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Short-Term Efficacy and Safety of Betamethasone Valerate 2.25 mg Medicated Plaster in Patients with Chronic Lateral Epicondylitis: Results of a Randomised, Double Blind, Placebo-controlled Study

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SUMMARY

Background. This placebo-controlled, double-blind study evaluated the short-term effects of betamethasone valerate (BMV) 2.25mg medicated plaster in patients with chronic lateral elbow tendinopathy (LET).

Methods. Adult outpatients with LET and on-movement pain intensity ≥50 mm at a 0-100mm visual analogue scale (VAS) were randomised to receive BMV (N=101) or placebo (N=98), 12 hours/day for 4 weeks. Pain decrease from baseline to Day 28 was the primary endpoint. Other endpoints were: patient-rated tennis elbow evaluation (PRTEE), use of rescue paracetamol, tolerability at the application site.

Results. Decrease in mean pain VAS from baseline to Day 28 was significantly higher with BMV vs. placebo: the difference between groups (intent-to-treat) was -8.57 mm (95% CI: -16.19 to -0.95 mm; p=0.028). Higher pain decreases in the BMV group over placebo were reported weekly during each control visit and daily in patients' measurements on diaries. Treatment with BMV also led to higher decreases vs. placebo in PRTEE total, pain and functional disability score. Use of paracetamol was minimal. BMV plaster was well tolerated for general and local adverse events.

Conclusions. BMV 2.25mg plaster was superior to placebo and well tolerated in patients with painful chronic LET.

KEY WORDS

betamethasone valerate; lateral elbow tendinopathy; pain relief; PRTEE

BACKGROUND

Primary disorders of tendons are common and account for a high proportion of referrals to rheumatologists and orthopaedic surgeons (1). The current evidence suggests that several proinflammatory agents may play a role in the development of tendon disorders, which include cytokines, proteolytic enzymes, growth factors and neuropeptides (2). However inflammation and degenerative changes often coexist in the course of tendon disorders and their relative contributions are difficult to dissect (3).

Lateral elbow tendinopathy (LET), or "tennis elbow," is a common painful musculo-tendinous degenerative disorder at the lateral humeral epicondyle, which is likely caused by repetitive occupational or athletic activities involving wrist extension and supination (4). LET affects middle-aged men and women in similar rate, and it is estimated that approximately 40% of people will experience this condition, with a reported point prevalence of up to 3% in the general population (5).

Corticosteroid injections are widely used for LET treatment and strong evidence suggests that they are beneficial in the short term for treatment of tendinopathy (6) but injection into the tendon might weaken its structure and increase probability of rupture, and cause other minor complications such as post-injection pain and subcutaneous atrophy (7, 8). Thus, the development of topical formulation of corticosteroids, which can maintain efficacy while minimizing adverse effects and discomfort due to intra-articular injection, might represent a therapeutic advance in the treatment of symptomatic tendinopathies. Studies using topically-applied steroids treatment have demonstrated their efficacy as pain reliever in tendon disorders (9, 10), including LET (11).

Among the currently available topical corticosteroids, betamethasone valerate (BMV) is largely used for the treatment of severe inflammatory disorders. IBSA Institut Biochimique S.A. has developed a medicated plaster containing 2.25 of BMV at a 0.1% concentration of the corticosteroid in the adhesive layer. This BMV medicated plaster is marketed in several European countries in the treatment of inflammatory skin disorders which do not respond to treatment with less potent corticosteroids, such as eczema and psoriasis, lichenification, lichen planus, granuloma annulare, palmoplantar pustulosis and mycosis fungoides (12).

In a phase II, placebo-controlled study (13), 102 patients with chronic LET and chronic Achilles tendinopathy were randomised to receive two different dose regimens (i.e., 12 or 24 hours of application/day) of BMV 2.25 mg medicated plaster over a maximum period of 4 weeks. The active plaster was effective and superior to placebo in pain relief, without significant difference between the two treatment regimens.

Based on the findings of the Phase II study and taking into consideration a trend toward a better local tolerability observed with the use of the 12-hour application, this regimen has been considered as the most appropriate for further development. LET has been chosen as the elective indication due to its higher prevalence compared to the other type of symptomatic tendinopathy (e.g. Achilles tendinopathy), which was also included and positively assessed in the phase II study.

The objective of this study was to evaluate the short-term efficacy of BMV 2.25 mg medicated plaster applied 12 hours/day for 4 weeks, as compared to placebo plaster, in reducing pain and functional disability in patients with chronic LET.

