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ORIGINAL RESEARCH

The "MESACA" Study: Methylsulfonylmethane and Boswellic Acids in the Treatment of Gonarthrosis

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ABSTRACT

Introduction: Osteoarthritis is a chronic rheumatoid disease mediated by metalloproteinases and inflammatory cytokines. Methylsulfonylmethane (MSM) and boswellic acids (BA) each show promise in the treatment of inflammatory processes, but the efficacy of combined treatment with these substances in the treatment of arthritis has not yet been studied. ***Methods:*** In this prospective randomized clinical trial, MESACA (for "methylsulfonylmethane and boswellic acids in the treatment of knee arthritis"), 60 subjects affected by arthritis of the knee were randomly assigned to an experimental group treated for 60 days with 5 g of MSM and 7.2 mg of BA daily, or a control group which was administered a placebo. At 2 and 6 months follow-up (FU), the efficacy of combined treatment with these two dietary supplements was assessed using the visual analog pain scale (VAS) and the Lequesne index (LI) for joint function, as well as monitoring the use of anti-inflammatory drugs (nonsteroidal anti-inflammatory drugs and anti-cyclooxygenase-2). ***Results:*** Pain, assessed with the VAS scale, was worse in the group treated with MSM and BA as compared with the placebo group at 2 months FU (3.8 vs. 2.7; P=0.04), whereas no difference between the two groups was observed at 6 months FU (2.7 vs. 3.6; P=0.2). No statistically significant differences were found in the LI between the two groups at either FU (2 months: 4.8 vs. 4.2; P=0.51; 6 months: 4.4 vs. 4.5; P=0.91). By contrast, a statistically significant difference in patients need for anti-inflammatory drugs was seen in the experimental as compared to the placebo group, even by 2 months FU (0.2 vs. 0.6 tablets/day; P<0.0001), that persisted up to the end of the study (0.1 vs. 0.6 tablets/day; P<0.0001). ***Conclusions:*** Although the combined administration of MSM and BA in the treatment of gonarthrosis was not shown to be more efficacious than placebo in the management of the clinical and functional

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picture, it significantly reduced patients need for anti-inflammatory drugs.

Keywords: arthritis; boswellic acids; cyclooxygenase-2 inhibitors; Lequesne index methylsulfonylmethane; nonsteroidal anti-inflammatory drugs; pain; visual analog scale

INTRODUCTION

Osteoarthritis (OA) is one of the most common forms of degenerative joint disease. It involves a degeneration of the joint cartilage structures, followed by the development of reactive proliferative phenomena at the level of the bone and surrounding cartilage.[1] From the pathophysiological standpoint, it is a complex process with multiple etiopathogenesis, caused by passive mechanisms of traumatic type, as well as active cell-mediated mechanisms that induce an anomalous response of the joint chondrocytes, leading to an imbalance between anabolic and catabolic processes that activates inflammatory processes.[2] Radiographic signs of OA are present in 80% of the population >65 years of age, and 60% have symptomatic disease.[1] The most common sites of localization are the knee, hip, spine, interphalangeal joints, and trapezo-metacarpal joint. From the clinical standpoint, symptomatic OA includes pain, stiffness, and functional limitation, that progressively worsen and can ultimately lead to a total loss of autonomy. This disease has high social and health-service costs, that are progressively rising, and causes a severe decline in the quality of life of affected patients. For these reasons it is obvious that all possible therapeutic strategies are adopted in patients at risk, both for primary prevention and secondary treatment.[3]

The administration of supplements can help in the management of the degenerative process.[4] Treatment of the symptomatic phase requires the administration of nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, and in more severe forms, opioid painkillers.[5] These drugs are fairly efficacious in reducing the pain and inflammation, but it has been amply demonstrated that long-term administration is associated with a high incidence of side effects.[6] This is why new alternative, safer strategies for the management of OA are urgently needed.

The aim of this work is to verify the clinical efficacy, in the treatment of moderate to severe gonarthrosis, of the combination of two dietary supplements (neutraceuticals), namely methylsulfonylmethane (MSM) and boswellic acids (BA), that have been shown to have an anti-inflammatory action in experimental and clinical studies,[7-9] as well as a good drug safety profile.[10-11]

MATERIALS AND METHODS

This prospective, randomized, double-blind placebo controlled trial, MESACA (for "methylsulfonylmethane and boswellic acids in the treatment of knee arthritis") was aimed at assessing the efficacy and duration of the effects of 5 g of MSM and 7.2 mg of BA, administered in the commercial formulas Lignisul® and Triterpenol® (Laborest Italia S.p.A., Nerviano, Milan, Italy), respectively. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee. Informed consent to take part was given by all participants. The knee was the chosen anatomical site to assess the efficacy of the active ingredients administered.

