Drug Saf (2015) 38:245–252
DOI 10.1007/s40264-015-0266-z

REVIEW ARTICLE

Benefit–Risk Assessment of Diacerein in the Treatment of Osteoarthritis

Elena Panova · Graeme Jones

Published online: 5 February 2015

Abstract Osteoarthritis (OA) is the leading musculoskeletal cause of disability. Despite this, there is no consensus on the precise definition of OA and what is the best treatment to improve symptoms and slow disease progression. Current pharmacological treatments include analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX) inhibitors. None of those treatments are disease-modifying agents that target the core pathological processes in OA. Diacerein, a semi-synthetic anthraquinone derivative, inhibits the interleukin-1-beta (IL-1β) cytokine which, according to animal studies, plays a key role in the pathogenesis of OA. Diacerein was synthesized in 1980 and licensed in some European Union and Asian countries for up to 20 years. It has shown modest efficacy and acceptable tolerability in a number of trials of low to moderate quality. Early this year, the European Medicines Agency (EMA) conducted a review and restricted the use of diacerein-containing medicines. This was because of major concerns about the frequency and severity of diarrhoea and liver disorders in OA patients. In addition, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) questioned the limited clinical benefits of diacerein, which, in their view, did not outweigh its risks. The aim of this review is to provide a benefit–risk assessment of diacerein in the treatment of OA, based on asystematic evaluation of the published efficacy and safety data. Overall, there is evidence that diacerein is modestly effective for symptoms and possibly for radiographic changes, but this needs to be balanced against higher rates of gastrointestinal toxicity.

E. Panova · G. Jones (✉)
Menzies Research Institute, Private Bag 23,
Hobart, TAS 7000, Australia
e-mail: g.jones@utas.edu.au

Key Points

There are limited therapeutic options for osteoarthritis, and interleukin-1, which is blocked by diacerein, is one potential target.

Clinical trials show that diacerein has a modest symptomatic benefit, with a controversial effect on radiographs in patients with knee and hip osteoarthritis.

Overall, diacerein is safe, apart from a substantially higher risk of diarrhoea, especially with longer-term use.

1 Introduction

Osteoarthritis (OA) is the most common form of arthritis. Its prevalence is increasing markedly because of an ageing population [1]. In all, 10 % of the world's population aged 60 years or older have pain or disability from OA [2]. The Osteoarthritis Research Society International (OARSI) recommendations for the treatment of hip and knee OA are divided into pharmacological, non-pharmacological and surgical treatments [3]. Current pharmacological treatment is mostly palliative, with analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase (COX) inhibitors, being the mainstay of therapy [4]. None of those treatments are disease-modifying agents that target the core pathological processes in OA. Research over the last two decades, primarily in animals, has shown that the cytokine interleukin-1-beta (IL-1β) plays a key local role in

cartilage degradation, subchondral bone remodelling, chondrocyte apoptosis and joint inflammation [5, 6], although it is only rarely detectable in the serum of patients with OA [7].

Diacerein inhibits production of IL-1β, and it has been suggested to have disease-modifying properties in experimental models and individuals with knee and hip OA [8, 9]. Diacerein was synthesized in 1980 and marketed as a tablet in some European Union and Asian countries from 1994 [2]. Following a review of diacerein, in March 2014, the European Medicines Agency (EMA) restricted the use of diacerein-containing medicines. The review was conducted at the request of the French medicines agency over concerns about the frequency and severity of gastrointestinal side effects, such as diarrhoea and liver disorders.

2 Overview of Osteoarthritis and Its Current Treatments

Despite OA being a leading musculoskeletal cause of disability in western society, it is still difficult to gain a precise definition of what OA actually is. OA is not a single disease but rather a collection of diseases with many causes [10]. It is well known that there is a modest correlation between X-ray changes and pain. However, for the knee joint structure, there is largely consistent evidence that bone marrow lesions, synovitis/effusions and cartilage defects are associated with knee pain and cartilage loss [1]. Thus, it would seem logical to regard knee (and perhaps other forms of) OA as an umbrella term for a number of different pathological processes that result in cartilage loss.

Currently, the definition of OA utilizes a combination of symptoms and radiographic criteria, but it is pain that drives patients to seek help. The main objectives of OA management are to reduce symptoms, minimize functional disability and limit the progression of structural changes, with the ultimate goal of avoiding arthroplasty [4].

