

A REVIEW ON RHEUMATOID ARTHRITIS: ITS DIAGNOSIS AND MANAGEMENT**Chaitanya Varma Bellamkonda*¹, Varada Chaitanya Vinnakota², Dr. Keerthana Tummuri³ and Dr. Pravilika⁴**¹Sr. Clinical Data Manager, IQVIA, New Jersey, U.S.A.²Director Sclin Soft Technologies Private Limited, Telangana, India.³Project Manager Sclin Soft Technologies Private Limited, Telangana, India.⁴Medical Writer, Sclin Soft Technologies Private Limited, Telangana, India.***Corresponding Author: Chaitanya Varma Bellamkonda**

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ABSTRACT

Blood and its constituent cells, such as platelets, white blood cells, and red blood cells, are essential to life. Identification of blood cells and a few other criteria is necessary for illness diagnosis. The advancement of technology has made it possible to diagnose and confirm diseases with high quality images. A chronic, debilitating autoimmune condition called rheumatoid arthritis can impair our immune system. It is a typical inflammatory joint disease that affects the body's joints, tendons, and bones and is characterised by articular damage. The hand, wrist, and knee joints are most frequently afflicted. Most people with rheumatoid arthritis are between the ages of 20 and 60, and their condition has an unpredictable course. Approximately 1% of people worldwide have rheumatoid arthritis. Additionally, women are two to three times more likely than men to have rheumatoid arthritis. The use of medicinal herbs is advised because of the negative consequences of allopathic medications. Traditional medicine is used by one-fourth of the global population. Herbal medicine has no adverse effects. In 1996, the first guidelines for managing rheumatoid arthritis and monitoring medication therapy were created. Since then, there has been a significant improvement in rheumatoid arthritis treatments. This review's main goal is to highlight the most significant recent developments in our knowledge of rheumatoid arthritis.

KEYWORDS: Rheumatoid arthritis, autoimmune disease, Herbal medicine, Joints, Diagnosis, Treatment, Management.

INTRODUCTION

Everyone has some degree of autoimmune disease. It is frequently not harmful and a universal truth of vertebrate existence. However, a wide range of human illnesses that are classified as autoimmune may have autoimmunity as their underlying cause. In industrialised countries, 5% of the population is affected by autoimmune illness. Out of them, 80% are now designated "auto-aggressive" disorders. Rheumatoid arthritis is one of the illnesses that affects them. In the early years of the 5th century BC, rheumatic sickness was recognised under the umbrella term of arthritis. Hippocrates, "the founder of modern medicine," is renowned as the disease in western nations. The illness was first identified in India in ancient times and was referred to as "vata vyadhi" in Ayurveda. The term "rheumatic arthritis" was proposed by scientist Garrod in 1859.^[1,2]

An autoimmune, inflammatory, chronic condition known as rheumatoid arthritis can cause a number of problems. The condition affects the body's tendons, bones, and joints. Wrists, knees, and hands are the joints most commonly affected. Swelling, discomfort, and the

deterioration of bone and cartilage are all side effects of rheumatoid arthritis. The World Health Organization estimates that 0.3–1% of people worldwide have rheumatoid arthritis. Rheumatoid arthritis affects women three times more frequently than it does men, and it is more common in women. Within two to three years following a diagnosis, 20 to 30 percent of patients with rheumatoid arthritis are permanently unable to work. Figure 1 shows a joint that is healthy and one that is impacted by rheumatoid arthritis.^[3,4]

The condition can be diagnosed using some laboratory testing and imaging investigations. Anti-rheumatic medications are advised for the treatment of rheumatoid arthritis. The disorders can also be treated with certain altering medications. For treatment, medications such as non-steroidal anti-inflammatory medicines, corticosteroids, and non-pharmacologic techniques are employed. Many human disorders are treated using medicinal plants due to the negative consequences of allopathic medications. Rheumatoid arthritis is treated with herbal medications such Harpagophytum procumbens, Bauhinia variegata, Leucas aspera, Phyllanthus amarus, and Acalypha indica. This review's

objective is to highlight the most significant recent developments in our knowledge of rheumatoid arthritis.^[5]