Inclusion Criteria

The inclusion criteria were as follows:

- men and women >45 and <85 years of age;

- a diagnosis of OA of the knee according to the criteria of the American College of Rheumatology;[12]
- grade 3 Kellgren and Lawrence radiographic staging,[13] in which the severity of the arthritis is assessed on a scale from 0-4, hypothesizing a sequential evolution from the manifestation of osteophytes through a reduction in the width of the joint space, to subchondral sclerosis and finally the formation of cysts;
- frequent joint pain (several days a week) for at least 6 months before recruitment;
- pain in the knee, scored at least 2 cm on a 10 centimetric visual analogic scale (VAS), where 0 means no pain and 10 is the worst pain possible;
- a score of >2 on the Lequesne pain-function index (LI).[14] The LI is a disease-specific validated questionnaire that poses a series of questions about pain in the knee (five questions on a scale from 0 to 2, where 0 indicates no pain and 2 intense pain), functional limitation (four questions, using the same scale) and maximum walking distance (one question, with a score from 0 to 6, where 0 indicates the ability to walk for an unlimited distance and 6, the inability to cover 100 m). The maximim worst final score was 24.

Lack of symptoms in other joints was not stipulated.

Exclusion Criteria

The exclusion criteria were as follows:

- previous surgery of the affected knee;
- disease processes such as rheumatoid arthritis, autoimmune diseases, systemic diseases, and tumors;
- obesity (BMI >30 kg/m^2);
- altered blood chemistry and kidney, liver, and metabolic (diabetes mellitus) function;
- intra-articular hyaluronic acid/cortisone infiltrations to the affected knee within 3 months before the start of the study;
- systemic cortisone treatment taken within 3 months before the start of the study;
- supplements (glucosamine, chondroitin sulfate, bromeline, etc) taken within 3 months before the start of the study (patients were also informed that they were not to be taken for the following 6 months).

A 7-day wash-out period for anti-inflammatory drugs was stipulated before the first recruitment visit.

Recruitment and Randomization

The required study population was 60 patients affected by gonarthrosis. Patients were randomized in a double-blind manner to two groups; experimental and control, each consisting of 30 patients. To ensure homogeneity, the following randomization criteria were adopted: sex (female/male), age (45-60 and 61-85 years old), smoker (yes/no). The clinician who conducted the patients recruitment and monitoring processes was blinded to the treatment administered (experimental or placebo), as the randomization was performed by a different physician. At recruitment, two homogeneous groups (determined by sex, age, and smoking habit) were randomly created.

Study Protocol

The study protocol included a clinical visit, medical history, and assessment using the VAS and LI at the time of recruitment (T0) and at the two follow-up (FU) visits at 2 months (T1) and 6 months (T2). If patients were in pain, they were allowed to take 500 mg of paracetamol, 20 mg of pyroxicam, or 50 mg of diclofenac, and a period of at least five times the half-life

of the drug was allowed to pass before assessing symptoms. Patients were asked to write down their use of NSAIDs and anti-COX-2 in a diary; the mean quantity of anti-inflammatory drug tablets/day was evaluated.

Pharmacological Treatment

All participants were asked to take one drug sachet every day for 60 days at the main meal. In the experimental group the sachet contained 5 g of MSM and 7.2 mg of titred BA, and in the control group, a placebo. The active ingredient has been commercially available since 2007 (Artrosulfur®, Laborest Italia S.p.A.). The purity of MSM was estimated by high resolution gas chromatography to be 99.9%.[15] The alpha and beta BAs were obtained by electromagnetic field extraction, resulting in the formation of free-form synergic macromolecular triterpene complexes.[16]

Outcomes Measures

The primary outcome measure was the response to treatment, defined as a decrease of pain on the VAS and an improvement in the patient's global assessment score on the LI from baseline to the 2 months FU, and finally the 6 months FU. The secondary endpoint was a reduction in patients need to take anti-inflammatory drugs.[17] All analyses were performed at each FU, comparing results within each group and between the two groups. Because the randomization had taken into account only age, sex, and a smoking habit, it was hypothesized that at subsequent FUs there might be a post-randomization imbalance in the clinical evaluations between the two groups. We decided to use any difference from baseline values in individual parameters, as well as absolute values, to compare the experimental group with the control group.

