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Letter to Editor

Oral hyaluronic acid in patients with knee osteoarthritis

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Summary. The international guidelines agree that management of knee osteoarthritis (OA) requires both non-pharmacological, and pharmacological approaches and suggest initiating a background therapy with chronic symptomatic slow-acting drugs for osteoarthritis (SYSADOAs), such as hyaluronic acid (HA). Oral HA treatment is now widely used because of its safety, good results in daily clinical practice, and relative low cost for knee pain. On the other hand, oral HA has been the source of much research in the last years. Several trials have evidenced the good efficacy of oral HA in reducing pain and improving joint functionality in mild to moderate knee osteoarthritis, but critical issues concerning the parameters used in these studies to measure the end points still persist. In few cases objective parameters (i.e. ultrasound) have been considered and no study correlated them with specific scales like visual analogue score (VAS) and Knee injury and Osteoarthritis Outcome Score (KOOS) to improve patient assessment. This could be the goal of future researches.

Key words: knee osteoarthritis, hyaluronic acid, outcome assessment

Dear Editor,

We read with great interest the manuscript published by Guadagna S et al (1) titled "Oral hyaluronan for the treatment of knee osteoarthritis: a systematic review" in the Vol 20 No 4 (2018) of this journal. The authors have done a well conducted analysis to describe the current state of the art of the treatment of mild to moderate knee osteoarthritis (OA) with oral hyaluronic acid (HA) products. The authors have also mentioned the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) recommendation to initiate a background therapy with chronic symptomatic slow-acting drugs for osteoarthritis (SYSADOAs), such as HA. The authors in their results evidenced the heterogenicity of HA preparations and that most trials used subjective measures (instead of objective parameters) to determine the efficacy of the HA treatment.

We argue that there are additional critical issues concerning the parameters used in the analysed clinical trials to measure the end points:

i) In the 7 trials performed in Japan, there were used only visual analogue scale (VAS) and/or scales for osteoarthritis symptoms tested on the Japanese population only, like Japanese Knee Osteoarthritis Measure (JKOM) and scoring of Japanese Orthopaedic Association (JOA) (2-4), and on no one a measurement using an objective tool, i.e. ultrasound (US) on isokinetic dynamometer; in the 10 trials conducted by the European and American investigators these instruments were used in only 4 of 10 studies.
ii) US (5-7) and isokinetic dynamometer (6-8) have given ambiguous results in several studies. US measurements evidenced a statistically significant difference with control group only in two trials (5,6) and it can be difficult to consider positive the results obtained in one of the three trials where the isokinetic test was used (statistically difference with control group only at isokinetic peak torque at 240° of the extensors) (2).
iii) The methods to apply and evaluate the US examination were not reported in two of the trials (5,7), while in the third study, the only US data collected was the synovial effusion in the suprapatellar recess measured in mm on the longitudinal axis (6), following the 2005 EULAR guidelines (9). Therefore, nei-

ther the recently proposed US score for large joints (10), nor the correlations between pain, radiological, and US findings (11), nor the several US features graded from 0 to 3 reported by Wu (12), were considered.

iv) The rationale to use the isokinetic test (Biodex Medical Systems, New York, USA) as primary efficacy assessment in 3 trials was that a decrease in knee OA pain could evidence an increased work, power and peak torque of leg muscles. Surely, this surrogate end point could be very useful to test HA on joint pain in trials with a different population, showing a clinical evidence i.e. in athletes with mean age 20 ±1.0 (13) or in soccer players with mean age 19.5 ±1.2 (14). Contrarily, the mean age of patients in the studies where isokinetic assessment was tested was 56.1±8.00 years (6), 42.38 ± 10.16 years (7), 59.6 ± 8.3 years (8); a difference, even statistically significant, in muscular strength obtained in a similar old population could not be considered important from a clinical point of view, because this parameter certainly did not modify patients' quality of life.

v) We agree with the authors when they say that the range of motion (ROM) of the knee joint measured with a goniometer is a simple tool and that it is commonly used in daily practices by orthopaedists. We also want to point out with the authors that ROM, unfortunately, has never been used as an end point in trials with oral HA, even if it could be easily correlated with specific scales like VAS and KOOS to improve patient assessment.

vi) No study has objectively evaluated the composite measurement of pain and basic activities like walking or performing daily activities. Tools able to record this data using accelerometery-based technology, are named actigraphs (15,16) and were already tested in clinical trials in patients affected by osteoarthritis of the knee. (17)

vii) When an Investigator is performing a ROM evaluation of the knee joint with a goniometer, overhead costs are near zero. The Biodex price is about 100 times the cost of a single actigraph; in addition, the Biodex system needs high qualified hospital centres and well-trained personnel. Finally, the ROM evaluation is part of the clinical practice of orthopaedics and the use of actigraphy is friendly with data collection by a standard personal computer (18). In this contest, Biodex system could represent the paradigm of the measurement tool not to be used in a pragmatic multicentre trial in a large population affected by pathologies like OA.

To address these topics we have planned a double blind randomized clinical trial (RCT) to compare a product based on oral HA with high molecular weight (Syalox® 300 Plus, River Pharma, Italy) versus placebo for a period of 4 months plus an optional period of 8 months; our goal will be to avoid the critical issues pointed out in the present letter, evidencing a correlation between improvements evaluated by subjective measurements (VAS, QoL) and by objective measurements (US and ROM). The project, extremely attractive from a scientific point of view, will be preceded by a pilot study (registered in clinicaltrials.gov as NCT 03421054) in order to assess the feasibility of the main study. This would save money, time and management for our team of investigators with limited resources.

We thank Guadagna S (Opera CRO) and the Progress in Nutrition journal for engaging in a challenging debate on the use of oral HA in knee osteoarthritis. We invite the authors of this systematic review to join and continue in this discussion. We also hope to collaborate with them to perform the future RCT, because our different and synergic competencies could contribute to define the correct role of oral HA as a new tool for the orthopaedists.

Disclosure

No potential conflict of interest relevant to this article was reported by the authors

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