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Diacerein in osteoarthritis: A systematic review of randomized controlled trials

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Abstract

Diacerein, an anthraquinone derivative, along with active metabolite rhein, inhibits the interleukin -1β synthesis and metalloproteases involved in cartilage breakdown in osteoarthritis (OA). It has been evaluated in multiple randomized controlled trials (RCTs) of knee and hip OA. In this systematic review, we included 13 RCTs assessing the efficacy and safety of diacerein in knee and hip OA. Current evidence from RCTs indicates diacerein is effective in reducing pain, and joint stiffness and improving functional index. Its efficacy is significantly better than placebo and is comparable to conventional analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs). It has an analgesic-sparing effect probably attributable to its activity in reducing the disease progression and carry-over effect even after discontinuation. Evidence suggests the carry-over effect can be seen up to 8 weeks after discontinuing diacerein. Gastrointestinal disturbances in terms of diarrhea, loose stools, and urinary discoloration are more common with diacerein but these are transient, mild to moderate in severity, and are often self-limiting. Evidence also indicates good tolerability with diacerein. In conclusion, given its efficacy, comparable tolerability, and inhibition of disease regreasing, diacerein can be considered an important treatment in the armamentarium of OA management. We consider that diacerein may also serve as an optional treatment in patients with contraindications for NSAIDs or paracetamol.

Keywords: osteoarthritis, diacerein, anthraquinone derivatives, analgesics, NSAIDs

Introduction

Globally, osteoarthritis (OA) is a major health concern. With increasing prevalence, disability associated with OA is also increasing. In the past three decades, there has been a nearly 10% increase in the age-standardized prevalence of OA [1]. Knee and hip joints, being the weight-bearing joints, are commonly affected in OA. OA manifests with pain, swelling, stiffness, and reduced joint mobility. In the management of OA, the primary objective is symptom relief, increased joint mobility, and halting the progression of structural damage [2]. Therapeutic approaches range from mild analgesics like acetaminophen to surgical interventions such as joint replacements. Non-steroidal anti-inflammatory drugs and steroids which are used as initial agents mainly reduce the pain without affecting the disease progress [3]. Symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) are the pharmacological interventions that are important in the non-acute phase of OA. SYSADOAs have shown promise in terms of pain reduction and reducing cartilage damage [4,5]. Glucosamine sulfate/hydrochloride, chondroitin sulfate, hyaluronic acid, diacerein, and avocado soybean unsaponifiable (ASU) are the commonly used SYSADOAs [6]. Diacerein, an anthraquinone derivative, rhein being an active metabolite, inhibits the interleukin-1β (IL-1β) and its signaling. It has been shown to effectively provide pain relief and improvement in physical function [5]. These findings are supported in various meta-analyses as well [7,8]. In this systematic review, we assess the current evidence from randomized controlled trials (RCTs) and provide opinions about the efficacy and safety of diacerein in the management of OA.

Diacerein – Brief history and pharmacology

Diacerein is an anthraquinone derivative that is found in the Cassia gender plant. Chemically, it is 4,5-diacetyl oxy-9,10-dioxo-anthracene-2-carboxylic acid. It has poor aqueous solubility resulting in 35% to 56% oral bioavailability. By deacetylation, diacerein is converted to its active metabolite rhein. After oral administration, urinary excretion occurs majorly as glucuroconjugated metabolite whereas a nearly equal proportion of excretion is of non-conjugated metabolite and sulphuronoconjugated metabolite [9].

Both diacerein and rhein, inhibit IL-1β cytokine synthesis and inhibits metalloproteases like collagenase and stromelysin that are involved in cartilage breakdown in OA. By reducing the concentration of pro-inflammatory cytokines, diacerein exerts an inhibitory effect on cartilage breakdown. It also upregulates transforming growth factors (TGF-β1 and TGF-β2) expression, antagonizes the downstream signalling of IL-1β i.e., inhibition of mitogen-activated protein kinase signalling cascades of articular chondrocytes and enhances the regeneration in articular cartilage [9]. The anti-catabolic effects on the synovial membrane are mediated via effects on IL-1β and pro-anabolic effects by increasing collagen and proteoglycans [10]. Table 1 enlists the different mechanisms by which diacerein acts in OA [9,10]. Diacerein was synthesized in the 1980s. It was used in 1994, in Asia and some European Union countries. Diacerein was approved by the United States Food and Drugs Administration in 1994 [9].

Mechanism of action of Diacerein:

- Inhibition of IL-1 and IL-1 induced expression of enzymes leading to reduced degradation of articular cartilage.

