VOLUME 52 · SUPPL. I TO No. 2 · JUNE 2010

PANMINERVA MEDICA

PRODUCT-EVALUATION REGISTRY OF MERIVA®, A CURCUMIN-PHOSPHATIDYLCHOLINE COMPLEX, FOR THE COMPLEMENTARY MANAGEMENT OF OSTEOARTHRITIS

G. BELCARO, M. R. CESARONE, M. DUGALL, L. PELLEGRINI, A. LEDDA, M. G. GROSSI, S. TOGNI, G. APPENDINO

EDIZIONI · MINERVA · MEDICA

PUBBLICAZIONE PERIODICA TRIMESTRALE - POSTE ITALIANE S.P.A. - SPED. IN A. P. D.L. 353/2003 (CONV. IN L. 27/02/2004 N° 46) ART. 1, COMMA 1, DCB/CN - ISSN 0031-0808 TAXE PERÇUE

PANMINERVA MED 2010;52(Suppl. 1 to No. 1):55-62

Product-evaluation registry of Meriva®, a curcumin-phosphatidylcholine complex, for the complementary management of osteoarthritis

G. BELCARO [1], M. R. CESARONE [1], M. DUGALL [1], L. PELLEGRINI [1], A. LEDDA [1], M. G. GROSSI [1], S. TOGNI [2], G. APPENDINO [3]

[1]*Irvine3 Labs*
Department of Biomedical Sciences
Chieti-Pescara University, Pescara, Italy
[2]*Indena S.p.A., Milano, Italy*
[3]*Dipartimento di Scienze Chimiche*
Alimentari, Farmaceutiche e Farmacologiche
Università del Piemonte Orientale, Novara, Italy

Aim. **A proprietary complex of curcumin with soy phosphatidylcholine (Meriva®, Indena SpA) was evaluated in a registry study to define its efficacy in 50 patients with osteoarthritis (OA) at dosages corresponding to 200 mg curcumin per diem.**

Methods. **OA signs/symptoms were evaluated by the WOMAC scores. Mobility was studied by walking performance (treadmill), and inflammatory status was assessed by measurements of C-reactive protein (CRP).**

Results. **After three months of treatment, the global WOMAC score decreased by 58% (P<0.05), walking distance in the treadmill test was prolonged from 76 m to 332 m (P<0.05), and CRP levels decreased from 168 ± 18 to 11.3 ±. 4.1 mg/L in the subpopulation with high CRP. In comparison, the control group experienced only a modest improvement in these parameters (2% in the WOMAC score, from 82 m to 129 m in the treadmill test, and from 175 ± 12.3 to 112 ± 22.2 mg/L in the CRP plasma concentration), while the treatment costs (use of anti-inflammatory drugs, treatment and hospitalization) were reduced significantly in the treatment group.**

Conclusion. **These results show that Meriva® is clinically effective in the management and treatment of osteoarthritis and suggests that the increased stability and better absorption of curcumin induced by complexation with phospholipids has clinical relevance and sets the stage for larger and more prolonged studies.**

KEY WORDS: Osteoarthritis – Curcumin - Meriva® - WOMAC – Joints – Pain - Anti-inflammatory drugs.

Over 2,500 preclinical investigations have validated the diarylheptanoid curcumin, the yellow pigment of turmeric (*Curcuma longa* L.), as a potential agent to treat chronic diseases such as inflammation, cancer, and Alzheimer's disease.[1] These pathologies are currently at the forefront of biomedical research because of their large incidence, suboptimal treatment, and growing financial burden to society. However, the clinical translation of these research findings has so far been hampered by the chemical instability of curcumin at intestinal pH values, by its low water solubility and poor oral bioavailability, and by its quick conjugation and excretion. Curcumin undergoes fast ($t_{1/2}$ <10 min) retro-Claisen hydrolytic cleavage at pH 7,[2] its overall oral absorption is dismally low, barely overcoming 50 ng/mL after administration of the clinically unrealistic dosage of 12 g/day,[3] and only phase II metabolites (sulfates and glucuronides) have been consistently detected in biological fluids (plasma, urine) after oral administration in humans.[3] Conjugation can stabilize curcumin in plasma, but its hydrolytical instability and insolubility, poor absorption, and quick elimination generate unfavorable conditions for therapeutic use. As a result, several human studies on curcumin have failed,[4] and the important clinical potential of this compound is still substantially untapped.[5-11]

To improve the poor oral pharmacokinetics of curcumin, two distinct strategies have been pursued. The first one is the co-administration of compounds that

Conflict of interest.—The Authors S. Togni and G. Appendino are managers of Indena S.p.A., producer and distributor of the product Meriva.

