

## Original Research Article

# A non-interventional, prospective, multicentric real life Indian study to assess safety and effectiveness of un-denatured type 2 collagen in management of osteoarthritis

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## ABSTRACT

**Background:** Osteoarthritis (OA) is the most common musculoskeletal condition affecting the quality of life. Undenatured collagen type II has emerged as one of the promising treatment options in treatment of OA. Despite being available in India, clinical safety and efficacy have not been evaluated. We performed a non-interventional, real-life study to determine its safety and efficacy in Indian population.

**Methods:** A non-interventional, real-life study was performed in patients with OA of knee by 18 orthopaedicians in India. Patients enrolled were followed-up at day 30 (visit 2), day 60 (visit 3) and day 90 (visit 4). Efficacy was assessed by Western Ontario McMaster Osteoarthritis Index (WOMAC) and Visual Analogue scale (VAS) on each visit. Safety was assessed by incidence of suspected adverse events (AEs), and abnormal laboratory parameters.

**Results:** Among 291 enrolled patients 226 patients completed the study. Mean age of the population was 56.2±8.7 years and 53.3% of them were females. In 291 patients included in safety analysis, at least one treatment emergent adverse event (TEAE) was seen in 4.47% patients. None of the AEs were serious or resulted in termination of patient from the study. Nausea (1.37%) and headache (1.03%) were the common AEs. Treatment with undenatured collagen type II was associated with significant reduction in WOMAC score ( $p < 0.0001$ ) and VAS scores ( $p < 0.0001$ ) from baseline to day 90.

**Conclusions:** Undenatured collagen type II is safe and efficacious in Indian patients with OA. This can be considered early in the initial management of OA.

**Keywords:** Osteoarthritis, Undenatured collagen, Efficacy, Safety, India

## INTRODUCTION

The global burden of osteoarthritis (OA) is enormous. The Centers for Disease Control and Prevention

estimated that 54.4 million adults (22.7%) in the United States are affected with arthritis.<sup>1</sup> The two most common forms of arthritis are rheumatoid arthritis (RA) and osteoarthritis (OA). OA of large joints (e.g. knee, hip) is the most common form of arthritis. Their presence in

Indian subcontinent is also substantial.<sup>2</sup> In India, the reported prevalence of OA is 28.7% in >40 years age group<sup>3</sup>. Further, in adults aged  $\geq 65$  years, it is estimated that nearly 45% of the women have symptoms and 70% have radiological evidence of OA. The disabling pain is associated with loss of daily activities in nearly 25% of them.<sup>4</sup> Being overweight/obese, lack of physical activity or sedentary lifestyle, and female sex are important risk factors of OA.<sup>3</sup> Pain and disease activity in OA can vary from mild to severe forms. Pain is the most troubling symptom and affects the quality of life of patients with OA.<sup>5,6</sup> Current treatment of OA includes exercise, heat/cold therapy, joint protection, weight loss, physiotherapy/occupational therapy and medications. The most common medications used for pain relief include NSAIDs. Although these drugs are effective for reducing pain associated with OA, they do not reverse the disease. In addition, there are considerable side effects associated with the use of these drugs. As a result, physicians have turned to adjunctive therapies to ease their pain and discomfort. These products are commonly used because they are well tolerated and considered safe.<sup>8</sup> The understanding of pathogenesis of OA has shifted from merely a degeneration of articular cartilage to pan-joint disease involving subchondral bone and synovium.<sup>9</sup> Recent evidence suggest that persistent low-grade systemic inflammation is an important risk factor for OA.<sup>10,11</sup>

In recent years, role of undenatured collagen type II (UC II) has been explored in management of OA. Oral administration of UC II induces oral tolerance to antigens and thereby lowers the T-cell mediated attack on the joint cartilage. It is also indicated to suppress IL-17 associated Receptor activator of nuclear factor kappa B ligand (RANKL) expression of CD4+ T cells.<sup>12,13</sup> Multiple clinical studies including randomized trials have proved the efficacy and safety of undenatured collagen in OA of knee.<sup>14,16</sup> It is available and being used in India for OA patients.