- Improve expression of TGF-β1 and TGF-β2 leading to Improved matrix synthesis and turnover in articular chondrocytes.
- Inhibits the binding of nuclear factor kappa B (NF-κB) and activator protein-1 (AP-1) thereby reducing the expression of various pro-inflammatory genes in chondrocytes.
- Reduced turnover of chondroitin-4-sulfate protecting proteoglycan aggrecan in articular cartilage improving compression ability of cartilage.
- Inhibit N-acylethanolamine-hydrolyzing acid amidase (NAAA) leading to increased palmitoylethanolamide (PEA) concentration thereby reducing inflammatory and neurodegenerative processes.
- Reduction in the chondrocyte's urokinase receptors.
- Reduction in the synovial fluid fibrinolytic activity.
- Decreases oxidative stress by reducing superoxide activity.
- Reduced macrophage migration and phagocytic activity

Literature search strategy

We searched the electronic PubMed database. In addition, a general search in the Google search engine was performed. Literature was searched using the terms such as Diacerein, Osteoarthritis, Knee, Hip, and a combination of these search terms. Literature inclusion criteria were randomized controlled trials (RCTs) published in these databases. Only studies in the English language were included. Unpublished articles and non-English language literature were excluded. As of March 10th, 2022, we observed 255 search results from PubMed. After excluding the non-relevant articles, we included 14 RCTs in the review (Figure 1).

Clinical evidence- Efficacy of Diacerein

1. Knee osteoarthritis

There were total of eight RCTs that evaluated diacerein in knee OA. Three RCTs evaluated diacerein against a placebo whereas an active drug was administered along with Diacerin and placebo in two RCTs (glucosamine and diclofenac sodium). A study by Pelletier *et al*. published in 2000 included 484 patients with knee OA. Diacerein was administered in three doses 50 mg, 100 mg, and 150 mg, twice daily for 16 weeks. A dose of 100 mg/day (50 mg twice a day) was observed to be the optimal dose that was efficacious in terms of the effect on WOMAC scores and safe in terms of adverse effects (AEs) [11]. Another study from Pavelka *et al*. reported significantly lower WOMAC pain and total score at 5 months after three months of diacerein treatment when compared to placebo. The effects were evident as early as one and two months for total score and pain score respectively [10]. In a single-blind, randomized, post-marketing trial, Bramhachari *et al*. assessed the effects of diacerein in 64 patients of knee OA. In comparison to the placebo, 8 weeks of treatment of diacerein was associated with a significant reduction in pain indicated by VAS score, and WOMAC function scores at 12 weeks. There was a significantly lower need for rescue medication and diacerein had significantly higher grades on the physician clinical global impression scale. Compliance was excellent in 85.7% and 92.5% of patients in the diacerein and placebo groups, respectively [12]. Another double-blind RCT from Singh *et al*. assessed 84 patients of knee OA and compared the effects of diacerein (50 mg once daily in the first month and twice daily for the next two months) to a placebo. Both groups received diclofenac sodium (75 mg sustained release once daily). At the end of three months, pain intensity and WOMAC function score were significantly lower in the diacerein group as compared to the placebo group. There was a persistent effect at four months and significantly lower consumption of rescue analgesic compared to placebo [13]. In another RCT from Kongtharvonskul *et al*., a combination of patented crystalline glucosamine sulfate (pCGS) and diacerein was compared to pCGS and placebo. At 24 weeks, there was no significant difference in the pain reduction indicated by VAS scores between the two groups. The mean difference was 0.09 (95% CI -0.75 to 0.94). Similarly, there was no significant difference in WOMAC pain score, stiffness score, and function score. Also, the minimal joint space width did not differ significantly (mean difference 0.04 mm, 95% CI -0.35 to 0.27) between the two groups [14].

In the remaining three RCTs, diacerein was compared to active drugs namely hyaluronic acid, piroxicam, and celecoxib. In the first double-blind RCT, Pham *et al*. assessed 301 patients aged above 50 years who had radiologically proven medial knee OA. Patients were randomized into three groups. Group 1 was intraarticular (IA) injection of hyaluronic acid (HA, NRD101) with an oral placebo, group 2 received IA saline injection with oral diacerein (100 mg/d) and group 3 had saline IA injection with an oral placebo. The study did not find any significant difference between the three groups for the change in pain VAS score, Lequesne's functional index, patient's global assessment of disease activity, and percentage of painful days during the previous months. Over the year, proportion progressors, defined by joint space narrowing >0.5 mm, was 17.7%, 18.9%, and 20.3% in the three groups, respectively. Though the study finds effective pain relief in all three groups, no intergroup difference was observed for structural or functional improvement [15]. The second study from Louthrenoo *et al*. compared diacerein 100 mg/d (n=86) and piroxicam 20 mg/d (n=85) in painful knee OA patients. After 16 weeks of treatment, the WOMAC pain score was reduced significantly and to a similar extent in both groups. After treatment discontinuation at 16 weeks, at the end of 20- and 24-week pain increased in piroxicam but not in the diacerein group. Thus, a significant carry-over effect of diacerein was observed for all three WOMAC scores and total WOMAC scores at both week 20 and week 24. Joint tenderness was also significantly lower in the diacerein group at week 24. Also, there was a significantly lower need for paracetamol medication at weeks 20 and 24 in the diacerein group. In assessing treatment efficacy, nearly 75% of patients in the piroxicam group rated it as effective by week 4 whereas diacerein was considered effective by nearly 60%. However, this proportion increased by end of 20 weeks with 89% rating diacerein treatment as effective compared to 73% in the piroxicam group. The proportion of patients remained significantly different by end of 24 weeks (86.4% vs. 64.1%, p=0.005) [16]. In the third study comparing diacerein (50 mg once daily for one month followed by twice daily, n=187) vs. celecoxib (200 mg once daily, n=193), Pelletier *et al*., found no significant between-group difference in WOMAC pain score reduction at 6 months. Thus, diacerein was observed to be non-inferior to celecoxib. Also, there was no significant difference in WOMAC total score, WOMAC stiffness score, WOMAC function score, and VAS pain score. These data indicate diacerein is as effective as celecoxib or piroxicam in knee OA. A carry-over effect has been demonstrated for nearly 8 weeks [17].

