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Review Article

Diacerein- A gold standard analgesic in management of osteoarthritis

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ABSTRACT

Diacerein is a symptomatic slow-acting drug in osteoarthritis (SYSADOA) with anti-inflammatory, reconstructive and anti-destructive properties on cartilage and synovial membrane. Recently, based upon its mechanism of action it has been shown that it has got pro-anabolic effect on subchondral bone remodelling. Based on a literature review of clinical trials and meta-analyses, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) declares that after the first month of osteoarthritic treatment the diacerein efficacy is superior to that of paracetamol and similar to that of non-steroidal anti-inflammatory drugs (NSAIDs). Additionally, once treatment was stopped diacerein has shown a prolonged effect on symptoms for several months, in view of its cumulative effects. Furthermore, similarly to other Symptomatic slow-acting drugs for OA (SYSADOAs), the ESCEO positions diacerein as a first-line pharmacological background treatment of osteoarthritis, particularly for patients in whom NSAIDs or paracetamol are contraindicated.

1. Introduction

Osteoarthritis (OA) is the most common and debilitating form of arthritis, and one of the leading caused of geriatric disability worldwide.[1] Osteoarthritis is a chronic inflammation of joint, which has predominantly two components, one is limitation of joint function if untreated it might lead to deformity of joint/limb, the other is pain, which varies from tolerable to intolerable intensities. Together with disability /deformities, pain contributes to a significant reduction in quality of life.

Osteoarthritis is an inflammation of joints that results from degeneration of cartilage caused by aging, heredity, injuries or inflammation secondary to inflammation. It is the most common chronic musculoskeletal disorder. Epidemiological studies shows this disorder claims 15% of world population.[2,3] In view of this ailment substantial burden on the family and economic issues are inevitable.

2. Background

Based on research osteoarthritis not only disrupt the articular cartilage, but it destroys the entire joint physiology.[4]

Normal adult cartilage is made up of extracellular matrix that contains majorly water, collagen, proteoglycans and chondrocytes[5] the turnover phase of collagen is relatively slow than proteoglycan due to its inbuilt physiology.[6]

Osteoarthritis results from imbalance in the above physiology i.e. failure of chondrocytes to maintain homeostasis between synthesis and degeneration of extracellular matrix.[6]

Breakdown molecules of collagen and proteoglycans are digested by synovial macrophages.

These macrophages engulfs the molecules releasing certain cytokines namely TNF (Tumor Necrosis Factor)-α, IL (Interleukin)-Iβ. Thus released cytokines binds the chondrocytes leading to further release of secondary inflammatory mediators like metalloproteinase, which degrades the structural proteins of the joint and inhibition of type II collagen production. This disruption of homeostasis

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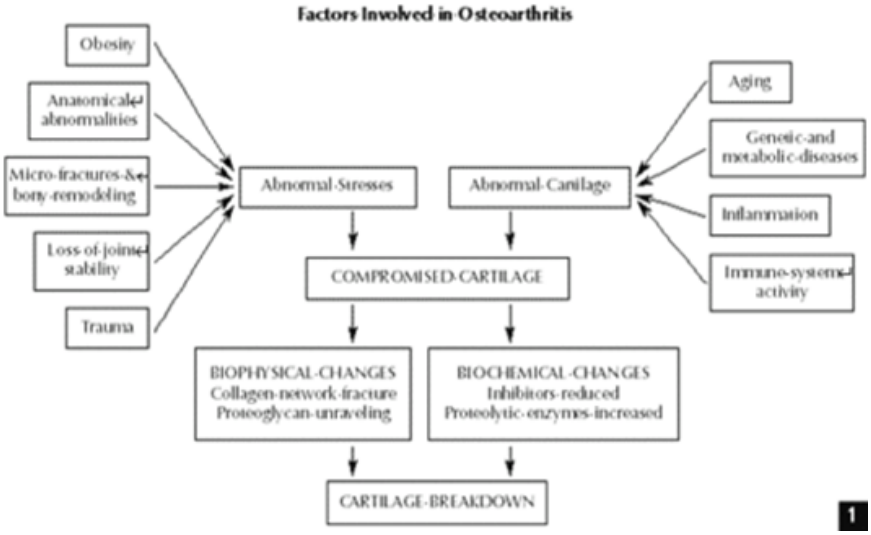

