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Review Article

HOW TO LIVE WITH RHEUMATOID ARTHRITIS???

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ABSTRACT
Rheumatoid Arthritis (RA) is a chronic auto-immune disease characterized by painful inflammation of the joints and surrounding tissues, leading to long term disability. Rheumatoid arthritis can begin at any age but has its peak between 35 to 55 years of age. RA shows hereditary linkage. Women and smokers are most often affected. The patient doesn't feel any symptoms during inactive state of the disease. RA progresses in a symmetrical pattern involving both the sides of the body. Once rheumatoid arthritis is confirmed by diagnosis, treatment should start as early as possible. The treatment for rheumatoid arthritis focuses initially on reducing the joint inflammation and pain with the use of analgesics and anti-inflammatory agents. In the next stage, joint function is restored by administering Disease Modifying Anti-rheumatic Drugs (DMARDs) thus preventing joint deformity. Treatment is generally based on the degree of severity of RA. Patients with mild RA are advised to take rest and are prescribed analgesics and anti-inflammatory medicines, which include fast acting drugs like NSAIDs. Slow acting drugs like (DMARDs) such as methotrexate, sulfasalazine, lelflunomide etc., and Body's reaction modifiers (BRMs) such as rituximab, anankinra, infliximab etc., are reserved for patients suffering from moderate to severe RA. The patient is advised to undertake regular exercises like walking, stretching, swimming or cycling, which are aimed at reducing body weight. The patient suffering from arthritis can carry out his normal day-to-day activities with the help of proper medication and regular exercise.
KEYWORDS: Rheumatoid arthritis, Auto-immune disease, Synovitis

INTRODUCTION

Patient's Narration

I considered myself lucky enough to have a government teaching job with handsome salary & sufficient leaves to look after my family. One day, suddenly, I noticed that I was not able to move my right hand. Fortunately, the next day my hand was alright & was functioning perfectly. Ten days later, something happened again, but this time it was my knee. I was not able to climb up the steps in the morning hours, while moving into the classroom. I was experiencing terrible pain in my knee joints. I conducted the class sitting in the chair & dictating the notes to the students. When all the students had left the classroom, I wished to return home fast. However, I realized that, I was not in a position to walk even a few steps that day due to swollen joints. I was terribly scared. I was wondering what was happening to me. I never wanted to be on wheel chairs at just 35 years of age. I prayed God that I would prefer ending my life, than leading a crippled life dependent on others. Soon, I requested one of my colleagues to take me to the nearby hospital to identify my health problem. Fortunately, my case was handled by a renowned orthopaedician. I was diagnosed to be suffering from RA, after a series of blood tests."

Background

Rheumatoid Arthritis (RA) is a chronic disease characterized by painful inflammation of the joints and surrounding tissues, leading to long term disability[1-3]. Chronic painful inflammation of synovial membrane and destruction of articular cartilage leads to muscle cachexia[4], joint destruction and permanent deformity[5]. Rheumatoid arthritis can begin at any age[6] but has its peak between 35 to 55 years of age[7].The term "rheumatoid arthritis" was coined by British rheumatologist Dr Alfred Baring Garrod, in the year 1859. It is also known as Rheumatoid disease (systemic illness)[8] as it can affect multiple organs of the body such as lungs, heart, eyes, blood vessels etc., in addition to the tissues around the joints, such as the tendons, ligaments, and muscles. Rheumatoid Arthritis is an auto-immune disease[9] in which body mistakenly considers some parts of its own system as pathogens and attacks them[10]. Damage to the joints can occur early in the disease and can be progressive.

Prevalence Of Rheumatoid Arthritis

Rheumatoid Arthritis (RA) predominantly occurs in females. The prevalence of RA is around 1%[11, 2, 3] worldwide, with women suffering 3-5 times more than men[8, 1, 6]. RA is a very common disease in India[12] affecting elderly ladies. The Indian prevalence rate (0.9%) almost equals the world prevalence rate. The variation in the level of sex hormones of women (estrogen and progesterone, which regulate the inflammatory process) is the main cause of the development of RA among them[13]. Globally, 1.3 million adults suffer from RA[14]. Persons having positive RF are more susceptible to develop RA. It is more prevalent among smokers than non-smokers but there is not enough evidence, which supports this correlation[6]. A study in 2010 found that those, who drank modest amounts of alcohol regularly were four times less likely to get rheumatoid arthritis than those who never drank. Scientists have found that postmenopausal women, who have more than 14 alcoholic drinks per week show reduced risk of rheumatoid arthritis. It can occur at any age[9], but its incidence increases with advancing age making it a disease of older persons.