Pharmacological treatments for OA are limited. Currently, first-line therapy in OA is purely symptomatic with analgesic agents and NSAIDs, including COX-2 inhibitors, and some guidelines recommend glucosamine or chondroitin. Although there is some controversial evidence for disease modification with the latter three therapies, none of these therapies have approval as disease-modifying agents; therefore, the need for a therapeutic agent that addresses symptoms of OA and has positive effects on joint structure remains high.

2.1 Role of Interleukin-1 in Osteoarthritis Pathogenesis

Although OA was widely considered by the rheumatology community to be a non-inflammatory disease, studies have shown that effusion and/or synovitis are common in OA, and inflammatory cytokines can be produced by synovial tissue cells and subchondral osteoblasts. IL-1β, IL-6 and tumour necrosis factor alpha (TNF-α) are key cytokines in the catabolic process of cartilage [2, 7]. IL-1 plays a major role in OA pathophysiology, as shown in Fig. 1 [6]. IL-1 also promotes expression of nitric oxide synthase, increasing release of prostaglandins and other interleukins that promote joint degradation [6]. Blocking IL-1 or its activity in animal models has been shown to be very effective in the prevention of cartilage destruction [9].

3 Diacerein

3.1 Pharmacology

Diacerein is an anthraquinone derivative, with a gradual onset of action (4–6 weeks) and a carry-over effect for a period of 4–8 weeks after cessation of treatment [4–8]. Diacerein has been shown to inhibit, in vitro and in vivo, the production and activity of IL-1 and the secretion of metalloproteinases, without affecting the synthesis of prostaglandins; therefore, diacerein does not have a deleterious effect on the upper gastrointestinal tract [4–9]. It also inhibits superoxide production, chemotaxis and phagocytic activity of neutrophils. Diacerein is entirely converted to rhein (the active metabolite) before reaching the systemic circulation, and rhein later gets eliminated via the renal route (20 %) or is conjugated in the liver to rhein glucuronide (60 %) and rhein sulphate (20 %); these metabolites are mainly eliminated via the renal route [11]. The optimal OA dose of diacerein is 100 mg/day (50 mg twice daily); there is no recommendation for dose reduction in patients with liver cirrhosis, but dose modification is required for mild to severe renal insufficiency [8].

3.2 Trial Review

Despite diacerein being on the market for 20 years, there is a relatively small number of acceptable-quality randomized controlled trials (RCTs) in OA. Those trials are limited to knee and hip OA and are of short duration, except for one, which followed patients for 3 years for structural outcome measures [9]. Several studies have concluded that diacerein is a slow-acting, symptom-modifying OA agent [4, 5, 8] with a carry-over effect; others have reported negative outcomes in regard to symptomatic [9] and structural effects [12]. The Cochrane Collaboration published the most comprehensive review in 2014, which included ten studies [2].

