

**EVALUATION OF EFFICACY AND SAFETY OF DIACEREIN IN  
OSTEOARTHRITIS OF KNEE JOINT****DILIP KUMAR RENAPURKAR\*<sup>1</sup>, SHOBANA MATHUR<sup>2</sup> AND K.L.  
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**ABSTRACT****Back Ground**

Diacerein, a New Drug for Osteoarthritis has already been in the market for last two years. This study is a post marketing survey of the drug Diacerein.

The Aims of this study are:

**Primary Objectives:**

1. To evaluate efficacy of Diacerein
2. To monitor adverse drug reaction

**Secondary Objectives:**

To know whether Diacerein brings about functional as well as structural improvement in osteoarthritis of knee joint.

**Study Design & Methods:**

120 male and female patients who were capable of giving written informed consent within an age range of 30 years to 80 years were selected. The study was done at Princess Esra Hospital affiliated to Deccan College of Medical Sciences, Hyderabad. Diacerein 50 mg tab was administered orally once daily to them for period of four months. Ethical committee approval and patient consents were obtained prior to the beginning of the trial. Ambulatory non pregnant females and males 30 to 80 years of age were included. Subjects are made to withdraw all NSAIDs except Diacerein. Severe Chronic cases in elderly debilitated patients were not included.

Treatment Safety / Efficacy study phase IV Eligibility criteria.

The patients were studied by 1986 criteria laid down by American College of Rheumatism.

**Findings :**

Out of the 120 cases seen for the period of four months all of them improved on the pain scale. No adverse effects were seen on Noranjo Scale. Improvements seen on the X-ray images were the characteristic findings.

#### **Interpretation :**

We can conclude from the results that Diacerein is very useful, disease modifying drug for Osteoarthritic patients bringing about structural and functional changes in the joints of OA patients with less adverse effects.

#### **Keywords:**

Osteoarthritis, DMOAD, Adverse drug reactions, Diacerein,

## **INTRODUCTION**

Osteoarthritis (OA) also known as degenerative arthritis or degenerative joint disease is a clinical syndrome in which low grade inflammation results in pain in the joints. Studies in United States estimate that 80% population will have radiographic evidence of OA by age 65 years although only 60% of those will be symptomatic. Osteoarthritis is derived from greek words "Osteo" meaning the bone, "ortho" meaning joint, and "itis" which means inflammation. OA affects nearly 21 million people in United states accounting for 25% of visits to primary care physicians and half of all NSAID prescriptions. There is hereditary susceptibility to this condition a number of studies have shown greater susceptibility in sibling and twins.

### **WHAT ARE THE TRIALS PUBLISHED UNTILL NOW**

In 1995, American College of rheumatology briefly mentioned preliminary studies on disease modifying osteoarthritic drugs (DMOAD) whose action is aimed at preventing break down of articular cartilage by matrix metallo-proteinases or stimulating the repair activity by chondrocytes. Drugs like Glucosamine, Chondroitin Sulfate and Diacerein are the ones which fall into this category.

The drugs used at present are divided into two groups having different modes of action.

The drugs of the first group, NSAIDS provide symptomatic relief .They have no influence on progress of the disease. The second group of drugs have different chemical structures and they act as disease modifying agents. They can prevent irreversible damage.

The most important drug in this group is Diacerein.

NSAIDS cause serious gastric damage. Recent study shows that they can accelerate the Arthritic disease<sup>1</sup>. [Rashads, Lancet, 1989, p 519-522]

Etiopathology has been re-studied and several new etiological factors which can be targeted for drug therapy have been found out. Research has shown that Cytokines and Chemokines are involved in joint degeneration. New drugs have the ability to target these. One of this kind of drugs is Diacerein.

