Clinical Efficacy and Safety of Diacerein in Osteoarthritis – A Review

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Abstract

First-line drug therapy in osteoarthritis (OA) is purely symptomatic, with analgesic agents such as acetaminophen and anti-inflammatory agents such as aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) being the most widely prescribed medications. However, these products need to be taken chronically, have serious side effects and may accelerate cartilage degradation. The ideal therapeutic agent in OA should have symptom-modifying effects with positive effects, or at least no negative effects, on cartilage structure. Research over the last two decades has identified several therapeutic targets in osteoarthritis. These include inflammation, cartilage breakdown, chondrocyte apoptosis and subchondral bone remodelling, and it is now widely accepted that the common factor in all of these processes is the key role played by the pro-inflammatory, pro-catabolic cytokine interleukin-1β (IL-1β). Interestingly, diacerein, an IL-1β inhibitor in OA, has been shown to influence both the anabolism and catabolism of chondrocytes in vitro. Its symptomatic effects have been demonstrated in several placebo-controlled clinical studies. In addition, it has demonstrated cartilage-sparing properties in animal models of OA and in a three-year structure-modifying clinical study in patients with hip OA, with a reasonable safety profile.

Keywords

Diacerein, efficacy, safety

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Osteoarthritis (OA) is a complex joint disorder that is a major cause of chronic musculoskeletal pain and joint dysfunction in elderly populations worldwide. The symptoms increase in severity with time, eventually leading to arthroplasty.

Although not all of the processes leading to the degeneration of the articular tissues have been fully elucidated yet, knowledge of the aetiopathogenesis of the disease has increased significantly. For decades, the destruction of articular cartilage was the focus of interest, whereas over the last few years evidence has shown that alterations in the subchondral bone metabolism may constitute an integral part of the disease process and progression. In vitro studies provide strong evidence that pro-inflammatory cytokines, especially interleukin-1β (IL-1β), contribute to inflammation and the degradation of cartilage and subchondral bone in OA. IL-1β stimulates the inflammatory and degradation processes in OA and suppresses cartilage-matrix synthesis. The overall result is a severe degradation of cartilage, subchondral bone remodelling and subsequent appearance of conditions characteristic of OA. A further finding that may increase the deleterious effect of IL-1β is that human OA cartilage may be more responsive to IL-1β than healthy cartilage.

In 2009, using a Delphi consensus approach, a European League Against Rheumatism (EULAR) task force generated 10 key recommendations regarding the diagnosis of knee OA. These were directly tested in two populations from the UK and The Netherlands. The results showed that three symptoms (persistent knee pain, limited morning stiffness and reduced function) and three signs (crepitus, restricted movement and bony enlargement) appeared to be most useful in knee OA diagnosis, with the probability of having radiographic knee OA increasing with an increasing number of positive features.

With respect to treatment options, numerous opinion-based guidelines were developed to assist physicians in their choice of therapy for the management of knee, hip and hand OA patients. However, no internationally agreed recommendations based on both literature evidence and expert opinions were available until the first EULAR recommendations for the management of knee OA were elaborated. These recommendations were updated, and subsequently recommendations for the management of hip OA were generated by this task force. In September 2005, Osteoarthritis Research International (OARSI) appointed an international, multidisciplinary committee of experts to produce up-to-date, evidence-based and globally relevant consensus recommendations for the management of knee and/or hip OA. Pharmacological treatment in OA can be broadly divided into two main categories: the symptomatic rapid-acting drugs in OA (SYRADOAs), e.g. non-steroidal anti-inflammatory drugs (NSAIDs) and...
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acetaminophen, and the symptomatic slow-acting drugs in OA (SYSADOAs), e.g. intra-articular hyaluronan, diacerein, glucosamine sulphate and chondroitin sulphate. SYSADOAs have a rapid onset of activity but symptoms reappear immediately once treatment is stopped; by contrast, SYSADOAs have a slow onset of efficacy but a carry-over effect once treatment has stopped.