Power Analysis and Statistical Analysis

The sample analysis of the study was conducted on the primary outcome of the study, ie, the pain, expressed as VAS, given the presence in literature of several studies on the effects of Boswellia serrata and MSM on knee arthritis.[7,15,18,19] Starting from two homogeneous groups determined by the mean value of VAS at baseline, we hypothesized a difference of two units, with ± standard deviation (SD) of two units, in the mean VAS value between the two groups, as from the second month of therapy. We established a margin of error of 5% and confidence intervals (CIs) of 95%; power calculation was carried out with the Raosoft sample size calculator. This yielded a minimum number of subjects per group of 26.

Statistical Analysis

Continuous variables are expressed as means and SDs, and categorical variables as proportions and 95% CIs. The chi-square test was used to compare categorical variables. The means of the LI and VAS scores within the two groups were compared by student *t* test for independent samples. To compare mean LI and VAS values in the two groups at recruitment and FU, student *t* test for paired samples was employed.

Given the relatively small sample size, we also relied on Cohen's *d*, a measure of effect size, to describe differences between the groups. Cohen's d is defined as the difference between two means divided by the pooled SD for those means, and is a useful way to conceptualize the magnitude of difference between groups when traditional parametric testing is not appropriate (eg, because of small sample size). Although interpretations of Cohen's d vary, most researchers consider 0.20-0.40 a small effect, 0.40-0.80 a medium effect, and >0.80 a large effect.[20]

Significance was set at a value of $P<0.05$. Stata software was used for data processing (Stata Corp, College Station, TX, USA).

RESULTS

The enrolled population consisted of 40 women (66.7%; 95% CI: 54.7-78.6) and 20 men (33.3%; 95% CI: 21.4-45.3). Mean age was 61.8 ± 8.5 years. Each group consisted of 20 women and 10 men. In the experimental group, mean age was 63.4 ± 8.2 years, and in the control group 60.2 ± 8.6 years (t=1.45; P=0.51). Smokers accounted for 13.3% (n=4; 95% CI: 1.2-25.2) of the experimental group and 16.7% (n=5; 95% CI: 3.3-30) of the control group (chi-square = 0.13; P=0.71). At recruitment, mean values were 7.2 ± 1.7 on the VAS, and 11.1 ± 3.7 for the LI. The mean VAS score was statistically homogeneous in the experimental group (7.5 ± 1.5) versus the control group (6.7 ± 1.9) (t=1.7; P=0.09), but the LI mean values were significantly worse in the experimental group (12.2 ± 2.7) than the controls (10.1 ± 4.2) (t=2.29; P=0.03). Daily intake of anti-inflammatory drugs was comparable in the experimental group (0.7 ± 0.4 tablets/day) and controls (0.7±0.4 tablets/day) (t=0.14; P=0.44) (Table 1). At FU there was one drop-out in the experimental group, for personal reasons not imputable to side effects of the treatment. No patient reported adverse effects due to daily ingestion of the sachet, nor complained of side effects.

Pain Control

In the experimental group, the VAS scores reduced significantly from T0 (7.5 ± 1.5) to T1 (3.8 ± 1.6) ($P<0.0001$) and then T2 (2.7 ± 2.5) (P=0.04). In the control group the VAS score was significantly reduced between T0 (6.7 ± 1.9) and T1 (2.7 ± 2.4) ($P<0.0001$), but the scores had worsened by T2 (3.6 ± 3.1) (P=0.14). Comparison between the VAS scores at 2 months showed a statistically significant worse mean in the experimental group than the controls (t=2.06; P=0.04; d=0.26, small effect size). By contrast, at the 6 months FU a better mean value was recorded in the experimental group, although this was not statistically significant (t=–1.2; P=0.2; d=0.33, small effect size).

Comparison of the percentage reduction in the VAS score was statistically significant in the control group than the experimental group at T1 (d=0.44, medium effect size) (Table 2) and in the experimental group than the controls at T2 (d=0.46, medium effect size) (P=0.04) (Table 3).