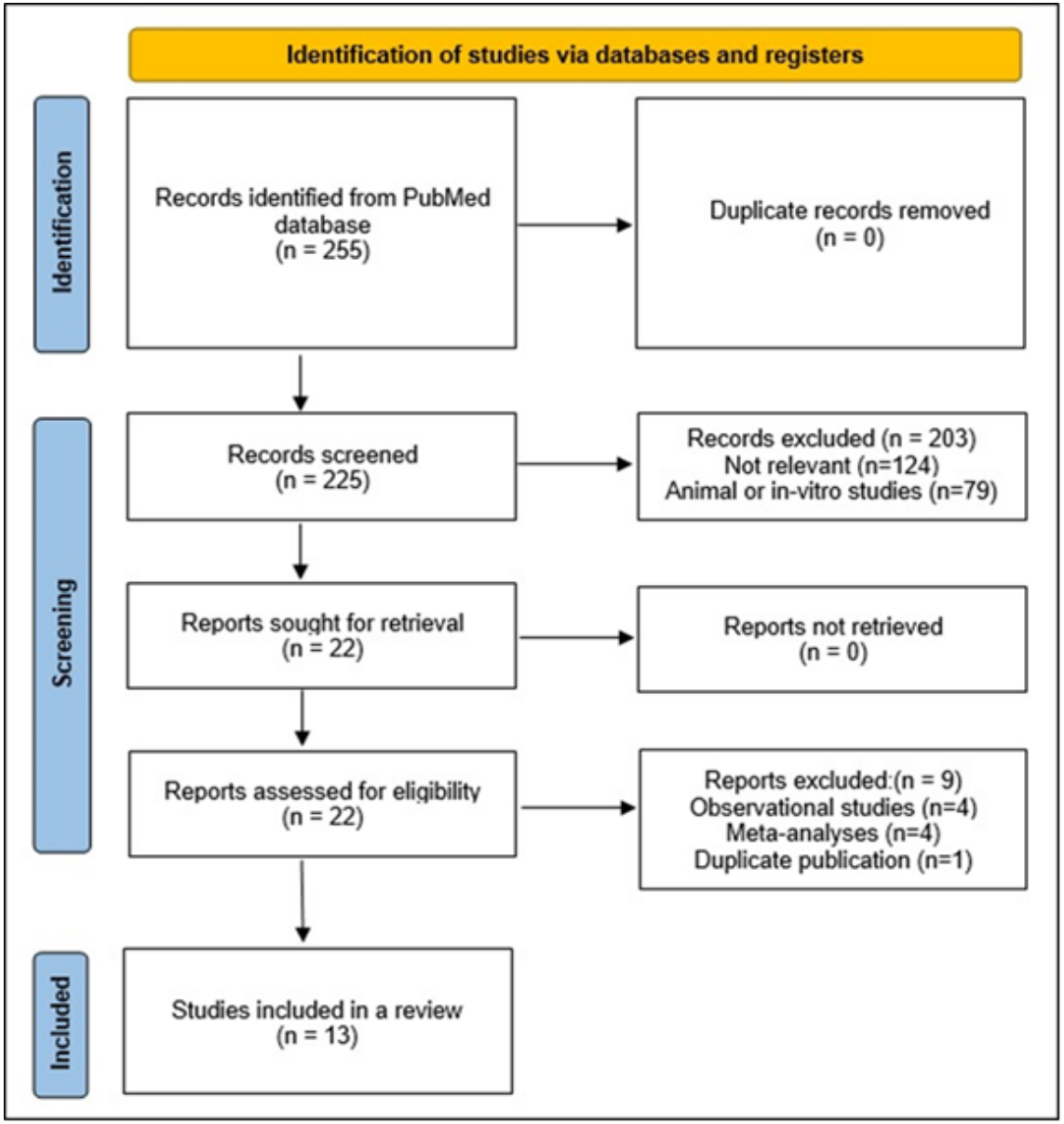

Fig 1: PRISMA study flow diagram

Table 1: Systematic review of randomized controlled trials

Author	Year	N	Population	Intervention	Comparator group	Follow-up	Outcomes	Adverse effects
Pelletier J *et al* [11]	2000	484	Knee OA	Diacerein (50 mg, 100 mg, and 150 mg per day)	Placebo	16 weeks	Significant improvements were observed in VAS pain score ($P < 0.05$).	Transient changes in bowel habits
Pavelka *et al* [10]	2007	165	Knee OA	Diacerein (50 mg)	Placebo	3 months followed by 3-month treatment free period	At 5 months: • WOMAC pain score and the overall WOMAC score significantly reduced (P 0.0001) • Superiority evident in 2nd month for pain and 1st month for overall score	Total AE rate: 35.7% Loose stools (14.3% vs. 8.3%) Diarrhea (15.5% vs. 8.3%) AE related drop out: 3 vs. 4 Global assessment of tolerability by the investigators- Good Tolerability: >90% vs. >94%
Bramhachari *et al*. [12]	2009	64	Knee OA	Diacerein (50 mg once daily for 10 days then twice daily till 8 week)	Placebo	8 weeks followed by 4-week treatment free follow-up	Significant reductions • VAS pain scores ($p < 0.01$) • WOMAC function scores ($p < 0.05$) - Significantly lower requirement for rescue medication - Significantly better CGI grades	• Significantly higher in diacerein ($p < 0.01$) • Most common: urine discoloration and soft stool • Mild to moderate intensity
Singh *et al* [13]	2012	74	Knee OA	Diclofenac +Diacerein 50 mg	Placebo and Diclofenac	3 months followed by observation at 4th month	At 3 months: • Significantly lower VAS pain score with diacerein (15.33±5.07 vs. 22.83±6.90) • Significantly better WOMAC functional score (15.9±2.40 vs. 36.8±2.92) At 4 months • Persistence of similar effects • Significantly Lower need of rescue medication (5.96±0.81 vs. 12.43±2.13)	Mild to moderate • Urine discoloration (33.3% vs. 3.3%) • Diarrhea (n=36.7% vs. 13.3%) • Dyspepsia (40% vs. 46.7%)