NSAIDs and acetaminophen are still preferentially prescribed in the management of OA pain, although the former are known to cause serious gastrointestinal, renal and vascular adverse events, while the latter may induce hepatotoxicity. Neither is known to improve the underlying structural damage and may, in the case of some NSAIDs, accelerate it. Therefore, the ideal therapeutic agent in OA should have symptom-modifying effects, i.e. reduce the patient’s symptoms, particularly pain and impaired physical function, with positive effects, or at least no negative effects, on cartilage structure, i.e. slow down disease progression.

Diacerein, a SYSADOA, was rated as a therapeutic option in OA with evidence level 1b within the EULAR recommendations for hip and knee OA, and was recommended class A according to the expert opinion.1,10

The Mechanism of Action of Diacerein in Osteoarthritis

IL-1β is found in the synovial membrane and synovial fluid of the OA joint and also in chondrocytes and the extracellular matrix of OA cartilage. In articular chondrocytes, IL-1β triggers several signalling cascades, including the sequential activation of various cytoplasmic protein kinases such as mitogen-activated protein kinases (MAPKs). This family is composed of extracellular signal-regulated kinases (ERK-1 and ERK-2), c-Jun N-terminal kinases (JNKs) and p38 kinase. MAPKs activate the DNA-binding activity of nuclear factor kappa B (NF-κB), c-Jun N-terminal kinases (JNKs) and p38 kinase. MAPKs activate the DNA-binding activity of nuclear factor kappa B (NF-κB) and activator protein-1 (AP-1), two transcription factors implicated in the transcription of many pro-inflammatory genes, including cytokines (such as IL-1β), tumour necrosis factor alpha (TNF-α), IL-6 and IL-8, cyclo-oxygenases (COX), prostaglandins, inducible nitric oxide (NOS) and metalloproteinases (MMPs), all of which are involved in cartilage degradation, synovial inflammation and subchondral bone remodelling. High NF-κB- and AP-1-binding activity has been found in the synovium of OA patients, suggesting the involvement of these factors in the pathogenesis of joint disease, the inflammatory process and degradation. The processes affecting the cartilage, bone or synovium overlap and collectively damage all the components of the joint.

IL-1β also downregulates the cartilage repair process by potently inhibiting chondrocyte proliferation and growth factors (such as transforming growth factor-beta [TGF-β]), thus suppressing the synthesis of cartilage matrix components including type II collagen and aggrecans. As a result, the repair potential of articular cartilage is limited. In addition, by acting in an autocrine or paracrine manner within cartilage, IL-1β can stimulate its own production and thus perpetuate cartilage damage. OA develops when the repair process fails to keep pace with the degenerative process.

The unifying hypothesis for the mechanism of action of diacerein and its active metabolite rhein is that they downregulate the production and activity of the pro-inflammatory, pro-catabolic cytokine IL-1β and IL-6, tumour necrosis factor alpha (TNF-α), IL-6 and IL-8, cyclo-oxygenases (COX), prostaglandins, inducible nitric oxide (NOS) and metalloproteinases (MMPs). The expression of genes coding for inflammatory cytokines, such as IL-1β, IL-6 and TNF-α, and several MMPs, including the collagenases MMP-1 and MMP-13, are also regulated by NF-κB activation. IL-1β-induced NO production in chondrocytes also plays a significant role in osteoarthritic chondrocyte death/apoptosis. Both diacerein and rhein inhibit NF-κB activation by inhibiting the degradation of inhibitor αB (IκBα).

By inhibiting IL-1β, diacerein and rhein therefore interfere with the cycle of events leading to inflammation, the production of cartilage-matrix-degrading enzymes and subchondral bone remodelling in the OA joint, while contributing to stimulate cartilage repair by upregulating the production of cartilage growth factors such as TGF-β1 and TGF-β2, even in the presence of IL-1β. A recent study using cultures of synovial tissue and cartilage derived from OA patients and also cultures of bovine and rabbit articular chondrocytes showed that rhein inhibits the proliferation of both synoviocytes and chondrocytes without inducing apoptosis. These studies employed rhein concentrations similar to therapeutic ones.

