Effectiveness of chondroitin sulphate in patients with concomitant knee osteoarthritis and psoriasis: a randomized, double-blind, placebo-controlled study

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SUMMARY
Objective: The aim of the trial was to assess the efficacy of chondroitin sulphate (CS) on symptomatic knee osteoarthritis (OA) associated to psoriasis.

Methods: In this randomized, double-blind, placebo (PBO)-controlled clinical trial 129 patients with symptomatic knee OA and concomitant psoriasis were randomized into two groups receiving 800 mg daily of CS or PBO for 3 months. The primary efficacy outcome for knee OA was the Huskisson’s visual analogue scale (VAS) and for psoriasis was the Psoriasis Area and Severity Index (PASI). Additionally, other secondary efficacy criteria for both conditions were assessed.

Results: After 3 months of treatment, CS was more effective than PBO, relieving pain VAS (CS 26.9/24.8 vs PBO 14.23/20.8 mm, $P < 0.01$), decreasing the Lequesne index (CS 4.8/3.4 vs PBO 3.3/3.5, $P < 0.05$) and reducing the number of patients using acetaminophen as rescue medication (CS 43% vs PBO 64%, $P < 0.05$). Regarding PASI, Overall Lesion Severity Scale and Physician’s Global Assessment of Change no statistically significant changes were detected in front of PBO. However, CS improved plantar psoriasis compared to PBO (CS 87% vs PBO 27%, $P < 0.05$). Quality of life improved significantly in CS-treated patients according to the Short Form-36 health survey and the Dermatology Life Quality Index (DLQI). CS tolerability was excellent. Adverse events were infrequent and evenly distributed among groups. The incidence of psoriatic flares did not increase after treatments.

Conclusions: This study confirms the efficacy and safety of CS as a symptomatic slow-acting drug in patients with knee OA and shows that CS improves plantar psoriasis. The use of CS could represent a special benefit in patients with both pathologies since non-steroidal anti-inflammatory drugs have been reported to induce or exacerbate psoriasis.

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Introduction

Osteoarthritis (OA) is a common, progressive condition, which is associated with severe pain, functional disability and impairment of health-related quality of life, causing a significant social and economic burden. OA of the hip or knee affects the majority of individuals over 60 years of age in developed countries. Irreversible damage to articular cartilage, osteophyte formation, alterations in the subchondral bone and synovial inflammation are characteristic features of the disease.

Chondroitin sulphate (CS) is a glycosaminoglycan, which is a major component of the extracellular matrix of many connective tissues including cartilage, bone, skin, ligaments and tendons. CS has been classified as a symptomatic slow-acting drug in OA (SYSADOA) and as a structure/disease modifying anti-OA drug (S/DMOAD). Randomized placebo (PBO)-controlled clinical trials in patients with knee OA have shown that CS reduces pain,
improves functional capacity, decreases non-steroidal anti-inflammatory drug (NSAID) or analgesic consumption, has a carry-over effect, reduces joint swelling and effusion, and is tolerated as well as the PBO. Moreover, CS prevents joint space narrowing of the knee and fingers more effectively than PBO.

The beneficial effects of CS in patients with OA result from its immunomodulatory effects reducing NF-kB nuclear translocation, from the stimulation of proteoglycan and hyaluronic acid synthesis in chondrocytes, from the anti-inflammatory activity and inhibition of proteolytic enzymes, of nitric oxide and other substances that contribute to damage the cartilage matrix and cause chondrocytes death. At the same time, CS has a positive effect on some of the pathological processes involving the synovial tissue and subchondral bone.

The beneficial effects elicited by CS in the treatment of OA, raise the hypothesis that CS might be effective in other chronic inflammatory processes such as psoriasis in which a deregulation of NF-kB plays an important role.

It is interesting to note that in a clinical series of 11 patients with knee OA and concomitant psoriasis, the use of CS as a symptomatic treatment for knee OA resulted in a marked clinical and histological improvement of the psoriatic lesions after 2 months of treatment. Taking into account these preliminary results, a double-blind, PBO-controlled pilot clinical trial was designed to assess the efficacy and safety of CS in patients with symptomatic knee OA and concomitant psoriasis.

Methods

Study design

A prospective, randomized, double-blind, PBO-controlled multicentre study was designed to assess the efficacy and safety of CS 800 mg daily compared to PBO in patients with both OA of the knee and concomitant plaque-type psoriasis. According to the response observed in a former exploratory study, the duration of the treatment period was limited to 3 months.

