PHYTOTHERAPY RESEARCH
Phytother. Res. (2012)
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/ptr.4639

A Randomized, Pilot Study to Assess the Efficacy and Safety of Curcumin in Patients with Active Rheumatoid Arthritis

Binu Chandran[1] and Ajay Goel[2]*

[1]Nirmala Medical Centre, Muvattupuzha, Kerala, India
[2]Baylor Research Institute and Sammons Cancer Center, Baylor University Medical Center, Dallas, TX, USA

Curcumin is known to possess potent antiinflammatory and antiarthritic properties. This pilot clinical study evaluated the safety and effectiveness of curcumin alone, and in combination with diclofenac sodium in patients with active rheumatoid arthritis (RA). Forty-five patients diagnosed with RA were randomized into three groups with patients receiving curcumin (500 mg) and diclofenac sodium (50 mg) alone or their combination. The primary endpoints were reduction in Disease Activity Score (DAS) 28. The secondary endpoints included American College of Rheumatology (ACR) criteria for reduction in tenderness and swelling of joint scores. Patients in all three treatment groups showed statistically significant changes in their DAS scores. Interestingly, the curcumin group showed the highest percentage of improvement in overall DAS and ACR scores (ACR 20, 50 and 70) and these scores were significantly better than the patients in the diclofenac sodium group. More importantly, curcumin treatment was found to be safe and did not relate with any adverse events. Our study provides the first evidence for the safety and superiority of curcumin treatment in patients with active RA, and highlights the need for future large-scale trials to validate these findings in patients with RA and other arthritic conditions.

Keywords: curcumin; diclofenac sodium; Disease Activity Score; American College of Rheumatology criteria.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that primarily affects various body joints and causes progressive destruction of articular structures, particularly, the cartilage and bone. Notably, the *joint destruction* is a prominent feature of the disease that not only distinguishes RA from other arthritic diseases but also determines its outcome in the majority of individuals affected (Shiozawa and Tsumiyama, 2009). The long-term prognosis of RA is poor with as much as 80% of patients affected becoming disabled after 20 yr and a concomitant reduction in life expectancy by an average of 3–18 yr. If the disease remains untreated, 20–30% of patients may become permanently work-disabled within 2–3 yr of diagnosis. Predictors of poor outcome for RA include relatively low functional disease activity scores early in the disease progression, lower socio-economic status and education level, strong family history of the disease, and early involvement of many joints (Rindfleisch and Muller, 2005; Schmajuk *et al*., 2011). Thirty per cent of the patients with severe forms of the disease typically remain unresponsive to any classic treatment intervention. Nonetheless, patients with milder forms of the disease may derive some level of benefit from early diagnosis and treatment (Breedveld, 2011).

Pharmacotherapy for rheumatoid arthritis generally involves treatment regimens including non-steroidal antiinflammatory drugs (NSAIDs) for the pain management, low-dose therapy using oral or intraarticular glucocorticoids, disease-modifying antirheumatic drugs (DMARD) and the newer biological treatments (Rindfleisch and Muller, 2005; Marks, 2011). Unfortunately, the majority of these drugs typically associate with severe side effects including gastrointestinal bleeding, increased blood pressure, accelerated osteoporosis, myelosuppression, hepatotoxicity, ocular toxicity, hypersensitivity and allergic reactions, as well as increased risk of infections (Lipsky *et al*., 2000; Newsome, 2002; Rahme and Bernatsky, 2010). Diclofenac belongs to the NSAID class of drugs and is used to relieve pain, tenderness, swelling and stiffness caused by osteoarthritis, rheumatoid arthritis and ankylosing spondylitis (Altman *et al*., 2009; Ruff *et al*., 2011). Since this drug constitutes the current standard of care for managing patients with RA, we selected diclofenac sodium as a reference drug for evaluating and comparing its efficacy with curcumin in RA patients in this study (Ruff *et al*., 2011).

Curcumin is the active component of the common spice turmeric, and exerts a wide spectrum of biological activities by modulating several transcription factors and signalling pathways (Aggarwal *et al*., 2007; Goel *et al*., 2008a,b). It possesses several functional groups that exhibit antioxidant activity (Goel *et al*., 2008a; Goel and Aggarwal, 2010), which permits curcumin to modulate redox-signalling pathways in cells. Curcumin can also activate the intracellular antioxidant defence system through stimulation of nuclear factor-erythroid-2-

* Correspondence to: A. Goel, Gastrointestinal Cancer Research Laboratory, Baylor University Medical Center, 3500 Gaston Avenue, Suite H-250, Dallas, TX 75246, USA.
E-mail: ajay.goel@baylorhealth.edu