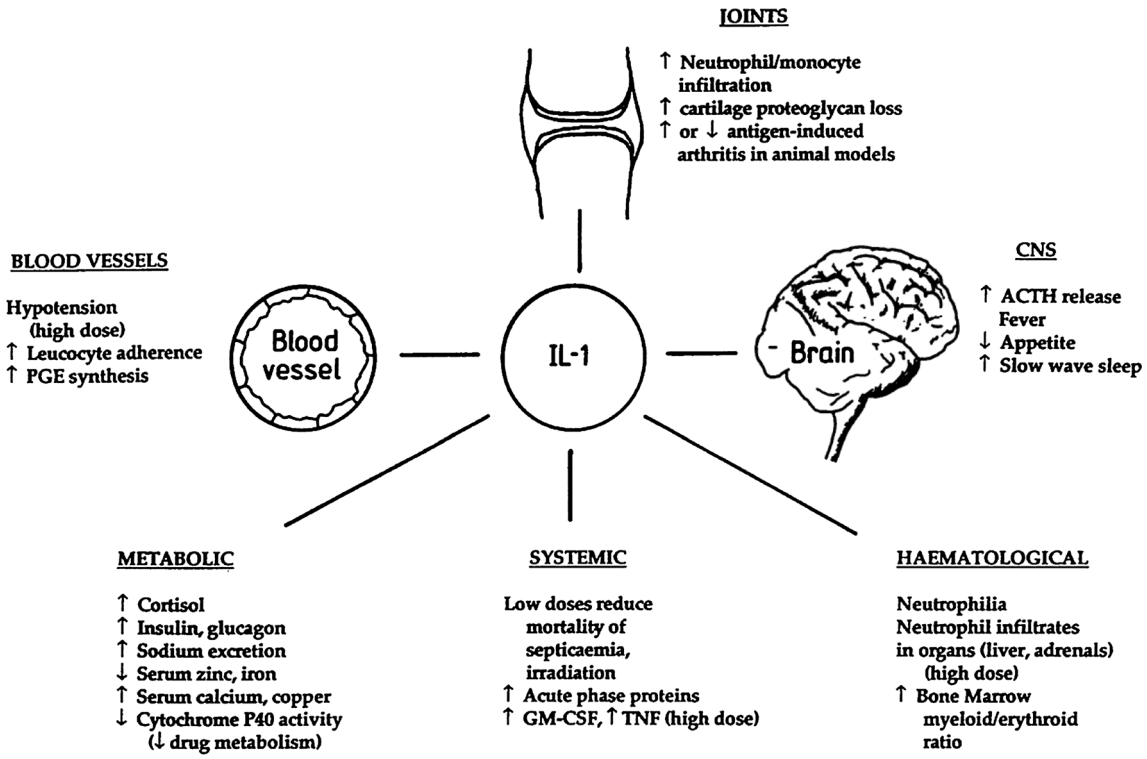

Fig. 1 Role of interleukin-1 in body systems, including joints. (Adapted from Kirkham [6], with permission)

3.2.1 Study Design and Analysis

We identified trials by using the search terms 'diacerein' and 'OA' and/or 'clinical trials' and/or 'meta-analysis', using Medline (search performed in June 2014). From this, we selected large clinical trials ($N > 100$) and the most up-to-date meta-analyses published in English. The included trials were RCTs comparing diacerein with placebo [5, 8, 9], as well as an NSAID comparator study [4], a trial of diacerein versus placebo and a hyaluronic acid compound [12], and two meta-analyses [2, 3]. Most reviewed RCTs had pain as their primary outcome, measured by a visual analogue scale (VAS) or the Western Ontario and McMaster Universities Osteoarthritis Index section A (WOMAC A). Secondary efficacy variables were joint stiffness (WOMAC B), physical function (WOMAC C), and the joint swelling grading, plus patient's and physician's global assessments [4, 5, 8, 9]. Some trials administered Short Form 36 (SF-36) health survey questionnaires and evaluated daily paracetamol (acetaminophen) and/or NSAID consumption [4, 12]. Only two trials had structural efficacy as their primary outcome: one for hip OA [9] and one for knee OA [12], which is discussed in the Sect. 3.2.3. One trial was designed to examine the carry-over effect of diacerein versus placebo [5]. Safety and adverse events (AEs) were evaluated in all trials as a secondary outcome. All reviewed RCTs used intent-to-treat (ITT) analysis.

The key trials had 161–480 patients randomized into 2–4 arms, depending on the study design. The durations of those trials ranged between 12 weeks and 12 months, most of them being on the shorter side. One trial went for 3 years and had almost 250 patients in each arm [9]. The study groups were well balanced at baseline, with appropriate inclusion criteria (symptomatic OA and a Kellgren and Lawrence score of 2/3). All trials allowed ongoing paracetamol use of up to 3 g/day in the case of severe pain. ECHODIAH allowed NSAID use in addition to or instead of analgesics as a rescue medication, with a washout period prior to the clinic visit [9]. No corticosteroid use was allowed. A 50 mg twice-daily diacerein regimen was used, except in the dose-ranging trial [8].

3.2.2 Symptomatic Efficacy

The key clinical trials are summarized in Table 1. The results are not consistent, with some showing substantial benefit and some showing virtually no difference in comparison with placebo.

The dose-ranging phase II study [8] analysed three populations, one for safety and two for efficacy. For

