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MANAGEMENT OF RHEUMATOID ARTHRITIS: AN OVERVIEW

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ABSTRACT

The word arthritis means inflammation of the joint ("arthr" meaning joint and "itis" meaning inflammation). Inflammation is a medical term describing pain, stiffness,redness and swelling. There are more than 100 types of arthritis. Some are caused by joint inflammation, while others are caused by progressive bone and joint damage. The major complaint by individuals who have arthritis is joint pain. Pain is often a constant and may be localized to the joint affected. The pain from arthritis is due to inflammation that occurs around the joint, damage to the joint from disease, daily wear and tear of joint, muscle strains caused by forceful movements against stiff painful joints and fatiguein the majority of cases arthritis causes pain and swelling in the joints.eventually a swollen joint can suffer severe damage. in some cases, arthritis can cause problems in the patient's eye, skin or other organs. Arthritis is not a single disease ,it is a term that covers over 100 medical conditions. Osteoarthritis (oa) is the most common form of arthritis and generally affects elderly patients. some forms of arthritis can affect people at a very early age. rthritis affects the musculoskeletal system, specifically the joints. It is the main cause of disability among people over fifty-five years of age in industrialized countries**.** Rheumatoid arthritis is characterised by persistent synovitis, systemic infl ammation, and autoantibodies (particularly to rheumatoid factor and citrullinated peptide). 50% of the risk for development of rheumatoid arthritis is attributable to genetic factors. Smoking is the main environmental risk. In industrialised countries, rheumatoid arthritis aff ects 0·5–1·0% of adults, with 5–50 per 100 000 new cases annually. The disorder is most typical in women and elderly people. Uncontrolled active rheumatoid arthritis causes joint damage, disability,decreased quality of life, and cardiovascular and other comorbidities.

Key Word- inflammation, Rheumatoid arthritis, Cartilage, joint.

INTRODUCTION

Arthritis (from greek arthro-, joint + -itis, inflammation; plural: arthritides) is a form of joint disorder that involves inflammation of one or more joints. says that if you have trouble moving around or feel pain and stiffness in your body, you could have arthritis. Rheumatoid arthritis (RA) is a form of arthritis in which the synovial tissues in the joints become inflamed. The search for the causes of RA has not led to any general agreement on the aetiology of RA (Fox, 1997). While approximately 150 studies have found dietary influences on RA (Panush, 1997; Henderson & Panush, 1999), the level of scientific methodology for most of the studies is such that generally they are not accepted by the medical establishment Often the studies were performed on a small group of subjects without adequate case control protocols.[1]Rheumatoid arthritis (RA) is an inflammatory disease that exerts its greatest impact on those joints of the body that are lined with synovium, a specialized tissue responsible for maintaining the nutrition and lubrication of the joint. The distribution of joints affected (synovial joints) is characteristic. It typically affects the small joints of the hands and the feet, and usually both sides equally in a symmetrical distribution, though any synovial joint can be affected. In patients with established and aggressive disease, most joints will be affected over time. The initial trigger for RA is unknown. There is evidence to suggest abnormalities in components of the immune system that lead to the body developing abnormal immune and inflammatory reactions, particularly in joints. These changes may precede the symptomatic onset of RA by many years. Whatever sets the pathology in motion results in a large increase in blood flow to the joint (giving heat and sometimes redness), proliferation of the synovial membrane with an increase in synovial fluid (swelling), and pain (due to stretching of pain receptors in the soft tissues around, and the bone on either side, of the joint). [2,3]Rheumatoid arthritis has 19th century roots and a 20th century pedigree. Although its name was introduced in the 1850s, classification criteria were only developed 50 years ago.[3] Observational studies in which these criteria are used portray treated rheumatoid arthritis as a serious long-term disease with dominant extra-articular features, limited treatment options, and poor outcomes.[4,5] Tumour necrosis factor (TNF) inhibitors and other biological agents have heralded a so-called therapeutic revolution, transforming the outlook for patients with rheumatoid arthritis. However, improved disease outcomes preceded biological agents, refl ecting early use of conventional drugs, ambitious treatment goals, and better management of comorbidities. An historic parallel is the 1950s revolution in

tuberculosis care, when improved conventional management followed by effective chemotherapy made tuberculosis curable .[4]