Received 14 October 2011
Revised 13 January 2012
Accepted 23 January 2012

related factor 2 (Nrf2), a transcription factor which binds to the antioxidant response element (ARE) in the regulatory region of several genes that code for intracellular antioxidants, cytoprotective and detoxification proteins (Scapagnini *et al*., 2011). Curcumin is a potent and established antiinflammatory dietary botanical component that inhibits all mediators of the inflammatory response such as cytokines, chemokines, adhesion molecules and growth factors, as well as other mediators such as cyclooxygenase-2, inducible nitric oxide, tissue factor and epigenetic alterations (Goel *et al*., 2001, 2008b; Reuter *et al*., 2011). These effects of curcumin are due to its ability to inhibit the NF-κB pathway and other proinflammatory signalling pathways including COX-2, AP-1, Egr-1, STAT (signal transducers and activators of transcription) members and mitogen-activated protein (MAP) kinases. Curcumin is both a chemopreventive and an anticancer agent (Aggarwal and Shishodia, 2006; Aggarwal *et al*., 2007). It inhibits cell proliferation, induces apoptosis and growth arrest in different phases of the cell cycle (depending on the cell type) and inhibits angiogenesis (Shishodia *et al*., 2007). Curcumin is able to exert such effects due to its ability to act on multiple targets and at multiple levels invoking several mechanisms, including activation of peroxisomal proliferator activated receptor gamma (PPARγ), degradation of p53, activation of proapoptotic genes (including caspases, Bax and Bak family members), down-regulating survival genes (e.g. Bcl-2) (Bhattacharyya *et al*., 2007; Shankar and Srivastava, 2007; Goel *et al*., 2008a,b). Owing to such multiple activities curcumin is currently being evaluated in several human clinical trials for several diseases, including cardiovascular diseases, type 2 diabetes, Alzheimer's disease, rheumatoid arthritis, multiple sclerosis and a variety of human cancers. In view of the overwhelming literature and promise for the potential benefits of curcumin-induced chemoprevention and treatment of several human diseases, the current study was a pilot effort to assess the efficacy and safety of curcumin compared with diclofenac sodium, and curcumin in combination with diclofenac sodium for 8 weeks in patients with mild to moderate rheumatoid arthritis.

MATERIALS AND METHODS

Patient characteristics: inclusion and exclusion criteria. The present study was conducted at Nirmala Medical Centre in Muvattupuzha, Kerala, India. Forty-five patients (38 female, 7 male; mean age 47.88 yr) with active RA were prospectively enrolled in this clinical trial. The clinical trial registration number is BCM HS 01–2008. Eligible patients were of 18–65 yr of age, and were diagnosed to have RA according to the revised 1987 American College of Rheumatology (ACR) criteria (with RA functional class I or II) and Disease Activity Score (DAS) > 5.1.

The exclusion criteria included patients with any of the several conditions listed as follows; concurrent treatment with any NSAID, DMARD or any anti-TNF-α therapy or other antiarthritic therapy, treatment with any investigational agent within 4 weeks of screening and intraarticular or parenteral corticosteroids within 4 weeks prior to the screening visit. Other criteria for exclusion were as follows: haemoglobin < 6.2 mmol/L (9.9 g/dL); neutrophil count $< 2 \times 10^9$/L; serum creatinine > 1.4 mg/dL for women or 1.6 mg/dL for men; aspartate transaminase (AST) or alanine transaminase (ALT) > 2.5 times the upper limit of normal; platelet count < 100000/μL; bone/joint surgery within 8 weeks prior to screening (including joint fusion), or joint surgery planned within 12 weeks of randomization; rheumatic autoimmune disease other than RA, or significant systemic involvement of secondary RA (e.g. vasculitis, pulmonary fibrosis or Felty's syndrome), past or current inflammatory joint disease other than RA (e.g. gout, reactive arthritis, psoriatic arthritis, sero-negative spondyloarthropathy, Lyme disease) or other systemic rheumatic disorders (e.g. systemic lupus erythematosus, inflammatory bowel disease, scleroderma, inflammatory myopathy, overlap syndrome); diagnosis of fibromyalgia or other chronic pain syndrome requiring daily narcotic treatment; patients having a secondary, non-inflammatory type of arthritis (e.g. osteoarthritis or fibromyalgia); a history of tuberculosis or positive chest X–ray for tuberculosis; uncontrolled diabetes mellitus or hypertension; history of severe allergic reactions to the type of drugs used in the study, uncontrolled diseases (such as asthma, psoriasis, or inflammatory bowel disease where flares are commonly treated with corticosteroids); evidence of significant concomitant diseases (such as cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine, cerebrovascular disease or gastrointestinal disorders); history of recurrent significant infection requiring hospitalization or treatment with antibiotics within 4 weeks of screening or oral antibiotics within 2 weeks prior to screening; history of or features of cancer (including solid tumours and haematologic malignancies and primary or secondary immunodeficiency); pregnant women or nursing (breast feeding) mothers; and history of alcohol, drug or chemical abuse within 6 months prior to screening.