Corresponding author: G. Appendino, Università del Piemonte Orientale, Dipartimento di Scienze Chimiche, Alimentari, Farmaceutiche e Farmacologiche, Via Bovio 6, 28100 Novara, Italy.
E-mail: appendino@pharm.unipmn.it

interfere with its metabolic process, such as the alkaloid piperine, a potent inhibitor of hepatic and intestinal transformations of xenobiotics.[6] However, since curcumin can already interfere with drug metabolism by inhibiting several classes of cytochromes,[4] severe reactions might occur when the curcumin-piperine association is administered with other drugs.[4] Furthermore, although an increased absorption has been shown for the curcumin-piperine combination,[7] its clinical efficacy and safety are still largely unknown. The second strategy to improve the oral absorption of curcumin is based on its tendency to form non-covalent adducts with phospholipids, host-guest complexes with cyclodextrins, and liposome inclusion products.[3-9] However, these formulation strategies intended to improve bioavailability also need clinical validation.

Curcumin has a high affinity for biological membranes and has the ability to rapidly penetrate them and form dimeric complexes that span the extra- to intracellular-length.[3-8] As a poorly water soluble phenolic, curcumin can form non-covalent links with phospholipids, and in particular phosphatidylcholine (PC).[9-12] The formation of these complexes could improve the curcumin pharmacokinetics by shielding curcumin from retro-Claisen hydrolysis and stabilizing it at intestinal pH values. Furthermore, capitalizing on the fast exchange of PC between biological membranes and the interstitial fluid, PC could also chaperone curcumin into cell membranes,[9-12] where, thanks to membrane fluidity, the PC-curcumin complex may next move from the luminal to the visceral side of enteric cells. In this way, a substantial increase of absorption could be foreseen.[3, 9-12]

Curcumin as PC complex (Meriva®) has shown promising results in terms of hydrolytical stability [10] and oral absorption.[11] Within its many possible clinical indications, curcumin could be particularly beneficial[1] in the management of osteoarthritis (OA), since it can affect most molecular processes involved in this condition.[12] The long-term side effects and costs of COX2-inhibitors have indicated the need for a complementary treatment in osteoarthritis,[13-15] prompting a registry study on Meriva® to evaluate and define its effects on osteoarthritic pain and its associated physical impairment.

Materials and methods

Two groups of subjects with symptomatic OA were defined: Group A was managed using the "best available treatment" as defined by patient's GP and by specialists; and Group B was managed using the "best available treatment" as above in association with Meriva® administered as a food supplement.

A total of 50 patients with osteoarthritis (confirmed by x-ray) were included in this study. Patients were recruited from the San Valentino Vascular Screening Project. For clinical homogeneity, the main localization of OA in these subjects and the source of most of their signs and symptoms were in either or both knees. Patients were informed about the aim of the study and management procedure and gave oral informed consent.

Meriva® (distributed by Indena SpA, Italy) is already included as an ingredient in over-the-counter food supplements marketed in the USA and Europe. In this study, a finished form in capsules prepared by Thorne Research Inc. (Dover, Idaho, USA) was used at a dosage of 1g Meriva® complex per day (corresponding to 200 mg curcumin per day). Curcumin [16-22] has been used in several clinical and preventive applications without side effects.

Inclusion criteria

Primary osteoarthritis in one or both knees was diagnosed by x-ray investigation. Subjects had mild to moderate pain not adequately or completely controlled with anti-inflammatory drugs. They had to be able to perform the treadmill walking test and to understand all questions from the WOMAC questionnaire.

Exclusion criteria

Exclusion criteria were cardiovascular disease requiring drug treatment, diabetes, BMI>25, severe metabolic disorders, surgery or arthroscopy within the 3 months before inclusion, and any oncological condition or severe bone or joint deformation or condition making the patient unable to walk.

