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Use of autologous conditioned serum (ACS-ORTHOKINE) for osteoarthrosic chronic pain and facet joint syndrome: a prospective observational study

Andrea Cortegiani[1], Mariachiara Ippolito[1], Giulia Spurio[1], Antonietta Alongi[2]

1 University of Palermo

2 Azienda Ospedaliera Universitaria Policlinico "Paolo Giaccone"

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Abstract

Osteoarthritis associated chronic pain is a highly disabling symptom with a strong impact on the quality of life of patients. Until now, no treatment can significantly reduce painful symptoms in the severe forms of osteoarthritis, except at the cost of important side effects. The purpose of our prospective observational monocentric study was to evaluate the effectiveness of the autologous conditioned serum (ACS) as a treatment for patients with 1 to 3 grade osteoarthritis and with facet joint syndrome, in reducing painful symptoms and slowing the progression of the disease.

We investigated a total of 26 patients treated with autologous conditioned serum injections in the target site. Patients were evaluated using validated outcome instruments to assess the intensity of painful symptomatology (VAS), joint function (WOMAC; Quick-DASH; ODI) and quality of life (SF36; Karnofsky Index). The evaluations were carried out before each injection of autologous conditioned serum (timepoints 0-3) and successively after one, three and six months from the last injections (timepoints 4-6).

The injections of autologous conditioned serum have shown promising results, reducing painful symptomatology, improving joint performance and quality of life, not only close and immediately following the infiltration itself, but also during the follow-up and up to six months after the last injection without significant adverse effects.

INTRODUCTION

The Autologous Conditioned Serum (ACS), known as Orthokine, is a new blood product, recently introduced as a conservative treatment in polydistrict grade 1 to 3 osteoarthritis, with many properties, that make it a potential first-choice treatment in osteoarthritis pathology and in facet joint syndrome.

The use of the autologous conditioned serum arises from the need to find an effective, well-tolerated, safe,

and lasting treatment that can alleviate the painful symptoms and slow, if necessary, the progression of the disease.

The autologous conditioned serum is obtained from a part of autologous venous blood, appropriately incubated in special test tubes containing crystal spheres, in contact with which the leukocytes release a series of anti-inflammatory cytokines. The serum obtained after this incubation can be stored, frozen, and it is then used for intra-articular injections in the sites to be treated, with the goal of extinguishing the inflammatory processes typical of the acuity phases of osteoarthritis, by reducing or blocking cartilage degradation and reducing the need for more invasive therapies.

The therapeutic properties of the autologous conditioned serum are mainly linked to the content of interleukins with regulatory and antiflogistic action, with reference to IL-1ra (antagonist of the IL-1 receptor).

IL-1, produced mainly by activated macrophages and lymphocytes, is a pro-inflammatory cytokine, highly expressed in osteoarthritis chondrocyte compared to normal chondrocyte. (1)

IL-1 contributes to the onset of painful symptoms and peripheral nociceptive sensitization, both indirectly through the perpetuation of the chronic inflammatory process, which directly through sensitization of sensitive neurons expressing receptors for the same interleukin. (2)

Until now, no treatments can significantly reduce painful symptoms without causing dangerous side effects for the patient.

It is therefore necessary to study a treatment that can give to the patient the highest relief from painful symptoms with the least number of side effects.

Our study aim was to evaluate the effectiveness and safety of treatment with the infiltration of autologous conditioned serum in patients with osteoarthritis of grade 1 to 3, not only at knee level, as already evaluated by previous scientific studies, but also at the level of the ankle, the hand, the shoulder and, above all, in patients with facet joint syndrome.

MATERIALS AND METHODS

The study, approved by the Palermo 1 Ethics Committee, was carried out on patients with osteoarthritis grade 1 to 3 and articular facet joint syndrome treated with injections of autologous conditioned serum, at the outpatient clinic for pain treatment of the Paolo Giaccone Hospital University of Palermo, from September 2020 to October 2021.

The patients were selected, after careful anamnestic analysis and objective examination, according to specific inclusion and exclusion criteria shown in **Table 1**.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age > 18 years	**Age < 18 years**
Polidistrict grade 1 to 3 osteoarthritis not responsive to treatment with platelet concentrate non-transfusioni use (CPuNT).	**Pregnancy**
Facet joint syndrome not eligible for corticosteroid infiltration	**Cancer pain**
	History of coagulopathy
	Infections in progress
	Immunodepression
	Diagnosis of rheumatoid arthritis

A written informed consent was collected from all the patients included in the study. Each patient was assigned a numerical alpha code, from α1 to α26, to ensure anonymity during data collection and data analysis.

Data collected regarded patients' age, weight, height, sex, comorbidity, age at the onset of the disease. All the data was collected using an electronic database, also used to register the outcome measures, evaluating pain reduction and improvement of joint function.