Besides these effects on the cartilage and the synovium, very recently diacerein and rhein were shown in vitro to also reduce, in a dose-dependent manner, IL-1β-induced MMP-13 production in OA subchondral bone. This effect occurred through the inhibition of ERK1/2 and p38. In osteoclasts, they significantly reduced the activity of MMP-13 and cathepsin K. Moreover, these drugs effectively blocked in vitro the IL-1β effect on the osteoclast differentiation process and the survival of mature osteoclasts.

The effects on pro-inflammatory, pro-catabolic cytokines seen in the in vitro studies mentioned above have been confirmed in vivo in the granuloma-induced cartilage breakdown model in the mouse. Diacerein significantly decreased plasma levels of NO in a dose-dependent manner in the rat adjuvant-induced arthritis model, while the comparative NSAID naproxen had no effects. Studies in different animal models of OA showed that diacerein consistently reduced cartilage loss in OA.

Given the key role IL-1 plays in the OA disease process and the results of the in vitro studies, diacerein may be considered an interesting compound for symptomatic as well as for disease-modifying treatment of OA.
Clinical Trials with Diacerein

Several randomised, double-blind, placebo- or NSAID-controlled symptomatic studies in patients with painful knee or/and hip OA showed that treatment with diacerein significantly reduced OA pain and improved function compared with placebo. These trials were performed over the last 20 years in different parts of the world.\textsuperscript{40–43} During a meta-analytic evaluation of these studies, these publications were rated for their quality according to the Jadad-score,\textsuperscript{44} which resulted in an overall average quality (score 3.2 on a 0–5 scale) as assessed by two raters with a high degree of congruence. \textsuperscript{45} More than two-thirds of the publications (69%) provided data on an intention-to-treat (ITT) basis,\textsuperscript{46} and, in contrast to studies on other SYSADOA compounds used in OA such as glucosamine sulphate and chondroitin sulphate, several studies on diacerein provided, at least in part, negative results.

In general, placebo-controlled symptom-modifying clinical studies with diacerein in patients with painful OA (pain ≥40mm on the 100mm visual analogue scale [VAS]) showed that the onset of diacerein efficacy is delayed, becoming significant compared with placebo at four weeks in knee OA patients\textsuperscript{47} and at six weeks in hip OA patients.\textsuperscript{48} Long-term treatment appears to be necessary as the plateau of diacerein’s efficacy was not reached after two months of treatment.\textsuperscript{49} Furthermore, in studies where a treatment-free follow-up period was included, a carry-over effect on symptoms persisting for up to three months after treatment discontinuation was suggested.\textsuperscript{50}

Proof of this carry-over effect was targeted – for the first time ever for any SYSADOA – in a recently published randomised, multicentre, double-blind, placebo-controlled six-month study in 168 patients with painful knee OA; treatment was either diacerein 50mg/day twice daily (BID) or matching placebo for three months.\textsuperscript{47} This was followed by an off-treatment period of three months to determine the carry-over effect of the drug.

The primary efficacy end-point was the percent change from baseline in pain on the Western Ontario and McMaster Osteoarthritis Index A (WOMAC A) at month five (i.e. two months after the end of treatment). The co-primary efficacy end-point was the percentage change from baseline in the total WOMAC score, also at month five. At this time-point, diacerein showed statistically significant superiority versus placebo as assessed by both WOMAC A (p<0.0001) and the total WOMAC (p<0.0001) scores, demonstrating the carry-over effect of the drug. This study, which was designed according to the latest guidelines for symptomatic studies in OA, can be considered as representative of the efficacy and safety of diacerein seen in most placebo-controlled studies.

