A Breakthrough Approach to Support Joint Health

Combination of undenatured type II collagen and tetrahydro iso-alpha acids help revitalize joint function and support an active lifestyle

JOINT DISCOMFORT

According to the 2006 National Health Interview Survey (NHIS) from the Centers for Disease Control and Prevention, nearly 30% of U.S. adults reported experiencing some type of joint pain during the preceding 30 days. Knee pain was the most common (18% of respondents), followed by pain in the shoulder, finger, and hip (*Figure 1*).[1]

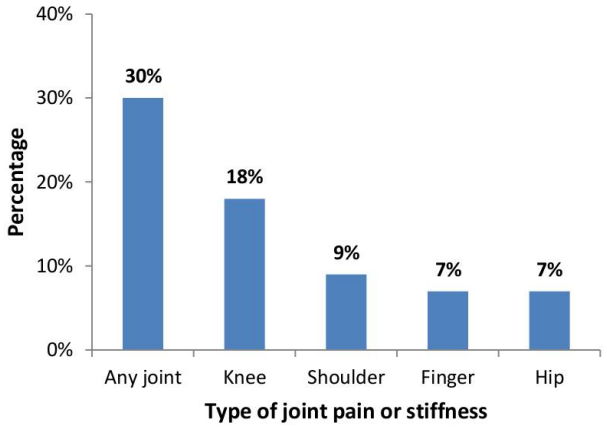


Figure 1. Percentage of U.S. adults reporting joint pain and stiffness in response to 2 questions in the 2006 NHIS: "During the past 30 days, have you had symptoms of pain, aching, or stiffness in or around a joint (exclude back or neck)?" and "Which joints are affected?"

Arthritis

Joint pain and stiffness can significantly affect the quality of day-to-day life. Many people's chronic pain is caused by arthritis (from Greek *arthro* "joint" and *itis* "inflammation"), which is the leading cause of disability in the U.S. According to the 2010-2012 NHIS, 52.5 million U.S. adults reported doctor-diagnosed arthritis, and 43.2% of them reported arthritis-attributable activity limitation.[2i] The prevalence of arthritis increases with age. Nearly half of adults aged ≥ 65 years reported having arthritis.[2]

Arthritis is not a single condition. In fact, there are more than 100 different forms of arthritis. The 2 most common types of arthritis, whose main feature is joint pain, are osteoarthritis (OA) and rheumatoid arthritis (RA).[ii] OA is a degenerative joint disease characterized by active bone remodeling, articular cartilage degradation, and synovial inflammation resulting in loss of joint function and angular deformity or malalignment.[3] In the U.S., nearly 27 million adults are affected by OA.[4] RA is a chronic, systemic autoimmune disease characterized by symmetric inflammation of synovial joints leading to progressive erosion of cartilage and bone.[5] Approximately 1.3 million U.S. adults are affected by RA.[6] Although OA and RA are defined and diagnosed differently, there are similarities in symptoms (e.g., joint pain and cartilage destruction), and recent research has found common underlying causes contributing to the pathogenesis of both conditions.

Immune response, synovial inflammation, and chondrocyte pathophysiology

The synovial membrane, also referred to as the synovium, is the soft tissue found between the joint capsule and the joint cavity of diarthrodial (freely movable) joints. It secretes lubricant called synovial fluid into the joint cavity to reduce friction and absorb shock between the articular cartilage of joints during movement.[7] Articular cartilage is populated exclusively by chondrocytes (from Greek *chondros* "cartilage" and *kytos* "cell") whose main function is to maintain the cartilage. Under normal physiological conditions, chondrocytes are quiescent with low turnover rate.

Under mechanical stress or chronic wear and tear, degraded cartilage fragments fall into the joint space. Upon contact, the synovial membrane treats the fragments as foreign bodies and triggers the innate immune response via pattern-recognition receptors known as Toll-like receptors.[8] It leads to activation of specific transcription factors—mainly NF-κB—resulting in production of pro-inflammatory mediators including

[i] Adults were defined as having doctor-diagnosed arthritis if they answer "yes" to "Have you ever been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?" Those who responded "yes" were also asked, "Are you now limited in any way in any of your usual activities because of arthritis or joint symptoms?" Those responding "yes" to both questions were categorized as having arthritis-attributable activity limitation.

[ii] Other types of arthritis whose primary feature is joint pain include gout, pseudo-gout, septic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, Still's disease, etc. These types of arthritis are beyond the scope of this research review.

cytokines and chemokines (e.g. IL-1, TNF-α).[8] Chondrocytes respond to the inflammatory environment and participate in the catabolic activities by producing metalloproteinases (MMPs) that cleave type II collagen (the major structural component of the articular cartilage), contributing to the degradation of cartilaginous matrix components.[9] Evidence also indicates that chondrocytes themselves exhibit elevated activities of NF-κB[10] and become the source of pro-inflammatory cytokines which increase tissue breakdown and suppress repair processes, amplifying further cartilage destruction.[11]

The inflamed synovial membrane and the innate immune response also recruit and activate macrophages, granulocytes, and lymphocytes (although the number of infiltrating immune cells is higher in RA than in OA).[12] As a result, several cytokines are produced, perpetuating a vicious cycle.

Not only does local synovial inflammation contribute to the development of arthritis, systemic inflammation also has an important role in either initiating or aggravating arthritis. For instance, elevated proinflammatory adipokines in circulation due to excess of central adiposity (as seen in metabolic syndrome and obesity) have been shown to mediate synovial tissue inflammation,[13,14] and many studies have found that the prevalence of metabolic syndrome or obesity is associated with higher incidence (and severity) of arthritis (OA or RA).[15-19]

Therapeutic options have long-term side effects

Currently there is no cure for arthritis. The most important benefit a patient seeks from medications is reducing pain in order to resume normal daily activities.[20] Though there are many palliative medications, nearly all have unwanted side effects (*Table 1*).[21,22] Even the most commonly used class, nonsteroidal anti-inflammatory drugs (NSAIDs), have serious health consequences when used long-term.[23]

Table 1. **Common Medications for Relieving Arthritis Symptoms**

	Class	Common side effects
OA	NSAIDs	Gastrointestinal toxicity (bleeding, ulcer, perforation), cardiovascular or cerebrovascular events (myocardial infarction, heart failure, stroke), and renal toxicity
	Acetaminophen	Hepatotoxicity (acute liver failure)
	Narcotics	Delirium, dependence, injuries (falls and fractures)
RA	NSAIDs	See above
	Steroids	Cataracts, weight gain, diabetes, osteoporosis
	Disease-modifying antirheumatic drugs (DMARDs)	Hepatotoxicity, bone marrow suppression, severe lung infections
	Immunosuppressants	Susceptibility to infection
	TNF-α inhibitors	Nausea, diarrhea, hair loss, risk of serious infections

Without targeting underlying causes, arthritis condition will only worsen. Once the first-line agents become ineffective, patients will have to move on to those with even more serious side effects. Therefore, newer and safer management approaches are needed.