Table 1 Key trial efficacy overview

Trial	Patients (*N*) (treatment arms)	Age (years; mean), female/male	Time on drug	Comparator	Pain: VAS/WOMAC scores [mm; mean (SD)]		X-ray change in JSW [mm]	*P* value
					Comparator	Diacerein		
Pelletier et al. [8]	484 (4 arms)	64, 80/20	16 weeks	Placebo	−14.2 (19.2)/ −56.5 (83.5)	−23.2 (18.2)/ −83.5 (83.4)	NA	<0.05
Dougados et al. [9]	507 (2 arms)	63, 60/40	3 years	Placebo	−3.0 (29.9)/ No WOMAC score	−3.0 (30.2)/ No WOMAC score	ITT $P = 0.036$	NSS
Pham et al. [12]	301 (3 arms)	65,	1 year	Hyaluronic acid	−33.5 (28.5)		−0.09	0.01
		70/30		Placebo	−34.5 (27.4)/ No WOMAC score	−33.9 (25.7)/ No WOMAC score		0.96
Pavelka et al. [5][a]	168 (2 arms)	64, 80/20	3 months	Placebo	No VAS score/ 192 (113.1)	No VAS score/ 148 (109.8)	NA	0.0001
Louthrenoo et al. [4]	161 (2 arms)	54, 90/10	16 weeks	NSAID	No VAS score/ 70.7 (70.0)	No VAS score/ 84.7 (85.8)	NA	0.85

P values versus comparator; diacerein dose 50 mg twice daily

ITT intent-to-treat, *JSW* joint space width (change is >0.5 mm), *NA* not applicable, *NSAID* non-steroidal anti-inflammatory drug (piroxicam), *NSS* not statistically significant, *SD* standard deviation, *VAS* visual analogue scale, WOMAC Western Ontario and McMaster Universities Osteoarthritis Index

[a] The Pavelka et al. trial [5] was a 6-month trial, in which patients received diacerein for 3 months, but outcome measures were reported at 6 months

efficacy, the aim was to detect a difference between treatment and placebo in VAS assessment of pain on movement of 10 mm. The safety population included all patients who were randomly assigned and who received at least one dose of medication. Two efficacy populations were ITT (everyone from the safety population who had at least one post-baseline VAS measure) and per protocol (PP) [all 16-week completers]. The results of the analysis of VAS assessment of pain on movement showed the superiority of diacerein versus placebo in the 100 mg/day group in both the ITT and PP populations. The other two diacerein groups (receiving 50 and 150 mg/day) showed a trend towards improvement, but it was not statistically significant versus placebo in the ITT analysis. In the PP population analysis, the improvement of pain was greater with the higher dose, but the same group had higher AE and discontinuation rates [8].

The ECHODIAH trial [9] was designed to primarily demonstrate a difference in the progression of joint space narrowing (JSN), with an α risk of 0.05 and power of at least 0.90 (by 2-tailed testing). However, the trial also measured pain as a secondary outcome, and it did not observe statistically significant improvements in VAS pain scores or functional impairment, measured by the Lequesne index, in either the ITT population or the completer population.

The trial, which aimed to test the diacerein carry-over effect [5], was designed to demonstrate, if present, moderate superiority of diacerein versus placebo at 6 months, with the last dose being administered at month 3. Statistically significant percentage changes in pain (measured using the WOMAC A score) and total WOMAC scores from baseline to 5 months were reported in both the ITT and PP populations. The differences became significant at month 2. The superiority of diacerein versus placebo was reached at 2 months as well and remained of similar magnitude until the end of the study.

There have been two meta-analyses published in the past 12 years. Zhang et al. [3] included diacerein as part of a systematic cumulative update of OARSI recommendations for the management of hip and knee OA [3]. The Cochrane meta-analysis, on the other hand, focused on diacerein only [2]. Zhang et al. [3] reviewed two diacerein trials from before 2002 and four RCTs from 2002 to 2006. They used the effect sizes (ES) and 95 % confidence interval (CI) as a measurement of efficacy and recorded the level of evidence (LoE). For the diacerein studies, the LoE was considered Ib. They found that the efficacy of diacerein for pain reduction was small, with an updated ES of 0.24 (95 % CI 0.08, 0.39), with considerable heterogeneity between trials. This was of the same order of magnitude as the efficacy of many other therapies, e.g. the efficacy of paracetamol was 0.14 and that of NSAIDs was 0.29 (Table 2).