EPIDEMIOLOGY

The prevalence of rheumatoid arthritis ranges from 0.3% to 1% worldwide (Figure 1). In women, rheumatoid arthritis is more prevalent. Three times as many women as men are impacted. Oral contraceptives have been shown to lessen the severity and activity of rheumatoid arthritis. Due to the fact that these drugs are also used for contraception, they can provide protection for women with rheumatoid arthritis.^[6] One of the most prevalent chronic illnesses is arthritis. And it results in impairments. 53 million US individuals suffered from arthritis in 2020. Using a demographic survey conducted by the World Health Organization-International League of Associations for Rheumatology (WHO-ILAR) Community Oriented Program for the Control of Rheumatic Diseases, Chopra et al. conducted a study on the hamlet of Bhigwan (Pune District, Maharashtra) in 1996. (COPCORD).^[7] Smokers are more likely to get rheumatoid arthritis than non-smokers. It is three times more common in smokers than in non-smokers, especially in men, heavy smokers, and people with a positive rheumatoid factor. According to a 2010 study, people who frequently drank a small amount of alcohol were 4 times considerably less likely to develop rheumatoid arthritis than those who never drank.^[8]

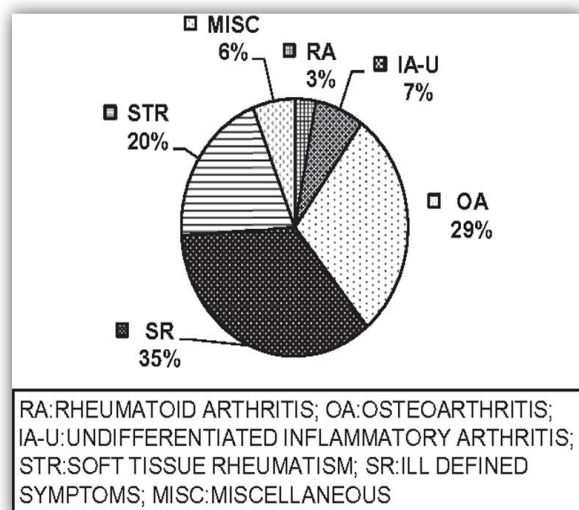


Figure 1: Prevalence of Rheumatoid Arthritis in India.

JOINTS

A wide range of morphological changes are brought on by RA. The joints show signs of the more severe. The synovium initially develops severely edematous, swollen, and hyperplastic, changing from a smooth shape to one with delicate, bulbous fronds. Infiltration of the synovial stroma by dense perivascular inflammatory cells, including B-cells, CD4+ T cells, plasma cells, and macrophages, is a distinctive histologic finding.

- Vasodilation and angiogenesis with surface hemosiderin deposit increase vascularity.
- A collection of arranged fibrin floating in the joint space and covering a part of the synovium.
- A buildup of neutrophils in the synovial fluid but not in the stroma of the synovium.
- Osteoclastic activity in the underlying bone, which allows the synovium to enter the bone and cause pannus, osteoporosis, and juxtra articular erosions. Which causes the degradation of the articular cartilage.

ETIOLOGY

The degeneration of cartilage is known as arthritis. The cartilage protects the joints, allowing for easy joint movement. In disease pathology, the articular cartilage is destroyed, and the joints become alkaline. Rheumatoid arthritis is a systemic autoimmune illness because it has an unknown origin yet autoimmunity plays a significant role in its chronicity and progression. Although the exact aetiology of rheumatoid arthritis is unknown, a combination of hereditary and environmental factors may play a role. About 50% to 60% of susceptibilities, severity, and the phenotype of the disease can be predicted using the genetic factor. Ageing, acquired genomic diversity, potential bacterial or viral triggers, and environmental variables are among non-genetic contributors. Smoking contributes significantly to the onset of rheumatoid arthritis. Another factor contributing to the onset of rheumatoid arthritis is ageing.^[9]

PATHOPHYSIOLOGY

An uncontrolled immune response that results in a revolutionary synovial infection and joint damage believed to be the root cause of rheumatoid arthritis. Numerous genetic and environmental factors that contribute to the phenotypic in particular combinations are linked to rheumatoid arthritis. Rheumatoid arthritis advances through the immune system, which is fueled by cytokines and affected by metalloproteinase. Through cell surface signalling, antigen-activated CD4+ T lymphocytes induce the production of cytokines, such as interleukin-1, interleukin-6, and TNF alpha, as well as the secretion of matrix metalloproteinase from monocytes, macrophages, and synovial fibroblast. In the early stages of rheumatoid arthritis, synovial fluid contains a large number of neutrophils. Immune complexes, which are IgG/anti IgG antigen-antibody complexes, are present in synovial fluid. IgG and IgA rheumatoid factors are the main pathogenic producers. In rheumatoid arthritis, osteoclast and proteolytic enzymes lead to bone erosion and cartilage breakdown. After triggering events such autoimmune or infectious lymphocyte infiltrates, perivascular areas and endothelial cells multiply, and then neovascularization occurs, joint damage in rheumatoid arthritis begins with the proliferation of synovial macrophages and fibroblast. Over time, tiny clots or inflammatory cells occlude blood arteries in the afflicted joint, and diseased synovial tissue begins to develop irregularly. This invasive pannus tissue

then invades and destroys bone and cartilage.^[10-12]

