REVIEW: A RHEUMATOID ARTHRITIS

P.Natarajan1*, R.Arunpandian1, G.Subramanian1, S.Ramarajan1, K.Sakthiraj, G.Ragunath1.

1Department of Pharmacology, Sankaralingam Bhuvaneswari College of Pharmacy, 3/77-C, Anaikuttam, Sivakasi-626130, Tamil Nadu, India

ABSTRACT

In present day, life of whole mankind has become mechanical, where people are supposed to afford many efforts both physically and psychologically. Our limbs and joints afford us much in our physical workouts and in return they are prime targets of our physical and mental stress. Irrespective of the age group, people are affected with various musculo-skeletal diseases. One among such diseases is Rheumatoid Arthritis (RA). According to survey of American College of Rheumatology, more than 1 million Americans suffer from rheumatoid arthritis. Uncontrolled rheumatoid arthritis causes joint damage, disability, decreased quality of life and cardiovascular and other comorbidities. Disease-modifying anti-rheumatic drugs (DMARDs) are the key of therapeutic agents to reduce synovitis and systemic inflammation and improve its function. The leading DMARD is methotrexate, which can be combined with other drugs of this type. The present study is on reviewing complicated rheumatic disorders and chronic degenerative diseases of musculo-skeletal system. Hence, an attempt has been made to discuss few old remedies for rheumatoid arthritis in modern science point of view.

KEY WORDS: Rheumatoid Arthritis, limbs, degenerative diseases.

INTRODUCTION

Rheumatoid arthritis has 19th century roots and a 20th century pedigree. Although its name was introduced in the 1850s. Arthritis - It is a Greek word, Arthro – Joint; itis - Inflammation. Quite literally, Arthritis means joint inflammation. Rheumatoid arthritis is an auto immune disease. It is a chronic complicated systemic inflammatory disorder and also affecting many tissues and organs. But flexible (synovial) joints are affected principally1. Rheumatoid
Arthritis is characterized by persistent joint synovial tissue inflammation.\textsuperscript{2,3} Joint damage in RA begins with the proliferation of synovial macrophages and fibroblasts after a triggering incident, possibly autoimmune or infectious.\textsuperscript{4} Over time, bone erosion and irreversible joint damage can occur, leading to permanent disability.\textsuperscript{5} Although most readily recognised by its articular manifestations, multiple organ systems may be affected and may result in shortened life expectancy, with increased deaths due to cardiovascular disease, infection and cancer.\textsuperscript{4} Systemic features may be associated with a poor prognosis, especially vasculitis, amyloidosis and pulmonary fibrosis.\textsuperscript{6}

Early diagnosis and management of RA presents an important opportunity to alter the course of this progressive disease. There is a window of opportunity within the first few months of disease onset to provide treatment that effectively limits structural damage and improves health outcomes.\textsuperscript{7} Such treatment involves:

1. The early introduction of disease modifying drug therapy
2. Education to assist individuals in the day-to-day management of their condition
3. Rehabilitation to restore function
4. Comprehensive multidisciplinary approach to the provision of care and
5. Support to manage the physical, social, emotional and occupational impact of the disease.

**Prevalence**

It is reported that RA occurs in all the ethnic groups all over the world. About 1% of total world’s population has RA, women are most often affected by RA than men. The prevalence of RA is lowest in Black Africans & Chinese where as it is found highest in Indians. It is around 1-1.5% with a female: male ratio 3:1 in Caucasians. Prevalence of RA increases with increase in age group with 5% of women & 2% of men over 55 years being affected. It is also reported that RA is uncommon in men under the age of 45 years while it is 6:1 female excess which is shocking. Onset of RA is most frequent between ages of 40&50 but people of any age group can also be affected by RA.

**Types Of Arthritis**

**Osteoarthritis**

Osteoarthritis occurs when cartilage, the tissue that cushions the ends of the bones within the joints, breaks down and wears away. In some cases, all of the cartilage may wear away, leaving bones that rub up against each other. Osteoarthritis can cause joint pain and stiffness.
Rheumatoid Arthritis

Rheumatoid Arthritis occurs when the immune system turns against parts of the body it is designed to protect, causing pain, swelling, stiffness, and loss of mobility in the joints. Inflammation most often affects the hands and feet. It tends to occur equally on both sides of the body.