Table 2 Comparison of effect sizes (ESs) and levels of evidence (LoEs) for pain relief with different modalities of therapy in 2006 and 2009

	ES (95 % CI); LoE	
	31 January 2006	31 January 2009
Self-management	0.06 (0.02, 0.10); Ia	0.06 (0.02, 0.10); Ia
Education/information	0.06 (0.02, 0.10); Ia	0.06 (0.03, 0.10); Ia
Exercise for knee OA		
Strengthening	0.32 (0.23, 0.42); Ia	0.32 (0.23, 0.42); Ia
Aerobics	0.52 (0.34, 0.70); Ia	0.52 (0.34, 0.70); Ia
Exercise for hip OA	NA	0.38 (0.08, 0.68); Ia
Exercise in water for knee and hip OA	0.25 (0.02, 0.47); Ib	0.19 (0.04, 0.35); Ia
Weight reduction	0.13 (−0.12, 0.36); Ib	0.20 (0.00, 0.39); Ia
Acupuncture	0.51 (0.23, 0.79); Ib	0.35 (0.15, 0.55); Ia
Electromagnetic therapy	0.77 (0.36, 1.17); Ia	0.16 (−0.08, 0.39); Ia
Paracetamol (acetaminophen)	0.21 (0.02, 0.41); Ia	0.14 (0.05, 0.22); Ia
NSAIDs	0.32 (0.24, 0.39); Ia	0.29 (0.22, 0.35); Ia
Topical NSAIDs	0.41 (0.22, 0.59); Ia	0.44 (0.27, 0.62); Ia
Opioids	NA	0.78 (0.59, 0.98); Ia
Intra-articular corticosteroid	0.72 (0.42, 1.02); Ia	0.58 (0.34, 0.75); Ia
Intra-articular hyaluronic acid	0.32 (0.17, 0.47); Ia	0.60 (0.37, 0.83); Ia
Glucosamine sulphate	0.61 (0.28, 0.95); Ia	0.58 (0.30, 0.87); Ia
Glucosamine hydrochloride	NA	−0.02 (−0.15, 0.11); Ib
Chondroitin sulphate	0.52 (0.37, 0.67); Ia	0.75 (0.50, 1.01); Ia
Diacerein	0.22 (0.01, 0.42); Ib	0.24 (0.08, 0.39); Ib
Avocado/soybean unsaponifiables	NA	0.38 (0.01, 0.76); Ia
Rosehip	NA	0.37 (0.13, 0.60); Ia
Lavage/debridement	0.09 (−0.27, 0.44); Ib	0.21 (−0.12, 0.54); Ib

Reproduced from Zhang et al. [3], with permission

CI confidence interval, *NA* not available, *NSAID* non-steroidal anti-inflammatory drug, *OA* osteoarthritis

The Cochrane review [2] included ten trials with 2,210 participants. It found that the majority of trials were of low quality, with incomplete outcome data and risk of bias in 80 % of the studies. It pooled six studies to assess pain reduction and found that diacerein had mild efficacy versus placebo, but this result was based on studies with large heterogeneity ($I^2 = 84$), meaning that pooling of studies was problematic. The mean ES of six studies of diacerein versus placebo for VAS pain was −8.65 (95 % CI −15.62, −1.68). Studies with larger participant numbers had no response (ES 0.0 for 507 patients) or lower response (−4.04 for 404 patients), while studies with smaller numbers had greater response (−28.60 for 55 patients). The authors concluded that diacerein has a small beneficial effect on pain (measured by VAS) at 3–36 months. Pain reduction was 9 % greater in the diacerein group than in the placebo group (mean difference −8.65; 95 % CI −15.62, −1.68). The clinical significance of this reduction was marginal. The Cochrane review analysed physical function and pooled four studies (totalling 1,006 participants), which failed to demonstrate any benefit from diacerein [2]. Thus, one can see that there is some variation in terms of clinical efficacy across the various trials.

3.2.3 *Structural Efficacy*

Two trials evaluated the structure-modifying effects of diacerein. ECHODIAH [9] was adequately powered and examined hip OA by measuring radiographic progression (JSN) as a primary endpoint. Statistical significance was reached only at the 3-year point. Furthermore, it was seen only in a modified ITT population (50.7 % with a diacerein group of 221 patients versus 60.4 % with a placebo group of 225 patients) and in the completer analysis (131 patients in the diacerein group and 138 in the placebo group) but not in the original ITT population (221 and 225, respectively).

In the original ITT population, the median values of the JSN rate were 0.23 mm/year for placebo versus 0.19 mm/year for diacerein. Thus, in a strict sense, this study did not reach its primary outcome. Achieving a small but statistically significant outcome in the modified ITT population makes the result questionable. In addition, the study looked at the requirement for total hip replacement (THR) of the signal hip. They found that the risk of a requirement for THR was 19.8 % in the placebo group versus 14.5 % in the diacerein group, but, again, this difference was not

statistically significant. Taking all of that into account, this study is best categorized as a negative study.