ENVIRONMENTAL FACTORS

The two main determinants of the autoimmune disease rheumatoid arthritis are genetics and environment. The rare historical accounts of rheumatoid arthritis prior to industrialization imply that evolving environmental factors might contribute to the condition's emergence. A detailed investigation of environmental factors is essential in rheumatoid arthritis. Environmental factors include things like cigarette smoking, workplace and air pollution, and a variety of infectious diseases. The DBRI'S common epitope has been connected to the risk factor for rheumatoid arthritis, which is long-term smoking. Epstein-Bar virus (EBV), mycobacterium tuberculosis, Escherichia coli, proteus mirabilis, retrovirus, and paravirus B19 are among the infectious etiologies.^[13]

Early research suggests a probable link between occupational and environmental agent's exposure and the onset of rheumatoid arthritis. In the Swedish era, Illar found that men who worked as electronic technicians, bricklayers, concentrate workers, and materials handlers

had a higher risk of getting rheumatoid arthritis than women who did assistance nursing and attendant labour.^[14]

TAXONOMY-(Figure-2)

Rheumatoid arthritis can be classified as:

- 1) Palindromic rheumatoid arthritis
- 2) Juvenile rheumatoid arthritis
- 3) Rheumatoid spondylitis
- 4) Ankylosing spondylarthritis
- 5) Osteoarthritis
- 6) Gout and gout arthritis
- 7) Infectious arthritis
- 8) Other types of arthritis

Osteoarthritis – It is classified into two types

- A Primary osteoarthritis – It develops in older persons.
- B. Secondary osteoarthritis – It develop at any stage.

Infectious arthritis – It is classified in four types

- A Supportive arthritis
- B. Tuberculous arthritis
- C. Lymph arthritis
- D. Viral arthritis