Randomized controlled trials (RCTs) are the "gold standard" for evaluating treatment outcomes providing information on treatments "efficacy". The strict and controlled conditions in which they are conducted, leads to low generalizability because they are performed in conditions very different from real life usual care. Conversely, real life studies inform on the "effectiveness" of a treatment, that is, the measure of the extent to which an intervention does what is intended to do in routine circumstances. Therefore, this non-interventional, real life multi-centre study was planned with the objective to assess the safety and effectiveness of UC II in Indian patients with OA under actual practice conditions.

## **METHODS**

The aim of the present non-interventional study was to assess the safety and effectiveness of UC II in Indian patients with OA in a 'real-life' scenario.

### **Study design**

This was an Indian multicentric non-interventional, real life study conducted by 18 orthopaedicians across India. The study was initiated on 2<sup>nd</sup> January 2017 and was completed on 15<sup>th</sup> November 2017.

### **Study population**

Two hundred and ninety-one patients, who were clinically &/or radiologically diagnosed to be suffering from knee OA and were prescribed UC II (as DUPACT<sup>®</sup> 40 mg capsules marketed by Wockhardt Ltd.) by investigating doctors were asked to participate in this study after provision of written informed consent for collecting their personal data.

### **Treatment**

Enrolled patients were prescribed with undenatured collagen type II (DUPACT<sup>®</sup>, Wockhardt Ltd., Mumbai) hard-gelatin capsules of 40 mg (which yields 1.2 mg of undenatured type 2 collagen per capsule) per day. All directions regarding general care, and concomitant medications were allowed.

### **Study visits**

All patients were assessed at baseline (visit 1) as per routine clinical practice for physical examination and baseline laboratory investigations. Activity level, diet history, medication/supplement use and medical history were recorded. OA signs and symptoms were assessed on Western Ontario McMaster Osteoarthritis Index (WOMAC) and Visual Analogue Scale (VAS) on each visit. Enrolled patients were followed-up at day 30 (visit 2), day 60 (visit 3) and day 90 (visit 4) in line with routine practice of monthly follow ups for OA knee patients.

### **Study endpoints**

At each visit, all the patients were evaluated for safety endpoints including the incidence of suspected adverse drug reaction (AR), suspected serious adverse drug reaction (SAR), significantly abnormal clinical signs and symptoms, significantly abnormal laboratory parameters observed during treatment with UC II and effectiveness endpoints including change in total WOMAC score from baseline and change in VAS score from baseline.

### **Concomitant medications**

All ongoing prescription & over-the counter medications consumed was recorded in the CRF.

### **Sample size**

A total of 291 patients were evaluated of which 226 patients completed the study.

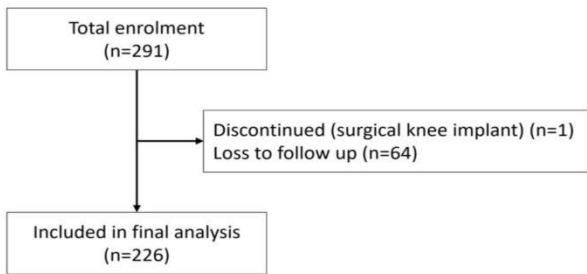
**Statistical analysis**

There was no formal sample size calculation. However, 291 evaluable patients were enrolled. The continuous data is presented as mean and standard deviation, whereas, categorical data is presented as frequency and percentage. The changes in WOMAC and VAS scores from baseline were compared by paired t-test.  $P < 0.05$  was considered statistically significant for all the comparisons.

**RESULTS**

**Patient disposition**

Total of 291 patients were enrolled in the study of which 64 patients were lost to follow-up and one patient underwent bilateral prosthetic transplant (Figure 1).



**Figure 1: Patient disposition.**

**Baseline characteristics**

The baseline characteristics of patients are shown in Table 1. Study population included equal representation of both genders with age observed to be in higher bracket of adulthood and elderly group. Mean body mass index (BMI) ranged from borderline overweight to obese in the study population.