The object of the intervention is to use one of these new disease modifying agents like Diacerein. Disease modifying agents like Glucosamine and Chondroitin Sulfate have been tried but their efficacy has been questionable. A meta-analysis R and C trial by Schererm et al (2007) "Of the knee or hip", meta-analysis by Richenbach, Chondroitin for Osteoarthritis by S. Sterchir found no benefit for chondroitin Sulfate<sup>2</sup>. (ANN.OFINTERN.MED.146[8]:580-90PMID17438317)

A Double-blind placebo controlled trial on Arthritis and Rheumatism was published in APLAR Journal of rheumatology in April 2006<sup>3</sup>. volume 43, Issue 10, pages from 2339 to 2348 dated 26 March 2001

### **DIACEREIN**

Diacerein is the drug to be proved as disease modifying agent. Diacerein [4,5-bis[acetyloxy]-9,10-dioxo-dioxo-2 -anthracene] is an Anthracene derivative. It is converted to active metabolite "Rhein" which has anti inflammatory effects through inhibition of Interleukin-1B. It reduces the fibrinolytic synovial Fibroblasts. It also dose – dependently inhibits chemotaxis and super oxide

anion production. It consequently reduces collagenase production in the intraarticular cartilage which spontaneously occurs in the body during destructive inflammation.

### COCHRANE REVIEW

Seven studies of moderate to high level of evidence were compared.

These studies compared people who took diacerein 100 mg to people who took placebo/NSAIDs/other slow acting drugs like Glucosamine and Chondroitin Sulfate. These studies ranged in duration from 2 months to 3 years

Pain does seem to improve better in people who took Diacerein. Pain decreased by about 5 more points on VAS SCALE for people who took Diacerein when compared to people who took placebo. Pain, stiffness physical function improved more in people who took Diacerein than placebo. Two studies which lasted 1 year and three years measured progress of disease on radiographically. These studies showed progress of Disease in osteoarthritis in hip. Other study showed that Diacerein did not show progress in OA of Knee joint. In our study we wanted to prove that diacerein is effective in OA of knee joint.

The study of literature suggests that Diacerein improves pain and also it slows the progress of OA in the Hip joint but shows no radiographic evidence regarding improvement in OA of Knee joint. Longer duration studies need to be done to determine the long term benefits and adverse effects of Diacerein.

### RESULTS

Seven identified studies included 2069 participants studied beneficial effects of Diacerein in OA of knee joint. Pain on visual analogue scale was evaluated [0-100mm]. In 1228 participants showed statistically significant difference with Diacerein. Confidence interval= 95%,  $p=0.04$ . But these studies did not show radiographic evidence. Cochrane Review points to small benefit from Diacerein. Usual Osteoarthritis treatment methods do not slow down the disease progression. Diacerein is being studied as Disease – Modifier for Osteoarthritis. More studies needed for Diacerein

*Ref : Dr. Zashin Said "At this time, there is no definitive evidence that Diacerein produces significant results as a disease – modifying drug for osteoarthritis. Further study is needed to establish the short and long term safety and effectiveness of Diacerein for osteoarthritis".*

## MATERIALS AND METHODS FOR THE STUDY

### *Criteria for Classification of Idiopathic Osteoarthritis (OA) of the Knee*

Clinical and Laboratory	Clinical and Radiographic	Clinical ±
Knee Pain	Knee Pain	Knee Pain
+ at least 5 of 9:	+ at least 1 of 3:	+ at least 3 of 6:
- Age > 50 Years	- Age > 50 Years	- Age > 50 Years
- Stiffness < 30 Minutes	- Stiffness < 30 Minutes	- Stiffness < 30 Minutes
- Crepitus	- Crepitus	- Crepitus
- Bony Tenderness	+ Osteophytes	- Bony tenderness
- Bony Enlargement		- Bony Enlargement
- No palpable warmth		- No palpable warmth
- ESR < 40 mm/hour		
- RF < 1:40		

- SF OA		
92% sensitive	91% sensitive	95% sensitive
75% Specific	86% Specific	69% Specific

ESR = Erythrocyte sedimentation rate (Westergren): RF = rheumatoid factor, SF OA = synovial fluid signs of OA (clear, viscous, or white blood cell count <2.000/mm<sup>3</sup>).

+ Alternative for the clinical category would be 4 of 6, which is 84% sensitive and 89% specific<sup>9</sup>.

R. Altman, E. Asch, D. Bloch, G. Bole, D. Borenstein, K. Brandt, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the knee. *Arthritis Rheum* 1986; 29:1039-1049

Sponsors : No Sponsors.  
 Drug Supplied By : REDDY LABS  
 Purpose : Whether Diacerein drug is effective in treating osteoarthritis and also to monitor adverse effect of the drug.