Preparation of the conditioned autologous serum

The conditioned autologous serum was prepared at the Immunohematology and Transfusion Medicine Unit of the Paolo Giaccone University Hospital in Palermo. A total of 40ml of venous blood was taken by patients, after screening for infectious diseases, using a standard needle syringe and then transferred to 2 EOT II syringes (as indicated by protocol Orthogen Lab Services Gmbh, Düsseldorf, Germany). In the laboratory, EOT II, was incubated for 6 hours at 37 C° and then centrifuged at 5000 rpm for 10 minutes. The supernatant, represented by the autologous conditioned serum, was divided into 4 aliquots of 2ml each into a 5ml syringe under a sterile laminar flow hood. The aliquots of autologous conditioned serum were stored in the freezer at a controlled temperature of -20 C° until use. At the time of administration each aliquot was defrosted separately at room temperature and used.

Administration of the autologous conditioned serum

The treatment consisted of four injections to the target site via intra-articular injection or local infiltration. Injections of 2ml of autologous serum were carried out weekly, for 4 weeks.

All the injections were performed by the same anesthesiologist, an expert in infiltrative therapy, and using ultrasound.

The injections were carried out in an appropriate outpatient environment according to the standards of good clinical practice, using sterile instruments and materials.

Clinical evaluation and follow-up

The patients were evaluated before each autologous conditioned serum injection (timepoints 0-3) and then after one, three and six months from the last injection (timepoints 4-6).

The data acquired in the study are represented by:

- Reduction of pain assessed by psychometric scale VAS, universally recognized, before each injection (timepoints 0-3), to 1 month (timepoint 4), 3 months (timepoint 5) and 6 months (timepoint 6) after.
- Improvement of symptomatology in polydistrict grade 1 to 3 osteoarthrosis not responsive to therapy with platelet concentrate for non-transfusion use (CPuNT) through evaluation score Western Ontario and Mc Master Universities Osteoarthritis Index (WOMAC), Disability of the Arm, Shoulder and Hand (quick-DASH) and Oswestry Disability Index (ODI)
- Safety of treatment measured at each injection and at the end of treatment as number of adverse events such as inflammation, redness or swelling of the injection point, hypotension, nausea, vomiting, fever, joint infections, hemarthrosis, persistent pain and anaphylactic shock

At each visit, patients were asked to describe the intensity of their pain through Visual Analogical Scale (VAS), the degree of functional limitation through different questionnaires depending on the articulation involved, for the lower limb was used the WOMAC score, for the upper limb the Quick-DASH and for patients with facet joint syndrome was used the ODI score. Finally, self-sufficiency and quality of life were assessed by the administration of the SF-36 questionnaire and the Karnofsky index.

Statistical analysis

The data were analysed using appropriate descriptive statistics, using medians and interquartile ranges for continuous variables and proportions and percentages for dichotomous and categorical variables. To compare outcomes to different timepoints, the Friedman test was used, assuming significance with $p<0.05$. The results of the analysis are presented in the form of tables and graphs, as appropriate. The analyses were performed using R 4.0.5 GUI 1.74 Catalina build (7950).

RESULTS

The study included 26 patients treated between September 2020 and October 2021. Patient characteristics are described in **Table 2**.

Table 2. Characteristics of the patients included (n=26)

Age (years), median [IQR]	63.5 [58.25-73]
Weight (kg), median [IQR]	71.5 [65-80.25]
Height (cm), median [IQR]	165 [160-170]
Male sex	35%
Hypertension	42%
Hypercholesterolemia	31%
MRGE	15%
Diabetes	11%
Thyroiditis	11%
Other comorbidity (at least one)	58%
Time from onset of symptom (years), median [IQR]	10 [7.25-13.75]
Previous treatment with cortisone infiltration	35%
Previous treatment with platelet gel	23%
Previous treatment with cortisone and hyaluronic acid infiltration	19%
Previous treatment with infiltrations with hyaluronic acid	11%
Other previous treatment (at least one)	23%
Anti-inflammatory and/or antalgic drug therapy	54%
T0 Quick-Dash (%), median [IQR]	65.9 [65.9-70.5]
T0 ODI, median [IQR]	41.2 [35-60]
T0 Womac (%), median [IQR]	62.5 [58.3-66.6]

Improvement of painful symptoms, joint function, and quality of life.

The Friedman test for differences between repeated measurements showed a significant difference between the VAS values ($P < 0.001$; $X2=50.009$; $df= 6$, $N = 26$), of Karnofsky performance status ($P < 0.001$; $X2=26.368$; $df= 6$, $N = 26$), of SF-36 sub-scale for mental health ($P < 0.001$; $X2=13.953$; $df= 3$, $N = 26$) at different timepoints, while no significant difference was observed for SF-36 sub-scales for physical health ($P=0.29$; $X2= 3.733$; $df=3$, $N = 26$) as showed in **Table 3**.