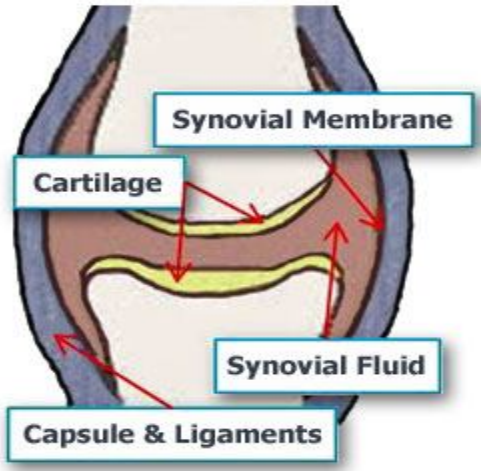
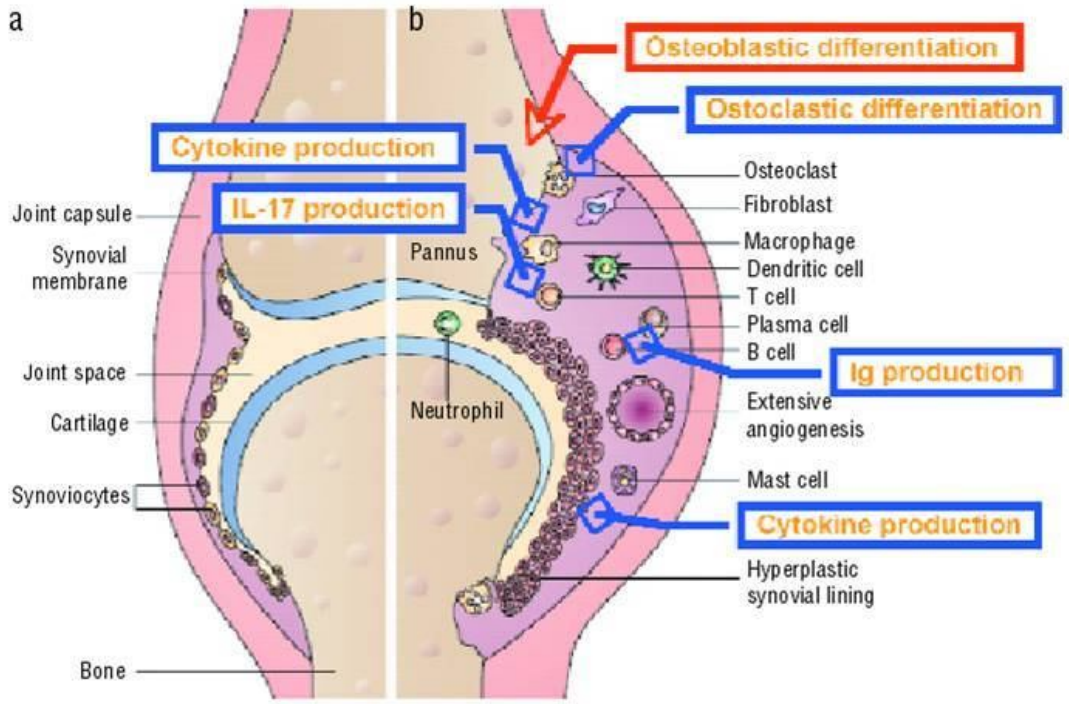


Figure 1 .Cause of Arthritis

Causes of arthritis

In order to better understand what is going on when a person suffers from some form of arthritis, let us look at how a joint works. Basically, a joint is where one bone moves on another bone. Ligaments hold the two bones together. The ligaments are like elastic bands, while they keep the bones in place your muscles relax or contract to make the joint move.Cartilage covers the bone surface to stop the two bones from rubbing directly against each other. The covering of cartilage allows the joint to work smoothly and painlessly a capsule surrounds the joint. The space within the joint - the joint cavity - has synovial fluid. Synovial fluid nourishes the joint and the cartilage. The synovial fluid is produced by the synovium (synovial membrane) which lines the joint cavity If you have arthritis something goes wrong with the joint(s). What goes wrong depends on what type of arthritis you have. It could be that the cartilage is wearing away, a lack of fluid, autoimmunity (your body attacking itself), infection, or a combination of many factors.RA is a condition that can affect several joints, most commonly the small joints in the hands and feet but does affect knees, hips and shoulder joints too. Several joints can be affected at the same time, usually on both sides of the body, symmetrically. RA causes the joint lining to become inflamed and swollen resulting in destruction of the joint surface, causing extreme tenderness and pain. RA is a 'systemic' (universal) disease which means that it can affect the whole body including the heart, lungs and eyes, but this is less common.[5, 6]



⇩ **Stimulate by Iguratimod** ⇧ **Inhibit by Stimulate by Iguratimod**

Figure 2. (A) In the Healthy Joint and (B) Rheumatoid Arthritis

Types of arthritis

There are over 100 types of arthritis. Here is a description of some common ones, together with the causes

Osteoarthritis

Is an extremely common condition and is often referred to as 'wear and tear' of the joints in the body. The surface of the joint is damaged and the surrounding bone grows thicker. The joints most commonly affected are the knees, hips, hands and spine cartilage loses its elasticity. If the cartilage is stiff it becomes damaged more easily. [7]The cartilage, which acts as a shock absorber, will gradually wear away in some areas. As the cartilage becomes damaged tendons and ligaments become stretched, causing pain. Eventually the bones may rub against each other causing very severe pain.[8]

Rheumatoid arthritis

The most common inflammatory arthritis – is a chronic disease that affects the joints, often in the wrists, fingers and feet. Common symptoms include pain, stiffness and fatigue.this is an inflammatory form of arthritis. The synovial membrane (synovium) is attacked, resulting in

swelling and pain. If left untreated the arthritis can lead to deformity. Rheumatoid is significantly more common in women than men and generally strikes when the patient is aged between 40 and 60. However, children and much older people may also be affected.During the first ten years after diagnosis; patients with rheumatoid arthritis have a higher risk of blood clots.

Infectious arthritis (septic arthritic)

an infection in the synovial fluid and tissues of a joint. It is usually caused by bacteria, but could also be caused by fungi or viruses.Bacteria, fungi or viruses may spread through the bloodstream from infected tissue nearby, and infect a joint.Most susceptible people are those who already have some form of arthritis and develop an infection that travels in the bloodstream.[9]

Psoriatic Arthritis

Psoriasis is an autoimmune disease that occurs when the immune system becomes confused and decides to "attack" the skin. This results in red (inflamed) patches of skin, which are covered with a silvery-white scale. Psoriasis can involve only a few small patches of skin to much larger areas of the skin. In most people, psoriasis tends to be mild and some don't even realize they have it at all. Psoriatic arthritis (PsA) is a type of inflammatory arthritis and an autoimmune disease. In PsA, the joints are the target of the immune attack. This causes swelling, pain and warmth (inflammation) in the joints.[10]

What are the signs and symptoms of arthritis?