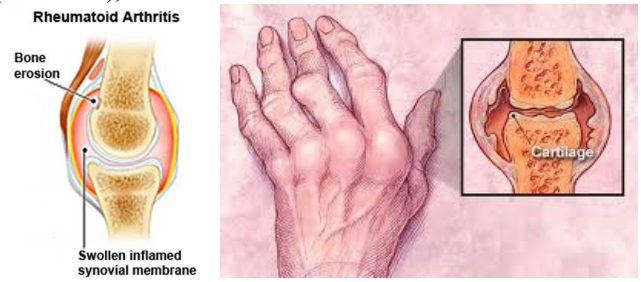
Causes

Till date there is no known cause of Rheumatoid Arthritis (RA). Lot of research is being done worldwide to identify the cause. According to Mistaken Identity Theory (molecular mimicry) an infection triggers an immune response, which releases antibodies in body, which in return results in an immune attack against the host's own body. Some researchers believe that the tendency to develop rheumatoid arthritis may be genetically inherited (hereditary) [6]. Organisms suspected of triggering rheumatoid arthritis are Mycoplasm, Erysipelothrix, Parvovirus, Rubella, Epstein – Barr virus (EBV) and Human herpes Virus (HHV-6). Furthermore, hormonal changes may also be linked to the disease, particularly in women. Environmental factors such as

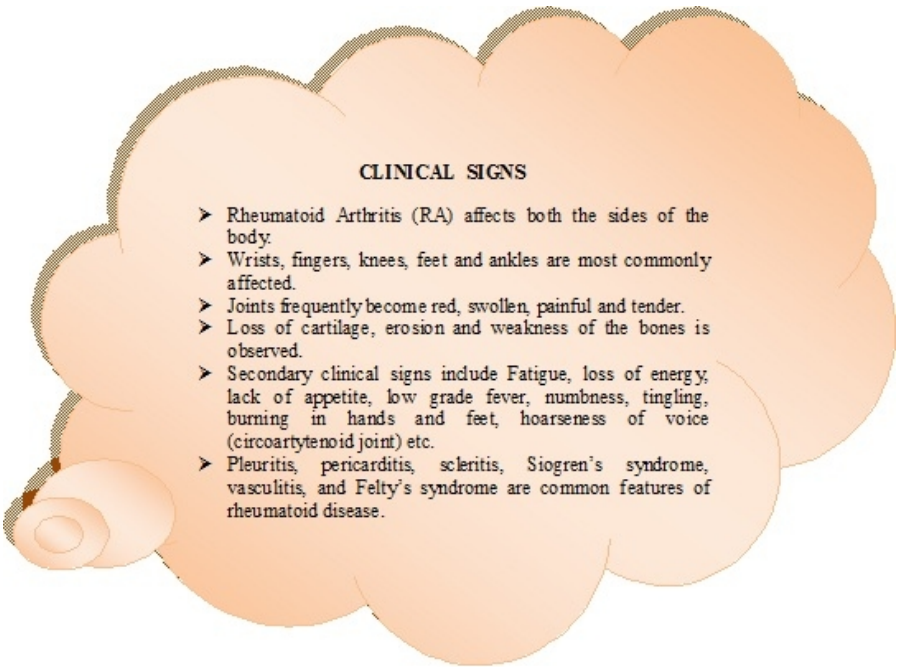
smoking tobacco increase the risk of developing rheumatoid arthritis.

Symptoms

Rheumatoid Arthritis (RA) may have 2 states, of which one is active (when the tissue is inflamed) and other is inactive (remission), when inflammation decreases.



