The Knee 21 (2014) 661–668

Contents lists available at ScienceDirect

The Knee

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

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ARTICLE INFO

Article history:
Received 1 July 2013
Received in revised form 1 January 2014
Accepted 3 February 2014

Keywords:
Osteoarthritis
Polynucleotides
Hyaluronic acid
Pain relief
COMP

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

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http://dx.doi.org/10.1016/j.knee.2014.02.010
0968-0160/

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),

Table 1
Protocol of treatment and clinical evaluation.

	Intra-articular injection of H or C	Clinical check-up	Filling KOOS schedule	COMP level determination (blood sample)
TO	✓(#1)	✓	✓	✓
T1	✓(tt2)	✓		
T2	✓(#3)	✓	✓	
T6		✓	✓	✓
T10		✓	✓	
TIB		✓	✓	
T26		✓	✓	✓

18 weeks (T18), and 26 weeks (T26) since the beginning of the treatment. Serum levels of COMP were determined at T0, T6, and T26.

Injections were performed by highly skilled medical staff, following all standard rules and all principles of asepsis for the administration of intra-articular injections.

To respect the double-blind condition, injections were performed by a different physician from the one who dealt with the following clinical evaluations.

All phases of the study were performed following the CONSORT 2010 Statement [15].

2.4. Outcome measurements

The first primary outcome of this study was represented by the evaluation of the results of KOOS (Knee Injury and Osteoarthritis Outcome Score), a universally accepted schedule used in order to determine the therapeutic efficacy during clinical investigations that regarded function in daily living, pain, function in sport and recreation, symptoms, and quality of life [16] and that was filled-in at the beginning of the treatment (T0) and during the follow-up (T2, T6, T10, T18, T26).

The other primary outcome of this study was the modification of pain level at rest, at weight-bearing and during physical activity, evaluated through the Visual Analogue Scale (VAS) [17] at T1, T2, T6, T10, T18, and T26.

As regards primary outcomes, two analyses have been performed: the first one consists of the evaluation of KOOS and VAS values at different time-points with respect to their baseline values considering the two treatments separately; the second one considers the KOOS and VAS values as a comparison between the effects of the two treatments at different time-points from T0 up to T26.

Secondary outcome measurements included the determination of COMP (Cartilage Oligomeric Matrix Protein) serum levels at T0, T6, and T26, NSAIDs consumption, crackling during movement, articular mobility limitation (LMA), and articular edema.

Details of follow-up intervals for primary and secondary end-points are summarized in Table 1.

2.5. Statistical data analysis

Among a total of 72 patients, 68 completed the study (Group H = 35 patients and Group C = 33 patients): one drop-out in group H was lost at follow-up and three drop-outs in group C (two due to adverse events not related to the product and one lost at follow-up) occurred before the end of the study.

Statistical data analysis of primary outcomes and of COMP levels was performed using a Student's t-test with a significance level of $p \leq 0.05$. Wilcoxon signed-rank and rank sum tests (with $p \leq 0.05$) were used for statistical analysis of all the other secondary measurements. Finally also χ^2 tests were performed in order to test the goodness of fits in particular of COMP analysis.

A power calculation for each t-test was performed and will be presented in the next section. Table 2 shows the a-priori mean difference with its standard deviation, the standardized mean difference, the calculated power, and the patients needed to calculate power for the T26 end-point (compared to baseline) in all KOOS and VAS parameters for both Condrotide and Hyalubrix. These specific t-tests were chosen for statistical analysis based on normality: the assessment of data normality was performed by creating a histogram for each parameter at each time-point both for C and H and by fitting them using a Gaussian function: the data were considered to be normal distributed if the reduced χ^2 resulted to be between 1 and 1.5. All the data resulted to be normally distributed.

2.6. Baseline analysis

In order to determine whether eventual imbalances were present between groups H and C, Table 3 shows the results of t-test comparing H and C T0 values (C-T0 minus H-T0) for all the KOOS and VAS parameters: the absence of imbalance is proved by the fact that there is no p-value < 0.05 and that all confidence intervals contain the zero value.