Any antiinflammatory, antirheumatoid, analgaesics, steroids or other drugs that in the opinion of the investigators would interfere with the study were not permitted for 4 weeks in the case of parenteral or intraarticular drugs and 2 weeks in the case of oral drugs before study enrolment and during the study period. This study was conducted in accordance with the International Conference on Harmonization guidelines (ICHG) for good clinical practice and the Declaration of Helsinki. Independent Ethics Committee, Aluva, Kerala, India approved the study protocol. Patients gave written informed consent before participating in the study.

Study design. The present study was a randomized, single-blinded, pilot study designed to determine the safety and effectiveness of twice daily oral therapy of curcumin 500 mg capsule and diclofenac sodium 50 mg tablet individually and in combination for 8 weeks in patients with active rheumatoid arthritis. Forty-five patients were randomized in 1:1:1 ratio using Random Allocation Software, to receive curcumin 500 mg (Group I) or curcumin 500 mg + diclofenac sodium 50 mg (Group II), or diclofenac sodium 50 mg (Group III) over a period of 8 weeks. Curcumin, in the form of BCM-95® (a patented and registered formulation of curcumin with enhanced bioavailability) for these studies was kindly provided by Arjuna Natural Extracts, Kochi, Kerala, India

(Antony *et al*., 2008). The purity of BCM-95® was assessed by HPLC analysis, in which the chromatograms from BCM-95® samples were compared with those of commercially available pure standards for different curcuminoids. The sample purity was determined by comparing the peak areas of individual peaks present in the standards versus BCM-95® samples. As shown in Fig. 1, HPLC analysis not only revealed absence of any impurities in the BCM-95® curcumin, but the ratios and retention times of various peaks in BCM-95® were parallel to those of the curcuminoid standards.

Eligible subjects were assigned a three-digit, unique randomization number. Data on demographic characteristics, medical history and prior and concomitant medications were also collected. Body weight and height were measured, physical examination was performed, and vital signs including blood pressure and heart rate were recorded. Laboratory examinations including haematology, blood chemistry, C-reactive protein (CRP), antistreptolysin-O (ASO), blood sugar and pregnancy test in women were performed. A 28 joint assessment was performed for a tender joint count, swollen joint count and duration of morning stiffness. Each patient underwent X-ray AP view of chest/hands/wrist/foot and 12-lead electrocardiography.

Efficacy and safety evaluation. The *primary end point* of the study was to determine the frequencies of the patients with good or moderate DAS28 response, as defined by the European League Against Rheumatism (EULAR) criteria, at week 8. The EULAR response criteria are based on the change from baseline in disease activity as assessed by the DAS28 (a composite index based on assessment of 28 joints), the erythrocyte sedimentation rate (ESR) and visual analog scales (VAS) on which the patient scored his/her global assessment of disease activity. The *secondary end point* was the proportion of patients achieving an ACR response of 20%, 50% or 70% (ACR20, ACR50, ACR70) at week 8 and an assessment of the severity of inflammation as judged by CRP values.

The ACR criteria measure improvement in tenderness or swollen joint counts and improvement in three of the following five parameters: patient global assessment – global assessment of disease activity on a 0–100 scale (0, best; 100, worst); physician assessment – global assessment of disease activity on a 0–100 scale (0, best; 100, worst); pain scale disability – visual analogue scale for pain (VAS; 0, no pain and 100, severe pain); functional questionnaire – HAQ (Health Assessment Questionnaire) includes four categories: dressing and grooming, arising, eating and walking, on a 0–3 scale (0, best; 3, worst); acute phase reactant (such as erythrocyte sedimentation rate, ESR). The ACR20 category is defined as a reduction in tender and swollen joint counts by 20%, ACR50 by 50% and ACR70 by 70%, from baseline. Efficacy evaluations were performed at biweekly intervals.

Monitoring of vital signs, physical examinations, laboratory parameters (haematology, blood chemistry,