In our study of 120 cases all the cases improved on pain scale

The pain scale selected were

1. Visual Analogue scale
2. Global scale
3. Ritchie index
4. Crepitations
5. Structural Improvement radiographically

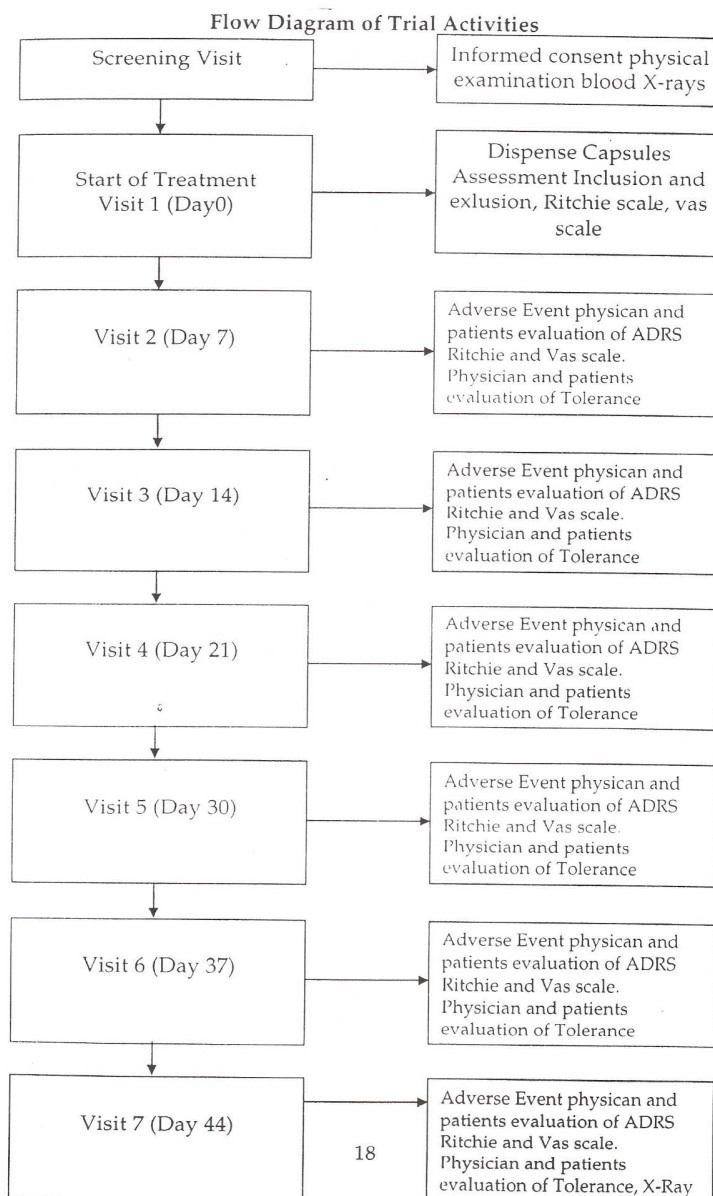
All the features improved on the VAS scale. Of the 120 we had 45 cases which were classified as very severe (more than 7.5 on VAS scale), 27 which were moderate cases (5-7.5) , 48 mild cases (< 5). All of the cases showed improvement on the VAS scale after administration of Diacerein 50mg for 2 months.

On the global scale the cases improved from worst category (71 cases) to better and 49 bad cases to better.

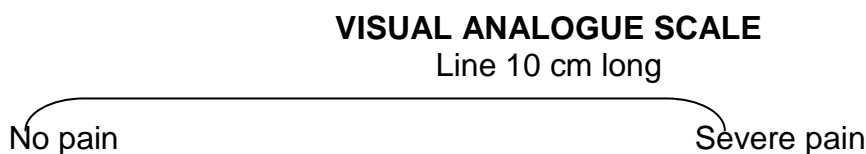
Another interesting conclusion was brought about – After giving Diacerein for 2 months we had structural improvement on radiographs. Variable reduction in Osteophytes and widening of the knee joint was seen radiographically.

The adverse effect in our series were Nil. Only two cases had red urine which is normal. We conclude that Diacerein is a safe drug with least side effects .

As far as possible the NSAIDs were avoided except during early phases when Diacerein administration was started. Diacerein is slow acting drug its effect is noticed after 7 to 15 days period. In our study Diacerein was given to patients in 50 mgs dosage. We noticed structural effects on the radiographic images after 2 months of treatment.



