RHEUMATOID ARTHRITIS: A REVIEW

Dr. H D Ramachandran. M.Sc. Ph.D*

Associate Professor, Department of Biochemistry, Bangalore University, Bangalore – 560001.

ABSTRACT

Rheumatoid arthritis is a form of arthritis, an autoimmune disease that causes pain, swelling, stiffness and loss of function in the joints and remains the most important form of arthritis seen in rheumatological practice in the developed world. The geographical distribution of the disease is remarkably homogeneous. Clinical progress has come from a better recognition of the natural history of the disease. The causes of rheumatoid arthritis are still unclear and a wide variety of factors namely genes, environment and hormones are suspected to contribute. Recent years have seen considerable advances in our understanding of both the clinical and basic-research aspects of rheumatoid arthritis. Treatments include medicine, lifestyle changes and surgery. These can slow or stop joint damage and reduce pain and swelling. The present review article aims to encompass all these aspects in detail.

Keywords: Rheumatoid arthritis, synovial fluid, pannus, autoimmunity, joint inflammation, Tumor necrosis factor, DMARDs, NSAIDs, juxta-articular osteopenia, adjuvant therapies.

INTRODUCTION

Rheumatoid Arthritis, the name is based on the term “Rheumatic fever”, an illness which includes joint pain and is derived from the Greek word rheuma (nom), rhematos (“flow, current”), the suffix –oid (“resembling”) translating as joint inflammation that resembles rheumatic fever.

Pre-History and History
The history of rheumatoid arthritis (RA) can be traced back to the dinosaurs and prehistoric man. It is an established fact that the dinosaurs suffered from arthritis. Remains of a herd of Iguanadons, small (three-ton) dinosaurs, 85,000,000 BC, found in Brussels, Belgium indicate...
that they had ankle osteoarthritis (OA).\[^1\] Also ample proof suggests that our earliest ancestors suffered from chronic aches and pains.\[^2\] According to the remains of Neanderthal man, a relative of modern man, who made his first appearance between 30,000 BC and 28,000 BC, individuals of this time developed secondary OA due to injuries and the difficulties of daily life.\[^3, 4\] Thus, there is evidence that arthritis has been in this world since the beginning of civilization, which makes it one of the oldest diseases in the universe.

Arthritis was evidenced in ancient Ötzi, name given to a mummy, popularly known as the iceman, who attempted to cross the Alps near the border of Italy and Austria in 3000BC. Although he was not successful in his venture, the mummified remains of his body, with the pouch of medicinal herbs that he carried with him, and his arthritic joints, provide valuable information even 5000 years after his death.\[^5\]

Although the earliest known appearance of RA was noted in skeletal remains of Native Americans Indians from 4500 BC found in what is now known as Tennessee and parts of modern-day Olathe, Kansas, USA, documented evidence was not found until much later. In 123AD, a text from India called ‘Charaka Samhita’ describes a disease where swollen, painful joints initially strike the hands and feet, then spread to the body, causing loss of appetite, and occasionally fever. This first written reference to arthritis points towards to what is now known as rheumatoid arthritis.

The first recognizable description of rheumatoid arthritis was made in 1800 by Dr. Augustin Jacob Landre-Beauvais (1772-1840) of Paris.\[^6\] The disease earned a proper name, when Sir Alfred Garrod, a London physician, coined the clinical term ‘rheumatoid arthritis’ in 1859 and the first reference came to be made in medical literature.

**Brief description:** Rheumatoid arthritis (RA) is a chronic, systemic inflammatory, autoimmune disorder\[^7\] that can affect many tissues and organs, but principally attacks synovial joints.\[^8\] The process produces an inflammatory response of the synovium (synovitis) secondary to hyperplasia of synovial cells, excess synovial fluid, and the development of pannus in the synovium. The pathology of the disease process often leads to the destruction of articular cartilage and ankylosis of the joints (wrists, shoulders, knees, ankles and feet). Rheumatoid arthritis can attack other parts of the body besides joints and also produce diffuse inflammation in the lungs, pericardium, pleura, and sclera, and also nodular lesions, most common in subcutaneous tissue. This results in a general fatigue even though there is no specific complaint or the person may experience pathology of the nervous
system, with accompanying sensory changes or even sensory losses. Although the cause of rheumatoid arthritis is unknown, autoimmunity plays a pivotal role in both its chronicity and progression, resulting in our own defenses aiding the activation of the disease. Therefore RA is considered a systemic autoimmune disease.\[^9\]

About 1\% of the world's population is afflicted by rheumatoid arthritis, women three times more often than men. The onset is more frequent between the ages of 40 and 50, but people of any age can be affected. RA can be a disabling and painful condition, which can lead to substantial loss of functioning and mobility if not adequately treated. The clinical diagnosis is made on the basis of symptoms, physical examination, radiographs (X-rays) and laboratory assays. The American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) publish diagnostic guidelines from time to time. Diagnosis and long-term management are typically performed by a rheumatologist, an expert in auto-immune diseases.\[^10\]

**Signs and symptoms**

The **signs and symptoms of RA include**

- Pain and stiffness lasting for more than 30 minutes in the morning or after a long rest.
- Tender, warm, swollen joints. Joint inflammation often affecting the wrist and finger joints closest to the hand; other affected joints can include those of the neck, shoulders, elbows, hips, knees, ankles, and feet. Rheumatoid nodules are sometimes present.
- Symmetrical pattern. For example, if one knee is affected, the other one is also.
- Fatigue, occasional fever, a general sense of not feeling well (malaise).
- Symptoms affecting other parts of the body besides the joints.\[^11\]