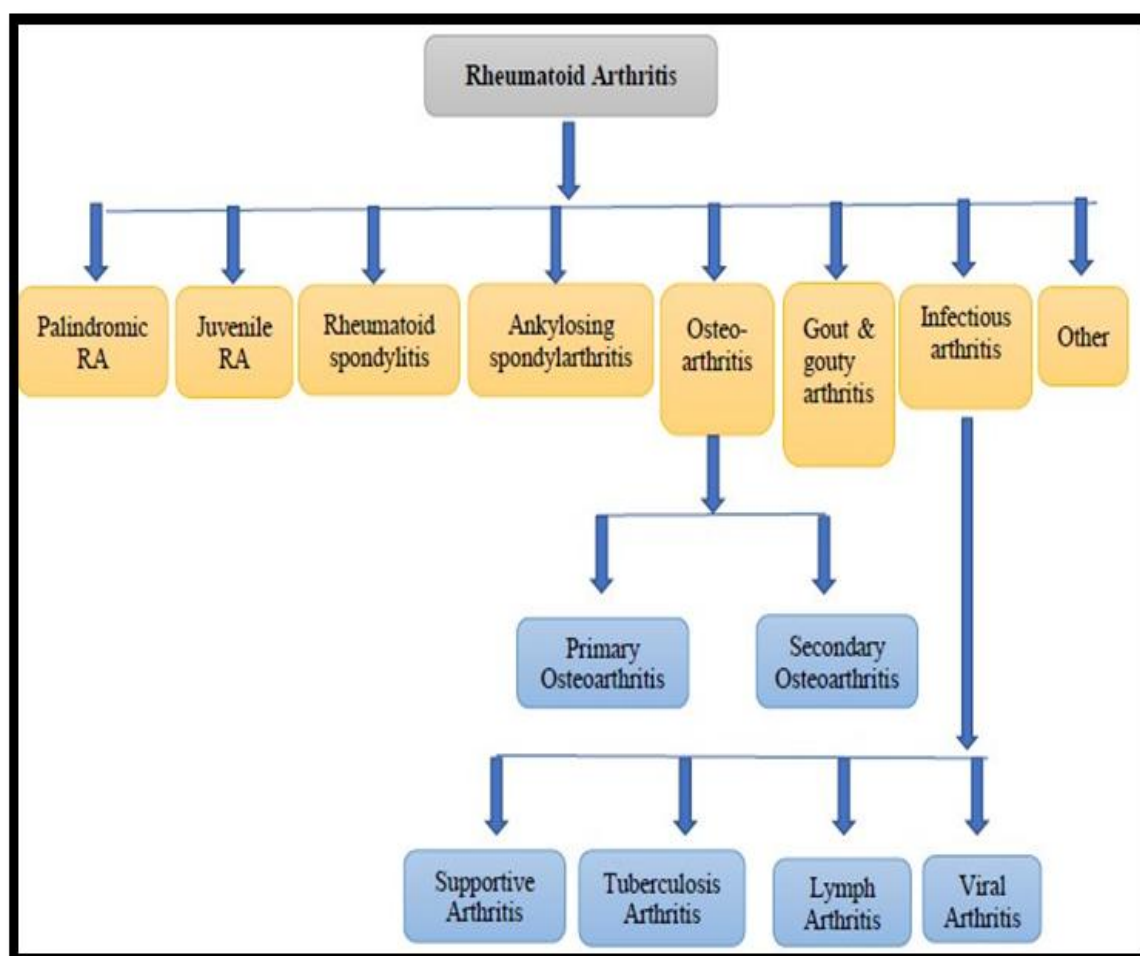


Figure 2: Taxonomy of Rheumatoid Arthritis.

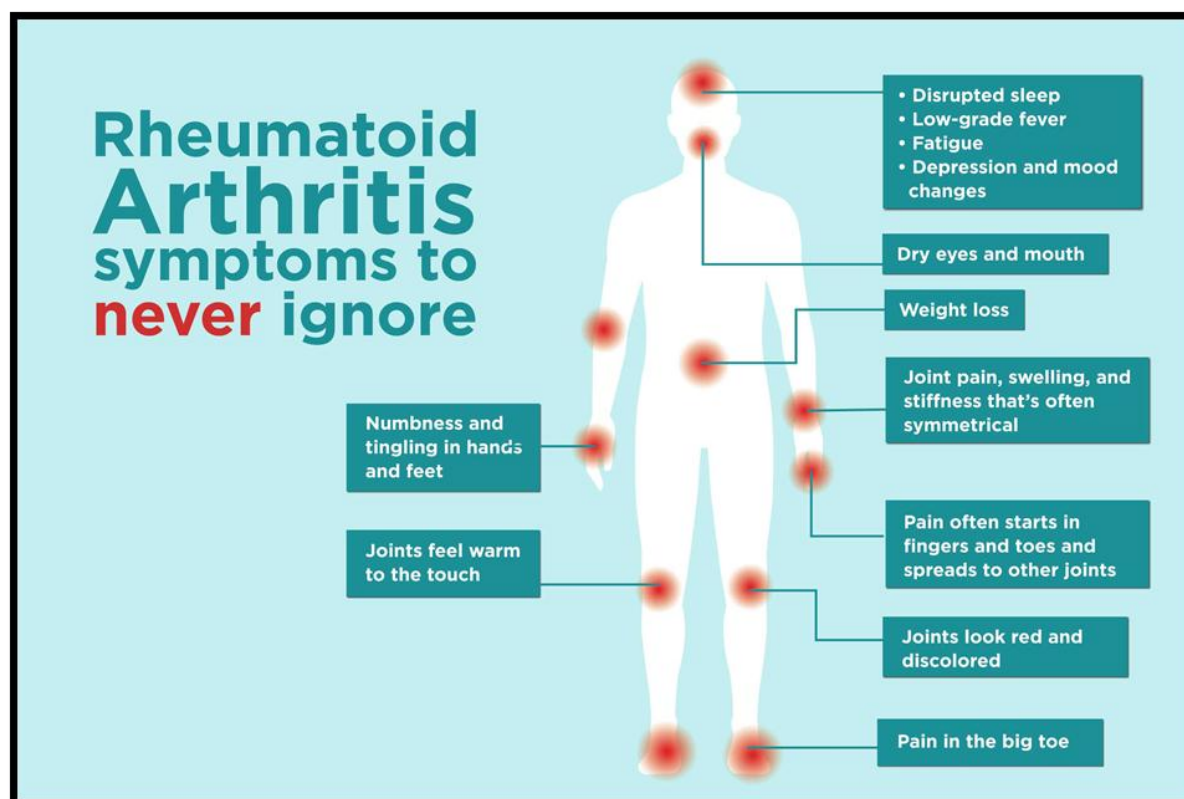


Figure 3: Sign and Symptoms of Rheumatoid Arthritis.

