Osteoarthritis is the most common joint disorder in the world. It is one of the most frequent causes of pain, loss of function and disability in adults. 2nd to Ischemic Heart Disease (IHD) (1). In India, the prevalence of OA has been suggested to be 24.9% (2). In one of our previous studies from Jammu region, it was recorded 42.4% (3). Till recently, osteoarthritis was classified as a mechanical wear and tear disorder of articular cartilage for which only pain modifying therapies such as analgesics were prescribed with little scientific attention focused on modification of course of disease leading to musculoskeletal disability and affecting quality of life. (4).

The current treatment of osteoarthritis is primarily focused on symptomatic relief by use of rapid action drugs (analgesics and NSAIDS) and newer cyclooxygenase (COX-2) specific inhibitors (5). NSAIDS use increases the risk of upper gastrointestinal adverse effects and does not effect the underlying pathogenesis of articular diseases (6), thus have minimal role in modifying disease course and improving quality of life. Although COX-2 inhibitors have reduced incidence of gastrointestinal adverse events but may have significant renal and cardiovascular toxicities (7). Hence, there is continuous search for new and better drug for OA.

Recently, there has been an increase in the use of symptomatic slow acting drugs /chondroprotective drugs /connective tissue structure modifying agents (e.g. chemically modified tetracyclines, glucosamine or chondritin sulphate and diacetylcrine (8-9). These drugs have gradual onset of action (4-6 weeks) but maintain their symptomatic effect for a period of 4-8 weeks after cessation of treatment (10).

**Diacerein** is newly introduced one of the symptomatic slow acting drug for OA. It is a semi-synthetic anthraquinone derivative extracted from certain plants.

**Mechanism of Action**: It directly inhibits IL-1 synthesis and release in vitro and down modulate IL-1 induced activities and have been shown to possess disease modifying effect in experimental models of osteoarthritis and in human subjects with finger joint and knee osteoarthritis (9). IL-1 plays a fundamental role in osteoarthritis pathophysiology and cartilage destruction as shown in figure 1&2 (11,12). IL-1 also promotes expression of inducible nitric oxide synthase, increase release of prostaglandin E2, IL-6,IL-8 in human osteoarthritis chondrocytes, which promote joint degradation (13). Hence, by inhibiting IL-1 diacerein retards all pathological prepossess initiated in OA (Fig:1-2). Diacerein also inhibits IL-1 induced expression of cartilage degrading enzymes. It also enhances expression of TGF BETA-1 and TGF BETA 2 thus favoring matrix synthesis and turnover in articular chondrocytes, thereby accounting for disease modifying property of diacerein as shown in fig-3 (12). It also inhibits superoxide production, chemotaxis and phagocytic activity of neutrophils in addition to effect on macrophage migration and phagocytosis (13). In contrast to NSAIDS, diacerein does not inhibit synthesis of prostaglandins; hence no gastroduodenal toxicity has been observed with diacerein (14). It is also demonstrated to be involved in prevention of loss of hydroxyproline and proteoglycans in the joint cartilage, an effect not observed with conventional NSAIDS or COX-2 inhibitors (10).

**Pharmacology**: Diacerein has efficacy on functional manifestations of osteoarthritis and on structural component. It exerts its pharmacologic action through its...
active metabolite-rhein (14). Diacerien is entirely converted to rhien before reaching systemic circulation and rhien later gets eliminated by renal route (20%) or conjugated in liver to rhien glucronide (60%) and rhien sulphate (20%), these metabolites are mainly eliminated by renal route. The pharmokinetics after a single oral dose are linear in normal therapeutic doses with equal efficacy in normal young and elderly volunteers. The absorption in systemic circulation is delayed with standard meal but is associated with 25% increase in amount absorbed. In contrast to other NSAIDS the interactions are minimal as highly binding of rhien to plasma proteins is not saturable (15). It dose not alter renal or platelet COX activity and can be tolerated easily by patients with prostaglandin dependent renal function (14). Though dose modification is required in mild to severe renal insufficiency [50% dose reduction in severe renal failure] (16), no reduction in initial dose is proposed in liver cirrhosis (17).

**Structural effect**: Various clinical trails have confirmed the efficacy of diacerein in patients with hip osteoarthritis. In a study (ECHODIAH) conducted to evaluate the effect of diacerein in a patient of hip Osteoarthritis over a 3 year period using progression of joint space narrowing as assessment criteria, it has been found that mean progression of narrowing was significantly less in patients treated with diacerein from 0.18 per year to 0.13 per year at the end of third year. For the first time significant structure modifying effect of diacerein as compared to placebo was demonstrated in this study (18,19). The effect of the drug in acute exacerbations of osteoarthritis of hip has been documented in approximately 30 studies. It is much superior to that of placebo and over a common NSAID tenoxicam at the 60th treatment day (20). Diacerein has been also shown to be effective in modification of symptoms and structure in patients of Knee OA (21).

**Safety profile**: Drug watch data and clinical trails have confirmed the safety and tolerability of diacerein. So there is no limitation on the duration of its use (8). The optimal daily dose which relief symptoms in osteoarthritis knee calculated from effect on VAS assessment criteria of pain on movement was found to be 100mg/day (21). Diacerein is well tolerated, the predominant adverse effect include transient change in bowel habits (14). It seems neither responsible for gastrointestinal bleeding nor for renal, liver nor hematological toxicities. Non significant discoloration of urine occurs during treatment because of urinary elimination of metabolites of diacerein. No allergic cutaneous reaction were reported in knee osteoarthritis trial (21). In 3 year hip osteoarthritis trial, rash or pruritis was noted in 3% patients on placebo and in 7% patients on diacerein 100mg daily (18). No severe allergic reaction has been reported till date.

**Conclusion**: In the current shift of understanding of pathogenesis from biomechanical to biochemical, diacerein holds a lot of promise in the treatment of osteoarthritis.
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