The study comprised patients from Barcelona (Spain) who were enrolled between October 2004 and February 2007 in two centres, the Instituto Poal de Reumatología and the Hospital del Mar. The study protocol was approved by the Ethical Review Board of the participating centres and was conducted in accordance with the principles of the Declaration of Helsinki and its amendments. Written informed consent was obtained from all participants prior to enrolment in the study.

Eligibility

Eligible patients were male and female subjects aged 40 years or over, with OA of the knee as defined by criteria of the American College of Rheumatology, with pain in the affected knee scoring ≥ 30 on a continuous 0–100 mm Huskisson’s visual analogue scale (VAS) and a confirmatory knee X-ray diagnosis (Kellgren–Lawrence grades I–III) associated to cutaneous plaque-type psoriasis with a Psoriasis Area and Severity Index (PASI) score of ≥ 5.

Key exclusion criteria were Kellgren–Lawrence grade IV, VAS ≥ 30 due to pain of any cause in other sites, non-plaque-type psoriasis forms, concurrent arthritic conditions that could confound evaluation of the index joint, presence of any clinically significant cutaneous disease that may interfere with the assessment of lesions during the study and presence of any medical condition judged by the investigator to preclude the patient’s inclusion in the study. The following medication washout periods before entering the study were requested: 6 months for intra-articular hyaluronic acid, 3 months for intra-articular corticosteroids and SYSADOAs; 1 month for oral corticosteroids, 1 week for oral NSAIDs; 1 month for high-potency topical corticosteroids, psoralen phototherapy and systemic treatment for psoriasis; 2 weeks for ultraviolet and topical treatment for psoriasis.

Treatment and patient evaluation

Study participants attended a screening visit, which included medical history, physical examination, VAS and PASI scores, and laboratory tests. Subjects were fully informed of the purpose of the study and signed the informed consent. They were instructed to discontinue or taper off gradually any systemic or topical treatment for both pathologies in accordance with eligibility criteria and were scheduled to return to the study centre for the baseline/randomization visit (visit 0). At baseline, physical examination was carried out, inclusion/exclusion criteria and results of laboratory tests were reviewed, and the following procedures were performed: assessment of knee pain using VAS and functional disability by the Lequesne index, assessment psoriasis severity by means of PASI and the Overall Lesion Severity Scale (OLS), radiographic confirmation of Kellgren–Lawrence grades I–III, and punch biopsy collection. Patients completed the Dermatology Life Quality Index (DLQI) and the Short Form-36 (SF-36) quality of life questionnaires. Patients were instructed to collect data of daily consumption of acitretin (500 mg) as rescue medication in the daily card. Adverse events arising after signing the informed consent were also documented.

All eligible participants were sequentially assigned by the researchers to one of the two masked products in a proportion of 1:1 per treatment group according to a pre-established computer-generated global randomization list provided by the statisticians. The randomization schedule was generated using the SAS PROC PLAN programme (Release 9.1.3 Service Pack 2) for a block size of 2 and a 1:1 ratio. Subjects were randomly assigned to receive daily either CS 800 mg (two capsules of 400 mg each) (Condrosan®), CS Bio-Active™, Bioibérica, S.A., Barcelona, Spain) or matched PBO capsules. Condrosan® is a prescription drug containing highly purified chondroitins 4 and 6 sulphate of bovine origin in a concentration not less than 98%. It has an average molecular weight of ~15–16 kDa and an intrinsic viscosity of ~0.02–0.06 m²/kg. This product has been approved as a prescription treatment for OA in many European countries. Subjects were instructed to take two capsules once a day. The study medication was dispensed to subjects at the baseline visit to cover the 3-month study period. Acetaminophen as rescue medication for osteoarthritic symptoms, syndet soap and moisturizing body milk for daily skin care were also provided.

