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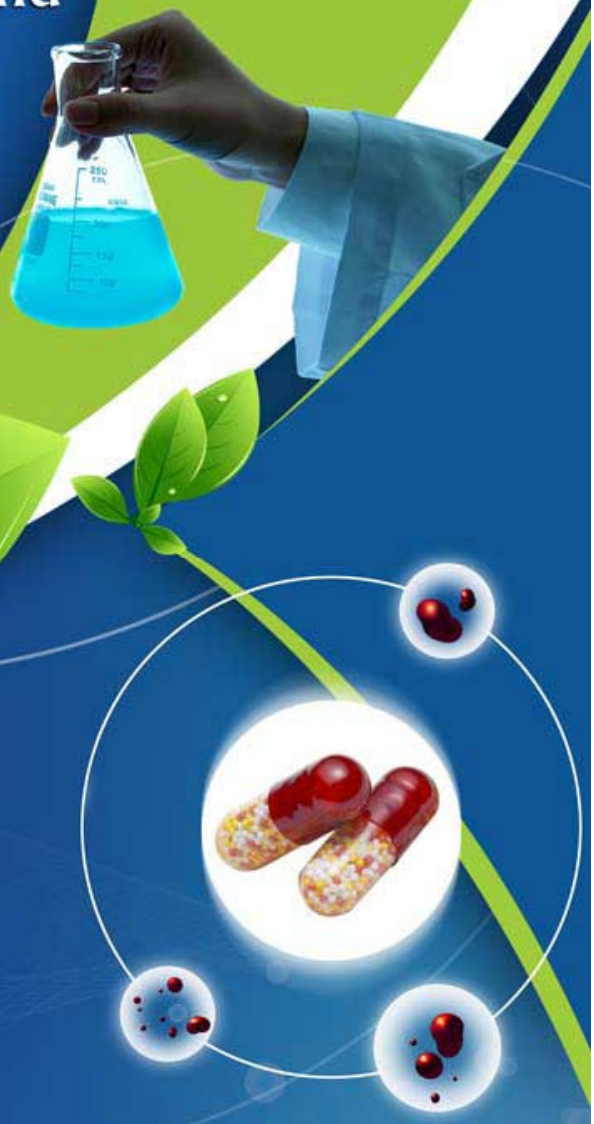

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Review Article

A REVIEW ON RHEUMATOID ARTHRITIS

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ABSTRACT:

RA is chronic, autoimmune, inflammatory disease that affects the skin, blood vessels, CVS, lungs and muscles but principally attacks the joints to destruction of the articular cartilage and ankylosis of the joints causing aching, pain, swelling and stiffness.The disease can affect at any age but old persons are mainly affected. There is no specific cause of RA but some factor may play important role in the progress of RA. A blood antibody called "rheumatoid factor" can be found in 80% of patients, is the principle factor for diagnosis RA. The drugs most commonly used in the therapy of RA are the disease modifying antirheumatoid drugs (DMARDS) and the NSAIDS.

Key words: *Rheumatoid arthritis, Rheumatoid factor, DMARDs*

INTRODUCTION

There are different types of small to large joints in the body which have following functions.

- Movement and locomotion of the body e.g. joints of extremities.
- Protection of important structures of body e.g. skull, chest cage.
- Maintenance of antigravity structure of body e.g. vertebral column.

Joints are the articular junction between two bones with a space between articular surfaces of bones [1].