The trial by Pham et al. [12] had a structural outcome measure as a primary outcome along with symptomatic measures. The study was powered to detect a difference of at least 0.40 mm with a standard deviation of 1 mm in the knee joint space width (JSW) change from baseline to the final visit between the groups. The analyses of JSN between baseline and the final visit and the percentage of patients with structural progression (JSN $>$ 0.50 mm) were performed using completer patients' data only. A significant deterioration in the JSW was observed during the study in all three groups, but the progression rates were not significantly different (17.7, 18.9 and 20.3 % in the hyaluronic acid, diacerein and placebo groups, respectively).

The Cochrane review [2] analysed both trials but used the ECHODIAH modified ITT population, not the original ITT population, for its analysis, and it found a small overall benefit, but it is unlikely that this would have been significant if the review had used the full ITT population. In its conclusion, the Cochrane review stated that the evidence favoured a small benefit of diacerein over placebo [risk ratio (RR) 0.85; 95 % CI 0.72, 0.99], with an absolute risk difference of −6 % (95 % CI −5, 2 %) and a number-needed-to-treat for an additional beneficial outcome (NNTB) of 14 (95 % CI 8, 203). The small benefit in terms of JSN reduction is of questionable clinical relevance and was observed only for hip OA. The review also reported uncertainty regarding the clinical significance, especially in terms of joint replacement outcome [2].

3.2.4 Safety

All shorter-duration RCTs [4, 5, 8, 12] found that the numbers of patients experiencing any AE were similar in the diacerein and comparator (placebo or active) groups. In the longer 3-year trial [9], there were higher AE rates in the diacerein group (95 %) versus placebo (84 %), $P = 0.001$.

This was largely due to a higher rate of diarrhoea (46 % in the diacerein group versus 12 % in the placebo group) and a statistically significant higher rate of skin and appendage disorders ($P = 0.024$) [9]. Similar findings were reported in the 1-year study by Pham et al. [12], where diarrhoea occurred in 41 %of the diacerein group and in 8 %of the placebo group, while the skin disorder rates were 8 and 1 %, respectively. Only those two longer-duration studies reported skin disorders as a significant AE. It seems likely that longer exposure to diacerein might trigger skin reactions in some patients.

In the majority of the key RCTs, the most common side effects with diacerein were diarrhoea and urine discolouration [4, 5, 9, 12]. Diarrhoea occurred within the first 2 weeks, and the rates ranged from 8 to 13.6 %in the placebo/comparator groups and from 15.5 to 46 % in the diacerein groups. The wide range of diarrhoea rates in the diacerein groups may have reflected differences in reporting but are most likely due to the lengths of the studies, with a lower percentage in the short term [5] and the highest percentage in the 3-year study [9]. The literature suggests that diarrhoea is a class effect with IL-1 blockade [6, 8]. A possible explanation for increased gut motility is an increase in prostaglandin levels, as diacerein has been shown to induce its synthesis [8]. All trials classified diarrhoea as mild to moderate and, except in the 3-year trial [9], it did not result in higher discontinuation rates. ECHODIAH reported a 12 % discontinuation rate due to diarrhoea in the diacerein group, compared with 2 % in the placebo group. In terms of the dose, there was a higher rate of diarrhoea in the 150 mg/day diacerein group, and diarrhoea was categorized as 'severe' in 13 patients in that group versus 2 in the placebo group and 2 in the 100 mg/day diacerein group. The same trial reported higher withdrawal rates due to diarrhoea in the 150 mg/day group versus the placebo and 100 mg/day diacerein groups, with 12, 3 and 3 withdrawals, respectively. Those observations lead to a conclusion that diarrhoea worsens with longer treatment duration and higher daily dosing.

Another common AE was urine discolouration; up to half of the participants experienced it, but it is a known class event due to elimination of diacerein metabolites via the kidney and is not of clinical significance [4, 6, 9].

All of the key trials collected blood and urine for various evaluations, including liver and kidney functions; all found no clinically relevant differences between the diacerein and comparator groups [5, 9, 12].

The Zhang et al. meta-analysis [3] reported diarrhoea as a significant problem; the RR versus placebo was 3.51 (95 % CI 2.55, 4.83).