Fig. 1: Factors involved in Osteoarthritis

results in hypoosmolarity and decrease in matrix containing rich type II collagen.[7]

Subchondral bone is separated from the articular cartilage by the zone of calcified cartilage. Osteoarthritis pathophysiology alters subchondral bone model also, leading to complete disruption of synovial joint architecture.[6]

Osteoarthritis patients manifest as synovial joint pain, with swollen joint, joint stiffness, joint crackling and loss of joint motion range.

Diacerein is a slow acting drug belonging to the class anthraquinone, which works by inhibiting the action of Interleukin-Iβ. Interleukin -Iβ, is a prime cytokine which is responsible for producing symptoms and destruction of joint architecture by inducing inflammation of tissues.[8]

The main action of diacerein is to block the action of interleukin-1β (IL-1β) system and its concomitant down streaming signals.[9] Diacerein decreases the production of interleukin-1 converting enzymes and thereby reduces the activation of interleukin-1β,[10] and also it decreases the interleukin-1 receptors on the cell surface of chondrocytes and thereby reducing the sensitivity of interleukin-1 actions. By this mechanism diacerein indirectly increases the IL-1 receptor antagonist production.[11] Diacerein inhibits the IL-1β-induced activation of transcription factor NF- κB, which stimulates pro-inflammatory cytokine expression.[12] On molecular studies of osteoarthritic synovial fluid, down regulation of interleukin-1 level has been documented.[13]

Besides its anti-inflammatory properties, diacerein has anti-destructive[14] and reconstructive effects[15] on cartilage and synovial membrane, as well as protective effects against subchondral bone remodeling.

2.1. Trial review

Despite Diacerein being nearly three decades in the market, few randomized controlled trial (RCT) in osteoarthritis have been done. Several studies have concluded that Diacerein is a slow acting symptom modifying agent.[16,17]

2.2. Study design

This review was conducted by using the search term: Diacerein, osteoarthritis, and/or clinical trial and/or metaanalysis in web. From this, trial done under long exposure (N>100), double blinded comparative studies involving the study drug with others like placebo, hyaluronic acid and NSAIDs were taken.[18–20] most reviewed RCT had relief from pain as their primary outcome, secondary efficacy variables being joint function improvement and relief from stiffness. Most of these RCT were done over a span of 3 months to 12 months. No steroid or paracetamol comparative studies were taken up.

2.3. Symptomatic efficacy

Trials are summarized in below table. Though the results were bit inconsistent there were substantial benefits to osteoarthritis patient.

The superiority of Diacerein versus placebo was reached at 2 months of therapy, similarly at the end of 3 months the efficacy were well established in hyaluronic acid comparative study.

Safety: Statistically significant adverse effects were observed in these comparative studies. Among which diarrhoea and skin rashes were more particular. Diarrhoea (46%) was experienced among the patients with Diacerein group. However, these adverse effects were self-limiting and treated symptomatically. Nearly 50% of the patient

Table 1:

Trial	Patients (N)	Age: Sex(F/M)	Duration (Months)	Comaparison	*P* Value
Pelletier et al	484	64:80/20	4	Placebo	<0.05
Pham et al	301	65:70/30	12	Hyaluronic Acid	0.01
Lautheranoo et al	161	54:90/10	4	NSAIDS	0.85

subjected to Diacerein drug suffered from diarrhoea and became asymptomatic when the drug was discontinued.[19,20]

Urine discolouration was another non-fatal manifestation among the Diacerein exposed patients. This discolouration was due to the metabolite of Diacerein. The renal functions were unaffected, concluding it be an renal safe drug.[18,20]

In long term study, skin rashes were evident in the Diacerein group, for which dermatological opinion was obtained.[20]

2.4. Clinical data on the safety of diacerein

2.4.1. Gastrointestinal (GI)

Diacerein belong to anthraquinone family, anthraquinone chemical structure possesses laxative property. Hence, the most frequently reported events with diacerein were loose stools and diarrhea.