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RHEUMATOID ARTHRITIS:

The "arthritis" was used in the days of Hippocrates, Old testament times, and the years 460 BC to about 380 BC. It literally means inflammation of joints – hot, red swollen, painful joints. This meaning remains quite applicable today. Any "inflamed" tissue is hot, red, tender and swollen. Thus, if a disease produces inflammation ("itis") in joints (arthron), it is arthritis. The word arthritis alone does not designate a disease but refers to the inflammation of a joint causing aching, pain, swelling and stiffness. The term arthritis describes over 100 different inflammatory or degenerative diseases that damage the joints [2].RA is chronic, systemic, autoimmune multisystem and inflammatory disease that affects the skin, blood vessels, cardiovascular system, lungs and muscles but principally attacks the joints producing a non supportive proliferative and inflammatory synovitis that

often progress to destruction of the articular cartilage and ankylosis of the joints (Abbas et al. 2007). Although the cause of the RA is unknown [3]. RA is characterized by progressive and irreversible damage of the synovial lined joints usually involving peripheral joints in a systemic distribution. The potential of the synovial inflammation to cause cartilage damage and bone erosions and subsequent changes in joint integrity & extra-cellular matrix degradation is a hallmark of RA, which is responsible for the typical destruction of cartilage, ligaments, tendons and bone [4].

RA is common rheumatic disease affecting 1% of the population worldwide [5]. It afflicts peoples of all races equally. The disease can begin at any age but most often onset is during the fourth and fifth decade of life after age of 40 to 60 years, with 80% of all patients developing the disease between the ages of 35 to 50, its incidence often increasing with age. The incidence of RA is more than six times greater in 60 to 64 year old women compared to 18 to 29 year old women [4]. The geographic distribution of RA is worldwide one of every six people have some form of arthritis in India, in female/male ratio 3: 1. A patient with a family history of RA had at least a 200% higher hazard of starting to suffer substantial damage. There is wide range of results on the association between familial RA and radiographic progression [6]. Attention has been called to the increased likelihood that the rheumatoid arthritis will be die of an infection and to associations with ulcerative colitis and psoriasis, though in recent years there has been some tendency to separate out “the arthritis of ulcerative colitis” and “psoriatic arthritis” as separate entities [7].

RA is the most common form of rheumatic diseases, and has a substantial social effect in terms of cost, disability, and lost productivity. The geographic distribution of RA is worldwide, with a notably low prevalence in rural Africa and high prevalence in specific tribes of Native Americans RA afflicts approximately 2.1 million individuals in the united states, 1.5 million being women [5].

ETIOLOGY:

The cause of rheumatoid of rheumatoid arthritis is unknown. Indeed, it is possible that many factors including genetic susceptibility, environmental influences, and the effects of advancing age on somatic changes in the musculoskeletal and immune system [5]. Nevertheless, current research is focusing on exogenous infectious candidates as the causative agent or agents, as well as endogenous substances, such as connective tissue proteins (e.g. collagen and proteoglycans) and altered immunoglobulins. Family studies indicate a genetic predisposition, For example, severe RA is found at approximately four times expected rate in first degree relatives of individuals with diseases associated with the presence of the autoantibody, rheumatoid factor; approximately 10% of patients will have an affected first degree relative [4]. Although epidemiologic associations have not been clearly established; smoking may increase the production of rheumatoid factor (RF) which often precedes the clinical presentation of RA [5].

There are two main groups of theories at present regarding this disease:

- That it is non-infective in character
- That it is infective

The non-infective factors fall into three categories:

- congenital predisposition
- Endocrine disturbances,
- Faulty alimentation.

The theory of infective is widely held, and there is much to be said in its favor. In simplest way it states “the joint has become hypersensitive, and in the event of any toxin reaching it from an infective focus, such as a single tooth with apical infection, reacts in an anaphylactic manner” [8].

Infectious Agents:

The similarities of rheumatoid arthritis to other arthritides such as Lyme disease for which an infectious cause has been established, continue to intrigue investigators. At various times in recent years other agents, including human T-

cell lymphotropic virus Type I, rubella virus, cytomegalovirus, herpes virus, and mycoplasma, have been proposed as the etiologic agent of rheumatoid arthritis, but none have received sustained scientific support**.** Alternatively, the microorganism or response to the microorganism might induce an immune response to components of the joints by altering its integrity and revealing antigenic peptides [4]. Epstein-Barr virus has been linked to rheumatoid arthritis for because of the following observations. Eighty percent of with rheumatoid arthritis have a circulating antibody directed against antigens specific for Epstein-Barr virus and the autoantibody response in rheumatoid arthritis enhances the response to these antigens. They also have increased numbers of circulating B cells infected with the virus and diminished cytotoxic T-cell response to immune responses induced by Epstein-Barr virus [9].