During inactive state of RA patient doesn't feel any symptoms of the disease. But, when disease relapses, symptoms start appearing (flare). RA progresses in a symmetrical pattern[15]. Multiple joints of both the sides of the body are affected simultaneously. Morning stiffness (generally occurs for 1hr), fatigue, loss of energy[3], lack of appetite and low-grade fever are the common symptoms associated with this disease[5]. Joints of wrists, fingers, knees, feet, and ankles are the most commonly affected. Aching and stiffness of joints[5] as well as muscles also take place. Joints frequently become red, swollen[5], painful[3, 5] and tender. Loss of cartilage, erosion and weakness of the bones [10] and joint deformity[5] are other consequences of RA. Patient finds it extremely difficult to perform day to day tasks. Symptoms of conventional Rheumatoid Arthritis should not be confused with the symptoms of Rheumatoid disease, which is a systemic disease affecting multiple organs of the body. It results into hoarseness of the voice[8] (when, it affects cricoarytenoid joint), spinal injury[16] (when neck bone is damaged) pleuritis[8] (inflammation of lining of lung) causing coughing and chest pain, which may develop into Rheumatoid lung disease, pericarditis[8] (inflammation of pericardium), scleritis[8] (inflammation of eyes white part), Siogren's syndrome (inflammation of glands of mouth & eyes), Felty's syndrome[8] (enlarged spleen) resulting into anemia, and very rarely vasculitis[8] (inflammation of blood vessels), which lead to necrosis and is often visible as tiny black areas around the nail beds. Rheumatoid nodules, which can become infected, can occur around the elbows and fingers and are found to be associated with a positive rheumatoid factor (RF). Occasionally, median nerves can be compressed at the wrists (in carpel tunnel) that results in carpel tunnel syndrome. RA is known as juvenile arthritis, when it occurs below the age of 16. Limping, irritability, crying, and poor appetite are the symptoms of juvenile arthritis, which are seen among children.



DIAGNOSIS

Many times, multiple tests are required to be performed to diagnose Rheumatoid Arthritis (RA). A single negative test doesn't indicate that RA is not present.

I) Imaging[6]: a) Ultrasonography b) Magnetic resonance Imaging (MRI) c) X- ray

II) Blood Tests: Immunological studies are done for the presence of a) Rheumatoid factor (RF) [17, 18] . It may be seropositive or seronegative depending on the presence or absence of the RF, respectively. b) The anti-citrullinated protein antibodies (ACPAs) [17, 19] and antinuclear antibody (ANA) are the powerful biomarkers for RA.

III) Other Tests are:

a) Anti-MCV assay (antibodies against mutated citrullinated Vimentin) [25]

b) Point of care test (POCT)

c) Erythrocyte Sedimentation Rate (ESR) [5, 19]

d) Complete blood count[19]

e) C-reactive protein

f) Antinuclear antibody

g) Renal function

h) Synovial fluid analysis

i) Liver function test

Pathophysiology

Rheumatoid Arthritis (RA) is an autoimmune disease[9]. It is driven primarily by activated T cells (TCD4 cells, T Helper cells, and Activated T Helper cells), giving rise to T cell-

derived cytokines, such as IL-1 and TNFα found in the rheumatoid synovium. Activation of B cells and the humoral response are also evident, although most of the antibodies generated are IgGs (IgM, IgA) apparently elicited by polyclonal activation of B cells rather than from a response to a specific antigen. Macrophages[20] enhance the cytokine production[21]. Antibodies also activate cytokines. Activated Interleukin-1[22] & Tumour necrosis factor α[15,4] augment the release of osteoclast[23], fibroblast and other cytokines [24] & chemokines[16] (NFkβ). This consequently shows a further increase in influx of inflammatory substance and secretion of lysosomal enzymes. Synovitis[10, 19] occurs due to inflammation of synovium and excessive production of synovial fluid All these factors damage the cartilage, decrease Bone Mineral Density[25] and cause bone erosion, which results into Rheumatoid Arthritis. [Figure 1]

Pharmacotherapy

Once Rheumatoid Arthritis (RA) is confirmed by diagnosis, treatment should start as early as possible. The treatment for rheumatoid arthritis focuses initially on reducing the joint inflammation and pain with the use of analgesics and anti-inflammatory agents. In the next stage, joint function is restored by administering Disease modifying anti-rheumatic drugs (DMARDs) thus preventing joint deformity. Treatment is generally based on the degree of severity of RA. Patients with mild RA are advised to take rest and are prescribed analgesics and anti-inflammatory medicines, which include fast acting drugs like NSAIDs. Slow acting drugs like Disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, sulfasalazine, lelflunomide etc., and Body's reaction modifiers (BRMs) such as rituximab, anankinra, infliximab etc., are reserved for patients suffering from moderate to severe RA.