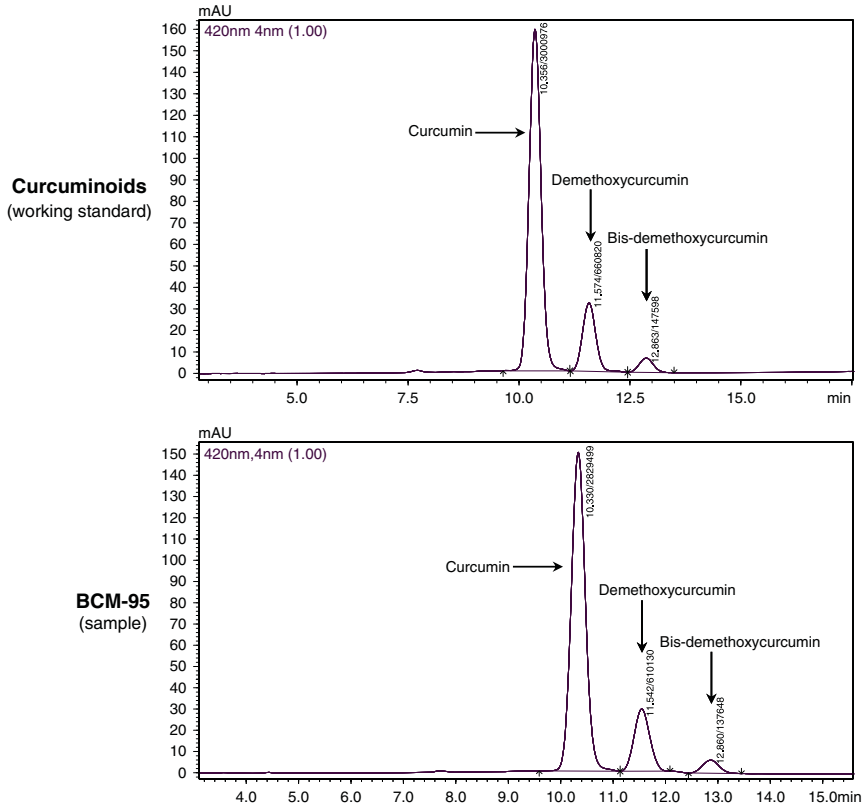

Figure 1. Representative HPLC chromatograms obtained from (upper panel) curcuminoid standards and (lower panel) BCM-95®. As shown, the BCM-95® sample was devoid of any impurities (as would be evidenced by the presence of any additional peaks), and the retention times for the peaks from the three curcuminoids (curcumin, demethoxycurcumin and bis-demethoxycurcumin) in the standard sample and BCM-95® were identical (10.3 min, 11.5 min and 12.8 min, respectively).

CRP, ASO, rheumatoid factor, blood sugar) were performed bi-weekly for safety evaluation. The occurrence of adverse events was the primary safety variable.

Statistical analysis. Thirty-eight subjects completed all visits in accordance with protocol and were selected for efficacy analysis. Primary and secondary endpoint measurements were analysed by calculating the change and percentage change from baseline to endpoint. All statistical tests were two-sided with a significance level of $\alpha = 0.05$. Data were summarized using descriptive statistics (number of subjects [*n*], means, standard deviation [SD]) for continuous variables, and using frequency and percentage (i.e. number and proportion of subjects – *n*, %) for discrete/categorical variables, unless specified otherwise. The ANOVA test was used to assess primary outcome of the trial between groups. Within the groups analysis for all parameters was carried out using an independent *t*-test. SPSS 10.0 was used for all analysis. The statistical power was calculated using a *post hoc* statistical power calculator for Student's *t*-test and the study had 95% power to detect a 37% change within the group.

The safety analysis was performed on all 45 patients. This included the collection of both adverse and serious adverse event data. Serious adverse events were defined as those presenting a significant hazard or side effect (e.g. any event that was fatal, life-threatening, required hospitalization, or resulted in persistent or significant disability).

RESULTS

Demographics and baseline characteristics

Forty-five patients who were enrolled into the study were randomized into three groups (15 in curcumin, 15 in curcumin + diclofenac sodium and 15 in diclofenac sodium alone). The mean age was 47.8 yr in the curcumin group; 47 in the curcumin + diclofenac sodium group; and 48.87 in the diclofenac sodium group. All RA patients had an active disease (with mean DAS scores in the curcumin group = 6.40, curcumin + diclofenac sodium group = 6.44 and diclofenac sodium group = 6.72). There was no significant difference in baseline characteristics including values for body mass index (BMI), disability index of the HAQ, positive rate of serum rheumatoid factor and baseline chemistry values (Tables 1 and 2).

Efficacy assessment: DAS28

All three treatments showed significant improvement in DAS28 scores, although the changes between individual groups were not statistically significant. However, among the three groups, the curcumin group showed the highest percentage of improvement. Among the components of DAS, ESR in all three groups showed similar mean baseline values (Table 3), while the percentage change from baseline was highest in the curcumin + diclofenac sodium group (13.3%). Mean VAS scores for pain in all groups were comparable at baseline, but the curcumin group showed the highest reduction in VAS score from baseline (59.9%). Percentage changes in VAS scores in all three groups were statistically significant. The results are summarized in Tables 4 and 5.

Efficacy assessment: ACR20, ACR50 and ACR70 response

A summary of ACR20, ACR50 and ACR70 at week 8 (end of study) shows that the highest percentage of ACR20 (93%), ACR50 (73%) and ACR70 (33%) was achieved by the curcumin alone group. Although the difference between treatment groups in the proportion of ACR20 responders was not significant, there was a marked trend towards ACR20 response rate in the curcumin group compared with the other two groups. The components of ACR response criteria showed significant changes from baseline to end of study in all three groups. However, CRP showed a statistically significant change only in the curcumin group. The results are summarized in Tables 6 and 7.

