ORIGINAL RESEARCH PAPER

Volume-7 | Issue-8 | August-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

PHYSIOLOGY, PATHOPHYSIOLOGY AND PHARMACOLOGICAL STUDY OF RHEUMATOID ARTHRITIS

Pharmacy

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation of the joints. Autoimmune disease is an illness that occurs when the body's tissues are mistakenly attacked by their own immune system. The non-antigen specific hypothesis of the initiation of rheumatoid synovitis is that an early and episodic release of Tumour Necrosis Factor α (TNFα) and granulocyte–macrophage colony-stimulating factor (GM-CSF) from synovial macrophages and fibroblasts are induced by minor trauma, allergic responses, infections and local immune complex deposition. The major chemokine in RA is IL-8 and other chemokines are found in the synovial fluid of patients with RA, including macrophage inflammatory protein 1 alpha and monocyte chemotactic protein1.The clinical features of rheumatoid arthritis includes , Joint pain, pain in the joints of the feet, hands, and knees, swollen joints, fever, limping, polyarthritis, loss of range of motion, tender joints, loss of joint function, stiff joints, fatigue, joint redness, rheumatoid nodules, anemia, joint warmth and joint deformity.

KEYWORDS

Inflammation, Immune System, Tnfα, Gm-csf, Macrophage Inflammatory Protein 1 Alpha And Monocyte Chemotactic Protein1.

1.INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation of the joints. Autoimmune disease is an illness that occurs when the body's tissues are mistakenly attacked by their own immune system. The immune system contains a complex organization of cells and antibodies designed normally to destroy the foreign bodies or microbes causing the infections. Patients with autoimmune diseases have antibodies and immune cells in their blood that target their own body tissues, where they can be associated with inflammation. While inflammation of the tissue around the joints is characteristic feature of rheumatoid arthritis, the disease can also cause inflammation and injury in other organs in the body, because it can affect other organs of the body. Rheumatoid arthritis is referred to as a systemic illness and is sometimes called rheumatoid disease. Rheumatoid arthritis that begins in people under 16 years of age is referred to as juvenile idiopathic arthritis (JIA) [1-3].

Inflamed synovium is central to the pathogenesis. The synovium shows increased angiogenesis, cellular hyperplasia, influx of inflammatory cells, changes in the expression of cell surface adhesion molecules, and many cytokines. The synovial lining becomes hyper plastic, with infiltration of the sublining with mononuclear cells including T-cells, B cells, macrophages, and plasma cells. This formation of locally invasive synovial tissue is characteristic and it is involved in causing the erosions seen in RA. Cytokines affect all phases of the inflammatory process and tumour necrosis factor (TNF), interleukin 1, and interleukin 6 seem to be the most abundant in the joint. Both are stimulators of proliferation, metalloproteinase expression, adhesion molecule expression, and further secretion of other cytokines. High levels of metalloproteinase activity are thought to contribute to joint destruction. Angiogenesis is active and leads to new blood vessels proliferating to provide for the hypertrophic synovium. This very inflammatory setting, when not treated, leads to the eventual destruction of the involved joint [4-6].

Although research into medications to treat rheumatoid arthritis (RA) is ongoing, there is no current cure for this condition. Still, a healthy diet, proper rest, stress management, and regular exercise can help to improve the quality of life. Over-the-counter medications and complementary treatments can also help to relieve pain and reduce inflammation [7].

2. PHYSIOLOGY

Cytokines can be classified according to their functions in the rheumatoid disease process. Cytokines are grouped under hematopoietic, immunoregulatory, growth and differentiation pro-inflammatory, anti-inflammatory and chemo tactic factors. However, it should be emphasized that any cytokine may function under more than one of these categories. Cytokine receptors are classified by their structural similarities, as well as by the use of common molecules of signal transduction. In general, the production of cytokines can be induced by bacterial and viral products, complement split products, immune complexes, fragments of connective tissue proteins, acute-phase proteins, or other cytokines themselves. The mechanisms by which excess production of IL-1 and TNFα is stimulated in the rheumatoid synovium remain unclear, but macrophages in the inflamed synovium appear to be the main source [8].

Initiation of rheumatoid synovitis

A number of cytokines are involved in early events in the rheumatoid synovium. The mechanisms by which rheumatoid synovitis is initiated remain unclear, but they may involve both antigen-specific and non–antigen-specific mechanisms. Activated T cells, expressing HLA–DR4 with the MHC-shared epitope, may initiate the pathophysiologic process. The responsible T cell antigens remain elusive, and they may be multiple, including viral or bacterial products. The activated T cells may cross-react with self-antigens, leading to the stimulation of macrophages both through the release of cytokines such as interferon gamma (IFNγ) and by direct cell-to-cell contact [9-13].

