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A randomized double-blind clinical trial on the treatment of knee osteoarthritis: The efficacy of polynucleotides compared to standard hyaluronian viscosupplementation

Laura S. Giarratana [a,*], Bruno M. Marelli [b], Calogero Crapanzano [c], Silvia E. De Martinis [a], Luca Gala [d], Marcello Ferraro [e], Niccolò Marelli [f], Walter Albisetti [g]

[a] Scuola di Specializzazione in Ortopedia e Traumatologia -Università degli, Studi di Milano, Italy
[b] Direttore Dipartimento Ortopedia e Traumatologia, Istituto Ortopedico Gaetano Pini, Milano, Italy
[c] Direttore U.O.C. Patologia Clinica, Istituto Ortopedico Gaetano Pini, Milano, Italy
[d] Specialista in Ortopedia e Traumatologia, Istituto Ortopedico Gaetano Pini, Milano, Italy
[e] Dirigente Medico, Istituto Ortopedico Gaetano Pini, Milano, Italy
[f] Facoltà di Medicina e Chirurgia, Università degli Studi di Milano, Italy
[g] Dipartimento di Scienze Biomediche, Chirurgiche ed Odontoiatriche, Università degli Studi di Milano, Italy

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ABSTRACT

Background: This randomized, double-blind, parallel-group clinical trial aims to assess the equivalence of intra-articular polynucleotides compared to standard hyaluronic acid (HA) viscosupplementation in the treatment of knee osteoarthritis (OA).
Methods: 75 patients affected by knee OA were assessed for eligibility and 72 were enrolled and randomized to receive either intra-articular polynucleotides (Condrotide-36 patients) or hyaluronic acid (Hyalubrix-36 patients) at the Orthopedic Institute "Gaetano Pini" (Milan).
All patients underwent three intra-articular injections of Condrotide or Hyalubrix with an interval of 1 week. Participants, care givers, and investigators responsible for outcome assessment were all blinded to group assignment. Primary outcome measurements (KOOS and pain level (1)at rest, (2)at weight-bearing and (3) during physical activity) were evaluated at baseline (T0) and after one (T1), two (T2), six (T6), ten (T10), and 26 (T26) weeks. Secondary measurements included the determination of COMP serum levels at T0, T6 and T26.
Results: The reduction of pain and the increase of KOOS values from baseline were statistically significant for both treatments; nevertheless, for parameter KOOS "symptoms" the treatment with Condrotide showed significant results already after two weeks (at T2 $p = 0.003$) while the results obtained with Hyalubrix became significant only after 18 weeks (at T18 $p = 0.01$).
No significant adverse events were reported.
Conclusions: Condrotide is as effective as Hyalubrix in reducing knee OA symptoms but showed an earlier response on pain reduction and can therefore be considered a valid alternative to the use of HA in the treatment of OA, avoiding the adverse events of NSAIDs and of intra-articular corticosteroids.

1. Introduction

Osteoarthritis (OA) is a highly prevalent, age-related degenerative disease of synovial joints that causes severe pain and disabilities, leading to a serious impact on the patient's quality of life [1].

OA is a multi-factorial disease due to mechanical and biological alterations and is mainly characterized by the degeneration of the articular cartilage and changes of the properties of the synovial fluid, whose elastoviscosity decreases [2,3].

The treatment of OA is still an open issue: the therapeutic options used so far include physiotherapy, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular steroids, oral supplementation with glucosamine or chondroitin, topical capsaicin, viscosupplementation with hyaluronic acid (HA) and surgical treatments [4,5].

During the last few years, the use of hyaluronian viscosupplementation has grown as a treatment of moderate-degree OA: the goal of this treatment method is to replace the quantity of intra-articular HA, that is reduced in patients affected by osteoarthritis, in order to restore the natural viscosity of the synovial fluid and therefore protect cartilage, relieving patient's pain [6].

The main result of HA viscosupplementation is a "cushion effect" that reduces articular attrition and provides a lubricant action on articular

* Corresponding author at: Istituto Ortopedico Gaetano Pini, Piazza Cardinal Ferrari 1 20121 Milano. Tel.: +39 0258296680; fax: +39 0258296523.
E-mail address: laura.giarratana@unimi.it (L.S. Giarratana).

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space: in this way, cartilage becomes more resistant to mechanical stresses and able to maintain its elasticity for a longer time after compression [7].

Different results have been obtained with the use of intra-articular HA in patients affected by OA but, according to the currently available evidence, the long-term clinical efficacy of intra-articular HA has not yet been proven [8].

The ideal intra-articular treatment for OA should not only mechanically protect the damaged cartilage surface, but also restore chondrocytes' homeostasis by reestablishing the physiological articular micro-environment.

The need to act on the whole altered intra-articular micro-environment and to restore the physiological conditions of cartilage led to the development of an innovative Class III, CE marked, Medical Device for the intra-articular treatment of degenerative chondral pathologies (product name: Condrotide).

