Original Article

Efficacy of Diacerein in the Treatment of Osteo-arthritis of Knee

Loitongbam L Sushil Singh[1], Handa Gita[2], Singh U[3], Yadav S L[4]

Abstract

Osteo-arthritis, the most common joint disease of human being, presents with pain and stiffness of the affected joints, feeling of instabilities, deformities and severe loss of function of the involved joint affecting activities of daily livings as well as economic burden.

The present study evaluates the efficacy and adverse effects of diacerein, an anti-inflammatory drug now being considered as a disease modifying drug in osteo-arthritis on 38 patients. After 6 weeks of intervention, diacerein showed statistically significant superiority versus aceclofenac as assessed with WOMAC A (P<0.0001), WOMAC B (P< 0.0001), WOMAC C (P<0.0001) and secondary efficacy variable like NSAIDs (aceclofenac) intake from the baseline and at the efficacy time point at 6 weeks and 12 weeks(P<0.0001), demonstrating the better efficacy of diacerein over aceclofenac. This superiority was already evident from 6th week for all the parameters. It was more significant after completion of the study.

Key words: **Osteo-arthritis, diacerein, WOMAC, aceclofenac, Kellgren- Lawrence grading.**

Introduction:

Studies by various investigators over the last few decades have demonstrated the inflammatory component in the pathogenesis of osteo-arthritis. Diacerein, a drug which inhibits the pathways and metabolism of inflammatory intermediates interleukin-1 and tumour necrosis factor in various studies[1,2] have shown diacerein to be as efficacious or even better than the commonly used analgesics and NSAIDs in the treatment of both knees without the unwanted side-effects of these medications, with a carryover effect of its benefits, which according to some studies extend up to 3 months. The present study has shown positive results of the efficacy and safety of the mentioned drugs.

Author's affiliation:
[1]*MD (PMR)*
[2]*Additional Professor*
[3]*Professor*
[4]*Additional professor*
Department of Physical Medicine and Rehabilitation,
All India Institute of Medical Sciences, New Delhi.

Citre as:
Loitongbam Sushil Singh, Handa Gita, Singh U, Yadav S L. Efficacy of diacerein in the treatment of osteoarthritis of knee. *IJPMR December 2013*; Vol **24(4)**: 92-8

Correspondence:
Dr. Sushil Singh Loitongbam, Room No. 2,
Department of Physical Medicine and Rehabilitation, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110029.
Phone Number: 9711474592.
E-mail address: drsushillongtongbam@gmail.com

Received on 16/07/2013, Accepted on 28/11/2013

Aetiology and pathophysiology of osteo-arthritis: Osteo-arthritis may be idiopathic, where causes are not identified, or may be secondary, which is attributable to an underlying cause, which may include[3] trauma to the joints, bony deformities, metabolic diseases, crystal deposition arthritides, fractures or loss of sensation to joints. Along with the above mentioned factors, the other risk factors for osteo-arthritis are age, female sex, race, genetic factors, repetitive stresses to the joints[4].

It follows that malfunction of a joint may result from either acute or chronic injuries that produce bio-mechanical and biochemical forces leading to anatomic alterations in the shape of articulating surface and leading to matrix synthesis, enzymatic degradation of the connective tissue matrices resulting from an inflammatory conditions (e.g. rheumatoid arthritis)

Moderate macroscopic and histological evidence of synovial inflammation was found in 55% of patients with knee osteo-arthritis and normal radiographs by arthroscopy[5]. Modest increases of the sensitive acute-phase proteins SAA and CRP have been observed in several studies of OA as well as in post-traumatic joint disease[6,7]. It may be argued that the chondrocyte in OA releases mediators very similar to activated macrophages. Cytokines and growth factors like interleukin-1B, tumour

necrosis factor-B, TPA (tissue plasminogen inhibitor) may function to activate enzymes involved in proteolytic digestion of cartilage. These enzymes, a family of matrix metalloproteins (MMPs), including stromelysin, collagenase and gelatinase can degrade all the components of the extracellular matrix at neutral pH / 10 4[1]. TIMP (tissue inhibitor of metalloproteinase) and PAI-1(plasminogen activator inhibitor) limit the degradative activity of the MMPs and plasminogen activators.