Non-steroidal Anti-inflammatory Drugs (nsaids)

NSAIDs provide symptomatic relief of pain, swelling & morning stiffness. They block the pain sensitizing mechanism induced by TNF, IL-1. They act by inhibiting Cyclooxygenase (COX) enzyme thereby diminishing the inflammation mediators [Figure 2]. At higher concentration NSAIDs are known to reduce superoxide radicals, induce apoptosis, inhibit the expression of adhesion pro-inflammatory cytokines, modify lymphocyte activity, and alter cellular membrane function. COX-2 is the major source of pro-inflammatory prostanoids and COX-1 accounts for only 10-15% of the prostanoids formation.

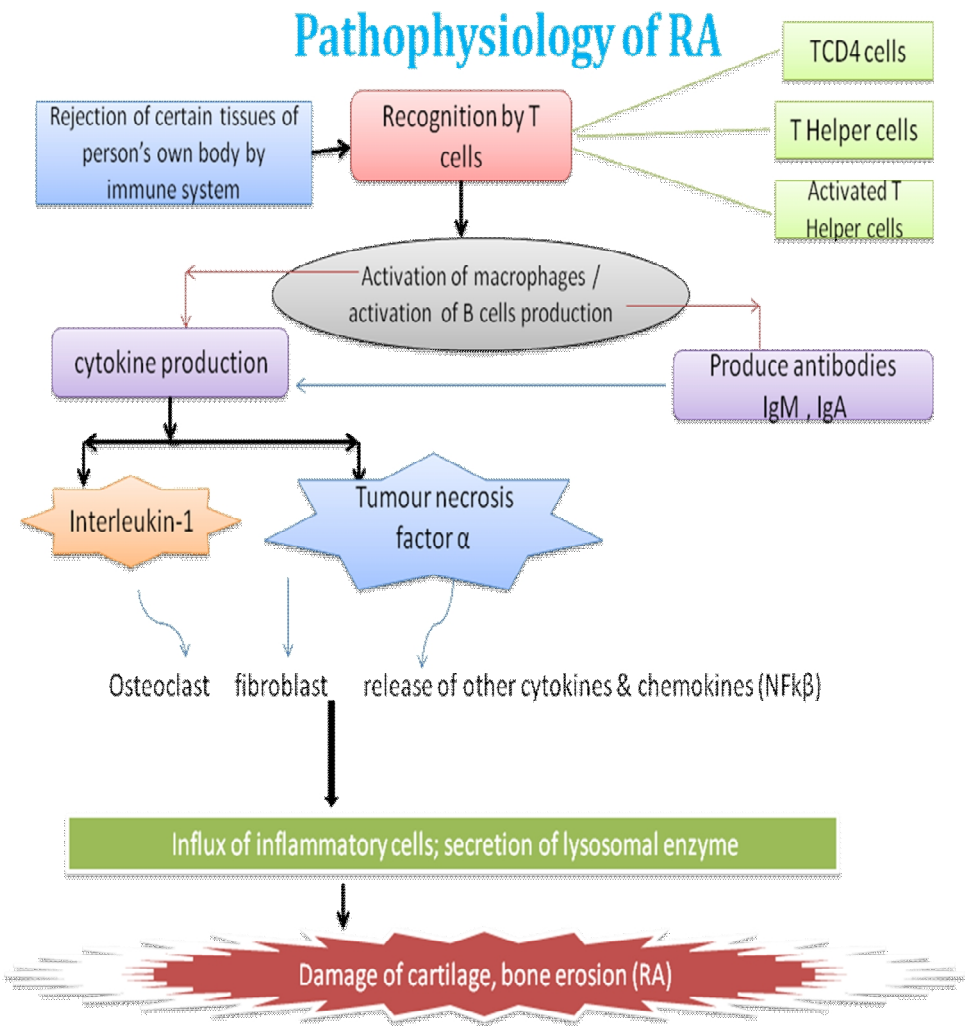


Figure 1: Pathophysiology of Rheumatoid Arthritis (RA)