This product is a gel composed of polynucleotides (20 mg/ml) of controlled natural origin (fish sperm) and highly purified, that are able to bind a high concentration of water molecules and to re-organize their structures and orientate water molecules in order to create a 3D gel that undergoes an enzymatic cleavage, releasing oligonucleotides of progressively smaller sizes into the articular cavity. The final products of this enzymatic degradation are simple nucleotides, nucleosides, and nitrogen bases which, as known from the literature, are physiologically present in the extracellular environment and which constitute fundamental substrates for cells [9,10]. The possibility to enrich the synovial fluid with these substrates might represent a real advantage of Condrotide by supplying chondrocytes with nucleotides, nucleosides, purine, and pyrimidine bases, therefore supporting the physiological repair processes of cartilage. This protective effect on cartilage is therefore additional to a lubricant and moisturizing action due to its high concentration of water molecules and to its high viscoelasticity.

A randomized, double-blind clinical trial published in 2010 on 60 patients assessed the efficacy and safety profile of intra-articular polynucleotides gel injection in the treatment of knee OA associated with persistent pain, showing a reduction of VAS (Visual Analogue Scale) values and an increase of KOOS (Knee Injury and Osteoarthritis Outcome Score) from baseline values comparable to those obtained with the use of HA [11].

This new randomized, double-blind clinical trial aims to investigate the evidence-based results obtained in the previously cited study [11]: the efficacy of an intra-articular preparation based on polynucleotides in the treatment of osteoarthritis (OA) associated with persistent pain was checked by comparing its effects with standard HA viscosupplementation. With respect to [11], this study was performed using a different injection posology and considering a longer follow-up. In addition, this study evaluated COMP (Cartilage Oligomeric Matrix Protein) serum levels: COMP is a 435,000 Da pentameric member of the thrombospondin protein family, initially isolated from cartilage and synthesized by chondrocytes. It is present in small amounts in the synovium and tendon and it is detectable in serum [12]. Although its mechanism of action is not completely understood, COMP showed to be predictive of subsequent MRI-determined cartilage loss in patients affected by knee OA, and could therefore be an important biomarker to predict OA progression [13]. This clinical trial, carried out from 2009 to 2012 at the Orthopedic and Traumatological Institute "Gaetano Pini" (Milan, Italy), was approved by the local ethic committee of this institute and followed the GCP guidelines. The trial was carried out according to 1964 Helsinki Declaration principles, and its subsequent endorsements.

2. Materials and methods

The product under study is a gel composed by polynucleotides, derived from natural sources (brood trout), whose trade name is Condrotide. It appears colorless, transparent, viscoelastic and it is provided in pre-filled glass sterile disposable syringes containing a solution of 2 ml (the concentration of polynucleotides is 20 mg/ml).

Standard hyaluronian viscosupplementation was perfomed using Hyalubrix that was provided in pre-filled glass sterile disposable syringes containing 30 mg of hyaluronic acid in 2 ml of buffered physiological saline solution. This study also evaluated the trend of COMP, whose serum levels were determined in blood samples during three different periods of the treatment.

2.1. Recruitment and eligibility

Seventy-five patients all affected by knee OA (diagnosis based on the ACR—American College of Rheumatology Classification [14]) were assessed for eligibility. Following the main inclusion criteria, patients had to be between 18 and 80 years, having followed at least five years of undergraduate school, having developed persistent pain for at least two months, having stated a VAS level less than or equal to four at the first clinical evaluation. Patients entered the study after having read and signed an informed consent form.

Exclusion criteria included alcohol or drug abuse, pregnancy or breastfeeding, hypersensibility to polynucleotides or hyaluronic acid, OA due to metabolic disorders, presence of severe pathologies at the first clinical evaluation, hyaluronic acid or steroid infiltration therapy ongoing or suspended since less than three months, systemic treatment with steroids ongoing or suspended since less than one month, fractures or severe traumatic episodes that affected the knee, presence of rheumatoid arthritis or other articular inflammatory pathologies and relevant hematological diseases.

The presence of inclusion and exclusion criteria was evaluated immediately before the first treatment (T0) and then, patients that were suitable for the treatment, were randomized in one of the two study groups (Group C or Group H) and followed for 26 weeks since the first clinical evaluation.

No restrictions were applied to NSAIDs consumption, but posology was recorded on the Case Report Form (CRF).

Three of 75 recruited patients were not declared as eligible since two had suspended steroid infiltration therapy since less than three months and one declined to participate.

2.2. Randomization and group assignment

A consecutive number (from one to 72) was assigned to each patient. Random number generator software was then used to assign treatments to patients. A set of numbered envelopes containing names of patients and the kind of assigned treatment was created and maintained closed until the end of the results analysis in order to keep the type of treatment unknown to experimenters. As a consequence participants, care givers, and outcome assessors were all blinded to group assignment.

Among the enrolled and randomized 72 patients, 36 were treated with Condrotide (Group C) and 36 were treated with Hyalubrix (Group H). Group C included 20 females and 16 males with a mean age of 64.92 years (range 31–80 years); group H included 21 females and 15 males with a mean age of 64.14 years (range 43–76 years). Since 3 patients from group C and one patient from group H were excluded, the efficacy set was composed by 33 patients for group C and 35 patients for group H.

2.3. Experimental intervention

As displayed in Table 1, all patients underwent three intra-articular injections of Condrotide or Hyalubrix with an interval of one week between each injection: the first one was performed at the beginning of the treatment (T0 = baseline time), the second one after one week (T1), and the third one after two weeks (T2); then patients returned for a clinical follow-up after six weeks (T6), ten weeks (T10),