A separate analysis of the treatment effect for pain (mean change in diacerein group minus mean change in placebo group, with a value >10mm on a 100mm VAS being considered clinically relevant according to Ehrich et al.),\textsuperscript{49} showed a clinically relevant treatment effect of diacerein from month three to month six.\textsuperscript{47} Responder rates in each treatment group were calculated according to the Outcome Measures in Rheumatology Clinical Trials, the OARSI-proposed set of responder criteria (see Figure 1). A treatment effect (i.e. the difference between responder rates) of 18.9% at month three and 30.1% at month six in favour of diacerein was detected. The response to placebo in this study was notably high, but consistent with data obtained in other clinical studies.\textsuperscript{49} Acetaminophen intake was similar in both groups during the treatment period but was significantly lower in the diacerein group during the follow-up period (p=0.0181, p=0.0018 and p=0.0124 at months four, five and six, respectively). The main side effect of diacerein in this trial was, as expected, diarrhoea, apart from which diacerein was safe and well tolerated. No serious or previously undocumented adverse events were observed during the study.

In comparative studies versus NSAIDs, the onset of action of diacerein is delayed compared with that of the NSAIDs, but the extent of pain reduction is similar with both treatments at about four weeks after the start of treatment.\textsuperscript{40–43} The 2007 study by Louthrenoo et al. is provided as an example of the results obtained in NSAID-controlled clinical studies with diacerein.\textsuperscript{47} This was a randomised, multicentre, double-blind, double-dummy, piroxicam-controlled, parallel-group phase III study in 171 patients with symptomatic knee OA (pain ≥40mm on VAS on two or more items of WOMAC A).

![Figure 1: Response to Treatment in the Diacerein and Placebo Groups](image1)

**Figure 1:** Response to Treatment in the Diacerein and Placebo Groups

- **Diacerein**
- **Placebo**

- **Month 1**
- **Month 2**
- **Month 3**
- **Month 4**
- **Month 5**
- **Month 6**

- **Per cent responders**

- **VAS improvement (%)**

- **p=0.0097**
- **p=0.0084**
- **p=0.0033**
- **p=0.0001**
- **p<0.0001**

**Figure 2: Course of Pain in Diacerein- and Piroxicam-treated Patients**

- **Piroxicam**
- **Diacerein**

- **Week**

- **0 4 8 12 16 20 24**

- **p=0.0065**

- **p<0.0001**

- **VAS improvement (%)**

- **p=0.0097**
- **p=0.0084**
- **p=0.0033**
- **p=0.0001**
- **p<0.0001**

**Table:**

<table>
<thead>
<tr>
<th>Week</th>
<th>VAS Improvement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-10.0</td>
</tr>
<tr>
<td>4</td>
<td>0.0</td>
</tr>
<tr>
<td>8</td>
<td>10.0</td>
</tr>
<tr>
<td>12</td>
<td>20.0</td>
</tr>
<tr>
<td>16</td>
<td>30.0</td>
</tr>
<tr>
<td>20</td>
<td>40.0</td>
</tr>
<tr>
<td>24</td>
<td>50.0</td>
</tr>
</tbody>
</table>

The primary efficacy parameter (pain on Western Ontario and McMaster Universities Osteoarthritis Index A [WOMAC A] decreased to a similar extent in both groups until week 16 (end of treatment). At week 20 (i.e. four weeks post-treatment), the improvement persisted for diacerein (79.3%), while it decreased from 84.9 to 37.7% for piroxicam (p=0.0066). At week 24 (eight weeks post-treatment), the per cent improvement remained stable for diacerein (80.6%), while it fell to 35.4% for piroxicam (p<0.0001). VAS = visual analogue scale.
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The primary efficacy parameter (pain on WOMAC A) decreased to a similar extent in both groups until week 16 (end of treatment). At week 24 (eight weeks post-treatment), the percentage improvement decreased slightly for diacerein (to 80.6%) and markedly for piroxicam (to 35.4%; p<0.0001) (see Figure 2). WOMAC C scores (function) showed a similar trend. The mean acetaminophen intake was similar in both groups until week 16; it remained stable during the follow-up period in the diacerein group but increased steadily in the piroxicam group until the end of the study (p=0.0247).