The symptoms of arthritis depend on the type, for example

- **Osteoarthritis** - The symptoms develop slowly and get worse as time goes by. There is pain in a joint, either during or after use, or after a period of inactivity. There will be tenderness when pressure is applied to the joint. The joint will be stiff, especially first thing in the morning.The patient may find it harder to use the joint - it loses its flexibility. Some patients experience a grating sensation when they use the joint. Hard lumps, or bone spurs may appear around the joint. In some cases the joint might swell.The most commonly affected joints are in the hips, hands, knees and spine.[11,12]

- **Rheumatoid arthritis** - The patient often finds the same joints in each side of the body are painfully swollen, inflamed, and stiff. The fingers, arms, legs and wrists are most commonly affected.Symptoms are usually worst on waking up in the morning and the

stiffness can last for 30 minutes at this time. The joint is tender when touched. Hands may be red and puffy. There may be rheumatoid nodules (bumps of tissue under the skin of the patient's arms).

Many patients with rheumatoid arthritis feel tired most of the time. Weight loss is common.

The smaller joints are usually noticeably affected first. Experts say patients with rheumatoid arthritis have problems with several joints at the same time.As the arthritis progresses it spreads from the smaller joints in your hands, wrists, ankles and feet to your elbows, knees, hips, neck, shoulders and jaw.[13]

- **Infectious arthritis -** The patient has a fever, joint inflammation and swelling. He will feel tenderness and/or a sharp pain. Often these symptoms are linked to an injury or another illness.Most commonly affected areas are the knee, shoulder, elbow, wrist and finger. In the majority of cases just one joint is affected.[14]

- **Juvenile rheumatoid arthritis -** The patient is a child. He will experience intermittent fevers which tend to peak in the evening and then suddenly disappear. His appetite will be poor and he will lose weight.There may be blotchy rashes on his arms and legs. Anemia is also common. The child may limp or have a sore wrist, finger, or knee. A joint may suddenly swell and stay larger than it usually is. The child may experience a stiff neck, hips or some other joint.[15]

Pathophysiology

Rheumatoid arthritis is best considered a clinical syndrome spanning several disease subsets.These different subsets entail several infl ammatory cascades,which all lead towards a fi nal common pathway in which persistent synovial infl ammation and associated damage to articular cartilage and underlying bone are present.Synovial joints, such as the knee, have the most flexibility due to unity of bones by connective tissue of an articular capsule and accessory ligaments. In RA, the immune response will be activated in an early stage of life. This immune response could be triggered by genetic and environmental factors. Once the immune system is unbalanced, subclinical inflammation will occur due to activation of T cells from an antigen-presenting cell. Once T cells are proliferated, a cascade of events occurs in the immune system: activation of B cells and macrophages, as well as other proinflammatory mediators such as tumor necrosis factor (TNF) and interleukin (IL). As the

immune system remains unchecked, symptoms associated with RA will occur and the criteria for the disease will be fulfilled. Once the diagnosis is confirmed, the pathologic inflammatory response can continue, resulting in joint destruction and extra-articular complications. Within a synovial joint, bone and cartilage erosion will occur, causing a swollen joint capsule and inflamed joint synovium. The extra-articular complications can occur over time and include infections, lymphomas, cardiovascular disease, and osteoporosis.[16, 17, 18]

Inflammation

One key inflammatory cascade includes overproduction and overexpression of TNF. This pathway drives both synovial infl ammation and joint destruction. TNF overproduction has several causes, including interactions between T and B lymphocytes, synovial-like fi broblasts, and macrophages. This process leads to overproduction of many cytokines such as interleukin , which also drives persistent infl ammation and joint destruction. Overproduction of other proinfl ammatory cytokines (eg, interleukin 1) diff ers from the process for interleukin 6 in that production is either less marked or is specifi c to one or more disease subsets, as best shown by the eff ects of interleukin 1 blockade in subforms of juvenile idiopathic arthritis or adult-onset Still's disease.[19,20]

Synovial cells and cartilage cells

The dominant local cell populations in joints aff ected by rheumatoid arthritis are synovial and cartilage cells. Synovial cells can be divided into fibroblast-like and macrophage-like synoviocytes. Overproduction of proinflammatory cytokines is believed to be led predominantly by macrophage-like synoviocytes.[21,22] Fibroblast-like synoviocytes show abnormal behaviour in rheumatoid arthritis. In experimental models, co-implantation of fi broblast-like synoviocytes with cartilage leads to fi broblasts invading cartilage, behaviour that correlates with joint destruction. Considerable information has accumulated about joint destruction and the role of osteoclast activation as a key process leading to bone erosion. This association is proven because specific inhibition of osteoclast activation can reduce joint destruction yet not aff ect joint inflammation.[23]We are unclear about whether arthritis starts as a primary problem in the bone and subsequently moves to the joint, or the other way around. One argument for rheumatoid arthritis starting in the joint is the observation that fi broblast-like synoviocytes showing altered behaviour can spread between joints, suggesting how polyarthritis might develop.[24] Regulation of immune infl ammation depends on balances between the number and strength of diff erent cell types. Control of arthritogenic

immunoresponses has been studied in mice in which the specifi c antigen is known. Infusion of low numbers of T cells with specifi c characteristics ameliorates arthritis in a rodent model of the disease, showing T cells can be protective. Ongoing research should translate these experimental findings into clinical practice.[25]