Kongtharvonskul *et al*. [14]	2016	148	Knee OA	pCGS 150 mg + Diacerein 50 mg	pCGS 150 mg + placebo	24 weeks	• No significant difference in pain reduction on VAS score in two groups (mean difference 0.0.9, p=0.710) • No significant difference in the mean WOMAC total, pain, function, and stiffness scores	• Abnormal urine color (87.7% vs. 66.2%) • Similar risk of diarrhea and dyspepsia in two groups
Pham T *et al* [15]	2004	301	Knee OA	Diacerein 50 mg + Saline intraarticular injection	Hyaluronic acid compound (NRD101) + oral placebo; Saline IA injection + oral placebo	12 months	No significant difference in three groups for • Change in pain VAS score • Lequesne's functional index • Patient's global assessment of disease activity • Percentage of painful days during the previous months	• AE rates: 81.7%, 84.7%, • and 81.2% respectively • Significantly more knee pain during or after IA • injection than diacerein group (p=0.0088) • Diacerein: more diarrhea ($p<0.0001$) and urine coloration (p=0.0009)
Louthrenoo *et al* [16]	2007		Knee OA	Diacerein 100 mg/d	Piroxicam	16 weeks followed by 8 weeks observation	• WOMAC Pain score • Week 16: significant decrease - Diacerein: -69.7±31.5% and piroxicam: -74.1±26.2% • Week 20: pain increased in the piroxicam group (-47%±47.8%) but not in diacerein group (-66.9± 35.9%)	Higher in diacerein • Urine abnormality (50.0% vs 8.2%) • Diarrhea (36.0% vs 10.6%) • Bowel motility disorders (12.8% vs 2.4%) Higher in piroxicam

