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Factors based treatment in curing Rhematoid Arthritis

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Abstract

Arthritis is a very common disease affecting the joints, skin and various internal organs. It causes pain, stiffness and sometimes swelling in or around joints. In normal bones, the ends are lined by cartilage, which provides 'cushioning' and allows a joint to move freely. The joint is enclosed in a capsule containing fluid, which provides nutrition, and lubricates the joint. Arthritis can occur when there is something wrong with this system. Rheumatoid arthritis is such a debilitating illness that much effort has been made to find the ideal therapeutic regimen that has a high efficacy but low toxicity rate. Developments in the treatment of rheumatoid arthritis (RA) have highlighted the need for objective disease activity indices applicable to both research and clinical settings and this area has become an important area of research. This review discusses each of these major disease indices and focuses on the most recent developments in their application to clinical care.

Keywords: Rhematoid arthritis, Synovial tissue, Interleukins, cyclo-oxygenase.

INTRODUCTION

Rheumatoid arthritis (RA) is a classic example of an autoimmune disorder, with chronic inflammation of the synovial membrane, and deterioration of cartilage and bone in the affected joints. The resultant pain, loss of function and permanent disability are also associated with increased morbidity and mortality. Although the symmetrical joint deformities are a predominant characteristic, the disease has many systemic features. It affects nearly 1% of the population worldwide. Studies have indicated that the development of RA is partly related to the excess production of reactive oxygen species and a lowered ability to remove oxidative stress. Plasma malondialdehyde, a degradation product of lipid peroxidation, level was significantly higher in the synovial fluid and serum of RA patients than that of control subjects [1,2].

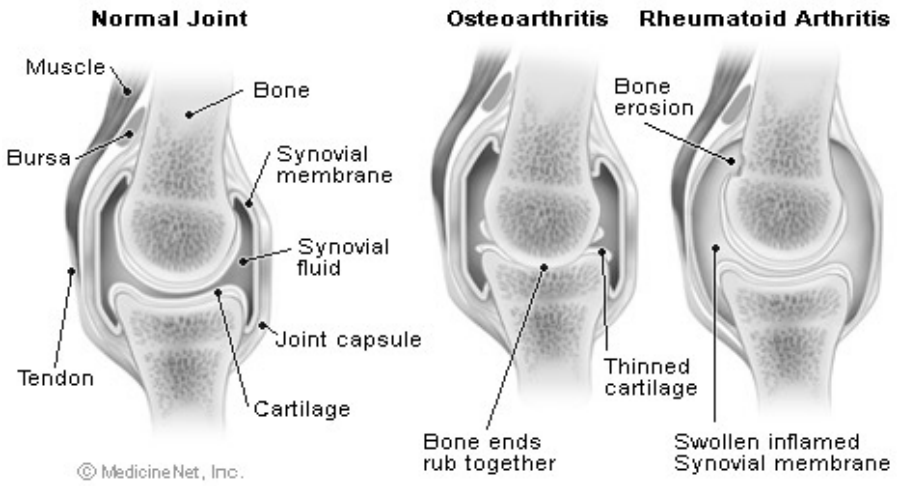

Fig:1. (Pictures from: www.medicinenet.com/rheumatoid_arthritis/article.htm)

It is principally affecting the synovial tissue (ST) of the joints. Its pathogenesis is complex and involves the collaboration of many cells of the immune system (**Fig. 1**). Although there has been argument regarding the relative importance of the various cell types and processes found in rheumatoid synovium, it is generally agreed that the disease process involves abnormal presentation of self antigen by antigen presenting cells (APC), leading to activation of autoreactive T lymphocytes, and that this autoimmunity is a fundamental element in the disease generation [3].

Main Symptoms

Painful and swollen joints, especially on hands, wrists, elbows, knees and feet Joint stiffness mainly in the morning or after long resting periods.
Fatigue
Muscular pain
Loss of appetite [4].

Epidemiology of RA

Rheumatoid arthritis is one of the most disabling types of arthritis, afflicting more than two million Americans. The prevalence of RA in most industrialized countries varies between 0.3% and 1%, whereas in developing countries it is at the lower end of this range. It affects approximately 1 per cent of world population including India [5, 6].