ECG, haematology and chemistry

There were no significant changes in ECG, haematology and chemistry parameters. However, serum glutamic oxaloacetic transaminase (SGOT) showed a 33.94% increase in the diclofenac sodium group.

Safety

Adverse events were reported more frequently in the diclofenac sodium group than in the curcumin and curcumin + diclofenac sodium groups. Three adverse events were reported in the diclofenac sodium group, namely: itching and swelling around the eyes, dimness of vision; worsening of condition; serum glutamic pyruvic transaminase (SGPT) and SGOT values increased, which were probably related to the drug. One adverse event, fever, was not related to the drug. Adverse events reported in the curcumin group were mild fever and throat infection. There was one case of worsening of condition in the curcumin + diclofenac sodium group.

Table 1. Demographics and baseline characteristics

	Curcumin (*n* = 15)	Curcumin + diclofenac sodium (*n* = 15)	Diclofenac sodium (*n* = 15)	Overall (*n* = 15)
Age (years)	47.8 ± 8.60	47 ± 16.22	48.87 ± 10.78	47.88 ± 12.03
BMI (kg/m^2)	24.52 ± 3.75	22.73 ± 3.65	21.99 ± 3.75	23.08 ± 3.79
Gender				
Male	2	4	1	7
Female	13	11	14	38

Table 2. Summary of mean change from baseline to end of treatment (EOT) in chemistry parameters

	Curcumin (n = 15)			Curcumin + diclofenac sodium (n = 15)			Diclofenac sodium (n = 15)		
Parameter	Baseline	EOT	% change	Baseline	EOT	% change	Baseline	EOT	% change
Blood urea	25.27 ± 6.66	23.8 ± 7.4	5.8	23.49 ± 5.10	25.14 ± 5.06	−7.02	25.27 ± 7.24	24.29 ± 7.57	3.87
Serum creatinine	0.89 + 0.10	0.88 + 0.15	1.1	0.88 ± 0.17	0.86 ± 0.15	2.27	0.89 ± 0.15	0.87 ± 0.17	2.24
Serum calcium	9.05 ± 0.38	9.48 ± 0.55	4.75	9.12 ± 0.52	9.53 ± 0.52	4.49	9.26 ± 0.49	9.31 ± 0.54	5.39
Serum phosphorus	4.91 ± 0.83	4.53 ± 0.43	7.73	4.47 ± 0.68	4.41 ± 0.49	1.34	4.54 ± 0.56	4.46 ± 0.42	1.76
Total bilirubin	1.08 ± 0.57	0.89 ± 0.07	17.59	0.89 ± 0.06	0.91 ± 0.13	2.24	0.88 ± 0.08	0.96 ± 0.20	9.09
Direct bilirubin	0.52 ± 0.21	0.47 ± 0.06	9.61	0.49 ± 0.08	0.46 ± 0.06	6.12	0.46 ± 0.06	0.49 ± 0.12	6.52
SGPT	30.4 ± 13.4	35.53 ± 22.24	16.87	41.36 ± 29.95	41.29 ± 19.48	0.16	36.21 ± 27.53	48.50 ± 52.18	33.94
SGOT	30 ± 8.56	28.13 ± 11.22	6.23	41.5 ± 30.19	34.79 ± 16.36	16.16	35.14 ± 13.97	35.43 ± 21.91	8.25
FBS	88.07 ± 12.18	89.07 ± 7.74	11.35	88.64 ± 14.23	92.86 ± 16.48	4.76	89.14 ± 10.49	97.64 ± 13.17	9.53

SGPT, serum glutamic pyruvic transaminase; SGOT, serum glutamic oxaloacetic transaminase; FBS, fetal bovine serum.

Table 3. Efficacy results – erythrocyte sedimentation rate (ESR)

Group	Baseline (n = 45)	End of treatment (n = 38)	% change	p value[a]
Curcumin (n = 14)	28 ± 23.7	24.86 ± 17.7	11.2	> 0.05
Curcumin + diclofenac sodium (n = 12)	28.75 ± 20.9	24.92 ± 22.6	13.3	> 0.05
Diclofenac sodium (n = 12)	27.08 ± 17.1	24.75 ± 13.5	8.6	> 0.05

[a]Analysis was within the group. Independent t-test was used.

Table 4. Treatment efficacy results – Disease Activity Score (DAS)

Group	Baseline (n = 45)	End of treatment (n = 38)	% change	p value[a]
Curcumin (n = 14)	6.40 ± 0.73	3.55 ± 0.73	44.5	< 0.05
Curcumin + diclofenac sodium (n = 12)	6.44 ± 0.51	3.58 ± 0.71	44.4	< 0.05
Diclofenac sodium (n = 12)	6.72 ± 0.87	3.89 ± 1.43	42.1	< 0.05

[a]Analysis was within the group. Independent t-test was used.