Table 1. Mean values (± SD) of visual analog scale (VAS), Lequesne index (LI), and anti-inflammatory drug usage in the two groups, at recruitment (T0) and the subsequent 2 (T1) and 6 months (T2) follow-up visits.

Group	Score	T0	T1	T2
Experimental	VAS	7.5 ± 1.5	3.8 ± 1.6	2.7 ± 2.5
	LI	12.2 ± 2.7	4.8 ± 3.0	4.4 ± 4.4
	NSAIDs and anti-COX-2 (tablets/day)	0.7 ± 0.4	0.2 ± 0.2	0.1 ± 0.2
Control	VAS	6.7 ± 1.9	2.7 ± 2.4	3.6 ± 3.1
	LI	10.1 ± 4.2	4.2 ± 3.6	4.5 ± 4.3
	NSAIDs and anti-COX-2 (tablets/day)	0.7 ± 0.4	0.6 ± 0.4	0.6 ± 0.3

COX-2=cyclooxygenase; NSAID=non-steroidal anti-inflammatory drugs.

Table 2. Mean values (± SD) of reduction (expressed as a percentage) of visual analog scale (VAS) at 2 months follow-up (T1) and statistical comparison between the two groups.

Group	VAS reduction (%) at T1	*t*	*P*
Experimental	49.5 ± 19.1	–1.67	0.04
Control	61.5 ± 34.2		

Table 3. Mean values (± SD) of reduction (expressed as a percentage) of visual analog scale (VAS) at 6 months follow-up (T2) and statistical comparison between the two groups.

Group	VAS reduction (%) at T2	*t*	*P*
Experimental	62.6 ± 33.9	1.76	0.04
Control	42.1 ± 53.7		

Table 4. Mean values (± SD) of reduction (expressed as a percentage) of Lequesne index (LI) at 2 months follow-up (T1) and statistical comparison between the two groups.

Group	LI reduction (%) at T1	*t*	*P*
Experimental	60.6 ± 22.4	–0.70	0.24
Control	64.9 ± 25.6		

Table 5. Mean values (± SD) of reduction (expressed as a percentage) of Lequesne index (LI) at 6 months follow-up (T2) and statistical comparison between the two groups.

Group	LI reduction (%) at T2	*t*	*P*
Experimental	64.7 ± 33.2	–0.39	0.34
Control	61.2 ± 34.2		

Functional Assessment

It was found that the experimental group had a statistically worse LI than the control group at baseline (Table 1). In the experimental group, the LI showed a significant reduction from T0 (12.2 ± 2.7) to T1 (4.8 ± 3.0) ($P<0.0001$). At T2 there was a trend toward a further improvement (4.4 ± 4.4) ($P=0.50$). In the control group, there was a significant improvement from T0 (10.1 ± 4.2) to T1 (4.2 ± 3.6) ($P<0.0001$), but a decline at T2 (4.5 ± 4.3) ($P=0.64$).

No statistically significant difference in the mean LI was found either at 2 months ($t=0.66$; $P=0.51$; $d=0.19$, negligible effect size) or 6 months FU ($t=–0.1$; $P=0.91$; $d=0.27$, small effect size) between the experimental group and the control group.

Comparison of the percentage reduction of the LI in the two groups was not statistically significant either at T1 ($d=0.19$, negligible size effect) (Table 4) or T2 ($d=0.10$, negligible size effect) ($P>0.05$) (Table 5).

Use of Anti-Inflammatory Drugs

In the experimental group, the use of anti-inflammatory drugs reduced significantly from T0 (0.7 ± 0.4 tablets/day) to T1 (0.2 ± 0.2 tablets/day) ($t=7.76$; $P=0.0001$) and then T2 (0.1 ± 0.2 tablets/day) (T1 vs. T2: $t=2.05$; $P=0.02$; T0 vs. T2: $t=7.46$; $P<0.0001$). In the control group, no statistically significant variation in anti-inflammatory drugs dosage was recorded from T0 (0.7 ± 0.4 tablets/day) to T1 (0.6 ± 0.4 tablets/day) ($t=1.57$; $P=0.06$), and T2 (0.6 ± 0.3 tables/day) (T1 vs. T2: $t=0.65$; $P=0.25$; T0 vs. T2: $t=1.74$; $P=0.04$) (Table 1).