The descriptive epidemiology of RA is suggestive of a genetic effect. The occurrence of RA is relatively constant with a prevalence of between 0.5 and 1.0%, a frequency that has been reported from several European and North-American populations .Specifically, native American-Indian populations have the highest recorded occurrence of RA, with a prevalence of 5.3% noted for the Pima Indians and of 6.8% for the Chippewa Indians . By contrast, there are a number of groups with a very low occurrence. Studies in rural African populations, both in South Africa and in Nigeria failed to find any RA cases in studies of 500 and 2000 adults, respectively.

Studies in populations from Southeast Asia , including China and Japan have similarly shown very low occurrences (0.2–0.3%).18).Epidemiological studies in Scandinavia have revealed an annual incidence of 25 per 100,000 and a prevalence of about 0.5% [7].

Etiology

Disease affecting approximately 0.5%–1% of the global adult population with an estimated annual incidence of 12.0–24.5 males and 23.9–54.0 females per 100,000. RA occurs two to three times more often in women than in men. The incidence is largely consistent racially and geographically, and the peak age of onset lies between the ages of 45 and 65 years. The etiology of RA is unknown but seems to be multifactor. There is a certain genetic susceptibility, and studies in twins indicate a concordance of about 15%–20%. As many as 70% of patients with RA express HLA-DR4. Environmental factors (smoking) or infectious agents are suggested to play a role in the etiology, but their contribution has yet to be defined .RA is regarded as an autoimmune disease in that in genetically susceptible patients, certain putative antigens that are presented by macrophages produce T-cell–mediated auto reactivity against a joint component [8,9].

Pathophysiology

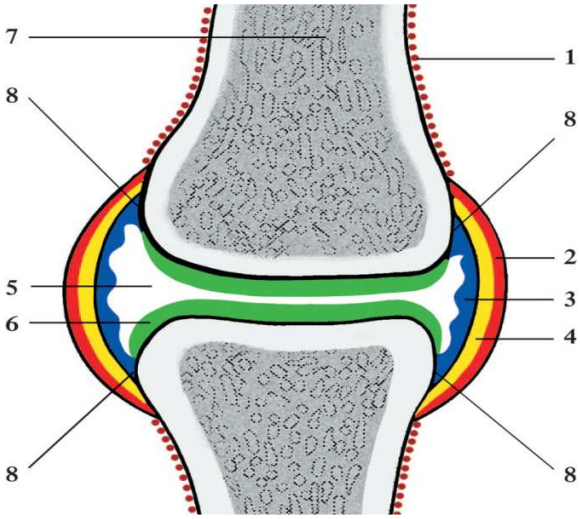

Fig: 2. Schematic drawing of a synovial joint. 1, periosteum, 2 outer fibrous layer of the capsule, 3 internal synovial layer of the capsule, 4 fat and loose soft tissue, 5 articular space, 6 cartilage, 7 bone, 8 bare area.

In RA, the synovium is the site of the pathologic process and synovial joints as well as tendon sheaths are involved. In the course of the disease, adjacent structures such as the bone, tendons, capsule, and ligaments typically are involved. In a synovial joint (Fig 2), the surface of the articulating bones is covered with cartilage except for a small region at the insertion of the joint capsule where—between the insertion of the fibrous capsule and the cartilage—the bone is covered by synovium only, the so-called “bare area.” Owing to the direct contact with the synovial tissue— without any protecting layer of cartilage—the bone surface in this location is very susceptible to synovitis-induced bone destruction. The periosteum is continuous with the fibrous outer layer of the capsule. The internal synovial layer is arranged in folds and is covered

by A cells derived from bone marrow and B cells of mesenchymal origin—the latter capable of phagocytosis. The two layers frequently are separated by fat [8].