**Etiology**

The etiology of RA\[^3\] is not fully understood despite extensive study of metabolic and nutritional factors, the endocrine system, and geographic, psychological, and occupational data. It now appears that an unknown antigen initiates the autoimmune response resulting in RA. This response supports the suspicion of an infectious origin of the disease process, which includes various bacteria and viruses, but without evidence of precipitating events. Even without this specific knowledge, treatment modalities have been developed that, while not curing the disease, can provide relief from the symptoms of the disease.\[^12\]
Evidence points to a complex interplay between environmental and genetic factors. In monozygotic twins, there is a more than 30 percent concordance rate for rheumatoid arthritis development, and 80 percent of whites with rheumatoid arthritis express the HLA-DR1 or -DR4 subtypes. These and other regions of the Major Histocompatibility Complex may confer susceptibility to more severe disease by causing a specific arthrogenic peptide to be presented to CD4+ T cells. Scientists are now focusing on the idea that it is a T-cell-mediated autosomal disease precipitated by both genetic and environmental factors.

Pathophysiology

The joint capsule is lined with a type of tissue called synovium, which produces synovial fluid. The synovial fluid secreted by the synovium is thought to serve two main purposes, lubrication of the joint and provision of nutrients to the avascular articular cartilage. The attack on a joint by the disease usually begins with the synovium. Joint damage in rheumatoid arthritis begins with the proliferation of synovial macrophages and fibroblasts after a triggering incident, either autoimmune or infectious. White blood cells that are part of the normal immune system travel to the synovium and cause a reaction. This reaction, or inflammation, is called synovitis, and it results in warmth, redness, swelling, and pain that are typical symptoms of RA. Lymphocytes infiltrate the perivascular regions, endothelial cells proliferate and these result in neovascularization. Thus early in the disease, edema begins to be seen in cells in the synovium and multiplication of synovial lining cells occur. During the inflammation process, the cells of the synovium grow and divide abnormally, making the normally thin synovium thick and resulting in a joint that is swollen and puffy to the touch.

Blood vessels in the affected joint become occluded with small clots or inflammatory cells. As the disease progresses, inflamed synovial tissue begins to grow considerably and irregularly, forming invasive pannus tissue. The pannus is a sheet of inflammatory granulation tissue that spreads from the synovial membrane and invades the joint in rheumatoid arthritis and destroys cartilage and bone ultimately leading to fibrous ankylosis. Pannus can be considered the most destructive element affecting joints in the patient with rheumatoid arthritis. Pannus can attack articular cartilage and destroy it. Further, pannus can destroy the soft subchondral bone once the protective articular cartilage is gone. There is chronic inflammation with lymphocytes and plasma cells that produce the blue areas beneath the nodular proliferations.
Multiple cytokines, interleukins, proteinases, and growth factors are released, causing further joint destruction and the development of systemic complications.[2,14]

In this disease process, an interaction between antibodies and antigens occurs, and causes alterations in the composition of the synovial fluid. Ultimately, digestants are formed in the fluid that attacks the surrounding tissue. Once the composition of this fluid is altered, it is less able to perform the normal functions noted above, and more likely to become destructive.[18] The changes in the synovium and synovial fluid are responsible for a large amount of joint and soft tissue destruction. The destruction of bone eventually leads to laxity in tendons and ligaments. Under the strain of daily activities and other forces, these alterations in bone and joint structure result in the deformities frequently seen in patients with rheumatoid arthritis. Considerable destruction of the joint can occur with pannus invading the subchondral bone.[19]

Bone destruction occurs at areas where the hyaline cartilage and the synovial lining do not adequately cover the bone. If the disease progresses to a more advanced stage, the articular cartilage may lose its structure and density resulting in an inability to withstand the normal forces placed on the joint.[20] In such advanced cases, muscle activity causes the involved ends of the bones to be compressed together causing further bone destruction. Further, the disease can irreversibly change the structure and function of a joint to a degree that other degenerative changes may occur, especially in the weight bearing joints of the body. Thus, joint destruction can progress to the degree that joint motion is significantly limited and joints can become markedly unstable.

While rheumatoid arthritis (RA) primarily affects joints, problems involving other organs of the body are known to occur. Extra-articular (outside the joints) manifestations other than anemia (very common) are clinically evident in about 15–25% of individuals with rheumatoid arthritis.[21] It is difficult to determine whether disease manifestations are directly caused by the rheumatoid process itself, or from side effects of the medications commonly used to treat it for example, lung fibrosis from methotrexate or osteoporosis from corticosteroids.

**Joints:** The arthritis of joints known as synovitis is inflammation of the synovial membrane that lines joints and tendon sheaths. Joints become swollen, tender and warm, and stiffness
limits their movement. With time, RA nearly always affects multiple joints (polyarthritis), most commonly small joints of the hands, feet and cervical spine, but larger joints like the shoulder and knee can also be involved. Synovitis can lead to tethering of tissue with loss of movement and erosion of the joint surface causing deformity and loss of function.\textsuperscript{[22, 23]}

Rheumatoid arthritis typically manifests with signs of inflammation, with the affected joints being swollen, warm, painful and stiff, particularly early in the morning on waking or following prolonged inactivity. Increased stiffness early in the morning is often a prominent feature of the disease and typically lasts for more than an hour. Gentle movements may relieve symptoms in early stages of the disease. These signs help distinguish rheumatoid from non-inflammatory problems of the joints, often referred to as osteoarthritis or "wear-and-tear" arthritis. In arthritis of non-inflammatory causes, signs of inflammation and early morning stiffness are less prominent with stiffness typically less than 1 hour, and movements induce pain caused by mechanical arthritis.\textsuperscript{[24]} In RA, the joints are often affected in a fairly symmetrical fashion, although this is not specific, and the initial presentation may be asymmetrical.