Comparison of the use of anti-inflammatory drugs in the two groups showed that at 2 months FU this parameter had a statistically significant lower value in the experimental group than in the control group ($t=4.88$, $P<0.0001$; $d=1.28$, large effect size). This statistically significant improvement persisted at the 6 month FU ($t=7.03$, $P<0.0001$; $d=1.84$, large effect size).

Size Effect

Estimating effect size using Cohen's *d* to compare the two groups in relation to the primary outcome resulted in similar values at 2 months FU for the VAS and at 6 months FU for both VAS and LI (small effect size). No significant difference was found for LI at the first FU (negligible effect size). When considering the percent reduction, we found better VAS scores in the experimental group than in controls at T1 and T2 (medium effect size), whereas no differences emerged between the two groups for LI at either FU (negligible effect size).

Estimating effect size in relation to the use of anti-inflammatory drugs resulted in important differences between the two study groups at the 2 months and 6 months FU (large effect size).

DISCUSSION

In recent years, many experimental and clinical studies have addressed the etiopathogenesis of OA and evaluated new therapeutic strategies for improving the management of the disease. The pathogenic mechanism underlying arthritic processes is complex: an initial lesion of the cartilage stimulates the mechanotransducers responsible for activating metalloproteinases (MMP) and local pro-inflammatory cytokines (CK) that trigger a cartilage degeneration process. This is then maintained by an increased cell expression of the corresponding membrane receptors and a local increase in inflammatory cells.[2]

Therapeutic guidelines for OA of the knee have been drawn up by various study groups, mainly the Osteoarthritis Research Society International (OARSI)[20] and the European League Against Rheumatism (EULAR).[21] Aims include education of the patient about the pathogenesis and management of OA, pain relief, functional improvement and a reduction of disability, disease prevention, and slowing of the disease process and its consequences. The different therapies for OA have been evaluated and evidence-based conclusions drawn. Regulating agencies such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have warned that caution should be used when prescribing NSAIDs and COX-2 inhibitors,[22] because these drugs can have serious side effects on the gastroenteric tract, the kidney, the cardiovascular system, the liver, and the hemostatic and immune systems, and allergic reactions have also been reported.[6] In addition, possible interactions must be taken into account between anti-inflammatory agents and other drugs that the patient may need to take for concomitant diseases such as corticosteroids, heparin, aminoglycosides, diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, digoxin, cisplatin, methotrexate, and oral anticoagulants. Neither the guidelines nor the regulating agencies indicate any drugs that are able to modify the degeneration of the joint structure and disease course. However, the EULAR guidelines stress that according to randomized studies, the strongest evidence of a beneficial effect on the symptoms of gonarthrosis has been obtained with the use of glucosamine sulfate.[23] In recent years, viscosupplementation with hyaluronic acid has yielded good results in research on efficacious strategies to improve pain control and joint mobility.[24] One or more treatment cycles can achieve pain relief and improved joint function lasting several months.[25] However, possible side effects, such as the risk of local infections, have been described, as well as a new acute onset of pain.[26]

The rationale for administering MSM and BA in arthritic patients was drawn from experimental studies showing that

neutraceuticals can modulate the pathogenic mechanisms underlying OA at several levels.[7-9] MSM is a sulfuric organic compound composed of 34% sulfur, due to the oxidation of dimethyl sulfoxide. Coffee, milk, meat, eggs, fish, wheat, leafy plants, and vegetables have a rich content of MSM and can restore the integrity of connective tissue, due to the sulfur content.[27] Experimental studies have demonstrated actions inhibiting various CKs involved in inflammatory processes.[7] Apart from these anti-inflammatory effects, MSM has been reported to have chemopreventive effects, inhibiting prostacyclin (PGI) synthesis, as well as an anti-sclerosis action, activating the metabolism of the eicosanoids and scavenging free radicals.[28] No side effects have been described even at doses of 5 to 7 times the maximum recommended dose.[10] Clinical applications of MSM in the treatment of hyperacidity, parassitosis, constipation, skeletal-muscle pain, arthritis, allergies, and immunomodulation have yielded promising results.[8] Many clinical studies support the efficacy of dietary supplements with MSM in patients with joint diseases such as OA, rheumatoid arthritis (RA) and lupus. In OA patients, the use of MSM in association with other supplements, such as glucosamine and chondroitin sulfate, has been shown to reduce pain and swelling and improve joint mobility and function.[29-31] Other authors conducting clinical studies to evaluate applications in the treatment of gonarthrosis have shown that MSM administered for 12 weeks alone or in association with glucosamine has effects on reducing pain and improving joint function that persist for 12 weeks after the end of treatment.[9] Apart from the above-described systemic applications, the efficacy of sulfur in the local treatment of arthrtitic disease has been amply described in experiences of bathing patients in mineral sulfate-bicarbonate-calcium water.[32]