The Cochrane Collaboration meta-analysis [2] summarized evidence from seven trials and concluded that the rate of AEs, mainly diarrhoea after 2–36 months, was significantly higher in the diacerein group than in the placebo group (RR 3.52; 95 % CI 2.42, 5.11), with an absolute risk increase of 24 % (95 % CI 12–35 %) and a number-needed-to-treat for an additional harmful outcome (NNTH) of 4 (95 % CI 3, 7). Table 3 summarizes those findings. With regard to comparisons with NSAIDs, three studies were reviewed, with 505 patients in total. Diacerein caused more lower gastrointestinal tract problems (diarrhoea RR 3.20; 95 % CI 1.58, 6.49) and less upper gastrointestinal tract problems (dyspepsia RR 0.67; 95 % CI 0.41, 1.11).

The Cochrane review did not find a statistical difference between the diacerein and comparator groups in participant withdrawals due to AEs. For the comparison of diacerein with placebo, the RR for dropout due to AEs was 1.29 (95 % CI 0.83, 2.01). For diacerein versus NSAIDs, the RR was 0.96 (95 % CI 0.38, 2.44) [2].

Table 3 Diarrhoea rates in diacerein trials

Trial	Age (years; mean)	Time on drug	Comparator	Diarrhoea rate (*n*/*N*)		RR (95 % CI)
				Comparator	Diacerein	
Pelletier et al. [8]	64	16 weeks	Placebo	17/125	33/111	2.19 (1.29, 3.70)
Dougados et al. [9]	63	3 years	Placebo	31/252	117/255	3.73 (2.61, 5.32)
Pham et al. [12]	65	1 year	Hyaluronic acid	11/131	34/85	4.76 (2.56, 8.88)
			Placebo	6/85	41/85	6.83 (3.06, 15.24)
Pavelka et al. [5]	64	3 months	Placebo	7/83	13/82	1.88 (0.79, 4,47)
Louthrenoo et al. [4]	54	16 weeks	NSAID	9/85	31/86	3.40 (1.73, 6.71)

The comparison figures were extracted from Fidelix et al. [2]

CI confidence interval, *NSAID* non-steroidal anti-inflammatory drug (piroxicam), *RR* risk ratio

With regard to hepatotoxicity, only two case reports were identified: one case of fatal hepatitis, published in 2001, and one case of acute hepatitis, published in 1997. These were both in French, with no abstracts available.

4 Benefit–Risk Assessment of Diacerein in Comparison With Other Therapies

Two key trials were reviewed, one versus an NSAID (piroxicam) [4] and one versus a new hyaluronic acid compound (NRD101); the latter had a placebo arm as well [12].

4.1 Diacerein Versus Piroxicam

A 16-week NSAID active comparator trial examined the efficacy, safety and carry-over effect of diacerein versus piroxicam for knee OA [4]. The study was designed to show non-inferiority of diacerein compared with piroxicam and appeared to be adequately powered. The results of the analyses of the ITT and PP populations were very similar. WOMAC A pain scores decreased to a similar (but perhaps biologically implausible) extent in both groups during the treatment period. At 16 weeks, the VAS score dropped from a baseline of 275.2 ± 65.0 mm to 84.7 ± 85.8 mm in the diacerein group and from 275.2 ± 63.0 mm at baseline to 70.7 ± 70.0 mm in the piroxicam group [4]. Piroxicam had a faster onset of action, demonstrating superiority at week 4, but the values were very similar at weeks 8, 12 and 16. The maintenance of the response in the diacerein group only at weeks 20 and 24 confirmed the carry-over effect.

The incidence of AEs was similar in both treatment groups, but more severe events were observed in the NSAID group, with one hospitalization due to gastrointestinal haemorrhage. More patients suffered from diarrhoea (36 versus 10.6 %) and urine discolouration (50 versus 8.2 %) in the diacerein group than in the piroxicam group. Dyspepsia (32.9 versus 22.1 %) and oedema (9.4 versus 4.7 %) were more common in the piroxicam group [4].

4.2 Diacerein Versus Hyaluronic Acid and Placebo

Pham et al. [12] focused on comparing a hyaluronic acid compound (NRD101) with diacerein and placebo in patients with knee OA. The study had a non-inferiority design and used the VAS pain change between baseline and the final visit for each group as a main criterion. The diacerein and placebo groups had smaller sample sizes than the hyaluronic acid group, but the study was adequately powered to detect a small effect. The primary structural outcome measures were JSN between baseline and the final visit, and the percentage of patients with structural progression (see details in the Sect. 3.2.3). There was a significant improvement in the VAS pain score from baseline in all three groups; however, no statistical or numerical difference was observed between the groups at 1 year in the ITT or completer populations.