DISCUSSION

The primary objective of this study was to undertake a pilot clinical study to ascertain the efficacy of curcumin alone, or in combination with diclofenac sodium in patients with rheumatoid arthritis. Since the study was a proof-of-principle and a pilot one, it had the limitations of being an open labelled study. The results from this 8-week randomized study in patients with active RA provide evidence that curcumin is safe, and has a significant efficacy in improving the DAS and ACR scores in patients with mild or moderate RA, when given alone or in combination with diclofenac sodium. In fact, patients who received curcumin achieved higher ACR response rates than the other two groups. For all three-treatment groups, the ACR response was significant. All components of ACR, namely total number of painful joints, total swollen joints, patient's GA, physician's GA, disability index and HAQ showed significant changes in all three groups. It is noteworthy that the acute phase reactant, CRP, showed significant improvement only in the curcumin group. Consistent with this, this group showed the most significant improvement in the DAS scores.

The findings of this study are significant, as these demonstrate that curcumin was not only safe and effective, but was surprisingly more effective in alleviating pain compared with diclofenac. Our findings are consistent with a previously published report by Kuptniratsaikul and colleagues in which they demonstrated the safety and efficacy of *Curcuma domestica* for the treatment of patients with knee osteoarthritis (Kuptniratsaikul *et al*., 2009). These investigators reported not only that both curcumin and ibuprofen had comparable efficacy in mitigating the clinical symptoms for osteoarthritis, but also that the rate of adverse events with curcumin was lower than that of ibuprofen (33.3% in curcumin group versus 44.2% with ibuprofen), an observation that has been independently validated in our present study in patients with rheumatoid arthritis. Although the molecular mechanisms for such efficacy of curcumin are unclear, it is reasonable to speculate that curcumin may differentially regulate molecular targets that control chronic pain versus the ones that mediate acute pain. Curcumin has been reported to be effective in alleviating chronic pain in different experimental models (Sharma *et al*., 2006, 2007; Maes *et al*., 2007; Tajik *et al*., 2007, 2008; Mittal *et al*., 2009), including neuropathic pain (Sharma *et al*., 2006, 2007), one of the most difficult forms of pain to treat. In an animal model of formalin-induced orofacial pain (Mittal *et al*., 2009), curcumin was found to potentiate a subanalgaesic dose (0.2 mg/kg) of diclofenac. In the present study, however, curcumin + diclofenac

Table 5. Treatment efficacy results – visual analog scale (VAS)

Group	Baseline (n = 45)	End of treatment (n = 38)	% change	p value[a]
Curcumin (n = 14)	68.57 ± 17.14	27.5 ± 9.35	59.9	< 0.05
Curcumin + diclofenac sodium (n = 12)	77.25 ± 9.65	34.29 ± 26.75	55.62	< 0.05
Diclofenac sodium (n = 12)	78.25 ± 11.25	39.17 ± 20.1	49.94	< 0.05

[a]Analysis was within the group. Independent t-test was used.

Table 6. Components of American College of Rheumatology (ACR) responses[a]

	Curcumin (n = 14)			Curcumin + diclofenac sodium (n = 12)			Diclofenac sodium (n = 12)		
Parameter	Baseline	EOT	p value[b]	Baseline	EOT	p value[b]	Baseline	EOT	p value[b]
Total painful joints	18.64	3.14	< 0.05	16.67	2.75	< 0.05	18.2	5.67	< 0.05
Total swollen joints	12.15	0.36	< 0.05	11.5	0.42	< 0.05	16.6	1.83	< 0.05
Patient's GA[c]	83.93	30.7	< 0.05	78.75	40.83	< 0.05	77.5	42.08	< 0.05
Physician's GA[c]	79.64	28.21	< 0.05	74.58	36.25	< 0.05	75.42	35.42	< 0.05
Disability index, HAQ[d]	4.41	1.06	< 0.05	3.95	1.53	< 0.05	3.79	1.51	< 0.05

EOT, end of treatment.

[a]Data presented as mean based on change from baseline;

[b]Analysis was within the group. Independent t-test was used.

[c]GA, global assessment of disease activity on a 0–100 scale (0, best; 100, worst).