The pharmacological and clinical properties of Boswellia extract have recently undergone a systematic study.[11] The main active pharmacological ingredients are alpha and beta BAs, that inhibit inflammatory processes, acting on cyclo- and lipo-oxygenases to produce a good anti-inflammatory and analgesic action, and reducing glycosaminoglycan (GAG) degradation of the joint cartilage.[33] The incidence of side effects, such as diarrhea, abdominal pain, and nausea, reported in some studies, did not seem to show appreciable differences between the treatment group and placebo controls.[11] In the rat, the absence of teratogenic effects has been ascertained.[33] Promising results have been obtained in clinical applications to treat asthma, RA, Crohn's disease, collagenous colitis, and arthritis.[11] Kimmatkar et al.[34] and Sontakke et al.[35] reported that in patients affected by gonarthrosis, the administration of Boswellia serrata extract for a period of between 6 weeks and 6 months improves the clinical and functional picture, and the results were stable 1 month after treatment.

The use of anti-inflammatory and analgesic drugs and bone mineral supplements is supported in literature, as well as physiokinesitherapy applications, to manage initial forms of arthritis and induce regression in symptomatic phases.[4]

A clinical study reported the efficacy of the combined administration of the these two dietary supplements in the treatment of degenerative joint disease, studying patients affected by dysfunctions of the temporomandibular joint. The efficacy of the supplements was assessed on pain management, improvements in the maximum mandibular range of movement, and magnetic resonance imaging (MRI) staging.[15] The treatment was shown to improve pain and joint function after 24 weeks, but no significant differences were found, as compared to the control group. The

comparable results were attributed to the use of NSAIDs. However, significant differences emerged in the treated group at mandibular MRI: in 12 of the 26 patients treated, there was an improvement in the structure of the inter-articular disk and reduced joint degeneration. These findings support the hypothesis that MSM and BA, by limiting the formation of free radicals and blocking leukotriene synthesis, may inhibit the inflammatory processes mediated by inflammatory CKs and MMP underlying the joint denegeration process.[7,8,31,34,36] It may be that they have an action stimulating cartilage formation, that could explain the improvements observed in the experimental group. Further studies are needed to examine their effects on different joint structures and in different diseases.

In view of the above-described experimental and clinical evidence, this first prospective randomized double-blind clinical trial was designed to evaluate the efficacy of combined treatment with MSM and BA in patients affected by gonarthrosis. Improvements of the clinical and functional picture were assessed by the VAS, to measure pain, and the LI, to quantify the severity of the functional limitation. Particular care was taken to monitor the use of anti-inflammatory drugs, bearing in mind the side effects of these drugs when taken for prolonged periods in chronic diseases like arthritis.[37] The primary endpoint of this study was to assess the efficacy of the treatment in terms of reducing pain and improving joint function. At the 2 month FU, a trend toward an improvement was observed in both groups. The fact that there seemed to be an improvement in symptoms also in the placebo group comes as no surprise in a prospective clinical study, in which one of the important problems is to prevent patient drop-out, since it involves a number of different clinical examinations and assessments.[38] In this study, patients were asked to note down their need to take anti-inflammatory drugs in a diary. In any case, the initial improvement in the VAS score and LI recorded in the placebo group was no longer present by the 6 months FU, whereas the experimental group showed a trend toward a further improvement by the end of the study, although this was not significant.