The non–antigen-specific hypothesis of the initiation of rheumatoid synovitis is that an early and episodic release of Tumour Necrosis Factor α (TNFα) and granulocyte–macrophage colony-stimulating factor (GM-CSF) from synovial macrophages and fibroblasts are induced by minor trauma, allergic responses, infections, vaccinations, or local immune complex deposition. These cytokines are differentiating resident dendritic cells into potent antigen-presenting cells, which are selectively present self-antigens for the induction of specific T cell responses. The presence of the shared epitop is decrease the threshold for the transformation of a mild reactive synovitis into a rapidly destructive synovial reaction by increasing the presentation of self-antigens by the dendritic cells.

Cytokines are intimately involved in the next phase of rheumatoid synovitis, which is characterized by the migration of inflammatory and immune cells from the blood into the synovial space and tissue. Interleukin-1 and TNFα, as well as IL-8 and GM-CSF, from stimulated macrophages up-regulate the expression of adhesion molecules on endothelial cells in synovial post capillary venules. Nucleated cells in the blood attach to these activated endothelial cells and, under the influence of chemokines, migrate into the synovium [14-18].

The major chemokine in RA is IL-8, but other chemokines are found in the synovial fluid of patients with RA, including macrophage inflammatory protein 1 alpha and monocyte chemotactic protein1. Chemokines in the rheumatoid synovium are derived primarily from macrophages and fibroblasts. These molecules then attract neutrophils, monocytes, and T cells into the rheumatoid synovium, where they are

stimulated by other cytokines. Neutrophils are found primarily in the synovial fluid, and monocytes and T cells are found in both the fluid and inflamed synovial tissue.

Establishment of chronic synovitis

The cytokines found in rheumatoid synovial tissue, and their roles in mediating events of inflammation and tissue destruction, have been well characterized over the past 10 years. The initial studies concluded that the major cytokines in the rheumatoid synovium were derived from macrophages and fibroblasts.

Systemic effects of cytokines

In addition to having local effects in rheumatoid synovitis, cytokines may also have prominent systemic effects in this disease. The acute-phase response includes an increase in the levels of proteins of the complement system, coagulation and fibrinolytic systems, antiproteases, transport proteins, and other proteins that participate in the inflammatory response, such as the cytokine IL-1Ra. These proteins are synthesized in the liver by hepatocytes that are stimulated by IL-6 and other cytokines that are present in acute and chronic inflammatory diseases as well as in malignancies and infections. The acute-phase proteins are largely anti-inflammatory, but IL-6 and other members of its family, such as IL-11, may have both pro-inflammatory and anti-inflammatory properties. Other systemic manifestations of RA, such as fever, fatigue, myalgias, muscle degradation, and weight loss, are induced primarily by IL-1 and TNFα [19-22].

Regulation of the cytokine network

The cytokine network is self-regulating, with cytokine antagonists, antibodies to cytokines, and soluble cytokine receptors all potentially acting to limit the injurious effects of inflammatory cytokines (Table 3). The major cytokines that have anti-inflammatory effects include IL-4, IL-10, IL-13, TGFβ, and IL-1Ra, with IL-10 and IL-1Ra being found in large amounts in the rheumatoid synovium. Interleukin 10 may suppress the production of IL-1 and TNFα in this tissue, while increasing the production of IL-1Ra. The therapeutic administration of IL-10 is currently being evaluated in patients with RA. TGFβ may have both pro-inflammatory and anti-inflammatory effects in animal models of arthritis. In patients with RA, TGFβ may suppress T cell functions, inhibit fibroblast proliferation and production of tissue-damaging enzymes, and increase the production of specific inhibitors of these enzymes [23].

3. PATHOPHYSIOLOGY

Rheumatoid arthritis (RA) is a chronic and usually progressive inflammatory disorder of unknown aetiology characterized by poly articular symmetric joint involvement and systemic manifestations. RA results from a dysregulation of the humoral and cell-mediated components of the immune system. Most patients produce antibodies called rheumatoid factors; these seropositive patients tend to have a more aggressive course than patients who are seronegative. Immunoglobulins can activate the complement system, which amplifies the immune response by enhancing chemo taxis, phagocytosis, and release of lymphokines by mononuclear cells that are then presented to Tlymphocytes. The processed antigen is recognized by the major histocompatibility complex proteins on the lymphocyte surface, resulting in activation of T and B cells.

Tumor necrosis factor (TNF), interleukin-1 (IL-1), and IL-6 are pro inflammatory cytokines important in the initiation and continuance of inflammation. Activated T cells produce cytotoxins, which are directly toxic to tissues, and cytokines, which stimulate further activation of inflammatory processes and attract cells to areas of inflammation. Macrophages are stimulated to release prostaglandins and cytotoxins. Activated B cells produce plasma cells, which form antibodies that, in combination with complement, result in accumulation of polymorphonuclear leukocytes. Polymorpho nuclear leukocytes release cytotoxins, oxygen free radicals, and hydroxyl radicals that promote cellular damage to synovium and bone.