UNDENATURED TYPE II COLLAGEN

Type II collagen is the major protein in articular cartilage. Because RA is classified as an autoimmune disease in which the immune system treats fragmented type II collagens in the joint as foreign bodies (antigens) and triggers an immune response leading to inflammation and cartilage degradation, researchers have been interested in preventing disease development by reducing specific antigenic responsiveness.

Oral tolerance

Undenatured type II collagen is a dietary ingredient derived from chicken sternum cartilage. Early experimental studies have confirmed that oral administration of undenatured type II collagen ameliorated RA in animal models.[24,25] Researchers believed that it worked through the mechanism of oral tolerance.[26] The concept of oral tolerance—the ability to induce antigen-specific peripheral immune tolerance by

oral administration of antigens—has been recognized for some time.[27] As orally ingested undenatured type II collagen reaches the small intestine, it interacts with gut associated lymphoid tissue (GALT), the gastrointestinal tract's immune system. Within GALT are aggregates of lymph tissue named Peyer's Patches where immune responses are generated.[28] In response to the presence of undenatured type II collagen, regulatory T cells in Peyer's Patches become activated and produce anti-inflammatory cytokines IL-4, IL-10, and transforming growth factor β (TGF-β), which help turn off T-cell attack on type II joint collagen, thereby reducing pain and inflammation.[29,30] Also, these inhibitory cytokines are important in restoring the cytokine balance and in shifting chondrocyte metabolism toward extracellular matrix replenishment.[31-33]

Denatured vs. undenatured collagen

Undenatured type II collagen retains its original triple-helical form and high molecular weight, making it resistant to digestion and absorption.[26] Its correct 3-dimensional structure is essential for the interaction with Peyer's Patches and the development of oral tolerance. In contrast, the denatured (or hydrolyzed) form of type II collagen no longer retains the tertiary structures, does not induce immunological hyporesponsiveness, and has not demonstrated an effect on reducing pain and inflammation.[24]

Clinical trials in RA

Oral administration of undenatured type II collagen ameliorated animal models of RA. Subsequently, open-label pilot studies and randomized controlled trials (RCTs) in RA patients were conducted in the 1990s, all demonstrating significant benefits without adverse events (*Table 2*).[34-36]

In the 1990s when undenatured type II collagen was evaluated for its efficacy in RA, OA was still viewed as an aging condition due to mechanical wear and tear to the joint. Today researchers have realized that synovial inflammation and the immune system are important factors in the development and progression of both OA and RA, although the number of infiltrating immune cells and the expression of proinflammatory cytokines are higher in RA than in OA synovial tissue.[12] This leads to the rationale that undenatured type II collagen may be effective in ameliorating OA as well.

Table 2. **Summary of Clinical Trials that Evaluated the Efficacy of Undenatured Type II Collagen in RA Patients**

Study	Dosage	Main results
Open-label pilot; 10 RA patients[36]	0.1 mg for 1 month and then 0.5 mg for 2 months	Substantial improvement in swollen and tender joint counts and other disease measures in 6 of the 10 subjects
RCT; 60 RA patients[36]	0.1 mg for 1 month and then 0.5 mg for 2 months	Significant improvements in symptoms in the treatment group compared with the placebo group
Open-label pilot; 10 juvenile RA patients[34]	0.1 mg for 1 month and then 0.5 mg for 2 months	Reductions in both swollen and tender joint counts in 8 of the 10 subjects
Multicenter RCT; 274 patients with RA[35]	0.02, 0.1, 0.5, or 2.5 mg/d for 24 weeks	39% of those receiving treatment vs. 19% taking placebo experienced significant improvement

Clinical trials in OA

The first RCT by Crowley et al. evaluated the safety and efficacy of undenatured type II collagen as compared to a combination of glucosamine and chondroitin—the 2 most commonly used neutraceuticals to alleviate pain associated with arthritis—in the treatment of OA of the knee.[37] A total of 52 subjects were randomly assigned to receive 40 mg/day UC-II® (a natural collagen concentrate derived from chicken sternum cartilage containing 25% undenatured type II collagen) or 1500 mg/day glucosamine HCl plus 1200 mg/day chondroitin sulfate for 90 days. The results indicate that UC-II treatment resulted in a significant reduction in all assessments from the baseline at 90 days, whereas this effect was not observed in glucosamine plus chondroitin group (*Figure 2*).