Autoimmunity*:*

Although the cause of RA remains unknown, adaptive immunity plays a pivotal role in its chronicity and progression. In autoimmune disorders such as RA, the cells of the adaptive immunity recognize self antigens and propagate a self directed autoimmune reaction. There is little question among most investigators that autoimmunity has a major role in the progression of rheumatoid arthritis, but data supporting autoimmunity as the initial cause of rheumatoid arthritis are less firm. Collagen and immunoglobulin G are the endogenous proteins most often implicated in these hypotheses. Autoimmunity involve in the development of synovitis [10].

Genetic Susceptibility:

The results of several studies have shown a higher disease concordance among monozygotic twins (12-15%) than dizygotic twins (4%), monozygotic twins are at least four times more likely to be concordant for RA than dizygotic twin influence of genetic factors [4]. Heritability analysis of these studies suggests that about 60% of a population's predisposition to rheumatoid arthritis can be accounted for by genetic factors, although on analysis of twin pairs concordant for rheumatoid arthritis, striking diversity in disease severity was noted. An association with HLA-DR4 has been noted in many populations, including North American and Europeans, South Americans, native Indians and kima Indians of North Americans. Genetic risk factors do not fully account for the incidence of RA suggesting that environmental factors also play a role in etiology [4].

Pathogenesis:

It is called a complex genetic disease, meaning that several genes, environmental factors and stochastic factors act in concernt to cause pathological events [11]. It is believed that RA is autoimmune disease triggered by exposure of a genetically susceptible host to an unknown arthritogenic antigen. The severity of the joint inflammation fluctuates over time, and the outcome of the uncontrolled disease is progressive joint destruction is progressive joint destruction, deformity and disability [12]. Two pathological processes may work simultaneously in RA patient's joints. One leads signs and symptoms of inflammation, and the other to direct joint destruction by synovial cells [6].

Therefore key considerations in pathogenesis of disease are

- The nature of autoimmune reaction
- The mediators of tissue injury
- Genetic susceptibility
- The anti arthritogenic antigens

There is immune complex deposition may play some role in the joint destruction [13].The role of antibodies in the diseases is suspected from a variety of experimental and clinical observations. About 80% of patients have serum IgM auto antibodies that bind to the Fc portion of their own IgG. These autoantibidies are called as rheumatoid factor (RF) they may form immune complexes with self-IgG that deposit in joints and other tissues, leading to inflammation and tissue damage [13].

T-cells:

Several lines of evidence implicate the participation of T-cells in the pathogenesis of rheumatoid arthritis. The predominant in filtering cell is the T lymphocyte. CD4+T cells are predominant over CD+8T cells a frequently

found in close proximity to HLA-DR 4+ macrophages and dendritic cells [4].

Cytokines:

The ability of T and B lymphocytes to mount an immune response following antigen stimulation is in large part governed by the production of cytokines. These are low-molecular-weight proteins and glycoprotein that regulate growth, differentiation, and functions of lymphocytes, phagocytes, and other cells in an autocrine, paracrine, and endocrine manner. Cytokines are classified into several groups, including interleukins (IL), tumor necrosis and IGE secretion factors (TNF), interferons (IFN), colony-stimulating factors (CSF), growth factors, and chemokines. The overproduction of specific cytokines, such as interleukin-1 (IL1), TNF-α, drives pathophysiological process that leads to the clinical symptoms of the RA. IL1 is produced by a variety of cells that are part of the innate immune system and IL1 causes inflammatory cells to move into the structures of joints and the synovium in patients who have RA. In animal models of RA IL1 and TNF-α play crucial part in causing the degradation of proteoglycans that can damage the joints. But in case of IL10 which is produced predominantly by monocytes and lymphocytes and has wide range of anti-inflammatory and immunoregulatory properties, including inhibition of synthesis of proinflammatory molecules such as IL1, IL6 and TNF-α [14, 15]. IL1 and TNF-α induce the production of G-CSF by human synovial fibroblasts and chrondocytes *in vitro* which produced by bone marrow stomatal cells, endothelial cells, macrophages and fibroblasts, and production induced by inflammatory stimuli. G-CSF may exert effect on macrophages, including expansion of monocytes macrophages number and enhancement of phagocytic function [16]. An important source of cytokines is helper T-lymphocytes. Two types of helper T lymphocytes have been identified, based on the nature of the cytokine they produce. T helper-1 (TH1) cells are activated by antigenic peptide and MHC II molecules on the surface of macrophages to produce IL-2 and interferon-gamma (IFN-γ). These cytokines activate neutrophils, macrophages, and lymphocytes and are effective mediators of delayed-type hypersensitivity reactions. TH 2 cells produce IL-4, IL-5, and IL-6, which promote B cell differentiation. In addition to T lymphocytes, cytokines are released from macrophages, monocytes, keratinocytes, and fibroblasts. The cytokine TNF has remarkable range of actions in RA. RNF occupies a pivot role position in a cytokine cascade that regulate the production of inflammatory mediators such as IL1 [17].

C - reactive protein (CRP):

The serum level of C - reactive protein (CRP), an acute-phase protein produced in the liver under the conditions of systemic inflammation, is increased in patients with clinically active RA. This protein is very useful marker of inflammation and a potential biomarker for the anti-inflammatory effect of a new therapy, because the half life remains unchanged under the conditions of health and disease. The serum CRP concentration directly reflects the intensity of the pathological process [18].

Oxidative Tissue Damage:

The primary oxidative mediators of cytotoxicity are H_2O_2 and HOCl, which are capable of oxidation of a variety of biologically important substances. Lipid peroxidation (i.e., oxidation of polyunsaturated fatty acids) is involved in membrane damage. ROS play a critical role in all aspects of the inflammatory process from initiation to resolution. Reactive oxygen intermediates (ROIs) are agents commonly produced by inflammatory cells during inflammatory processes, including those occurring in arthritis and glomerulonephritis. Superoxide is a more potent inducer of COX-2 than H_2O_2. In addition, NADPH stimulated COX-2 expression and an inhibitor of NADPH oxidase blocked COX-2 expression induced by TNF-α. These studies demonstrate that oxidant stress is a specific and important inducer of COX-2 gene expression. Thus induction may contribute to the deleterious amplication of prostanoids in inflammation (Carolina et al., 2003). One important consequence of excessive production of ROS is lipid peroxidation. The patients with RA had shown elevated plasma levels of hydroperoxides,

estimated as Malondialdehyde (MDA), increased concentration of MDA in plasma has been considered as an indicator of elevated ROS production, a reflexion of the extent of lipid peroxidation and probably the severity of damage [19].

Morphology:

A broad spectrum of morphologic alterations is seen in RA ; the most severe occur in the joints. RA is typically presents as symmetric arthrtis, principally affecting the small joints of the hands and feet, ankles, knees, wrists, elbows and shoulders. Typically, the proximal interphalangeal and macrophalangeal joints are affected, but distal interphalangeal joints are spared.