Diacerein is a pro drug which gives the active metabolite rhein. Rhein can effectively inhibit the IL-1 activated MAPK pathway and the binding of NF–Kappa and AP-1 transcription factors, two key factors involved in the expression of several pro-inflammatory genes by chondrocyte 8, 9-52, 53. In addition the drug can reduce the pro-catabolic effect of the cytokine, by reducing the MMP-1 synthesis and enhance the synthesis of matrix components such as type II collagen and aggrecan[8,9]. It increases the production of transforming growth factor-b (TGF-b1 and TGF-b2) that stimulates chondrocyte proliferation and stimulates the production of collagen II, proteoglycan synthesis and increase matrix components.

The pharmacokinetic behaviour of diacerein is the same in young and elderly people with normal renal function after a single dose (50 mg) or repeated doses (25 to 75mg) twice daily. Taking diacerein with a standard meal delays systematic absorption but is associated with a 25% increase in the amount absorbed. Hence it is advisable to administer the drug with a major meal.· Though dose modification is required in mild to severe renal insufficiency (50% reduction in severe renal failure) tab[10], no reduction in initial dose is proposed in liver cirrhosis tab[11].

Two adverse effects of diacerein are important to note. The first is a laxative effect, associated with diarrhoea or soft stools in 20% to 30% of patients after the first few doses whose frequency decreases with the continuation of treatment. The second adverse effect is yellow-brown discolouration for which the patient needs to be advised to prevent unnecessarily feeling of fear or anxiety.

Table 1 gives an analysis of efficacy and adverse effects of diacerein in the treatment of osteo-arthritis of knee as published by the various authors[12-15].

Materials and Methods:

A prospective, randomised, controlled clinical study was carried out in the Department of Physical Medicine and Rehabilitation, AIIMS, New Delhi. A total of 76 patients were included in the study, divided into two groups, A and B, 38 patients in group A given diacerein and aceclofenac and 38 patients in group B only aceclofenac in predetermined doses. All the patients of both groups were given home bound strengthening exercises for the quadriceps and hamstrings muscles in the following protocol-straight leg rise, short arc extensions (knee), 30 repetitions, initially with ½ kg weight for resistance and gradually increased by ½ kg for every 4 weeks up to 2 kg in leg (B/L), 6 seconds holding time in each, twice in a day, to continue throughout the study. Physical modalities were also advised to reduce pain.

In group A, the patients were given diacerein 50 mg once daily for 4 weeks, then 50 mg twice daily for the next 2 months. Along with it, they were given aceclofenac 100 mg twice daily for 1 week then continued aceclofenac 100mg on SOS basis. In the group B, the patients were given aceclofenac 100 mg twice daily for 1 week then continued aceclofenac 100 mg on SOS basis.

Each patient was given a questionnaire page to answer the assessment questions, according to their subjective feelings about pain, stiffness and difficulties in functional activities using VAS and WOMAC scale at the initiation of study, at the 6th week and finally at the 12th week. Along with it, the frequency of intake of aceclofenac was monitored in the two groups. At the end of three months, the final assessment was taken and the desired study results were analysed using SPSS software.

Assessment:

The symptoms and functional disabilities on performance of activities of daily living of the two groups of patients were assessed using The Western Ontario and McMaster Universities (WOMAC) osteo-arthritis index. The Western Ontario and McMaster Universities (WOMAC) osteo-arthritis (OA) index is a tested questionnaire to assess symptoms and physical functional disability in patients with OA of the knee and the hip. The WOMAC is a patient-centred, self-reported measures which provides opportunity to evaluate consequences of osteo-arthritis, that are important and relevant to patients with the condition[16,17]. The questionnaire contains 24 questions, targeting areas of pain, stiffness and physical function, and can be completed in less than 5 minutes. The self-rating instrument consisting of 24 items of which 5(P1-P5) relate to pain, (S1-S2) to joint stiffness, and 17(F1-F17) to the function scale. All items are rated

on a numerical rating scale of 0(no symptoms/disability) to 10(maximal symptoms/ disability).The unweighted arithmetic mean of at least 4/5 pain, 1/2 stiffness and 14/ 17 disability items make up the WOMAC scales.