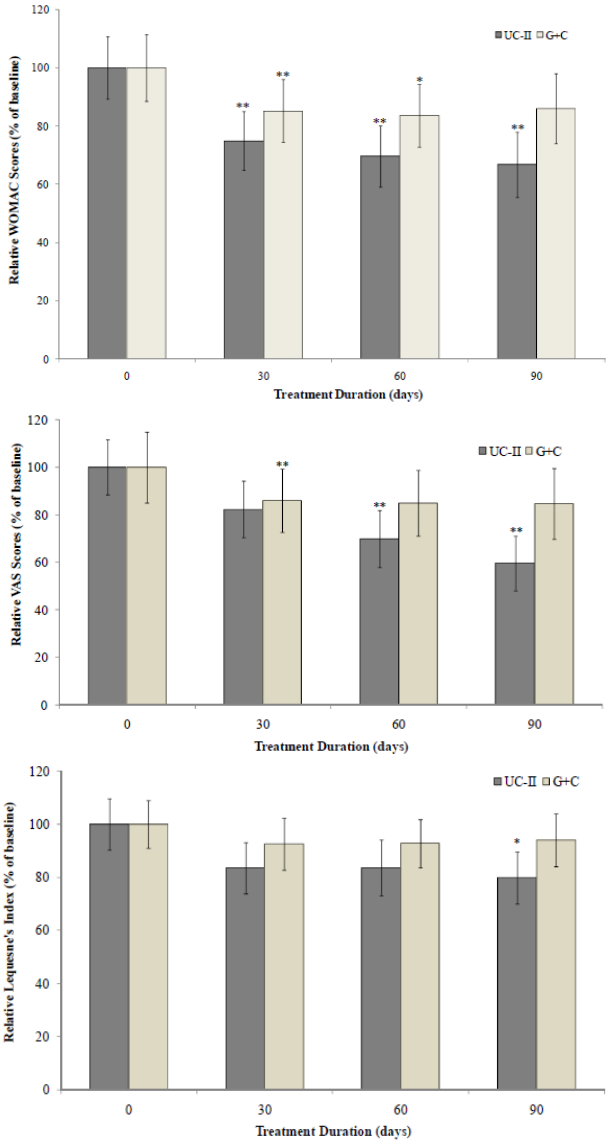


Figure 2. Changes in WOMAC scores (assessing physical function, stiffness, and pain in the knee), VAS scores (assessing general level of moving and resting pain), and Lequesne functional index (assessing pain, maximum walking distance, and some activities of daily living) at Day 90 from baseline. Values are mean ± SEM. *P<0.05, **P<0.005 indicate significantly different from baseline.

The second RCT by Lugo et al. was conducted in 55 healthy subjects who experienced joint discomfort within 10 minutes of physical activity. Subjects were randomized to receive 40 mg/day UC-II or placebo for 120 days.[38] At the end of the trial, the UC-II group exhibited a statistically significant improvement in average knee extension compared with placebo group. Compared with baseline, the UC-II cohort showed significant change in knee extension at day 90, and exercised longer before experiencing any initial joint discomfort at day 120 (*Figure 3*).

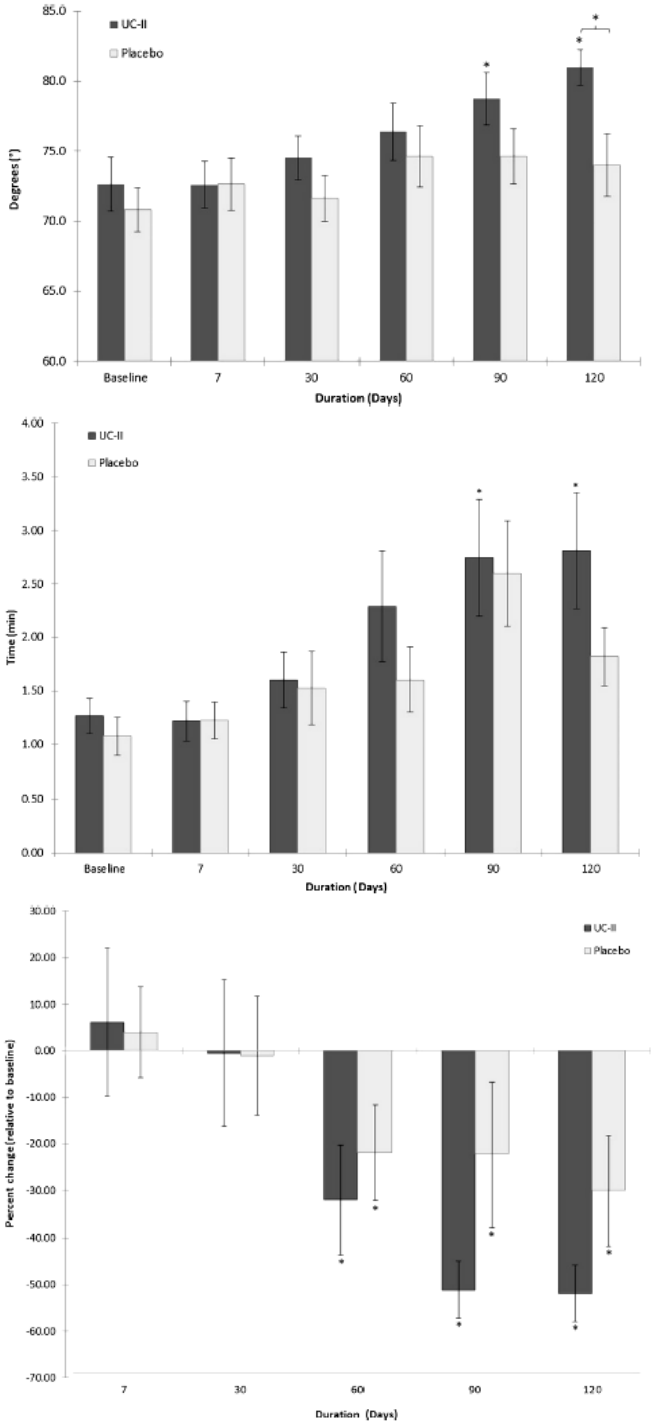
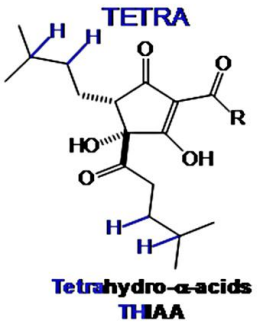


Figure 3. Knee extension, minimum time to onset of joint discomfort, and percent change in time to complete recovery from pain in UC-II group and placebo group. Values are mean ± SEM. *P<0.05.

TETRAHYDRO ISO-ALPHA ACIDS (THIAA)

Humulus lupulus L. (hops), a plant that has been used for medicinal purposes for centuries and is currently widely used in the brewing industry, contains several classes of compounds with various biological activities. A modified hops extract that contains reduced iso-alpha acids has demonstrated anti-inflammatory potential by inhibiting lipopolysaccharide-stimulated prostaglandin E_2 (PGE_2) production in RAW 264.7 macrophages.[39] Among the reduced iso-alpha acid families, tetrahydro iso-alpha acids (THIAA) possess the most potent anti-inflammatory activity in vitro.[40] THIAA are a mixture of 3 major (co-, n-, and ad-) related compounds that share a similar chemical structure (i.e., congeners).[40]