Natural Killer Cells and Their Role in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease determined by an inflammation of the synovial membrane leading to destruction of cartilage and bone [26]. The interaction between genetic and environmental factors can contribute to RA occurrence . RA is more prevalent among women than men [27].It has been demonstrated that osteoclasts are crucial mediators of all forms of bone loss inRA . TNF-α induces synovial fibroblasts and macrophages to release IL-1. TNF-α, IL-1 and, RANKL promote osteoclast activation and osteolysis in RA . Recent studies have indicated that HLA-DRB1 SE alleles are associated with a severe course of RA, and a parameter that can be measured is bone destruction [28]. It has been indicated that RA patients expressing a combination of two SE-associated HLA-DRB1 alleles exhibit the most severe small joint damage in the initial stages of the disease and suffer a high proportion of long-term large joint destruction [29]. Plasma soluble HLA-G levels are lower in RA patients than in controls, and low soluble HLA-G indicates that T and natural killer (NK) cell activities are not inhibited by soluble HLA-G molecules in RA [30]. The accumulation of NK cells has been demonstrated in the synovial fluid in patients with RA as show in (fig 2). [31]Hence, knowledge of NK cells and NK cell receptors maybe of great interest for their role to RA. In this review, we focus on current knowledge regarding NK cells and NK cell receptors in human autoimmune diseases such as RA.

Natural Killer Cells

Natural killer (NK) cells were defined by their ability to spontaneously kill tumor cells and virally infected cells To date, we know that these cells are capable of recognizing and destroying a wide variety of target cells, including transplanted, virally infected, antibody-coated, stressed, and transformed cells [33,34]. NK cells constitute the third major population of lymphocytes together with T and B cells. The majority of NK cells are believed to be relatively short lived, although more long-lived subpopulations of NKcells have been identified in lymph nodes (LNs) and thymus .[35] There are about 2 billion NK cells in adults and they are mostly found in the blood, bone marrow (BM), spleen, liver, LNs, thymus, lung, peritoneum, and in the uterus during gestation. The two major functions of NK cells are

cytotoxicity and cytokine production (Figure 1). NK cells display heightened cytotoxicity when activated by cytokines, such as IL-2 or IL- 15. NK cells are capable of performing antibody-dependent cellular cytotoxicity (ADCC) through CD16 (low-affinity Fcγ receptor IIIA). CD16 binds to the Fc tail of antibodies. When target cells are coated with antibodies, they may induce ADCC. NK cells may kill tumors and virally infected cells through the induction of apoptosis. Perforin is stored in cytoplasmic granules that are released upon NK cell activation. Perforin monomers are inserted into the plasma membrane of target cells and polymerize into a pore through which granzyme A and B enter and induce apoptosis.Perforin is constitutively expressed in NK cells but its expression is enhanced by IL-2 stimulation. [36] NK cells also express TNF-related apoptosis-inducing ligand (TRAIL)and FasL, which are important mediators of apoptosis. TRAIL is only expressed by subpopulations of resting NKcells, but is generally expressed after stimulation by IL-2, IFN-α/β, or IL-15. Fas is a transmembrane protein expressed by abnormal cells and may induce apoptotic signals afterbinding to FasL on NK cells. NK cells also produce cytokines, of which IFN-γ is critically important both in the innate and adaptive immune responses. It has both immunostimulatory andimmunomodulatory effects. It induces TH1 responses and upregulates MHC-I expression on a variety of cells, such as antigen presenting cells (APCs). Subpopulations of NK cells may also produce TNF-α, GM-CSF, IL-5, IL-13, IL- 10, and TGF-β. It has been reported that some cytokines, including IL-2, IL-12, IL-15, and IL-18 may stimulate cytokine production by NK cells .[37, 38]

Management of Arthritis

Rheumatoid arthritis (RA) affects nearly 1% of the adult Indian population and is the commonest inflammatory joint disease seen in clinical practice. It is an autoimmune disorder of unknown aetiology characterized by joint erosions and destruction. The disease follows a chronic course and, in addition to morbidity, results in a shortened life span.[39]

Analgesics and non-steroidal anti-inflammatory drugs

Analgesics

Analgesics in early RA should only be used as an adjunct to non-steroidal anti-inflammatory drugs (NSAIDs) and DMARD therapy. There is evidence that both paracetamol and codeine are effective in reducing pain in RA.8These trials were carried out more than 25 years ago, are in small patient numbers and of short duration.[40,41]

Non-Steroidal Anti-Inflammatory Drugs

NSAIDs provide some relief of pain and stiffness in RA (but do not influence radiographic progression) by inhibiting cyclo-oxygenase (COX).49,50 There are at least two COX isoforms and non-selective NSAIDs inhibit both COX-1 and COX-2 in differing ratios. Selective COX- 2 inhibitors or coxibs were designed to avoid gastroduodenal ulceration which arises due to inhibition of COX-1 by NSAIDS.[42]

Efficacy

There is no difference in the efficacy of non-selective NSAIDs. A health technology assessment concluded that selective COX-2 inhibitors have a similar efficacy to NSAIDs.[43]

Side Effects of Nsaids

Side effects of NSAIDs are dose and duration of therapy dependent.[44]The gastrointestinal (GI) and cardiovascular side effects are of particular concern. Other less common but equally serious side effects include renal disease and hypersensitivity (including asthma).