MATERIALS AND METHODS

The study population included outpatients of either sex aged ≥ 18 years with chronic (i.e. for ≥12 weeks) symptomatic lateral elbow tendinopathy. To be eligible for study participation, patients were required to have a pain intensity ≥ 50 mm on a 0-100 mm Visual Analogue Scale (VAS) as perceived on a standardized movement (according to Cozen's or Mill's test).

Patients with any of the following conditions were excluded from the study: use of non-steroidal anti-inflammatory drugs (NSAIDs), opioids or narcotic analgesics in the last 7 days; local injections of corticosteroids for the tendinopathy in the last 6 months or for any other conditions in the last months; use of systemic corticosteroids in the last month; use of physiotherapy (except for cold or hot patch application and/or use of braces for casting), electro-medical Tecar therapy, laser therapy or iontophoresis in the last 3 months; history of fractures or ruptures of tendon or surgical treatment in the affected area; presence of skin lesions or dermatological diseases in the affected area that could interfere with the application of the plaster; history of musculoskeletal, neurological disorders or other systemic diseases potentially affecting the outcome of the study; pregnancy or breast-feeding.

The study was conducted according to a phase III, randomized, double blind, parallel-group, placebo-controlled design. The study plan included a screening/randomisation visit (Day 1), three follow-up visits on a weekly basis (Days 4, 14 and 21) and a final visit at Day 28. Visits were performed in the morning at approximately the same time of the day.

Eligible patients were randomised to receive 2.25 mg of BMV medicated plaster (IBSA Institut Biochimique S.A.) or matched placebo, topically applied once a day for 4 weeks

on the most painful area of the lateral epicondyle. Patients renewed the plaster application in the morning of each day, approximately at the same time of the day, and removed the plaster in the evening, approximately 12 hours after. An elastic loose net was supplied to keep the plaster adhered to the skin. However, the use of any kind of occlusive bandage over the entire medicated plaster was forbidden. Subjects were instructed to take their shower/bath during the treatment-free period, and to carefully dry the to-be-treated skin area before any new plaster application.

During the entire study period, NSAIDs, local (intra-tendinous or intra-articular injections) or systemic corticosteroids, physiotherapy, electro-medical Tecar therapy, laser therapy, iontophoresis, manipulation and acupuncture were not permitted.

The primary efficacy endpoint of the study was the pain decrease from baseline to Day 28, as scored by the patient using a 0-100 mm VAS (0 = no pain, 100 = worst imaginable pain) while performing the standardized movement. The secondary efficacy endpoints were: pain decrease at Day 7, 14 and 21; patient-rated tennis elbow evaluation (PRTEE) score;[14] sum of pain intensity difference (SPID) defined as the sum of differences from baseline to any follow-up visit; morning, evening and mean daily pain based on daily patients' diary of VAS; patient's self-perceived level of improvement based on a 6-points Likert scale (completely recovered/much improved/improved/no change/worse/much worse); rate of success (i.e. completely recovered or much improved as defined above) at Day 28; use of rescue medication, i.e. paracetamol (dose and rate of users).

Safety parameters were: treatment-emergent adverse events (TEAEs) and vital signs (heart rate and blood pressure). Skin irritation at the plaster application site was scored using a 5-point scale: 0=none, i.e. no evidence of irritation; 1=mild, i.e. presence of minimal erythema, barely perceptible; 2=moderate, i.e. presence of definite erythema, readily visible or minimal oedema or minimal papular response; 3=severe, i.e. presence of one or more of the following signs: erythema and papules; definite oedema; erythema, oedema, and papules; vesicular eruption; 4=very severe, i.e. presence of a strong reaction spreading beyond the application site. Presence of skin atrophy at the plaster application site was assessed by the investigator at least 20 minutes after the plaster removal using a 5-point scale: 0=no change from normal skin; 1=slight increase in skin transparency; 2=moderate increase in skin transparency and presence of telangiectasia just visible with the naked eye; 3=marked skin thinning and increase in transparency, with marked telangiectasia; 4=very severe thinning of the skin with vasculature appearing to be directly under the surface and very severe telangiectasia with large blunt vessels. The study protocol, the patient information leaflet and the informed consent document were first submitted to and approved by the reference Independent Ethic Committee (IEC) of the coordinating centre (Unit of Orthopaedics and Traumatology, General Hospital, Legnano - MI, Italy) and were then approved by the reference IEC of each investigational study site prior to the start of any study-related procedure. Patients gave their written informed consent to study participation. The study met the ethical standards of the Muscle, Ligaments and Tendons Journal (15).