In vitro research has shown that THIAA inhibit IL-1β-activated PGE_2, MMP-3, IL-6, IL-8, and monocyte chemotactic protein 1 (MCP-1) in human RA synovial fibroblasts.[41] In vivo research has shown that THIAA reduce paw swelling in a mouse model of acute inflammation; the effect is similar to that of aspirin. Also, in a mouse model of RA, THIAA significantly reduce the arthritis index (a standardized score reflecting the severity of arthritis; *Figure 4*) and decrease bone, joint, and cartilage degradation; serum concentrations of the IL-6 in these mice are inhibited in a dose-dependent manner.[41]



analog	R	MW
n-		366
ad-		366
co-		352

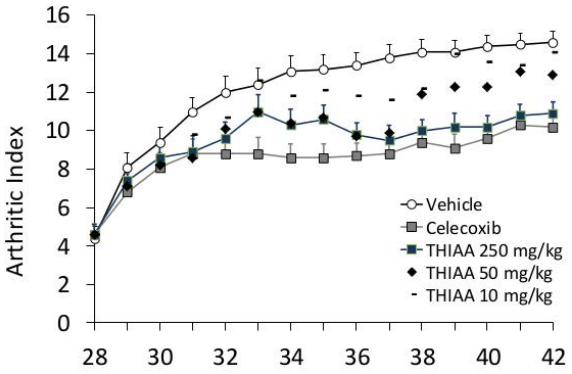


Figure 4. Effects of THIAA on the inhibition of arthritis index in a mouse model of RA. RA was induced and developed in mice by day 28. Treatments were initiated and continued from day 28 to 42. Values are mean ± SEM.

Mechanistically, THIAA target inflammatory signal transduction by modulating multiple kinases involved in the NF-κB pathway without affecting constitutive COX-2 enzymes.[40] This tissue specific inhibition should reduce PG up-regulation in inflamed tissues without affecting constitutively produced COX-2 and PGs in non-target tissues, thus minimize potential side effects, such as gastrointestinal toxicity.

FMRC CLINICAL EXPERIENCES: CASE SERIES

Through different mechanisms of action, undenatured type II collagen and THIAA together may form a unique approach in managing arthritis and joint discomfort. An open-label case series was devised to evaluate the efficacy and safety of this combination formula at the Functional Medicine Research Center® (FMRC; Gig Harbor, WA), the clinical research facility at Metagenics. Eligible subjects were adults with arthritis, including symptomatic OA involving any joint or combination of joints and RA. Each received 20 mg undenatured type II collagen as UC-II and 300 mg THIAA twice daily for 12 weeks. At each clinic visit, subjects completed a series of quality-of-life and arthritis-related questionnaires[iii] including:

- VAS-P: Visual Analog Scale for Pain
- MSQ: Medical Symptoms Questionnaire, including joint/muscle score and total score
- MOS-SF36: Health and Wellness Outcome Questionnaire, including physical component and mental component
- AIQ: Arthritis Impact Questionnaire, including arthritis symptoms score and daily living score
- HAQ-DI: Health Assessment Questionnaire; Q26 indicates overall pain over previous week
- AIMS2: Arthritis Impact Measurement Scales 2

At 12 weeks, each subject also rated product efficacy using VAS-E: Visual Analog Scale for Efficacy.[iv] Analgesic use by subjects at baseline and at 12 weeks was also recorded. Two sided paired t-tests were used to compare each subsequent clinic visit with baseline. Data are expressed as mean ± SE.

[iii] For VAS-P, MSQ joint/muscle, MSQ total, AIQ daily, HAQ-DI;Q26, and AIMS2, reduced score indicates improvement. For MOS-SF36 physical, MOS-SF36 mental, and AIQ arthritis, increased score indicates improvement.

[iv] For VAS-E, 0 indicates no efficacy whereas 10 indicates highest efficacy.

Results

Seventeen consecutive Caucasian subjects (12 women and 5 men), ranging in age from 39 to 69 presented with joint pain presumably due to OA. Four of the subjects also had RA. Joint symptoms had been present from 9 months to 30 years. All subjects were followed for 12 weeks. Analyses were done on the entire dataset of 17 subjects (OA + RA) and on the dataset of 13 subjects with only OA.

OA + RA combined data (N=17)

Among subjects with any arthritis, significant improvements compared with baseline were observed in every questionnaire measured. Statistically significant improvements began at 4 weeks for VAS-P score, and at 2 weeks for MSQ joint/muscle and MSQ total scores (*Figure 5A*).

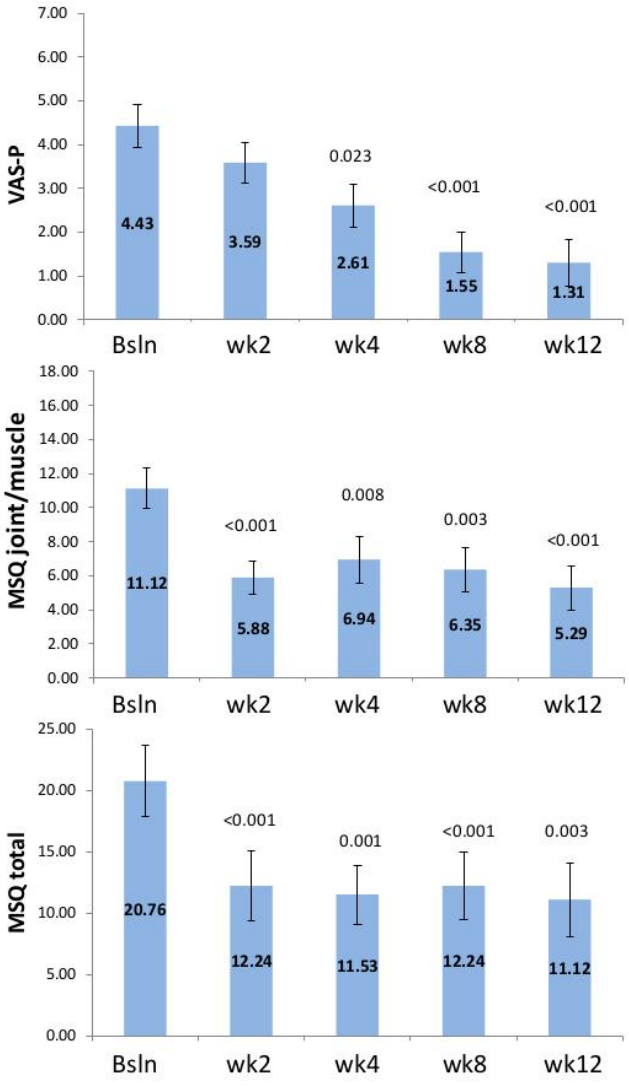


Figure 5A. Changes in VAS-P, MSQ joint/muscle, and MSQ total scores from baseline to 12 weeks among 17 subjects with arthritis.