							• Week 24: pain increased in the piroxicam group (-26.8±60.6%) but not in the diacerein group (-69.5±33.7%) • Significant carry-over effect of diacerein was observed for all three WOMAC scores and total WOMAC score at both week 20 and week 24	• Dyspepsia (32.9% vs 22.1%) • Oedema (9.4% vs 4.7%)
Pelletier J *et al* [17]	2020	288	Knee OA	Diacerein 50 mg once a day for 1 months followed by twice daily	Celecoxib	6 months	Mean decrease in the WOMAC pain score from baseline • Diacerein: –11.1 (0.9) • Celecoxib: -11.8 (0.9) No significant differences in • WOMAC stiffness score • WOMAC function score • VAS pain score • Consumption of rescue medication	AEs: 26.3% vs. 17.4% Diarrhoea: 10.2% vs. 3.7% • Mild: 4.8% vs. 2.6% • Moderate: 4.8% vs. 1.1% • Severe: 0.5% vs. 0% Diarrhea associated discontinuation: 4.8% vs. 1.6%
Nguyen *et al* [18]	1994	288	Hip OA	Diacerein (100 mg/d) + placebo, Diacerein + tenoxicam	Tenoxicam +placebo, placebo + placebo	8 weeks	• Diacerein had a slow-acting response (6-week) • Diacerein has revealed no interaction with tenoxicam • Tenoxicam had clinically significant rapid effect (within 2 weeks)	Diarrhea: higher in diacerein than placebo (37% vs. 4%)
Dougados *et al*. [19]	2001	507	Hip OA	Diacerein 50 mg twice a day	Placebo	3 years	• Reduced joint space loss of at least 0.5 mm. compared to patients who were given a placebo. • Joint space narrowing reduced with diacerein (0.18±0.25 mm/year against 0.23±0.23 mm/year, p=0.042)	AEs related discontinuation: 25% vs. 12% Diarrhea (46% vs. 12%) Discoloration of urine (31% vs. 2%)
Kay *et al* [20]	1980	12	Knee and hip OA	Diacerein 50 mg twice a day	Placebo	12 weeks (4 weeks placebo followed by 4 weeks diacerein followed by 4 weeks placebo)	• Six patients improved in terms of pain score, walking time, and the number of 'rescue' analgesic pills (paracetamol) administered • Four remain unchanged • Two deteriorated	-
Chantre *et al*. [21]	2000	122	Knee and hip OA	Diacerein (100 mg/d)	Harpadol [Harpagophytum procumbens powder capsule (435 mg, 6 cap/d)]	16 weeks	• No significant difference in pain reduction, and Lequesne functional Index • Significantly lower requirement for rescue medication with Harpadol	Significantly lower in the Harpadol Diarrhea • 8.1% in Harpadol • 26.7% in Diacerein
Shin *et al* [22]	2013	86	Hand OA	Diacerein 50 mg/d	Placebo	12 weeks	No difference in the AUSCAN pain score, stiffness score and physical score at 4 weeks and 12 weeks At 4 weeks, there was an improvement in physician global evaluation (per-protocol analysis, (P = 0.004).	Diarrhea (21% vs. 20%) Urine coloration (88% vs. 20%) Headache (29% vs. 39%) Liver function abnormality (2% vs. 11%)

AE: Adverse event, AUSCAN: Australian/Canadian Osteoarthritis Hand Index, CGI: Clinical global impression, OA: Osteoarthritis, WOMAC: The Western Ontario and McMaster Universities Osteoarthritis Index

2. Hip osteoarthritis

In hip OA, two RCTs evaluated diacerein against placebo and tenoxicam. In the first RCT, Nguyen *et al*. randomized 288 patients of painful hip OA to placebo + placebo, tenoxicam (20 mg/d) + placebo, diacerein (100 mg/d) + placebo, and diacerein + tenoxicam. Efficacy was assessed with pain reduction on VAS score, a functional improvement on the Lequesne index, and analgesic consumption. They defined improvement as Improvement in the change of scores by >30% from the baseline. Over 8 week's observation, tenoxicam showed clinically significant and rapid (within 2 weeks) and persistent improvement. Similarly, diacerein had slow (6 weeks) but persisting improvement. The concomitant administration of two drugs did not significantly affect the efficacy and safety of each other [18]. In the second ECHODIAH study, Dougados and colleagues compared diacerein (100 mg/d, n=255) and placebo (n=252) in patients with primary hip OA. Radiographic progression (joint space loss of at least 0.5 mm) over 3 years was significantly lower with diacerein in the intention-to-treat population (50.7% vs. 60.4%, p=0.036) and completed population (47.3% vs. 62.3%, p=0.007). Also, the rate of joint space narrowing was significantly lower with diacerein. There was no significant difference between the two groups in terms of clinical symptom relief and consumption of rescue analgesics [19]. These studies show that diacerein is efficacious in reducing the radiographic progression of hip OA and might have an equivalent effect on NSAIDs such as tenoxicam in terms of pain reduction and functional improvement.

