EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2015.0019

Original Investigation

Short-term effect of the combination of hyaluronic acid, chondroitin sulfate, and keratin matrix on early symptomatic knee osteoarthritis

Felice Galluccio, Tatiana Barskova, Marco Matucci Cerinic

Abstract

Objective: In the last years, symptomatic slow-acting drugs for osteoarthritis (SYSADOA) have been vastly studied and have generated considerable interest among clinicians. SYSADOA are generally used as a ground therapy with the main rationale to reduce the consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) and thus limit the related adverse events.

Material and Methods: In this study, we evaluated the short-term effect of an oral combination of hyaluronic acid, chondroitin sulfate, and keratin matrix on early symptomatic knee osteoarthritis. Forty patients were treated for 1 month and were allowed to assume analgesics or NSAIDs if necessary.

Results: At 2 months, the mean reduction of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score was 36% ($p<0.001$), and the mean reduction of the WOMAC pains score was 40% ($p<0.001$). Only two patients reported a sporadic need to assume analgesics; no patient reported any side effect during the study period.

Conclusion: This data demonstrates that the oral combination of hyaluronic acid, chondroitin sulfate, and keratin matrix is safe, well tolerated, and shows a rapid action reducing pain and improving joint function and stiffness in early symptomatic knee osteoarthritis.

Keywords: Knee osteoarthritis, SYSADOA, hyaluronic acid, chondroitin sulfate, piperine, manganese

Introduction

The prevalence of osteoarthritis (OA) is significantly increasing because of aging of the population (1). A variety of genetic and environmental risk factors and pathophysiological processes contribute to the progression of the disease resulting in typical OA features. Until recently, OA was considered a degenerative disorder caused by the breakdown of articular cartilage. However, OA affects the whole joint structure, including the synovium, subchondral bone, ligaments, and joint capsule (2). The disease is thus characterized by the degradation of the articular cartilage, the formation of osteophytes, a subchondral sclerosis and/or meniscal degeneration sometimes with bone marrow reaction, and synovial proliferation (3).

Increasing evidence has shown that inflammation, characterized by the contribution of cytokines, and metalloproteinase overproduction and release into the synovial joint are involved in cartilage degeneration (4), which is the pathological hallmark of the disease. The role of the inflammatory cascade in the development and progression of OA is now the new frontier of research. A variable grade of inflammation occurs at different OA stages.

Currently, no targeted or disease-modifying drugs are available for treating OA, and there are significant differences between the most important guidelines published until now (5-10) on pharmacological and non-pharmacological management. In the last years, symptomatic slow-acting drugs for OA (SYSADOA) have been vastly studied and have generated considerable interest among clinicians. SYSADOA such as hyaluronic acid (HA), chondroitin sulfate (CS), and glucosamine are natural compounds composed of repeating disaccharides and are prescribed as a ground therapy with the main rationale of reducing the consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) and thus limiting the related adverse events in the gastrointestinal tract, kidney, and cardiovascular system.

In this study, we evaluated the short-term effect of an oral formulation of HA, CS, keratin matrix, manganese and piperine on knee OA.

Material and Methods

The charts of all OA patients with knee OA from an outpatient clinic were reviewed, and 40 Caucasian patients were chosen according to the following inclusion criteria: adult patients with symptomatic knee OA

Department of Clinical and Experimental Medicine, Division of Rheumatology, University of Florence, Firenze, Italy

Address for Correspondence: Felice Galluccio, Department of Clinical and Experimental Medicine, Division of Rheumatology, University of Florence, Firenze, Italy

E-mail: felicegalluccio@gmail.com

Submitted: 13.02.2015
Accepted: 13.05.2015

Copyright 2015 © Medical Research and Education Association

grade I–II according to Kellgren and Lawrence. Patients with previous surgery, infiltrative therapy in the previous month both with HA and corticosteroids, or oral or topical therapy with NSAIDs or corticosteroids were excluded. The study was approved by the local ethics committee, and all patients signed an informed consent form to participate in the study.

This study was conducted over a period of 2 months, during which the rheumatologist advised the patients to assume the oral formulation of HA, CS, keratin matrix, manganese, and piperine (Ialoral 1500™, PharmaSuisse Laboratories Srl., Milan, Italy) for 1 month. The patients were also allowed to assume analgesics or NSAIDs if necessary.

The primary objective of this study was to retrospectively evaluate the effect of 1-month therapy with Ialoral 1500™ in patients with knee OA. The secondary objective was to evaluate the tolerability and adherence to the therapy and consumption of analgesics.