[d]HAQ, Health Assessment Questionnaire, which includes four categories: dressing and grooming, arising, eating and walking, on a 0–3 scale (0, best; 3, worst);

Table 7. Treatment efficacy results – C-reactive protein (CRP)

Group	Baseline (n = 45)	End of treatment (n = 38)	% change	p value[a]
Curcumin (n = 14)	5.34 + 4.12	2.56 + 1.8	52	< 0.05
Curcumin + diclofenac sodium (n = 12)	9.11 + 9.93	6.66 + 6.87	26.9	> 0.05
Diclofenac sodium (n = 12)	3.3 + 2.4	3.35 + 2.5	−1.5	> 0.05

[a]Analysis was within the group. Independent t-test was used.

combination was slightly less efficacious than curcumin alone, even though the curcumin dose remained unchanged. On the contrary, the diclofenac sodium group experienced several adverse events that were probably a direct consequence of the use of this drug. Supplementation of curcumin alone provided significant overall improvement in patients with active RA, and this efficacy was better than that provided by diclofenac sodium, and was not associated with any adverse events. Our findings are of further interest considering that although curcumin has long been known to possess a wide spectrum of activities including antioxidant, antiinflammatory and anticancer properties in different preclinical and clinical models, poor absorption and bioavailability of this phytonutrient has severely limited its application to various diseases. In this study, we were able to overcome this shortcoming by using a proprietary preparation of curcumin, BCM-95®, which is not only all natural, but has six- to eight-fold enhanced bioavailability as reported previously (Antony *et al*., 2008). Our observations that curcumin alone was able to alleviate symptoms of rheumatoid arthritis in this study are quite encouraging, and these results provide an ideal springboard for investigating the potential of curcumin in other chronic diseases arising in the setting of dysregulated chronic inflammation.

The study was designed as a 2-month trial, which is probably not long enough to detect radiographic changes. However, since both DAS and ACR are the indicators of the physical functioning in RA, the significant improvement in both parameters would suggest that radiographic progression was likely inhibited in these patients. The study shows that curcumin can provide significant improvement in treatment efficacy in active RA. The reported findings are especially relevant in view of recent reports of monotherapy failure in RA(Combe *et al*., 2009; van der Heijde *et al*., 2006; Zintzaras *et al*., 2008; Breedveld *et al*., 2006).

In conclusion, curcumin was generally safe and well-tolerated in most subjects when given up to 8 weeks. Although our present data are very encouraging they are a platform only for future planning of long-term studies with the drug in combination with existing standard therapies in RA, which will provide a complete picture of the utility of curcumin. Curcumin has activities similar to the anti-TNF drugs, but without their serious side-effects and a study comparing these two drugs is warranted. Taken together, our present results provide a clear proof-of-principle for the superiority of curcumin, and the lack of any synergistic or additive efficacy when used in conjunction with diclofenac strongly favours the safe

and effective application of curcumin alone in clinical settings for the management of rheumatoid arthritis, and other proinflammatory diseases including cancer in the future.

Acknowledgements

The authors deeply acknowledge Dr T. N. B Kaimal for his valuable suggestions and Arjuna Natural Extracts Limited for providing curcumin capsules (BCM-95®). The study was supported by a pilot project grant from the Nirmala Medical Center, Kerala, India.

Conflict of Interest

The authors have declared that there is no conflict of interest, financial or otherwise.

REFERENCES

Aggarwal BB, Shishodia S. 2006. Molecular targets of dietary agents for prevention and therapy of cancer. *Biochem Pharmacol* **71**: 1397–1421.

Aggarwal BB, Sundaram C, Malani N, Ichikawa H. 2007. Curcumin: the Indian solid gold. *Adv Exp Med Biol* **595**: 1–75.

Altman RD, Dreiser RL, Fisher CL, Chase WF, Dreher DS, Zacher J. 2009. Diclofenac sodium gel in patients with primary hand osteoarthritis: a randomized, double-blind, placebo-controlled trial. *J Rheumatol* **36**: 1991–1999.

Antony B, Merina B, Iyer VS, Judy N, Lennertz K, Joyal S. 2008. A pilot cross-over study to evaluate human oral bioavailability of BCM-95CG (Biocurcumax), a novel bioenhanced preparation of curcumin. *Indian J Pharm Sci* **70**: 445–449.

Bhattacharyya S, Mandal D, Saha B, Sen GS, Das T, Sa G. 2007. Curcumin prevents tumor-induced T cell apoptosis through Stat-5a-mediated Bcl-2 induction. *J Biol Chem* **282**: 15954–15964.

Breedveld F. 2011. The value of early intervention in RA – a window of opportunity. *Clin Rheumatol* **30**(Suppl. 1): S33–S39.

Breedveld FC, Weisman MH, Kavanaugh AF *et al*. 2006. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* **54**: 26–37.

Combe B, Codreanu C, Fiocco U *et al*. 2009. Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study. *Ann Rheum Dis* **68**: 1146–1152.

Goel A, Aggarwal BB. 2010. Curcumin, the golden spice from Indian saffron, is a chemosensitizer and radiosensitizer for tumors and chemoprotector and radioprotector for normal organs. *Nutr Cancer* **62**: 919–930.

Goel A, Boland CR, Chauhan DP. 2001. Specific inhibition of cyclooxygenase-2 (COX-2) expression by dietary curcumin in HT-29 human colon cancer cells. *Cancer Lett* **172**: 111–118.

Goel A, Jhurani S, Aggarwal BB. 2008a. Multi-targeted therapy by curcumin: how spicy is it? *Mol Nutr Food Res* **52**: 1010–1030.