Evaluation of signs/symptoms of osteoarthritis

The questionnaire developed by the Western Ontario and McMaster Universities was applied to describe and rate the symptoms of OA. The questionnaire gives scores for the diverse symptoms of OA (WOMAC scores).[13-15] The status of OA signs/symptoms was evaluated by the investigator together with the patient at inclusion and after at least 3 months of treatment.

TABLE I.—*WOMAC scoring and interpretation. Each response is associated with a conventional score expressed in points, as follows.*

Response	Points
None	1
Slight	2
Moderate	3
Severe	4
Extreme	5

Table I shows the types of responses and the attribution of the WOMAC score.

Evaluation of physical performance

Patients were able to walk on a treadmill (as tested in two tutorial tests). At inclusion and after 3 months performance was evaluated by treadmill at a speed of 3 km/h and an inclination of 10%. The total distance that could be covered without pain was recorded.

Evaluation of associated treatments needed to manage osteoarthritis

A diary was kept to record the use of any other drug prescribed by the patient's GP, the use of which was free (with a warning not to use excessive amounts).

Evaluation of costs and side effects

The costs of treatment and other costs occurring during the trial period (including work disruption and hospital admission) were recorded in a file specifically designated for costs.

Evaluation of edema

Lower limb edema [23-25] was evaluated using an edema score (0-4) as previously defined:

0) no edema;

1) distal, below-knee minimal edema visible only after prolonged standing (all day); not present every day; completely resolving after rest; no other symptoms;

2) below-knee edema visible only after long standing (>3 hours); disappearing after rest and leg elevations; minimal symptoms. Present every day;

3) edema present every day; only partially regressing with night rest; important symptoms; requires pharmacological treatment;

4) edema present day and night not reversible without pharmacological treatment. Impairs daily activities. Often extending proximal to knees and visible also in other body parts (i.e.hands).

Edema was present at inclusion in most patients (88%) as a consequence of reduced activity associated to pain and walking impairment.

Evaluation of plasma C-reactive protein

C reactive protein (CRP) [26] was evaluated by laser nephelometry. Diagnostic use CRP is used mainly as a marker of inflammation. Apart from liver failure, there are few known factors that interfere with CRP production.[16] Measuring C-reactive protein values is useful in determining disease progression or the effectiveness of treatments.

Reference ranges for blood tests

CRP was quantified with laser nephelometry. The test gives results in 30 minutes and is sensitive enough to detect 0.04 mg/L. CRP concentration in healthy subjects is usually lower than 10 mg/L, slightly increasing with age. Higher levels are found in late stages of pregnancy, mild inflammation and viral infections (10–40 mg/L), active inflammation, bacterial infection (40-200 mg/L), and severe bacterial infections and burns (>200 mg/L). Viral infections tend to give a lower CRP level than bacterial infection. In our population normal reference ranges for blood tests were less than 5-6mg/L.

Standards

All test were performed according to our standards defined in several publications. [27, 28]

Statistical analysis

The results were evaluated using analysis of variance (ANOVA with the Bonferroni correction) and the non-parametric Mann-Whitney U test.

TABLE II.—*Main patient characteristics.*

Response		Points
Age	44.4 SD 7.2 range 40-53	45.3 SD 8.6 range 44-53
Male / female ratio	12:11	13:12
BMI	23.6; 1.4	23.7;1.1

TABLE III.—*Details of the variations in score for each WOMAC item (score at inclusion, with SD, in comparison with the score at 2 AND 3 months of treatment). The comparative decrease in controls was significantly lower with minimal, non-significant variations between two and three months.*

