



A REVIEW ON RHEUMATOID ARTHRITIS AND ITS MEDICATION

Amol V. Supekar*, Vikram S. Sarukh, Anil B.Badnale, Yogesh P.Nikam, Sandip S.Khandagale.

Abasaheb kakade College of B.Pharmacy Bodhegaon, Ahmednagar 414503, Maharashtra, India.

ABSTRACT:

Rheumatoid arthritis is a chronic inflammatory disorder that may effect on joints. In some people, the condition can damage a good kind of body systems, including the skin, eyes, lungs, heart and blood vessels. An autoimmune disease, rheumatoid arthritis occurs when your system mistakenly attacks your own body's tissues.

A current choice like steroids and DMARD'S (disease modifying anti-rheumatic drugs) is that the cornerstone in therapy of the disease, but has their own limitation. New drugs and better methods for management of rheumatoid arthritis are still evolving. The present review highlights the possible involvement of Montelukast, an antagonist of leukotriene receptors and Cetirizine, an antihistaminic drug in betterment of the progression of the disease.

KEYWORDS: Montelukast, cetirizine, rheumatoid arthritis, leukotriene, histamine.

INTRODUCTION-

Arthritis is known as a form of joint disorder which involves inflammation of one or more joints. There are more than 100 kinds of arthritis are available. Out of them few are common like osteoarthritis, rheumatoid arthritis, gout, ankylosing spondylitis, and juvenile idiopathic arthritis. Arthritis affects the musculoskeletal system, especially the joints. A joint is that the area within the body where two bones meet and helps within the movement of the body parts. It usually causes joint pain. It is classified as a rheumatic disease. Rheumatoid arthritis is chronic progressive autoimmune disease characterized by symmetric erosive sinusitis (1).The prevalence of rheumatoid arthritis (RA) is comparatively constant in many populations, at 0.5–1.0%.The exact etiology behind rheumatoid arthritis is unknown till now. There is a genetic role in disease risk. Studies have thus far shown that the familial recurrence risk in RA is little compared with other autoimmune diseases.

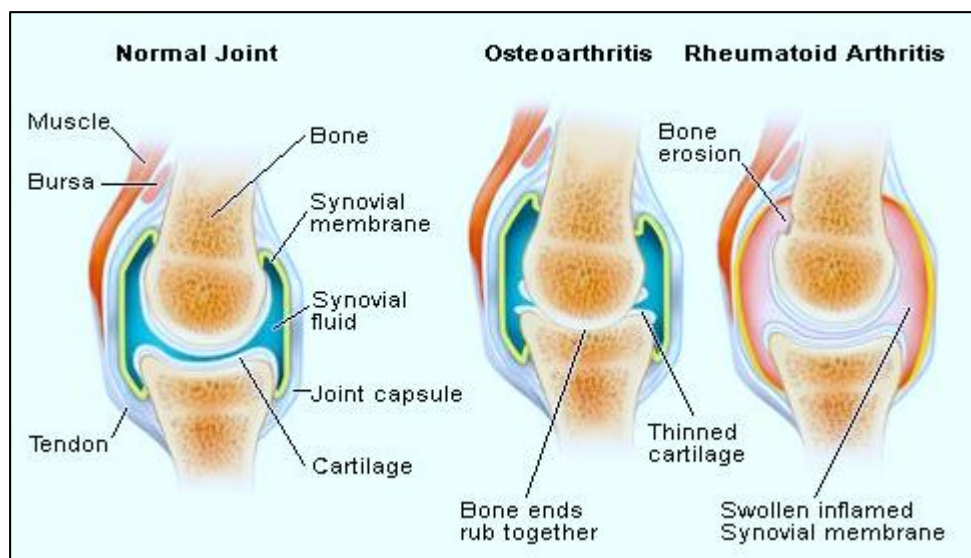


Figure 1. Types of Arthritis

There are two types of arthritic condition for joints. One is rheumatoid arthritis and another is osteoarthritis. Diagram shows the difference between osteoarthritis and rheumatoid arthritis. In osteoarthritis, cartilage is getting eroded. Two bone's ends rub together, causes pain and inflammation. In rheumatoid arthritis synovial membrane is inflamed. Bone erosion is a central feature of rheumatoid arthritis.

Progression of rheumatoid arthritis:

The figure 2 shows progression of rheumatoid arthritis. In rheumatoid arthritis there are three phases of progression:

1. Initiation
2. Inflammation
3. Destruction

First stage is initiation of disease. In this stage destructive changes are not seen. At this stage innate immunity activators get activates. In progression of disease FLS, mastocyte, dendritic cells and macrophages are involved. Activators activates chemokines, cytokines, and adhesion molecule. Second stage is inflammation; in this joint deformities are not seen but limitation of joint mobility may be present. Adjacent muscle atrophy, extra-articular soft tissue lesions can be seen. Joint destruction gets started. Osteoclast has formed. Auto antibodies, prostaglandins, and proteases get activated. Third stage is destruction; cartilage and bone destruction is seen. Extensive muscle atrophy and joint deformities are symptoms. Here panus is formed and aggressive FLS formed.