Signs and symptoms

The stiffness and discomfort at the joints are the primary signs and symptoms of rheumatoid arthritis. The onset of symptoms is slow. The first and most prevalent symptom of our RA is seen in the fingers and toes and other minor joints. It then has an impact on the shoulders and knee. Rheumatoid arthritis symptoms are shown in Figure 3.^[15] The main symptoms are as follows.

1. Morning stiffness: The area around the affected joints feels stiff. After some joint initiative, this symptom lasts for 45 to 60 minutes.
2. Fatigue: The majority of people experience this symptom. One of them is experiencing excessive fatigue because our body begins to use all of its energy fighting the inflammation.
3. Weight loss: This is one of the initial signs of unexplained weight loss. Fever and fatigue decrease appetite, which ultimately results in weight loss.
4. Arthritis at the joint: Swelling or fluid-filled soft tissue is seen. This usually happens at the proximal interphalangeal (PIP), metacarpophalangeal (MCP), and metatarsophalangeal (MTP) joints, but it can also happen at the wrist, elbow, knee, and ankle.
5. Puffed hands: Some RA patients experience puffy or swollen hands, which is a symptom of increased blood flow to the area that is inflamed.
6. Warmth: RA joints are warm, squishy, and painful to the touch. The temperature of the area rises as a result of the increased blood flow at the affected joints.

DIAGNOSIS AND MANAGEMENT OF RA

One of the key steps in identifying any disorders is diagnosis. It is possible to make an assumption without being able to substantiate it by looking at the symptoms people exhibit. Therefore, a diagnostic or check-up are required to confirm the presence of any condition. It might be challenging to diagnose RA by examining its symptoms because, in its early stages, these symptoms can resemble those of many other illnesses. Therefore, blood tests become the primary diagnostic tool that provide correct condition information and aid in the confirmation of disorders.

Blood Analysis:

Blood tests are used to determine whether an inflammatory condition is present in the body by measuring high erythrocyte sedimentation rate (ESR or SED) or C-reactive protein (CRP). Other blood tests include those for rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies. Hemoglobin levels, changes in WBC and platelet counts are also taken into consideration when RA is diagnosed.

Imaging Analysis

X-rays are taken to monitor the development of RA in joints over time. In addition to X-rays, other procedures including magnetic resonance imaging (MRI) and ultrasounds are performed to determine the severity of the disease.^[16]

THERAPEUTIC PRESENTATION

A polyarticular symmetric illness, RA affects several joints on both sides of the body. Pain and swelling in the hands and feet are typical symptoms of RA in patients. The wrists, metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal joints are where the swelling is most prominent. Joint stiffness in the morning that lasts more than 30 minutes, typically up to several hours, is present along with this. Synovitis and effusion usually cause the swelling to be "soft," as opposed to the "hard" (bony) swellings of osteoarthritis. When the fingers are affected, the swelling (fusiform) is localised to the joint rather than covering the entire digit (a "sausage digit"), as is the case with psoriatic arthritis. Although the distal inter phalangeal joints are infrequently impacted, both small and big joints may be afflicted. Metacarpophalangeal, metatarsophalangeal, proximal interphalangeal, and wrist joints are examples of small joints.

The ankle, knee, elbow, and shoulder joints are examples of large joints. Extra-articular symptoms of RA may develop if it is not well treated. Rheumatoid nodules are the most prevalent (firm subcutaneous lumps near bony prominences such as the elbow). Rheumatoid vasculitis, a necrotizing inflammation of small or medium-sized arteries that primarily affects the skin and vasa nervorum and occasionally arteries in other organs, is a more significant symptom. Many comorbidities may have an impact on RA patients. Cardiovascular disease is the main cause of death in RA patients and is a typical side effect of chronic inflammation. Cardiovascular disease is more closely linked to disease activity than to conventional cardiovascular risk factors in RA patients. Targeted biologic therapy lowers the risk of

cardiovascular disease.^[17,18] Interstitial lung disease may be a RA symptom or a side effect of RA medications like methotrexate and leflunomide. Physical performance, productivity, and quality of life are all impacted by RA. If the condition is not adequately treated, 40% of patients will become disabled within 10 years of the disease's inception, and 80% of patients will have misaligned joints.^[19-21] According to the 36-Item Short Form Health Survey, the quality of life is on par with or worse than that caused by diabetes and cardiovascular disease. All daily activities are impacted by RA.^[22,23]