The subsynovial tissue is rich in vessels. The interchange of fluid between vessels and the intraarticular space is facilitated due to lack of a basal layer under the synovialocytes. Synovial fluid is a dialysate of plasma, containing cells such as Europhiles and phagocytes. The content of fibrinogen and protein is lower compared with that in plasma. It acts both as a lubricant and as a nutrient. The nutrition of cartilage is provided through diffusion from the synovial fluid, by blood vessels that pass from the subchondral bone plate into the deep layers of the cartilage, and via blood vessels at the synovium-cartilage interface . Synovial hyperplasia and formation into pannus is the fundamental pathogenesis of RA. This process is mediated by production of various cytokines, for example, tumor necrosis factor (TNF-) and interleukin 1 (IL-1) by antigen presenting cells and T cells.

Hyperemia and pain induced inactivity lead to collateral changes involving the osseous compartment early on. Synovial tissue is invaded by local macrophages, fibroblasts, and activated lymphocytes. The next step in the pathophysiologic cascade is the invasion of the articular cartilage and bone by secretion of degrading enzymes, mainly metalloproteinases. TNF- and IL-1 also play a prominent role in bone destruction .Intraarticular loose bodies may develop as a consequence of the inflammatory process, thus perpetuating the inflammation themselves. If ineffectively treated, the disease may be disabling and mutilating, producing ankylosis, deformity, and severe secondary degenerative osteoarthritis [8].

Mechanism of joint destruction

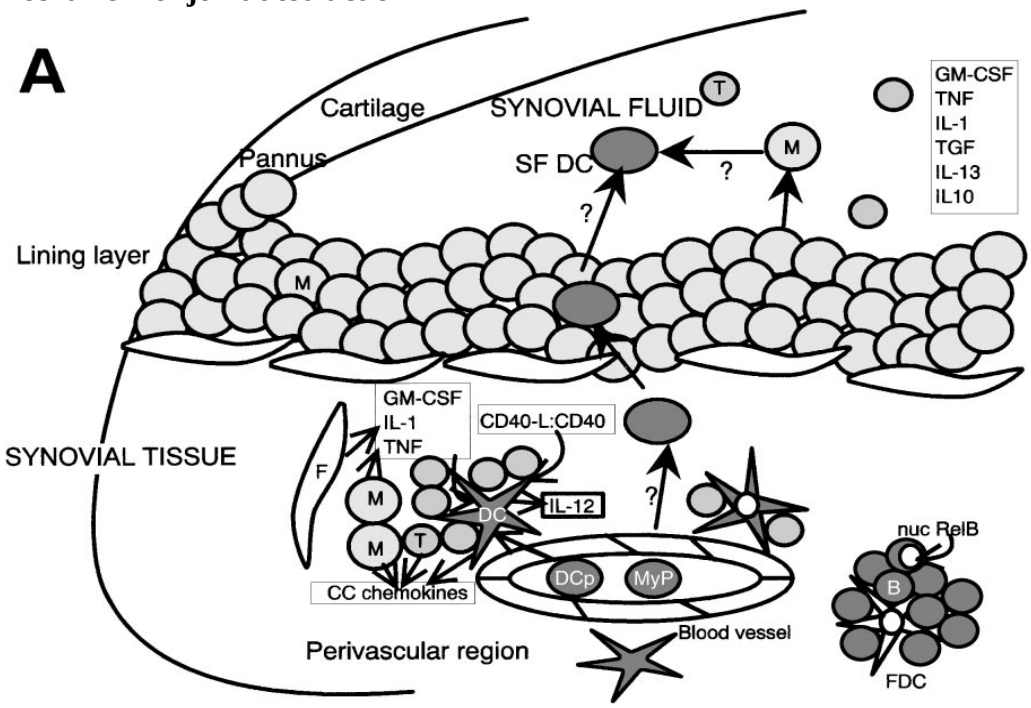

Fig:3. A model of APCs in rheumatoid synovium. T, T cells; B, B cell; DCp, precursor DC; MyP, myeloid progenitor; M, monocyte/macrophage; F, fibroblast; FDC, follicular DC; SF DC, synovial fluid DC.