3. Knee and Hip osteoarthritis

In total, two RCTs assessed diacerein in both knee and hip OA. One RCT compared diacerein with a placebo and one Harpagophytum. Among the two RCTs compared against a placebo, the first by Kay *et al*. conducted in 1980 was a single-blind, placebo-controlled study. During the 12 weeks, 12 patients received a placebo plus rescue analgesic (4 weeks), diacerein (50 mg/d for 4 weeks), and placebo (4 weeks). At the end of 4 weeks of diacerein treatment, six improved as indicated by a reduction in pain score, improved walking time, and need for rescue analgesics, 4 remained unchanged and two deteriorated. The onset of action was slower and the effect persisted for 2 weeks to 3 months after discontinuation [20]. Another RCT compared diacerein to Harpagophytum, Chantre *et al*. randomized 122 patients of knee and hip OA to herbal medication Harpadol®, 6 capsules/day, each containing 435 mg of powdered cryoground powder Harpagophytum procumbens) and diacerein (100 mg/d). By 4 months, both treatments reduced pain on VAS score as well as improved Lequesne's functional index [21].

4. Hand osteoarthritis

A study conducted by Shin *et al*. compared diacerein (100 mg/d, n=42) with placebo (n=44) in patients with hand OA. At the end of 4 weeks, the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) pain score, stiffness score, and physical score did not differ in the two groups. However, physician global assessment at 4 weeks showed significantly better improvement with diacerein than with placebo (p=0.004) [22].

Safety of diacerein

In the included studies, the duration of follow-up has varied from 8 weeks to 3 years. Table 1 describes the incidence of various AEs in different studies. Compared to the placebo, the rates of AEs remained higher with diacerein. Bramhachari *et al*. reported a significantly higher rate of AEs with diacerein than with a placebo. Gastrointestinal upset or motility disorder is common with diacerein. Urine abnormality or discoloration, and diarrhea were the most common AEs reported in most studies. The incidence of diarrhea varied from 15% to 46% [12]. Over a period of 3 years, the ECHODIAH study reported that the treatment discontinuation due to AEs was higher in the diacerein group than placebo (25% vs. 12%) whereas those due to inefficacy was higher in the placebo group than diacerein (14% vs. 7%). Among AEs, diarrhea (46% vs. 12%), and discoloration of urine (31% vs. 2%) were seen in a significantly higher proportion of patients in the diacerein group. However, all these were mild to moderate in severity and were often self-limiting. With a lower dose of (50 mg/d), the incidence of diarrhea was similar between the diacerein and placebo group (21% vs. 20%) [19].

Overall, tolerability was observed to be good. A study by Pavelka *et al*. observed investigators reported good tolerability in >90% of patients in diacerein and >94% of patients in placebo groups [10].

Various studies had active comparators such as glucosamine sulfate or NSAIDs like piroxicam. Compared to pCGS, Kongtharvonskul *et al*. reported nearly one-third of all AEs related to the GI system. The risk of diarrhea, as well as dyspepsia, was similar in the two groups. Also, both groups had a similar rate of skin reactions (10%). No patient discontinued the drug due to AE [14]. In a study from Pham *et al*., IA injection-associated knee pain during and after injection was in a significantly lower proportion of patients in the diacerein group than in NDR101 and placebo groups (9 vs 24 and 19, p=0.0088). Diarrhoea (P<0.0001) and GI upset (p=0.07) were more common in the diacerein group. Overall, rates of AEs in NDR101, diacerein, and placebo groups were 81.7%, 84.7%, and 81.2% respectively with intensity being mild to moderate [15]. In a comparison of diacerein to piroxicam, Louthrenoo *et al*. reported a significantly higher proportion of patients with GI disturbances in the diacerein group. However, dyspepsia (32.9% vs 22.1%) and edema (9.4% vs 4.7%) were higher in the piroxicam group. Premature treatment withdrawal due to AEs was reported in 3.5% and 7.1% of patients in the diacerein and piroxicam groups, respectively. The tolerability was judged to be good to very good in 88.9% and 92.3% of patients in the two groups, respectively. Compared to celecoxib, the proportion of AEs was higher with diacerein (26.3% vs. 17.4%) [16].

Compared to herbal preparation containing Harpagophytum procumbens, the incidence of diarrhea was 26.7% in the diacerein group compared to 8.1% in the herbal medicine group [20].

Discussion

This systematic review brings out important discussion pointers in terms of efficacy, dosing strategy, the need for rescue medication, carry-over effect, safety, and tolerability of diacerein. The evidence from the thirteen RCTs indicates that diacerein is an effective SYSADOAs that reduces pain, improves functional mobility, and reduces stiffness. The