**Table 1: Baseline characteristics (n=291).**

Parameters	Observation
<b>Age (years) (range)</b>	56.2±8.7 (28 to 79)
<b>Gender</b>	
Male (%)	136 (46.7)
Female (%)	155 (53.3)
<b>Weight (kg)</b>	69.7±9.5
<b>BMI (kg/m<sup>2</sup>)</b>	26.6±3.7

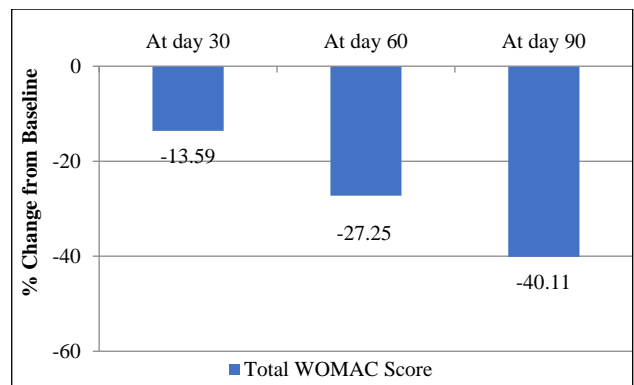
**Safety assessment**

Thirteen (4.47%) patients reported at-least one treatment emergent adverse events (TEAE). Nausea (n=4, 1.37%) and headache (n=3, 1.03%) were the most commonly observed AEs. Seven AEs were considered of moderate intensity and eight were at least considered to be related to the study medication. There were no serious AEs or AEs leading to treatment discontinuation (Table 2).

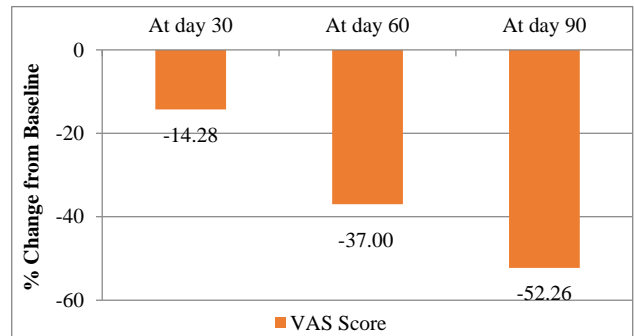
**Table 2: Safety assessment (n=291).**

Parameters	N (%)
<b>At least one TEAE</b>	13 (4.47)
<b>Nausea</b>	4 (1.37)
<b>Headache</b>	3 (1.03)
<b>Loose motion</b>	2 (0.69)
<b>Diarrhoea</b>	2 (0.69)
<b>Burning sensation in epigastrium</b>	1 (0.34)
<b>Gastritis</b>	1 (0.34)
<b>Terminated due to TEAE</b>	0 (0.00)
<b>Moderate or severe TEAE</b>	7 (2.41)
<b>At least one serious TEAE</b>	0 (0.00)
<b>At least one TEAE which is related to study medication</b>	8 (2.75)

TEAE- treatment emergent adverse event.



**Figure 2: Percentage changes in mean total WOMAC at each visit.**



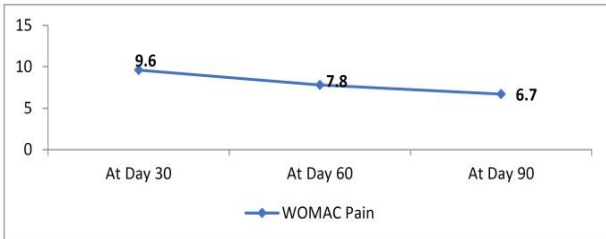
**Figure 3: Percentage changes in mean VAS scores at each visit.**