3. Results

3.1. Primary outcome measurements

The evaluation of the results of KOOS included function in daily living, pain, function in sports and recreation, symptoms, and quality of life [16].

In the first analysis, the KOOS parameters in Group C and Group H were considered separately, observing the trend of their values at different time-points with respect to their baselines. The most remarkable result was achieved for the parameter "Symptoms": in fact the outcome obtained with the treatment with Condrotide was statistically significant already after 2 weeks since the beginning of the treatment (at T2 $p = 0.003$), while the results achieved with Hyalubrix became significant only after 18 weeks (at T18 $p = 0.010$). Another important result concerns the parameters "pain" and "Function in sports and recreation": Condrotide showed statistically significant results after 6 weeks (for KOOS "pain": at T6 $p = 0.03$; for KOOS "Function in sports and recreation": at T6 $p = 0.012$) since the beginning of the treatment, while Hyalubrix outcome became significant only after 18 weeks (for KOOS "pain": at T18 $p = 0.0001$; for KOOS "Function in sports and recreation": at T18 $p = 0.003$). Finally, considering the parameters "Function in daily living" and "Quality of life", the results of both treatments became statistically significant after 6 weeks. The calculated power ($1-\beta$) for all the performed t-tests lies between 0.94 and 0.999, showing a low rate of false positives.

Fig. 1 shows the obtained mean differences with respect to baseline (columns) as well as 95% t-test confidence intervals (bars) for all the KOOS parameters considering C and H separately.

Concerning the comparison between Condrotide and Hyalubrix at different time-points a statistically significant difference in favour of Condrotide was observed at T10 for parameters "Pain", "Function in daily living", and "Function in sports and recreation". In all the other cases the efficacy of both treatments can be considered equal.

In order to summarize the comparison results between the two treatments, Fig. 2 shows the obtained mean and standard deviation (error bars) as a function of time for both C and H and for all the above described KOOS parameters.

As regards parameters "Symptoms" and "Pain", the linear fit of group C is clearly steeper, showing that Condrotide has a faster effect on their reduction if compared to Hyalubrix. Concerning the other parameters, the slopes of groups C and H are similar, illustrating that both treatments almost perform in the same way. Finally, a detailed analysis of the T26 end-point for KOOS (together with power calculation) has been performed and is presented in Table 2.

The analysis of primary measurements was completed using the evaluation of pain at rest, at weight-bearing, and during physical activity from T0 to T26 using the Visual Analogue Scale (VAS) [17].

Table 2
Study of the primary endpoint (T26) with respect to baseline for both treatments (C and H) for all KOOS and VAS parameters. The power calculation and the number of needed patients are reported.

KOOS primary endpoint (T26-baseline)						
Treatment	Parameter	A-priori mean difference	Std. dev. of the a-priori difference	Standardized mean difference	Number of patients needed	Power
C	KOOS function and daily living	15.61	2.65	5.88	32	0.980
C	KOOS sport and recreation	17.49	3.61	4.85	32	0.999
C	KOOS pain	18.47	2.70	6.83	32	0.999
C	KOOS quality of life	19.04	3.45	5.52	32	0.999
C	KOOS symptoms	16.52	2.46	6.72	32	0.999
H	KOOS function and daily living	17.27	2.60	6.26	34	0.990
H	KOOS sport and recreation	20.05	3.15	6.42	34	0.999
H	KOOS pain	18.00	2.51	6.85	35	0.999
H	KOOS quality of life	22.36	2.99	7.58	34	0.990
H	KOOS symptoms	11.09	2.40	4.13	35	0.999
VAS primary endpoint (726-baseline)						
C	VAS at rest	−1.33	0.29	4.57	33	0.999
C	VAS standing	−2.12	0.32	6.69	33	0.999
C	VAS walking	−3.39	0.40	8.50	33	0.990
H	VAS at rest	−1.57	0.41	3.83	35	0.999
H	VAS standing	−2.09	0.41	5.04	35	0.990
H	VAS walking	−2.57	0.41	6.31	35	0.999

Fig. 3 shows the obtained mean and standard deviation (error bars) as a function of time for both C and H and for all the above described VAS parameters. It is possible to observe that all VAS values decrease with time for both treatments.