The following are the results obtained on relative risk ratio for developing diarrhoea when the patients are subjected to study with diacerein and placebo.

On retrospective analysis, Diarrhoea occurred in the first fortnight of treatment and was mild to moderate in its severity.[24] In almost all cases, the diarrhoea induced by diacerein was reversible after stopping the treatment. Furthermore, diarrhoeal symptoms decreased in most cases after continuous treatment.[25]

The post-marketing surveillance of diacerein showed that 25 serious cases of diarrhoea were reported. Three of them concerned elderly patients, who experienced dehydration and electrolyte disorders; one case was fatal and occurred in a 79-year-old female with a medical history of arterial hypertension and cardiac arrhythmia.[26]

2.4.2. Cutaneous

On reviewing15 published articles, the cutaneous manifestations were evident ranging from simple rashes to high grade skin inflammations, reflecting its incidence from 1.8% to 9.4%.[20,27] The present review identified rash, pruritus and eczema as the most common cutaneous reactions reported in clinical trials. They are appropriately reflected in the product information with a frequency of >1/100 and <1/10).

Based upon post-marketing statistics, data revealed a few severe cases of cutaneous events: four erythema multiform, two Stevens-Johnson syndrome (SJS) and three toxic epidermal necrolysis (TEN).[26]

2.4.3. Hepatic

Among the 15 published clinical trials evaluating diacerein, only Zheng et al.[28] reported the occurrence of a hepatic adverse event: one treatment discontinuation due to increase in hepatic enzymes. The Pharmacovigilance Risk Assessment Committee (PRAC) performed a more complete analysis of available data and retrieved seven clinical trials showing abnormalities of liver tests. These were mostly characterized by mild/moderate liver enzyme increase (ALT, AST <5 ULN) without increases in bilirubin.[26]

A total of 89 cases within the post-marketing surveillance were considered as hepatic reactions. The most frequent reactions were liver function test abnormalities (41 cases).[26] One case of hepatic failure had a fatal outcome and a close temporal association with diacerein.[29]

The extensive preclinical animal toxicology data with diacerein indicated that the liver was not a target organ for toxicity. The mechanism of action of this hepatic toxicity is not fully understood, but an idiosyncratic mechanism is suggested.

2.4.4. Cardiovascular

Diacerein is a relatively cardiovascular safe drug. Based on ICHS (International Community Health Services) 7A guidelines, a study was designed on dog subjects, where 5 and 30 mg/kg/day for 7 consecutive days and at 60 and 200 mg/kg/day for 4 and 3 consecutive days were administered and studied. Results revealed diacerein was relatively cardiovascular safe drug with absolutely no adverse effects on cardiovascular system. Furthermore, the dosage administered was nearly 3.6 to 143 times the recommended dose on humans (1.4 mg/kg/day based on a 70 kg person).[30]

More significantly, no signal from post-marketing surveillance for acute coronary syndromes or myocardial infarctions was reported in more than 20 years of experience with diacerein.

3. Conclusion

Diacerein has a modest but significant effect on pain management in osteoarthritis. Its comparative efficacy seems to be statistically significant enough for its inclusion in the management of osteoarthritis. The main toxicity is mild to moderate diarrhoea which has linear relationship with the dosage and duration of the therapy. The concerned

Table 2:

Bartels et al.[21]	3.51 (95 % CI 2.55–4.83).
Fidelix et al.[22]	3.52 (95 % CI 2.42–5.11)
Rintelen and co-authors[23]	39% patient under diacerein, 12% under placebo

authorities advised that patient should start half the normal dose initially and titrate to the therapeutic level and discontinue once the significant adverse effect sets in. i.e. to start 50mg/day instead 100mg/day initially.

The other recommendation is to have screening test for liver dysfunction. It can be concluded that Diacerein does have a role in patient with gastrointestinal disorder, heart disease and renal disorder, where NSAIDs are avoided.

Patients with cardiac, renal and GI disorders form a major bulk of the population suffering from osteoarthritis; Diacerein by virtue of possessing a safe profile with respect to these co-morbidities, is a valueable addition to the pain physician's armamentarium.

4. Source of funding

None.

5. Conflict of interest

None.

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