Assessments were performed at 30 days (visit 1), 60 days (visit 2) and 90 days (visit 3, final visit) after initiation of the treatment. At follow-up visits, the same procedures as those described for visit 0 were performed except for laboratory tests and skin biopsy, which were only performed at the final visit. Changes in psoriatic lesions according to the Physician’s Global Assessment of Change (PGA) method, as well as the patient’s and investigator’s efficacy and tolerability of treatment were also assessed at each follow-up visit. The PGA categorizes the global response to therapy of all clinical signs and symptoms of the disease relative to baseline using all the available information for the assessment including, registration of the different body areas with psoriatic lesions and photographs taken at each visit under standardized conditions. Treatment compliance by capsule count and use of acitretin (500 mg, maximum allowed 3 g/day) by inspection of daily cards was also checked at each visit. Non-compliance was defined as taking less than 75% of the prescribed course of the study drug.
Punch biopsy specimens of 4 mm were taken under local anaesthesia at visits 0 and 3 from the same psoriatic plaque from each subject. All biopsies were examined by two independent pathologists who were unaware of the purpose of the study and origin of the biopsy specimens. Quantitative, semiquantitative and qualitative histological variables were assessed. Quantitative variables included the thickness of the epidermis, of the stratum corneum and the thickness from stratum basale to the stratum corneum. Semiquantitative variables were psoriasis activity and inflammation. Qualitative variables included orthokeratosis or parakeratosis, presence of CD1a+ Langerhans cells, CD31+ endothelial cells, CD4+ and CD8+ T lymphocytes, CD57+ natural killer cells, triptase + mastocytes, and keratinocyte proliferation (Ki67 staining).

Efficacy and safety parameters

The primary efficacy endpoints were the decrease in pain intensity assessed by VAS and the clinical improvement of psoriasis determined by the PASI score at the end of treatment as compared with baseline. Secondary efficacy parameters included pain relief and function improvement in the knee using the Lequesne algo-functional index\textsuperscript{26}. acetaminophen consumption, OLS score, histopathological data, changes in psoriatic lesions according to PGA, assessment of efficacy by patients and investigators and quality of life measured with SF-36 and DLQI.

Tolerability and safety parameters were the incidence and severity of adverse events reported throughout the study, changes in laboratory tests including complete blood cell count, biochemical profile and urinalysis and patient's and investigator's assessment of tolerability.

Statistical analysis

The sample size calculation was determined to guarantee the statistical power for the more restrictive of the two co-primary endpoints, the PASI outcome. For that variable, a sample size of 60 evaluable patients provided an 80% power to detect a difference of 4 points assuming an SD of 7 points, with a two-sided alpha level of 5%. Therefore, a total of 120 evaluable patients (60 per group) were required to analyze the co-primary endpoints of the study and approximately 130 patients were predefined to be randomized considering a dropout rate of less than 10%.

The efficacy analysis was performed for the intention-to-treat (ITT) population defined as all randomized patients who met the inclusion/exclusion criteria, received the study medication and from which data of the primary endpoints for the baseline visit and at least one follow-up visit were available. The last observation carried forward (LOCF) method was used to replace missing values for co-primary outcomes as long as there was at least one post-baseline value available. In case there were no values available from the immediately following visit, the selection value was used instead. All other variables were treated using the Available Data Only (ADO) approach. Primary efficacy variables were also analyzed in the per-protocol (PP) population to assess the robustness of the results obtained in the ITT data set. The PP population was defined as all patients randomized who met the inclusion/exclusion criteria, received the study medication, and had data from the primary endpoints for the baseline visit and at least one follow-up visit and who did not present major protocol deviations. Major protocol deviations included lack of fulfillment of the selection criteria, non-compliance with the study medication or use of any systemic or topical medication other than the study drugs or acetaminophen. The safety population included all randomized subjects who received at least one dose of the study drug.

Both VAS and PASI were evaluated following an ANCOVA model with the baseline value as a covariable for each visit. Adjusted means and their CI 95% bilateral for the mentioned variables (EAV, PASI and their respective differences from baseline) were calculated using ANCOVA. We also performed an additional post-hoc sensitivity analysis of the two co-primary outcomes following Mixed Models for Repeated Measurements (MMRM) using a restricted maximum likelihood based approach, including in the model the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous fixed covariate of baseline. For all secondary efficacy variables comparability was performed using Fisher exact test, Student’s t-test and Mann–Whitney U-test, according to the variables nature. When applied, variables were evaluated similarly as primary variables using an ANCOVA model.

![Fig. 1. Flow-chart of the distribution of study patients.](image-url)
with the baseline value as a covariate. Statistical significance was set at \( P \leq 0.05 \).