As regards VAS "at rest" since T2 both groups C (at T2 $p = 0.043$) and H (at T2 $p = 0.043$) showed a statistically significant difference, that was also later maintained.

Analyzing VAS values "standing" and "walking", Condrotide showed a statistically significant difference earlier than Hyalubrix (T1 for group C vs T2 for group H). The calculated power ($1-\beta$) for all the performed t-tests lies between 0.97 and 0.999 showing a low rate of false positives.

Fig. 4 shows the obtained average differences with respect to baseline (columns) as well as 95% t-test confidence intervals (bars) for all VAS parameters considering C and H separately.

Concerning the comparison between Condrotide and Hyalubrix at different time-points, a statistically significant difference in favor of Condrotide was observed at T6 for VAS "at rest", at T1, T2, and T6 for VAS "standing" and in T6 and T10 for VAS "walking", underlining that Condrotide shows an earlier effect on the reduction of pain. Finally, a detailed analysis of the T26 end-point (together with power calculation) for VAS has been performed and is presented in Table 2.

4. Secondary outcome measurements

Secondary outcome measurements included the determination of COMP serum levels at T0, T6 and T26, NSAIDs consumption, crepitus during movement, articular mobility limitation (LMA) and articular oedema.

The evaluation of COMP showed a statistically significant reduction of its serum levels since the beginning to the end of the treatment (T26-T0) in group H ($p = 0.001$), while the treatment with Condrotide caused a mild increase of COMP levels at T6 with a new successive reduction. Besides, the comparison between the two treatments did not show any statistical significance (Fig. 5).

A χ^2 test was performed in order to understand if C values can be better fitted by a constant function ($y_1(x) = P_0$, shown as a dotted line in Fig. 5) or by a linear function ($y_2(x) = P_1 + P_2x$) with P_0, P_1, and P_2 to be determined through the fitting procedure. Since this analysis shows that reduced χ^2 (y_1) = 4.48 and reduced χ^2 (y_2) = 0.30, it is possible to conclude that a linear fit (with $P_1 < 0$) better approximates the data. In addition, since reduced χ^2 (y_2) < 1, it is also possible to state that the C error bars are over-estimated.

The limited number of patients could be the main cause of overestimation of the error bars.The angular coefficient of the linear fit of H group (−0.09) is about 1.5 times larger than that of the one of the linear fit of C group (−0.06), thus meaning that COMP levels decrease 1.5 times faster in H than in C group.

A clear reduction of NSAIDs consumption was observed at T10 in group C and at T18 in group H, but the comparison between the two treatments did not show any statistical significant difference. Finally, the clinical evaluation of the treated joint (crackling during movement, articular mobility limitation and articular edema) showed similar results for both treatments, without enlightening any statistically significant difference between the two groups.

5. Discussion

During the last few years, hyaluronian viscosupplementation has been introduced in the treatment of OA as an alternative to the use of NSAIDs and intra-articular steroid injections [18].

Hyaluronian has been used as a pain reliever in patients with OA, particularly in the knee joint, since it causes a stimulation of the

Table 3
Determination of baseline imbalances.

Parameter (C–H)	Estimate	p-Value	95% CI		T-estimate	Power
			Lower	Upper		
KOOS function and daily living	4.026	0.316	−3.856	11.909	1.714	0.954
KOOS sport and recreation	3.863	0.422	−5.590	13.317	1.207	0.884
KOOS pain	1.322	0.731	−6.251	8.896	0.622	0.732
KOOS quality of life	3.206	0.466	−5.445	11.857	1.269	0.895
KOOS symptoms	−2.136	0.557	−9.291	5.018	−0.908	0.183
VAS at rest	−0.806	0.078	−1.704	0.092	2.034	0.977
VAS standing	−0.782	0.111	−1.744	0.181	2.034	0.977
VAS walking	−0.025	0.963	−1.096	1.046	0.077	0.530

