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ZAFIRLUKAST AND FEXOFENADINE MAY AMELIORATE PROGRESSION OF RHEMATOID ARTHRITIS

*KOMAL PHARATE[1] VIKRAM V NIMBALKAR[2], PANDURANG M GAIKWAD[3], SHITAL PHARATE[4],SWATI NAVGHARE[5].

Department of pharmacology,

PDVVP college of pharmacy, villad ghat Ahmednagar. (MS) India. 414111.Affiliated to savitribai phule pune university, Pune, India.

ABSTRACT:

Rheumatoid arthritis (RA) is autoimmune systemic disorder caused by unknown etiology and characterized by chronic inflammation and synovial infiltration of immune cells. The risk factors include age, gender, genetics, and environmental exposure (cigarette smoking, air pollutants, and occupational). Cytokines such as IL-1, IL-10, IL-4, and TNF-α that are present in the synovium produce inflammation and joint-destroying enzymes such as serine protease, matrix metalloproteinase, etc. current options like steroids and DMARD's (Disease modifying anti-rhematic drugs) are the cornerstones therapy of disease. The presence reviews high lights the possible involvement of zafirlukast, an antagonist of leukotriene receptors and fexofenadine, an antihistaminic drug in amelioration of the progression of the disease.

KEYWORDS: zafirlukast, fexofenadine, rheumatoid arthritis, leukotriene, histamine.

INTRODUCTION:

Rheumatoid arthritis is an autoimmune disorder that causes chronic inflammation of the joints. Autoimmune diseases occur when the body's tissues are mistakenly attacked by their own system. The system contains a fancy organization of cells and antibodies designed normally to "seek and destroy" invaders of the body, particularly infections. Patients with autoimmune diseases have antibodies in their blood that concentrate on their own body tissues and results in inflammation.10 Animal models of arthritis are used extensively in research on pathogenesis of inflammatory arthritis and within the pharmaceutical industry within the testing of potential anti-arthritic agents. Important criteria in selection of a model include 1) capacity to predict efficacy of agents in humans, 2) simple performing the model, reproducibility of knowledge, reasonable duration of trial period and 3) similar pathology and/or pathogenesis to it of human disease.2

Progression of Rheumatoid arthritis:

Figure1 shows progression of autoimmune disease . In autoimmune disorder there are three phages of progression:

1. Initiation
2. Inflammation
3. Destruction

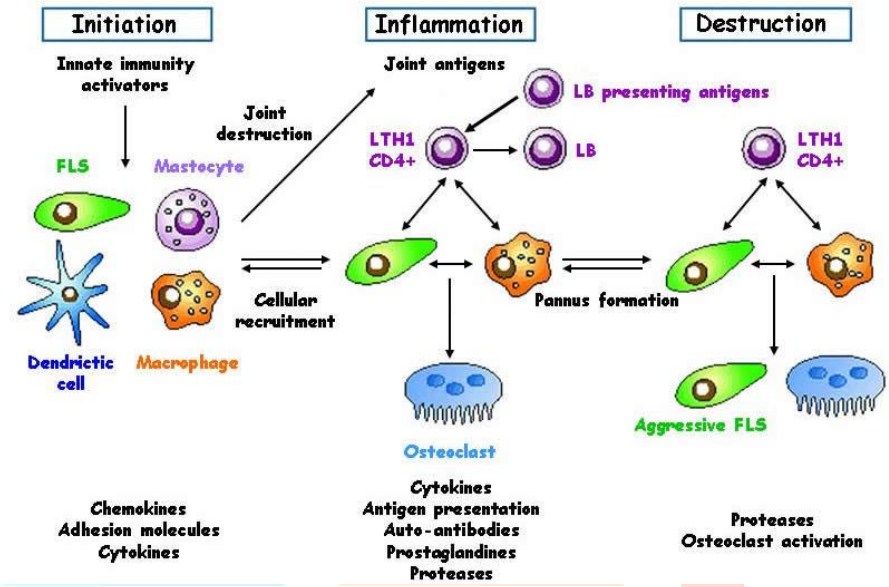

Figure2. Diagram of disease mechanisms that likely occur in various phases of rheumatoid arthritis