The sample size calculation was based on the results of the previous phase II study (*Frizziero et al, 2016*) (13) in which the mean difference observed between BMV and placebo in pain reduction at 28 days ranged between 16 and 19 mm depending on the plaster dose regimen and application duration (12 or 24 hours daily). In this study, it was hypothesized that a sample size of 86 patients in each group would have had a 90% power to detect a difference of 15 mm between BMV and placebo in mean pain reduction at Day 28, assuming a standard deviation (SD) equal to 30 mm and using a two group t-test with a 0.05 two-sided significance level.

All statistical analyses and data processing were performed using SAS® Software release 9.2 for Windows (SAS Institute, Inc., Cary, North Carolina, USA). All efficacy variables were analysed in the intent-to-treat (ITT) population, which included all randomised patients. Analysis of the primary efficacy endpoint was repeated in the per-protocol (PP) population, which included all ITT patients who completed the treatment without any major protocol deviation and those patients who interrupted prematurely the treatment due to specific reasons such as lack of efficacy of study drug or adverse drug reactions (ADRs). The analysis of safety endpoints was performed in the safety population, which included all randomized patients who received at least one dose of study medication.

At each post-baseline visit, mean and SD of the change from baseline in pain VAS score were calculated with the relative 95% confidence interval (CI). The comparison between groups was performed with an analysis of covariance (ANCOVA) model with change from baseline as dependent variable, treatment and centre as fixed effects, and baseline value as covariate. The same ANCOVA model was used for the comparison between groups in SPID and PRTEE questionnaires scores. The comparison between treatment groups in weekly means of diary pain values (daily, morning and evening) was performed using a mixed model for repeated measures (MMRM) with the change from baseline at each inter-visit period as dependent variable, treatment and treatment*visit interaction as fixed effects and baseline, centre and baseline*visit interaction as covariates.

A Chi-square test was used for the comparison between groups of proportion of successes, incidence of adverse events, and severity scores of skin irritation and skin atrophy. The comparison between groups in total dose and mean daily dose of rescue medication was performed using an analysis of variance (ANOVA) model.
The last observation carried forward (LOCF) method was applied for missing values in all analyses that required complete patient data (ANCOVA models).

RESULTS

A total of 200 patients were screened in 16 Orthopaedic sites in Italy and 199 were randomized to the assigned treatment: 101 patients were randomised to receive BMV and 98 were randomised to placebo. One patient was a screening failure. Eight (7.9%) patients in the BMV group and 8 (8.2%) patients in the placebo group prematurely discontinued the study; consent withdrawal was the primary reason for discontinuation (7 and 3 patients, respectively in the two groups).
Fifteen patients (8 in the BMV group and 7 in the placebo group) did not complete the treatment period or had major deviation from the protocol and were therefore excluded from the PP population (93 and 91 patients, respectively in the two groups).
Demographic and characteristics at baseline, including pain intensity and PRTEE scores, were comparable in the two groups (**table I**) except for a longer time since first symptoms in the BMV group compared to the placebo group.
Figure 1 shows the results of pain VAS in the ITT population. The decrease from baseline in mean VAS score was higher in the BMV group than in the placebo group at any post-baseline time point. The difference between adjusted mean changes from baseline

Table I. Demographic and baseline characteristics of patients (ITT population).