The linear distance from “no pain” mark to the patient’s mark measures the pain Improvement defined as improvement on visual analogue scale and patients ability to do work [global assessment scale]. The most important point we want to prove is structural improvement on X-ray images.



Improvement is defined as improvement in the

1. Visual analogue scale and other scales
2. Structural improvement in radiographic images.

Ritchie Index  
(Recommended by European League against Rheumatism)

Tenderness to firm pressure on joints. The magnitude of discomfort ranging from No pain to very severe pain is recorded

Global assessment of the patient

Patient is characterized as being:

- Much worse
- Worse
- The same
- Better

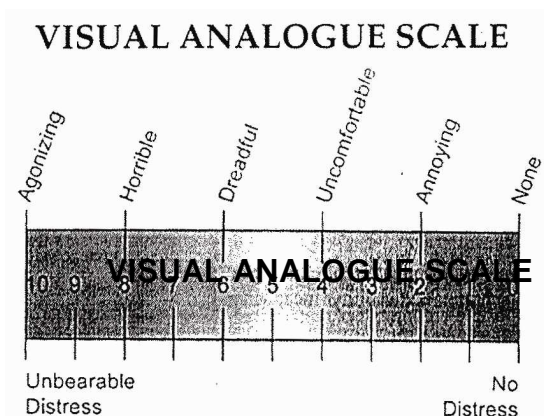
### STUDY PROTOCOL

Name of the patient :  
 Identification no :  
 Age :  
 Sex :  
 Address :  
 Identification marks :  
 Diagnosis :  
 Duration of illness :  
 Drugs the patient on :  
 Duration the patient :  
 Is taking the drug :  
 Highest dosage :  
 Duration of treatment :  
 Current dosage :  
 Duration :  
 Assessment :  
 Visual analogue scale :  
 ESR :  
 Radiographs :  
 Any adverse event :

### VAS

#### RESULTS : VISUAL ANALOGUE SCALE

During the 4 month period 120 cases of Osteoarthritis were seen out of which 30 were males, 90 Females



48 cases mid

27 cases moderate

45 cases severe

Every week Diacerin capsules 50 mgs were given and patient was assessed. Before recruiting the patient all the essential criteria was met with Ethical Committee Permission. The recruiting criteria for the patients American College of Rheumatology Criterion.

### COMPARATIVE IMPROVEMENT IN VISUAL ANALOGUE SCALE

Day 0 Diacerein Started	Day 15 supplied	Day 30 Diacerein Supplied	Day 37 Diacerein Supplied	Day 44 Diacerein Supplied	Day 60 Diacerein Supplied
<b>48 Cases mid</b>	Progressive improvement 2.5 - 5 cm	Progressive improvement	Progressive improvement	Progressive improvement	Complete improvement NIL
<b>28 Cases Moderate</b>	Progressive improvement 7.5 cms	Progressive improvement	Progressive improvement	Progressive improvement	Complete improvement NIL
<b>45 Cases Severe</b>	Progressive improvement 8 – 10 cms	Progressive improvement	Progressive improvement	Progressive improvement	Complete improvement NIL

### GLOBAL FUNCTIONAL SCALE

Out of the 90 females seen 58 were above 50 years of age and diagnosed with Osteoarthritis, 32 cases were below 50 years. In total 84 cases were diagnosed with OA (both male and female) were above 50 years.

Global Functional Scale is the assessment of patient's perception of pain as worst or bad. On improvement a perception of better should be made by the patient. Out of 71 worst pain cases:

### GLOBAL ASSESSMENT

	1 <sup>st</sup> Week	15 days	30 days	40 days	50 days
<b>71 Worst Pain</b>	Improvement	Improvement	Improvement	Improvement	Better
<b>Bad 49 Cases</b>	Improvement	Improvement	Improvement	Improvement	Better

### RITCHIE ARTICULAR INDEX

All the 120 cases demonstrated positive Bony tenderness mostly medial epicondyle. After taking Diacerin for 1½ to two months all cases improved progressively.

	Zero	7 days	15 days	1 month	1 ½ month	2 months
<b>120 cases follow up</b>	Bony Tenderness	Improved	Improved	Improved	Improved	Improved

All of the 120 cases show crepitation. It was crepitations which improved during the first and second weeks after starting Diacerein.