**Efficacy assessments**

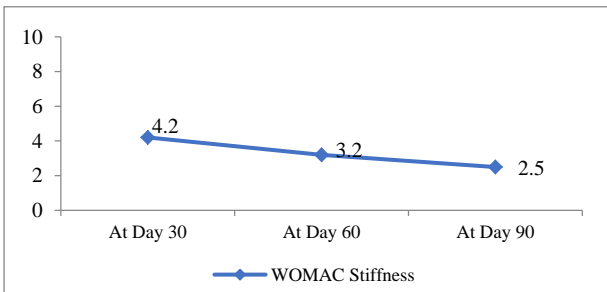
Significant reductions (Mean±SD) were observed in WOMAC and VAS scores from baseline to day 90 with mean change of  $-20.7 \pm 12.6$ , ( $p < 0.0001$ ) and  $-3.3 \pm 1.8$ , ( $p < 0.0001$ ), respectively (Table 3). Percent reduction in mean total WOMAC score and mean total VAS score also declined from day 30 to day 60 and further at day 90 as demonstrated in Figure 2 and 3. WOMAC subscales scores assessed on day 30, 60 and 90 indicated a trend of continuous decline (Figure 4a-c). Mean WOMAC-pain

score was  $9.6 \pm 3.9$  at day 30, which reduced to  $7.8 \pm 4.1$  and to  $6.7 \pm 4.9$  at day 60 and 90, respectively. WOMAC-stiffness score was  $4.2 \pm 2.2$  at day 30, which reduced to  $3.2 \pm 1.9$  at day 60 and to  $2.5 \pm 2.1$  by day 90. Physical function score reduced from  $39.2 \pm 15.4$  at day 30 to  $36.6 \pm 16.4$  at day 60 and  $33.8 \pm 17.9$  by day 90.

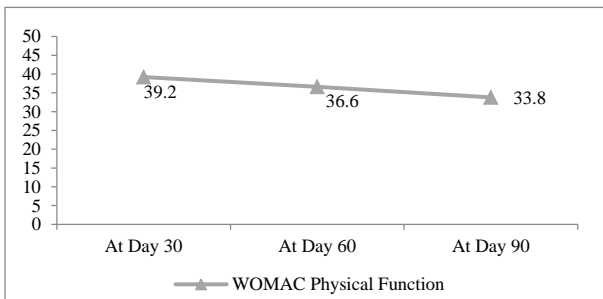
a. WOMAC - Pain



b. WOMAC - Stiffness



c. WOMAC – Physical function



**Figure 4: Changes in mean WOMAC scores (a) pain, (b) stiffness and (c) physical function at different visit.**

**Table 3: Efficacy assessment (n=226).**

Parameter	Total WOMAC score	VAS score
<b>Baseline</b>	$59.7 \pm 19.6$	$6.5 \pm 1.4$
<b>Change from baseline</b>		
<b>At day 30</b>	$-8.3 \pm 11.36$ ( $p < 0.0001$ )	$-0.9 \pm 1.14$ ( $p < 0.0001$ )
<b>At day 60</b>	$-14.8 \pm 12.9$ ( $p < 0.0001$ )	$-2.2 \pm 1.6$ ( $p < 0.0001$ )
<b>At day 90</b>	$-20.7 \pm 12.6$ ( $p < 0.0001$ )	$-3.3 \pm 1.8$ ( $p < 0.0001$ )

**DISCUSSION**

OA is major musculoskeletal disease affecting adults and elderly. The pain, restriction of joint movements and limitation of physical movements affects the quality of life of patients with OA. Despite various treatments being available to manage pain and joint stiffness, none of these have any effect on OA pathogenesis. Chronic low-grade systemic inflammation has been identified as pathogenic factor in OA.<sup>10</sup> Thus, targeting immune modulation seems effective approach to affect the OA disease course. UC II has been found to affect the disease pathogenesis by inducing the immune tolerance. Oral use of UC II with all epitopes is presented to the gut-associated lymphoid tissues and causes antigen desensitization and therefore minimizes the T-cell induced articular damage.<sup>12</sup> Modulation of immune system in such way can reduce the joint damage and thereby provide symptomatic relief.

