ORAL HYALURONIC ACID ADMINISTRATION FOR KNEE OSTEOARTHRITIS

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ABSTRACT

Introduction
Knee osteoarthritis (OA) represent the most common OA localization, highly prevalent among people over 50 years, affecting more than 250 million people worldwide. On 2014, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) has recommended several non-pharmacological treatments for knee OA a background therapy with chronic symptomatic slow-acting drugs for osteoarthritis. Part of this class of natural compounds, Hyaluronic acid (HA) has evidenced its efficiency after intra-articular administration in patients with knee OA in more than 137 studies. This paper presents the feasibility of oral HA administration in relieving knee pain but present several inconsistencies, leading to the need of a trial to test the efficacy of the oral administration of HA and the implementation of objective measurements for conclusive results.

Methods
The study trial was planned to test on a limited scale (8 subjects) the feasibility of a large scale testing on subjects administering oral high-molecular-weight HA 300 mg + AKBA 10 mg (SYALOX 300 PLUS - RiverPharma - Italy) for 4 months. Then, the subjects bloods (n=8) evaluated with mild knee OA administered the nutritionacal product daily for 8 weeks and the symptoms were assessed using specific questionnaires and scales (KOAS, VAS, and imaging and orthopaedic tests). The study was approved by the local Ethical Committee and registered in www.ClinicalTrials.gov. The protocol was registered on ClinicalTrials.gov - NCT03421054.

Study Objectives
The primary objective of this trial was to assess the feasibility of implementing Ultrasonography and Range of motion (ROM) as objective measures to improve the knee mobility with the pain reduction of the affected knee in the patients suffering from knee OA. The secondary objective was to assess the feasibility of implementing Actigraphy as objective measurement to correlate the improvement of the knee mobility with the self-assessed quality of life and to evaluate the enrollment rate in one month while the collection of the laboratory data on efficacy of the tested product was only an exploitative objective.

Methods
The study population included a number of 8 participants aged between 65 and 70 years, each suffering from knee OA and pain due to osteoarthritis. The protocol was approved by the local Ethical Committee and registered in www.ClinicalTrials.gov. Each patient signed the informed consent form at the screening visit.

Inclusion criteria:
- Any gender
- Age from 65 to 70 years
- Symptomatic osteoarthritis (OA) of the knee with mild joint pain in daily life activities; not affecting the mobility of activities; subjects diagnosed with bilateral knee OA will be asked to specify the most affected knee at baseline, and the knee was evaluated throughout the study period.
- Age-related and related conditions within the previous 6 months (diagnosis of Kellgren/Lawrence score 2) at the enrollment visit.

Exclusion criteria:
- Subjects who have any inflammatory arthritic condition (different from the OA of the knee: fibromyalgia, multiple sclerosis or autoimmune disease.
- Treatment with NSAIDs or corticosteroids within 4 weeks before screening.
- Non-atroicial reactions of HA or corticosteroids in the target joint within 3 months before screening.
- Treatment with anti-inflammatory or chondroprotective drugs (chondroitin sulfate, glucosamine, methylsulfonylmethane, HA) within 2 weeks before.
- HA-containing nutritional supplements or cosmetics during the month before the study.
- Previous surgical treatment of knee joint(s) or any other diagnosis for osteoarthritis (high surgical osteoarthritis, arthroplasty), complications necessary for hospitalization and surgical treatment.
- Significant injury to the target joint within the past 6 months prior to screening (identified from medical history).
- Subjects taking an energy-restricted diet for weight loss.
- Pregnant women, nursing mothers, or women (only if childbearing potential) not using adequate methods of contraception.

References

Results
Eight patients were enrolled and administered oral SYALOX 300 PLUS for 8 weeks. All objectives planned were achieved:
- i) Ultrasonography and ROM were tested and evaluated as objective measurements for the improvement of the knee mobility with the pain reduction of the affected knee.
- ii) Actigraphy evidenced the possibility to follow the increasing of patient mobility and the decrease of the symmetric pain during the study period and also the possibility to be considered as a useful tool for the early detection of side effects.
- iii) Data regarding recruitment capability (8 patients/week) as well resulting sample characteristics and study procedures were collected. Therefore, it is possible to obtain a realistic estimation of time and budget for the future study.
- iv) Preliminary and positive data on efficacy and safety of SYALOX 300 PLUS oral formulation were obtained.

Conclusions
The results of the feasibility questions clearly and evidenced the performance of oral SYALOX 300 PLUS - RiverPharma - Italy in knee OA symptoms, exceeding the objectives of a simple pilot trial to some extent. Thanks to these results, it will be possible to implement a future main RCT where these parameters will be evaluated in a large population.

The chief movements, flexion and extension, were measured to calculate the knee Range Of Motion. Table 1 shows increases in both situations, active (helped by the clinician) and passive knee extension and flexion respectively.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Baseline</th>
<th>4 weeks</th>
<th>Delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKE</td>
<td>-2.3°</td>
<td>-0.6°</td>
<td>+1.7°</td>
</tr>
<tr>
<td>PFE</td>
<td>3.3°</td>
<td>-1.1°</td>
<td>+2.1°</td>
</tr>
<tr>
<td>PRO</td>
<td>128.1°</td>
<td>130.3°</td>
<td>+2.1°</td>
</tr>
<tr>
<td>PKF</td>
<td>125.7°</td>
<td>130.4°</td>
<td>+4.3°</td>
</tr>
</tbody>
</table>

Table 1

KQOS questionnaire was used to subjectively collect patient's change in opinion between visits. All six domains (symptoms, stiffness, pain, function, daily life activities, sports and recreational activities and quality of life) showed improvements. For example, at question #4 ‘Can you stanch your knee fully?’ of 6 patients (50%) positively responded to the nutricratical administration after just 4 weeks. A similar situation was found for question #9 ‘How soft is your knee joint stiffness after first walking in the morning’ were 5 of 6 (83.3%) subjects were pleased with the results.

At the question #1 ‘How often do you experience knee pain?’ of 7 of 8 (87.5%) subjects showed a decrease in the level of pain suffered from knee osteoarthritis while 5 of 8 (62.5%) subjects answered in positively manner on function and daily living question ‘#9. Putting on socks/stockings’. Overall, more than 50% of the responses in the KQOS questionnaire were either positive or neutral, in regard to the change from baseline to the 4 weeks of Oral HA nutricratical product administration.

Safety
No adverse events occurred during the 4 weeks administration with 100% very good results according to Investigator’s Global Assessment of Safety. In fact, one of the patients declared that observed a slight improvement in the limitations of the joint pain.

Conclusion
Results obtained, after only 4 weeks of oral hyaluronic acid (Syalox 300 PLUS) administration for knee osteoarthritis, showed a promising perspective to extend or implement a future main clinical trial in a larger population using the same parameters proved feasible from the pilot study.

Conflicts of interest
No conflict of interest for the authors; Barattini DF and Dogaru DE are members of the CRO involved by the Sponsor of the trial.

**Figure 1** presents graphically the change in knee extension ROM from baseline visit to 4 weeks after administration of SYALOX 300 PLUS.

**Figure 2** presents graphically the change in knee flexion ROM from baseline visit to 4 weeks after administration of SYALOX 300 Plus.