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 diseaseFLS,mastocyte, dendriatic cells and macrophages are involved.Activators activates chemoines , cytokines,cytokines,and adhesion molecules.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 present. Joint destruction gets started. osteoclast has formed. Auto antibodies, prostaglandins, and proteases get activated. Third stage is destruction; cartilage and bone destruction are seen. Extensive muscle atrophy and joint deformities are symptoms. here panus is formed and aggressive FLS formed.[3]

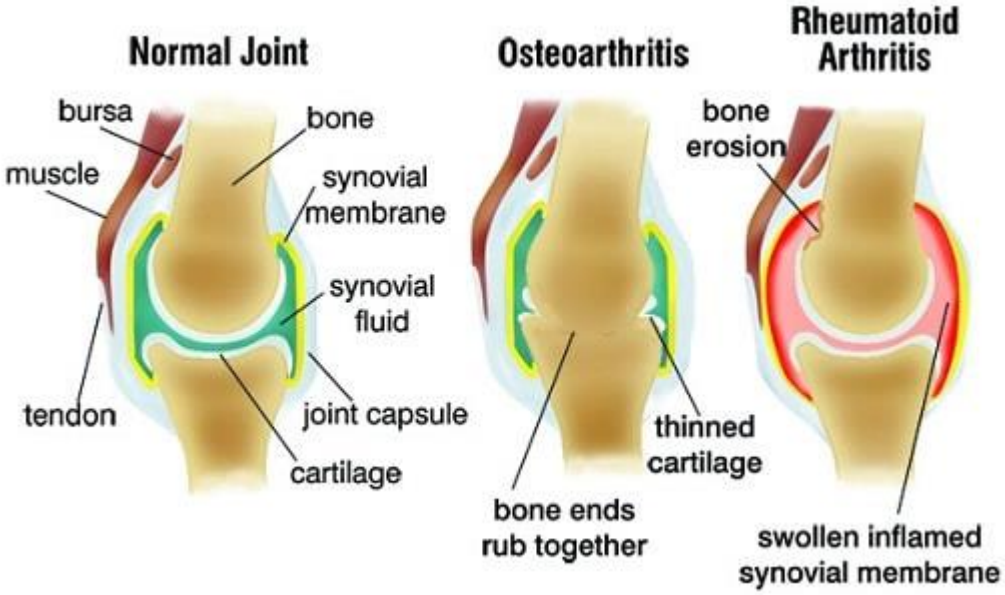

Figure 2 . Types of Arthritis

Arthritis means joint inflammation, but the term is employed to explain around 200 conditions that affect joints, the tissues that surround the joint, and other animal tissue. it's a rheumatic condition.

The most common variety of arthritis is osteoarthritis. Other common rheumatic conditions associated with arthritis include gout, fibromyalgia, and arthritis (RA).

Rheumatic conditions tend to involve pain, aching, stiffness, and swelling in and around one or more joints. The symptoms can develop gradually or suddenly. Certain rheumatic conditions may also involve the system and various internal organs of the body.4 There are two forms of arthritis condition for joints one is arthritis and also the another is osteoarthritis . Diagram shows the difference between two types. In osteoarthritis, cartilage is getting eroded. Two bone's ends rub together, causes pain and inflammation . in arthritis tissue layer is inflamed .Bone erosion could be a central feature of autoimmune disorder. Bone continuously undergoes remodelling by action of bone resorbing osteoclasts and bone forming osteoclasts. one in all the most trigger of bone erosion within the joints within the arthritis is inflammation of the synovium, caused partially by the assembly of proinflammatory cytokines and receptor activator of nuclear factor kappa B ligand (RANKL), a cell surface protein present in Th17 cells and osteoblasts.(4) Osteoclast activity is directly induced by osteoblasts through the RANK/RANKL mechanism.5

Current Drug Treatment:

A. Disease modifying anti rheumatic drugs (DMARD's)

a. Nonbiological drugs

1. Immunosuppressants: Methotrexate, Azathioprine, Cyclosporine
2. Sulfasalazine
3. Chloroquine or Hydroxychloroquine
4. Leflunomide

b. biological agents

1. TNF α inhibitors: Etanercept, Infliximab, Adalimumab

2. IL-1 antagonist: Anakinra II.

B. Adjuvant drugs Corticosteroids: Prednisolone et al.6

3.Zafirlukast:

3.1. Structure:

Zafirlukast could be a selective and orally administered leukotriene receptor that inhibits the cysteinyl leukotriene cysLT1 receptor.

