Monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, and curcumin: A randomized, double-blind placebo-controlled cross-over 4g study and an open-label 8g extension study

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Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) represent useful models for studying multiple myeloma precursor disease, and for developing early intervention strategies. Administering a 4g dose of curcumin, we performed a randomised, double-blind placebo-controlled cross-over study, followed by an open-label extension study using an 8g dose to assess the effect of curcumin on FLC response and bone turnover in patients with MGUS and SMM. 36 patients (19 MGUS and 17 SMM) were randomised into two groups: one received 4g curcumin and the other 4g placebo, crossing over at 3 months. At completion of the 4g arm, all patients were given the option of entering an open-label, 8g dose extension study. Blood and urine samples were collected at specified intervals for specific marker analyses. Group values are expressed as mean ± 1 SD. Data from different time intervals within groups were compared using Student's paired *t*-test. 25 patients completed the 4g cross-over study and 18 the 8g extension study. Curcumin therapy decreased the free light-chain ratio (rFLC), reduced the difference between clonal and nonclonal light-chain (dFLC) and involved free light-chain (iFLC). uDPYD, a marker of bone resorption, decreased in the curcumin arm and increased on the placebo arm. Serum creatinine levels tended to diminish on curcumin therapy. These findings suggest that curcumin might have the potential to slow the disease process in patients with MGUS and SMM. Am. J. Hematol. 87:455–460, 2012. © 2012 Wiley Periodicals, Inc.

Introduction

Multiple myeloma is a progressive, neoplastic disease and is characterized by high bone turnover, significant bone loss, and pathological fractures, resulting in significant morbidity and a high mortality. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) are asymptomatic plasma cell disorders which can progress to multiple myeloma. Both MGUS and SMM are suitable for studying multiple myeloma precursor disease and to develop early intervention strategies [1]. While MGUS is largely considered a benign condition, a number of studies have shown that patients with MGUS are at increased risk of high bone turnover and fractures even before progression to myeloma [2–5]. Despite these findings, the cornerstone of managing multiple myeloma precursor disease is a "watch and wait" strategy.

Because symptomatic myeloma may not evolve for as long as 20 years, it is currently not possible to predict the clinical course of MGUS or SMM. Features predicting patients at highest risk include the size and type of M-protein, with IgA having a higher risk compared to IgG paraprotein, % plasma cell dyscrasia, and abnormal serum-free light chain ratio. A number of studies [6–9], have shown that independent of the size and type of the serum M-protein, an abnormal free light-chain (FLC) ratio increases the risk of progression. Serum free light chain analysis is now recommended for prognosticating plasma cell dyscrasias [9]. The International Myeloma Working Group has therefore recommended that serum-free light chain analysis be performed in combination with serum protein electrophoresis and immunofixation when evaluating plasma cell disorders.

Given the uncertainty of disease progression with MGUS and SMM, early intervention aimed at reducing the abnormal protein load and the potential negative effects on the skeleton might be therapeutic [10]. *Curcuma longa* (turmeric) is a tropical plant native to southern and southeastern tropical Asia. It is a perennial herb belonging to the ginger family. The most active component in turmeric is curcumin [11]. Curcumin has been shown to inhibit the proliferation of multiple myeloma cells through the downregulation of IL-6 and NF-kB. It has also been shown to inhibit osteoclastogenesis and to reduce bone turnover. Bharti et al. showed that curcumin suppresses proliferation and induces apoptosis in multiple myeloma cells [12] and inhibits osteoclastogenesis through the suppression of RANKL signaling [13].

Based on its antimyeloma cell activity, we have previously shown that oral curcumin at a dose of 4 g daily can, in a select group of MGUS patients, decrease paraprotein load and bone resorption [14]. We now present the results of a randomized, double-blind placebo-controlled cross-over 4g study and an open-label 8g extension study of the effects of curcumin on paraproteinemia, serum-free light chains, and bone turnover in MGUS and SMM patients.

Patients and Methods

Nineteen patients with MGUS (serum M-protein value of <30 g/L, bone marrow plasma cells $<10\%$, no or small amount of M-protein in the urine, and absence of lytic bone lesions, anemia, hypercalcemia, or renal insufficiency) and 17 patients with SMM (serum M protein level $\geq$ 30 g/L and/or bone marrow plasma cells $\geq 10\%$, plus no anemia, hypercalcemia, renal failure, or lytic bone lesions) [15] who were not

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Additional Supporting Information may be found in the online version of this article.