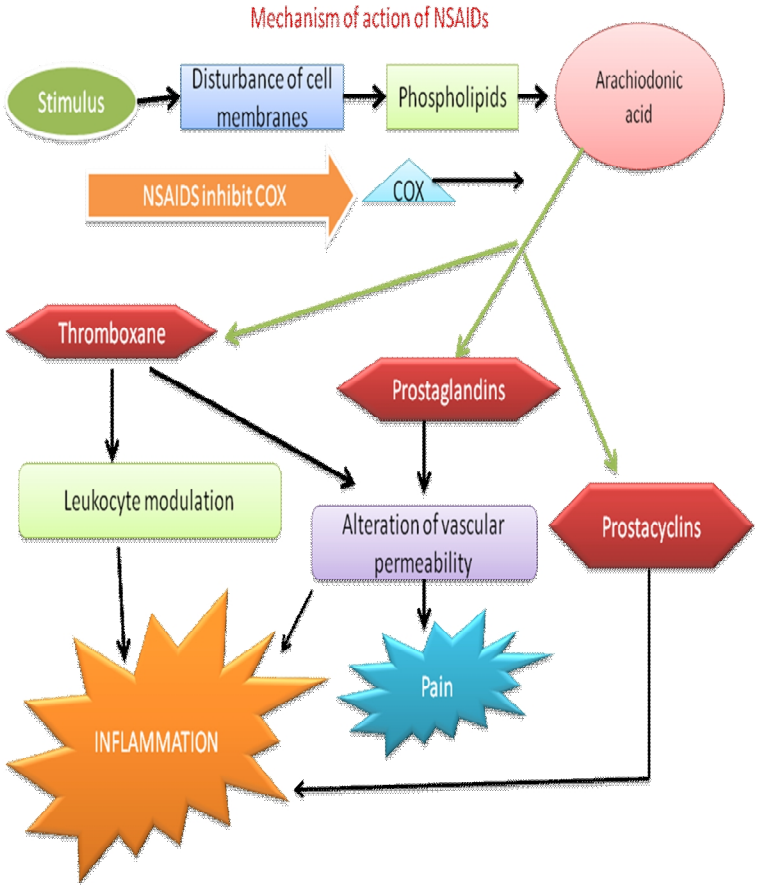


Figure 2: Mechanism of action of Non-steroidal Anti-inflammatory Drugs (NSAIDs)

COX-1 derived products play a dominant role in the initial phase of acute inflammatory response, while COX-2 derived products play role for a long period in producing chronic inflammation. COX-1 inhibition leads to harmful as well as beneficial effects. COX-1 inhibition produces increased acid secretion through increased LT production as well as cardio protection mediated through diminished synthesis of TxA_2. Different types of COX inhibitors are used as NSAIDs. Non-selective COX inhibitors used for RA are Aspirin (350mg t.i.d), Ibuprofen (400-600 mg t.i.d), Diclofenac (100 to 200 mg, t.i.d) & Naproxen (prescribed for juvenile arthritis, 250mg t.i.d. The most common side effect of this category of drug is gastrointestinal disturbance. Celecoxib (100 to 200 mg bid), a selective COX-2 inhibitor shows lesser g.i.t side effects than aspirin but is found to cause cardiac toxicity mediated through reduced release of PGI_2 and PGE_2 on chronic use. Another drug, Meloxicam (15 mg once daily), which is a preferential COX-2 inhibitor, is less cardio toxic. The newer NSAIDs are just as effective as aspirin in reducing inflammation and pain, but differ in their pharmacokinetic profile.