Gastrointestinal side effects

Ulceration of the gastrointestinal tract, particularly of the stomach and duodenum, arises due to the systemic inhibition of prostaglandins. Symptoms correlate poorly with GI ulceration which can occur throughout the length of the GI tract. GI bleeding, perforation and gastric outlet obstruction are recognised complications of ulceration. [45]The risk of GI bleeding is the most frequent complication of GI ulceration and occurrence differs between NSAIDs. Although the frequency of gastroduodenal ulceration is less with selective COX-2 inhibitors compared to non-selective NSAIDs the case for reduced GI ulcer complication rates is unproven.[46]

Medications for arthritis

NSAIDs

NSAIDs (nonsteroidal anti-inflammatory drugs) are the most commonly prescribed drugs for arthritis patients. These may be either prescription or over-the-counter (OTC). At low doses NSAIDs help a vast range of ailments, from headaches, muscle aches, to fever and minor pain. At a higher dose prescription dose -NSAIDs also help reduce joint inflammation. There are three main types of NSAIDs and they all work by blocking prostaglandins hormone-like substances that trigger pain, inflammation, muscle cramps and fever.[46,47]

Traditional NSAIDs

these are the largest subset of NSAIDs. As is the case with most drugs, they do carry a risk of side-effects, such as stomach upset and gastrointestinal bleeding. The risk of side effects is significantly higher if the patient is over 60. A patient should take this type of drug at high doses under the supervision of a doctor.

NSAID Risks

Arthritis Research UK says that people who have had a heart attack or stroke, have heart disease, or have peripheral vascular disease are unlikely to be prescribed NSAIDs. Doctors should be cautious about prescribing NSAIDs to patients with hypertension (high blood pressure), hyper lipidemia (high cholesterol),diabetes.[47,48,49]

COX-2 inhibitors

These also reduce pain and inflammation. However, they are designed to have fewer stomach and gastrointestinal side-effects.

Salicylates

Includes aspirin which continues to be the preferred medication of many doctors and patients. Patients need to consult their doctor if they plan to take aspirin more than just occasionally.Long term high dosage usage of aspirin carries with it a significant risk of serious undesirable side effects, such as kidney problems and gastrointestinal bleeding. For effective control of arthritis pain and inflammation frequent large doses are needed. Nonacetylated salicylate is especially designed to have fewer side effects than aspirin. Some doctors may prescribe nonacetylated salicylate if they feel aspirin is too risky for their patient. However, nonacetylated salicylate does not have the chemical aspirin has which protects against cardiovascular disease. Some doctors prescribe low dose aspirin along with nonacetylated salicylate for patients who they feel need cardiovascular protection. [47, 48]

Glucocorticoids are anti-inflammatory steroids and are very effective at combating inflammation and can be extremely helpful when used properly. The patient needs to consider the potential for undesirable side-effects with this type of drug.

Minocycline an antibiotic that is sometimes used as antibiotic therapy for rheumatoid arthritis. Its use is controversial.

Methotrexate works by blocking the metabolism of rapidly dividing cells. It is commonly used for treating more serious types of inflammatory arthritis. Methotrexate of the DMARDs, methotrexate (Rheumatrex) is the most widely prescribed. It is indicated for the treatment of rheumatoid arthritis and psoriasis; it is also used for psoriatic arthritis, systemic lupus erythematosus, and sarcoidosis. It is generally as efficacious as the other agents, with a low incidence of serious side effects when prescribed on a low-dose weekly schedule. At the low doses used in the therapy of rheumatoid arthritis,methotrexate appears to be acting more as an antiinflammatory agent than as an immunosuppressant. Methotrexate inhibits folate-dependent enzymes involved in adenosine degradation, increasing concentrations of extracellular adenosine. Adenosine acts via cell surface receptors to inhibit the production of inflammatory cytokines such as TNF-**α** and IFN-**α** .Methotrexate also decreases the production of inflammatory prostaglandins and proteases, though a direct action on the COX enzymes.[49,50]

Sulfasalazine

Sulfasalazine (Azulfidine) is approved for the treatment of rheumatoid arthritis and ulcerative colitis. It is also used to treat ankylosing spondylitis and Crohn's disease. Comparisons of sulfasalazine with other DMARDs suggest that it is more effective than hydroxychloroquine, azathioprine, and oral gold compounds. It is at least as effective as intramuscular gold and penicillamine. It has a greater degree of toxicity than hydroxychloroquine but less than gold compounds and penicillamine. After 5 years, approximately 75% of patients have discontinued sulfasalazine therapy, primarily because of a lack of efficacy as opposed to intolerable side effects

Azathioprine

Used for severe forms of inflammatory arthritis. Azathioprine also blocks the metabolism of rapidly dividing cells.

Antimalarials

Hydroxychloroquine (Plaquenil) and chloroquine (Aralen) are 4-aminoquinoline antimalarial drugs that possessmodest DMARD activity. Anti-malarials, such as hydroxychloroquine and chloroquine are commonly used for treating mild inflammatory arthritis. They are indicated for the treatment of rheumatoid arthritis and systemic lupus erythematosus; their use as antimalarials The onset of action of these drugs is longer than that of other DMARDs, and

their side effects are relatively mild. Because of this, these agents show promise as ingredients of combination therapies for rheumatoid arthritis.