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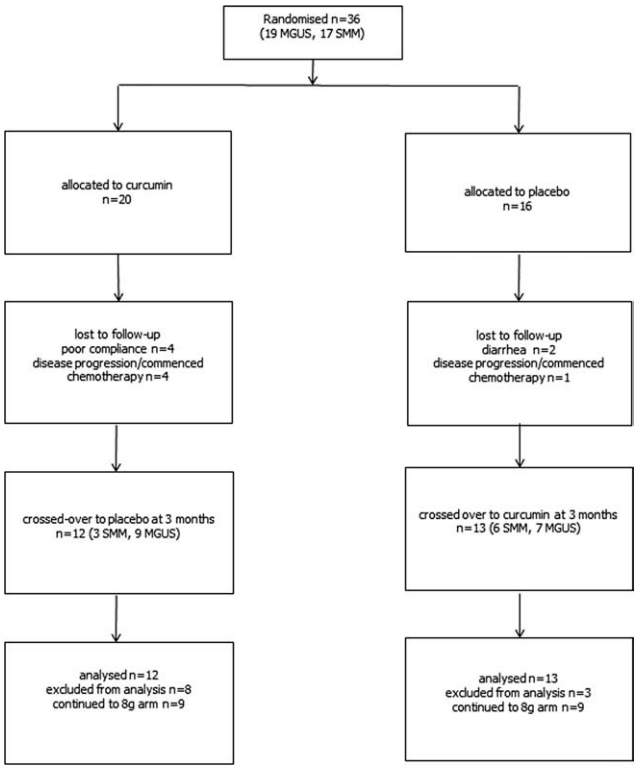

Figure 1. Trial profile.

receiving chemotherapy or bisphosphonates, were randomized into the study between January and September 2010. Patients were selected on the basis of an elevated paraprotein level (>20 g/L), an abnormal free light chain ratio or both. No patients had evidence of previous thyroid, parathyroid, renal, or metabolic bone disorders. All patients were Caucasian and aged more than 45 years. The study was performed in the Department of Endocrinology at St George Hospital, Sydney, and approved by the local ethics committee. Written informed consent was obtained from each patient before enrolment. The study was registered with the Australian Clinical Trials Registry (ACTRN12610000962033).

Formulation, dose, and study design. Patients were randomized into two groups (Fig. 1): Group A ($n = 20$) were given 4 g curcumin at the start of the study and crossed over to placebo at 3 months. Group B ($n = 16$) were given 4 g placebo initially and crossed over to curcumin at 3 months. All patients were given the option, after completion of the 4g arms, of entering the open-label, 8g extension study for a further 3 months.

A curcumin dose of 4 g has been defined as the dose at which plasma levels of curcumin can be measured and pharmacodynamic effects demonstrated in vivo [16]. Phase 1 clinical trials indicate tolerability and safety at doses as high as 8 g/day [17,18]. This study was designed to determine whether a dose of 4 or 8 g would provide benefit to patients with myeloma precursor disease.

Four gram of "C3" curcuminoid granule stick-packs (Allepey finger turmeric) and 4 g of placebo granule stick-packs were supplied by the Sabinsa Corporation (Piscataway, NJ). Each "curcumin" stick-pack contained 4,000 mg of curcuminoids (3,600 mg of curcumin, 320 mg of desmethoxycurcumin, and 80 mg of bisdesmethoxycurcumin), confirmed by high performance liquid chromatography (HPLC). This formulation is referred to as "curcumin." Placebo granules contained micro crystalline cellulose, dicalcium phosphate, PVPK 30, Sodium starch glycolate, and magnesium stearate. This formulation is referred to as "placebo." Patients consumed one stick-pack daily (half in the morning, half in the evening as divided dose) of 4 g of curcumin or placebo, administered with a diet containing some fat (such as yoghurt to maximize drug absorption—personal communication) and were crossed over at 3 months. The total duration of the crossover study was 6 months. For the 8g extension study, patients consumed two stick-packs of curcumin daily (divided dose) for an additional 3 months.