Juvenile Rheumatoid Arthritis

The most common form of arthritis in childhood, causing pain, stiffness, swelling and loss of function of the joints. It may be associated with rashes or fevers and may affect various parts of the body.
Fibromyalgia
A chronic disorder that causes pain throughout the tissues that support and move the bones and joints. Pain, stiffness and localized tender points occur in the muscles and tendons, particularly those of the neck, spine, shoulders and hips. Fatigue and sleep disturbances may be experienced. Fibromyalgia makes you feel tired, causes muscle pain and "tender points." Tender points are places on the neck, shoulders, back, hips, arms or legs that hurt when touched.

Gout
Gout occurs when there is a build-up of too much uric acid in the body causing hard, crystal-like deposits to go to the joint. Affected areas are very sore, red, warm and swollen.

Systemic lupus erythematosus (SLE)
Also known as lupus or SLE is an autoimmune disease. This can result in inflammation of and damage to the joints, skin, kidneys, heart, lungs, blood vessels and brain.

Spondyloarthropathies
This group of rheumatic diseases principally affects the spine. One common form, ankylosing (chronic inflammatory disease of axial skeleton), spondylitis, affects the spine but may also affect the hips, shoulders and knees as the tendons and ligaments around the bones and joints become inflamed, resulting in pain and stiffness.

Diagnosis Of Arthritis
All the above mentioned symptoms say morning stiffness, swelling of joints and pain inflexation of joints, rheumatoid nodule, any four or more of these symptoms may half reveal that RA has been attacked. Still it is difficult to diagnose RA as many other conditions resemble the symptoms of RA. Blood tests and radiological examination may not reveal the changes occurred for months even after the onset of RA.

1. Elevated ESR
Erythrocyte sedimentation rate, it measures the rate of sedimentation of red blood cells in a fine glass tube filled with patient’s blood. Elevated ESR severely does not help in determining how active the condition within. Presence of rheumatoid factors along with the evidence of bone damage on x-rays suggests a change for progressive joint damage. Presence
of RF (rheumatoid factors) does not completely several RA attack but most often 80% of RA cases show positive test for rheumatoid factor\(^1\).

2. C Reactive Protein (CRP)
Increased CRP levels indicate the condition of active inflammation. But a medical practitioner should also consider a patient’s body mass index (BMI) because obesity also leads to increased level of CRP\(^2\).

3. Anti-CCP Antibody (cyclic citrullinated peptides)
In the combination of test for RF, CCP antibody test is known to be a best predictor for patients to develop severe RA. The presence of CCP, cyclic citrullinated peptides help in identifying RA even before its symptoms arises. Generally, x-rays are not much helpful in detecting the early stages of RA, as the soft tissue images cannot be seen on x-rays. Also, anemia is associated with progressive RA\(^3\).

4. Synovial Fluid (SF)
Colour of SF is changed to dark pink in RA cases. Volume of SF is also quietly inclined in RA cases. The blood tests should be carried out to determine the levels of liver enzymes like- Serum alanine Transaminase (SAT), Aspartame amino Transaminase (AST), Alkaline posphatase (ALT), \(\gamma\)- glutanyltranspeptidase (GGT), Total Bilirubin, Albumin, Urea, Uric acid, Creatinine, Superoxide dismutase, Glutathione Peroxidase (GSH-PX), Malondialdehyde (MDA), Xantine Oxidase (XOD), Prostaglandin in serum are carried out as many of above liver enzymes tend to increase in RA cases\(^4\).

**Treatment To Arthritis**

**Treatment of symptoms**
Analgesic reduces pain and non-steroidal anti-inflammatory drugs (NSAIDs) lessen pain and stiffness. But both groups of drugs are used widely to control symptoms of rheumatoid arthritis. Evidence for use of analgesic is modest but uncontroversial support for use of NSAIDs is considerably stronger\(^5,6\). NSAIDs have lost their historical role as first-line treatment because of concerns about their limited effectiveness, inability to modify the long-term course of disease, gastrointestinal and cardiac toxic effects.\(^7\) These agents should be given with proton-pump inhibitors for gastro protection, with short-acting drugs administered for short periods to minimize risks.
Drug used for the treatment of RA

The goal of therapy in RA is that,
1. To reduce the pain
2. To reduce swelling
3. To reduce joint stiffness
4. To prevent articular cartilage damage
5. To prevent bony erosion
6. To prevent deformity of the joints
7. To preserve the joint function

Physical therapy and drug therapy are commonly used for RA. Physical therapy is used as a supportive step for drug therapy.