efficacy of diacerein in OA has been proved in multiple previous meta-analyses [5,6]. Through various studies, the efficacy of diacerein in knee and hip OA was observed to be better than placebo and equivalent to NSAIDs such as piroxicam, tenoxicam, celecoxib as well as hyaluronic acid, and glucosamine sulfate. One study in hand OA reported no difference compared to placebo. It is probably because of a lower dose used (50 mg/d). Another reason for non-efficacy in hand OA is probably hand joints are not weight-bearing joints. Also, the duration of the study was 16 weeks which is perhaps shorter to establish the effect on hand joints as diacerein has a slower onset of action (~4 weeks). In addition, the severity of hand OA, and the number and types of joints involved might also affect the efficacy [22]. Nonetheless, the most effective dose is observed to be 100 mg/d (administered as 50 mg twice daily). The dosing strategy adopted varied in some studies [11,12]. They used 50 mg once daily dose for an initial period (10 – 30 days) and then escalated to 100 mg/d. The reasons for such a dosing strategy remains unclear. One possible explanation is that GI upset is common with diacerein. The use of a lower dose in the initial treatment phase might allow for a lower risk of GI disturbances allowing the patient to remain compliant. However, the actual implications of such a dosing strategy need to be studied further. In other studies, including the long-term ECHODIAH study [19], a dose of 100 mg/day was observed to be an effective dose that was used from the beginning of the study. The efficacy is further supported by the significantly better physician clinical global impression scores. The consumption of rescue medication (paracetamol) was significantly lower with the use of diacerein in comparison to the placebo, which was comparable to that of NSAIDs. This is probably because of its effect on the disease activity. Studies observed decreased rate of joint space loss and reduction in the joint space narrowing indicating reduced radiographic progression of OA [19]. Thus, diacerein possibly can halt the disease progression. A separate analysis of the ECHODIAH cohort observed that the use of diacerein was associated with reduced progression of OA compared to placebo (55% vs. 64%, relative risk 0.72, 95% CI 0.54 to 0.96, p=0.0274) [23]. Thus, diacerein not only provides symptomatic and functional relief but also has the potential to reduce OA progression.

Diacerein has demonstrated a significant carry-over effect even after discontinuation of the drug. Current data indicate carry-over effect can last for up to 8 weeks after stopping the medication. Such carry-over effect is not only observed against the placebo but also in comparison to NSAIDs. The previous meta-analysis also supports this finding [5]. This effect is a beneficial component of diacerein that can be useful in patients who have tolerability issues. In terms of safety, diacerein is definitely associated with a higher incidence of urine discoloration and diarrhea. Urine discoloration is not due to the presence of red blood cells but due to the excretion of its active metabolite rhein. Such an effect can be reduced with adequate intake of fluids. Diarrhea is often mild to moderate in intensity, often self-limiting but might lead to treatment discontinuation in some patients. The ECHODIAH study reported AE-related discontinuation rates of 25% with diacerein and 12% with placebo [19]. This AE of diarrhea should not limit the use of diacerein and patient counseling should be done in routine clinical practice. The rate of treatment withdrawals due to AEs is not significantly different from diacerein. In comparison to NSAIDs, dyspepsia is lower with diacerein. Other AEs such as headache, liver enzyme abnormalities, and edema, are reported with lower frequency. The tolerability is rated to be good to excellent in some studies indicating it is well-tolerated. The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) expert report identifies that the benefits of diacerein outweigh the risks associated with it and that diacerein can be considered a potential therapy in the treatment of OA. Further consideration of diacerein as the initial choice of treatment is advised in patients with contraindications to NSAIDs or paracetamol [10].

Conclusion

In patients with knee and hip osteoarthritis, diacerein is effective in pain relief, and functional improvement and is associated with a lower need for analgesic therapy. The efficacy is comparable to commercially available NSAIDs. It can be considered as a treatment of choice where conventional analgesics such as NSAIDs and paracetamol are contraindicated. The advantage of diacerein is its carry-over effect that can be observed till 8 weeks after the discontinuation. It has the potential to reduce the progression of the disease. The safety concern is only diarrhea which is mild to moderate and is self-limiting. Thus, combined with its efficacy and good tolerability, diacerein offers an alternative to existing treatments for the effective management of OA with a good carry-over effect post-treatment.

References

1. Safiri S, Kolahi AA, Smith E, Hill C, Bettampadi D, Mansournia MA, *et al*. Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the Global Burden of Disease Study 2017. Ann Rheum Dis,2020:79(6):819-828.
2. Newberry SJ, FitzGerald J, SooHoo NF, Booth M, Marks J, Motala A, *et al*. Treatment of Osteoarthritis of the Knee: An Update Review [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2017 May. Report No.: 17-EHC011-EF. Available from: https://www.ncbi.nlm.nih.gov/books/NBK447530/ Accessed 30 March 2022
3. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: the chronic osteoarthritis management initiative of the US bone and joint initiative. InSeminars in arthritis and rheumatism,2014:43(6):701-712.
4. Towheed TE, Maxwell L, Anastassiades TP, Shea B, Houpt J, Robinson V, *et al*. Glucosamine therapy for treating osteoarthritis. Cochrane Database Syst Rev,2005:2:CD002946.
5. Rintelen B, Neumann K, Leeb BF. A meta-analysis of controlled clinical studies with diacerein in the treatment of osteoarthritis. Arch Intern Med,2006:166(17):1899–906.
6. Kongtharvonskul J, Anothaisintawee T, McEvoy M, Attia J, Woratanarat P, Thakkinstian A. Efficacy and safety of glucosamine, diacerein, and NSAIDs in osteoarthritis knee: a systematic review and network meta-analysis. Eur J Med Res,2015:20(1):24.