Clinical, hematological, and biochemical measurements. Blood and urine samples were collected at baseline (V1), Week 1 (V2), Month 1 (V3), Month 3 (V4–crossover), Month 6 (V5-crossover) (end 4g arm), and Month 9 (V6–8g arm) after initiating therapy. Serum paraprotein and immunoglobulin-electrophoresis were quantitated by agarose gel (Sebia, Cedex, France). Serum calcium was measured using standard autoanalyser methods and serum 25-hydroxyvitamin D3 by radioimmunoassay (DiaSorin, Stillwater, MI). Patients who were vitamin D deficient (<50 nmol/L) were given supplemental 1,000 IU daily (Phytologic Pty Ltd—vitamin D3) before commencement of the study. Serum B2 microglobulin was measured using Beckman instruments (Beckman Instruments, Fullerton, CA). Serum parathyroid hormone (PTH) was determined by an immunoradiometric assay (Nichols Institute, San Clemente, CA).

FLC analysis. This was performed by immunonephelometry using specific antibodies (the binding site) on a BNII nephelometer (Dade Behring, Deerfield, IL).The FLC assay consists of two separate measurements, one to detect free-kappa (normal range, 3.3–19.4 mg/L) and the other to detect free-lambda (normal range, 5.7–26.3 mg/L) light chains. In addition to measuring the absolute levels of FLC, the test also allows the assessment of clonality based on the ratio of kappa–lambda light chain levels (normal reference range, 0.26–1.65). Patients with a kappa–lambda FLC ratio <0.26 are typically defined as having monoclonal lambda FLC and those with ratios >1.65 are defined as having a monoclonal kappa FLC. If the FLC ratio is >1.65, kappa is the "involved" FLC (iFLC) and lambda the "uninvolved" FLC, and vice versa if the ratio <0.26.

Marker of bone turnover. Urinary deoxypyridinoline (u-DPYD), a marker of bone resorption, was measured by a chemiluminescence immunometric assay (Diagnostic Products, Los Angeles, CA; %coefficient of variation (CV) = 15% at 30 nmol/L and 10% at 100 nmol/L). The u-DPYD excretion rate was expressed as nmol/mmol urinary creatinine.

Statistical evaluation. Group values are expressed as the mean ± 1 standard deviation. Group comparisons were made using Student's unpaired *t*-test. Data from different time intervals within groups were compared using analysis of variance and Student's paired t-test. Statistical significance was assigned as $P < 0.05$. Stepwise regression analysis was performed (using SPSS, version 19) to determine the most important predictors of outcome measures such as the free light chain ratio and uDPYD excretion rates. The variables entered into the analysis included baseline paraprotein, rFLC iFLC, dFLC, total protein, B2M, PTH, albumin, and creatinine. Data from our previous study was used to calculate the number of patients required to show a benefit from curcumin on FLC. We determined that a minimum of 34 patients, 17 in each arm were required to achieve a statistical endpoint (95% CI, 90% power).

Results

Baseline characteristics of the cohort

There were 19 men and 17 women with a mean age of 69.8 (range 43–90). The mean duration of disease was 61 ± 50.3 months. The mean baseline clinical data and serum biochemistry of the cohort are outlined in Table I (column 1). The paraprotein level was 24.7 g/L, the FLC ratio (rFLC) was 32.3 (range 0.02–260.29, normal = 0.3–1.7), involved free light chain (iFLC) equal to 210.4 mg/L and difference between " involved" and "uninvolved" light chains (dFLC) equal to 222.1 mg/L.

The baseline characteristics for the 19 MGUS and 17 SMM patients are separately illustrated in Table I (columns 2 and 3). There were two patients with IgA paraproteinemia (one kappa, one lambda) and 34 with IgG paraproteinemia. Of the 34 patients with IgG paraproteinemia, 24 were IgG kappa and 10 were IgG lambda. Globulin, gamma globulin, random urinary protein, and total protein levels were elevated. Mean serum 25OHD (77.9 nmol/L) and PTH (5.4 pmol/L) concentrations were normal in all groups. There were three patients with hyperparathyroidism but normal serum calcium levels (one patient had slightly raised serum creatinine (135 μmol/L) and two patients had probable mild normo-calcemic primary hyperparathyroidism). Bone turnover markers P1NP and uDPYD were within normal ranges, as were hemoglobin, beta-2-microglobulin, calcium, creatinine, lactate dehydrogenase (LDH), and albumin.