As the pathology progresses, inflammatory activity leads to tendon tethering and erosion and destruction of the joint surface, which impairs range of movement and leads to deformity. The fingers may suffer from almost any deformity depending on which joints are most involved, namely ulnar deviation, boutonniere deformity, swan neck deformity and "Z-thumb," (not significant for diagnosis, since they occur in osteoarthritis as well).

\textbf{Skin}

The rheumatoid nodule, which is often subcutaneous, is the cutaneous feature most characteristic of rheumatoid arthritis. The initial pathologic process in nodule formation is unknown but may be essentially the same as the synovitis, since structural features in both are similar. The nodule has a central area of fibrinoid necrosis that may be fissured and which corresponds to the fibrin-rich necrotic material found in and around an affected synovial space. Surrounding the necrosis is a layer of palisading macrophages and fibroblasts, corresponding to the intimal layer in synovium and a cuff of connective tissue containing clusters of lymphocytes and plasma cells, corresponding to the subintimal zone in synovitis. The typical rheumatoid nodule may be a few millimetres to a few centimetres in diameter and is usually found over bony prominences, such as the olecranon, the calcaneal tuberosity, the metacarpophalangeal joint, or other areas that sustain repeated mechanical stress. Nodules are
associated with a positive RF (rheumatoid factor) titer and severe erosive arthritis. Rarely, these can occur in internal organs or at diverse sites on the body.

Several forms of vasculitis occur in rheumatoid arthritis. A benign form occurs as microinfarcts around the nailfolds. More severe forms include livedo reticularis, which is a network (reticulum) of erythematous to purplish discoloration of the skin caused by the presence of an oblitative cutaneous capillaropathy.

Other, rather rare, skin associated symptoms include: pyoderma gangrenosum, a necrotizing, ulcerative, noninfectious neutrophilic dermatosis; Sweet's syndrome, a neutrophilic dermatosis usually associated with myeloproliferative disorders; drug reactions; erythema nodosum; lobular panniculitis; atrophy of digital skin; palmar erythema; diffuse thinning (rice paper skin), and skin fragility (often worsened by corticosteroid use).

Lungs
Fibrosis of the lungs is a recognized response to rheumatoid disease. It is also a rare but well recognized consequence of therapy (with methotrexate and leflunomide). Caplan's syndrome describes lung nodules in individuals with rheumatoid arthritis and additional exposure to coal dust. Pleural effusions are also associated with rheumatoid arthritis. Another complication of RA is Rheumatoid Lung Disease. It is estimated that about one quarter of patients with RA develop Rheumatoid Lung Disease.[25]

Kidneys
Renal amyloidosis can occur as a consequence of chronic inflammation.[26] Rheumatoid arthritis may affect the kidney glomerulus directly through a vasculopathy or a mesangial infiltrate but this is less well documented. Treatment with Penicillamine and gold salts are recognized causes of membranous nephropathy.

Heart and blood vessels
People with rheumatoid arthritis are more prone to atherosclerosis, and risk of myocardial infarction (heart attack) and stroke is markedly increased.[27] Other possible complications that may arise include: pericarditis, endocarditis, left ventricular failure, valvulitis and fibrosis.[28] Many people with rheumatoid arthritis do not experience the same chest pain that others feel when they have angina or myocardial infarction. Cardiovascular risk can be reduced by maintaining optimal control of the inflammation caused by rheumatoid arthritis.
and to use exercise and medications appropriately to reduce other cardiovascular risk factors such as blood lipids and blood pressure.\(^{[29]}\)

**Psychological factors**

There is no evidence that physical and emotional effects or stress could be a trigger for the disease. The many negative findings suggest that either the trigger varies, or that it might in fact be a chance event inherent with the immune response.\(^{[30]}\)

**Continued abnormal immune response**

The factors that allow an abnormal immune response, once initiated, to become permanent and chronic, are becoming more clearly understood. The genetic association with HLA-DR4, as well as the newly discovered associations with the gene PTPN22 and with two additional genes\(^{[31]}\), all implicate altered thresholds in regulation of the adaptive immune response. It has also become clear from recent studies that these genetic factors may interact with the most clearly defined environmental risk factor for rheumatoid arthritis, namely cigarette smoking.\(^{[27, 32]}\) Other environmental factors also appear to modulate the risk of acquiring RA, and hormonal factors in the individual may explain some features of the disease, such as the higher occurrence in women, the not-infrequent onset after child-birth, and the (slight) modulation of disease risk by hormonal medications. Exactly how altered regulatory thresholds allow the triggering of a specific autoimmune response remains uncertain. However, one possibility is that negative feedback mechanisms that normally maintain tolerance of self are overtaken by aberrant positive feedback mechanisms for certain antigens such as IgG Fc (bound by RF) and citrullinated fibrinogen (bound by ACPA).

Once the abnormal immune response has become established (which may take several years before any symptoms occur), plasma cells derived from B lymphocytes produce rheumatoid factors and ACPA of the IgG and IgM classes in large quantities. These are not deposited in the way that they are in systemic lupus. Rather, they appear to activate macrophages through Fc receptor and perhaps complement binding. This can contribute to inflammation of the synovium, in terms of edema, vasodilation and infiltration by activated T-cells (mainly CD4 in nodular aggregates and CD8 in diffuse infiltrates). Synovial macrophages and dendritic cells further function as antigen presenting cells by expressing MHC class II molecules, leading to an established local immune reaction in the tissue. The disease progresses in concert with formation of granulation tissue at the edges of the synovial lining (pannus) with extensive angiogenesis and production of enzymes that cause tissue damage. Modern
pharmacological treatments of RA target these mediators. Once the inflammatory reaction is established, the synovium thickens, the cartilage and the underlying bone begin to disintegrate and evidence of joint destruction accrues.