	BMV 2.25 mg N=101	Placebo N=98	Total N=199
Age (years)			
Mean (SD)	49.4 (11.0)	49.9 (9.6)	49.7 (10.3)
Median (range)	50.0 (23-77)	50.5 (23-76)	50.0 (23-77)
Sex, N (%)			
Male	52 (51.5%)	53 (54.1%)	105 (52.8%)
Female	49 (48.5%)	45 (45.9%)	94 (47.2%)
Ethnic origin, N (%)			
Caucasian	100 (99.0%)	97 (99.0%)	197 (99.0%)
Asiatic	1 (1.0%)	1 (1.0%)	2 (1.0%)
BMI (kg/m^2)			
Mean (SD)	24.99 (3.503)	25.00 (3.701)	24.99 (3.593)
Median (range)	24.93 (18.71-34.29)	24.82 (17.57-40.56)	24.91 (17.57-40.56)
Affected elbow, N (%)			
Left	31 (30.7%)	35 (35.7%)	66 (33.2%)
Right	70 (69.3%)	63 (64.3%)	133 (66.8%)
Duration of tendinopathy (weeks)			
Mean (SD)	62.9 (93.8)	42.0 (54.7)*	52.7 (77.7)
Median (range)	28.0 (12-521)	24.0 (13-349)	25.5 (12-521)
Pain evaluation (VAS)			
Mean (SD)	70.1 (10.7)	67.9 (11.1)	69.0 (10.9)
Median (range)	69.0 (52-100)	67.0 (50-98)	68.0 (50-100)
PRTEE total score			
Mean (SD)	58.2 (15.9)	59.0 (15.9)	58.6 (15.9)
Median (range)	58.5 (24-100)	61.0 (18-87)	59.0 (18-100)
PRTEE Pain score			
Mean (SD)	29.8 (7.9)	29.3 (8.0)	29.5 (7.9)
Median (range)	29.0 (13-50)	30.0 (9-44)	30.0 (9-50)
PRTEE Functional Disability score			
Mean (SD)	28.4 (9.1)	29.7 (8.8)	29.0 (9.0)
Median (range)	29.0 (8-50)	30.8 (9-47)	29.5 (8-50)

N = number of patients
*One patient had missing value

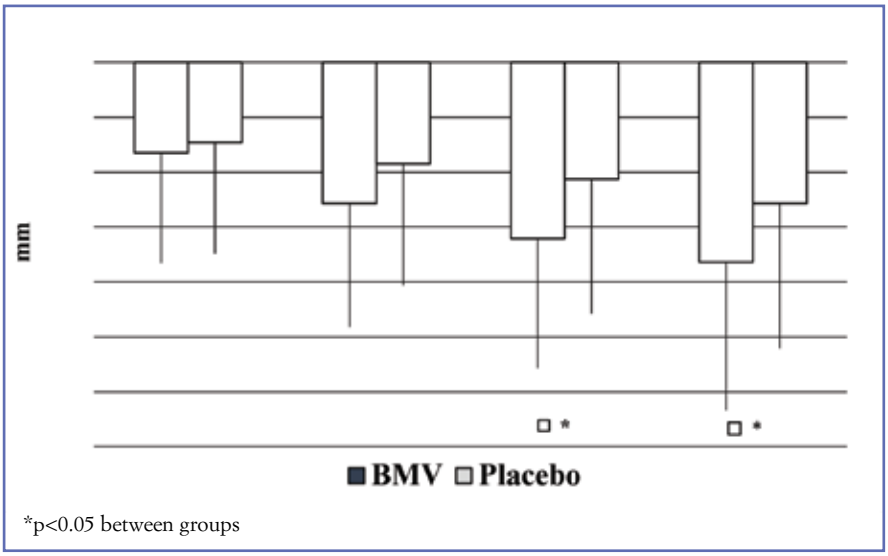

Figure 1. Results of pain VAS. Data are mean changes from baseline with SD in bars.

to Day 28 in the BMV (-32.47 mm; 95% CI: -37.96 to -26.98 mm) and in the placebo group (-23.90 mm; 95% CI: -29.47 to -18.33 mm) was -8.57 mm (95% CI: -16.19 to -0.95 mm) and was statistically significant (p=0.028), in favour of BMV. The comparison between groups at the other time points showed that the difference between adjusted means of BMV and placebo at Day 21 was -8.00 mm (95% CI: -14.80 to -1.20 mm) and was statistically significant (p=0.021), in favour of BMV, whereas the difference between groups at Day 7 and Day 14 was not statistically significant. In the PP population, the difference between adjusted means of BMV -33.68 mm (95% CI: -39.28 to -28.08 mm) and placebo -23.24 mm (95% CI: -28.94 to -17.55 mm) was -10.44 mm (95% CI: -18.22 to -2.65 mm) and was statistically significant (p=0.009), in favour of BMV.