TABLE I. Baseline Clinical Data and Biochemistry of All 36 Patients Randomized into the Study (Mean ± 1 SD)

Variables	Baseline (Group $n = 36$)	Baseline (MGUS $n = 19$)	Baseline (SMM $n = 17$)
Mean age (years)	69.8 ± 12.2	67.1 ± 12.7	73 ± 12.2
M:F	19:17	12:7	7:10
% plasma cells	16.9 ± 14.4	6.4 ± 2.5	25.9 ± 15
Paraprotein (g/L)	24.7 ± 9.5	20.8 ± 5	29.3 ± 8.8
Free light chain ratio (0.3–1.7)	32.3 ± 62.4	11.5 ± 32.4	57.8 ± 88
dFLC (mg/L)	222.1 ± 360.5	97.9 ± 228.7	367.7 ± 443.3
iFLC (mg/L)	210.4 ± 351.8	106.9 ± 228.1	374.7 ± 443
Albumin (37–50 g/L)	42.1 ± 4.1	43.4 ± 3.9	40.6 ± 3.8
Globulin (22–38 g/L)	45.2 ± 9	40.9 ± 5.7	50.1 ± 9.3
Gamma globulin (7–16 g/L)	26.7 ± 8.8	24.2 ± 4.9	29.6 ± 10.9
Random urinary protein (g/L)	0.27 ± 0.38	0.14 ± 0.25	0.32 ± 0.42
Total protein (64–83 g/L)	87.2 ± 8.3	84.4 ± 4.6	90.6 ± 10.1
Hemoglobin (119–160 g/L)	123.9 ± 20	133.9 ± 13.8	112.5 ± 19.2
Beta 2 Microglobulin (0–3 mg/L)	2.7 ± 1.1	2.6 ± 1.1	3.1 ± 1.1
Calcium (2.15–2.55 mmol/L)	2.4 ± 0.2	2.4 ± 0.14	2.5 ± 0.3
25-OH Vitamin D (nmol/L)	77.9 ± 29.2	74.6 ± 23.1	81.6 ± 36.9
Creatinine (45–90 μmol/L)	86.5 ± 16	83 ± 14.4	92.6 ± 18.5
±PTH (1.6–6.9 pmol/L)	5.4 ± 3	4.7 ± 2.4	6.4 ± 3.7
LDH (120–250 μ/L)	164.2 ± 31.4	161.3 ± 30.3	166.8 ± 32.3
P1NP (μg/L)	35.1 ± 14.7	36.6 ± 11.1	33.9 ± 17.8
uDPYD (3.0–7.4 nmol/mmol)	5.6 ± 1.8	5 ± 1.3	6.1 ± 2.1

Results of the 4g arm of the study

A total of 25 (16 MGUS and nine SMM, i.e., 69%) patients completed the 4g arm, 12 (of 20, 60%) in Group A and 13 (of 16, 81%) in Group B. All but one (patient entered into study after first documentation) of these 25 patients had stable (within a range of 2–4 g/L) paraprotein levels for 3–24 months before entry into the study.

Group A—4g curcumin to placebo. Of the 20 patients randomized into this group, only 12 (three SMM and nine MGUS) completed the 4g crossover arm (Table II, Supporting Information Fig. 2). The data of four patients with poor compliance and four patients with progressive SMM were excluded (their paraprotein/ B2M or rFLC progressively increased and they commenced chemotherapy. Two patients stopped taking curcumin after 1 month and two elected to continue with the curcumin while on chemotherapy). All 12 had IgG parapoteinemia, 10 (83%) had kappa chains (rFLC > 1.7) and two lambda chains. All three markers of free light chains decreased after 3 months of curcumin and continued to decrease despite crossover to placebo. The changes from baseline were rFLC (−26.1%,), iFLC (−9.1%), and dFLC (−9%) at 3 months and rFLC (−35.5%), iFLC (−10.8%), and dFLC (−10.9%) at 6 months. These changes did not reach statistical significance. The random urinary protein (−37.1%, $P = 0.03$) and serum creatinine (−4.4%, $P = 0.14$) decreased on curcumin. There were no significant changes noted in paraprotein concentrations. While the uDPYD (−13.1%, $P = 0.18$) decreased on curcumin, it increased (+18.4%, $P = 0.09$) on crossover to placebo.