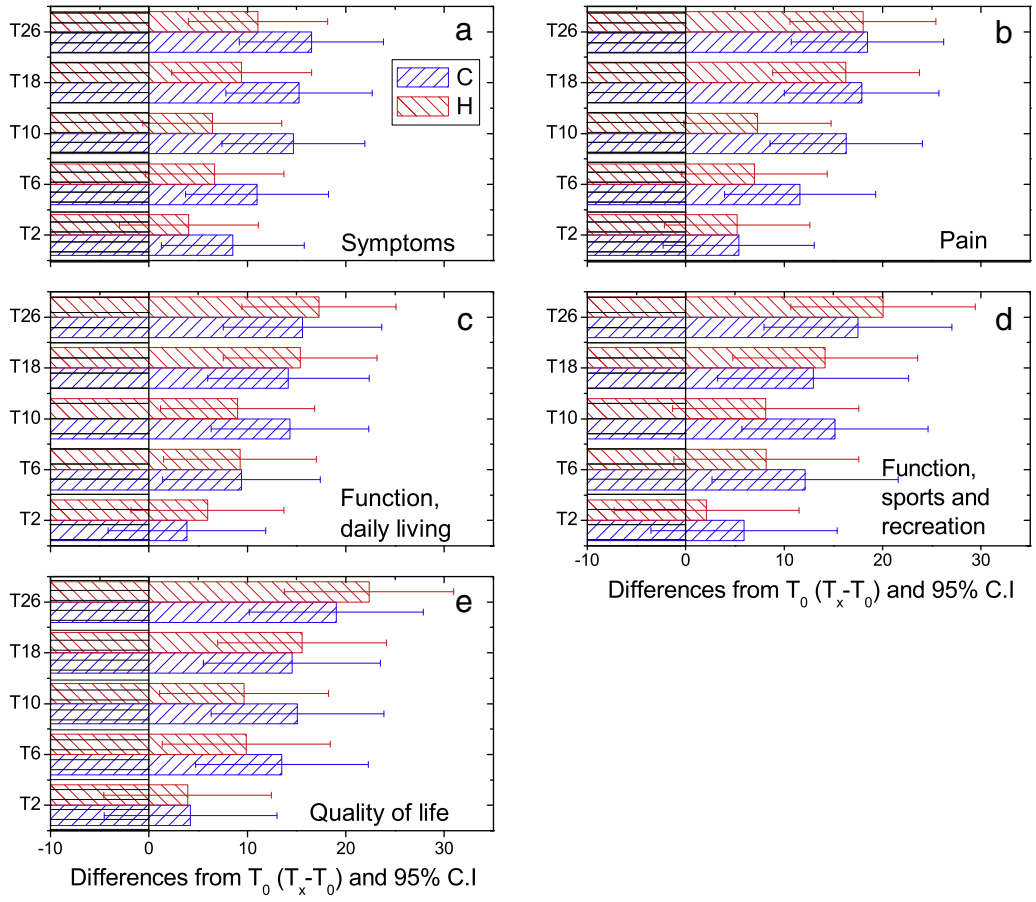

Fig. 1. Mean differences from baseline for all KOOS parameters as well as 95% t-test confidence interval considering C and H separately.

synthesis of endogenous hyaluronian [19], the reduction of inflammatory degradation products in the joint and the improvement of the viscoelastic function of the synovial fluid. In addition, HA showed to decrease osteophyte formation [20] and to promote reparative processes of articular cartilage [21], highlighting a biological activity on rabbit models of OA.

There is evidence in the literature that the employment of some kinds of highly cross-linked HA in the treatment of OA showed even better results at 6 months needing only one or two intra-articular injections; besides, the efficacy of highly cross-linked HA increases in combination with other drugs [22,23].

Nevertheless, the results of meta-analyses about the long-term efficacy of HA are still equivocal [24–26].

Condrotide is an innovative medical device, conceived in order to satisfy a double mechanism of action: a mechanical protection of the damaged cartilage, and the substitution of the flogistic synovial fluid and to the restoration of an ideal microenvironment for matrix production [11].