Basic Pharmacology

Hydroxychloroquine and chloroquine are similar in activity; however, hydroxychloroquine has a lower incidence of ocular side effects and is used more frequently. These drugs are weak bases that enter and interfere with the functioning of lysosomes and other subcellular compartments of T- and B-lymphocytes, monocytes, and macrophages. This in turn inhibits the ability of these cells to produce and release inflammatory cytokines and hydrolytic enzymes.[51]

Adverse Effects

Skin rashes and pruritus are common adverse effects of the 4-aminoquinoline antimalarials, as are GI effects. The incidence of the most serious toxic reaction, irreversible retinopathy with resultant blindness, is dose related and can be minimized by maintaining a daily dose of hydroxychloroquine less than 6.5 mg/kg or chloroquine less than 4 mg/kg. Eye examinations should be performed regularly during treatment with these drugs. Severe hematological toxicity (neutropenia, thrombocytopenia, aplastic anemia) is rare.

Contraindications

The aminoquinolines accumulate in lung, kidney, and liver; thus, any preexisting pathology in these tissues contraindicates their use. Similarly, any ocular pathology precludes their use. Psoriasis and porphyria are frequently exacerbated by the administration of the aminoquinolines.

TNF α Inhibitors

Two recently introduced biological therapies were designed to interfere with the inflammatory cascade initiate by TNF-**α**Etanercept (Enbrel) is indicated for the treatment of moderate to severe rheumatoid arthritis in individuals over age. Infliximab in conjunction with methotrexate (Remicade) is approved for use by adults in the treatment of rheumatoid arthritis. It is also indicated for therapy of Crohn's disease. Over the short term, the efficacy of these drugs in the treatment of rheumatoid arthritis appears to be superior to that of methotrexate alone; however, their ability to prevent bone erosion for longer than 24 months must be further studied. The cost of both drugs is significantly higher than that of the other DMARDs.[47, 48, 51]

Basic Pharmacology

Etanercept is a recombinant fusion protein produced in Chinese hamster ovary cells. It consists of the intracellular Ligand-binding portion of the human p75 TNF receptor linked to the Fc portion of human immunoglobulin (Ig) G1.Two p75 molecules are attached to each Fc molecule. Etanercept binds to soluble TNF- **α** and TNF- **α** and forms inactive complexes, effectively lowering circulating levels of these cytokines. It is administered subcutaneously, generally twice weekly. Infliximab is a chimeric monoclonal antibody targeted against TNF- **α**. It consists of a human IgG1 Fc heavy chain and partial _-light chain fused to a murine hypervariable region. Infliximab binds to both soluble and transmembrane forms of TNF and inhibits their ability to bind to TNF receptors. It does not inhibit TNF- **α** , which binds to the same receptors as TNF- **α**. Infliximab is administered intravenously, usually at 4- to 8-week intervals[47,48]

Adverse Effects

The most common adverse reaction to etanercept is mild to moderate erythema, pain, or pruritus at the injection site (37%). Headaches and abdominal pain can also occur. New positive autoantibodies, such as antinuclear antibodies (ANA), anti-dsDNA antibodies, and anticardiolipin antibodies, can develop in patients treated with etanercept. Although there is so far no association between this and the development of autoimmune diseases or malignancies, long-term studies have yet to be done. Rare cases of pancytopenia may be associated with this drug. Although clinical trials showed no increased risk of infection with etanercept treatment, postmarketing reports of serious infections, sepsis,and associated fatalities exist .[48,49]

Gout medications - some physicians may use gout medications to treat some forms of arthritis.

Leflunomide - used to treat rheumatoid arthritis and psoriatic arthritis. It also blocks cell metabolism. However, biologic therapy is gradually taking over.

Cyclosporine -an immunosuppressant drug - it makes your immune system less aggressive. Cyclosporine is commonly used by transplant patients so that their bodies do not reject their transplanted organs. Cyclosporine is usually used in combination with methotrexate for arthritis patients. Although effective, this may be limited by its toxicity. [47, 49, 50]

Gold Compounds

Gold compounds (chrysotherapy) are the oldest of the DMARDs in use to treat rheumatoid arthritis. Parentally administered gold is generally believed to be somewhat less effective than methotrexate; oral gold is less effective than parenteral preparations. Gold compounds take several months to produce a measurable effect. Among patients who can tolerate this therapy, some benefit will be obtained in about 80%, and complete remission will be induced in 20% of cases. Remissions are maintained for varying periods after discontinuing therapy, with a relapse rate as high as 80%. Relapse is usually less severe in such patients, and a second course of gold therapy usually produces beneficial effects[49, 50]

Basic Pharmacology

The gold preparations available in the United States include two preparations administered via intramuscular injection: gold sodium thiomalate (GSTM, Myochrysine, Aurolate) and aurothioglucose (gold sodium thioglucose, GSTG, Solganal), and an oral preparation, auranofin. (Ridaura). Although called gold salts, these compounds contain monovalent gold bound to sulfur, a bond that is at least partly covalent. For this reason, these complexes are termed gold preparations Generally, 2 months of multiple dosing of gold compounds is required to reach steady-state levels. Auranofin therapy produces lower steady-state blood gold concentrations than does treatment with parenteral gold compounds, but it also produces a lower incidence of adverse effects.[49, 50,51]

CONCLUSION

Rheumatoid arthritis is a chronic autoimmune disease characterized by joint inflammation and bone destruction. Excessive cytokine production driven by cell-cell interactions within the joint contributes to the disease progression. For the management of RA, the goal is to slow disease progression and prevent disability, such as loss of physical function. If approved, the emerging therapies for RA may not change the algorithm for RA and approval by FDA may be several years from the present time. Treatment guidelines, however, have been updated to support the use of early, aggressive treatment for a patient with RA. On the downside, economic considerations may be a drawback to existing, advanced therapies and emerging therapies. Additional evidence will be needed given that clinical trials with RA have exhibited wide variability in the patient population, clinical outcomes, and interventions. Long-term benefits remain to be seen, and more comparative studies with standard of care are needed. - See more at: RA is a chronic, progressive polyarthritis associated with substantial

disability. The traditional pyramidal approach that envisaged the sequential use of rest, physiotherapy and NSAIDs, with DMARDs being reserved for refractory cases, has been abandoned. Present day treatment protocols advocate the early use of DMARDs.