Group B—4g placebo to curcumin. Of the 16 patients randomized to this group, 13 (six SMM and seven MGUS) completed the 4g crossover arm (Table III, Supporting Information Fig. 3). The data on three patients were excluded, two withdrawing from the study due to diarrhea and one with progressive disease (SMM). All patients had IgG paraproteinemia, and six (46%) had kappa chains and seven lambda chains. In other words, a greater proportion of patients in Group A had kappa chains compared to Group B ($X^2 = 3.74$; 1 df; $P = 0.05$). In contrast to the decreases seen in rFLC, iFLC, and dFLC on curcumin/placebo therapy in Group A, all three free light chains showed small increases at 3 months after placebo therapy (+2.4, +3, and +3.5%, respectively). There were no significant changes seen after crossover to curcumin 4 g, but decreases did occur after crossover to the 8g arm ($n = 9$). These decreases, compared with baseline, in rFLC (−36%), iFLC (−6.7%), and dFLC (−8.5%) at this higher dose were similar to the changes with 4 g curcumin arm in Group A. A small nonsignificant decrease (−9.4%, $P = 0.37$) in uDPYD occurred on placebo and continued to decrease after crossover to curcumin (−22.5% from baseline, $P = 0.07$). Similarly, serum creatinine showed a small nonsignificant decrease on placebo (−6.8%, $P = 0.14$) and continued to decrease after crossover to curcumin (−9.5% from baseline, $P = 0.03$).2

Individual changes at the 4 g dose are categorized for MGUS and SMM patients in Supporting Information Table IV (a and b).

Results of the 8g arm of the study

Combined data of 18 patients completing 8g arm. Nine patients from Group A and nine patients from Group B (seven SMM and 11 MGUS) completed the 8g arm (Table IV, Supporting Information Fig. 4). Each patient in this group received, in total, 4g curcumin therapy, 4g placebo therapy, and 8g curcumin over 9 months. Significant reductions in rFLC (−36.8%, $P = 0.03$), total protein (−3.4%, $P = 0.04$), and random urinary protein (−26.7%, $P = 0.04$) were evident (final compared to baseline). Similarly, there were also reductions in the iFLC (−8.4%, $P = 0.48$), dFLC (−10.1%, $P = 0.43$), uDPYD (−9.5%, $P = 0.09$), and PTH (−19.8%, $P = 0.002$) after 9 months of therapy. No significant effects of curcumin (4 and 8 g dose) were evident on serum albumin, B2 microglobulin, or hemoglobin levels.

Individual changes at the 8 g dose are categorized for MGUS and SMM patients in Supporting Information Table VI (a and b).

Regression analysis

Stepwise regression analysis showed that the baseline rFLC ($P < 0.0005$) and baseline total protein ($P < 0.005$) were the most important determinants of the rFLC response, while the baseline creatinine ($P < 0.05$) was the most important determinant of the uDPYD excretion rates.

Results of both the 4g and 8g arms based on free light chain ratio (abnormal or normal) at baseline

As stepwise regression analysis showed that baseline rFLC was an important determinant of FLC response, the cohort of patients were divided into those with an abnormal free light chain ratio (<0.3 or >1.7) at baseline (Supporting Information Table VIIa and b) and those with a normal ratio (0.3–1.7) at baseline. Of the 25 patients who completed the 4 g arm of the study, 17 (nine MGUS (56%) and eight SMM (89%)) had an abnormal ratio, while 8 (seven MGUS (44%) and one SMM (11%)) had a normal ratio.