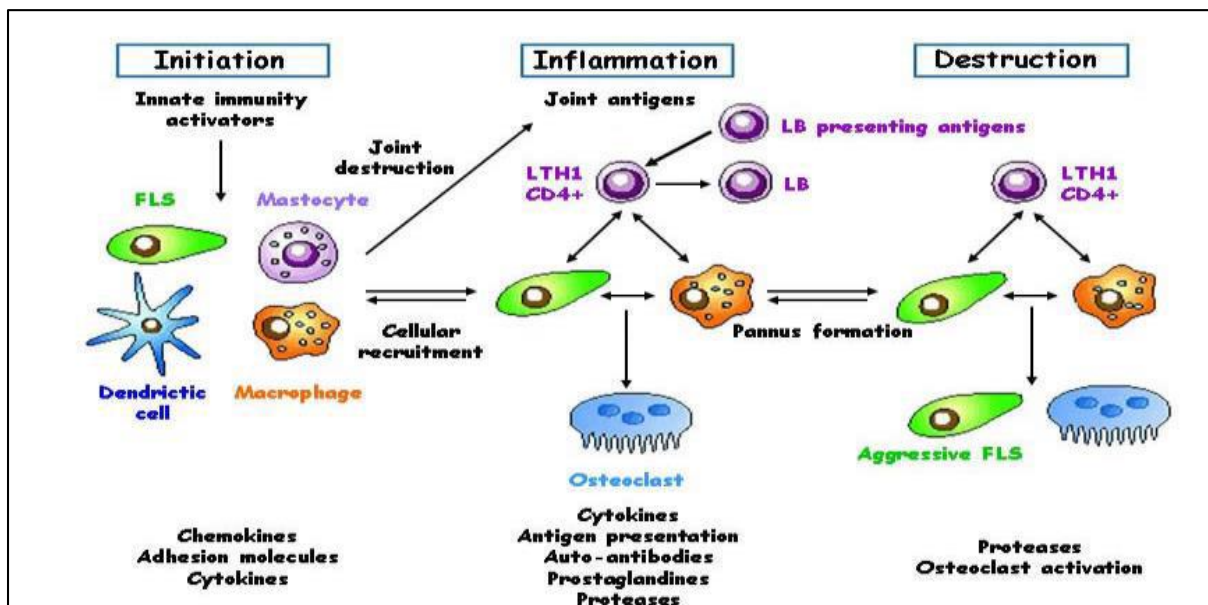


Figure 2. Schematic diagram of mechanisms of disease in various phases of rheumatoid arthritis.

Treatment approaches:

Rheumatoid arthritis is an autoimmune disease, so it is not just the treatment of disease but it is a management of disease. The main objective of treatment is to relieve the symptoms, restrict the articular damage, stop the progression of disease, and improve the standard of life. There are 5 main principles

1. Relief of pain
2. Reduction of inflammation
3. Protection of articular structure
4. Maintenance of function
5. Control of systemic involvement

Current drug treatments:

A. Disease modifying and rheumatic drugs (DMARDs)

1. Immunosuppressant: Methotrexate, Azathioprine, Cyclosporine
2. Sulfasalazine
3. Chloroquine or Hydroxychloroquine
4. Leflunomide
5. Thiomalate, Auranofin
6. d-Penicillamine

B. biologic response modifier:

1. TNF – α inhibitor - Etanercept, Infliximab, adalimumab
2. IL-1 antagonist – anakinara

C. Adjuvant drugs:

Corticosteroids, prednisolone, and other

Treatments and safety issues:

Rheumatoid arthritis is a chronic disorder, so patients need to take therapy for long period of time.

It will increase the risk factors of drugs to the patients. Few common side effects of traditional drugs are listed below.

Table 1. Treatment approach

NSAID's	Indigestion gastrointestinal disturbance Stomach ulcers
COX 2 inhibitors	Increased risk of cardiovascular events aggravation of hypertension
Corticosteroids	Weight gain cushingoid appearance increased blood pressure, increased blood sugar level Osteoporosis
DMARD'S	Hepatic cirrhosis Interstitial pneumonitis Severe myelosuppression Cancer risk with methotrexate
Biologics	Systemic lupus erythromatus Injection or infusion site reactions
JAK inhibitors	Infection and malignancy Gastrointestinal perforation

❖ Montelukast:

- ❖ Structure: Montelukast sodium is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene CysLT1 receptor.