Pain	Inclusion		2 months		P1	P2	3 months	
	T	C	T	C			T	C
1) walking	3.1;1	3.2;0.8	2;0.8	3.3;1.2	S	ns	2.1;0.4	3.2;0.9
2) stair climbing	3.4;1.1	3.1;1.1	1.5;1.1	2.1;0.8	S	S	1.5;0.6	2.2;1
3) nocturnal	3.3;1.1	3.2;1	1.4;0.6	2.1;1.1	S	S	1.1;0.4*	2.2;0.8
4) rest	3.6;1	3.1;1.1	1.6;1.2	2.6;1.2	S	S	1.5;1	2.5;0.4
5) weight bearing	3.3;1.2	3.4;1	2.6;1.1	3.4;1.1	S	ns	2.3;0.4*	3.2;0.4
	16.9	*16*	*9,1*	*13.4*	*S*	*ns*	*8.5*#*	*13.3 ns*
Stiffness:								
1) morning stiffness	3.8;1.1	3.6;1.2	2.2;1.2	3.4;1	S	ns	2.1;1	3.5;1.1
2) stiffness late in day	3.6;1.1	3.2;1.3	1.4;0.8	3.1;2	S	ns	1.2;0.5*	3.2;1
	7.4	*6.8*	*3.6*	*6.5*			*3.3*#*	*6.7 ns*
Physical function:								
1) descending stairs	3.2;1	3.3;1.1	1.8;1	2.9;1.1	S	S	1.1;0.3*	2.8;1
2) ascending stairs	3.6;1.1	3.4;1.2	1.1;1.1	2.9;1.1	S	S	1.05;0.6	3;1.1
3) rising from sitting	3.7;1.2	3.5;1.2	1.3;0.9	3.2;1.1	S	S	1.23;0.5	3.3;1
4) standing	3.6;1.1	3.5;1.1	1.5;1	3;1.4	S	S	1.4;0.4	3.2;1
5) bending to floor	3.8;1.2	3.7;1.3	2;1.2	3;1.1	S	S	2.1;0.3	3.2;1
6) walking on flat	3.7;1.1	3.3;1.2	1.6;0.9	3.4;1.2	S	ns	1.5;0.4	3.3;0.8
7) getting in/out (car)	3.9;1	3.6;1.1	1.1;0.4	2.8;1	S	S	1;0.4	2.9;1
8) going shopping	3.7;1.2	3.8;1.2	1.4;0.3	3.1;1.1	S	S	1.2;0.4	3.6;1.1
9) putting on socks	3.8;1	3.9;1.1	2;1.2	3.1;1.2	S	S	1.5;0.4*	3.2;1
10) rising from bed	3.9;1.3	3.7;1.2	2.8;1.2	3.3;1.1	S	S	2.5;1	3.4;1.3
11) taking off socks	3.7;1.1	3.8;1.2	1.5;0.7	3.5;1.4	S	S	1.1;0.5*	3.7;1.1
12) lying in bed	2.7;0.5	2.7;1	1.1;1.1	2.6;1.1	S	ns	1;0.3	2.8;0.4
13) sitting (a)	2.8;1.1	2.7;1.3	1.3;0.8	2.8;1.1	S	ns	1.1;0.3	2.9;0.9
14) sitting (b)	2.4;1	2.5;1.3	1.2;1.1	2;0.7	S	S	1.1;0.5	2.5;0.4
15) getting on/off toilet	3.3;1.1	3.3;1.2	2;0.5	3.3;1.1	S	ns	1.3;0.3*	3.6;1
16) heavy house duties	3.5;1.1	3.4;0.5	2.1;1.2	3.5;1.2	S	ns	1.7;1*	3.8;0.4
17) light house duties	3.8;1	3.7;0.7	1.8;0.4	3.6;1.4	S	ns	1.1;0.5*	3.8;0.8
Total	59.1	57.8	28.4	55.3			22.98*#	58.8 ns
WOMAC Score	83.4	80.6	41.1	75.2			34.8*#	78.8 ns

Interpretation of the table: the first numbers (T) indicate the score relative to patients using active treatment (AVERAGE AND SD); C-column numbers indicate controls. P1: significance: inclusion value VS after (2 months) value. P2: significance: treatment vs controls at 2 months. Results at 3 months: *difference between 2 and 3 months; # difference between groups.

At least 50 subjects should have been observed in the study (with at least 20 completing the study/observation period in each group). This number was chosen to overcome spontaneous or intra-individual variations and to overcome inter-individual variability. A condition such as OA may have periods of high-level signs/symptoms followed by other periods of low-level signs/symptoms. These variations may be due to several factors including individual inflammatory situations as well as environmental and climate changes, working or standing patterns, etc.

Results

Table II shows details of the patients. The treatment and control groups were comparable for age, sex distribution, and presence and intensity of their signs/symptoms. Routine hematochemical tests (hematocrit, hepatic and renal function tests, including blood and urinary Ca) were within normal limits at inclusion and at the end of the study.