Patients who sustain irreversible joint damage will never regain normal physical function, even if clinical remission (i.e., absence of signs of inflammation such as joint swelling and elevated CRP levels) is subsequently achieved. Disability results from the accumulation of joint damage, which is irreversible in RA, in long-standing, inadequately treated disease. Joint damage cannot be reversed, not even with the most successful treatments. The progression of radiographic findings spans from joints with minor abnormalities to severe destructive alterations manifested as bone erosions and joint space narrowing, indicating cartilage changes (changes in cartilage can only be observed indirectly because it is radiotranslucent).^[24] More cartilage damage than bone damage results in permanent impairment.

TREATMENT

The major focus of treatment is on lowering the level of inflammation or lowering the drug's activity. Additionally, it reduces joint damage. Correct medical care can enhance our quality of life and physical health. We have three options for treatment: surgery, allopathic drugs, and natural drugs (Figure 4).^[25]

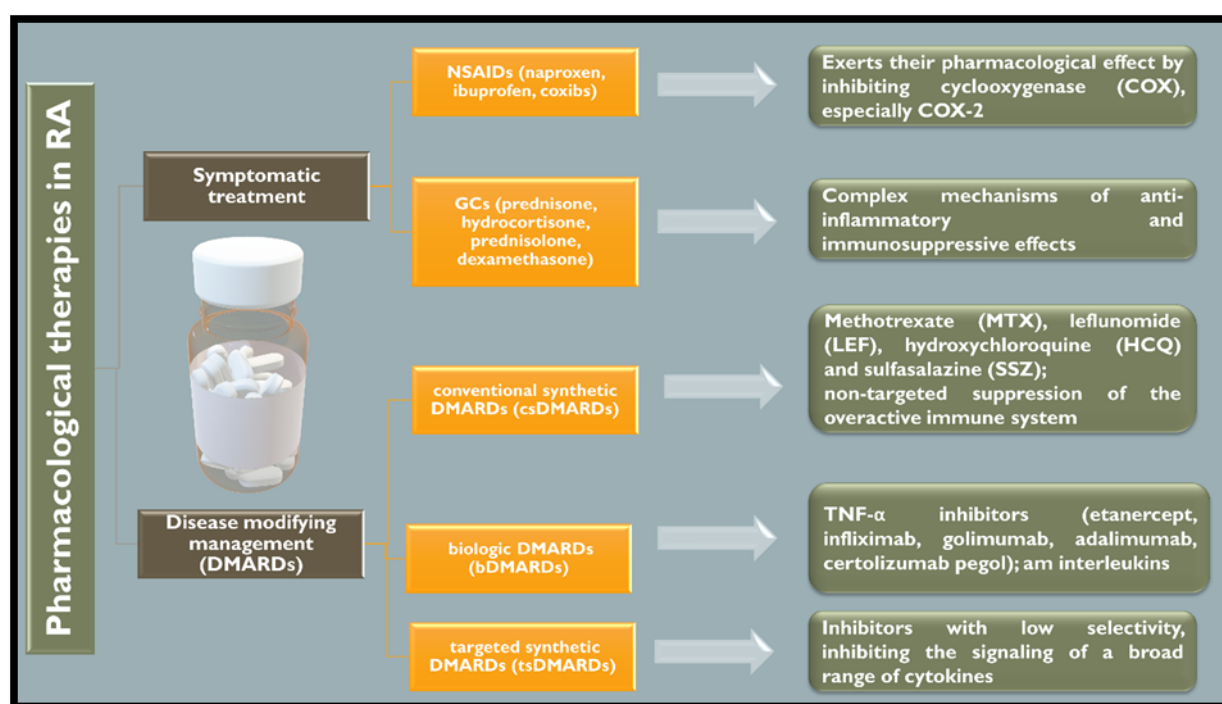


Figure 4: Treatment of Rheumatoid arthritis.

a. ALLOPATHIC DRUGS

The drug used in treatment of rheumatoid arthritis Acetaminophen (tylenol), aspirin, ibuprofen naproxen, Methotrexate, gold salts, penicillamine, sulfasalazine, and hydroxychloroquine, hydroxychloroquine, methotrexate sulfasalazine, Sulfasalazine hydroxychloroquine and methotrexate – hydroxychloroquine sulfasalazine, Paracetamol, ibuprofen, naproxen, meloxicam, etodolac, nabumetone, sulindac tolmetin, choline magnesium salicylate, diclofenac, diflunisal, indomethacin, ketoprofen, oxaprozin, and piroxicam.