The key pieces of evidence relating to pathogenesis are
1. A genetic link with HLA-DR4 and related allotypes of MHC Class II and the T cell-associated protein PTPN22.
2. A link with cigarette smoking that appears to be causal.[33]
3. A remarkable deceleration of disease progression in many cases by blockade of the cytokine TNFα (Tumor Necrosis Factor).
4. A similar dramatic response in many cases to depletion of B lymphocytes, but no comparable response to depletion of T lymphocytes.
5. A more or less random pattern of whether and when individuals predisposed are affected.
6. The presence of autoantibodies to IgGFc, known as rheumatoid factors (RF), and antibodies to citrullinated peptides (ACPA).

These data suggest that the disease involves abnormal B cell–T cell interaction, with presentation of antigens by B cells to T cells via HLA-DR eliciting T cell help and consequent production of RF and ACPA. Inflammation is then driven either by B cell or T cell products stimulating release of TNF and other cytokines. The process may be facilitated by an effect of smoking on citrullination but the stochastic (random) epidemiology suggests that the rate limiting step in genesis of disease in predisposed individuals may be an inherent stochastic process within the immune response such as immunoglobulin or T cell receptor gene recombination and mutation.[34, 35]

If TNF release is stimulated by B cell products in the form of RF or ACPA-containing immune complexes, through activation of immunoglobulin Fc receptors, then RA can be seen as a form of Type III hypersensitivity.[36, 37] If TNF release is stimulated by T cell products such as interleukin-17 it might be considered closer to type IV hypersensitivity although this terminology may be getting somewhat dated and unhelpful.[38] The debate on the relative roles of immune complexes and T cell products in inflammation in RA has continued for 30 years. There is little doubt that both B and T cells are essential to the disease. However, there is good evidence for neither cell being necessary at the site of inflammation. This tends to favour immune complexes (based on antibody synthesised elsewhere) as the initiators, even if not the sole perpetuators of inflammation. Moreover, work by Thurlings and others in Paul-
Peter Tak's group and also by Arthur Kavanagh's group suggest that if any immune cells are relevant locally they are the plasma cells, which derive from B cells and produce in bulk the antibodies selected at the B cell stage.\[39\]

Although TNF appears to be the dominant, other cytokines (chemical mediators) are likely to be involved in inflammation in RA. Blockade of TNF does not benefit all patients or all tissues (lung disease and nodules may get worse). Blockade of IL-1, IL-15 and IL-6 also have beneficial effects and IL-17 may be important. Constitutional symptoms such as fever, malaise, loss of appetite and weight loss are also caused by cytokines released in to the blood stream.

As with most autoimmune diseases, it is important to distinguish between the cause(s) that trigger the process, and those that may permit it to persist and progress.

**Possible infectious triggers**

It has long been suspected that certain infections could be triggers for this disease. The "mistaken identity" theory suggests that an infection triggers an immune response, leaving behind antibodies that should be specific to that organism. The antibodies are not sufficiently specific, though, and set off an immune attack against part of the host. Because the normal host molecule "looks like" a molecule on the offending organism that triggered the initial immune reaction. This phenomenon is called molecular mimicry. Some infectious organisms suspected of triggering rheumatoid arthritis include Mycoplasma\[40\], Erysipelothrix, parvovirus B19 and rubella, but these associations have never been supported in epidemiologic studies. Nor has convincing evidence been presented for other types of triggers such as food allergies.

Epidemiological studies have confirmed a potential association between RA and two herpesvirus infections: Epstein-Barr virus (EBV) and Human Herpes Virus 6 (HHV-6) \[41\]. Individuals with RA are more likely to exhibit an abnormal immune response to the Epstein-Barr virus.\[42, 43\] The allele HLA-DRB1*0404 is associated with low frequencies of T cells specific for the EBV glycoprotein 110 and predisposes one to develop RA.\[44\]

In a recent study we have shown that patients with rheumatoid arthritis (RA) that adopted a Cretan Mediterranean diet obtained a reduction in inflammatory activity, an increase in
physical function and in vitality, whereas no significant changes were seen in the control group, who followed their habitual diet.\cite{45}

For a long time the beneficial effects of the Mediterranean diet have primarily been attributed to its lipid profile. However, recently attention has been drawn to the antioxidants.\cite{46, 47, 48} Vegetables, fruit and olive oil have a central position in the Mediterranean diet and these food items contain a variety of compounds with an antioxidant capacity, such as vitamin C and E, carotenoids and polyphenols.\cite{46}

There is evidence indicating that a low antioxidant status is associated with a higher risk of developing RA.\cite{49} Furthermore, the rheumatoid inflammation is associated with an increased generation of oxidants (reactive oxygen and nitrogen species), which play an important role in the inflammatory process and contribute to tissue destruction.\cite{50} Antioxidant defenses limit the damages caused by oxidants, such as those formed during inflammation. In addition, in vitro-studies and animal studies have shown that antioxidants also possess anti-inflammatory properties.\cite{51, 52, 53, 54} This implies that antioxidative defence mechanisms are of particular importance for patients with RA and that the effects of antioxidative nutrients ought to be further investigated.