Comparison of the effect of the therapy between the two groups demonstrated that the mean VAS score was statistically worse in the experimental group at the 2 month FU, whereas there were no significant differences regarding the VAS score at 6 months, and the LI at both 2 and 6 months. Analysis of the primary outcome measure did not therefore reveal a greater efficacy of the two supplements. The discordance between the clinical results obtained in this study and the improved results reported in literature may be correlated to patients more severe disease within the study (moderate-severe grade of Kellgren and Lawrence radiographic staging[13]) as compared to the patients recruited in previous studies (mild-moderate grade).[15,30]

The clinical effect of therapy with MSM and BA was assessed by considering the minimal clinically-important difference (MCID); that is, the smallest difference in an outcome score which a patient perceives as beneficial.[39] For knee OA Tubach et al.[40] defined it as –1.99 cm on the VAS. At the end of our study the difference for the VAS between the experimental group and control group was 3.6 cm versus 2.7 cm, ie, a difference of only –0.9 cm, and therefore not clinically significant in the light of the MCID. Also, in terms of effect size, the patients treated with MSM and BA showed similar symptoms to those of the placebo group (small effect size).

For the LI, no MCID reference value was found in the literature to help compare the groups; in any case, estimates of effect size

suggest that the functional picture was similar in both groups at the end of the study (small effect size).

These results call into question the need to analyze the second study endpoint; in other words, the patients need to take anti-inflammatory drugs. To monitor this use, patients were instructed to take these drugs in case of need, noting this down in a diary. Of note, there was a statistically and clinically significant difference in the need to take NSAIDs and anti-COX-2 between the patients in the experimental group and the controls, with a large size effect.

On this basis, we may hypothesize that the trend toward a clinical improvement may be justified, in the placebo group, by the continued administration of NSAIDs and anti-COX-2, and in the experimental group, by the administration of MSM and BA. This supports the hypothesis that the combined administration of these two supplements can assist in the management of the clinical and functional symptoms of the patient with gonarthrosis in substitution of the use of anti-inflammatory drugs. Estimating effect size in relation to the use of anti-inflammatory drugs confirms a significant reduction in the use of NSAIDs and anti-COX-2 in the experimental group.

Thus, although the primary endpoint was not satisfied, further studies with a longer lasting, different design, and of larger populations, are needed to establish whether the administration of MSM and BA can replace that of NSAIDs and anti-COX-2 in the management of the OA patient. In fact, despite the similar clinical-functional picture in the two groups, as emerged by valuation of the MCID and by calculation of the size effect, the use of anti-inflammatory drugs was significantly different. The two supplements were shown to induce a significantly reduced need for anti-inflammatory drugs even after 2 months, and this effect still persisted at 4 months after suspension of the dietary supplementation. A trial specifically designed to directly compare MSM and BA with NSAIDs would be needed in order to assess whether they could be regarded as the preferred medication in OA.

A strong point of this work is the longer period of verification of the effects of MSM than has previously been described; up to 4 months after the end of treatment. Kim et al.[30] monitored the beneficial effects induced by MSM during 12 weeks' administration, while Usha and Naidu[19] reported the persistence of MSM effects at FU, 12 weeks after the end of treatment. We hypothesized that administration of BA could contribute to a longer duration in the combined supplement administrated in this study, since the effects of these acids have been shown to be long-lasting. In fact, although Sengupta et al.[36] monitored improvements only during the 90 days of administration of BA, Sontakke et al.[35] described stable effects at 6 months after the end of treatment.

Limitations of this study include the absence of a control group treated with supplements and the small study population, which could explain the statistically significant differences in the LI at baseline between the two groups. It is important to note that patients need to be constant and collaborative, and take the dietary supplement daily for a long period of time, although in this study the treatment was well tolerated and compliance was high (29/30 patients in the experimental group), with no side effects being reported. Besides, the present trial explored effects on patients with gonarthrosis using clinical and functional scales but not imaging tests, since previous experiences with bone mineral supplements did not reveal visible tissue modulation at such

tests.[34] In view of the findings of Castroflorio et al.,[15] it would now be interesting to explore the effects of MSM and BA at the cartilage level by imaging tests. Although the use of a low LI (>2) in the inclusion criteria could be considered another weak point of our study, resulting in the recruitment of asymptomatic patients or those with only minor functional symptoms, the low percentage (<10%) of patients with a low LI allows the study to exclude the presence of a floor effect in the patient population.

CONCLUSION

Given the putative mechanisms of action, the use of MSM and BA could be supported in the treatment of OA. Evidence of efficacy when administered singly has been reported, but this is the first study to assess the efficacy of combined treatment of MSM and BA in the management of gonarthrosis. Although these results did not reveal a greater efficacy than the placebo, it was found that they significantly reduced patients need to take anti-inflammatory drugs. Further studies are needed to investigate this potential effect.

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