Visual analogue scale (VAS):[18] The VAS is a self-report instrument that consists of a 10 cm straight line of either horizontal or vertical orientation. The line is anchored by two extremes of pain. "no pain" and pain as bad as it could be. Possible score ranges from 0 to 10. The resulting measure represents the patient's level of pain.

Score: 1-4=mild, 5-6=moderate pain, 7-10=severe pain.

Table 1: *Efficacy and Adverse Effects of Diacerein in Various Studies*

Authors with study	Efficacy, dosage recommendations	Safety profile and recommendation
Bernhard Rintelin *et al*[12] in their meta-analysis of 19 studies	Diacerein was significantly superior to placebo during the active treatment phase (Glassgow score, 1.50 [95% confidence interval, 0.80-2.20]. Diacerein, showed a carryover effect, persisting up to 3 months after treatment, with a significant analgesic-sparing effect during the follow-up period (Glassgow score, 2.06 [95% confidence interval, 0.66-3.46)]	Tolerability assessment revealed no differences between diacerein and NSAIDs, although the latter showed more severe events
Zheng *et al*[13] on a study with 223 patients satisfying the ACR criteria for OA knee, to look for the efficacy rates with patient's/physician's overall assessment on diclofenac alone versus diclofenac with diacerein after 12 weeks of treatment.	Consumption of paracetamol was significantly lower in diacerein group than in the diclofenac group during the follow-up	Adverse events were 35.7% in diacerein and 45.1 % in the diclofenac group
Pelletier *et al*[14] Randomised, double-blind, placebo-controlled,, parallel study group with 3 diacerein dosages of 50 mg/ day, 100 mg/day and 150 mg/day (administered twice daily).	Diacerein dosage of 100 mg/day was significantly superior (P<0.05) to placebo using the primary criterion (VAS assessment of pain) and the secondary criteria, which included the Western Ontario and McMaster Universities OA Index (WOMAC), and the VAS assessment of handicap	The best daily dosage of diacerein was 90.1 mg. Mild-to-moderate transient changes in bowel habits were the most frequent adverse effects, increasing with the dosage
Brahmachari *et al*[15]. Efficacy and safety of diacerein in early knee osteo-arthritis:a randomised placebo-controlled trial	Diacrein showed highly significant (P<0.01) reductions in VAS pain scores, significant in WOMAC physical functional scores, significant lower requirements for rescue medications	Incidence of AE was significantly higher in diacerein arm(27 patients on diacerein experienced AE versus eight with placebo; p<0.01) with yellow discolouration of urine, soft stool, dyspepsia, mild to moderate intensity abdominal cramp, and skin rash being most common events
Pavelka *et al*[2]. A randomised, multicenter, double-blind, placebo-controlled study on 168 patients with primary end points at two months after the end of a three-month treatment period	At month 5, diacerein showed statistically significant superiority versus placebo as assessed with both the WOMAC A (*P* <0.0001) and the total WOMAC (*P*<0.0001), demonstrating the carryover effect of the drug. This superiority was already evident from month 2 for pain (*P* =0.001) and month 1 for total WOMAC (*P* _ 0.0021)	Diacerein was safe and well tolerated. No serious orpreviously undocumented adverse events were observed during the study

Results and Observations:

Demographic and clinical variables of study subjects: The age at presentation of patients in group A varied from 41 to 68 years with mean age of 54.57% and in group B from 41 years to 72 years with mean age of 53.06%. The maximum number of patients was in the age group of 50 to 59 years. Female patients were more than male in both the groups, 22 females (62%) in group A.