REFERENCE

1. William B. Grant , The Role Of Meat In The Expression Of Rheumatoid Arthritis, Review Article, British Journal Of Nutrition (2000), 84, 589±595:1-76
2. What Is Arthritis? What Causes Arthritis?Http://Www.Medicalnewstoday.Com/Articles/7621.
3. Http://En.Wikipedia.Org/Wiki/Arthritis
4. Scott David L, Frederick Wolfe, and Huizinga Tom W. J, Rheumatoid Arthritis, and Www.Thelancet.Com Vol 376 September 25, 2010:15-15.
5. Http://Www.Bda.Uk.Com/Foodfacts, Diet and Rheumatoid Arthritis, Bda the British Dietetic Association BDA January 2012. Review Date January 2015:1-2
6. Http://Www.Arthritisresearchuk.Org/
7. Thomas K.J, Coleman P, Use of Complementary or Alternative Medicine in A General Population In Great Britain. Results from the National Omnibus Survey. Journal of Publichealth 2004; 26:152–57.
8. Http://Www.Arthritisresearchuk.Org/, Arthritis Research UK Complementary And Alternative Medicines, H Dicin Published Oct 2012 ISBN 97-81-901815-13-9:1-64
9. Arthritis.Webmd.Com/Septic-Arthritis-Symptoms-Diagnosis-And-TreatmentSeptic Arthritis: Symptoms, Diagnosis, And Treatment -Webmd
10. Thompson Andy, M .D Frcpc Psoriatic Arthritis, The Arthritis Society, The Arthritis Society Gratefully Acknowledges University Of Western Ontario, For Writing Psoriatic Arthritis – Know Your Options. This Brochure Was Reviewed And Edited By Dr. David Bell, Md, Frcpc., The Arthritis Society Http://Www.Arthritis.Ca/, 2011:1-11
11. Www.Health.Com/Health/Gallery/0,,20464354,00.Html Signs And Symptoms Of Rheumatoid Arthritis - Health.Co
12. Www.Arthiritis Care .Org.Uk.Published By Arthiritis Care ,Last Reviewed In 2011,Isbn 978-903419-37-3:1-44
13. Www.Arthritisresearchuk.Org/Arthritis.../Arthritis/Symptoms.Aspx What Are The Symptoms Of Arthritis? | Arthritis Research UK
14. Www.Nytimes.Com/Health/Guides/Disease/Arthritis/Arthritis - Symptoms, Diagnosis, Treatment Of Arthritis - NY Times ...

15. Www.Webmd.Com/Osteoarthritis/Guide/Understanding-Arthritis-Symptoms Symptoms Of Arthritis - Webmd.
16. O 'Dell JR, Rheumatoid Arthritis. In: Goldman L, Schafer AI, Eds. Goldman's Cecil Medicine, 24th Ed. Philadelphia, PA: Saunders Elsevier; 2011:1681–1689
17. Firestein G.S, Etiology And Pathogenesis of Rheumatoid Arthritis. In: Firestein GS, Budd RC, Harris ED Jr, Et Al, Eds. Kelley's Textbook of Rheumatology, 8th Ed. Philadelphia, PA: Saunders Elsevier; 2008:1035–1086.
18. Harris E.D Jr, Firestein G.S, Clinical Features Of Rheumatoid Arthritis. In: Firestein GS, Budd RC, Harris ED Jr, Et Al, Eds. Kelley's Textbook of Rheumatology, 8th Ed. Philadelphia, PA: Saunders Elsevier; 2008:1087–1118.
19. Van Der Helm-Van Mil AHM, Huizinga T. W. J., Advances In The Genetics Of Rheumatoid Arthritis Point To Subclassifi Cation Into Distinct Disease Subsets. Arthritis Res Ther 2008- 10: 205.
20. Van Oosterhout M, Bajema I, Levarht EW, Toes RE, Huizinga TW, Van Laar JM., Diff Erences In Synovial Tissue Infi Ltrates Between Anti-Cyclic Citrullinated Peptide-Positive Rheumatoid Arthritis And Anti-Cyclic Citrullinated Peptide-Negative Rheumatoid Arthritis. Arthritis Rheum 2008; 58: 53–60.
21. Feldmann M, Brennan FM, Maini RN, Rheumatoid Arthritis. Cell 1996; 85: 307–10.K
22. Choy EH, Isenberg DA, Garrood T, Et Al. Therapeutic Benefi T of Blocking Interleukin-6 Activity With An Anti-Interleukin-6 Receptor Monoclonal Antibody In Rheumatoid Arthritis: A Randomized,Double-Blind, Placebo-Controlled, Dose-Escalation Trial.Arthritis Rheum 2002; 46: 3143–50.
23. Tolboom T .C .A., Van Der Helm-Van Mil AHM, Nelissen RGHH, Breedveld FC, Toes REM, Huizinga TWJ. , Invasiveness of Fi Broblast-Like Synoviocytes Is An Individual Patient Characteristic Associated With The Rate of Joint Destruction In Patients Withrheumatoid Arthritis. Arthritis Rheum 2005; 52: 1999–2002.
24. Schett G, Firestein GS,Classic And Alternative Views On The Pathogenesis Of Rheumatoid Arthritis. 2010; 69: 787–89.
25. Lefèvre S, Knedla A, Tennie C, Et Al. Synovial Fi Broblasts Spread Rheumatoid Arthritis to Unaff Ected Joints. Nat Med 2009; 15: 1414–20.
26. Sabatino Di A, Calarota S. A, Vidali F, Macdonald T. T, And Corazza G. R., “Role of IL-15 In Immune-Mediated And Infectious Diseases,” Cytokine And Growth Factor Reviews, Vol. 22, 2011: 19–33.