TABLE II. Group A (Curcumin to Placebo)—4g Data (n=12)

Variables	Baseline	Three-month Curcumin	% Change at three months from baseline	P	Three-month placebo	% Change at three months from curcumin	P	% Change from baseline	P
FLCratio	8.25 ± 9.9	6.1 ± 6.5	−26.1	0.10	5.3 ± 5.5	−12.8	0.28	−35.5	0.07
iFLC (mg/L)	79.8 ± 89.3	72.6 ± 78	−9.1	0.28	71.1 ± 72.6	−2.0	0.73	−10.8	0.34
dFLC (mg/L)	74.8 ± 88	68.1 ± 76.6	−9.0	0.31	66.7 ± 71.2	−2.2	0.73	−10.9	0.38
Paraprotein (g/L)	23.5 ± 6.6	23.4 ± 5.7	−0.6	0.85	23.4 ± 5.2	+0.2	0.95	−0.3	0.95
Albumin (37–50 g/L)	43.7 ± 3.8	42.1 ± 2.7	−3.6	0.12	42.1 ± 3.1	0	1	−3.6	0.12
B2M (0−3 mg/L)	2.1 ± 0.5	2.1 ± 0.51	+2.4	0.37	2.2 ± 0.57	+4.3	**0.03**	+6.9	**0.04**
Random urinary protein (g/L)	0.32 ± 0.35	0.21 ± 0.28	−37.1	**0.03**	0.24 ± 0.3	+18.1	0.25	−25.8	**0.04**
uDPYD (nmol/mmol)	5.4 ± 1.5	4.7 ± 1.8	−13.1	0.18	5.6 ± 1.6	+18.4	0.09	+2.9	0.70
Creatinine (μmol/L)	79.7 ± 10.5	76.2 ± 11.6	−4.4	0.14	76.9 ± 14.2	+1.0	0.78	−3.5	0.34

Significance of bold values is $P < 0.05$ ie assigned value of significance.

TABLE III. Group B (Placebo to Curcumin—4g Data (n = 13)

Variables	Baseline	Three-month placebo	% Change from baseline	P	Three-month curcumin	% Change from placebo	P	% Change from baseline	P
FLC ratio	12.1 ± 27.1	12.3 ± 27.9	+2.4	0.65	13 ± 28.2	+5.6	0.43	+8.2	0.48
iFLC (mg/L)	102.1 ± 188.6	105.2 ± 192.8	+3.0	0.37	109.3 ± 195.9	+3.9	0.13	+7.1	0.17
dFLC (mg/L)	139.4 ± 232.3	144.2 ± 243.4	+3.5	0.62	135.3 ± 213.3	−6.2	0.40	−3.0	0.77
Paraprotein(g/L)	24.3 ± 10.1	23.5 ± 9.4	−3.1	0.38	23.4 ± 9.1	−0.3	0.89	−3.4	0.46
Albumin (37–50 g/L)	41.8 ± 4.5	41.1 ± 4.5	−1.8	0.17	41.8 ± 4.3	+1.7	0.26	−0.2	0.89
B2M (0–3 mg/L)	2.4 ± 0.9	2.5 ± 1	+4.6	0.23	2.4 ± 0.9	−1.9	0.66	+2.6	0.56
Random urinary protein (mg/L)	0.28 ± 0.43	0.15 ± 0.15	−45.8	0.27	0.22 ± 0.3	46.7	0.23	−20.5%	0.41
uDPYD(nmol/mmol)	5.5 ± 2.0	5 ± 1.8	−9.4	0.37	4.3 ± 1.4	−14.5	0.25	−22.5	**0.07**
Creatinine (μmol/L)	90.2 ± 18.3	81.6 ± 13	−6.8	0.14	81.6 ± 13.1	−2.8	0.18	−9.5	**0.03**

Significance of bold values is $P < 0.05$ ie assigned value of significance.

Patients with an abnormal ratio at baseline showed a decrease in rFLC, dFLC, iFLC, paraprotein, and uDPYD at both doses with significant reduction in rFLC at 8 g and uDPYD at both doses. Of interest was the significant increase in the uninvolved light chain (uiflc) at the higher dose of 8 g. At the 4 g dose, there was no increase seen in the level of uninvolved free light chain in patients with abnormal ratios.

Patients with a normal FLC ratio at baseline demonstrated minimal change in their ratios at either the 4 or 8 g dose. An increase in paraprotein was seen in these patients but this increase did not reach significance at either dose. There was a significant decrease in the involved free light chain at 8 g, and the uDPYD showed a small decrease at both doses. Individual patient responses are shown in Supporting Information Table VIII.