Progression of the disease: We had found that 20%, 51.42%, 22.85%, 5.71 % respectively of the patients in group A had disease progression measured as stages I, II, III and IV according to the Kellgren-Lawrence staging of knee OA. The corresponding figures in the group B were 22.22 %, 58.33%, 22.22% and 5.81% respectively. After comparison of all history of both the groups, we found there was statistically no significant difference between the two groups at the inclusion of the study.

Duration of the disease: We had found that the average duration of disease in group A was 38.29 months and 39.39 months in group B. Maximum number of patients were those who have been having the disease for 2-3 years in both the groups, 9 (25.71%) in group A and, 10 (27.77%) in group B. There was no statistically significant difference between the groups in relation to the duration of knee pain (p=.666).

Joint compartments involvement: There were 48.50% of patients in group A and 44.44% patients in group B had bilateral compartments involvement, whereas only 17.14% and 27.77% respectively of patients in group A and group B had unilateral compartment involvement, remaining 34.25% in group A and 27.72% in group B had involvement of all the compartments of the knee. They were compatible at both groups. There was no statistically significant difference between the groups, p=1.0

Intensity of knee pain and stiffness: Table 2 shows the changes in the various sub-scores over the period of time. The mean VAS score of pain on the sub-score (pain while walking) were 4.80, 3.06 and 1.80 at 0, 6th and 12th weeks respectively for patients in the group A which was statistically significant (p=0.00). The findings of the other sub-scores are also shown in the table. This was reduced over the period of time and was highly significant at the completion of the study (p=0.000). At the end of the study, the p-value was 0.000 which was also statistically significant between both the groups.

Stiffness of knee joint: In Table 3, where we compared the numerical rating scale (0-10) in stiffness at early morning time and stiffness later at the day within the group and between the groups at inclusion 0 week, 6th week and at the completion of the study. They were comparable within the groups and in both group A and group B at the starting of the study. And in between the groups, they were comparable but after 6 weeks of time (p=0.000). Here it was found significant difference between both the groups (p=0.00). The improvement was better with group A over group B at the end of the study.

In Table 2, we have compared the difficulty level in

Table 2: *Mean Vas Score of Pain*

Variable	Group	0 week	After 6 weeks	After 12 weeks	p-value
		Mean VAS score	Mean VAS score	Mean VAS score	
P1 Pain while walking	A	4.80	3.06	1.80	0.000
	B	4.78	3.33	2.56	0.000
P2 Climbing wtairs	A	6.86	4.77 1.087	2.94	0.000
	B	6.83	4.92	3.67	0.000
P3 In bed at night	A	1.83	1.40	1.09	0.000
	B	1.94	1.44	1.08	0.000
P4 Sitting or lying	A	2.00	1.46	1.11	0.000
	B	1.94	1.39	1.14	0.000
P5 Standing	A	5.69	3.89	2.29	0.000
	B	5.25	3.81	3.03	0.000

Table 3: *Numerical Rating Scale*

Variable	Group	0 week	After 6 weeks	After 12 weeks	p-value
		Mean RS	Mean RS	Mean RS	
S1	A	3.11	1.94	1.31	0.000
	B	2.78	1.81	1.39	0.000
S2	A	2.57	1.69	1.43	0.000
	B	2.86	2.00	1.83	0.000

carrying out the various activities of daily livings as according to the WOMAC scale. At the beginning of the study, the mean numerical rating scale (0-10) of the various parameters are compared within the groups and between the groups and was comparable in between the groups and among the groups. Over the course of time, the improvement was much better with group A than that with the group B in all the parameters, p=0.000 **.**

Reduction in the intake of NSAIDs: The average number of NSAIDs (tablets) taken by the patients in the group A and group B and their gradual decrease over the period of twelve weeks after starting treatment with diacerein is shown in the Figs 1 and 2 and Tables 4 and 5. The reduction has been found to be statistically significant (p=0.000) in both the groups. Comparing the reduction among the two groups, patients in the group A had lesser number of NSAIDs intake as compared to the group B as shown in the Figs 1 and 2.