Most controlled studies investigating the therapeutic use of antioxidant supplementation have not shown any significant effects on RA symptoms.\cite{55} In contrast to these studies, in a placebo-controlled trial, vitamin E was reported to have a mild, but significant, analgesic effect.\cite{56} Since many of the antioxidant compounds interact in the body, supplementation with individual antioxidants may not be the best way to strengthen the antioxidant defence. In a small study, supplementation with a combination of antioxidants, in addition to standard treatment, gave better results regarding clinical indices of RA compared to standard treatment alone.\cite{57} This indicates that supplementation with a combination of antioxidants, or a diet providing a cocktail of different antioxidants, may be more effective than supplementation with single nutrients. Therefore, the beneficial effect of the Cretan Mediterranean diet, which we recently tested on patients with RA,\cite{58} could, at least in part, be attributable to the high content of antioxidants in this diet. Since this needs to be investigated further, the aims of the present study were to examine our patients with respect to their antioxidant intake, their plasma level of antioxidants, and by means of a marker of oxidative stress (malondialdehyde).
Risk factors

Female sex, a positive family history, older age, silicate exposure, and smoking are associated with an increased risk for developing rheumatoid arthritis.\cite{33, 59, 60} Consumption of more than three cups of coffee daily particularly decaffeinated coffee also may contribute to RA.\cite{61} High vitamin D intake, tea consumption\cite{62}, oral contraceptive use\cite{63} are associated with decreased risk.

The association between smoking and rheumatoid arthritis (RA) has been widely reported.\cite{33, 59, 60, 61, 62, 63, 64, 65, 66} The specific association between smoking and rheumatoid factor (RF)-positive RA is well known and meets the Bradford Hill criteria for causation\cite{67} namely strength, consistency, plausibility, experimental evidence, coherence, temporality, and biologic gradient of association.\cite{67, 68, 69}

The term 'interaction' refers to a conditional relationship between an independent variable and the dependent variable. An interaction exists when the relationship between an independent variable \(x\) and an outcome variable \(y\) varies according to the value of another covariate \(z\). The presence of a statistically significant interaction would suggest the presence of an underlying biologic effect modification and provide epidemiologic clues to the etiology and pathogenesis.\cite{70}

Among women, hormonal risk factors for RA include age at menarche, progestin use\cite{71} oral contraceptive use\cite{72}, termination of pregnancy, lactation\cite{73}, and short fertile period\cite{77}. Three in four women with rheumatoid arthritis experience significant improvement in symptoms when pregnant, usually with a recurrence after delivery.\cite{59} Systematic review\cite{66} of 24 studies did not support a link between breast implants and connective tissue disorders. Epidemiologic studies do not consistently show that smoking confers an increased risk among women. Indeed, even a protective effect of smoking on risk for developing RA has been described among women.\cite{75} The smoking–RA risk is more consistent across studies on men.\cite{76} Thus, the risk for RA conferred by smoking depends on the sex of the patient.

Diagnosis

Imaging

X-rays of the hands and feet are generally performed in people with polyarthritis.\cite{77} In rheumatoid arthritis, there may be no changes in the early stages of the disease, or the x-ray may demonstrate juxta-articular osteopenia, soft tissue swelling and loss of joint space. As
the disease advances, there may be bony erosions and subluxation. X-rays of other joints may be taken if symptoms of pain or swelling occur in those joints.

Other medical imaging techniques such as magnetic resonance imaging (MRI) and ultrasound are also used in rheumatoid arthritis.\cite{78,79,80}

There have been technical advances in ultrasonography.\cite{81} High-frequency transducers (10 MHz or higher) have improved the spatial resolution of ultrasound images; these images can depict 20% more erosions than conventional radiography. Also, color Doppler and power Doppler ultrasound, which show vascular signals of active synovitis depending on the degree of inflammation, are useful in assessing synovial inflammation. This is important, since in the early stages of rheumatoid arthritis, the synovium is primarily affected, and synovitis seems to be the best predictive marker of future joint damage.\cite{82,83}

**Blood tests**

When RA is clinically suspected, immunological studies are required, such as testing for the presence of rheumatoid factor (RF, a non-specific antibody).\cite{24} A negative RF does not rule out RA; rather, the arthritis is called seronegative. This is the case in about 15% of patients.\cite{84} During the first year of illness, rheumatoid factor is more likely to be negative with some individuals converting to seropositive status over time. RF is also seen in other illnesses, for example Sjögren's syndrome, Hepatitis C, chronic infections and in approximately 10% of the healthy population, therefore the test is not very specific.

Because of this low specificity, new serological tests have been developed, which test for the presence of the anti-citrullinated protein antibodies (ACPAs) or anti-CCP. Like RF, these tests are positive in only a proportion (67%) of all RA cases, but are rarely positive if RA is not present, giving it a specificity of around 95%.\cite{85} As with RF, there is evidence for ACPAs being present in many cases even before onset of clinical disease.

The most common tests for ACPAs are the anti-CCP (cyclic citrullinated peptide) test and the Anti-MCV assay (antibodies against mutated citrullinated Vimentin). A serological point-of-care test (POCT) for the early detection of RA is an assay that combines the detection of rheumatoid factor and anti-MCV for diagnosis of rheumatoid arthritis and shows a sensitivity of 72% and specificity of 99.7%. \cite{86,87}
Several other blood tests are usually done to allow for other causes of arthritis, such as lupus erythematosus. The erythrocyte sedimentation rate (ESR), C-reactive protein, full blood count, renal function, liver enzymes and other immunological tests (antinuclear antibody/ANA) are all performed at this stage. Elevated ferritin levels can reveal hemochromatosis, a mimic RA, or be a sign of Still's disease, a seronegative, usually juvenile, variant of rheumatoid.