The patients were assessed according to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score (11) at baseline (T0) and after 2 months (T2).

Data are presented as mean±standard deviation and as numbers or percentage. D'Agostino and Pearson normality test T-test for paired data was used to compare data. Statistical analyses were performed with GraphPad Prism 6.0 (GraphPad Software Inc, La Jolla, California, United States).

Results

The mean age of the patients was 62.7±10.35 years; 63% of the patients were female and the patients had an average onset of symptoms of 3.55±1.32 months.

At the beginning of the treatment, the mean WOMAC score was 44.2±4.14. At the end of the observational study period, the mean reduction in the WOMAC score was 36% (28.3±3.94; $p<0.001$). The subanalyses of the WOMAC pain score showed a reduction of approximately 40% (8.6±0.48 vs. 5.2±0.97; $p<0.001$).

All patients had taken regular treatment for 30 days, and none of them reported any side effects or symptoms related to the drug. Only two patients reported the sporadic need to assume acetaminophen or acetaminophen–codeine combination. No patient showed the need to take topical NSAIDs and systemic corticosteroids.

Discussion

In literature, there are many studies evaluating the efficacy of SYSADOA with an increasing evidence of their beneficial effects on OA (12). Moreover, recent advances on the biochemical and molecular aspects of the pathogenic process of the disease support the hypothesis that the long-term intake of these compounds can slow the progression of the disease, thereby reducing both pain and joint stiffness.

Unfortunately, there is still a disagreement on the use of SYSADOA in published guidelines. The European League against Rheumatism and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis recommend this therapy with a high level of evidence, which is in contrast to the latest guidelines of American College of Rheumatology, the Osteoarthritis Research Society International, and the National Institute for Health and Care Excellence (5-10).

This study demonstrated that Ialoral 1500™ was not only safe and well tolerated by patients with grade I-II KL knee OA but also showed also a rapid action reducing pain and improving joint function and stiffness.

These data were obtained from the patients with a low degree knee OA (I-II KL) and with a symptom onset 6 months prior. The aim was to evaluate whether these drugs elicited a rapid response in patients frequently treated with NSAIDs and steroids.

Synovial inflammation and structural and molecular changes of the joint system should be the target of OA therapies. However, currently, therapy with HA, a constituent of the synovial fluid and that has viscoelastic properties (13), has been proposed. Previous studies have shown that HA has a low bioavailability orally (14), and for this reason, it is generally administered via intra-articular injections with the aim of restoring the viscoelasticity of the synovial fluid and inhibiting the secretion of inflammatory mediators and neuropeptides via CD44 and ICAM1 and blocking the binding of extracellular matrix fragments (ECM-f) (15). Despite controversies on its efficacy in the current guidelines, it is a diffuse and common practice. The therapeutic effect of oral HA also occurs without intestinal absorption binding the intestinal toll-like receptor 4 (TLR4) exerting a proinflammatory cytokine suppression (16). On the other hand, the effect of CS seems to be due by the inhibition of both the nuclear translocation of NF-kβ and targeting TLR4 and CD44, thus preventing ECM-f from unleashing the inflammatory cascade (15). Another important role of CS is to increase the expression of TGF-β1 on the extracellular matrix (17) and to promote the synthesis of HA and collagen type II (18-19). The mechanism of action of HA and CS seems to be complementary, developing a synergistic effect that could explain the results obtained in this study. Moreover, the addition of manganese, a trace element cofactor in the biosynthesis of glycosaminoglycan (20), and piperine, the active phenolic component of black pepper extract with its anti-inflammatory activity (21), may play a key role in the fast action of this compound.

We can also assume that the rapid response to the treatment was mainly due to the fact that we targeted only patients at an early OA stage and with the onset of symptoms of less than 6 months, when the inflammation cascade more closely triggered the pathophysiological process.

A limitation of this study is the absence of a control group and the subjective assessment with the WOMAC scale only, but the purpose of this work was to evaluate the rapidity of action of this compound and not its efficacy versus placebo or standard therapy.

In conclusion, we suggest that the combination of SYSADOA is more effective than monotherapy in the early phase of OA, in particular. In this phase, the clinical features of the disease can be significantly attenuated by the combined use of SYSADOA.

Because OA is a chronic disease, it is of importance to educate both patients and general practitioners that anti-inflammatory drugs are not the only rapid and effective treatment choices and that they should not be used/abused. As reported by other experts, we recommend the use of only high-quality compounds that can guarantee product contents and pharmacological properties.