One patient in group A dropped out due to allergic reaction to diacerein like skin rashes, itching. The symptoms subsided after stopping diacerein. Although soft stool, diarrhoea and mild abdominal discomfort occurred in few patients, none of the patients dropped out due to these symptoms. These symptoms also subsided within a few days even in continuing with the drug. Some had abdominal pain and discomfort which may be due to side-effects of aceclofenac, which was later treated with PPIs (proton pump inhibitors). The dropout were due to various reasons like missing the drug in between and few of them could not come on time mainly those who were from very far off places.

Discussion:

Osteo-arthritis is one of the most frequent causes of pain, loss of function and disability in adults second to ischaemic heart disease. In India the prevalence of osteo-arthritis has been suggested at 24.9%[19] till recently, osteo-arthritis was classified as a wear and tear disorder of articular cartilage for which only pain reducing medications, physiotherapy and other joint injections with corticosteroids were the mainstay of treatment. Very little scientific consideration has given on the modification of course of disease activity leading to musculoskeletal disability and affecting quality of life.

The present treatment of osteo-arthritis revolves around the use of analgesics and NSAIDs and newer cyclooxygenase-2 inhibitors. But these medications increases the risk of upper gastro-intestinal adverse effects and may have significant renal and cardiovascular toxicity especially NSAIDs including the COX-2 inhibitors[20]. Moreover, they don't have the disease course modifying effect. Recently, the used of symptomatic slow acting drugs or chondroprotective drugs like glucosamine, chondroitin sulphate and diacerein[21]. These drugs have gradual onset of action (4-6 weeks) but maintain their symptomatic effect for a period of 4-8 weeks after cessation of treatment.

Diacerein acts by inhibiting the inflammatory mediators like IL-1, and MMP-1 and by enhancing the synthesis of matrix components such as type II collagen and aggrecan[8,9]. It increases the production of transforming growth factor-b (TGF-b1 and TGF-b2) that stimulates chondrocyte proliferation and stimulates the production of collagen II, proteoglycan synthesis and increases matrix components. Diacerein has been found to be safe and can be given to those with liver diseases but reduction of dose is needed to those with severe renal failure.

In our study, the group of patients (group A) who were given diacerein at the dose of 50 mg daily for one month to be followed by 50 mg twice daily for another two months were compared to the group of patients (group B) who were not given diacerein. Both groups of patients were prescribed a uniform exercise regime to be followed at home on a regular basis, joint care and protection advice given and physical modalities suitable to the

Table 4: *Average Number of Aceclofenac 100mg Tablets Taken per Week in Group A*

Weeks	Mean	Std. Deviation
A (1-2) weeks	6.46	1.221
B (2-3) weeks	4.80	1.079
C (3-4) weeks	4.66	0.968
D (4-5) weeks	3.89	0.993
E (5-6) weeks	2.63	1.165
F (6-7) weeks	2.14	1.141
G (7-8) weeks	2.09	1.197
H (8-9) weeks	1.49	0.853
I (9-10) weeks	1.46	0.950
J (10-11) weeks	1.23	0.973
K (11-12) weeks	1.00	0.840

Table 5: *Average Number of Aceclofenac 100mg Tablets Taken per Week in Group B*

Weeks	Mean	Std. Deviation
A (1-2) weeks	6.92	1.251
B (2-3) weeks	5.83	1.082
C (3-4) weeks	5.33	1.195
D (4-5) weeks	4.83	1.000
E (5-6) weeks	4.97	1.028
F (6-7) weeks	4.75	0.874
G (7-8) weeks	4.36	0.990
H (8-9) weeks	3.69	0.920
I (9-10) weeks	3.56	0.969
J (10-11) weeks	3.33	0.535
K (11-12) weeks	3.22	0.797