Interleukin-1 (IL-1) plays an important role in mediating joint inflammation and destruction in RA. The IL-1 gene family contains three related genes, *IL-1A*, *IL-1B* and *IL-1RN*, which encode the proinflammatory cytokines IL-1a, IL-1b and their naturally occurring antagonist, interleukin-1 receptor antagonist (IL-1Ra), respectively. Il-1Ra acts by competitive blockade of IL-1 receptor without affecting downstream signaling6. IL-1Ra knockout mice spontaneously develop inflammatory arthritis resembling RA, and exogenous administration of IL-1Ra prevents bone damage in animal models and joint erosion in patients of rheumatoid arthritis [7].

Potential mechanisms of joint destruction in rheumatoid arthritis (RA) were examined by studying the regulation of mitogen-activated protein kinases and collagenase gene expression in fibroblast-like synoviocytes (FLS). The three main mitogen-activated protein kinase families [p38, Jun N-terminal kinase (JNK), and extracellular signal-regulated kinases (ERKs)] were constitutively expressed in RA and osteoarthritis (OA) FLS. p38 and ERK1/2 were readily phosphorylated in both RA and OA FLS after interleukin-1 (IL-1) stimulation. JNK was phosphorylated in RA FLS but not OA FLS after IL-1 stimulation. Reverse transcription-polymerase chain reaction studies suggested that JNK2 is the major isoform of the JNK family expressed by FLS. Northern blot analysis of collagenase gene expression demonstrated that RA FLS contained significantly more collagenase mRNA than OA FLS after IL-1 stimulation. The roles of JNK and p38 kinase were evaluated with the p38/JNK inhibitor SB 203580 [10].

Causes of Rheumatoid Arthritis

The exact cause of RA is unknown. It is considered a condition where multiple factors need to converge in an individual susceptible to the disease for it to develop The following are factors related to disease development.

Genes (passed from parent to child)
Environment
Hormones [11].

Genetic Factor (inheritance)

There is extensive evidence for a role for genetic factors in RA. Studies of monozygotic twins have revealed increased concordance rates of RA compared to dizygotic twins. The 2- to 3-fold higher prevalence of the disease in women, primarily due to an increased female incidence before menopause, has been interpreted as indicating a role for hormonal or reproductive factors; about 70% of patients with RA are women [12].

Environmental Factor

The term ‘environment’ is frequently used to describe all those susceptibility factors leading to disease that are not explicable on the basis of an identifiable genetic marker. There are environmental triggering factors which, together with the genetic factor, determine disease development. These factors include: geographic location/climate, level of development, smoking, hormonal level and some infections, mainly viral ones. These diseases are not a direct consequence of an infection; in fact, the infection alters the immune system cells. These cells, called lymphocytes, are in charge of producing antibodies, which are an important part of the body’s “defense” system. Viruses make cells work improperly, so they produce abnormal

antibodies which, instead of defending the organism, cause damage to other cells and body organs [5, 13].

Gender and Smoking Factor

This disease, like any other, may appear in different stages of life; most cases, however, start between age 30 and 50 in both sexes, although it is more common in women. A potential risk factor is cigarette smoking. Smoking is a well-established risk factor for the development of RA and also seems to be a predictor of disease severity. Interestingly, a recent study found smoking to be a predictor primarily in the subset of patients with RA-associated *HLA-DRB1* genotypes, indicating that genetic and environmental factors could interact in predisposing to RA.

In a strict sense, however, environment could be taken to refer to those factors external to the individual; for example, factors associated with diet, water or air-borne exposures. It is also important to consider factors implicated with diseases that are internal to the subject without an obvious genetic basis. An appropriate term for this group of factors is ‘non genetic host factors [5, 14].

Non genetic host factors: hormonal and pregnancy factors

The increased risk of RA in females has lead to considerable effort in examining the role of hormonal and pregnancy factors in disease occurrence. In general, male sex hormones, particularly testosterone, are lower in men who have RA by contrast levels of female sex hormones are not different between RA cases and controls. Pregnancy itself has been investigated as a risk factor in RA development. A number of studies have suggested that women who are nulliparous are at increased risk of developing the disease, although there is no increased risk in women who are single .It would thus appear that sub fertility highlights a group at higher risk [5].