Histological Changes:

An inflamed synovium is central to the pathophysiology of rheumatoid arthritis. It is histologically striking, showing pronounced angiogenesis; cellular hyperplasia; an influx of inflammatory leucocytes; and changes in the expression of cell-surface adhesion molecules, proteinases, proteinases inhibitors, and many cytokines. A synovial change in Rheumatoid arthritis varies with disease progression. In the first weeks of the disease, tissue oedema and fibrin deposition are prominent and can manifest clinically as joint swelling and pain. Within a short period, the synovial lining becomes hyperplastic, commonly becoming ten or more cells deep and consisting of type A (macrophage-like) and type B (fibroblast-like) synoviocytes. The sub lining also undergoes striking alterations in cellular number and content, with prominent infiltration of mononuclear cells including T-cells, B-cells, macrophages, and plasma cells. Synovial-vessel endothelial cells transform into high endothelial venules early in the course of the disease. High endothelial venules are specialized post-capillary venules found in secondary lymphoid tissue or inflamed non-lymphoid tissues; they facilitate the transit of leucocytes from the bloodstream into tissues. The formation of locally invasive synovial tissue pannus – is a characteristic feature of rheumatoid arthritis. This tissue is involved in the joint erosions seen in rheumatoid arthritis. Pannus is histologically distinct from other regions of the synovium and shows phases of progression initially, there is penetration of the cartilage by synovial pannus composed of mononuclear cells and fibroblasts with high-level expression of matrix metalloproteinase by synovial lining cells. In later phases of the disease, cellular pannus can be replaced by fibrous pannus comprised of a minimally vascularised layer of pannus cells and collagen overlying cartilage. The tissue derivation of pannus cells has not been fully elucidated, although they are thought to arise from fibroblast-like cells (type B synoviocytes). In-vitro work shows that these fibroblast-like synoviocytes have anchorage-independent proliferation and loss of contact inhibition, which phenotypes are shown by transformed cells. However, the molecular pathogenic mechanisms driving pannus formation remain poorly understood [13].

CLINICAL FEATURES:

The range of presentations of RA is broad, but disease onset is insidious in most cases, and several months can elapse before a firm diagnosis can be ascertained. The predominant symptoms are pain, stiffness, and swelling of peripheral joints. The clinical course of the disorder is extremely variable, ranging from mild, self-limiting arthritis to rapidly progressive multisystem inflammation with profound morbidity and mortality.

DIAGNOSIS:

A careful history-taking and physical examination are essential for making the diagnosis of RA. The doctor reviews the history of symptoms, examines the joints for inflammation and deformity, the skin for rheumatoid nodules, and other parts of the body for inflammation. Certain blood and x-ray tests are often obtained. The diagnosis will be based on the pattern of symptoms, the distribution of the inflamed joints, and the blood and x-ray findings. Abnormal blood antibodies can be found in patients with rheumatoid arthritis. A blood antibody called "rheumatoid factor" can be found in 80% of patients. Citrulline antibody (also referred to as anti-citrulline antibody, anti-cyclic citrullinated peptide antibody, and anti-CCP) is present in

most patients with rheumatoid arthritis. It is used in the diagnosis of rheumatoid arthritis when evaluating patients with unexplained joint inflammation. A test for citrulline antibodies is most helpful in looking for the cause of previously undiagnosed inflammatory arthritis when the traditional blood test for rheumatoid arthritis, rheumatoid factor, is not present. Citrulline antibodies have been felt to represent the earlier stages of rheumatoid arthritis in this setting. Another antibody called "the antinuclear antibody" (ANA) is also frequently found in patients with rheumatoid arthritis.

Radiographic evaluation:

Joint x-rays may be normal or only show swelling of soft tissues early in the disease. As the disease progresses x-rays can show bony erosions typical of rheumatoid arthritis in the joints. Joint x-rays can also be helpful in monitoring the progression of disease and joint damage over time. Bone scanning, a radioactive test procedure, can demonstrate the inflamed joints. Use of scored radiographs as an outcome measure can help estimate the progression of rheumatoid arthritis (RA). Radiographs not only provide permanent records with which to evaluate RA serially, but can also be randomized and blinded, a major advantage in clinical trials [20].