The numbers of patients experiencing any AE were similar in the three groups. Most of these events were mild to moderate. Knee pain during or after injection was significantly greater in the NRD101 group ($P = 0.0088$), and diarrhoea and urine discolouration were more common in the diacerein group ($P < 0.0001$ and $P = 0.0009$), respectively, than in the other two groups [12].

A comparison of ESs and LoEs for pain between diacerein and other different modalities of therapy has been summarized in Table 2 [3].

5 Opinion and Conclusions

Diacerein has a modest but significant effect on pain in OA. Its effects on function are unclear. Overall, it may have a small effect on structural progression as assessed by radiographs, but this result is questionable. Its comparative efficacy is similar to those of many current OA therapies.

The main toxicity is mild to moderate diarrhoea, of which there is an increasing risk with increasing dose and duration. Discontinuation rates due to diarrhoea do not increase in the short term but do in the longer term. The EMA has removed the indication for patients aged 65 years and above, but there was no change in efficacy or increased risk of diarrhoea in this age group, so the reasons behind this decision are unclear. The EMA also advised that patients should start treatment on half the normal dose (i.e. 50 mg/day instead of 100 mg/day) and should stop taking diacerein if diarrhoea occurs. In addition, it advised that diacerein-containing medicines must not be used in patients with liver disease or a history of liver disease, and that patients should be monitored for early signs of liver problems. We would conclude that diacerein does have a role in the treatment of knee and hip OA in certain patient groups. These include patients with known upper gastrointestinal problems or heart disease where NSAIDs and COX-2 inhibitors cannot be used. Diacerein should be avoided in patients with a known tendency towards diarrhoea and should be discontinued in those with persistent and troublesome diarrhoea (but may be of benefit in those with constipation). A 4-week trial would be appropriate in the first instance, and it may be reasonable to interrupt therapy for up to 8 weeks, given the carry-over therapeutic effect.

Acknowledgments No sources of funding were used in the preparation of this review. Elena Panova and Graeme Jones have no conflicts of interest that are directly relevant to the content of the review.

References

1. Jones G. Sources of pain in osteoarthritis: implications for therapy. Int J Clin Rheumatol. 2013;8:335–46.
2. Fidelix TS, Macedo CR, Maxwell LJ, Fernandes Moça Trevisani V. Diacerein for osteoarthritis. Cochrane Database Syst Rev. 2014;2:CD005117.
3. Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III. Changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage. 2010;18:476–99.
4. 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):605–14.
5. Pavelka K, Trc T, Karpas K, Vítek P, Sedlácková M, Vlasáková V, Böhmová J, Rovenský J. The efficacy and safety of diacerein in the treatment of painful osteoarthritis of the knee: a randomized, multicenter, double-blind, placebo-controlled study with primary end points at two months after the end of a three-month treatment period. Arthritis Rheum. 2007;56(12):4055–64.
6. Kirkham B. Interleukin-1, immune activation pathways, and different mechanisms in osteoarthritis and rheumatoid arthritis. Ann Rheum Dis. 1991;50:395–400.
7. Stannus O, Jones G, Cicuttini F, et al. Circulating levels of IL-6 and TNF-α are associated with knee radiographic osteoarthritis and knee cartilage loss in older adults. Osteoarthritis Cartilage. 2010;18:1441–8.
8. Pelletier JP, Yaron M, Haraoui B, et al. Efficacy and safety of diacerein in osteoarthritis of knee: a double-blind, placebo controlled trial. The Diacerein Study Group. Arthritis Rheum. 2000;43(10):2339–48.
9. Dougados M, Nguyen M, Berdah L, et al. Evaluation of structure modifying effect of diacerein in hip osteoarthritis: ECHODIAH, a three-year, placebo-controlled trial evaluation of the chondromodulating effect of diacerein in osteoarthritis of the hip. Arthritis Rheum. 2001;44(11):2539–47.
10. Lane NE, Brandt K, Hawker G, et al. OARSI–FDA initiative: defining the disease state of osteoarthritis. Osteoarthritis Cartilage. 2011;19:478–82.
11. Spencer CM, Wilde MI. Diacerein. Drugs. 1997;53(1):98–106.
12. 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):1611–7.