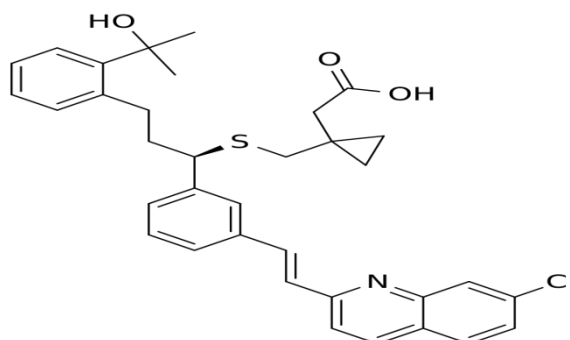


Figure 3. Structure of Montelukast

Pharmacology:**Pharmacodynamics:**

Montelukast is a leukotriene receptor antagonist used as an alternative anti-inflammatory medication in the management and chronic medication of asthma and exercise induced bronchospasm (EIB). Unlike zafirlukast, Montelukast does not inhibit CYP2C9 or CYP3A4 and is, therefore, not expected to affect the hepatic clearance of drugs metabolized by these enzymes.

Pharmacokinetics:

The leukotriene-modifying drugs are administered orally. Montelukast is absorbed rapidly, with ~60–70% bioavailability. At therapeutic concentrations, it is highly protein-bound (99%). It is metabolized extensively by CYP3A4 and CYP2C9. The $t_{1/2}$ of Montelukast is 3–6 hours, with volume of distribution of 8 to 11 lit.

Clinical uses:

Montelukast sodium, a cysteinyl leukotriene receptor antagonist, is approved for the treatment of asthma. Leukotrienes are one of the main inflammatory mediators released during the body's reaction to allergen exposure. They are produced from arachidonic acid via the 5-lipoxygenase pathway and include LTC₄, LTD₄, and LTE₄. They are released by many inflammatory cells, including eosinophils, mast cells, monocytes, basophils, and neutrophils. Montelukast, primarily a cysteinyl leukotriene (CysLT1) receptor antagonist, exhibited previously undocumented, secondary, neutrophil-directed anti-inflammatory properties, which appeared to be cAMP dependent.

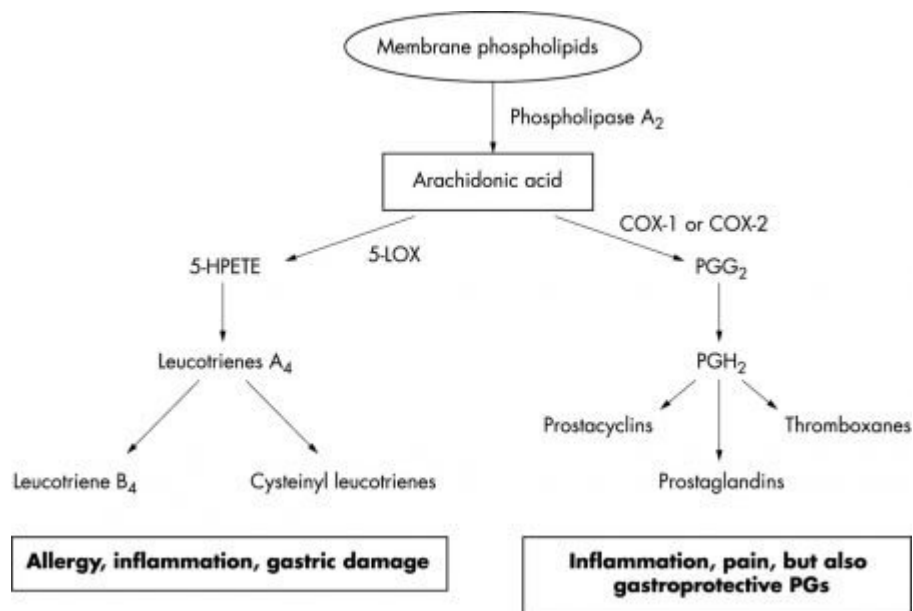


Figure 4. Leukotriene Formation

Side effects:

Montelukast is very safe with few side effects like:

- 1) Headache,
- 2) Rashes.
- 3) Eosinophilia and neuropathy are infrequent.

Cetirizine:

Structure:

Cetirizine is a potent second-generation histamine H₁ antagonist that is effective in the treatment of allergic rhinitis, chronic urticaria, and pollen-induced asthma. Unlike many traditional antihistamines, it does not cause drowsiness or anticholinergic side effects.