Studies in vitro and in vivo have been carried out in order to verify the effects of polynucleotides on cartilage: Gennero et al. estimated the efficacy of polydeoxyribonucleotides (PDRNs) on cartilage degradation in vitro, finding out that PDRNs are suitable for a long-term cultivation of in vitro cartilage and have therapeutic effects on chondrocytes by protecting cartilage [27]. An in vivo study performed by Bitto et al. investigated the effects of PDRNs in collagen-induced arthritis in mice. The results of this work show that PDRNs treatment improves clinical signs of arthritis and histological damage, reduces cartilage expression and circulating levels of HMGB-1, TNFα, and IL-6 and reduces cytokine production from stimulated human chondrocytes, thus representing a valid alternative for the treatment of arthritis [28].

Finally, a clinical trial carried out by Vanelli et al. compared for the first time the efficacy of intra-articular polynucleotides (Condrotide) and HA (Sinovial) in the treatment of knee OA of 60 patients that underwent five weekly intra-articular knee injections (30 with Condrotide-Group A and 30 with Sinovial-Group B); a three months follow up was planned after the end of the treatment. This work pointed out a statistically significant increase of KOOS for both groups A and B and a statistically significant decrease of VAS for both groups with a faster reduction of pain at rest in group A, showing that intra-articular polynucleotides are a valid alternative to traditional hyaluronian supplementation [11].

The aim of our study is to evaluate the efficacy of intra-articular polynucleotides (Condrotide) in the treatment of osteoarthritis (OA) associated with persistent pain employing a different injection posology (three intra-articular injections instead of five) and considering a longer follow-up (26 weeks instead of three months) with respect to [11].

The results of this work showed how the use of both treatments (Condrotide vs Hyalubrix) determined a favorable effect on the analyzed parameters, in particular pointing out a reduction of pain and an improvement of the activities of daily living and, therefore, of the quality of life.

The outcome of this study did not show any statistically significant difference between the two treatments; nevertheless, an earlier clinical efficacy of Condrotide with respect to Hyalubrix was observed.

In the literature, good clinical results with the use of polynucleotides were obtained by Saggini et al. [29], who tested the two months efficacy of three weekly intra-articular injections of Condrotide in 75 patients affected by OA. In particular they obtained, in both groups, a pain decrease of more than 6 points of score from 7.88 to 1.74 and a substantial improvement of R.O.M. from 0–84° to 0–111°.

Although in this study a shorter follow-up was considered with respect to our investigation, it shows an even higher response to the treatment with Condrotide in the short-term period.