**Results**

*Study population*

Of the 181 potential participants, 52 were not enrolled because of lack of eligibility at the screening visit \((n = 20)\), flare of psoriasis during the washout period \((n = 3)\) and patient’s decision \((n = 29)\). Therefore, a total of 129 patients were randomized to the study arms, 64 of which were assigned to treatment with CS and 65 to PBO. However, one patient assigned to the PBO group did not take at least one dose of the study medication and was excluded from the safety data set. Twelve patients, four in the CS group and eight in the PBO group, were excluded from the ITT population because the primary endpoint data was lacking for at least one follow-up visit \((n = 9)\) or because of no fulfillment with inclusion criteria \((n = 3)\). In seven other patients, major protocol violations occurred and were excluded from the PP data set. The disposition of patients is shown in Fig. 1.

Baseline characteristics were similar among patients in both groups (Table I). The mean VAS score for the intensity of pain in the affected knee was 57.8 ± 16.0 mm and the Lequesne index score was 9.5 ± 3.5. The mean PASI score at baseline for the entire study cohort was 12.9 ± 5.7. Seven (6%) patients reported a psoriasis worsening after NSAID consumption (Table I).

**Efficacy**

*Knee OA*

Regarding the primary efficacy variable, treatment with CS was superior to PBO in reducing the intensity of pain throughout the study period. Absolute differences in VAS scores were statistically significant after 1 month of treatment \((CS − 14.6 ± 19.5 \text{ mm vs PBO} − 7.2 ± 11.7 \text{ mm}, P < 0.05)\) and at the final visit at 3 months \((CS − 26.9 ± 24.8 \text{ mm vs PBO} − 14.2 ± 20.8 \text{ mm}, P < 0.01)\) (Table II, Fig. 2). The additional post-hoc sensitivity analysis following the MMRM approach gave similar results confirming the conclusions obtained with the LOCF analysis \((P = 0.002)\).

The administration of CS was associated with a steady improvement in Lequesne index scores over the 3-month study period. At the end of the treatment, absolute differences were statistically significant as compared with the PBO group \((CS − 4.8 ± 3.4 \text{ vs PBO} − 3.3 ± 3.5, P < 0.05)\) (Table II, Fig. 3). Acetaminophen consumption was scarce and very similar in both treatment groups. At the end of the treatment, no statistically significant differences were detected among treatment groups \((CS 38.2 ± 42.6 \text{ vs PBO 30.2 ± 33.8}, P > 0.05)\) (Table II). However, at the final visit, a significantly higher percentage of PBO-treated patients than CS-treated patients consumed acetaminophen \((CS 43% \text{ vs PBO 64%}, P < 0.05)\).

According to the patient’s opinion, the efficacy of CS treatment was rated more favourably than the efficacy of treatment with PBO, with statistically significant differences after 1 \((P < 0.05)\) and 3 months \((P < 0.05)\) of treatment. Efficacy was considered ‘good’ by 61% of patients in the CS group and 38% of patient in the PBO group at visit 1, whereas 44% of patients in the CS group and 20% in the PBO group rated efficacy of treatment as ‘very good’ at visit 3 (Table II). Treatment efficacy was considered ‘very good’ by 48% of investigators in the case of CS and by 24% in the case of PBO after 3 months of treatment \((P < 0.05)\) (Table II). Regarding health-related quality of life, differences between study groups were observed in the physical function scale of the SF-36 questionnaire at the final visit in favour of CS treatment compared with PBO \((mean \text{ score CS } 85.6 ± 2.19 \text{ vs PBO } 78.3 ± 2.19, P < 0.05)\).

*Psoriasis*

In relation to the primary efficacy variable, CS-treated patients experienced a reduction of 33% in the PASI after 3 months of treatment; without achieving statistically significant differences as compared with PBO (Table III). The additional post-hoc sensitivity analysis following the MMRM approach \((P = 0.759)\) confirmed the results obtained by the predefined LOCF analysis \((P = 0.842)\).

There were no significant differences in the OLS; although at months 2 and 3, ‘very severe’ psoriatic lesions were observed in 6% and 4% of patients in the PBO group and in none of the CS group (Table III). In the PGA method, although lesions improved in both study groups, 12% of patients treated with PBO and 2% of patients treated with CS scored ‘worse’ after the 3-month treatment course (Table III).

When psoriatic lesions at different body sites were assessed, a significant reduction in the percentage of patients with psoriasis among those treated with CS compared with PBO was observed. After the second month of treatment, 33% of patients treated with PBO had plantar psoriasis as compared with 16% of patients treated with CS. At the final visit, plantar psoriasis was

![Table I](null)
present in 22% of patients treated with PBO and in 4% of patients treated with CS (P < 0.05) (Fig. 4).