Disease Modifying Anti-rheumatic Drugs (DMARDS)

Exact mechanism of action of these drugs is not known, but these drugs can reduce the disease activity of RA and retard the progression of arthritic tissue destruction. DMARDs require 4 to 6 months of treatment for a full response. Sulfasalazine (500mg/d) was developed originally as a therapy for rheumatoid arthritis. Efficacy of this drug is modest, in RA. It is split by colonic bacteria of the intestine into two moieties 5-aminosalimcylic acid & sulfapyridine. Sulfapyridine inhibits cytokines, IgA, IgM, rheumatoid factor (RF) and suppresses T cells, TNFα, NFkβ, which are chemotactic factors causing inflammation. It is generally well tolerated. Since RA is an autoimmune disease, immunosuppressants are commonly employed in the management of RA. These medicines inhibit i) Cytokine production, ii) Chemo taxis, iii) Cell mediated immune reaction, iv) B & T Cell function, and interleukin production, thus suppressing the auto-immune response. Methotrexate (7.5mg/week) is a favorite among physicians. It is used in combination therapy with other medicines for treating RA. Azathioprine, Cyclosporine, Chloroambucil & Cyclophosphamide are some other immunosuppressive agents used for RA. Bone marrow depression is the most common side effect of immunosuppressive agents. Chloroquine (150mg/day) or Hydroxychloroquine (400mg/day) is used in those cases of RA, where only few joints are involved. They are commonly employed for non-erosive disease. The underlying mechanism of action of Chloroquine appears to be mediated through suppression of T lymphocytes, inhibition of IL-1 & B lymphocyte, stabilization of lysosomes and as a free radical scavenger. Chloroquine is a popular anti-malarial drug which may take weeks or months for showing their benefits in RA. It shows retinal damage, corneal opacity, rashes and graying of hairs, therefore it is less preferred by physician for RA.

Leflunomide (100mg for 3 days followed by 20mg per day) is the most commonly used among DMARDs for RA, despite its adverse effects like thrombocytopenia, loss of hairs & headache. It is actively converted to a metabolite, A77-1726, which inhibits dihydroorotate dehydrogenase and results in suppression of ribonucleotide synthesis. The whole mechanism leads to inhibition of T cell proliferation and production of auto-antibody. The net result is arresting of auto-immune response of the body. Gold therapy is reserved for severe cases of RA because of its adverse effects like

dermatitis, bone marrow depression & liver damage. Patients, who do not obtain satisfactory relief from NSAIDs and who cannot tolerate the immunosuppressant or cytokine receptor antagonists are prescribed with these drugs. Gold Sodium Thiomalate, Auranofin and Aurothimalate are the medicines of this category, which are given in a dose of 6mg/day (orally) or 5-25mg i.m. The underlying mechanism of action of gold therapy is mediated through i) Reduction in cell mediated immunity and histamine release, ii) Alteration of morphology & functional capabilities of human macrophages, and iii) Inhibition of IL-1, Monocyte, chemotactic factor 1 and Vascular endothelial growth factor. Gold therapy should not be used if the disease is mild. d-Penicillamine shows adverse effects like myasthenia gravis and loss of taste. Efficacy of d-Penicillamine is also less than other drugs. So, it is rarely used in selective cases of RA.

Combinations of DMARDs, such as Methotrexate +sulfasalazine, Methotrexate +Leflunomide, Methotrexate + Chloroquine, Methotrexate + Sulfasalazine + Hydroxychloroquine are indicated for patients with moderate or severe RA or for those, who fail to respond to a single compound.