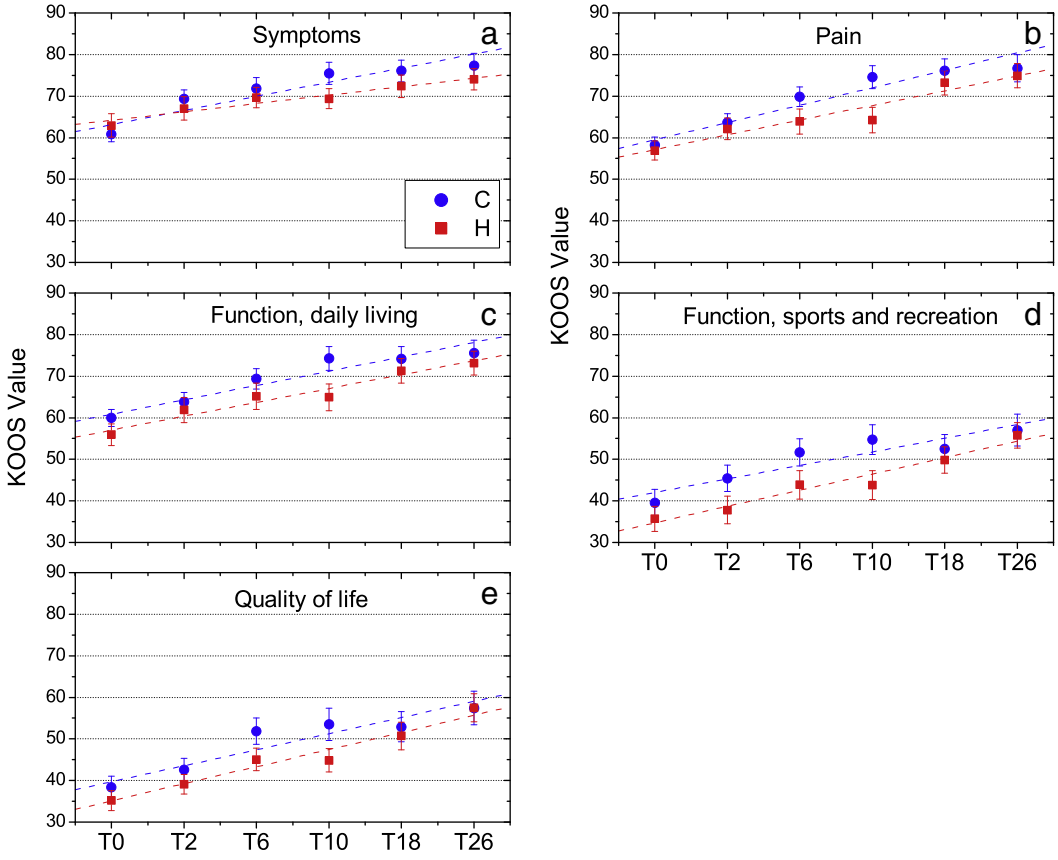

Fig. 2. C and H KOOS mean values as a function of time for the five considered parameters. Error bars represent standard deviation.

The results obtained in our study about the efficacy of HA are comparable to those described in literature whose state of art shows that the clinical efficacy of HA occurs between five and 13 weeks after the beginning of the intra-articular treatment and lasts up to 24 weeks [30,31] but with a longer lasting efficiency. Our study demonstrates that Condrotide is at least as effective as HA but with a shorter silent period before acting on the reduction of pain.

In addition, our work proves that a lower number of injections with respect to [11] (three instead of five) has the same impact on OA symptoms.

A real breakthrough in the treatment of OA might be represented by the identification of biomarkers that could actually change OA prediction, OA management, trials of therapies and that could increase our understanding of its pathogenesis [32]. Among the possible studied biomarkers, COMP, a protein detectable in serum, showed to be predictive of subsequent MRI-determined cartilage loss in patients affected by knee OA [13]. This hypothesis seems to be confirmed by the observation that COMP levels were highly

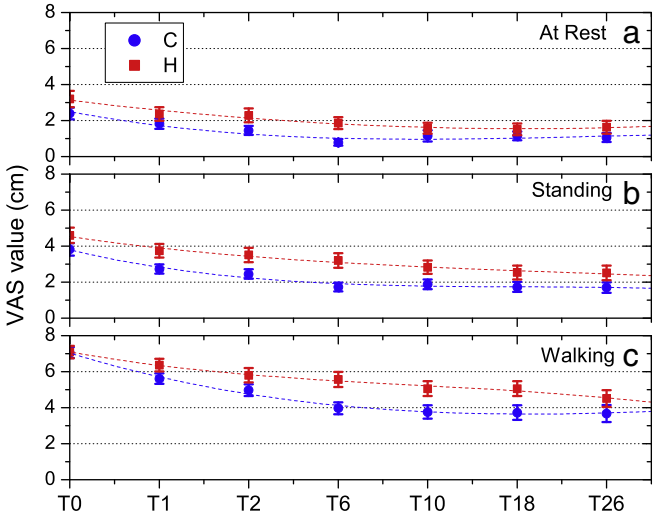

Fig. 3. C and H VAS mean values as a function of time for the three considered VAS parameters. Error bars represent standard deviation.

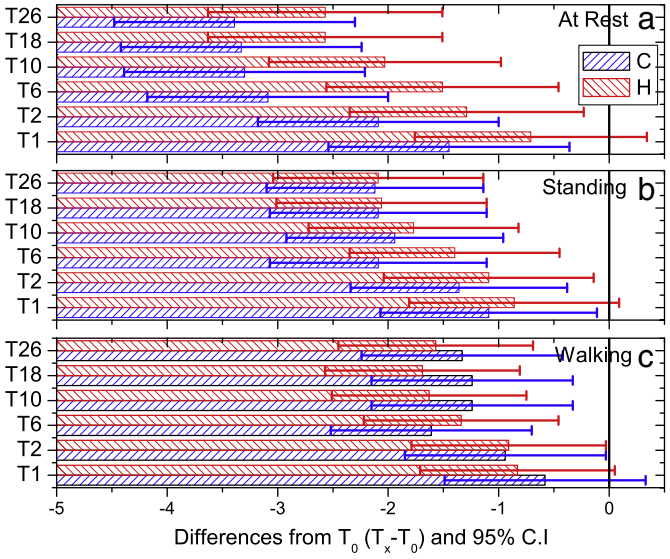

Fig. 4. Mean differences from baseline for all VAS parameters as well as 95% t-test confidence interval considering C and H separately.