Histopathologically, neither biopsies from CS-treated patients nor biopsies from those treated with PBO showed changes in quantitative, semiquantitative and qualitative histological variables, except for CD1a+ Langerhans cells, which showed a trend to decrease with CS treatment (CS 5.13 ± 0.42 vs PBO 6.26 ± 0.43, P = 0.06).

Patients rated similarly the efficacy of treatment with CS and PBO throughout the study period (Table III). In the DQLI, both study groups showed decreases from baseline to the end of treatment in the overall score as well as in the six subscales, with a statistically significant difference for the work/school domain in favour of CS treatment (CS 0.01 ± 0.06 vs PBO 0.19 ± 0.02, P < 0.05).

The analyses for the PP population supported the results obtained in ITT patients, as similar results for all efficacy variables related to knee OA and psoriasis were found in the PP population.

Safety and tolerability

Adverse events were infrequent and evenly distributed among groups. Adverse events of mild to moderate intensity were recorded in 31 patients in each group. The most common adverse events that occurred in both CS and PBO groups were common cold with a frequency of six and seven cases, respectively; back pain with a frequency of one and five, respectively; pruritus with two cases in each treatment group, and dental pain with a frequency of one and three, respectively. Treatment tolerability was excellent in both study groups. At the final visit, tolerability of treatment with both CS and PBO was considered ‘very good’ by near 90% of physicians and 80% of patients. The incidence of psoriatic flares did not increase after treatments.

No clinically significant laboratory abnormalities or pattern changes in vital signs were observed during CS treatment.

### Table II

<table>
<thead>
<tr>
<th>Variable</th>
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<td>Efficacy of treatment, % of patients</td>
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<td>Very good</td>
<td>10.2 vs 10.9</td>
<td>28.1 vs 18.0</td>
<td>44.0 vs 20.0</td>
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<td>42.1 vs 52.0</td>
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<td>4.0 vs 8.0</td>
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<tr>
<td>Very bad</td>
<td>0.0 vs 3.6</td>
<td>1.8 vs 0.0</td>
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<td>Good</td>
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<td>Very bad</td>
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<td>0.0 vs 0.0</td>
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<tr>
<td>P value</td>
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<td>0.109</td>
<td>0.517</td>
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</table>

* CS vs PBO.
Treatment compliance was above 90% in both groups at each time point, with a mean compliance rate of 97%.

Discussion

This randomized, double-blind, PBO-controlled study presents the results of a 3-month clinical trial conducted in patients with knee OA and concomitant psoriasis receiving oral CS, 800 mg on a daily basis.

Although multiple controlled trials since the 1980s have examined the use of oral CS in patients with symptomatic OA of the knee, the benefits in terms of pain reduction, improvement of functional disability and decrease in NSAID consumption are still debated.

The results of this study, designed to assess the clinical effects of CS on pain amongst other outcomes, confirm previous positive results obtained with CS used for the symptomatic treatment of human OA. In this clinical trial CS elicited a significant reduction of pain intensity as compared with PBO after the first month of treatment, providing further evidence for CS as a SYSADOA.

The effect of CS increased progressively over time, achieving a maximal effect after 3 months of treatment. The results from the secondary efficacy parameters in OA confirmed the effect of CS with statistical significance at several endpoints. A significantly higher increase in physical function than in the PBO arm was also observed after 3 months of treatment with CS. The global assessment by the investigators and patients was also significant better in the CS group.

In agreement with the effect of CS on pain and function, CS was also able to improve the patient’s health-related quality of life according to the SF-36 questionnaire. This finding is relevant for clinical practice as knee OA has been described to have one of the worst quality of life patterns among musculoskeletal disorders.

With reference to psoriasis, CS did not reach statistically significant results in the primary outcome together with OLS and PGA. However, it is noteworthy that CS at dose of 800 mg/day demonstrated a statistically significant improvement of plantar psoriasis. At the end of treatment, only 2% of patients in the CS group complained of plantar psoriasis compared with 22% of those treated with PBO. Palmoplantar psoriasis is one of the most invalidating forms of psoriasis that impacts activities of daily living and affects the hands or feet (or both) with very dry, thickened skin, fine desquamation, often involving splitting and cracking and a silvery appearance.
Patients with palmoplantar involvement report significantly greater physical disability and physical discomfort than patients without palmoplantar involvement. In this clinical trial and in accordance with the former results, the substantial clinical response to treatment was correlated with an improvement of patient’s quality of life according to DLQI.