**CREPITATIONS : OSTEOARTHRITIS**

	First Week of Diacerein	2 <sup>nd</sup> Week of Diacerein	3 <sup>rd</sup> Week of Diacerein	One month of Diacerein
<b>120 cases of Crepitation</b>	Crepitations disappeared first in 80 cases out of 120	Progressive disappear same in another 20	Disappear in all cases	

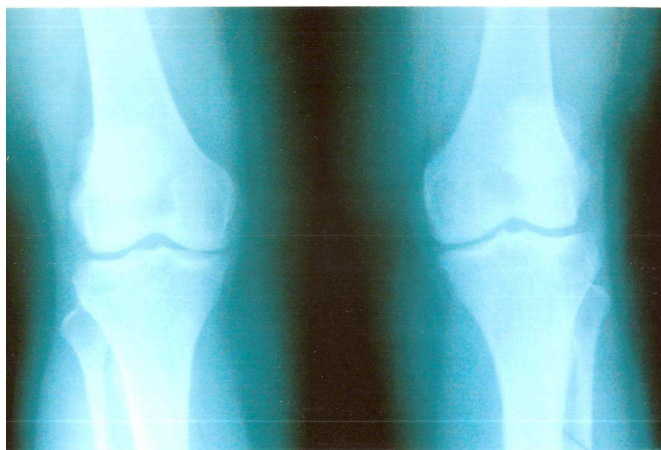


**Figure 1: Radiograph of case No. 1 before starting Diacerein**



**Figure 2: Radiograph of case No. 2 before starting Diacerein**





**Figure 3: Radiograph of case No. 3 before starting Diacerein**

### RADIOGRAPHS

<b>BEFORE TREATMENT</b>	<b>AFTER TREATMENT</b>
All 120 cases had pre-treatment radiographs which showed osteophytes. Radiographs also showed narrowing of joints	3 cases recorded (because of financial constraints and poor patient follow-up) who show improvement on radiographs such as, widening of joint spaces reduction of osteophytes

### RADIOGRAPHIC RESULTS

One of the criteria considered for admission and diagnosis of cases was joint changes on X-rays. X-rays show narrowing of Joints and Osteophytes before treatment.



**Figure 4: Radiograph of case No. 1 after Treatment with Diacerein**



**Figure 5: Radiograph of case No. 2 after Treatment with Diacerein**



**Figure 6: Radiograph of case No. 3 after Treatment with Diacerein**

### **ADVERSE EVENTS**

Noranjo Scale<sup>10</sup> followed and in only two cases reddish urine was recorded. Drug Diacerein sometimes gives Reddish tinge to urine. This is due to metabolic product in urine which is not of any adverse effect.

## ADVERSE EVENTS

Adverse events can be studied by Naranjo Algorithm

Question:	Yes	No	Do not know
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did adverse event appear after the suspected drug was administered?	+2	-1	0
3. Did the adverse reaction improve when The drug was discontinued or a specific Antagonist was administered?	+1	0	0
4. Did the adverse reaction reappear when The drug was re-administered?	+2	-1	0
5. Are there alternative causes (other than drugs) that could on their own have caused the reaction?	-1	+2	0
6. Did the reaction appear when a placebo Was given?	-1	+1	0
7. Was the drug detected in the blood in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was increased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0
Total Score=			
1 to 4 points	:	ADR possible	
5 to 8 points	:	Probable	
More than 9 points	:	Definite	

(Naranjo C A, Busto U, Sellers E M et al (1981), A Method of Estimating the Probability of Adverse Drug Reaction. Clinical Pharmacology and Therapy 30: 239-245.)

## CONCLUSIONS

In our study of 120 cases all the cases improved on pain scale. All the features improved on the VAS scale, global scale Ritchie index, crepitations. Another interesting conclusion that was brought about after administration of Diacerein for 2 months was the structural improvement seen on radiographs. The structural improvement includes reduction in osteophytes and widening of joint spaces. The adverse effect in our series were nil. Only two cases had red urine which is normal consequence. We conclude that Diacerein is a safer drug with least

side effects and which could result in beneficial structural changes in the joints.

## ACKNOWLEDGEMENTS

We thank Dr. Reddy's Labs for supply of Diacerein capsules (HILIN Capsules).

We thank Department of Orthopedics, Princes ESRA Hospital.

We thank our own Department of Pharmacology, Deccan College of Medical and Sciences.

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