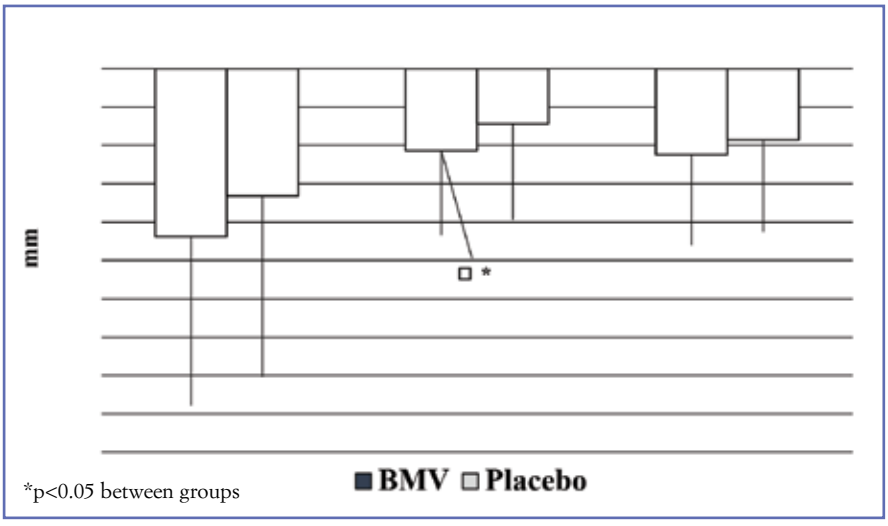

Figure 2. Results of PRTEE total score, pain score and functional disability score. Data are mean changes from baseline to Day 28, with SD in bars.

The mean decrease in PRTEE total, pain and functional disability scores from baseline to Day 28 were higher in the BMV group than in the placebo group (**figure 2**). The difference between BMV and placebo in adjusted mean changes from baseline to Day 28 was -5.689 mm (95% CI: -11.73 to 0.35 mm; p=0.065) for PRTEE total score, -3.085 mm (95% CI: -6.13 to -0.04 mm; p=0.047) for PRTEE pain score and -2.48 mm (95% CI: -5.63 to 0.67 mm; p=0.122) for PRTEE functional disability score.

The adjusted mean SPID was 789.37 mm (95% CI: 652.02 to 926.02 m) in the BMV group and 613.39 mm (95% CI: 474.06 to 752.72 mm) in the placebo group. The difference between adjusted means of BMV and placebo was 175.98 mm (95% CI: -14.70 to 366.65 mm; p=0.070).

The results of mean daily pain, morning pain and evening pain (**figure 3**), as measured by patients on the daily diary, showed higher decreases from baseline in the BMV group than in the placebo group at any post-baseline time interval. Statistically significant differences between groups, in favour of the BMV group, were observed at Day 15-21 (p=0.013) and Day 22-28 (p= 0.014) for mean daily pain, Day 8-14 (p=0.043), Day 15-21 (p=0.008) and Day 22-28 (p=0.008) for morning pain, and Day 15-21 (p=0.021) and Day 22-28 (p=0.025) for evening pain, as well as in the overall study period for mean daily pain, morning pain and evening pain.

A better perception of level of improvement was reported in patients in the BMV group compared to those in the placebo group. At Day 28, rates were completely recovered in 8 (7.9%) patients, much improved in 29 (28.7%), improved in 29 (28.7%),

