MONTELUKAST AND CETRIZINE MAY AMELIORATE PROGRESSION OF RHEUMATOID ARTHRITIS

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INTRODUCTION

Arthritis is a form of joint disorder which involves inflammation of one or more joints. There are more than 100 forms of arthritis 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 the area in the body where two bones meet and helps in the movement of the body parts. It usually causes joint pain. It is classified as a rheumatic disease.

Rheumatoid arthritis is chronic progressive autoimmune disorder characterized by symmetric erosive synovitis (1). The prevalence of rheumatoid arthritis (RA) is relatively 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 so far shown that the familial recurrence risk in RA is small compared with other autoimmune diseases. The main genetic risk factor of RA is the HLA DRB1 alleles, and this has consistently been shown in many populations throughout the world. The strongest susceptibility factor so far has been the HLA DRB1*0404 allele. Tumor necrosis factor alleles have also been linked with RA. However, it is estimated that these genes can explain only 50% of the genetic effect. A number of other non-MHC genes have thus been investigated and linked with RA.

Environmental factors have also been studied in relation to RA. The geometric distribution of disease is homogenous.

Disease occurrence is more in identical twins. Females are more prone than male. Female sex hormones may play a protective role in RA; for example, the use of the oral contraceptive pill and pregnancy are both associated with a decreased risk. However, the postpartum period has been highlighted as a risk period for the development of RA. (2), (3).

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 two types. 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. Bone continuously undergoes remodeling by actions of bone resorbing osteoclasts and...
bone forming osteoblasts. One of the main triggers of bone erosion in the joints in rheumatoid arthritis is inflammation of the synovium, caused in part by the production of pro-inflammatory cytokines and receptor activator of nuclear factor kappa B ligand (RANKL), a cell surface protein present in Th17 cells and osteoblasts. Osteoclast activity can be directly induced by osteoblasts through the RANK/RANKL mechanism.

**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, dendriatic 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.

**2.1 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 relief the symptoms, restrict the articular damage, stop the progression of disease, and improve the quality 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

**2.2 Current drug treatments.**

**A. Disease modifying ant rheumatic drugs (DMARDs)**
1. Immunosuppressant: Methotrexate, Azathioprine, Cyclosporine
2. Sulfasalazine
3. Chloroquine or Hydroxychloroquine
4. Leflunomide
5. Gold sod. 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

**2.3 Treatments and safety issues**
Rheumatoid arthritis is a chronic disease, so patients need to take therapy for long time. It will increase the risk of side effects of drugs to the patients. Some common side effects of traditional drugs are listed below.

<table>
<thead>
<tr>
<th>Treatment approach</th>
<th>Side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID’s</td>
<td>Indigestion gastrointestinal disturbance Stomach ulcers</td>
</tr>
<tr>
<td>COX inhibitors</td>
<td>Increased risk of cardiovascular events aggravation of hypertension</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Weight gain cushingoid appearance increased blood pressure, increased blood sugar level Osteoporosis</td>
</tr>
<tr>
<td>DMARD’S</td>
<td>Hepatic cirrhosis Interstitial pneumonitis Severe myelosuppression Cancer risk with methotrexate</td>
</tr>
<tr>
<td>Biologics</td>
<td>Systemic lupus erythromatus Injection or infusion site reactions</td>
</tr>
<tr>
<td>JAK inhibitors</td>
<td>Infection and malignancy Gastrointestinal perforation</td>
</tr>
</tbody>
</table>

**3. Montelukast:**

**3.1 Structure:** Montelukast sodium is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene CysLT1 receptor. Montelukast sodium is described chemically as [R-(E)]=[1-[[[1-[3-[2-(7-chloro-2 quinoliny] ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl] phenyl] propyl] thio] methyl] cyclopropanecacetic acid, monosodium salt. The empirical formula is C35H35CINaO3S, and its molecular weight is 608.18.
The structural formula is:

![Figure 3. Structure of Montelukast](image)

3.2 Pharmacology:
3.2.1 Pharmacodynamics:
Montelukast is a leukotriene receptor antagonist used as an alternative to anti-inflammatory medications in the management and chronic treatment 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.

3.2.2 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 t1/2 of Montelukast is 3–6 hours, with volume of distribution of 8 to 11 lit.

3.3 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. (10) (11).

3.4 Side effects: Montelukast is very safe with few side effects like headache, rashes. Eosinophilia and neuropathy are infrequent.

4 Cetirizine:
4.1 Pharmacology:
4.1.1 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 allergic rhinitis and for chronic urticaria.

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

4.2 Clinical uses: Cetirizine is an antihistamine that reduces the natural chemical histamine in the body. Histamine can produce symptoms of sneezing, itching, watery eyes, and runny nose. Cetirizine is the 2nd generation H1 receptor blocker. The prevalence of allergic conditions and the relative safety of the drugs contribute to heavy use of it.

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

4.3 Side effects: Less common toxic effects of systemic use include excitation and convulsions in children, postural hypotension, and allergic responses. (12)

4.4 Mechanism of action: Cetirizine competes with histamine for binding at H1-receptor sites on the effector cell surface, resulting in suppression of histaminic edema, flare, and pruritus. The low incidence of sedation can be attributed to reduced penetration of cetirizine into the CNS as a result of the less lipophilic carboxyl group on the ethylamine side chain.
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. 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. (13)

**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. Leukotrienes 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 will further produce leukotriene C4 (LTC4) and leukotriene B4 (LTB4). These leukotriene triggers inflammatory responses, so that 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. 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. Cetirizine may prove benefit in improvement of rheumatoid arthritis.

**CONCLUSION**

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

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