Goel A, Kunnumakkara AB, Aggarwal BB. 2008b. Curcumin as 'Curecumin': from kitchen to clinic. *Biochem Pharmacol* **75**: 787–809.

Kuptniratsaikul V, Thanakhumtorn S, Chinswangwatanakul P, Wattanamongkonsil L, Thamlikitkul V. 2009. Efficacy and safety of Curcuma domestica extracts in patients with knee osteoarthritis. *J Altern Complement Med* **15**: 891–897.

Lipsky PE, van der Heijde DM, St Clair EW *et al*. 2000. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study group. *N Engl J Med* **343**: 1594–1602.

Maes M, Mihaylova I, Bosmans E. 2007. Not in the mind of neurasthenic lazybones but in the cell nucleus: patients with chronic fatigue syndrome have increased production of nuclear factor kappa beta. *Neuro Endocrinol Lett* **28**: 456–462.

Marks WH. 2011. Tripterygium wilfordii Hook F. versus Sulfasalazine in the treatment of rheumatoid arthritis: a well-designed clinical trial of a botanical demonstrating effectiveness. *Fitoterapia* **82**: 85–87.

Mittal N, Joshi R, Hota D, Chakrabarti A. 2009. Evaluation of anti-hyperalgesic effect of curcumin on formalin-induced orofacial pain in rat. *Phytother Res* **23**: 507–512.

Newsome G. 2002. Guidelines for the management of rheumatoid arthritis: 2002 update. *J Am Acad Nurse Pract* **14**: 432–437.

Rahme E, Bernatsky S. 2010. NSAIDs and risk of lower gastrointestinal bleeding. *Lancet* **376**: 146–148.

Reuter S, Gupta SC, Park B, Goel A, Aggarwal BB. 2011. Epigenetic changes induced by curcumin and other natural compounds. *Genes Nutr* **6**: 93–108.

Rindfleisch JA, Muller D. 2005. Diagnosis and management of rheumatoid arthritis. *Am Fam Physician* **72**: 1037–1047.

Ruff CT, Morrow DA, Jarolim P *et al*. 2011. Evaluation of NT-proBNP and high sensitivity C-reactive protein for predicting cardiovascular risk in patients with arthritis taking longterm nonsteroidal antiinflammatory drugs. *J Rheumatol* **38**: 1071–1078.

Scapagnini G, Sonya V, Nader AG, Calogero C, Zella D, Fabio G. 2011. Modulation of Nrf2/ARE pathway by food polyphenols: a nutritional neuroprotective strategy for cognitive and neurodegenerative disorders. *Mol Neurobiol* **44**: 192–201.

Schmajuk G, Trivedi AN, Solomon DH *et al*. 2011. Receipt of disease-modifying antirheumatic drugs among patients with rheumatoid arthritis in Medicare managed care plans. *J Am Med Assoc* **305**: 480–486.

Shankar S, Srivastava RK. 2007. Bax and Bak genes are essential for maximum apoptotic response by curcumin, a polyphenolic compound and cancer chemopreventive agent derived from turmeric, *Curcuma longa*. *Carcinogenesis* **28**: 1277–1286.

Sharma S, Kulkarni SK, Agrewala JN, Chopra K. 2006. Curcumin attenuates thermal hyperalgesia in a diabetic mouse model of neuropathic pain. *Eur J Pharmacol* **536**: 256–261.

Sharma S, Chopra K, Kulkarni SK. 2007. Effect of insulin and its combination with resveratrol or curcumin in attenuation of diabetic neuropathic pain: participation of nitric oxide and TNF-alpha. *Phytother Res* **21**: 278–283.

Shiozawa S, Tsumiyama K. 2009. Pathogenesis of rheumatoid arthritis and c-Fos/AP-1. *Cell Cycle* **8**: 1539–1543.

Shishodia S, Chaturvedi MM, Aggarwal BB. 2007. Role of curcumin in cancer therapy. *Curr Probl Cancer* **31**: 243–305.

Tajik H, Tamaddonfard E, Hamzeh-Gooshchi N. 2007. Interaction between curcumin and opioid system in the formalin test of rats. *Pak J Biol Sci* **10**: 2583–2586.

Tajik H, Tamaddonfard E, Hamzeh-Gooshchi N. 2008. The effect of curcumin (active substance of turmeric) on the acetic acid-induced visceral nociception in rats. *Pak J Biol Sci* **11**: 312–314.

Van der Heijde D, Klareskog L, Rodriguez-Valverde V *et al*. 2006. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum* **54**: 1063–1074.

Zintzaras E, Dahabreh IJ, Giannouli S, Voulgarelis M, Moutsopoulos HM. 2008. Infliximab and methotrexate in the treatment of rheumatoid arthritis: a systematic review and meta-analysis of dosage regimens. *Clin Ther* **30**: 1939–1955.