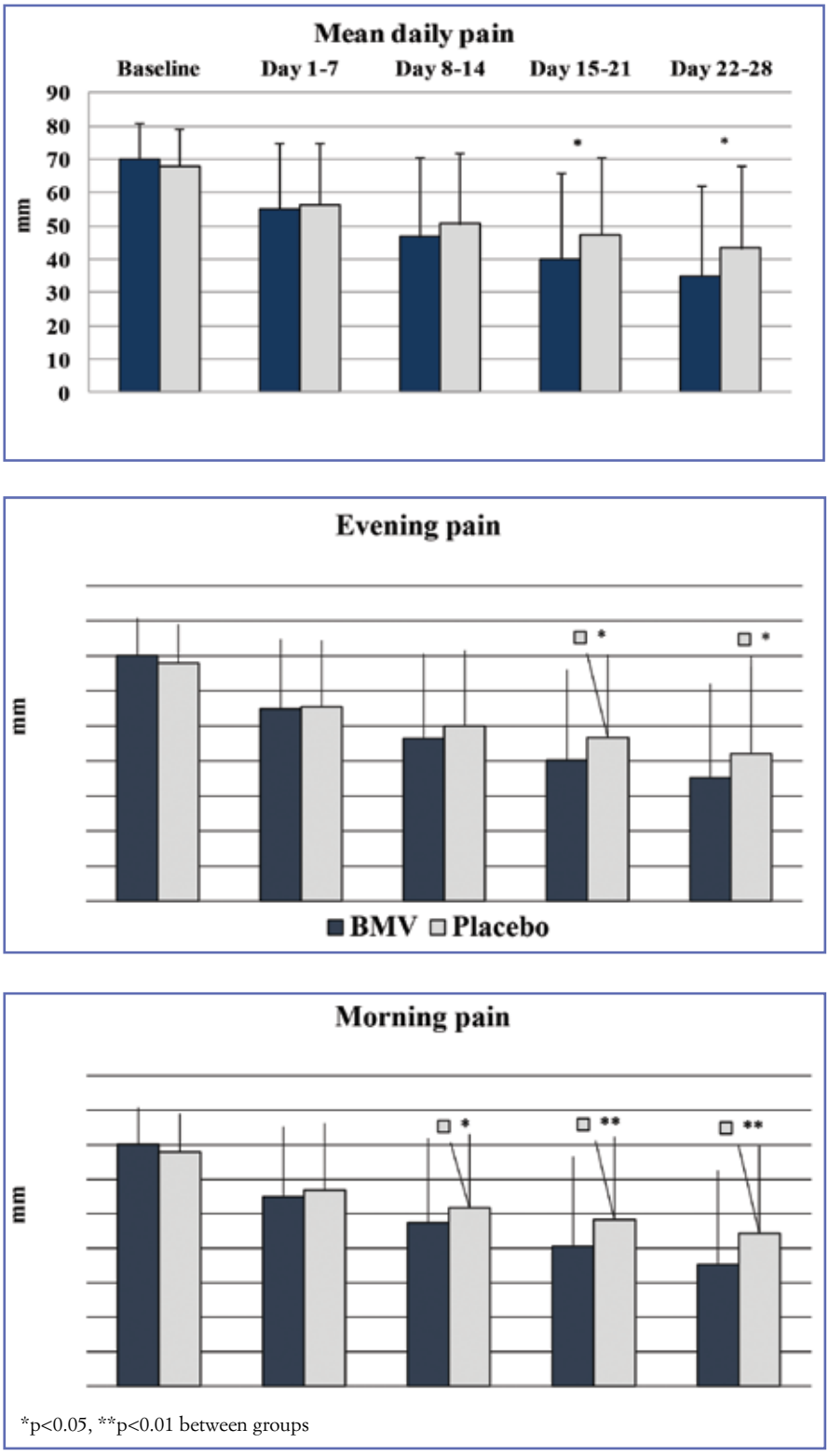

Figure 3. Results of weekly means of daily pain, morning pain and evening pain. Data are mean values with SD in bars.

no change in 25 (24.8%) and worsened in 3 (3.0%) patients in the BMV group, and were completely recovered in 5 (5.1%) patients, much improved in 22 (22.4%), improved in 25 (25.5%), no change in 35 (35.7%) and worsened in 3 (3.1%) patients in the placebo group. Success at end of treatment was reported by 37 (36.6%) patients in the BMV group and 27 (27.6%) in the placebo group (p=0.183 between groups).

Thirty-one (30.7%) patients in the BMV group and 31 (31.6%) in the placebo group used rescue medication during the study. The mean (± SD) total number of used tablets of rescue medication was 2.50 ± 6.27 in the BMV group and 3.38 ± 11.06 in the placebo group (p=0.488 between groups) and the mean (± SD) daily number of used tablets of rescue medication was 0.09 ± 0.21 and 0.11 ± 0.37, respectively in the two groups (p=0.499 between groups).

TEAEs were reported in 17 (16.8%) patients in the BMV group and in 16 (16.3%) patients in the placebo group. None was serious, and ADRs (i.e. treatment-related TEAEs) were reported in 4 (4.0%) and 3 (3.1%) patients, respectively in the two groups (**table II**). Local adverse effects at the site of plaster application were the most common ADRs. One patient in the BMV group (palpitation) and 2 in the placebo group (hypertension in one patient and application site erythema and pruritus in the other one) discontinued the study due to adverse events.

Table III shows the results of skin irritation and skin atrophy in the two groups. There was no evidence of skin irritation or skin atrophy following treatment with BMV. The skin irritation score was equal to 0 (none, i.e. no evidence of irritation) in the vast majority (> 90%) of patients in both groups at any post-baseline time point, as well as the vast majority (> 90%) of patients in both groups reported a

Table II. Summary of treatment-emergent ADRs by system organ class (SOC) and preferred term (PT) according to MedDRA (safety population).