Ethics Committee Approval: Ethics Committee approval was received for this study from Careggi University Hospital of Florence.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.G.; Design - F.G.; Supervision - M.M.C.; Materials - F.G.; Data Collection and/or Processing - T.B.; Analysis and/or Interpretation - F.G.; Literature Review - F.G.; Writer - F.G.; Critical Review - M.M.C.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The author declared that this study has received no financial support.

References

1. Bijlsma JW, BerenbaumF, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. Lancet 2011; 377: 2115-26. **[CrossRef]**
2. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum 2012; 64: 1697-707. **[CrossRef]**
3. Liu-Bryan R, Terkeltaub R. Emerging regulators of the inflammatory process in osteoarthritis. Nat Rev Rheumatol 2015;11: 35-44. **[CrossRef]**
4. Pereira D, Peleteiro B, Araújo J, Branco J, Santos RA, Ramos E. The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review. Osteoarthritis Cartilage 2011; 19: 1270-85. **[CrossRef]**
5. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, et al. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003; 62: 1145-55. **[CrossRef]**
6. Bruyère O, Cooper C, Pelletier JP, Branco J, Luisa Brandi M, Guillemin F, et al. An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: A report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Semin Arthritis Rheum 2014; 44: 253-63. **[CrossRef]**
7. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res 2012; 64: 465-74. **[CrossRef]**
8. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part III: changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage 2010; 18: 476-99. **[CrossRef]**
9. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014; 22: 363-88. **[CrossRef]**
10. National Clinical Guideline Centre. Osteoarthritis: Care and Management in Adults. Clinical guideline 2014; CG177.
11. Salaffi F, Leardini G, Canesi B, Mannoni A, Fioravanti A, Caporali L, et al. Reliability and validity of the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index in Italian patients with osteoarthritis of the knee. Osteoarthritis Cartilage 2003; 11: 551-60. **[CrossRef]**
12. Henrotin Y, Marty M, Mobasheri A. What is the current status of chondroitin sulfate and glucosamine for the treatment of knee osteoarthritis? Maturitas 2014; 78: 184-7. **[CrossRef]**
13. Caligaris M, Canal CE, Ahmad CS, Gardner TR, Ateshian GA. Investigation of the frictional response of osteoarthritic human tibiofemoral joints and the potential beneficial tribological effect of healthy synovial fluid. Osteoarthritis Cartilage 2009; 17: 1327-32. **[CrossRef]**
14. Hisada N, Satsu H, Mori A, Totsuka M, Kamei J, Nozawa T, et al . Low-molecular-weight hyaluronan permeates through human intestinal Caco-2 cell monolayers via the paracellular pathway. Biosci Biotechnol Biochem 2008; 72: 1111-4. **[CrossRef]**
15. du Souich P. Absorption, distribution and mechanism of action of SYSADOAS. Pharmacol Ther 2014; 142: 362-74. **[CrossRef]**
16. Asari A, Kanemitsu T, Kurihara H. Oral administration of high molecular weight hyaluronan (900 kDa) controls immune system via toll-like receptor 4 in the intestinal epithelium. J Biol Chem 2010; 285: 24751-8. **[CrossRef]**
17. Campo GM, Avenoso A, Campo S, D'Ascola A, Traina P, Samà D, et al. Purified human plasma glycosaminoglycans reduced NF-kappaB activation, pro-inflammatory cytokine production and apoptosis in LPS-treated chondrocytes. Innate Immunol 2008; 14: 233-46. **[CrossRef]**
18. Nishimoto S, Takagi M, Wakitani S, Nihira T, Yoshida T. Effect of chondroitin sulfate and hyaluronic acid on gene expression in a three-dimensional culture of chondrocytes. J Biosci Bioeng2005; 100: 123-6. **[CrossRef]**
19. Gouttenoire J, Valcourt U, Ronzière MC, Aubert-Foucher E, Mallein-Gerin F, Herbage D. Modulation of collagen synthesis in normal and osteoarthritic cartilage. Biorheology, 2004; 41: 535-42.
20. McNamara PS, Johnston SA, Todhunter RJ. Slow-acting, disease-modifying osteoarthritis agents. Vet Clin North Am Small Anim Pract 1997; 27: 863-81. **[CrossRef]**
21. Ying X, Chen X, Cheng S, Shen Y, Peng L, Xu HZ. Piperine inhibits IL-β induced expression of inflammatory mediators in human osteoarthritis chondrocyte. Int Immunopharmacol 2013; 17: 293-9. **[CrossRef]**