Zafirlukast could be a synthetic, selective peptide leukotriene receptor antagonist (LTRA), with the chemical name 4-(5-cyclopentyloxy carbonylamino-1-methyl-indol-3-ylmethyl)-3-methoxy-N-o-tolylsulfonylbenzamide.

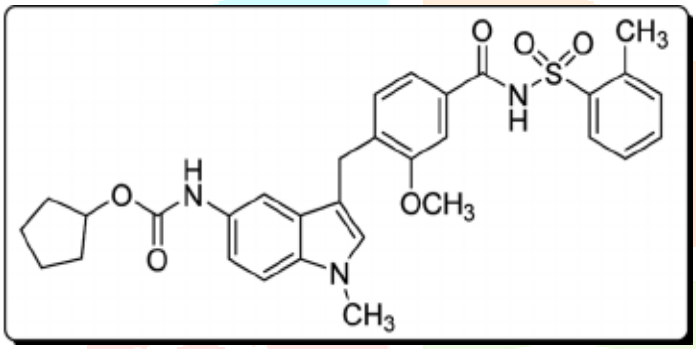

Figure 3.Structure of Montelukast

3.2 Pharmacology:

3.2.1.Pharmacodynamics:

Zafirluast could be a leuotriene receptor antagonist used as alternative to anti- inflammatory medications within the treatment and management of asthma and exercise induced bronchospasm (EIB). Zafirlukast is employed to stop asthma symptoms. Zafirlukast is in a very class of medicines called leukotriene receptor antagonists (LTRAs). It works by blocking the action of certain natural substances that cause swelling and tightening of the airways.

3.2.2 Pharmacokinetics:

The pharmacokinetics of zafirlukast are best described by a two-compartment model. Maximum plasma concentrations (Cmax) were achieved 3 hours after one oral dose of 20 or 40 mg to healthy volunteers. absolutely the bioavailability of zafirlukast is unknown. However, coadministration of zafirlukast with food reduces bioavailability by approximately 40%. The drug binds to plasma proteins (>99%), predominantly to albumin, and encompasses a mean terminal elimination half-life of roughly 10 hours in both healthy volunteers and patients with asthma. Zafirlukast undergoes extensive hepatic metabolism. Hydroxylation by cytochrome P450 (CYP) 2C9 is that the major biotransformation pathway. The metabolites of zafirlukast contribute little to its overall activity. Zafirlukast is principally eliminated within the faeces, while urinary excretion accounts for <10% of an orally administered dose.[7]

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3.3: Clinical use:

4-(5-cyclopentyloxycarbonylamino-1-methyl-indol-3-ylmethyl)-3-methoxy-N-o-tolylsulfonylbenzamide, a cysteinyl lecoptrine receptor antagonist, is approved for the treatment of asthma. the leukotrienes play a vital role within the underlying inflammatory processes of asthma, zafirlukast represents a brand new antinflammatory option available in an oral dosage form. it's clear that this agent has therapeutic activity in patients with asthma[8]

Leukotriene formation:

leukotrienes don't exist preformed in cells. they're formed from the breakdown of arachidonic acid, a polyunsaturated 20 carbon acid. In its esterified form, arachidonic acid is sure to the phospholipids of the cell membranes.[9]