SOC and PT	BMV (N=101)		Placebo (N=98)	
	N (%)	No. of ADRs	N (%)	No. of ADRs
Any ADR	**4 (4.0%)**	**7**	**3 (3.1%)**	**4**
Cardiac disorders	**1 (1.0%)**	**2**	**0 (0.0%)**	**0**
Palpitations	1 (1.0%)	1	0 (0.0%)	0
Tachycardia	1 (1.0%)	1	0 (0.0%)	0
Gastrointestinal disorders	**1 (1.0%)**	**1**	**0 (0.0%)**	**0**
Nausea	1 (1.0%)	1	0 (0.0%)	0
General disorders and administration site conditions	**2 (2.0%)**	**3**	**2 (2.0%)**	**3**
Application site atrophy	1 (1.0%)	1	1 (1.0%)	1
Application site erythema	1 (1.0%)	1	1 (1.0%)	1
Application site irritation	1 (1.0%)	1	0 (0.0%)	0
Application site pruritus	0 (0.0%)	0	1 (1.0%)	1
Psychiatric disorders	**1 (1.0%)**	**1**	**0 (0.0%)**	**0**
Mood swings	1 (1.0%)	1	0 (0.0%)	0
Vascular disorders	**0 (0.0%)**	**0**	**1 (1.0%)**	**1**
Hypertension	0 (0.0%)	0	1 (1.0%)	1

skin atrophy score equal to 0 (no change from normal skin) at any post-baseline time point. There were no statistically significant differences between groups for both skin irritation and skin atrophy.

In both groups, there were no important changes from baseline in heart rate and blood pressure.

DISCUSSION

The results of this study have shown that treatment with BMV 2.25 mg medicated plaster in patients with LET was associated with a significantly greater improvement of VAS for pain from baseline to Day 28 (primary endpoint) compared to matched placebo. The result was consistent in both the ITT and the PP populations. The pain reduction at Day 21 was also significantly higher in the BMV group than in the placebo group, whereas the difference between groups in pain reduction at Day 7 and Day 14 was not statistically significant, despite the higher pain decreases in the BMV group than in the placebo group. Data of pain daily measured by patients confirmed the findings from measurement at the clinics. The SPID during the 4-week treatment period was also higher (although not significantly) in the BMV group than in the placebo group. Moreover, treatment with BMV was associated with higher decreases in mean PRTEE total score, pain score and functional disability score from baseline to Day 28 compared to placebo, and a statistically significant difference between groups was observed for PRTEE pain score. A better perception of level of improvement was reported at Day 21 and Day 28 in patients in the BMV group as compared to placebo recipients. At the end of treatment (Day 28), more patient (although not significantly) in the BMV group than in the placebo group achieved a complete recovery or a significant improvement, as compared to baseline. The use of rescue paracetamol was very limited and similar in the two groups and therefore had no impact on results.

Compared with findings observed with the same BMV regimen used in the previous phase II study,[13] there was a lower pain reduction with BMV, however not compromising the clinically and statistically significant superiority of BMV over placebo. The longer mean duration of tendinopathy in the BMV arm compared to placebo (62.9 and 42.0 months, respectively) and to that observed in the same arm in the phase II study (49.4 months) suggests that a significant proportion of patients in the BMV arm might have had a long-lasting chronic form of tendinopathy, in which corticosteroids have limited effects (16).

Consistently with findings of the previous study (13), BMV was as well tolerated as placebo in terms of adverse events

Table III. Results of skin irritation and skin atrophy in the two groups (safety population).