Table 3. Trends in outcomes at different timepoints

	T0 (n=26)	T1 (n=26)	T2 (n=26)	T3 (n=26)	T4 (n=26)	T5 (n=26)	T6 (n=14)	P-value
VAS	8 [7-9]	6 [4.3-7]	5 [4-6]	3 [3-4]	4 [2-5.8]	5 [2-7]	5.5 [3-6]	<0.01
Karnofsky	90 [80-90]	90 [80-90]	90 [80-90]	90 [90-90]	90 [90-90]	90 [90-90]	90 [80-90]	<0.01
SF-36 ISF	27.5 [22.5-32.5]	NA	NA	NA	37.5 [27.5-41.8]	31.5 [27.3-43.5]	32 [28.3-37.3]	0.29
SF-36 ISM	35.5 [32-39]	NA	NA	NA	41.5 [35-45]	41 [35-47.8]	41-5 [39.3-47.8]	<0.01

Data are reported as median [IQR]. NA, Not assessed

Focusing exclusively on the VAS of patients with facet joint syndrome we saw, as shown from **Figure 1**, an

even more evident reduction of painful symptoms along the entire period elapsed since the first injection (median VAS value of 7.5), up to 6 months after the last injection, reaching the VAS median value of 2.

Figure 1. Trend of VAS in patients (n=13) with facet joint syndrome

The Friedman test showed a significant difference between the values of the WOMAC scales ($P < 0.001$; $X2=18.468$; df= 6, N = 9), ODI ($P < 0.001$; $X2=20.247$; df= 6, N = 13), and Quick-Dash ($P < 0.001$; $X2=27.707$; df= 6, N = 5), to the different timepoints as can be seen in Table 4.

Table 4. Trend of the outcomes specific for joint district to the various timepoints

	T0	T1	T2	T3	T4	T5	T6	P-value
WOMAC (n=9)	62.5 [58.3-66.6]	54.2 [39.5-61.4]	44.8 [36.4-52.1]	32.8 [28.6-41.1]	40.6 [28.9-53.6]	40.6 [37.5-46.9]	44.75 [40.6-54.4]	<0.01
ODI (n=13)	41.2 [34.9-60]	35.5 [29.8-55.5]	31.1 [24.4-44.4]	25.5 [16-33.5]	15.5 [8-28.9]	22.2 [13.3-38.3]	20 [13.3-22.2]	<0.01
Quick-Dash (n=5)	65.9 [65.9-70.4]	47.7 [47.7-56.8]	40.9 [34.1-45.5]	29.1 [21.8-40.1]	34.1 [25-40.9]	27.3 [25-27.3]	31.8 [30.7-34.1]	<0.01

Data are reported as median [IQR].

Toxicity and adverse events

No immediate or delayed adverse events, such as inflammation, redness or swelling of the injection point, hypotension, nausea, vomiting, fever, joint infections, hemarthrosis, persistent pain and anaphylactic shock, were observed during all infiltrations.

Furthermore, no toxicity was observed.

DISCUSSION AND CONCLUSIONS

The main result of our study was a significant reduction of painful symptoms and an improvement of joint function and quality of life in patients receiving treatment with autologous conditioned serum, not only immediately following the treatment itself, but also during the follow-up and up to 6 months after the last injection.

In particular, the median of the VAS scale at timepoint 0 was 8 [IQR 7-9] up to 5.5 [IQR 3-6] at timepoint 6. An even greater reduction of VAS was observed in patients with facet joint syndrome, whose VAS scores decreased from an initial median value of 7.5 at timepoint 0, up to the final value of 2 at timepoint 6. This result assumes relevance when considering the presence of only anecdotal literature on the treatment with autologous conditioned serum in patients with osteoarthritis involving the facet joints.

In a similar way, the mental health index (ISM) improved, which at timepoint 0 was 35 [IQR 32-39] to reach 41.5 [IQR 39.3-47.8] at timpepoint 6, unlike the physical health index (ISF) which did not reach any significant difference.

These results are hopeful for the use of injections with autologous conditioned serum in patients with osteoarthritis but especially in patients with facet joint syndrome, to obtain maximum effectiveness, in terms of reduction of painful symptoms, in a prolonged period with minimal side effects, both in the short and long term.

In conclusion, our study, although preliminary and still in progress, provided the basis for considering a new treatment for patients with osteoarthritis grade 1 to 3, with the purpose of reducing painful symptoms and improving the quality of life. However, our study is monocentric and involved a small sample of patients. Furthermore, the observational nature of the design limits the generalizability of the results. Multicentric studies, with appropriate design, will be required to study our research hypothesis and consider possible confounding factors in order to consider treatment with autologous conditioned serum for clinical practice.

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