Fig 1- *Average Number of Aceclofenac 100mg Tablets Taken per Week in Group A*

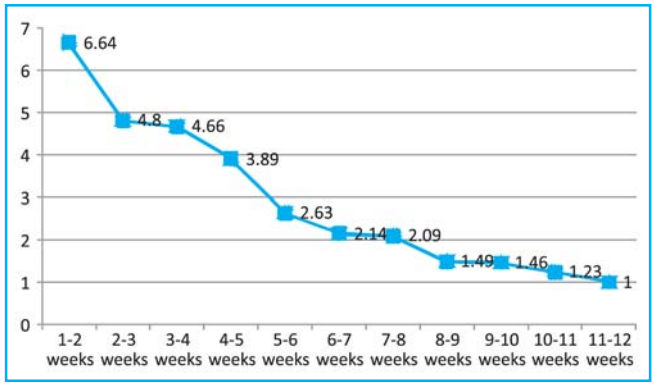
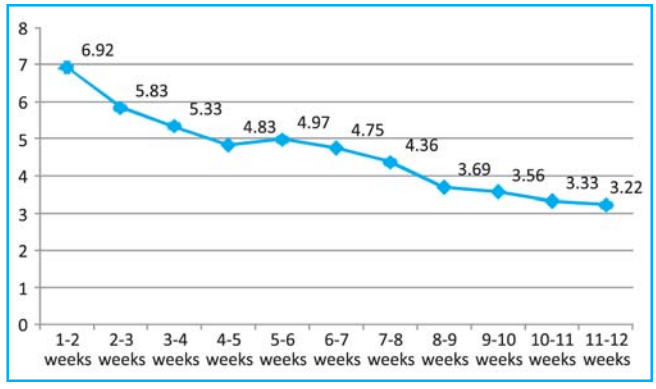


Fig 2- *Average Number of Aceclofenac 100mg Tablets Taken per Week in Group B*



patients were also recommended. The mean VAS score of pain on the sub-score (pain while walking) were 4.80, 3.06 and 1.80 at 0, 6th and 12th weeks respectively for patients in the group A which was statistically significant (p=0.00). Significant changes were seen on the other sub-scores of pain, stiffness and difficulty in functional activities included in the WOMAC scale. The effects of diacerein were observable by 6th week period and sustained at the end of the third month.

The average number of NSAIDs (aceclofenac 100 mg tablets) taken by the patients in the group A and group B has been found to be decreased and were statistically significant (p=0.000) in both the groups. Comparing the reduction among the two groups, patients in the group A had lesser number of NSAIDs intake as compared to the group B.

One patient in the diacerien group dropped out due to skin rashes and itching which might be due to allergic reaction to diacerein. The symptoms subsided after stopping diacerein. Soft stools, diarrhoea and mild abdominal discomfort occurred in few patients, these would subside within a few days, but none of the patients dropped out due to these symptoms. The dropout was due to various reasons like missing the drug in between and few of them could not come on time mainly those who were from very far off places.

Summary and Conclusion:

Both the patients were statistically comparable, at the initiation of the interventions in relation to age, sex distribution, height, body mass index, occupations, socio-economic status, dietary and family history, duration of the knee pain, clinical features.

In both the patient groups, medications were not only helpful in improving the symptoms, but also activities of daily living of the patient with primary osteo-arthritis of knee. But those patients who were taking diacerein along with aceclofenac, pain, stiffness and activities of

daily living were much better with them than with aceclofenac alone. Most of the adverse effects of diacerien were mild and easily tolerable. To conclude, diacerein is an effective drug for osteo-arthritis of the knee with minimal side-effects and possible NSAIDs sparing effect which might be very helpful in preventing renal and gastric involvements in patients with a chronic disease like osteo-arthritis.