OA + RA combined data (N=17)

Statistically significant improvements began at 8 weeks for AIQ arthritis score, at 12 weeks for MOS-SF36 mental score, and at 4 weeks for MOS-SF36 physical score (*Figure 5B*).

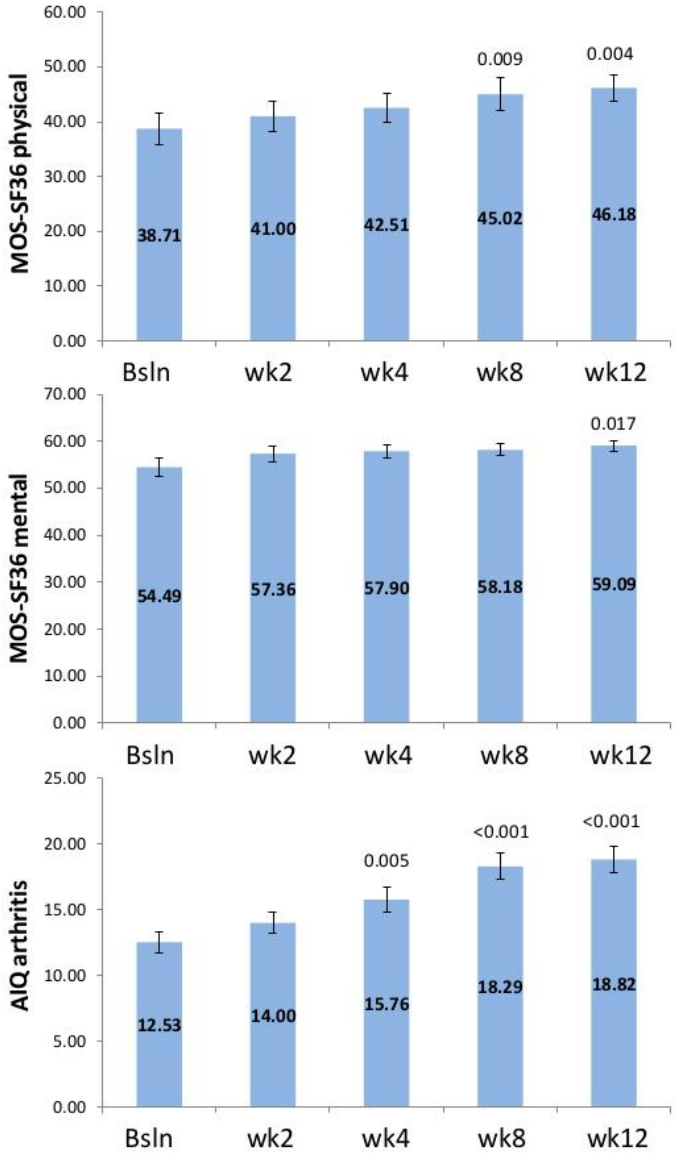


Figure 5B. Changes in MOS-SF36 physical, MOS-SF36 mental, and AIQ arthritis scores from baseline to 12 weeks among 17 subjects with arthritis.

OA + RA combined data (N=17)

Statistically significant improvements began at 2 weeks for AIMS2 and HAQ-DI;Q26 scores, and at 4 weeks for AIQ daily score (*Figure 5C*).

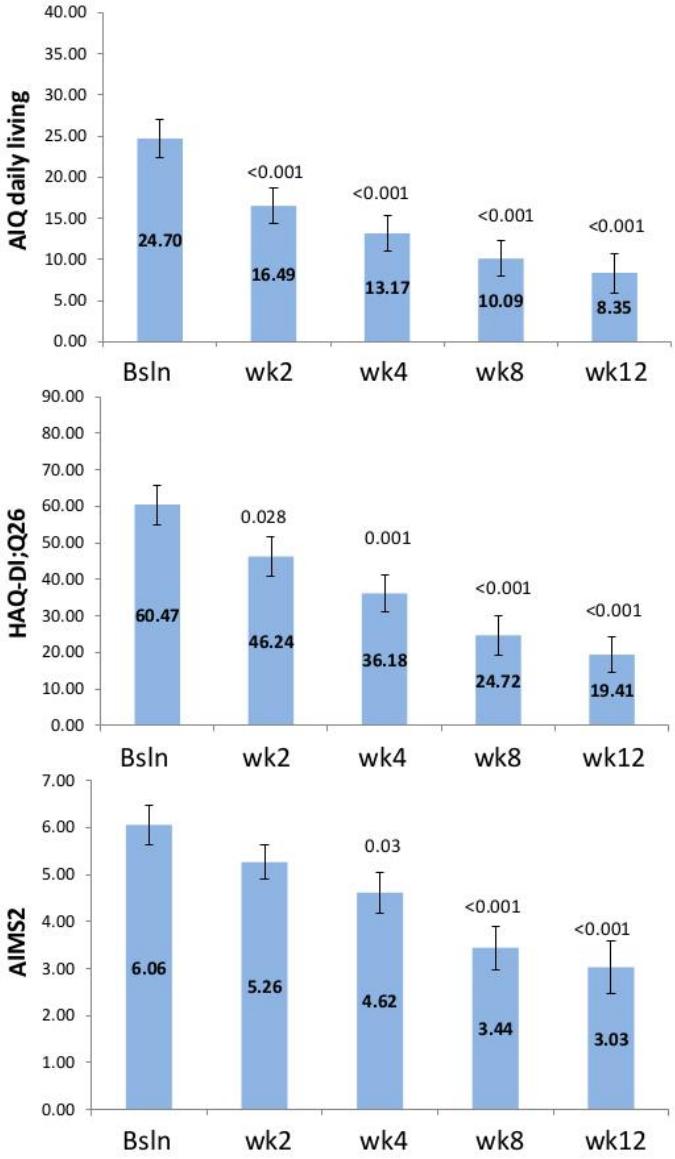


Figure 5C. Changes in AIQ daily living, HAQ-DI;Q26, and AIMS2 scores from baseline to 12 weeks among 17 subjects with arthritis.