Vasoactive substances (histamine, kinins, and prostaglandins) are released at sites of inflammation, increasing blood flow and vascular permeability. This causes edema, warmth, erythema, and pain and makes it easier for granulocytes to pass from blood vessels to sites of inflammation. Chronic inflammation of the synovial tissue lining the joint capsule results in tissue proliferation. Pannus invades cartilage and eventually the bone surface, producing erosions of bone and cartilage and leading to joint destruction. The end results may be loss of joint space, loss of joint motion, bony fusion, joint subluxation, tendon contractures and chronic deformity [24-28].

Stages of rheumatoid arthritis:

The American College of Rheumatology has developed a system for classifying rheumatoid arthritis that is primarily based upon the X-ray appearance of the joints. This system helps medical professionals classify the severity of rheumatoid arthritis with respect to cartilage, ligaments, and bone.

Stage I

- No damage seen on X-rays, although there may be signs of bone thinning
- Stage II
- On X-ray, evidence of bone thinning around a joint with or without slight bone damage
- Slight cartilage damage possible
- Joint mobility may be limited; no joint deformities observed
- Atrophy of adjacent muscle
- Abnormalities of soft tissue around joint possible

Stage III

- On X-ray, evidence of cartilage and bone damage and bone thinning around the joint
- Joint deformity without permanent stiffening or fixation of the joint
- Extensive muscle atrophy
- Abnormalities of soft tissue around joint possible

- **Stage IV**
- On X-ray, evidence of cartilage and bone damage and osteoporosis around joint
- Joint deformity with permanent fixation of the joint (referred to as ankylosis)
- Extensive muscle atrophy
- Abnormalities of soft tissue around joint possible
- Rheumatologists also classify the rheumatoid arthritis in the people as follows:

Class I: completely able to perform usual activities of daily living
Class II: able to perform usual self-care and work activities but limited in activities outside of work (such as playing sports, household chores)
Class III: able to perform usual self-care activities but limited in work and other activities
Class IV: limited in ability to perform usual self-care, work, and other activities.

Symptoms:

Rheumatoid arthritis is an autoimmune disease that causes chronic inflammation of the joints and other areas of the body [29-31].

Rheumatoid arthritis symptoms and signs include:

Joint pain, such as in the joints of the feet, hands, and knees,Swollen joints, fever, limping, polyarthritis,loss of range of motion,tender joints,loss of joint function,stiff joints, fatigue, joint redness, rheumatoid nodules,anemia,joint warmth,joint deformity, and symptoms and signs that affect both sides of the body (symmetry). Rheumatoid arthritis is a chronic disease characterized by periods of disease flares and remissions. In rheumatoid arthritis, multiple joints are usually, but not always, affected in a symmetrical pattern. Chronic inflammation of rheumatoid arthritis can cause permanent joint destruction and deformity. Damage to joints can occur early and does not always correlate with the severity of RA symptoms [32-34].

4. CURRENT STRATAGIES:
(Pharmacological study of rheumatoid arthritis drugs)

I.NSAIDs:

Non steroidal anti-inflammatory drugs (NSAIDs) can relieve pain and reduce inflammation. Over-the-counter NSAIDs include ibuprofen (Advil, Motrin IB) and naproxen sodium (Aleve). Stronger NSAIDs are available by prescription. Side effects may include ringing in your ears, stomach irritation, heart problems, and liver and kidney damage.

II.Steroids:

Corticosteroid medications, such as prednisone, reduce inflammation and pain and slow joint damage. Side effects may include thinning of bones, weight gain and diabetes. Doctors often prescribe a corticosteroid to relieve acute symptoms, with the goal of gradually tapering off the medication.

III.Disease Modifying Antirheumatic Drugs (DMARDs)
DMARDs

Disease-modifying antirheumatic drugs (DMARDs) are used to decrease inflammation. Unlike other medications that temporarily ease pain and inflammation, DMARDs can slow the progression of RA. These drugs can slow the progression of rheumatoid arthritis and save the joints and other tissues from permanent damage.

The most common DMARDs used to treat RA include:

- Hydroxychloroquine (Plaquenil)
- Leflunomide (Arava)
- Methotrexate (Trexall)
- Sulfasalazine (Azulfidine)
- Minocycline (Minocin)

Biologics are injectable drugs. They work by blocking specific inflammatory pathways made by immune cells. This reduces inflammation caused by RA. Doctors prescribe biologics when DMARDs alone aren't enough to treat RA symptoms. Biologics aren't recommended for people with compromised immune systems or an infection. This is because they can raise risk of serious infections.