**Diacerein and Structure Modification**

Two long-term studies, one evaluating hip OA and another evaluating knee OA, analysed structural progression under diacerein treatment with radiographic measurements of joint space. The principal objective of the first trial, Evaluation of the Chondromodulating Effect of Diacerein in OA of the Hip (ECHODIAH), was to evaluate the structure-modifying potential of diacerein compared with placebo.50

The study was conducted in 507 patients with primary hip OA. Patients received diacerein (50mg BID) or placebo (n=255 and n=252, respectively) over a three-year period, using the post hoc co-variate analysis of joint space narrowing (JSN) as the assessment criterion. Two hundred and thirty-eight patients (47%) discontinued the study, mainly because of adverse events in the diacerein group (25% diacerein versus 12% placebo) and because of inefficacy in the placebo group (14% placebo versus 7% diacerein).

Deterioration, expressed as JSN of at least 0.5mm, occurred in significantly fewer patients in the diacerein group than in the placebo group both in the ITT analysis and in the completer analysis. Moreover, importantly, deterioration occurred significantly later in the diacerein group. In the population of patients who completed at least three years of treatment, the sparing effect on JSN was 32% greater in the diacerein group compared with placebo; however, no evident effect on OA symptoms was found in this study. This is understandable as the study was powered according to its primary end-point, namely structural deterioration. Nevertheless, a post hoc co-variate analysis that took into account the use of analgesics and anti-inflammatory drugs showed an impact of diacerein on the Lequesne functional index. Although more patients stopped treatment in the diacerein group due to side effects, the compound can be regarded overall as being well tolerated during the three-year study. The most frequent adverse events were diarrhoea, transient changes in bowel habits and dyspepsia. No serious or previously undocumented adverse events were observed during this long-term study.

The second trial was a one-year prospective, multicentre, randomised, double-blind, placebo-controlled symptom- and structure-modifying study in which knee OA patients were randomly assigned into three groups receiving:

- three courses of three intra-articular (IA) injections of a new hyaluronan NRD101 (HA) + oral placebo.
- IA injections of saline solution + diacerein 100mg/day; or
- IA injections of saline solution + oral placebo.

Efficacy criteria were changes in JSN and the percentage of progressors (JSN >0.5mm). In addition, pain, Lequesne’s index, patient’s global assessment of disease activity and percentage of painful days were recorded. There was no significant difference between groups for joint space width (JSW) deterioration and the percentage of progressors. Pain improvement was significant and regarded as clinically relevant, but no differences between the treatment groups could be found in this respect either. Thus, the overall conclusion was that a weak but statistically significant structural deterioration occurred over one year, together with clinically relevant symptomatic improvement in patients regardless of the type of treatment. Concerning the lack of significant differences between the groups for symptomatic effects, it is well accepted that there is a notoriously high placebo effect with IA injections of saline (as a placebo) in knee OA studies. An arthrocentesis was performed prior to IA injections of HA or placebo, and this alone can be considered as a form of short-term symptomatic treatment per se as the altered inflammatory synovial fluid is removed.

This study could not demonstrate structural effects for either the new HA compound (NRD101) or diacerein. It should be considered that the study duration (one year) may not have been sufficient to demonstrate a structure-modifying effect of both compounds in comparison. For example, the results of the ECHODIAH study showed that the annual JSN rate (median values) was steady in the placebo group at 0.19mm/year every year for three years, whereas it progressively declined in the diacerein group (0.18mm/year at the end of the first year, 0.14mm/year at the end of the second year and 0.13mm/year at the end of the third year).51