At 12 weeks, subjects rated product efficacy at 7.8 ± 0.47 out of 10. At baseline, 13 of 17 subjects were using analgesics for joint pain. At 12 weeks, only 4 subjects were using analgesics for joint pain; 2 of the 4 had reduced the dosage of analgesics.

OA data (N=13)

Among subjects with OA, significant improvements compared with baseline were observed in every questionnaire measured. Statistically significant improvements began at 8 weeks for VAS-P score and at 2 weeks for MSQ joint/muscle and MSQ total scores (*Figure 6A*).

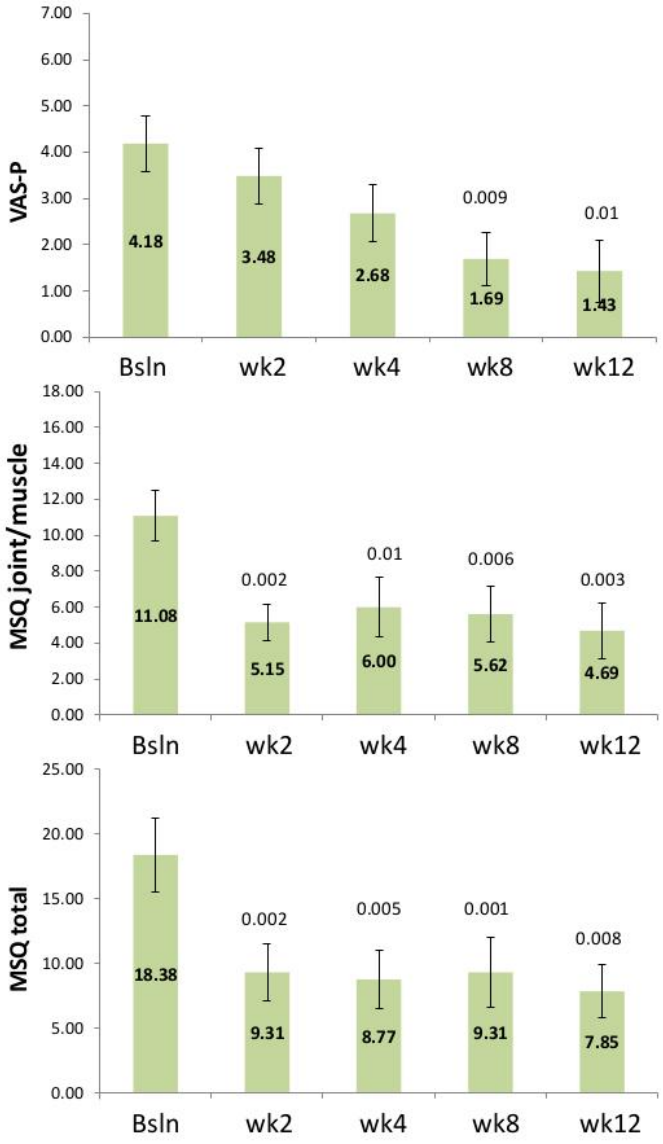


Figure 6A. Changes in VAS-P, MSQ joint/muscle, and MSQ total scores from baseline to 12 weeks among 13 subjects with OA.

OA data (N=13)

Statistically significant improvements began at 8 weeks for AIQ arthritis and MOS-SF36 mental scores, and at 4 weeks for MOS-SF36 physical score (*Figure 6B*).

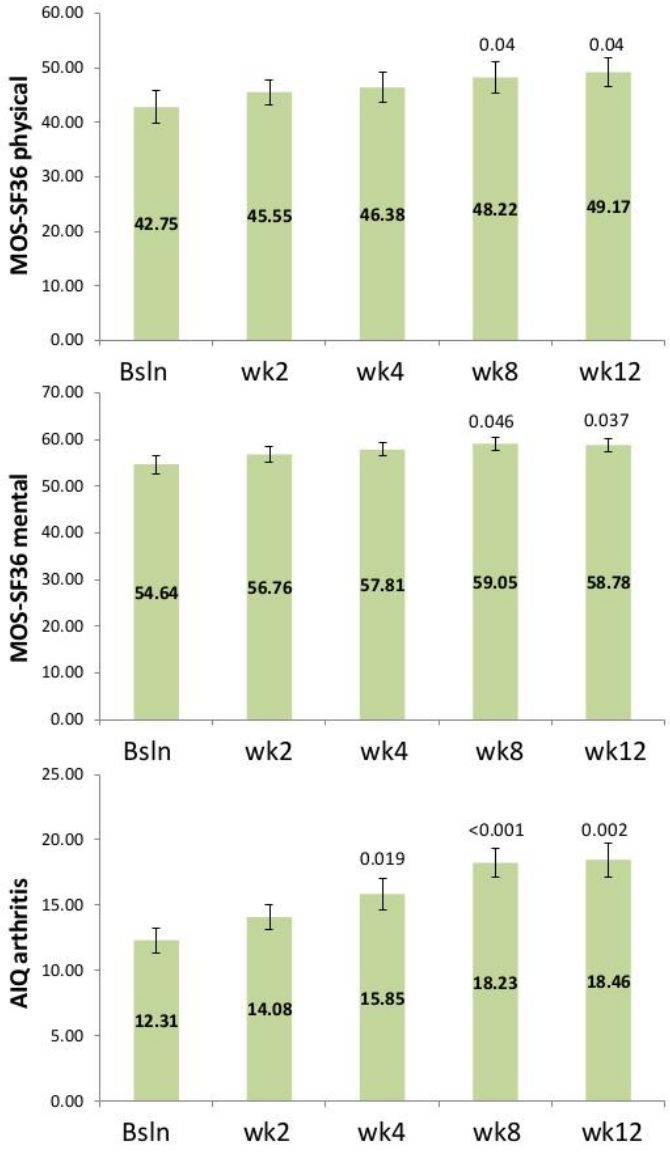


*Figure 6B***.** Changes in MOS-SF36 physical, MOS-SF36 mental, and AIQ arthritis scores from baseline to 12 weeks among 13 subjects with OA.

OA data (N=13)

Statistically significant improvements began at 2 weeks for AIMS2 score, at 4 weeks for HAQ-DI;Q26 score, and at 8 weeks for AIQ daily score (*Figure 6C*).