There are 4 types of therapy used in treatment of rheumatoid arthritis are

1. over the counter drug therapy,
2. Disease modifying anti-rheumatic drugs (DMARDs) therapy,
3. non-steroidal anti-inflammatory drugs (NSAIDs) therapy and
4. biological agent therapy.

b. SURGERY

One may choose surgery to restore the injured joint if herbal and allopathic medications are unable to prevent or halt joint damage. The procedure has restored the joint's capacity to move. Additionally, surgery is typically performed to treat abnormalities and lessen pain.

1. Synovectomy—In this procedure, the inflammatory synovium—the joint's lining—is removed. Wrist, finger, elbow, knee, and hip joints are all treated with synovectomy.
2. Tendon repair: The tendons are built to withstand joint damage and inflammation before they loosen or rupture. Surgery is used to mend these tendons.
3. Total joint replacement - During this procedure, the doctor removes the joint's damaged portion and inserts a metal prosthesis in its place.
4. Joint fusion - This procedure involves joining two or more joints together to stabilise them and to relieve pain when replacing joints is not an option.

c. HERBAL MEDICINES

Due to an allopathic drug's side effect, herbal medications are employed as a form of treatment. The following are some plants that have anti-rheumatic properties.^[26]

1. *Harpagophytum procumbens*: It also goes by the name "devil claws" plant. Southern Africa's Kalahari Desert and Namibian steppes are home to this plant. In both the acute and chronic phases of Freund's adjuvant-induced arthritis in rats, the root of this plant exhibits anti-inflammatory and analgesic activity. Other tests, such as behavioural assessments, body weight measurements, hot-plate assessments, and paw volume measurements, are also performed. This drug's extract made animals' "delay of paws" withdrawal symptoms worse, and it

also has a protective effect that lessens pain. This medicine is used to treat both acute and chronic rheumatoid arthritis.

2. *Variegated Bauhinia*: Utilizing in vivo animal models, the *Bauhinia variegata* leaf has anti-inflammatory efficacy. The petroleum ether fraction of this medication contains more of the medicine's activity. The treatment of both acute and chronic inflammatory conditions was part of this plant's traditional use.
3. *Leucas aspera*: Utilized as an analgesic, antipyretic, anti-rheumatic, anti-inflammatory, and antibacterial medication is *Leucas aspera*. Inflamed areas are treated externally with the medication paste. The complete cartilage regeneration is generated as a result of this herbal medicine treatment, and the joint is close to normal.
4. *Phyllanthus amarus*: The *Phyllanthus amarus* extract (PAE), which contains 2.5% phyllanthin and hypophyllanthin, was tested against rats that had been given the Freund's complete adjuvant to induce arthritis. Measurements included arthritis evaluation, joint diameter, mechanical hyperalgesia, and nociceptive threshold. With regard to arthritis index, paw volume, and joint diameter, PAE significantly reduced arthritis. Additionally, the mechanical hyperalgesia and nociceptive threshold were greatly improved. Additionally, the histopathology identified the control in irritation with PAE.
5. *Acalypha indica*: The anti-arthritis potentials of *Acalypha indica* (AI) methanol extract, including inhibition of protein denaturation, proteinase inhibitory motion, and anti-hyaluronidase activity, were examined using three different in-vitro models. DMSO was used to arrange quantities of 10 to 200 g/ml of AI methanol extract. Diclofenac was utilised as a quality control drug. Every in-vitro analysis had been carried out in triplicate. All three models showed a dose-dependent increase in the percent inhibition. The inhibitory concentration (IC₅₀) for the protein denaturation assay was found to be 52 g/ml, for the proteinase inhibitory action to be 37 g/ml, and for the anti-hyaluronidase activity to be 18 g/ml. The drug's traditional use is that it has excellent anti-arthritis properties.
6. **Alternative and complementary medicine (CAM)**: The definition of complementary and alternative medicine (CAM) is a "diagnosis, treatment and/or prevention which complements conventional medicine by adding to a shared whole, by meeting a need not addressed by conventional medicine, or by diversifying the conceptual frameworks of medicine." These days, CAM therapies are being used more frequently not only in North America, Europe, and Australia but also in