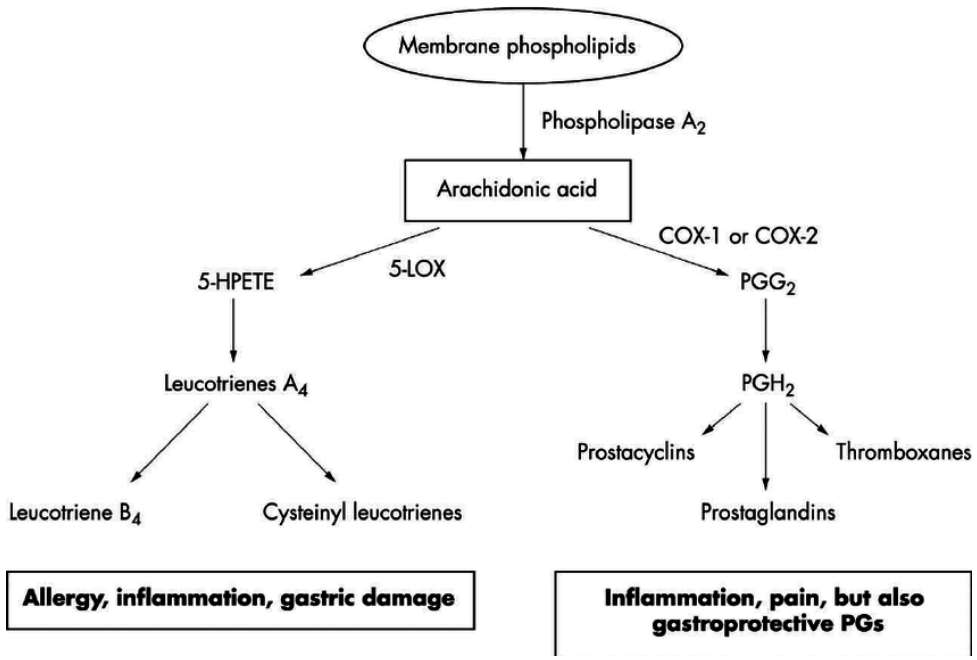

Figure 4. Leukotriene Formation

3.4: side effects:

Zafirlukast is very safe with few side effect like headache, sore throat ,cold symptoms, nausea, diarrhea

4.fexofenadine:

Structure: Fexofenadine is a potent second –generation histamine H1 antagonist that is effective in the treatment of allergic rhinitis, urticarial hay fever. Fexofinadine described chemically as (±)-4-[1 hydroxy-4-[4-(hydroxydiphenylmethyl)-1- piperidinyl]-butyl]-α, α-dimethyl benzene acetic acid hydrochloride. The molecular formula is C32H39NO4 with molecular weight is 501.7 g/mol