**Meta-analyses**

Systematic reviews and meta-analytical methods are common approaches to the assessment of treatment modalities and have been used in the development of the above-mentioned recommendations. The approach to performing meta-analysis is not uniform and this can affect the overall results and hence the recommendations on whether to use a particular treatment modality. Current minimum standards require a pre-defined meta-analysis protocol with a clear hypothesis, objective and method of systematic review, a collection of as comprehensive a set of reports as possible of relevant randomised controlled trials, a search for all potential relevant data and clear documentation of all search methods and sources. The quality of each study should be reviewed and scored according to accepted and validated criteria (e.g. the Jadad criteria) by more than one reviewer (reviewers should be specialists in the field), and treatment effect sizes should be calculated. Most importantly, the randomised controlled trials in OA chosen for meta-analysis should be reviewed not only for the design and robustness of the data but also for the indication, treated joint, treatment modalities and possible bias due to study design. For example, the inclusion of purely structure-modifying studies (i.e. with no requirement for the patients to be symptomatic at entry into the study) into analyses targeting the symptom-modifying effects of a drug needs to be re-examined as this could bias the results of the meta-analysis and hence wrongly bias the recommendation to use the evaluated drug in the indication.

In 2006 we published a meta-analysis on diacerein identifying a total of 23 studies, 19 of which were ultimately included in the analysis with a total of 2,637 recruited patients (1,328 diacerein-treated patients and 1,309 patients in the comparator groups). Of the studies included, eight (42%) were placebo-controlled and 11 (58%) were...
active (mainly NSAID)-controlled. Forty-two per cent of the studies were conducted in patients with knee OA and 11% in those with hip OA, and 47% dealt with both OA localisations. The result of the quality scoring was 3.2 on the five-point Jadad score.

Diacerein was significantly superior to placebo during the active treatment phase (Glass score 1.50, 95% confidence interval [CI] 0.80–2.20). Both diacerein and NSAIDs were similarly efficacious during the treatment period; however, diacerein, but not NSAIDs, showed a carry-over effect persisting up to three months after treatment, with a significant analgesic-sparing effect during the follow-up period (Glass score 2.06, 95% CI 0.66–3.46). The patient global tolerability ratings at the end of active treatment showed no statistically significant differences between other active treatments and diacerein. As expected, a significant inferiority of diacerein versus placebo was observed regarding patient tolerability, also indicating the reproducibility of the results obtained here. The most frequent adverse event was diarrhoea, followed by discoloration of the urine.

Simultaneously, Fidelix et al. published a Cochrane review on diacerein in OA. They included seven of the identified studies (namely those with the highest-quality scoring according to the Jadad score), which included 2,069 participants. This meta-analysis demonstrated a small, consistent beneficial effect of diacerein on pain in the treatment of OA. Compared with placebo, pain assessment on a VAS (0–100mm) evaluated in 1,228 participants showed a statistically significant difference in favour of diacerein (weighted mean difference [WMD] -5.16, 95% CI -9.75 to -0.57) with an absolute change of five points on the scale; however, significant heterogeneity of the studies was found. When analysed separately by hip OA and knee OA, no difference was detected. The 1,006 patients evaluated on the Lequesne Impairment Index for function did not show improvement in the whole group or in the subgroup analysis, with homogeneity in all results. In summary, the authors concluded that there is ‘gold-level’ evidence that diacerein has a small, consistent benefit in terms of improvement of pain, a result that is very much in line with those of our meta-analysis. The most frequent adverse event was diarrhoea, followed by discolouration of the urine.

Most recently—three years after the other meta-analyses were conducted—a prospective, randomised, open-design, multicentre, pragmatic medico-economic analysis of diacerein was carried out in France in the treatment of OA of the hip and knee compared with standard therapy (ST) alone. Patients with X-ray evidence of hip and/or knee OA and requiring treatment with NSAIDs, analgesics or slow-acting anti-OA drugs were included in this study. Patients scheduled for hip or knee prosthesis within the year following study entry were excluded.

The treatment scheme was as follows. One group received ST for nine months. Treatment was left to the discretion of the physician, who could prescribe various therapies including NSAIDs, analgesics and slow-acting anti-OA drugs. A second group was treated with diacerein according to the following scheme: one group received diacerein in the active treatment phase only (25 mg twice daily for 6 months); the second group received diacerein in the active treatment phase and the 3-month follow-up period. The treatment was continued for another 6 months in the open phase.