Table III shows details of the variations in score for each WOMAC item. There was a significant decrease at 2 months ($P<0.05$) with a further, significant decrease at 3 months ($P<0.05$). Pain, stiffness, and physical function were all positively affected by treatment ($P<0.05$). In treatment patients the WOMAC score (median 83.4 at inclusion vs. 80.6 in controls) decreased to 41.1 (vs. 75.2 in controls) at 2 months and was down to 34.8 at 3 months (vs. 78.8 in controls) ($P<0.05$).

Table IV shows performance concerning social func-

TABLE IV.—*Performance of social functions and the status of emotional function.*

Social function	Inclusion		2 months		P1	P2	3 months	
Negative alterations in:								
1) in leisure activities	T 3.3;1	C 3.4;2)	T 2.2;1	C 3.2;2	S	S	T 2.1;0.3	C 3.5;1
2) community events	3.5;1.1	3.2;1.1	2.2;1	3.3;1.1	S	ns	2;0.1	3.2;1.1
3) church attendance	3.5;1.1	3.6;1	1.8;1.1	3.5;1.1	S	ns	1.1;0.5*	3.6;1
4) with spouse	3.5;1	3.6;1.3	1;1.2	2.1;1.2	S	S	1.1;0.6	2.3;1.1
5) with family	3.6;1.1	3.5;1.2	1.4;1.1	3.3;1.1	S	S	1.3;0.4	3.2;1
6) with friends	3.4;0.8	3.3;0.7	1.4;0.8	3.3;1.2	S	ns	1.1;0.3	3.6;1.2
7) with others	3.7;1	2.1;1.4	1.3;0.5	3.2;0.9	S	S	1.2;0.3	3.3;1
Total	24,5	22.8	11.3	21.9	*	**	9.9	22.7
Emotional function:								
1) anxiety	3.7;1.1	3.6;1	1.1;0.4	3.4;1	S	ns	1;0.3	3.5;1.1
2) irritability	3.8;1.1	3.7;1.2	1.3;0.4	3.6;1.1	S	ns	1.1;0.7	3.4;1.2
3) frustration	3.5;1.1	3.6;1.2	1.1;0.2	3.7;1.3	S	ns	1;0.3	3.6;0.4
4) depression	3.3;1	3.3;1.2	1.4;0.8	3.1;0.8	S	ns	1.1;0.4*	3.3;1
5) relaxation	2.8;0.3	2.7;0.4	1.1;0.3	2.9;1	S	ns	1;0.3	3.4;3
6) insomnia	2.9;1.1	2.8;1	1.1;0.4	2.8;1.1	S	ns	1.1;0.2	3.1;0.7
7) boredom	3.6;1	3.3;1.2	1.1;0.3	3.3;1.3	S	ns	1;0.2	3.4;0.4
8) loneliness	3.6;1.2	3.6;1	1.2;0.4	3.4;0.5	S	ns	1.1;0.2	4.1;1
9) stress	3.9;1	3.8;1.1	2;1.1	3.9;0.6	S	ns	1.2;0.4*	4.3;1.1
10) well-being#	3.8;1	3.7;1.1	1;0.3	3.9;1.2	S	ns	0.9;0.4	3.8;0.8
Total	34.9	34.1	13.4	37.9	*	**	10.5*#	35.9

#Indicates alterations in well being. Score = SUM (points for relevant items). Average score = (total score) / (number of items). Interpretation: minimum total score: 0; maximum total score: 96; minimum pain subscore: 0; maximum pain subscore: 20; minimum stiffness subscore: 0; maximum stiffness subscore: 8; minimum physical function subscore: 0; maximum physical function subscore: 68.

TABLE V.—*Results of the exercise tests (median and range). The treadmill test was performed with the treadmill at the speed of 3 km/hour, with an inclination of 10%.*

Treatment	Controls	Time differ.	Groups differ.
Inclusion			
76 m (15-188)	82m (19-210)	NS	*
2 months			
229 m (106->400) (+201%)#	104m (38-336) (+26.8%) #	P<0.05	*
3 months			
331 (112- >400) +44% *vs* 2-month data	129 (44-383) +24% *vs* 2-month data	P<0.05	*

Difference before-after#.