**Criteria**

In 2010 the 2010 ACR / EULAR Rheumatoid Arthritis Classification Criteria were introduced. These new classification criteria overruled the "old" ACR criteria of 1987 and are adapted for early RA diagnosis. The "new" classification criteria, jointly published by the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) establish a point value between 0 and 10. Every patient with a point total of 6 or higher is unequivocally classified as an RA patient, provided he has synovitis in at least one joint and given that there is no other better diagnosis explaining the synovitis. Four areas are covered in the diagnosis:

- **Joint involvement** – depending on the type and number of joints: up to 5 points
- **Serological parameters** – including the rheumatoid factors as well as ACPA – "ACPA" stands for "anti-citrullinated protein antibody": up to 3 points depending on titre level
- **Acute phase reactants**: 1 point for elevated erythrocyte sedimentation rate, ESR, or elevated CRP value (c-reactive protein)
- **Duration of arthritis**: 1 point for symptoms lasting six weeks or longer

The new criteria accommodate to the growing understanding of rheumatoid arthritis and the improvements in diagnosing RA and disease treatment. In the "new" criteria serology and autoimmune diagnostics carries major weight, as ACPA detection is appropriate to diagnose the disease in an early state, before destruction of joints occur. Destruction of the joints viewed in radiological images was a significant point of the ACR criteria from 1987. This criterion no longer is regarded to be relevant, as this is just the type of damage that treatment is meant to avoid.

The criteria are not intended for the diagnosis for routine clinical care; they were primarily intended to categorize research (classification criteria). In clinical practice, the following criteria apply: two or more swollen joints; morning stiffness lasting more than one hour for at
least six weeks; the detection of rheumatoid factors or autoantibodies against ACPA such as autoantibodies to mutated citrullinated vimentin can confirm the suspicion of rheumatoid arthritis.\[93\] A negative autoantibody result does not exclude a diagnosis of RA.

**Differential diagnoses:** Several other medical conditions can resemble RA, and usually need to be distinguished from it at the time of diagnosis: Crystal induced arthritis (gout, and pseudogout) – usually involve particular joints and can be distinguished with aspiration of joint fluid if in doubt.\[94, 95, 96, 97, 98\] Osteoarthritis – distinguished with X-rays of the affected joints and blood tests; Systemic lupus erythematosus (SLE) – distinguished by specific clinical symptoms and blood tests (antibodies against double-stranded DNA); one of the several types of psoriatic arthritis resembles RA – nail changes and skin symptoms distinguish between them; Lyme disease causes erosive arthritis and may closely resemble RA – it may be distinguished by blood test in endemic areas; Reactive arthritis (previously Reiter's disease) – asymmetrically involves heel, sacroiliac joints, and large joints of the leg. It is usually associated with urethritis, conjunctivitis, iritis, painless buccal ulcers, and keratoderma blennorrhagica; Ankylosing spondylitis – this involves the spine and is usually diagnosed in males, although a RA-like symmetrical small-joint polyarthritis may occur in the context of this condition; Hepatitis C – RA-like symmetrical small-joint polyarthritis may occur in the context of this condition. Hepatitis C may also induce Rheumatoid Factor autoantibodies.

**Rarer causes that usually behave differently but may cause joint pains:** Sarcoidosis, amyloidosis, and Whipple's disease can also resemble RA; Hemochromatosis may cause hand joint arthritis; acute rheumatic fever can be differentiated from RA by a migratory pattern of joint involvement and evidence of antecedent streptococcal infection; Bacterial arthritis (such as streptococcus) is usually asymmetric, while RA usually involves both sides of the body symmetrically; Gonococcal arthritis (another bacterial arthritis) is also initially migratory and can involve tendons around the wrists and ankles.\[99\]

**Treatment:** Historic treatments for RA have also included: rest, ice, compression and elevation, acupuncture, apple diet, nutmeg, some light exercise every now and then, nettles, bee venom, copper bracelets, rhubarb diet, extractions of teeth, fasting, honey, vitamins, insulin, magnets, and electroconvulsive therapy (ECT).\[100\] Most of these have either had no effect at all, or their effects have been modest and transient, while not being generalizable.\[22\]
There is no known cure for rheumatoid arthritis, but many different types of treatment can alleviate symptoms and/or modify the disease process. Recommendations of the American College of Rheumatology (ACR), published in 2008, follow a trend in supporting earlier, more aggressive treatment of RA, and reflect heightened expectations of treatment effectiveness, including remission or substantial alleviation of symptoms for a rising percentage of patients.\textsuperscript{[101]}

**Pharmacotherapy**

Pharmacological treatment of RA can be divided into 3 which are required to halt the underlying immune process & present long term damage and which have increased treatment options.\textsuperscript{[102]}

1. **Analgesics** - pain killers.\textsuperscript{[103, 104]} Analgesics include - paracetamol (acetaminophen in US and Canada): opiates; diproqualone; lidocaine topical.

2. **Anti-inflammatory agents:**
   (a) steroids to suppress the symptoms – glucocorticoids. Cortisone therapy became a controversial medical solution because even though it can provide great relief, there are some questions as to the usefulness of the procedure over a long period of time \textsuperscript{[105].}
   (b) Non-steroidal anti-inflammatory drug (NSAIDs, most also act as analgesics). Pharmacotherapy for rheumatoid arthritis generally involves a nonsteroidal anti-inflammatory drug (NSAID) for control of pain.\textsuperscript{[22]} NSAIDs used in the treatment of RA include ibuprofen, naproxen, meloxicam, etodolac, nabumetone, sulindac, tolementin, choline magnesium salicylate, diclofenac, diflusinal, indomethicin, ketoprofen, oxaprozin, and piroxicam.