Treatment for RH

In the fifties and early sixties, the treatment of RA revolved around the use of high-dose aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. These drugs provided symptomatic relief but did not have any significant effect on the underlying disease process. In addition, they caused a fair degree of side effects. Subsequently, disease modifying ant rheumatic drugs (DMARDs) [15].

Analgesics

These are painkillers, they aim at pain relief rather than reduction of inflammation. The most commonly prescribed analgesic is paracetamol. Codeine is another analgesic, which is sometimes prescribed as a combined medicine with paracetamol. This is known as co-codamol.

Non-steroidal anti-inflammatory drugs (NSAIDs)

The last 4 years or so have seen the advent of several new therapeutic agents for RA. Firstly, safer NSAIDs or ‘Coxibs’ have become available. The list which began with celecoxib seems to be expanding fast with the addition of rofecoxib, valdecoxib and etoricoxib etc.they relieve pain while they can also reduce stiffness and inflammation.

However, they don't affect disease progression. They act by blocking the action of the enzyme cyclo-oxygenase. This enzyme, and especially its second form (i.e. COX-2), produces prostaglandins which are involved in the inflammatory cascade of RA .Specific Cox-2 inhibitors were introduced into clinical practice recently. They reduce the incidence of serious gastro-intestinal events by about 80% of that observed with conventional NSAIDs. Patients likely to benefit most with Cox-2 inhibitors include elderly, those taking steroids or anticoagulants and those with past history of peptic ulcers. However, these agents lack antiplatelet effect. This has important implications in the context of RA. Recent work has shown that increased mortality in RA is because of higher incidence of atherosclerosis.

At present there is uncertainty about the efficacy of even conventional NSAIDs as substitutes for low dose aspirin in coronary artery disease (CAD) prophylaxis. Patients taking low dose aspirin for CAD or stroke must not discontinue it. Coxibs have renal adverse effects similar to those of conventional NSAIDs [15, 16 and 17].

Corticosteroids

Drugs such as prednisone and methylprednisolone are used to reduce pain and inflammation and can also reduce joint damage .They are usually used when NSAIDs fail to provide relief. Such drugs act directly on the immune system and lower its response to the antigen. Other side effects of corticosteroids include weight gain, osteoporosis, easy bruising, muscle weakness, and thinning of the skin. They can also worsen diabetes and glaucoma and increase risk for cardiovascular diseases [18].

Disease modifying anti-rheumatic drugs (DMARDs)

These included gold, d-penicillamine, chloroquine and hydroxychloroquine. These drugs had their limitations. Sulphasalazine was designed for the treatment of RA but failed in its initial trials to produce benefit. The drug was rediscovered about 30 years later and became an important addition to the other DMARDs. Methotrexate, sulfasalazine, hydroxychloroquine and cyclosporine, either alone, or in combination, have been the principal therapies for RA in the last decade .It is now well established that early therapy with DMARDs is critical for better long term outcome in RA. Also, combinations of DMARDs are well tolerated and result in better outcome than immunotherapy.

Leflunomide is an oral antimetabolite which has shown efficacy in the treatment of RA. It is a pro-drug which is rapidly converted to its active form, which inhibits dihydro-orotate dehydrogenase, the rate limiting enzyme for de novo synthesis of pyramiding nucleotides. Three large clinical trials [showed the clinical efficacy and safety of this drug as equivalent to that of methotrexate and sulfasalazine.

Currently, the drug merits the status of a very good alternative to methotrexate. Combination of leflunomide with methotrexate has been found to be superior to methotrexate alone The side effects of the drug in general include nausea, diarrhoea, drug rash, reversible alopecia, transient mild transaminitis and hypertension. It is advisable to monitor the blood pressure and liver functions [15, 19, 20 and 21].

Biologics

Secondly, interventions designed specifically to target pathogenic cytokines have reached the clinic. These include most notably, anti-TNF antibody or 'infliximab', soluble TNF-a receptor or 'etanercept' and interleukin-1 receptor antagonist or 'anakinra'. The other very important new agent is leflunomide [15, 22, 23 and 24].