Body's Reaction modifying agents (BRMs) or Biological Agents

BRMs are reserved for the patients, who show poor prognosis such as functional impairment, radiographic bony erosions, extra-articular disease and positive rheumatoid factor. NSAIDs are commonly used in combination with these agents. They are designed to affect the immune system, that play role in disease process of RA. These are administered either s.c or i.v. TNFα inhibitors are very expensive medicines. They are effective both ways as monotherapy as well as in combination with other drugs. They inhibit TNFα (produced by macrophages and lymphocytes), which causes joint damage. TNF receptor protein or antibody is present on T cell surface, which causes joint damage and bone erosion. TNFα inhibitors act on these proteins to inhibit inflammation and also slow down bony erosions. Drugs included under this category are Etanercept (50mg once weekly), Infliximab (chimeral monoclonal, 3-5mg/kg infused i.v every 4-8 weeks), Adalimumab (40mg every 2 weeks), Golimumab (fully human anti-TNF monoclonal anti-body), Certolizumab pegol (humanized Fab-fragment fused to polyethylene glycol (PEG)) etc. IL-1 Antagonist such as Anakinra (recombinant human IL1, 100mg daily) is commonly employed in those cases, where patient stops responding to DMARDs. Anakinra inhibits the Interleukin that causes cartilage degradation, stimulate osteoclast and bone erosion, thus suppressing mediators of RA. IL-2 antagonists act by inhibiting the chain of IL-2 receptor and by blocking receptors on the T helper cells. Basiliximab (a murine human chimeric monoclonal antibody) and Daclizumab (human IgG_1 chimeric antibody) are the medicines, prescribed from this class, for treating RA. IL-6 inhibitor, Toclizumab blocks the downstream effects of IL-6 (a cytokine that contributes to the inflammation cascade in RA). It inhibits the function of neutrophils, T cells, B cells, monocytes, and osteoclasts. T cell Co stimulatory blockade is caused by Abatacept (fusion protein). This drug binds to CD28 on the T cell surface and thus inhibits T cell response and production of TNF is blocked. B- Cells stimulate the production of antibodies, which is one of the causes of inflammation. B- Cell depletors like Rituximab (1000mg i.v at a gap of 3-4 hr), binds to B cells leading to their removal from circulation, these biological agents are very effective, but should be taken carefully. They are generally preferred by a physician in combination therapy with methotrexate. People taking these drugs must be watched for the occurrence of consequences such as infection from bacteria, viruses, and fungi, Leukemia or lymphoma, psoriasis, hypersensitivity reactions.

Corticosteroids

Corticosteroids (mainly glucocorticoids) are often prescribed to patients suffering from severe joint pain & inflammation. But, they should not be given as first line drugs because of their several side effects. They are not suitable for long term use because of adrenal suppression. Corticosteroids have anti-inflammatory and immunosuppressant properties. They down regulate the induced expression of COX-2 but not COX-1. Symptomatic relief is prompt, but they do not arrest the RA process. Joint destruction may be slowed. Bony erosion is delayed and the appearance of new bone erosions is slowed down. At low dose, Corticosteroids act as Disease Modifying Agents. Drugs commonly used under this category are Prednisone, Methyl prednisone and Intra-articular corticosteroid like Triamcinolone. They can be given orally or injected directly into the tissues and joints. Serious side effects, usually encountered with corticosteroids are osteoporosis, weight gain, Cushing's syndrome, muscular weakness, hyperglycemia, peptic ulceration, psychiatric disturbances etc. [6]

Drugs From Natural Sources

Mycophenolate Mofetil is a semi-synthetic derivative of fungal antibiotic. It is converted in body to Mycophenolic acid, which inhibits proliferation of T & B lymphocytes, which are the key cause of RA. Medicines obtained from nature for RA include *Harpagophytum procumbens*, *Tripterygium wilfordii*, *Uncaria tomentosa*, emu oil, fish oil, gamma-linoleic acid, vitamin-E, vitamin-C, apple diet, nutmeg, bee venom, copper, rhurbarb and honey.

Non Drug Therapy

The patient is advised to undertake regular exercises like walking, stretching, swimming, or riding a bicycle, which are aimed at reducing body weight. This can slow down the progression of the disease. It helps in suppressing the flares[4]. Occupational therapy includes the services provided by occupational therapist[2], whose primary aim is to help the people with arthritis and to develop their skills and capacity, so they are able to master the tasks essential at home and work. In Physiotherapy, a physiotherapist[2] prescribes range-of-motion exercises and exercise programs which helps a person to cope up with the consequences of the disease. Hydrotherapy is also known as pool therapy. It is a very good way of exercising arthritic joint. Psychological support can help in regaining person's positive attitude and strength to fight the depression associated with RA[8, 18]. Chronic disease is generally associated with depression, which could be overcome by psychological treatment[20].Immunoadsorption therapy, Acupressure, Reflexology, Rest (8-10 hr of sleep) and Thermal modalities are some nondrug therapies commonly employed for RA. Orthotist is wearing of appropriate, comfortable, supportive footwear, which can eliminate pain while walking.