Asian nations like India. Ayurveda, homoeopathy, siddha, and unani medicine are the main alternative systems used in India and have been around for a while. Other therapies that can be found in India include magnet therapy, massage, acupuncture, yoga asana, and pranayama. The key benefits of CAM are that it is less expensive, more efficient, and has no adverse effects. When compared to Ayurveda in India, the practise of yoga asana and pranayama is more prevalent.^[27]

MANAGEMENT AND RECOMMENDATIONS

For the treatment of RA, many methods are used. Among them DMARDs (disease-modifying antirheumatic drugs), NSAIDs (Nonsteroidal anti-inflammatory drugs), Therapies and surgery are used mainly. Generally speaking, remission or low disease activity are the outcomes that are targeted by ACR70 and EULAR69. As a result, while the ACR does not advise against the use of biologic DMARD monotherapy, the EULAR recommends combining both targeted synthetic and biologic DMARDs with methotrexate. Patients should be categorised according to ACR and poor prognostic indicators, according to EULAR recommendations.

Every time a standard synthetic DMARD is started, EULAR strongly advises the short-term prescription of glucocorticoids. More so than EULAR, ACR advises combining typical synthetic DMARDs with one another. Each medication only partially relieves symptoms, with up to 40% of RA patients experiencing low disease activity and up to 20% experiencing remission. Therapy must be changed if a particular medication fails to meet the treatment objectives. For patients who did not respond to the first course of medication, biologic DMARDs and targeted synthetic DMARDs should be added to methotrexate or other conventional synthetic DMARDs rather than switching to biologic

DMARD monotherapy in order to maximise the effects of treatment. After the initial DMARD course, about 50% to 60% of patients will not achieve their treatment objectives, and more than 60% of these patients will need at least a third DMARD course. For more than 75% to 80% of RA patients, however, low disease activity or remission is currently a realistic goal with the right treatment plan. All biologic DMARDs and targeted synthetic DMARDs have similar efficacy when taken with methotrexate, as shown by randomised trials and indirect comparisons. JAK inhibitors may be an exception (eg, tofacitinib and baricitinib). Adalimumab was less effective when combined with methotrexate than baricitinib. Adalimumab plus methotrexate was superior, whereas tofacitinib plus methotrexate was not.^[28] You need more information. Upadacitinib, a third JAK inhibitor, inhibits JAK 1 and possibly JAK 2 and has shown significant efficacy in phase 3 trials for methotrexate insufficient responders (patients who did not achieve the goal of low disease activity or remission, regardless of whether they had slightly improved with

methotrexate) as well as for anti-TNF insufficient responders and as a monotherapy^[29], but it is still being studied. Phase 3 clinical trials are examining filgotinib, a JAK 1 selective inhibitor.^[30]

SCENARIO IN INDIA

With an uncertain course, this inflammatory disease primarily affects adults between the ages of 20 and 60. According to the WHO, RA affects between 0.3 to 1% of the world's population overall and affects women two to three times more frequently than men. According to certain reports, Europe and North America may have higher prevalence rates than Asia. If RA affected entire populations, it would affect roughly 7 million patients in India. Although probands from multicase families have been observed to be as frequently males as women, the frequency of women against men with RA has generally been shown to be approximately 3:1. According to reports, the prevalence of RA in adults ranges from 0.15 to 1.37% in males and from 0.15 to 3.8% in women.

CONCLUSION

Rheumatoid Arthritis is a debilitating, chronic, inflammatory disease, capable of causing joint damage as well as long-term disability. The treatment for RA has been greatly enhanced by recently gained understanding about the pathophysiology, ideal management, and ideal outcome measurements of RA. Early diagnosis and intervention are essential for the prevention of serious damage and loss of essential bodily functions. When RA is diagnosed early, doctors can quickly recommend methotrexate as the first DMARD, halting the progression of the disease in a significant number of patients. Measures of disease activity, such as the CDAI, should be used to closely monitor the effects of treatment. Treat-to-target guidelines advise changing the course of therapy if there is no remission or little disease activity. Biologic DMARDs or JAK inhibitors should be administered if methotrexate (in combination with short-term glucocorticoids) does not result in remission, especially in individuals with persistently high disease activity, the presence of autoantibodies. With advances in the field of molecular medicine and with a better understanding of disease mechanisms which can aid in the designing of more effective treatments. Old treatment modalities have been optimized and new ones have been produced. It is foreseen that treatment methods will face tremendous improvements in the management of RA. RA patients today can live a healthy and productive life. Current medicines used can relieve pain and swelling and, in some cases, put the disease in remission, preventing bone damage or deformity in arthritis patients.

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