References:

1. Meyers SL, Brandt KD, *et al*. Synovial inflammation in patients with early osteoarthritis of the knee. *Rheumatology* 1990; **17:** 1662-9.
2. Pavelka K, *et al*. The efficacy and safety of diacerein in the treatment of painful osteoarthritis of the knee. *Arthritis Rheum* 2007; **56:** 4055-64.
3. Hernborg JS, Nilsson BE *et al*. The natural course of untreated osteoarthritis of the knee. *Clin Orthop* 1977; **123:** 130-1.
4. Brandth KD, Fauci AS, Braunwald E, Issalbacher, KJ, *et al*. Harrison's principles of internal medicine. 14th ed. New York: MacGraw-Hill, 1989: 1935-41.
5. Fell HB, Jubb RW. The effect of the synovial tissue on the breakdown of articular cartilage in organ culture. *Osteoarthritis Cartilage* 1977; **20:** 1359-71.
6. Sukeniks, Henkin J *et al*. Serum and synovial fluid levels of serum amyloid A protein and C-reactive protein in inflammatory and non-inflammatory arthritis. *J Rheumatol* 1988; **15:** 942-5.
7. Spector TD, *et al*. Low level increase in serum, C-reactive protein are present in the early osteoarthritis of the knee and predict progressive disease. *Arthritis Rheum* 1997; **40:** 723-7.
8. Falgarone G, Dougados M, *et al*. Diacerein as a disease-modulating agent in osteo-arthritis. *Curr Rheumatol Rep* 2001; **3:** 479-83.
9. Domagala F, Martin G, *et al*. Inhibition of IL-1 B- induced activation of MEK/ ERK pathway and DNA binding of N F kappa B and AP-1: potential mechanism of diacerein in osteo-arthritis. *Biorheology* 2006; **43:** 577-87.
10. Nicholas P, Tod M, padion C. Clinical pharmacokinetics of diacerein. *Clin Pharmacokinet* 1998; **35:** 347-59.
11. Magnard O, Louchahi K, Tod M, *et al*. Pharmacokinetics of diacerein in patients with liver cirrhosis. *Biopharm Drug Dispos* 1993; **14:** 401-8.
12. Rintelen B, Neumann K, *et al*. A meta-analysis of controlled clinical studies with diacerein in the treatment of osteo-arthritis. *Arch Intern Med* 2006; **166:** 1899-906.
13. Zheng WJ, *et al*. Efficacy and safety of diacerein in osteoarthritis of the knee: a randomized, multicenter, double-dummy, diclofenac-controlled trial in China. *APLAR J Rheumatol* 2006; **9:** 64-9.
14. Pelletier JP, *et al*. Efficacy and safety of diacerein in osteo-arthritis of the knee: a double-blind, placebo-controlled trial. The Diacerein Study Group. *Arthritis Rheum* 2000; **43:** 2339-48.
15. Brahmachari B, Chatterjee S, Ghosh A. Efficacy and safety of diacerein in early knee osteo-arthritis. *Clin Rheumatol* 2009; **15**.
16. Bellamy N, Buchanan WW, *et al*. Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy. *J Rheumatol* 1988; **15:** 1833-40.
17. Bellany N. The WOMAC knee and hip osteoarthritis Indices: Development, validation, globalization and influence on the development of the AUSCAN Hand Osteoarthritis Indices. *Clin Exp Rheumatol* 2005; **23:** 148-53.
18. Hiskisson EC: Visual Analogue Scales. In Melzack R, editor. Pain Measurement and Assessment. New York: Raven Press 1983; 33-40.
19. Provvedini D, Cohen P. Efficacy of diacerein on the symptoms and radiographic progression of osteoarthritis. *Medicine* 2002; **31:** 4S13-5.
20. Mahajan A. Cox-2 inhibitors: cardiovascular safety. *JK Sci* 2005; **7:** 61-2.
20. Verbruggen G. Chondroprotective drugs in degenerative joint diseases. *Rheumatology (Oxford)* 2006; **45:** 129-38.
21. Hochberg MC, Dougados M. Pharmacological therapy of osteoarthritis. *Best Pract Res Clin Rheumatol* 2001; **15:** 583-93.