TABLE VI.—*CRP variations.*

	Treatment	Controls
Inclusion	168 (SD18)mg/Lt	175 (12.3)
8 weeks	10.2 (SD 3.51)*	132 (18.2)
12 weeks	1.31 (SD 4.11)	112 (SD22.2)

* p <0.05 (Mann Whitney).

tion and the status of emotional function. These aspects were also improved in treatment patients as the score decreased at 2 months from a median value of 34.9 (vs 34.1 in controls) down to 13.4 (P<0.05) in comparison with 37.9 in controls. At 3 months there was a further decrease down to a median value of 10.5 (P<0.05) in Meriva® patients vs. 35.9 (not significant) in controls.

Table V shows the results of the exercise (treadmill) tests (median and range). The treadmill (at a speed of 3 km/hour, with a 10% inclination) indicates an improvement of 201% of the initial distance (P<0.05) at 2 months (vs. a 26% increase in controls) and a further increase (+44% at three months) for a total of 336% compared to value at inclusion vs. a total increase of 30.8% in controls (the difference between the two increases is significant; p<0.05). Meriva® treatment produced an increase 5.568 times greater than "the best treatment" when considering physical performance.

Edema was on average 2.81(sd 0.33) in Meriva® patients in comparison with 2.76(0.4) in controls. At 3 months it was reduced in both groups: 1.2 (0.3) in Meriva® patients compared with 2.13 (p<0.05 between groups) in controls.

Table VI shows the variations in CRP in a subgroup

TABLE VII.—*Other observations during the study (median).*

	Meriva®	Controls
1) Decrease in use of nsaids/painkillers	63%	13%
2) Decrease in gastrointestinal complications	69%	15%
3) Decrease in use of other drugs/treatments	38%	11%
4) Decrease in management costs	49%	3%
5) Distal edema decrease	65%	5%
6) Hospital admissions, consultation and tests decrease	38%	6%
7) Specific decrease in non-drug treatment (i.e. physiotherapy), costs due to different complications, new consultations, test et cet.	44%	8%

of subjects treated with Meriva®. Twelve patients in the treatment group (age 43.3;5.1; 8 females) and 11 (age 44.2;4.8; 6 females) in controls had increased CRP at inclusion. The average decrease in CRP values of these subgroups of patients at inclusion and at 8-12 weeks is shown in the table. The decrease in CRP was significant in both groups at 8 weeks with a limited, not significant further decrease at 12 weeks; the decrease in CRP was significantly greater in the Meriva® group ($P<0.05$).

Table VII shows other observations concerning several aspects of the treatment of OA. The decrease in NSAIDs and painkillers during the study was, globally, 63% in the treatment group vs. 12% in controls ($P<0.05$).

The decrease in gastrointestinal complications was 38% in Meriva® patients vs. 15% in controls ($P<0.05$). The decrease in the use of other drugs/treatment was 38% in treatment subjects vs. 11% in controls ($P<0.05$). The global decrease in management costs was 49% in Meriva® patients compared to a decrease of 3% (not significant) in controls (difference between groups: $P<0.05\%$).

The median decrease in distal edema was 65% vs. 5% in controls ($P<0.05$). The presence of edema in these patients is mainly associated with a combination of inflammation, forced reduced activity (caused by pain on motion), and relative impaired limb mobility altering the venous pump function and the venous return, particularly of the lower limbs.

Hospital admissions, consultation and radiological, imaging or instrumental tests decreased (median) 38% ($P<0.05$) in comparison with a 6% (not significant) decrease in controls (difference between groups: $P<0.05$).

The specific decrease in non-drug treatment (i.e. physiotherapy) costs due to different types of complications, new consultations or blood tests was 44% ($P<0.025$) in Meriva® patients vs. 8% (not significant) in controls (the difference between the two groups was significant: $P<0.05$).

Discussion

Curcumin is one of the most extensively investigated products of natural origin. Its broad spectrum of bioactivity and low oral toxicity have expanded its use to several clinical conditions.[1, 12] Many potential beneficial properties of the natural product have not produced effective clinical results because curcumin shows a poor water solubility and stability, a low and unpredictable oral absorption, and a quick metabolism. All these problems have hampered the clinical development of curcumin as a drug as well as an efficacious health food ingredient.

The clinical trials of curcumin reported so far are characterized by a small number (<50) of participants, large doses (>1 g) of the natural product [4] and, often, controversial results.