3. **Disease-modifying antirheumatic drugs** (DMARDs): Pharmacotherapy for rheumatoid arthritis generally involves a NSAID and initiation of a DMARD.\textsuperscript{[106]}

In past decades, pharmacologic treatment of rheumatoid arthritis was managed using a pyramid approach: symptom-alleviating treatment was started at diagnosis, and only with progression of symptoms were dosages changed or additional medications added. However, a “reverse pyramid” approach now is favored, in which DMARDs are initiated quickly to slow disease progression as early as possible.\textsuperscript{[107]} This change of approach is a result of several research findings: (1) joint damage begins early in the disease;\textsuperscript{[108]} (2) DMARDs have significant benefits when used early; (3) the benefits of DMARDs may be enhanced when the
drugs are used in combination\[^{109, 110, 111, 112, 113}\] a number of new DMARDs are available, with good evidence of beneficial effect.\[^{114}\]

The term DMARD, originally meant a drug that affects biological measures such as ESR and haemoglobin and autoantibody levels, but is now usually used to mean a drug that reduces the rate of damage to bone and cartilage.\[^{106}\] DMARDs have been found both to produce durable symptomatic remissions and to delay or halt progression. This is important as such damage is usually irreversible. Anti-inflammatories and analgesics improve pain and stiffness but do not prevent joint damage or slow the disease progression.

There is an increasing recognition among rheumatologists that permanent damage to the joints occurs at a very early stage in the disease. In the past it was common to start with just an anti-inflammatory drug, and assess progression clinically and using X-rays. If there was evidence that joint damage was starting to occur then a more potent DMARD would be prescribed. Ultrasound and MRI are more sensitive methods of imaging the joints and have demonstrated that joint damage occurs much earlier and in more sufferers than was previously thought. People with normal X-rays will often have erosions detectable by ultrasound that X-ray could not demonstrate. The aim now is to treat before damage occurs.

There may be other reasons why starting DMARDs early is beneficial as well as prevention of structural joint damage. From the earliest stages of the disease, the joints are infiltrated by cells of the immune system that signal to one another in ways that may involve a variety of positive feedback loops (it has long been observed that a single corticosteroid injection may abort synovitis in a particular joint for long periods). Interrupting this process as early as possible with an effective DMARD (such as methotrexate) appears to improve the outcome from the RA for years afterwards. Delaying therapy for as little as a few months after the onset of symptoms can result in worse outcomes in the long term. There is therefore considerable interest in establishing the most effective therapy with early arthritis, when they are most responsive to therapy and have the most to gain.\[^{115}\]

Disease-modifying anti-rheumatic drugs have been used in the treatment of rheumatic arthritis for a long time now. Over 90% of rheumatologists now use combination therapy of multiple disease modifying drugs for rheumatoid arthritis as it has become apparent that using combination of these drugs does not increase their relative toxicity profiles.\[^{116}\] Common combinations of DMARDs include methotrexate – hydroxychloroquine,
methotrexate – sulfasalazine, sulfasalazine – hydroxychloroquine, and methotrexate – hydroxychloroquine – sulfasalazine.\textsuperscript{117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127}

In order to be effective, disease-modifying anti-rheumatic drugs must be administered before the deformities appear or the erosive disease occurs. Usually, rheumatologists do not wait for the fulfillment of the criteria for classification of RA as published by the American College of Rheumatology (ACR) and start treatment with this type of drugs if the pain and synovitis persist and the function is compromised.\textsuperscript{46}

**Chemically synthesised DMARDs include**

**\textbf{(a) traditional small molecular mass drugs namely:** azathioprine, ciclosporin (cyclosporine A), D-penicillamine, gold salts, hydroxychloroquine, leflunomide, methotrexate (MTX)\textsuperscript{128} aminocycline, sulfasalazine (SSZ), Cytotoxic drugs, Cyclophosphamide.

The most important and most common adverse events relate to liver and bone marrow toxicity (MTX, SSZ, leflunomide, azathioprine, gold compounds, D-penicillamine), renal toxicity (cyclosporine A, parenteral gold salts, D-penicillamine), pneumonitis (MTX), allergic skin reactions (gold compounds, SSZ), autoimmunity (D-penicillamine, SSZ, minocycline) and infections (azathioprine, cyclosporine A).

**\textbf{(b) Biological agents (biologics) namely:** tumor necrosis factor alpha (TNF\(\alpha\)) blockers\textsuperscript{109, 114, 129} – etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi); Interleukin 1 (IL-1) blockers – anakinra (Kineret); monoclonal antibodies against B cells – rituximab (Rituxan);\textsuperscript{130} T cell costimulation blocker – abatacept (Orencia); Interleukin 6 (IL-6) blockers – tocilizumab (an anti-IL-6 receptor antibody) (RoActemra, Actemra)

In patients with rheumatoid arthritis, the risk of infection is increased. Therefore, prior to introduction of TNF\(\alpha\) antagonists, a retrospective study showed a twofold increase in the risk of serious infections among RA patients compared with non-RA patients.\textsuperscript{131} Factors that increase the risk of infections in RA include disease-related immune dysfunction (involving T cells such as T-helper type 1 cells and, as described more recently, T-helper type 17 cells)\textsuperscript{132} and immunosuppressive effects of drugs used to treat the disease, such as long-term glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), and TNF\(\alpha\)
antagonists.\textsuperscript{[133, 134]} Other factors including immobility, skin breaks, joint surgery, leukopenia, diabetes mellitus, and chronic lung disease, may be involved.