Physical therapy
1. Is done by the balanced rest and exercise are given to the patient
2. Heat is one of the important things in relieving the muscular pain.
3. Heating pads or paraffin bath is usually advised to use

Non-Steroidal anti-Inflammatory Drugs (NSAIDs)

NSAIDs are the first line drugs used for the treatment of rheumatoid arthritis. The drugs can reduce the pain and stiffness of the patient with rheumatoid arthritis. As a brief history about the drugs, sodium salicylate was the first NSAIDs used for fever in 1875. Its magical effect lead to invent all the drugs belongs to this series. And these drugs are available in market like COX 1 and COX 2 drugs and selectively COX 2 inhibitors.

DMARDs (Disease modifying Anti-rheumatic drugs)

Immunosuppressants

These are the drugs that can suppress cellular and humoral activity or both. These drugs are used in organ transplantation and auto immune diseases. The main drugs used are as follows.

Methotrexate

Methotrexate is one of the oldest and effective anticancer drugs. This drug is a dihydrofolatereductase inhibitor or simply folate antagonist. It blocks the conversion of dihydrofolic acid to tetrahydrofolic acid which is essential coenzyme required for purine synthesis. As an anticancer drug it kills cells in S phase and inhibits DNA synthesis. It can also inhibit RNA and protein synthesis. The drug is used as immunosuppressant and anti-
inflammatory. It can inhibit cytokinin production and cell mediated immune reaction. These abilities make the drug a good antirheumatoid arthritic drug. Methotrexate is orally absorbable and excreted unchanged in urine. Toxicities include megaloblastic anaemia in low doses and pancytopenia in high dose.

**Azathioprine**
It is a purine antagonist. Azathioprine has effect on T-lymphocytes and suppresses cell mediated immunity. It is used as immunosuppressant in organ transplantation and rheumatoid arthritis. Main toxicities include bone marrow depression and jaundice.18

**Biological Response Modifiers (BRMs)**
BRMs used for the treatment of rheumatoid arthritis are derived from the human genes which are the genetically engineered proteins. These specifically inhibit the particular component of the immune system which acts as the key cause of inflammation in arthritis. These includes a group of monoclonal antibodies or recombinant proteins that can inhibit TNFα and IL-6 and thus beneficial for rheumatoid arthritis and many other autoimmune diseases.

**TNFα inhibitors**
TNFα can act by activating membrane bound receptors i.e. TNFR1 and TNFR2. TNFα inhibitors can neutralise this action. TNFα inhibitors can be classified as first generation and second generation. The first generation drugs include Etanercept which is a recombinant protein, Infliximab and Adalimumab which are the monoclonal antibodies. The second generation drugs include Certolizumab and Golimumab.

**IL-6 antagonist**
Anakinra is a recombinant human IL-1 antagonist which is less active than TNFα inhibitors.

**Corticosteroids**
These are the potent immunosuppressant’s and anti-inflammatory agents that can be used at any stage of rheumatoid arthritis. Cortisone is a hormone of our body that regulates the inflammatory process. In 1950, the Physicians found out that if the patients with rheumatoid arthritis are administered with extra cortisone, the symptoms get relieved fast.19

**Prevention**
With respect to primary prevention, decreasing the number of people who smoke within the populations should reduce risk of rheumatoid arthritis developing, and this initiative is a
realistic preventive strategy with wide health benefits\textsuperscript{20}. Modification of diet to prevent rheumatoid arthritis is an area of speculation; however, at present, insufficient evidence exists to support this idea looking at secondary prevention of disease. 5–15\% of patients with rheumatoid arthritis from historical studies (treated less intensively than nowadays) achieved drug-free remission. Modern, intensive, very early treatment aims to increase the frequency of drug-free remission and achieve long-term disease modification. Benefits of this approach must be offset against risks of overtreatment of patients with mild self-limiting disease\textsuperscript{21}.

CONCLUSION
As rheumatoid arthritis is considered one of the major and life threatening diseases, it should be treated adequately after its prediction. Although many unresolved difficulties exist for people with rheumatoid arthritis, continuing introduction of innovative treatments can overcome many of them. One key need is definition of disease subsets in individuals with early arthritis so that intensive treatment regimens can be targeted at patients who most need them and are likely to respond. We also need to move beyond long-term suppressive treatment towards short intensivetherapeutic courses that result in remission. This progression requires improved drugs and biomarkers that accurately predict the patients.

REFERENCE
7. Nell VP, Machold K, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease modifying anti-rheumatic drugs in patients