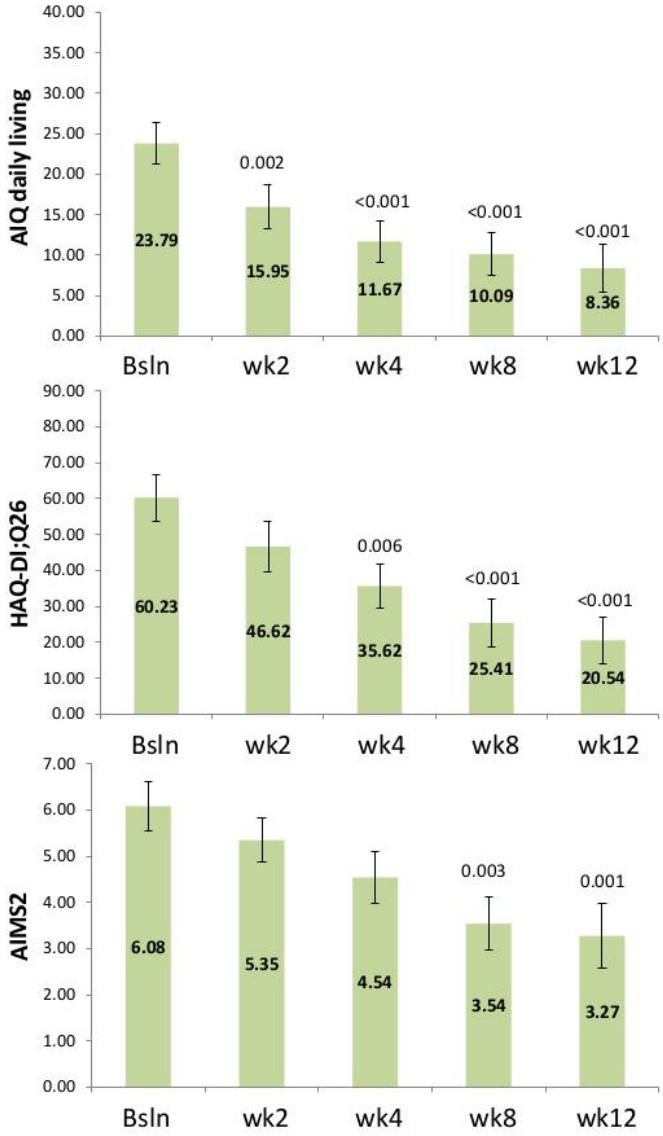


Figure 6C. Changes in AIQ daily living, HAQ-DI;Q26, and AIMS2 scores from baseline to 12 weeks among 13 subjects with OA.

At 12 weeks, subjects rated product efficacy at 7.6 ± 0.59 out of 10. At baseline, 10 of 13 subjects were using analgesics for joint pain. At 12 weeks, only 3 subjects were using analgesics for joint pain; 1 of the 3 had reduced the dosage of analgesics.

RA data (N=4)

Due to limited sample size (N=4), no statistical analyses were performed in RA subjects. There was an indication toward improvement (a decrease in score) in VAS-P score over the study period (*Figure 7A*).

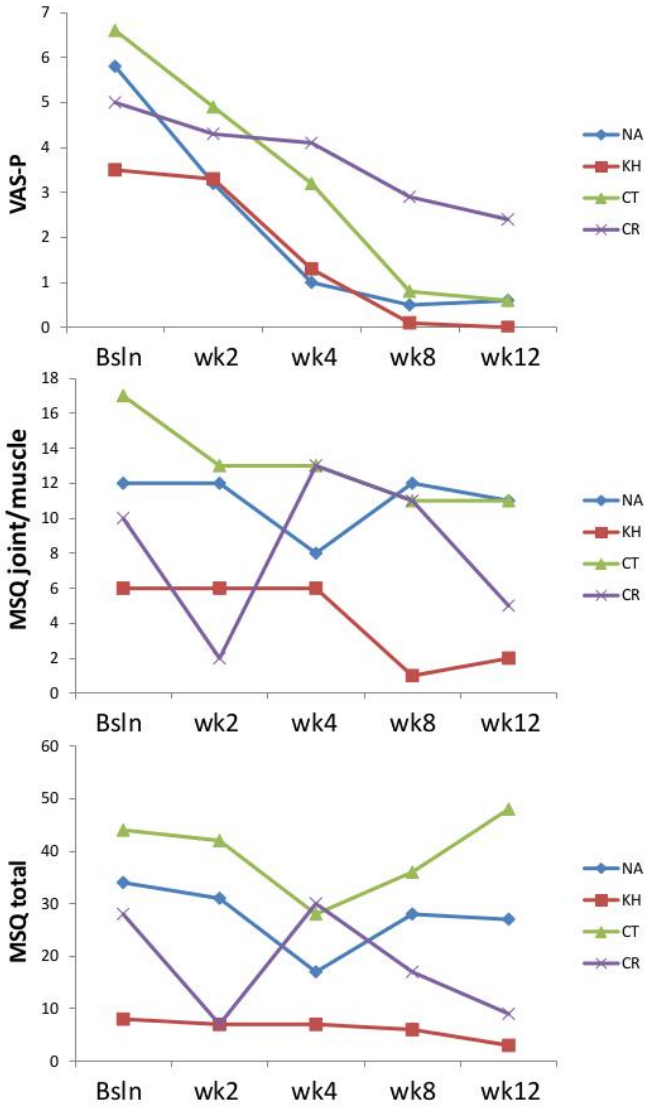


Figure 7A. Changes in VAS-P, MSQ joint/muscle, and MSQ total scores from baseline to 12 weeks in subjects with RA. (Each line represents 1 subject; letters in figure legends are the initials of subjects.)

RA data (N=4)

There appeared to be a trend toward improvement (an increase in score) in AIQ arthritis and MOS-SF36 physical scores over the study period (*Figure 7B*).