The infections encountered in RA patients affect a variety of sites (upper and lower respiratory tracts, lungs, joints, bone, skin, soft tissues, and so forth)\textsuperscript{[135]} and can be caused by bacteria, viruses, fungi, or mycobacteria. RA patients may experience reactivation of latent infection such as tuberculosis, which is the most commonly reported granulomatous infection in patients treated with TNF\textsubscript{\alpha} antagonists.\textsuperscript{[136]} Preventive strategies have been developed to identify patients at risk for latent tuberculosis.\textsuperscript{[137, 138, 139]} Other infections occurring during TNF\textsubscript{\alpha} antagonist therapy include legionellosis, listeriosis, pneumocystosis, histoplasmosis, and aspergillosis.\textsuperscript{[140, 138]} A recent warning issued by the Food and Drugs Administration and supported by the American College of Rheumatology Drug Safety Committee draws attention to histoplasmosis and other invasive fungal infections, including fatal cases, reported in RA patients taking TNF\textsubscript{\alpha} antagonists.\textsuperscript{[141]}

**Adjuvant therapies**

A number of additional, nonpharmacologic treatments for rheumatoid arthritis have been tried. Therapeutic fasting, dietary supplementation of essential fatty acids, and journaling have shown benefit,\textsuperscript{[142]} as have spa therapies\textsuperscript{[143]} and exercise.\textsuperscript{[144]} Patient education\textsuperscript{[145]} and a multi-disciplinary approach to patient care\textsuperscript{[143]} provide at least short-term benefits. Evidence is inconclusive regarding herbal medications,\textsuperscript{[146]} acupuncture\textsuperscript{[147]} and splinting.\textsuperscript{[148, 149]}

**Surgery**

Surgery is to be considered when pain is unacceptable, loss of motion is significant, or functional impairment is severe.\textsuperscript{[148]} In early phases of the disease, an arthroscopic or open synovectomy may be performed. It consists of the removal of the inflamed synovia and prevents a quick destruction of the affected joints. In older patients, the yttrium synovectomy may be performed. It is successful in approximately half of patients. The surgery is mostly done on knee, elbow, shoulder, ankle or tarsal joints. It has to be performed before the destruction of the cartilage.\textsuperscript{[150]} Severely affected joints may require joint replacement surgery, such as knee replacement.

**Ayurveda**

A traditional form of Indian Medicine, is another source of treatment, and while it is popular in India there are no studies to show that it benefits patients with RA.\textsuperscript{[151]}
Physiotherapy
It is always necessary, postoperatively. Special tools to improve hand movements (e.g., special tin-openers) have also been put to use.

Immunoadsorption therapy
The ProSORBA column blood filtering device (removing IgG) was approved by the FDA in 1999\textsuperscript{152} for treatment of RA, however it was discontinued at the end of 2006.

Other therapies
Other therapies include regular exercise, weight loss, orthoses, occupational therapy, podiatry, and joint injections.

Regular exercise is important for maintaining joint mobility and making the joint muscles stronger. A Cochrane Review of studies determined that exercise programs designed to improve strength and stamina were safe and led to moderate benefits for RA sufferers.\textsuperscript{153} According to one study, the effectiveness of treating RA with acupuncture is inconclusive, and "more rigorous research seems to be warranted".\textsuperscript{154}

One study of 873 patients with RA found that those who drank some alcohol (not more than 10 units of alcohol a week) had reduced severity of symptoms compared to those who drank no alcohol\textsuperscript{155}. However, a spokeswoman for the Arthritis Research UK (who co-funded the study) warned that some RA treatments, like methotrexate, could damage the liver when taken with large amounts of alcohol.\textsuperscript{156}

DURATION OF TREATMENT
Rheumatoid arthritis tends to be a lifelong illness. Combinations of methotrexate and the new biologic agents can lead to remission in 30 to 40 percent of patients with rheumatoid arthritis, but for most patients, significant disease persists despite treatment.\textsuperscript{157, 158} Complete remission rarely occurs. In clinical trials, improvement has been tracked using the ACR improvement criteria, most often ACR 20, ACR 50, or ACR 70. The numbers represent the percentage of improvement in the following criteria: number of tender joints, number of swollen joints, global disease activity (as assessed by the patient or by an observer), pain level, physical disability score, and acute phase response (as measured by CRP or ESR).\textsuperscript{159} For the individual patient, health assessment questionnaires may be a more useful means of evaluating disease progression, such as European League against Rheumatism response
criteria for rheumatoid arthritis and various daily activity score surveys. Radiologic assessment scales are also useful. Treatment should be guided by individual clinical response to various interventions. Although changes in hemoglobin, ESR, and CRP may serve as helpful indicators of response to treatment, platelet count and rheumatoid factor levels have been found not to correlate well.

In most cases of RA, the patient has remissions and exacerbations of the symptoms. This means that there are periods of time when the patient "feels good" and times when the patient "feels worse". There are likely times that a patient with RA "feels cured". It is important to understand that there are very few patients that have complete remission of the disease and it is essential that the RA patient does not stop the treatment program established by knowledgeable health care practitioners. Rarely does the disease "go away", although at times the symptoms might temporarily remit.

CONCLUSION
Scientists are making rapid progress towards understanding the complexities of rheumatoid arthritis: how and why - it develops, some people get it and others do not, some people get it more severely than others? Results from research are having an impact today, enabling people with rheumatoid arthritis to remain active in life, family, and work far longer than was possible 20 years ago. In the future hope lies in the fact as researchers begin to apply new technologies such as stem cell transplantation and novel imaging techniques. These and other advances will lead to an improved quality of life for people with rheumatoid arthritis and also provide for a holistic approach and cure for the same.

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