Discussion

In this randomized, double-blind placebo-controlled cross-over study, curcumin (4 and 8 g daily) decreased the rFLC (−35 and −36%), iFLC (−8 and −10%), and dFLC (−9 and −11%) in both MGUS and SMM patients. Significant reductions were also seen in both total serum protein ($P = 0.04$) and random urinary protein concentrations ($P = 0.04$), but not in the serum paraprotein concentration. To our knowledge, this is the first randomized study to show a beneficial effect of curcumin on light chains in MGUS and SMM patients. Normalization of the FLC ratio has previously been shown in myeloma patients after chemotherapy and have been reported to be highly predictive of achieving a complete response [19,20].

The highly sensitive serum FLC assay enables the quantitation of free kappa and lambda chains (i.e., light chains that are not bound to intact immunoglobulin). An abnormal kappa/lambda FLC ratio is indicative of an excess of one light chain type over the other and is regarded as a surrogate for clonal expansion. Rajkumar et al. [6] noted such findings in patients with MGUS and SMM. They suggested that the risk of progression to MM was significantly higher in those patients with an abnormal FLC ratio. Siegel et al. [9] on the other hand, have recommended serial monitoring of serum FLC during chemotherapy as a real-time evaluation of tumor kill. They have also suggested that serial changes in the iFLC or dFLC rather than the FLC ratio alone should be used to evaluate treatment responses.

Serum FLC have a much shorter circulating half-life (only 2–6 hr) than monoclonal immunoglobulins (20–25 days) [21] and allow for shorter time intervals for assessing treatment responses. We monitored serial responses in rFLC, iFLC and dFLC at 1 week and at 1, 3 and 6 months post curcumin therapy. We found a continuous decrease in all three markers despite crossover to placebo. The lingering effect of curcumin on serum FLC response while on placebo may have been due to a prolonged tumor suppressor effects, altered tumor kinetics or persistent circulating active curcumin metabolites. We did not monitor curcumin blood levels during our study.

The effects of curcumin may vary according to the FLC ratio. In the regression analysis the baseline rFLC was the most important variable affecting the response to curcumin supplementation. Patients with an abnormal rFLC at baseline showed a greater response (decrease) in the various parameters measured than patients with a normal rFLC. A decrease in rFLC was accompanied by a significant increase (at 8 g) in the uninvolved free light chain. This may explain the reduction in the ratio, i.e., an increase in the clones secreting the normal free light chain or a decrease in the clone secreting the abnormal free light chain.

Kappa-secreting plasma cells may be more sensitive to the tumorcidal effect of curcumin than lambda-secreting cells. Patients in Group A as compared to Group B demonstrated a better response on 4 g dose. A possible explanation may be that 9/12 (75%) patients in Group A had an abnormal baseline FLC ratio compared with only 7/13 (54%) patients in Group B. On the other hand, 10/12 (83%) patients in Group A had kappa chains (rFLC > 1.7) compared with 6/13 (46%) in Group B.

In addition to a decrease in FLC ratios, both total serum protein and random urinary protein concentrations

TABLE IV. Combined Data for 18 Patients Who Completed the 8g Arm of the Study

Variables	Baseline mean ± SD	Final mean ± SD	Change (mean ± SD)	Change (%)	*P*	95% Confidence intervals
Free light chain ratio	14.0 ± 23.8	8.9 ± 15.6	−5.2 ± 8.9	−36.8	**0.03/0.02 (wilcox)**	0.58 to 9.74
IFLC (mg/L)	103.7 ± 168	95.7 ± 168	−8.02 ± 46	−8.4	0.481	−15.5 to31.6
dFLC (mg/L)	98.0 ± 167	89 ± 166	−9.03 ± 46	−10.1	0.430	−14.6 to 32.6
Paraprotein (g/L)	25 ± 9.6	24.7 ± 9.3	−0.32 ± 3.2	−1.3	0.69	−1.3 to 1.98
Albumin (37–50 g/L)	43.4 ± 4.1	42.1 ± 3.8	−1.2 ± 2.9	−2.8	0.1	−0.28 to 2.75
B2M (0–3 mg/L)	2.2 ± 0.8	2.3 ± 1	+1.4 ± 0.44	+7.1	0.17	−0.38 to 0.07
Globulin (22–38 g/L)	45.4 ± 10.5	43.6 ± 9.8	−1.8 ± 5.3	−3.9	0.2	−9.5 to 4.48
Total protein (64–83 g/L)	88.7 ± 9	85.7 ± 8.5	−3 ± 5.5	−3.4	**0.04**	0.18 to 5.8
Random urinary protein ($n = 11$)	0.19 ± 0.12	0.14 ± 0.12	−0.05 ± 0.07	−26.7	**0.04**	0.01 to 0.1
UDPYD (3.0–7.4 nmol/mmol)	5.8 ± 2	5.2 ± 1.5	−0.5 ± 1.2	−9.5	0.09	−0.11 to 1.21
PTH (1.6–6.9 pmol/L)	5.1 ± 1.8	4.1 ± 1.2	−1 ± 1.1	−19.8	**0.002**	0.42 to 1.58
Creatinine (45–90 μmol/L)	83.9 ± 14.4	80.9 ± 16.8	−3 ± 11.0	−3.6	0.28	−2.7 to 8.7