27. Alamanos Y. And Drosos A.A., "Epidemiology of Adult Rheumatoid Arthritis," Autoimmunity Reviews, Vol. 4, No. 3, 2005:130–136.
28. Vries De R. R. P, Huizinga T. W. J, And Toes R. E. M., "Redefining The HLA And RA Association: To Be or Not To Beanti-CCP Positive," Journal Of Autoimmunity, Vol. 25, 2005: 21–25.
29. Valenzuela A, Gonzalez-Escribano M. F, Rodrigue Z R., Moreno I, Garcia A., "Association of HLA Shared Epitope with Joint Damage Progression In Rheumatoid Arthritis," Human Immunology, Vol. 60, No. 3:250–254.
30. Verbruggen L. A, Rebmann V, Demanet C, De Cock S , And Grosse-Wilde H. ,"Soluble HLA-G In Rheumatoid Arthritis," Human Immunology, Vol. 67, No. 8, 2006: 561–567.
31. Laszlo P, "Do NK Cells Regulate Human Autoimmunity?"Cytokine, Vol. 32, No. 2, 2005:76–80.
32. Lanier L. L., "NK Cell Recognition," Annual Review of Immunology, Vol. 23, 2004 : 225–274 .
33. Santo Di J. P., "Natural Killer Cell Developmental Pathways: A Question Of Balance," Annual Review Of Immunology, Vol. 24 2006: 257–286.
34. Wu J. And Lanier L. L., "Natural Killer Cells and Cancer," In Advances In Cancer Research, F. George, Ed., Vol. 90, Academic Press, 2003.
35. Colonna M., "Interleukin-22-Producing Natural Killer Cells and Lymphoid Tissue Inducer-Like Cells in Mucosal Immunity,"Immunity, Vol. 31, No. 1, 2009: 15–23.
36. Raulet D. H. And Guerra N., "Oncogenic Stress Sensed By the Immune System: Role Of Natural Killer Cell Receptors," Nature Reviews Immunology, Vol. 9, No. 8, 2009:568–580.
37. Yokoyama W.M And Plougastel B. F. M., "Immune Functions Encoded By The Natural Killer Gene Complex," Nature Reviews Immunology, Vol. 3, No. 4 , 2003.:304–316.
38. M. B. Lodoen and L. L. Lanier, "Viral Modulation Of NK Cell Immunity," Nature Reviews Microbiology, Vol. 3, No. 1, 2005:59– 69.
39. Handa R., Management Of Rheumatoid Arthritis, The National Medical O Journal Of India , Vol. 17, No. 3, 2004:1-9
40. Grigor C, Capell H, and Stirling A, Et Al. Effect Of A Treatment Strategy Of Tight Control For Rheumatoid Arthritis (The Ticora Study): A Single-Blind Randomised Controlled Trial. Lancet 2004; 364(9430):263-9.
41. Huskisson EC. Simple Analgesics for Arthritis. BMJ 1974; 4(5938):196- 200.

42. Brooks Pm, Day Ro., Nonsteroidal Antiinflammatory Drugs-Differences and Similarities. N Engl J Med 1991; 324(24):1716-25.
43. Chen YF, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, Et Al. Cyclooxygenase-2 Selective Non-Steroidal Anti-Inflammatory Drugs (Etodolac, Meloxicam, Celecoxib, Rofecoxib, Etoricoxib, Valdecoxib And Lumiracoxib) For Osteoarthritis And Rheumatoid Arthritis: A Systematic Review And Economic Evaluation. Health Technol Assess 2008;12(11):1-278.
44. Wolfe MM, Lichtenstein DR, Singh G., Gastrointestinal Toxicity of Nonsteroidal Antiinflammatory Drugs. N Engl J Med 1999; 340(24):1888-99.
45. Fries JF, Spitz PW, Williams CA, Bloch DA, Singh G, Hubert HB. A Toxicity Index for Comparison Of Side Effects Among Different Drugs. Arthritis Rheum 1990; 33(1):121-30.
46. Emery P, Gibson T. A., Double-Blind Study of the Simple Analgesic Nefopam In Rheumatoid Arthritis. Br J Rheumatol 1986; 25(1):72-6.
47. Http://Www.Medicalnewstoday.Com
48. Michelle A ,Clark ,Richard A.,Lipincott's Iiiustrated Review ,Pharmacology 5th Edition ,Published By Wolters Kluwer(India)Pvt Ltd,Isbn :13:978-81-8473-573-4:539
49. Barar F.S.K ,Essential Of Pharmacotherapeutics,Published By S.Chand&Company Ltd,Fifth Edition 2007,Isbn:81-219-0444-7:134-136
50. Rang H.P , Dale M.M. Pharmacology International Seventh Edition,British Library Cataloguing In Publication Elsevier Isbn-13978-1-4377-1933-8:255-256.
51. Charles R, Craig Robert E, Stitzel, Modern Pharmacology With Clinical Applications,Fifth Edition ,Section 5:423-441.