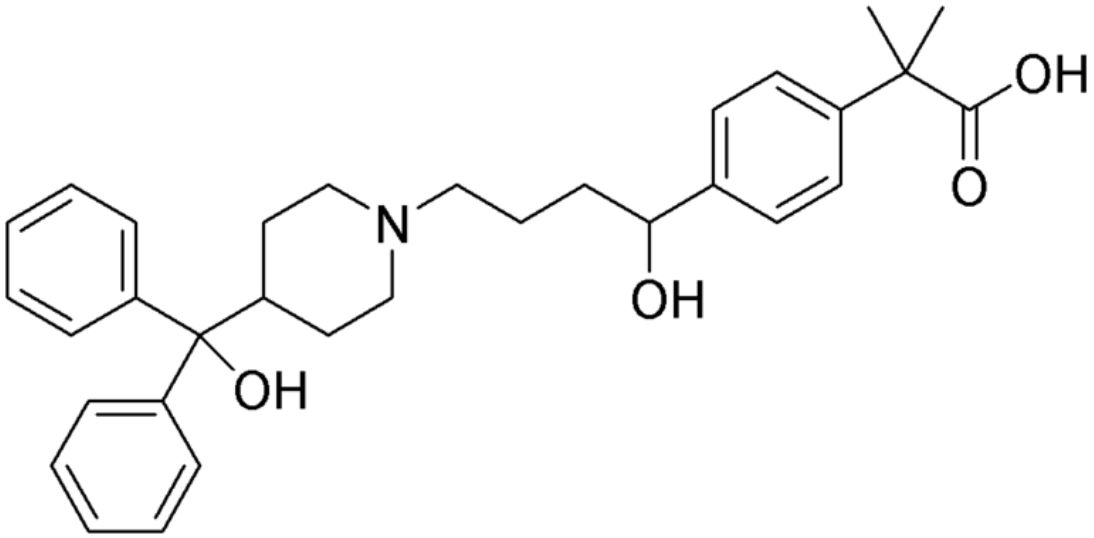

Figure 5. Structure of cetirizine

4.1. Pharmacology:

4.1.1 Pharmacodynamics:

The mechanism of action of fexofenadine is to selectively antagonize H1 receptors on the surface of cells on multiple different organ systems. it's a second-generation H1 receptor blocker and is non-sedating. Fexofenadine also affects inflammatory mediators. Fexofenadine blocks the results of histamine and reduces these symptoms.10(clinical pharmacokinetics review paper, 2008, Vol. 47, No. 4 (pp. 217-230)

4.1.2 Pharmacokinetics

: Fexofenadine hydrochloride was rapidly absorbed, reaching peak concentrations in 0.83 to 1.33 hours.[11]

4.2 Clinical uses:

Fexofenadine is an antihistamine that reduces chemical histamine within the body. Fexofenadine is that the 2nd generation h1 receptor blocker. The prevalence of allergic conditions and also the relative safety of the drugs. it's heavily employed in

1. hypersensitive reactions

2.watery eyes,

3. runny nose,

4.itching eyes/nose,

5.sneezing, hives,

6. itching.

4.3 Side effects:

common side effect includes convulsions in children, allergic responses, headaches, feeling sleepy, dry mouth, feeling sick and dizziness.[12]

4.4. Mechanism of action:

Fexofenadine 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 may be attributed to reduced penetration of cetirizine into the CNS as a results of the less lipophilic chemical group on the ethylamine side chain.[13]

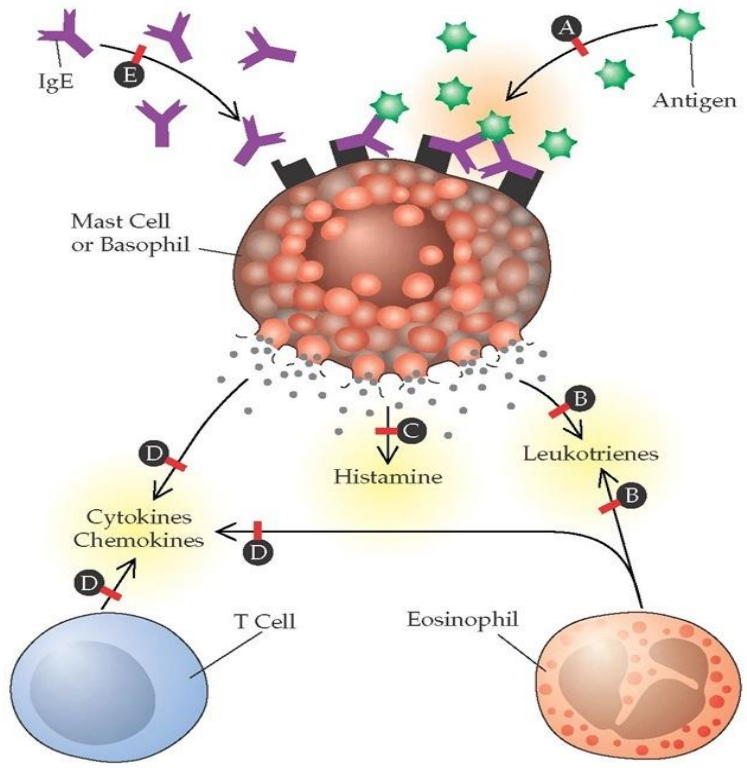

Figure6. Inflammatory mediators

Fexofenadine, presupposed to inhibit DNA binding activity of NF-Kapp B, inhibits the expression of adhesion molecules on immunocytes and endothelial cells and therefore the production of IL-8 and LTB4, two potent chemo attractants, by immune cells. It induces the discharge of PGE2, a suppressor of antigen presentation and MHC class II expression, from monocyte/macrophages and reduce the quantity of tryptase positive mast cells in inflammation sites. Tryptase may be a chemo attractant, generates kinins from kininogen, activates mast

cells, triggers maturation of dendritic cells and stimulates the discharge of IL-8 from endothelial cells and therefore the production of TH1 lymphokines by mononuclear immunocytes.[14]