To overcome the problematic use and dosage of the natural product, a phospholipid complex (Meriva®) was developed by combining curcumin and phosphatidylcholine in a 1:2 ratio.[9] Complexation with phospholipids led to an improved aqueous stability and oral absorption of curcumin.[10, 11]

The management of OA is one of the best clinical possibilities for the use of curcumin in the light of ethno-pharmacological data and its mechanisms of action. Thus, turmeric is used in Asian medicine to treat inflammation and joint pain; curcumin protects chondrocytes from the catabolic action of inflammatory cytokines (IL-1beta, AP-1, NF-kB) and enzymes

(MMP-3, collagenases) and may block proteoglycane degradation.[12]

Curcumin has shown high potency in animal models of rheumatoid arthritis [18] and in a clinical trial that compared its activity with that of the non-steroid anti-inflammatory drug phenylbutazone.[19] This study was the first indication of its clinical efficacy in OA.[20]

Meriva® shows a marked improvement in hydrolytic stability and oral absorption in comparison with non-complexed curcumin.[9-11]

In this product-evaluation registry, a dosage (200 mg) much lower than those employed in previous or current clinical studies (usually greater than 1g/day) was employed.[20]

This dosage was only slightly higher than the dietary intake of curcumin (up to 2 mg/Kg die) in the Indian diet,[20] where turmeric is mainly consumed in an oily matrix favoring the absorption of curcumin.[3]

Meriva® (with curcumin embedded in a phospholipid complex) is a comparable molecular translation of this healthy dietary habit.

This product evaluation registry in patients with OA used the WOMAC [29] score (now considered a standard of evaluation for these clinical problems) for the evaluation of physical performance, which is the most bothersome problem for most patients and leads to an inability to take care of themselves (as, for example, the inability to shop alone). Some secondary outcomes (i.e. consumption of NSAID, management costs, and overall quality of life) are less predictable and may reflect the social context and the possibility offered by healthcare providers.

In this pilot registry a very significant decrease of WOMAC scores was observed, which was associated with an improvement in walking. These results suggest that Meriva® can be used as a complementary treatment in the management of OA, particularly to relieve pain and increase the mobility of patients. Meriva® improves their quality of life and physical function, but it may also produce a significant decrease in treatment costs. The reduced use of NSAID, physical treatments and hospitalization was observed in the treatment group. Curcumin is generally a gastroprotective agent[19] that might protect from the adverse gastric side effects of many anti-inflammatory drugs.

At this stage, it is difficult to define whether the improved physical performance observed with Meriva® is due to a better control of inflammation, pain and rigidity, or to a direct action on muscular function. In the subpopulation with higher CRP, there was a decrease from abnormally increased values (168 ± 18 mg/L) to almost normality (11.3 ±. 4.1 mg/L), suggesting a possible important decrease of inflammation by Meriva®.

Conclusions

These results suggest that Meriva® is effective in OA as a complementary management tool, and the study provides a clinical validation of the effectiveness of phospholipid complexation to improve the hydrolytic instability and poor oral absorption of curcumin.

References

1. Aggarwal BB, Sung B. Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. Trends Pharmacol Sci 2009;30:85-94.
2. Wang Y-J, Pan M-H, Cheng, A-L, Lin, L-I, Ho Y-S, Hsieh C-Y, Lin J-K. Stability of curcumin in buffer solutions and characterization of its degradation products. J Phar Biomed Anal 1997;15:1867-76.
3. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: Problems and promises. Mol Pharm 2007;4:807-18.
4. Mancuso C, Barone E. Curcumin in clinical practice: myth or reality? Trends Pharmaco Sci 2009;30:333-4.
5. Goel A, Kunnumakkara, AJ, Aggarwal BB. Curcumin as "curecumin": From kitchen to clinic. Biochem Pharmacol 2008;75:787-809.
6. Srinivasan K. Black pepper and its pungent principle-piperine: a review of diverse physiological effects. Crit Rev Food Sci Nut 2007;47:735-48.
7. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med 1998;64:353-6.
8. Barry J, Fritz M, Brender JR, Smith PES, Lee D-K, Ramamoorthy, A. Determining the effects of lipophilic drugs on membrane structure by solid-state NMR spectroscopy: the case of the antioxidant curcumin. J Am Chem Soc 2009;131:4490-8.
9. a) Kidd PM. Bioavailability and activity of phytosome complexes from botanical polyphenols: The silymarin, curcumin, green tea and grape seed extracts. Alt Med Rev 2009;14: 226-46. b) Semalty A, Semalty M, Rawat MA, Franceschi F. Supramolecular phospholipids-polyphenolics interactions: The Phytosome® strategy to improve the bioavailability of phytochemicals. Fitoterapia 2009. In press.
10. Giori A, Franceschi F. Unpublished: Indena: investigator's brochure: data on file. 2005.
11. Marczylo TH, Vershoyle RD, Cooke DN, Morazzoni P, Steward WP, Gesher AJ. Comparison of systemic availability of curcumin with that of curcumin formulated with phosphatidylcholine. Cancer Chemother Pharmacol 2007;60:171-7.
12. Henrotin,Y, Clutterbuck AL, Allaway D, Lodwig EM, Harris PM, Mathy-Harterty M, *et al*. Biological actions of curcumin on articular chondrocytes. Osteoarthritis Cartilage 2010;18:141-9.