It is worth mentioning that psoriasis is a disease with evident NF-κB activation. The deregulation of NF-κB appears to play an important role in skin inflammatory processes, such as psoriasis. The nuclear expression of NF-κB is detected in 66% of psoriatic lesions and over-expressed in psoriasis compared with normal skin. Moreover, the NF-κB-dependent proinflammatory cytokines, IL-1β and TNF-α, have a crucial role in the appearance and progression of psoriasis and psoriatic arthritis. Further supporting the role of NF-κB in psoriasis are the reports showing that effective treatment of psoriasis diminishes NF-κB nuclear translocation. For instance, one study showed that etanercept produced a significant down-regulation of phosphorylated NF-κB/RelA effect that correlated with decreases in epidermal thickness, restoration of normal markers of keratinocyte differentiation, and clinical outcomes. Furthermore, the anti-psoriatic effect of avarol-3-thiosalicylate, dimethyl fumarate and tacrolimus is closely associated to the down-regulation of NF-κB activity. Recent studies have reported that CS is able to inhibit the nuclear translocation of NF-κB in chondrocytes and synoviocytes and therefore, to explain CS in some patients with psoriasis, we may postulate that CS may also reduce nuclear translocation of NF-κB in psoriatic skin cells.

The therapeutic efficacy of CS may have implications in clinical practice since palmoplantar psoriasis is usually resistant to most of the available therapeutic modalities. Results of this clinical trial are encouraging and warrant further studies in patients with psoriasis to assess the effects of CS treatment for a longer period of time.

Current therapies for psoriasis are limited, therefore there is a need for effective and safe treatment options. The need for alternative therapies is reinforced by the demographic change in age distribution that will lead to more elderly people with psoriasis with an increasing number of coexisting conditions, and so it may be expected that a large percentage of patients with psoriasis will suffer from OA in adulthood. Moreover, the need for new therapeutic approaches to treat patients with both pathologies is further emphasized by the fact that some anti-inflammatory medications, commonly used in the management of OA are considered potential risk factors for psoriasis, in particular, propionic acid derivatives, as NSAIDs may induce psoriasis flares or aggravate preexisting lesions. The data available on the beneficial effect of CS in psoriasis and the results observed in the present clinical trial suggest that CS could represent a therapeutic alternative for many patients.

In conclusion, the daily administration of 800 mg/day of CS for 3 months improved OA-associated pain, physical function, and plantar psoriasis, and enhanced quality of life of patients with OA and psoriasis.

Competing interests

Authors’ contributions

Ingrid Möller was the coordinator of the study, participated in the conception and design of the study protocol, recruitment and care of patients, interpreted study findings and wrote the manuscript.

Montserrat Pérez was one of the principal investigators, participated in the design of the protocol, recruitment and care of patients, interpreted the study findings, wrote the manuscript and approved the final draft.
Jordi Monfort was one of the principal investigators, participated in the design of the protocol, recruitment and care of patients, interpreted study findings, wrote the manuscript and approved the final draft.

Pere Benito was one of the principal investigators, participated in the conception and design of the study protocol, in the recruitment and care of the patients, interpreted study findings, reviewed the manuscript for intellectual and scientific content and approved the final draft.

Jesús Cuevas and Cristian Perna contributed to the design of the study, examined skin biopsies, carried out histopathological assessments, reviewed the manuscript and approved the final draft.

Marta Herrero, Eulalia Montell and Josep Vergés are employees of Bioibérica, S.A., Barcelona, Spain, manufacturer of a proprietary CS product and sponsor of this work. They contributed to the study design, monitored the study, provided logistic support, reviewed the manuscript and approved the final draft.

Conflict of interest

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Jesús Cuevas: “Conflict of Interest Disclosure: None declared.”

Cristian Perna: “Conflict of Interest Disclosure: None declared.”

Marta Herrero: full employee, Clinical Research Unit, Bioibérica, S.A., Barcelona, Spain, that provided the study drug (Condrosan®).

Eulalia Montell: full employee, Head of the Medical Area, Bioibérica, S.A., Barcelona, Spain.

Josep Vergés: full employee as Scientific and Medical Director of Bioibérica, S.A., Barcelona, Spain.

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