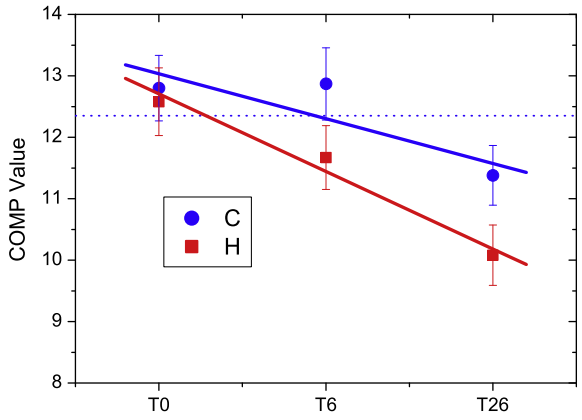

Fig. 5. C and H COMP values as a function of time. Constant and linear fit of C and linear fit of H data are also shown.

increased after strong articular stresses, for example in marathoners after a race [33].

Although evidences are accumulating about the existence of a correlation between COMP serum levels and cartilage degradation in OA progression [34–36], little is known about the modifications of COMP serum levels in response to its treatment, while several studies face this aspect in rheumatologic diseases as rheumatoid arthritis (RA) [37,38].

As a consequence, one of the aims of this study was to link, for the first time, the trend of COMP serum levels with the efficacy of intra-articular injections of Condrotide or Hyalubrix.

The slight increase of COMP levels in the first part of the Condrotide data curve (Fig. 5) could be explained as a consequence of a faster improvement of symptoms in patients treated with Condrotide if compared to patients treated with Hyalubrix. This precocious reduction of pain could in fact induce patients of group C to an earlier increase of physical activity that causes articular overwork with a resulting augmented stress on cartilage. Nevertheless, a wider number of patients may be needed in order to confirm these results.

The reduction of NSAID consumption observed during both treatments is linked to the efficiency of C and H in timely reducing pain.

Finally, the clinical evaluation of the treated joint (crepitus during movement, articular mobility limitation and articular oedema) showed similar results for both treatments, agreeing with the results obtained for the other parameters.

Moreover, no significant adverse events connected to the employment of both products were reported.

6. Conclusions and future perspectives

This study confirms that Condrotide is as effective as Hyalubrix in reducing knee OA symptoms, but it shows an earlier response on pain reduction, determining a faster improvement of the activities of daily living and, therefore, of a patient's quality of life.

The intra-articular use of Condrotide might therefore represent a favorable alternative to the use of HA in the treatment of OA connected to persistent pain, avoiding the adverse events due to the use of NSAIDs and intra-articular corticosteroids that, until some years ago, represented the gold-standard therapy for OA. Besides, in clinical practice, the advantages of Condrotide as regards pain relief could be better exploited by extending the interval between the different injections, thus reducing the rate of infiltrations.

However, more studies are needed to broaden present knowledge. Condrotide efficacy on knee OA should be investigated in larger cohorts of patients and planning a longer follow-up period of at least one or two years.

Further studies are also necessary in order to clarify the link between cartilage degradation and COMP levels, whose understanding could better explain OA pathogenesis. Besides, COMP levels determination could be performed at several time-points (less than or equal to four).

Finally, a new randomized, double-blind clinical trial could be developed in order to compare Condrotide to intra-articular corticosteroids, in particular as regards their short-term efficacies in patients affected by knee OA.

Conflict of interest

The authors disclose no conflict of interest.

Acknowledgments

This paper is warmly dedicated to the memory of dear Prof. Albisetti, who sadly and prematurely left us.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.knee.2014.02.010.

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