also known as steroids, also can help with pain and inflammation. They include prednisone and cortisone.

## **Disease-modifying antirheumatic drugs (DMARDs):**

Unlike other NSAIDs, DMARDs actually can slow the disease process by modifying your immune system. Your provider may prescribe DMARDs alone and in combination with steroids or other drugs. Common DMARDs include:

- Methotrexate.
- Hydroxychloroquine.
- Sulfasalazine.
- Leflunomide.

## **Janus kinase (JAK) inhibitors:**

JAK is a group of tyrosine kinases that participate in intracellular signal transduction for hematopoiesis and immune cell function. JAK inhibitors (such as tofacitinib) reduce the production of cytokines and are approved as second-line agents for the treatment of RA.

## **Biologics:** <sup>(13)</sup>

If you don't respond well to DMARDs, your provider may prescribe biologic response agents (biologics). Biologics target the molecules that cause inflammation in your joints. Providers think biologics are more effective because they attack the cells at a more specific level. These products include.

## **What is the safest drug for rheumatoid arthritis?**

The safest drug for rheumatoid arthritis is one that gives you the most benefit with the least amount of negative side effects. This varies depending on your health history and the severity of your RA symptoms. Your

healthcare provider will work with you to develop a treatment program. The drugs your healthcare provider prescribes will match the seriousness of your condition.

## VACCINATION CONSIDERATION:

When you have you may worry about getting vaccines After all, RA involves a malfunctioning immune system, and vaccines work by activating the immune system. It is fair to wonder whether the combination of the two effects may be harmful or contradictory.

In many cases, it is absolutely safe to be vaccinated if you have RA, but there are exceptions and a few precautions you may need to take.

## Benefits of Vaccination:

Both RA and the immunosuppressant drugs used to treat RA may increase your susceptibility to vaccine-preventable diseases like influenza; shingles, pneumococcal pneumonia, and others.<sup>1</sup> Some studies suggest that the risk may be as high as two-fold compared to people without RA.<sup>2</sup> Moreover, if your RA is severe, you are more likely to experience frequent flares and severe infections compared to those who have their condition under control.<sup>1</sup>

## Recommendations:

The benefits of vaccinations almost always outweigh the risks in people with RA. Even so, experts recommend the following precautions:

- Get vaccines updated before starting DMARDs whenever possible.
- Avoid vaccinations during flares.
- Live attenuated vaccines can be considered after careful consultation with your healthcare provider.
- If you took biologics during the second half of pregnancy, your baby shouldn't receive a live attenuated vaccine until they're 6 months old.

## SURGERY:

Most people with RA never have surgery but—like people with osteoarthritis—people with rheumatoid arthritis may elect to have surgery to reduce joint pain and improve everyday function. The most common surgeries are joint replacement, arthrodesis and synovectomy.



## Joint Replacement

Patients may elect to have joint replacements for large joints such as shoulders, hips, or knees as well as smaller joints in the fingers and toes. Joint replacement surgery involves removing either all or part of a damaged joint and inserting a synthetic replacement.

## Undergoing Total Knee Replacement for Knee Arthritis:

Joint replacements are typically major surgeries with considerable risks, but one study showed that RA patients seemed to do better than osteoarthritis patients during hospital recovery, perhaps because of physician's hyper-vigilant screening of RA patients.<sup>1</sup>

## Arthrodesis:

In arthrodesis, the damaged joint is removed and the neighbouring bones are fused together. The procedure greatly limits movement but increases stability and reduces pain in the affected joints.

## Ankle Osteoarthritis Surgery:

Arthrodesis is most commonly used to treat arthritic ankles, toes, wrists, or finger joints. It can also be used to stabilize painful joint(s) in the spine (called spinal fusion). Arthrodesis sometimes requires using bone grafts retrieved from the patient's own pelvis.

## Synovectomy:

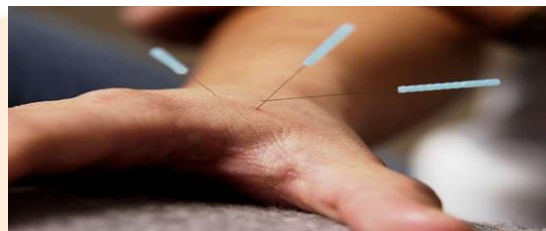
During this procedure, the surgeon removes the inflamed synovial tissue around the joint. By removing the affected tissue, the surgeon hopes to reduce or eliminate the patient's symptoms. Not all of the tissue can be removed, however, so inflammation, swelling and pain can recur.

## OTHER THERAPIES:

### Herbs and Supplements

Are your joints sore and stiff? Some herbal remedies and supplements might help bring down swelling and ease pain. Here are a few to ask your doctor about:

- Boswellia (Indian frankincense)
- Cat's claw



### Acupuncture

Practitioners of this ancient Chinese method stick tiny needles into your skin to reroute your body's flow of energy. Acupuncture may lower levels of substances like tumour necrosis factor (TNF), which cause joint swelling. It also triggers the release of natural painkillers.