13. Read SJ, Dray A. Osteoarthritic pain: a review of current, theoretical and emerging therapeutics. Expert Opin Investig Drugs 2008;17: 619-40.
14. Söderman P. On the validity of the results from the Swedish National Total Hip Arthroplasty register. Acta Orthop Scand Suppl 2000;71: 1-33.
15. Baron G, Tubach, F, Ravaud P, Logeart I, Dougados M. Validation of a short form of the Western Ontario and McMaster Universities Osteoarthritic Index function subscale in hip and knee osteoarthritis. Arthritis Rheum 2007;57:633-8.
16. Krishnaswamy K. Traditional Indian spices and their health significance. Asia Pac J Clin Nutr 2008;17:265-8.
17. Funk JL, Oyarzo JN, Frye JB, Chen G, Lantz RC, Joland SD, *et al*. Turmeric extracts containing curcuminoids prevent experimental rheumatoid arthritis. J Nat Prod 2006; 69:351-5.
18. Deodhar SD, Sethi R, Srimal RC. Preliminary studies of antirheumatic activity of curcumin (diferuloyl methane). Ind J Med Res 1980;70:632-4.
19. Jurenka JS. Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. Altern Med Rev 2009;14:141-53.
20. Thimayamma VS, Rao P, Radhaiah G. Use of spices and condiments in the diet of urban and rural families. Ind J Nut Diet 1983;20:153-62.
21. Mahattanadul S, Nakamura T, Panichayupakaranant P, Phdoongsombut N, Tungsinmunkong K, Bouking P. Comparative antiulcer effect of bisdemethoxycurcumin and curcumin in a gastric ulcer model system. Phytomedicine 2009;16:342-51.
22. DeSanctis MT, Cesarone MR, Incandela L, Belcaro G, Acerbi G. Methods of evaluation and quantification of microangiopathy in high perfusion microangiopathy (chronic venous insufficiency and diabetic microangiopathy). J Cardiovasc Pharmacol Ther 2002;Suppl 1:S3-6.
23. Cesarone MR, Belcaro G, Nicolaides AN, Arkans E, Laurora G, De Sanctis MT *et al*. The edema tester in the evaluation of swollen limbs in venous and lymphatic disease. Panminerva Med 1999;41:10-4.
24. Cesarone MR, Laurora G, De Sanctis MT, Steigerwalt R, Belcaro G. Edema tester. Assessment of edema of the legs. Minerva Med 1998;89: 309-13.
25. Stuard S, Cesarone MR, Belcaro G, Ledda A, Cornelli U, Di Renzo A *et al*. Screening nelle farmacie: documento e linee guida 2008. Lo studio clinico NPT. Minerva Cardioangiol 2008;56(5 Suppl):11-20.
26. Thompson D, Pepys MB, Wood SP. The physiological structure of human C-reactive protein and its complex with phosphocholine. Structure 1999;7:69-77.
27. Belcaro G, Nicolaides AN. Noninvasive Investigations In Vascular Diseases. Imperial College Press, London; 2001.
28. Belcaro G, Nicolaides AN, Stansby G. The venous Clinic. Imperial College Press, London; 2002.
29. Nilsdotter AK, Isaksson F. Patient relevant outcome 7 years after total hip replacement for OA - a prospective study. BMC Musculoskelet Disord 2010;11:47.