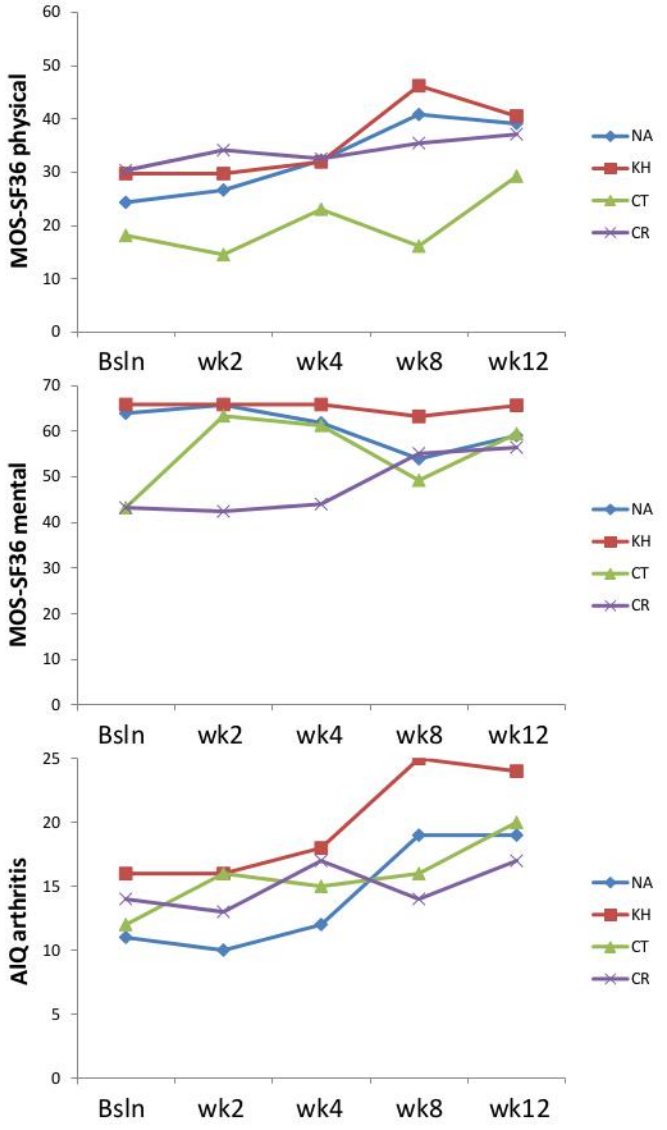


Figure 7B. Changes in MOS-SF36 physical, MOS-SF36 mental, and AIQ arthritis scores from baseline to 12 weeks in subjects with RA. (Each line represents 1 subject; letters in figure legends are the initials of subjects.)

RA data (N=4)

There appeared to be a trend toward improvement (a reduction in score) in AIMS2, HAQ-DI;Q26, and AIQ daily scores over the study period (*Figure 7C*).

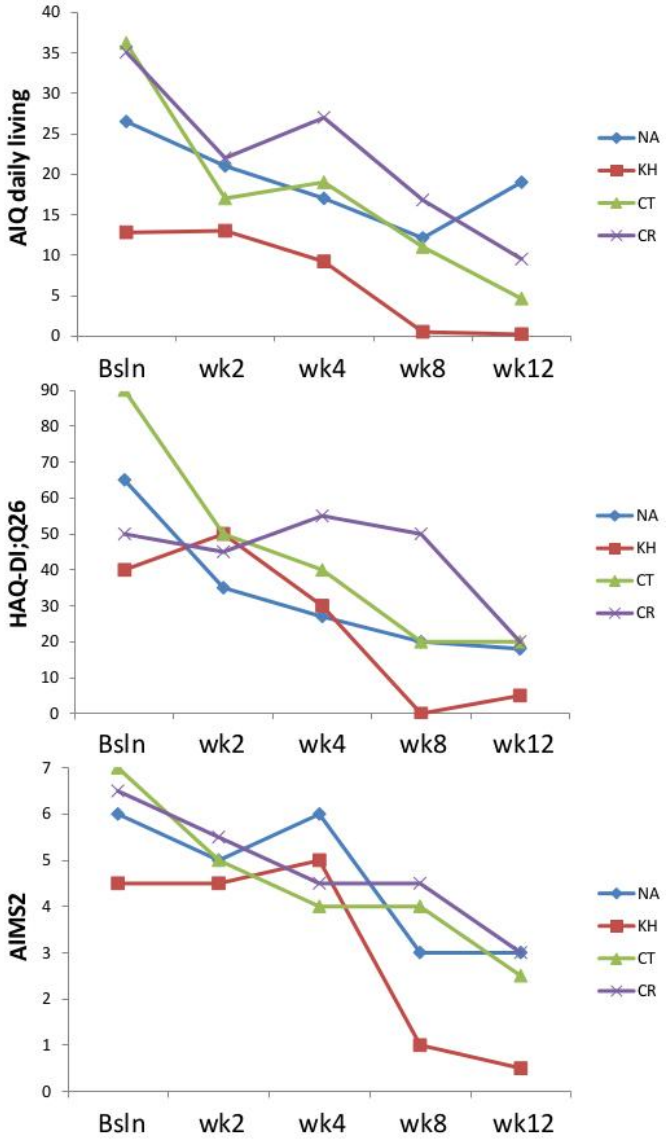


Figure 7C. Changes in AIQ daily living, HAQ-DI;Q26, and AIMS2 scores from baseline to 12 weeks in subjects with RA. (Each line represents 1 subject; letters in figure legends are the initials of subjects).

Serious adverse events

The UC-II and THIAA combination was well tolerated and no serious adverse events occurred during the course of 12 weeks.

Conclusion

The FMRC case series demonstrates that a UC-II and THIAA combination is safe and efficacious in the short-term management of a small group of subjects with arthritis with improvement in most subjects experienced as early as 2 weeks.

SUMMARY

Undenatured type II collagen has been shown to induce immune hyporesponsiveness that down-regulates a wide range of immunologic and proinflammatory activities in the joint, effectively ameliorating joint pain and swelling in subjects affected by RA. Undenatured type II collagen as UC-II® has been shown to improve symptoms and quality of life in subjects affected by OA, and improve knee joint extension and alleviate joint discomfort in healthy subjects who experienced joint pain due to exercise. In experimental studies, THIAA inhibit various markers of inflammation via modulating multiple kinases involved in the NF-κB pathway. In a mouse model of RA, THIAA reduce bone, joint, and cartilage degradation. In the FMRC case series, subjects affected by arthritis received UC-II and THIAA and experienced improvements as early as 2 weeks. Through different mechanisms of action, these 2 ingredients form a unique and safe approach in managing arthritis and joint discomfort.

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