	Skin irritation			
	Day 7	**Day 14**	**Day 21**	**Day 28**
BMV (N=101)				
N	97	94	94	94
Mean (SD)	0.0 (0.1)	0.0 (0.0)	0.0 (0.1)	0.0 (0.1)
Median (range)	0.0 (0-1)	0.0 (0-0)	0.0 (0-1)	0.0 (0-1)
Score distribution, N (%)				
None (0)	96 (95.0%)	94 (93.1%)	93 (92.1%)	93 (92.1%)
Mild (1)	1 (1.0%)	-	1 (1.0%)	1 (1.0%)
Severe (3)	-	-	-	-
Placebo (N=98)				
N	96	95	92	90
Mean (SD)	0.0 (0.3)	0.0 (0.1)	0.0 (0.1)	0.0 (0.0)
Median (range)	0.0 (0-3)	0.0 (0-1)	0.0 (0-1)	0.0 (0-0)
Score distribution, N (%)				
None (0)	94 (95.9%)	94 (95.9%)	90 (91.8%)	90 (91.8%)
Mild (1)	1 (1.0%)	1 (1.0%)	2 (2.0%)	-
Severe (3)	1 (1.0%)	-	-	-
	Skin atrophy			
	Day 7	**Day 14**	**Day 21**	**Day 28**
BMV (N=101)				
N	98	95	94	94
Mean (SD)	0.0 (0.0)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)
Median (range)	0.0 (0-0)	0.0 (0-1)	0.0 (0-1)	0.0 (0-1)
Score distribution, N (%)				
No change (0)	98 (97.0%)	94 (93.1%)	93 (92.1%)	93 (92.1%)
Slight (1)	-	1 (1.0%)	1 (1.0%)	1 (1.0%)
Placebo (N=98)				
N	97	95	92	90
Mean (SD)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)
Median (range)	0.0 (0-1)	0.0 (0-1)	0.0 (0-1)	0.0 (0-1)
Score distribution, N (%)				
No change (0)	95 (96.9%)	94 (95.9%)	91 (92.9%)	89 (90.8%)
Slight (1)	2 (2.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)

N = number of patients

and ≤ 4% of patients in both groups had treatment-related adverse TEAEs. Evidence of minimal erythema or slight increase in skin transparency at plaster application site was only occasionally reported. Only one case of mild erythema was reported in the BMV group, and more severe skin irritation was only reported in one placebo-treated patient.

Treatment of LET is mainly based on conservative measures such as physical therapy (17). Corticosteroid injections given in addition to physiotherapy are effective for short-term pain control but have not demonstrated long-term benefit (18). There is also limited evidence on the effects of non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of pain in elbow tendinopathy (19). Furthermore, there is some evidence on the efficacy of topical formulations of corticosteroids or NSAIDs when used in combination with iontophoresis and phonophoresis, two methods of

driving topically applied substances across tissues by utilization of electric current or ultrasound, respectively (5). Overall, the existing literature does not provide conclusive evidence that there is one preferred method of non-surgical treatment for this condition (20).

Compared to marketed dermatological formulations for topical use, such as creams/ointments, BMV medicated plaster may offer many advantages: it is formulated in a highly-standardised, fixed-dose plaster form, also representing a user-friendly delivery system for self-medication. The occlusive nature of the medicated plaster makes it possible to improve the steroid absorption in the site of action and possibly enhance its penetration in target connective tissues. Furthermore, the BMV medicated plaster may increase the patient adherence to treatment by reducing the sensation of greasy skin and avoiding its removal by clothes and dressings spots, typical of cream, gels and unguents, while avoiding at the same time the dispersion of active substance on unaffected areas, with potential advantages in terms of local safety. Finally, the use of BMV medicated plaster is less costly and time consuming compared to physical therapy, alone or associated with modalities such as iontophoresis, ultrasound, phonophoresis, or low-level laser treatment.

Despite the clear benefits observed with BMV 2.25 mg medicated plaster, this study has some limitations and some unanswered questions might be the matter for future research. Neither the previous phase II study (13) nor this study has included an actively-treated control group and therefore it is not possible to compare the extent of the effects of BMV medicated plaster with other alternative therapies. Moreover, the lack of a comparative alternative treatment has not allowed a reliable evaluation of the facility and convenience of use of the BMV formulation. During the choice of the study design, it was considered that the use of a comparative active arm would have compromised the blindness of the study, which is important to strengthen outcomes in variables subjectively measured by patients. Furthermore, the period of observation lasted with the end of treatment, without any follow-up period aimed at investigating whether the effects of BMV medicated plaster may be extended beyond the end of treatment and its efficacy in preventing symptoms relapse.

In conclusion, findings of this placebo-controlled study have provided confirmatory evidence of the efficacy of a 28-day treatment with BMV 2.25 mg medicated plaster applied 12 hours/day as pain reliever in patients with LET. BMV medicated plaster was as well tolerated as placebo. Further comparative trials would be helpful to better understand the advantages of BMV 2.25 mg medicated plaster over standard therapies in terms of convenience of use, duration of effects and improved compliance.

CONFLICTS OF INTERESTS

Stefano Rovati and Valeria Frangione are employees of IBSA Institut Biochimique SA, the sponsor of the study.

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