Botanical Medicines

One of the most supportive botanical medicines for the patient with RA may well be curcumin or turmeric (*Curcumaonga*). Notable for its ability to act as an antioxidant and anti-inflammatory, curcumin seems well suited for treating this condition. More recent research suggests that curcumin is a potent inhibitor of the signaling pathway utilized by a specific type of IL-6, called oncostatin M. If not inhibited via this pathway, oncostatin M signaling results in the transcription/ translation of metalloproteinases and their inhibitors. An imbalance between metalloproteinases and their inhibitors may represent one of the mechanisms of joint damage in RA. To be able to slow metalloproteinase expression down may represent one of the many recently discovered mechanisms of efficacy of an ancient herb.

A second botanical option recently reported in the botanical literature is the Ayurvedic herbal combination Maharasnadhi Quathar (MQR). In a 3-month study that involved 45 patients with this herbal combination and a second group treated with another traditional preparation, the patients in the MQR-treated group demonstrated significant increases in the activity of the antioxidant enzymes superoxide dismutase, catalase, and glutathione peroxidase. 56 Another finding of the study was that lipid peroxidation was reduced by 34 percent in the MQR-treated group. MQR is a combination of 26 herbs, with the bulk (70 percent) of its composition accounted for by alpinia galangal (*Alpinia calcarata*), but also including a variety of other plants, such as ginger (*Zingiber officianale*), tropical almond (*Terminalia chebula*), tribulus (*Tribulus terrestrin*), ashwagandha (*Withania somnifera*), and coriador also called Chinese parsley (*Coriandrum sativum*). Oleoresin gum extracts of boswellia (*Boswellia serrata*), with 37.5–65 percent boswellic acid, exert potent anti-inflammatory actions via inhibition of proinflammatorie s such as leukotrienes.

The recommended boswellia dose is 150 mg 3 times per day. Bromelain, a commonly used proteolytic enzyme, has direct clinical application for treating RA, as do other enzymes. Select results have yielded upward of 73-percent positive results, ranging from good to excellent.58 Ginger extracts have demonstrated benefit as well, with good pain relief, with proposed mechanisms conjectured to include one or more of the following mechanisms of action: thromboxane synthetase inhibition and prostacyclin agonists and prostaglandin synthesis inhibition. These herbs and numerous others show promise for alleviating symptoms and potentially modulation of pathophysiologic changes. Other select herbs that have been used in the treatment of RA include: cayenne *(Capsicumf rutescens)*, feverfew (*Tanacetumparthenium*), devil's claw (*Harpagophytum procumbens*), stinging nettle (*Urtica dioica)*, thunder god vine *(Tripterygium wilfordi)*, and yucca (*Yucca glauca*) [25].

Animal models of RA

Animal models of RA such as collagen-induced arthritis (CIA) in DBA/1 strain of mice, adjuvant- induced arthritis in Lewis rats and antigen induced arthritis in rabbits have been

essential in understanding the possible pathogenic mechanisms of this disease. They have been also served as basic models for the development of therapeutic strategies [26].

Over the past several decades, many inductive models of inflammatory polyarthritis, such as collagen-induced arthritis (CIA) and adjuvant-induced arthritis, have been employed to study immune responses in arthritis. These animal models of arthritis have contributed significantly to our understanding of cellular and molecular events that may be relevant to RA. Recently, several models of spontaneous arthritis have been identified due to perturbations in the TCR and alterations of cytokine regulation. Recent data from these animal models emphasize that inflammatory arthritis can be engendered by T-cell auto-reactivity through pathways that also require participation of other arms of both the innate and adaptive immune responses, ranging from production of autoantibodies by B cells to elaboration of proinflammatory cytokines [27,28].

CONCLUSION

As rheumatoid arthritis is caused by an autoimmune disorder care should be taken in the treatment of RA by using immunosupresants as it may affect the natural immune system of the body thus making the body prone for easy attack of different microorganisms. Therefore in the treatment of RA primarily analgesics are preferred for symptomatic treatment for relieving pain and is continued by a usage of a immunosupresant in the form of herbal drug as our body is already genetically habituated to herbal drugs therefore they act as immunomodulators rather than as immunosupressants. Thus this article has provided animal models for the young scientists so that they can fasten the search for herbal immunomodulaters.

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