In this real life study, we observed that most of the patients were in higher bracket of adulthood and elderly group (mean  $56.2 \pm 8.7$  years). OA may not be only restricted to this population, but may also involve young adults. Diagnosis of OA in the young group would be more challenging considering their increased threshold of bearing pain.<sup>17</sup> Age group affected also is dependent on exposure to multiple factors like injuries, occupational activities, and obesity. In general, across all ages, females are more frequently affected than males in OA.<sup>18,19</sup> However, in our study equal distribution of gender was observed in enrolled patients. This could be due to lack of awareness about medical treatment by the female counterparts in India and opting for home-made remedies to relieve the symptoms.<sup>20</sup> The BMI of study patients was in range of borderline overweight to obese suggesting association of obesity with development of OA. Obesity has been long identified risk factor for OA. But, current concept pointing to presence of low-grade systemic inflammation in obese individuals suggest that obesity’s association with OA is beyond the wear and tear causing joint damage.<sup>21</sup> Hence promotion of weight loss and modulation of inflammation should be included in treatment algorithm of OA.

Safety of UC II is well established. The incidence of at least one TEAE was seen in  $<5\%$  patients. This suggests good tolerability of UC II. Out of 291 enrolled patients, only 13 patients had TEAE during the period of 3 months. None of the patient had a serious TEAE or discontinued due to TEAE. The TEAEs reported in our study included nausea, diarrhoea, gastritis, burning in epigastrium and headache indicating gastrointestinal disturbances as commonest reason. Nausea and vomiting were the only adverse events with frequency above 1%. Seven of total 13 AEs were moderate in intensity, rest being mild. Eight of them were considered possibly related to the UC II consumption. Lugo in his evaluation of the efficacy and tolerability of UC II in knee OA found only 8 subjects reporting AEs (12.7%) during the treatment period, out of which 3 (4.76%) were related to

gastrointestinal disturbances and none were considered related to UC II consumption.<sup>15</sup> Conversely, another study by Crowley et al. reported AEs in 11.4% patients possibly related with UC II consumption with most common being constipation and headaches (intermittently) that seem to be in line with our observations.<sup>16</sup>

The Western Ontario and McMaster Universities (WOMAC) index is the most widely used outcome measure in assessment of OA. It assesses pain, joint stiffness and functional capacity of patients with OA. Use of this index has been found to be a useful screening tool in patients with OA.<sup>22</sup> Besides this, visual analogue scale (VAS) score is used to assess pain intensity in multiple disorders. We observed that there was significant reduction in WOMAC index total scores and VAS score at each visit (days 30, 60 & 90), suggesting effectiveness of UC II. A study by Crowley et al. observed similar significant reductions in WOMAC index total (at days 30, 60 & 90) and VAS score (at days 60 & 90) in patients with knee OA.<sup>16</sup> A study by Lugo compared UC II with placebo in OA and found that WOMAC index total were significantly lower in UC II group at days 60, 90, 120, 150 and 180.<sup>15</sup> In another study, Lugo et al, found that even in absence of OA, healthy individuals who had joint discomfort after physical activity, UC II improved joint movements and increased the time for pain free strenuous exercise.<sup>14</sup> Thus, UC II not only diminishes pain and joint stiffness but also seems to enhance functional mobility in patients with OA. Hence indicating that its use even in patients with mild to moderate form of OA that usually is associated with no or less pain can also be helpful. This is important factor as early use of UC II can possibly stall the disease pathogenesis of OA in a safe and effective way converse to current approach of symptomatic treatment till joint condition worsens.

## CONCLUSION

Evidence form this Indian real-life study suggests that UC II is safe and effective in treatment of OA in routine clinical practice. Its consumption is associated with reduction in pain, stiffness and improved functional mobility of patients with OA which can improve their quality of life. Given the disadvantages with long-term use of NSAIDs, UC II has potential to bridge the therapeutic gap in management of OA by providing safer therapeutic option that potentially stalls the disease pathogenesis through a unique mechanism.

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