IV.Biological agents.

Also known as biologic response modifiers, these are newer class of DMARDs (Disease Modifying Anti Rheumatic Drugs).These drugs can target parts of the immune system that trigger inflammation that causes joint and tissue damage. These types of drugs also increase the risk of infections.Biologic DMARDs is usually most effective when paired with a nonbiologic DMARD, such as methotrexate. The most common biologics include: tocilizumab (Actemra), anakinra (Kineret), adalimumab (Humira), etanercept (Enbrel)infliximab,(Remicade), certolizumab pegol (Cimzia) golimumab (Simponi) abatacept (Orencia) and rituximab (Rituxan)

V.Surgery

If medications fail to prevent or slow joint damage, you and your doctor may consider surgery to repair damaged joints. Surgery may help restore your ability to use your joint. It can also reduce pain and correct deformities.

Rheumatoid arthritis surgery may involve one or more of the following procedures:

Synovectomy:

Surgery to remove the inflamed synovium (lining of the joint). Synovectomy can be performed on knees, elbows, wrists, fingers and hips.

Tendon repair:

Inflammation and joint damage may cause tendons around your joint to loosen or rupture. Your surgeon may be able to repair the tendons around your joint.

Joint fusion:

Surgically fusing a joint may be recommended to stabilize or realign a joint and for pain relief when a joint replacement isn't an option.

Total joint replacement:

During joint replacement surgery, surgeon removes the damaged parts of joint and inserts a prosthesis made of metal and plastic. Surgery carries a risk of bleeding, infection and pain. Discuss the benefits and risks with doctor [35-38].

VI.Alternative medicine

Some common complementary and alternative treatments that have shown promise for rheumatoid arthritis include:

Fish oil: Some preliminary studies have found that fish oil supplements may reduce rheumatoid arthritis pain and stiffness. Side effects can include nausea, belching and a fishy taste in the mouth. Fish oil can interfere with medications, so check with your doctor first.

Plant oils: The seeds of evening primrose, borage and black currant contain a type of fatty acid that may help with rheumatoid arthritis pain and morning stiffness. Side effects may include nausea, diarrhoea and gas. Some plant oils can cause liver damage or interfere with medications, so check with your doctor first.

Tai chi: This movement therapy involves gentle exercises and stretches combined with deep breathing. Many people use tai chi to relieve stress in their lives. Small studies have found that tai chi may reduce rheumatoid arthritis pain. When led by a knowledgeable instructor, tai chi is safe. But don't do any moves that cause pain.

5. SUMMARY

This review has summarized the physiology of some cytokine pathways in RA, emphasizing the redundant and synergistic nature of this network. However, it is important to understand that this system is self-regulating through the action of anti-inflammatory cytokines, opposing cytokines, cytokine receptor antagonists, and possibly naturally occurring antibodies to cytokines (Figure 1). Disease results when an imbalance in the cytokine network develops, either from excess production of pro-inflammatory cytokines or from inadequate presence of natural anti-inflammatory mechanisms. The current therapeutic approaches to RA that are aimed at restoring this balance include the use of monoclonal antibodies to TNFα, soluble TNFα receptors, and IL-1Ra. Other therapeutic agents that interfere with the cytokine network are in various stages of preclinical and clinical evaluation.

6. CONCLUSION:

A marked increase in plasma levels of leptin, adiponectin and visfatin was noted in patients with rheumatoid arthritis, whereas resistin levels were similar to those observed in healthy controls. Coordinated roles for adiponectin, leptin and visfatin are suggested in the modulation of the inflammatory environment in patients with rheumatoid arthritis, whereas the lack of modulation in resistin levels is predictive of an irrelevant role for this peptide, suggesting that resistin level is probably not one of the main signals associated with the pathogenesis of this disease.

The pathogenic advances described here, the effective therapies and remarkable improvement in clinical outcomes have been observed. Severe disease manifestations, such as vasculitis, nodule formation, scleritis, and amyloidosis that are associated with persistent, uncontrolled inflammation have become rare. There is a need to understand the factors that lead to loss of tolerance and that cause localization of inflammation in the joint. There is a need to find the ways to promote immunologic resolution or homeostasis and repair of damaged joints. There must elucidate the mechanisms driving the various systemic disorders that contribute substantially to reductions in the quality and length of life. Ultimately, must strive to develop curative and preventive therapeutics that will transform the notion of rheumatoid arthritis as a chronic disease.

7. ACKOWLEDGEMENT

I sincerely thankful to coauthors during the work in SIMS college of Pharmacy and Dr.S.Manohar babu, Principal of SIMS College of pharmacy, Mangaldas Nagar, Guntur, A.P, for providing required facilities during review work.

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