Treatment of arthritis:

The drugs most commonly used in the therapy are the disease modifying antirheumatoid drugs (DMARDS) and the NSAIDS. The NSAIDS reduce the symptoms of rheumatoid diseases but do not retard the progress of the disease. The therapy of Rheumatoid arthritis is revolutionized by the technology to target specific mediators of disease. There are different targeted therapies are as follow:

i) T- cell specific therapies
ii) Targeting cytokines
iii) Targeting B cells [21].

Anti rheumatoid drugs:

• NSAIDS : Aspirin, Ibuprofen, Indomethacin, Piroxicam,Diflunisal,Naproxen,Sulindac, Fenoprofen, Diclofenac etc.

• Gold compounds : - Sodium aurothiomalate, Auranofin, Aurothioglucose.

• DMARDS: - Sulfasalzine, Penicillamine, Chloroquine, Methotrexate.

• TNF-α Antagonist : - Etanercept, Infliximab, Adalimumab, Certolizumab.

Nonsteroidal anti-inflammatory drugs (NSAIDS):

The primary drugs used in the treatment of arthritis, particularly rheumatoid and osteoarthritis is nonsteroidal anti-inflammatory (NSAIDS). In most cases, these drugs have proven to be of only limited value. Many of them inhibit prostaglandin biosynthesis by inhibiting cyclooxygenase (COX). COX is a key enzyme in the synthesis of prostaglandins and thromboxanes. Some NSAIDS have additional actions, including inhibition of leukocyte migration (Ritter et al., 1999). These are also called as slow acting antirheumatoid drugs (SAARDS) because they taken long time**.** However NSAIDS cannot reduce or arrest the progress of disease. Aspirin, generally, they are recommended for only short periods of time since prolonged use carries the risk of significant side effects [22].

DMARDS: (Disease modifying anti rheumatic drugs)

They are the class of diverse groups of compounds that share common pattern of clinical response when used to treat arthritis .After weeks or months old their administration .The suitable onset of clinical benefit may appear and with the continued administration complete suppression of some or all disease manifestation may occur in some patients, but if the drug is discontinued disease manifestations gradually reoccur. Their use is frequently associated with serious side effects hence they are reserved for patients with severe, progressive or life threatening disease manifestation. Generally only one DMARD is used at a time along with background therapy of NSAIDs [23].

DMARD's act by following mechanisms of action,

I. Suppress immune responses: Azathiopurine, Cyclophosphamide.

II. Normalizes the immune system: Levamisole, Methotrexate

III. Others with no specific effect: Gold, Penicillamine, (Sulfasalzine), 6-Mercaptopurine, Leflunomide.

TNF-α Antagonist

TNF-α is a cytokine central to many aspects of the inflammatory response, TNF-α also stimulate production of acute phase proteins, has proteolytic effects. RA illustrates central role of TNF-α in the pathophysiology autoimmune disorder [24].

Adverse effects of Anti rheumatoid drugs: [4, 5, 22, 23]

S.No.	*Drugs*	*Side effects*
1	NSAIDS	Tinnitus (ringing in the ears), gastric irritation ,NSAID induced peptic ulcer, allergic reactions, easy bleeding and bruising, salt and water retention, acute interstitial nephritis, hepatitis, haematemesis , abdominal cramps, gas, nausea, vomiting, diarrhea, urinary tract infection, heart failure, headache, depression, dizziness, weight gain or loss.
2	Corticosteroids	Cataracts and glaucoma, suppresses the normal functioning of the adrenal glands, suppresses the production of their natural hormones, multiple injection cause joint destruction, weight gain, impaired wound healing
3	Immunosuppressant	Blood dyscrasias, carcinogenesis, alopecia, nausea, hypertension & hyperkalemia
4	Gold salts	Rashes, nephritic syndrome, Blood dyscrasias, diarrhea
5	Penicillamine	Proteinurea, urticaria , Blood dyscrasias

CONCLUSION

Many drugs that can help to stop the progression of RA including NSAIDs and DMARDs but these drugs could not help in the complete remission of the RA as well as they

produced the intolerable side effects after prolong use.

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