HYPOTHESIS

As we seen earlier, progression of disease goes through three steps; Initiation, Inflammation, and destruction. In second stage inflammation, interleukins play important role. Zafirlukast act as leukotriene receptor antagonist. leukotriene 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 trigger to inflammatory responses. in order that one can restrict the progression of disease at second stage only. this can be new approach for the treatment of autoimmune disorder.

Fexofenadine is incredibly popular anti-histaminic drug , fexofenadine restrict the activity of histaminic .fexofenadine, speculated to inhibit DNA binding activity of NF-Kappa B, inhibits the expression of adhesion molecule on immunocytes and endothelial cells and therefore the production of IL-8 andLTB4, two potent champ attractants , boby immune cells .It induces the discharge of PGE2, a suppressor of antigen presentation and MHC class II expression from monocyte/macrophages and reduces the amount of tryptase positive mast cells in inflammation sites . Tryoptase may be a chemo attractant, generate kinnins from kininogen, activates mast cells triggers maturation of dendritic cells and stimulates the discharge of IL-8 from endothelial cells and therefore the production of Th1 lymphokines by mononuclear immunocytes. fexofenadine may prove benefit in improvement of arthritis.

CONCLUSION:

Rheumatoid arthritis is an autoimmune disease; there's lacuna in proper management of disease. This study puts forth a brand-new approach of Zafirlukast and fexofenadine in treatment of rheumatoid arthritis. It also highlights the probable mechanism of action involved in treatment of disease.

REFERENCE:

1. A. Krishna Sailaja An overall review on autoimmune disorder Journal of Current Pharma Research 4 (2), 2014, 1138-1143.
2. A.M. Bendele Animal models of atrophic arthritis J Musculoskel Neuron Interact 2001; 1(4):377-385.
3. Angelica Gierut,1 Harris Perlman,1,3 and Richard M. Pope immunity and atrophic arthritis 2010 may;36(2):271-2
4. Hannah Nichols What are the causes and kinds of arthritis? November 14, 2017)
5. Hee Yeon Won,
6. Prominent Bone Loss Mediated by RANKL and IL-17 Produced by CD4+ T Cells in TallyHo/JngJ Mice March 25, 2011)
7. K.D. Tripath, ‘essential of medical pharmacology by K.D. Tripathi’,JAYPEE BROTHERS,5,203.
8. P N Richard Dekhuijzen 1, Peter P Koopmans Pharmacokinetic profile of zafirlukast 2002;41(2):105-14.)
9. J S Kelloway Zafirlukast: the primary leukotriene-receptor antagonist approved for the treatment of asthma 1997 Sep;31(9):1012-21.)
10. Stella R. O'Donnell Leukotrienes - biosynthesis and mechanisms of action 1999; 22:55-)
11. clinical pharmacokinetics review paper, 2008, Vol. 47, No. 4 (pp. 217-230)
12. T Russell 1, M Stoltz, S Weir Pharmacokinetics, pharmacodynamics, and tolerance of single- and multiple-dose fexofenadine hydrochloride in healthy male volunteers 1998 Dec;64(6):612-21.
13. David Axelrod and Leonard Bielory Fexofenadine hydrochloride within the treatment of allergic disease: a review 2008; 1: 19–29.)

14. Fexofenadine hydrochloride within the treatment of allergic disease: A review September 2008 Journal of Asthma and Allergy 1(1):19-29)
15. Kari L. Craun; Mark P. Schury. Fexofenadine. November 20, 2020.)