The results of these meta-analyses must also be viewed in the context of recently published results about the efficacy of placebo for symptom relief in OA patients. This paper also excellently demonstrated that the effect size of placebo was highly dependent on whether it was administered in an ‘impressive’ way (e.g. intra-articularly), resulting in a high placebo response.

### Cost-effectiveness of Diacerein Treatment

A prospective, randomised, open-design, multicentre, pragmatic medico-economic analysis of diacerein was carried out in France in 1998 to assess the advantages (in terms of public health and health economics) of using diacerein together with standard therapy in the treatment of OA of the hip and knee compared with standard therapy (ST) alone. Patients with X-ray evidence of hip and/or knee OA and requiring treatment with NSAIDs, analgesics or slow-acting anti-OA drugs were included in this study. Patients scheduled for hip or knee prosthesis within the year following study entry were excluded.

The treatment scheme was as follows. One group received ST for nine months. Treatment was left to the discretion of the physician, who could prescribe various therapies including NSAIDs, analgesics and slow-acting anti-OA drugs. A second group was treated with diacerein according to the following scheme: one group received diacerein in the active treatment phase only (25 mg twice daily for 6 months); the second group received diacerein in the active treatment phase and the 3-month follow-up period. The treatment was continued for another 6 months in the open phase.

### Table 1: Inter-group Comparison Between Σ of Total Outpatient Costs and Total Hospitalisation Cost Over 250 Days of Treatment (1998 costs)

<table>
<thead>
<tr>
<th>Categories of Costs</th>
<th>Diacerein (US$)</th>
<th>Usual Therapy (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra visits to doctors (GPs and specialists)</td>
<td>11.25</td>
<td>14.12</td>
</tr>
<tr>
<td>Intra-articular injections</td>
<td>2.68</td>
<td>7.61</td>
</tr>
<tr>
<td>Nursing care (injections)</td>
<td>0.79</td>
<td>2.55</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>52.34</td>
<td>89.21</td>
</tr>
<tr>
<td>Diagnostic imaging</td>
<td>8.00</td>
<td>5.37</td>
</tr>
<tr>
<td>Hydrotherapy</td>
<td>35.72</td>
<td>49.76</td>
</tr>
<tr>
<td>Drugs (except diacerein and treatment of side effects)</td>
<td>89.52</td>
<td>180.01</td>
</tr>
<tr>
<td>Treatment of side effects and gastro-protectors</td>
<td>22.55</td>
<td>39.90</td>
</tr>
<tr>
<td>Diacerein</td>
<td>180.75</td>
<td>0</td>
</tr>
<tr>
<td>Total (outpatient care)</td>
<td>403.64</td>
<td>388.53</td>
</tr>
<tr>
<td>Total (hospital costs)</td>
<td>0</td>
<td>853.29</td>
</tr>
<tr>
<td>Overall total</td>
<td>403.64</td>
<td>1,241.82</td>
</tr>
</tbody>
</table>

(p=0.01) was based on a small amount of heterogeneity (I²=11%); however, the authors queried the clinical effect size of -0.14.
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analgesics, slow-acting anti-OA drugs (except diacerein) and physiotherapy. The second group received diacerein 100mg daily (in two divided doses) combined with standard therapy for the treatment of OA (with the exception of the slow-acting anti-OA drugs) for six months. Diacerein was then discontinued and patients were monitored for a further three months to assess any residual treatment effects.

All patients were assessed at inclusion (day 0), on days 15 and 45 and at three, six and nine months for clinical efficacy and safety and quality of life Arthritis Impact Management Scales (AIMS2) parameters. Health costs were also calculated. A total of 207 patients were enrolled, 98 in the standard therapy arm and 109 in the diacerein plus ST arm. Patients in the two treatment arms were well matched on inclusion, particularly with respect to NSAID and analgesic consumption.