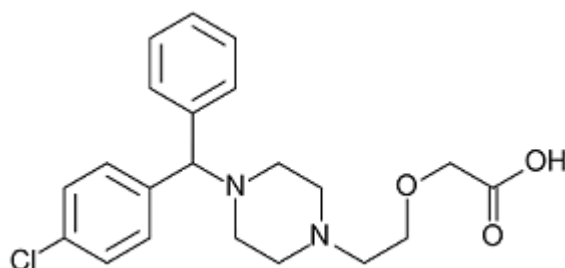


Figure 5. Structure of Cetirizine

Pharmacodynamics:

Cetirizine is a metabolite of hydroxyzine and a selective peripheral histamine H₁- receptor antagonist. It is used for symptomatic treatment of seasonal and perennial rhinitis and for chronic urticaria.

Pharmacokinetics:

Cetirizine is orally absorbed. Its half-life is 8.3 hours with clearance rate of 53 mL/min.

Clinical uses:

Cetirizine is an antihistamine that reduces the natural chemical histamine within the body.

1. Allergic Reactions
2. Motion Sickness and Vestibular Disturbances
3. Nausea and Vomiting of Pregnancy

Side effects:

Less common toxic effects of systemic use include excitation and convulsions in children, orthostatic hypotension, and allergic responses.

Mechanism of action:

Cetirizine competes with histamine for binding at H1-receptor sites on the effector cell surface, leading to suppression of histaminic edema, flare, and pruritus. The low incidence of sedation are often attributed to reduced penetration of cetirizine into the CNS as a results of the less lipophilic group on the ethylamine side chain.

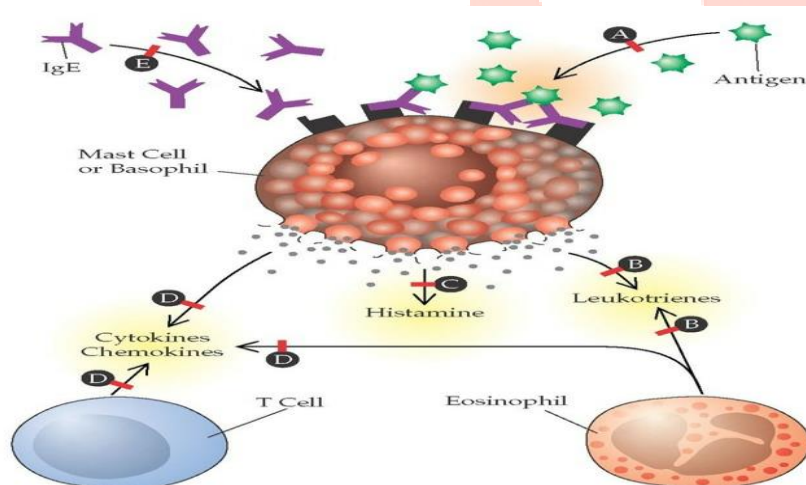


Figure 3. Inflammatory mediators

Cetirizine, supposed to inhibit DNA binding activity of NFkappa B, inhibits the expression of adhesion molecules on immunocytes and endothelial cells and the production of IL-8 and LTB4, two potent chemo attractants, by immune cells. It induces the release of PGE2, a suppressor of antigen presentation and MHC class II expression, from monocyte/macrophages and reduces the number of tryptase positive mast cells in inflammation sites. Tryptase is a chemo attractant, generates kinins from kininogen, activates mast cells, triggers maturation of dendritic cells and stimulates the release of IL-8 from endothelial cells and the production of Th1 lymphokines by mononuclear immunocytes.

HYPOTHESIS:

As we seen earlier, progression of disease goes through three steps; Initiation, inflammation, and destruction. In second stage inflammation, interleukins plays important role. Montelukast acts as leukotriene receptor antagonist. Leukotriene's are produced by many cells of the body and mediate many aspects of the inflammatory response. Arachidonic acid is converted into leukotriene A4 (LTA4), which can further produce leukotriene C4 (LTC4) and leukotriene B4 (LTB4). These leukotriene triggers inflammatory responses, so one can restrict the progression of disease at second stage only. This will be new approach for the treatment of rheumatoid arthritis.

Cetirizine is very popular anti-histaminic drug. Cetirizine restrict the activity of histamine. Cetirizine, supposed to inhibit DNA binding activity of NF-kappa B, inhibits the expression of adhesion molecules on immunocytes and endothelial cells and the production of IL-8 and LTB4, two potent chemo attractants, by immune cells. Cetirizine may prove benefit in improvement of rheumatoid arthritis.

CONCLUSION:

Rheumatoid arthritis is an autoimmune disease; there is space in proper management of disease. This study puts forth a new approach of Montelukast and Cetirizine in treatment of rheumatoid arthritis. It also highlights the probable mechanism of action involved in treatment of disease.

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