Significance of bold values is $P < 0.05$ ie assigned value of significance.

decreased in response to 8 g dose ($P = 0.04$). Our pilot study (14) showed that curcumin was able to decrease paraprotein load by 12–30% in a select group of MGUS patients. While some patients in this study showed a similar response, the serum paraprotein concentrations (serum M-protein) showed no significant response to either curcumin dose. All patients completing this study had an IgG paraproteinemia and may have required longer treatment periods to demonstrate a response. Similar findings have been reported by Vadhan-Raj [22] in myeloma patients treated with curcumin over a 12-week period. While some patients showed an increase in paraprotein on curcumin therapy, this was accompanied by a decrease in rFLC, dFLC, iFLC, and uDPYD (data not shown) suggesting that these patients were not at increased risk of progression while taking curcumin.

The effect of curcumin on the serum vitamin D/PTH axis has not previously been evaluated. In our study, no significant changes were seen with respect to serum calcium or vitamin D concentrations. The serum creatinine levels decreased to a greater extent after the 4-g curcumin dose, while the serum PTH concentrations decreased by 19.8% ($P = 0.002$) after 8-g curcumin dose. Although there are no known direct effects of curcumin on renal or parathyroid cell function, a possible calcimimetic effect warrants further investigation. The decrease in the serum creatinine levels might have occurred due to the decrease in circulating FLC through the glomeruli.

In multiple myeloma, there is an uncoupling between bone formation (usually suppressed) and bone resorption (usually increased). Bone remodeling may be similar in MGUS and SMM as compared to myeloma, with a predilection for a high bone turnover state. Biochemical markers have been used for monitoring the bone activity in patients with plasma cell dyscrasias and assessing their responses to bisphosphonates and chemotherapy [23]. There are several in vitro reports that curcumin may inhibit osteoclast differentiation and activity and promote apoptosis in myeloma cells [24–26]. The data in animal models have been more controversial [27]. In our study, curcumin decreased the uDPYD excretion by 9–14% ($P = 0.09$). This decrease may have been related to the direct effects of curcumin on osteoclasts or indirectly due to the suppression of PTH secretion; however, regression analysis showed that only serum creatinine was a determinant of uDPYD excretion. A similar effect was noted in our previous study where 27% of patients demonstrated a more than 25% decrease in crosslinked N-telopeptides of Type 1 collagen after curcumin therapy.

The majority of MGUS patients (75–90%) will not develop myeloma or a related disorder in their lifetime. The risk of progression is 1.1% per year. In the higher risk SMM group (high serum M protein and an abnormal FLC ratio), the risk of progression is 3% per year. Such a low risk of disease progression, the potential for drug-related toxicity and the failure to achieve a complete remission would weigh against the use of conventional chemotherapy in patients with MGUS and SMM. In this study, we have shown that curcumin may benefit some but not all patients with MGUS or SMM. It would appear that patients with an abnormal ratio benefit most from curcumin administration and an increased effect was seen at the higher dose of 8 g/day. None of the 25 patients who completed the 4g study (which includes the 18 on 8 g/day) have progressed to active disease 1 year after the study has been completed.

The drawbacks of our study are the small patient numbers and its short duration. Our data suggest that future studies should assess the role of curcumin in patients at risk of transformation.

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