7. Bartels EM, Bliddal H, Schondorff PK, Altman RD, Zhang W, Christensen R. Symptomatic efficacy and safety of diacerein in the treatment of osteoarthritis: a meta-analysis of randomized placebo-controlled trials. Osteoarthr Cartil,2010:18(3):289–296.
8. Fidelix TS, Macedo CR, Maxwell LJ, Fernandes Moca Trevisani V. Diacerein for osteoarthritis. Cochrane Database Syst Rev,2014:2:CD005117.
9. Kaur D, Kaur J, Kamal SS. Diacerein, its beneficial impact on chondrocytes and notable new clinical applications. Brazilian J Pharma Sci,2019:8:54.
10. Pavelka K, Bruyère O, Cooper C, Kanis JA, Leeb BF, Maheu E, *et al*. Diacerein: Benefits, Risks and Place in the Management of Osteoarthritis. An Opinion-Based Report from the ESCEO. Drugs Aging,2016:33(2):75-85.
11. Pelletier JP, Yaron M, Haraoui B, Cohen P, Nahir MA, Choquette D, *et al*. Efficacy and safety of diacerein in osteoarthritis of the knee: a double-blind, placebo-controlled trial. The Diacerein Study Group. Arthritis Rheum,2000:43(10):2339-2348.
12. Brahmachari B, Chatterjee S, Ghosh A. Efficacy and safety of diacerein in early knee osteoarthritis: a randomized placebo-controlled trial. Clin Rheumatol,2009:28(10):1193-1198.
13. Singh K, Sharma R, Rai J. Diacerein as adjuvant to diclofenac sodium in osteoarthritis knee. Int J Rheum Dis,2012:15(1):69-77.
14. Kongtharvonskul J, Woratanarat P, McEvoy M, Attia J, Wongsak S, Kawinwonggowit V, *et al*. Efficacy of glucosamine plus diacerein versus monotherapy of glucosamine: a double-blind, parallel randomized clinical trial. Arthritis Res Ther,2016:18(1):233.
15. Pham T, Le Henanff A, Ravaud P, Dieppe P, Paolozzi L, Dougados M. Evaluation of the symptomatic and structural efficacy of a new hyaluronic acid compound, NRD101, in comparison with diacerein and placebo in a 1 year randomised controlled study in symptomatic knee osteoarthritis. Ann Rheum Dis,2004:63(12):1611-1617.
16. Louthrenoo W, Nilganuwong S, Aksaranugraha S, Asavatanabodee P, Saengnipanthkul S, Thai Study Group. The efficacy, safety and carry-over effect of diacerein in the treatment of painful knee osteoarthritis: a randomised, double-blind, NSAID-controlled study. Osteoarthritis Cartilage,2007:15(6):605-614.
17. Pelletier JP, Raynauld JP, Dorais M, Bessette L, Dokoupilova E, Morin F, *et al*. An international, multicentre, double-blind, randomized study (DISSCO): effect of diacerein vs celecoxib on symptoms in knee osteoarthritis. Rheumatology (Oxford),2020:59(12):3858-3868.
18. Nguyen M, Dougados M, Berdah L, Amor B. Diacerhein in the treatment of osteoarthritis of the hip. Arthritis Rheum,1994:37(4):529-536.
19. Dougados M, Nguyen M, Berdah L, Maziéres B, Vignon E, Lequesne M, *et al*. Evaluation of the structure-modifying effects of diacerein in hip osteoarthritis: ECHODIAH, a three-year, placebo-controlled trial. Evaluation of the Chondromodulating Effect of Diacerein in OA of the Hip. Arthritis Rheum,2001:44(11):2539-2547.
20. Kay AG, Griffiths LG, Volans GN, Grahame R. Preliminary experience with diacetylrhein in the treatment of osteoarthritis. Curr Med Res Opin,1980:6(8):548-551.
21. Chantre P, Cappelaere A, Leblan D, Guedon D, Vandermander J, Fournie B. Efficacy and tolerance of Harpagophytum procumbens versus diacerhein in treatment of osteoarthritis. Phytomedicine,2000:7(3):177-183.
22. Shin K, Kim JW, Moon KW, Yang JA, Lee EY, Song YW, *et al*. The efficacy of diacerein in hand osteoarthritis: a double-blind, randomized, placebo-controlled study. Clin Ther,2013:35(4):431-439.
23. Mazières B, Garnero P, Guéguen A, Abbal M, Berdah L, Lequesne M, *et al*. Molecular markers of cartilage breakdown and synovitis at baseline as predictors of structural progression of hip osteoarthritis. The ECHODIAH Cohort. Ann Rheum Dis,2006:65(3):354-359.