The results showed that the mean NSAID consumption fell by 1.7 in the diacerein group versus 1.1 in the ST group between baseline and six months. This reduction in NSAID consumption continued in favour of the diacerein group between month six and month nine, with a reduction of 1.6 points in the diacerein group and 1.2 points in the ST group. Analgesic consumption between baseline and month six was 41.1% lower in the diacerein group than in the ST group. This difference was statistically significant (p=0.005) over the entire six-month period.

The Lequesne index fell by 2.2 points (-24%) and 1.2 points (-13%) in the diacerein group and the ST group, respectively, in the ITT population (using the last observation carried forward method). The difference between the two groups was statistically significant during the period from baseline to month six (p=0.01) and from baseline to month nine (p=0.001).

The various quality of life components of the AIMS2 and Nottingham Health Profile (NHP) scales showed a trend favouring diacerein over ST alone. Significant results in favour of diacerein were observed for the NHP scale and for the ‘symptoms’ component of the AIMS2 scale.

The costs of outpatient care and hospitalisation were compared in the two groups and the results are presented in Table 1. The overall cost (total outpatients costs plus total hospitalisation costs) was three times higher for patients in the ST group than for those in the diacerein group.

Safety of Diacerein
The most frequently reported and dose-related side effects of diacerein treatment are loose stools and diarrhoea and, to a lesser extent, abdominal pains – effects that are related to the structure of the active ingredient and may affect up to 42% of the treated patients. These events commonly appear during the first two weeks of treatment and abate on continuing treatment, but have resulted in a low incidence of patient withdrawals in clinical studies. These events are reversible on stopping treatment. Urine discoloration is also reported but to a lesser extent. This effect is due to the elimination of rhein metabolites via the urine and is of no clinical significance; it may also be dependent on general fluid intake. A few cases of skin reactions have been reported, but these resolve on stopping treatment. A short literature research targeting publications about a drug rash (or reaction) with eosinophilia and systemic symptoms (DRESS) syndrome under diacerein treatment revealed no results.

Unlike NSAIDs and analgesics, as it does not interfere with prostaglandin E₂, diacerein does not cause gastrotoxicity as demonstrated by endoscopy, and is well tolerated at the level of the kidney. Cardiovascular adverse events in patients treated with diacerein can be considered very rare. In France, over a period of 11 years (from September 1994 to November 2005) and with more than 14 million prescriptions of diacerein, only nine cases of cardiovascular adverse events with diacerein were spontaneously reported (information collected by the Drug Safety Department, Negma-Lerads, Toussus-Le-Noble, France). In particular, no acute coronary syndromes or myocardial infarctions were reported.

By contrast, NSAIDs exert a risk of several more severe adverse effects, including cardiovascular, severe gastrointestinal, hepatotoxicity and nephrotoxicity events, as well as rare events of adverse effects on the central nervous system. Thus, with respect to tolerability, in patients at risk of NSAID toxicity diacerein may have some advantages compared with the medium- or long-term application of NSAIDs.

Summary and Conclusion
There is robust evidence from in vitro studies that diacerein acts as an IL-1β inhibitor in OA, mediated by inhibition of NF-κB activation. The key role of this mediator in inflammatory processes in general, and in OA in particular, makes diacerein a rational therapeutic option in OA patients. The majority of clinical trials and meta-analyses have consistently shown a positive effect on pain and, with some restrictions, also on function in patients with knee and hip OA. However, evidence for other OA localisations, particularly hand OA, is lacking. One study revealed evidence for a structure-modifying effect of diacerein in patients with hip OA.

OA is the most common arthritis in elderly patients, who are often in need of polypragmatic pharmacological treatment. Diacerein has been shown to be as efficient as NSAIDs in treating OA pain and thus may constitute a reasonable alternative for OA patients in whom NSAIDs are contraindicated. Further research, including patients at risk on NSAIDs and also individuals suffering from OA of other locations than the knee or hip, is needed to underline the above hypothesis and to fully understand the effects of diacerein.

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