Studies haven't yet proven that acupuncture helps with RA pain and swelling. More research is needed.



### Massage:

This could be just the thing to bring relief when your joints feel stiff and achy. Research finds an arm and hand massage can ease pain and improve your grip strength. A good rub-down can also knock out anxiety and help you sleep better. Before your first session, see your rheumatologist to make sure it's safe for you. And let the massage therapist know you have RA.

### Aromatherapy:

You'll breathe in fragrant plant oils, or a massage therapist can rub them onto your skin. It's not clear whether aromatherapy works for RA because so little research has been done. But evidence suggests it may relieve pain and fatigue and boost your mood.

- \* Some other include
- \* Tai chi
- \* Healthy eating

- \* Yoga
- \* Hot and cold treatment

## NEWER MEDICATION:

The past 20 years have brought many new ways to treat RA, and there are more around the corner. Here's how the face of treatment has changed. Then: Twenty years ago, your doctor told you to take over-the-counter or prescription to relieve pain and reduce inflammation. You got a corticosteroid shot. The doctor waited to prescribe stronger medicines -- and choices were limited back then -- until your RA got worse. The approach was to treat flares, not the disease itself.

**Now:** You and your rheumatologist tackle RA head-on -- and early. You'll take powerful medicine from the start -- prescription drugs that work to stop the disease before it causes major damage. There are several to choose from or combine if the first ones don't work.

## Promise for the Future:

There's still much to learn about why and how RA happens. Building on recent discoveries, areas under study include:

- Researchers are looking at genes to see why some people get RA and some don't, and why some cases are worse than others. This data can lead to biologics -- like JAK inhibitors -- that fight the causes of RA at a cellular level. Several such drugs are in the works.
- Another area of RA research focuses on proteins made to target molecules that affect your immune system. They're called monoclonal antibodies, and several are approved by the FDA for use in RA. New ones are under study, too
- Statins, commonly used to lower cholesterol and prevent heart disease, are being studied to if they can lessen the symptoms of rheumatoid arthritis.
- Medical and dental researchers are revisiting the link between joint disease and gum disease.

## DIET:

A varied and balanced diet can help control the inflammation that causes RA symptoms. It can also help a person manage their weight, reducing joint stress.

A Mediterranean diet is a good option for many people with RA. This diet focuses on inflammation-fighting foods, such as:

- Plenty of fresh fruits and vegetables, which are rich in antioxidants.
- Fatty fish, such as salmon or tuna, which are high in omega -3 fatty acids.
- Olive oil which has heart-healthy monounsaturated fats
- Nuts, which are also a great source of monounsaturated fats and other nutrients.

## PREVENTION:

**Some of the known risk factors for RA include:**

- Advancing age, with most cases beginning when a person is in their 60s
- Female sex, especially those who have never given birth
- Genetics, with a high association with human leukocyte antigen (HLA) class II genotypes
- Smoke early in life
- Low income

## HISTORY: (14,15)

The first recognized description of RA in modern medicine was in 1800 by the French physician Dr Augustin Jaco Landré-Beauvais (1772–1840) who was based in the famed Salpêtrière Hospital in Paris. The name "rheumatoid arthritis" itself was coined in 1859 by British rheumatologist Dr Alfred Baring Garrod.

The art of Peter Paul Rubens may possibly depict the effects of RA. In his later paintings, his rendered hands show, in the opinion of some physicians, increasing deformity consistent with the symptoms of the disease.(14) RA appears to some to have been depicted in 16th-century paintings. However, it is generally recognized in art historical circles that the painting of hands in the 16th and 17th century followed certain stylized conventions, most clearly seen in the Mannerist movement. It was conventional, for instance, to show the upheld right hand of Christ in what now appears a deformed posture. These conventions are easily misinterpreted as portrayals of disease.

## ROLE OF PHARMACIST:

The majority of RA cases are diagnosed and treated on an outpatient basis. Pharmacists in ambulatory care settings (e.g., clinics, community pharmacies) have pivotal opportunities to counsel patients and ensure that RA drugs are administered appropriately. An example of such a drug is MTX, which should be taken once weekly, along with folic acid supplementation.

## CONCLUSION:

RA is a chronic disease that requires interventions to modify disease progression. While initial presentations are related to joint inflammation, long-term sequelae can include extra-skeletal manifestations. The most recent RA guidelines are from ACR 2015 and EULAR 2016. There are specific differences between the guidelines, based on the respective region/population studied. A future update of the ACR guidelines may contain commentary regarding the roles of baricitinib and sarilumab, as well as other promising therapies for RA.

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