Surgery

Surgery includes removal of the joint lining (synovectomy), or Total joint Arthroplastices (total knee, hip, ankle or shoulder replacement). It is done in severe cases of RA, where drug therapy as well as non-drug therapy has failed to provide any relief.

Future Treatments

Future treatment of RA is mainly concerned with the blockade of special inflammatory factors like ILs, WBC cells and TNFα. Drugs, which are currently under study are Tofacitinib and Fostamatinib.

Notable Victims

- **Drothy Hodgkin**: [Nobel Prize winning scientist] Developed sever deforming rheumatoid arthritis at age 28.
- **Billy Bowden:** [international cricket umpire], who had to retire from active play because of rheumatoid arthritis.
- **Christiaan Barnard:** [the first surgeon to perform a human-to- human heart transplant] had to retire because of severe RA.
- **Sandy Koufx**: [an American Hall-of-Fame baseball pitcher]
- **Raoul Dufy:** [French artist, 1877–1953] Continued to paint despite RA.
- **James Courbon:** [an actor] Claimed to have healed the condition using pills containing a sulfur-containing compound.
- **Melvin Franklin:** [bass singer of the Temptations] treated his RA with cortisone shots.
- **Matt Iseman:** [licensed physician and professional comedian, and host of Style Network's Clean House]
- **Auguste Renoir:** [impressionist painter]

Table 1: PHARMACOKINETIC PROFILE OF SELECTED NSAIDS

Drug	Pharmacokinetic profile
Aspirin (Micropyrin) Nicholas Piramal	Orally ingested, absorption occurs by passive diffusion , distributed throughout the body tissues and transcellular fluids, 80% to 90% of the salicylate in plasma is bound to proteins, biotransformation occurs in hepatic endoplasmic reticulum and mitochondria, excreted in the urine , half life: 3-5 hrs
Ibuprofen (BRUFEN) Abbot	Absorbed rapidly, bound to protein, and undergoes hepatic metabolism and renal excretion of metabolites. The half-life is 2hrs. Enters brain synovial fluid and crosses placental barrier
Diclofenac (DICLONAC) Lupin	Absorbed orally, 99 % protein bound, metabolized and excreted both in urine and bile, plasma half life: 2hrs
MELOXICAM (MEL-OD) Cadila Healthcare	Rapidly and completely absorbed, 99%plasma protein bound, largely metabolized in liver by hydroxylation and glucuronide conjugation; excreted in urine and bile
Celecoxib (CELIB) Unichem	Celecoxib is slowly absorbed, 97% plasma protein bound and metabolized primarily by CyP2C9 with a half life-10 hours, drug is excreted unchanged in the urine and faeces

Table 2: PHARMACOKINETIC PROFILE OF SELECTED DMARDS

DRUG	PHARMACOKINETIC PROFILE
Methotrexate (BIOTREXATE) Biochem	Oral bioavailability is variable, affected by food, it is 50% plasma protein bound, little metabolized, excreted through urine
Sulfasalazine (Salazar) Cadila Healthcare	10-20% absorbed, undergoes enterohepatic recirculation, excreted unchanged in urine, half life: 6-17 hrs.
Leflunomide	Given orally , metabolized in intestine, excreted in urine; half life: 2 weeks
(ARAVA) Aventis	

KEY POINTS

- Rheumatoid Arthritis (RA) is an autoimmune disease.
- Women are most commonly affected (female: male, 3:1).
- RA is more prevalent among smokers and individuals having family history.
- RA can occur at any age.
- RA is a systemic disease with potential of serious manifestation.
- It shows symmetrical progression, with pain and swelling of joints of both the sides.
- Treatment of RA should begin as early as possible.
- DMARDs should follow the initial treatment with NSAIDs.
- Efforts directed to reduce weight have yielded wonderful results in managing RA.
- Mild to moderate exercises such as walking, stretching, swimming or cycling yield best results.
- Wearing cushioned arthritis friendly footwear greatly helps in reducing the pain while walking.

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