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Autologous conditioned serum (ACS) for intra-articular treatment in Osteoarthritis: Retrospective report of 28 cases

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ABSTRACT

Introduction: Autologous conditioned serum (ACS) is a novel blood product developed for intra-articular injection as a novel therapy for Osteoarthritis (OA).

This study is a retrospective evaluation of 28 cases (25 Knee-OA and 3 hip-OA) treated with ACS between November 2013 and February 2016.

Materials and methods: ACS was prepared according to standards in an accredited Cell Manipulation Lab, and applied by an expert clinician (2 ml injection once weekly over 4 weeks). At any injection visit (Timepoints 1–4), and after a follow-up of 1 (Timepoint 5) and 6 months (Timepoint 6), patients were asked to describe the intensity of their pain with the VAS (visual analog scale) psychometric scale, and the objective parameter ROM (Range Of Motion) was recorded in case of injection in the knee.

Results: Pain (VAS) reduced in all cases since the first injection up to Timepoint 5.

A significant improvement was observed in VAS between Timepoint 1 and 6 (primary objective), with a median VAS decrease of 60 mm (range 20–100, $p < 0.01$).

A significant difference was also recorded in ROM between Timepoint 1 and 6 (secondary objective), with a median increase of 25° (range 5–40, $p < 0.01$).

Ten out of 14 patients (71%) who were undergoing a chronic therapy to relieve pain were able to interrupt it. No serious adverse events were recorded.

Conclusions: Treatment with ACS produced a rapid decline in pain, accompanied by a large improvement in ROM. These results suggest that ACS is a valid option for the treatment of OA.

1. Introduction

Over the last decades, major evolutions have taken place in the production of blood biomaterials and components for not-transfusion use, with novel spectra of clinical indications, especially in the field of reparative and regenerative medicine [1].

Autologous conditioned serum (ACS) is a blood product developed in the 1990s in an attempt to generate an injectable material as a novel therapeutic for Osteoarthritis (OA) [2–4].

Osteoarthritis is a slowly progressive, disablingand degenerative joint disease characterized by destruction of articular cartilage, remodeling of the subchondral bone, joint marginal osteophyte formation and synovitis [5].

Among the cytokines identified in the development of OA, IL-1 appears to be of special importance [6]. Many attempts have been done to exploit the therapeutic use of IL-1 inhibitors in such disease; this led to the development of new biological treatments such as IL-1 receptor antagonist (Ra), soluble forms of IL-1 receptors, and type 1 cytokines (IL-4, IL-10, IL-13) that inhibit the synthesis of IL-1 and increase the synthesis of IL-1Ra.

The history of ACS began when Meijer and colleagues firstly developed a method for stimulating IL-1Ra synthesis in human blood [4]. According to their method, peripheral blood was drawn into a syringe containing glass beads treated with chromium sulfate, to which blood monocytes and other adherent cells had the opportunity to attach. The syringe and its contents were then incubated at 37° for several hours, during which platelets degranulated and mononuclear cells synthesized and secreted IL-1Ra (100–1000 times more than after a standard exposure to glass) along with a variety of additional anti-inflammatory products [6,7], without significant increase of IL-1β and Tumor

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Necrosis Factor-α (TNF-α) [8,9].

ACS was firstly used clinically in 1997. Beginning from 2001, ACS was manufactured as Orthokine in a Good Manufacturing Process (GMP) facility.

In current times, physicians are directly provided with syringes, known as EOTII syringes (Orthogen Lab Services GmbH), containing glass beads treaded on their surface, for ACS preparation in the local GMP[10].

Baltzer et al. [11] published the first clinical uses of ACS for the treatment of OA of the knee, firstly in a nonrandomized study on 1000 patients, and subsequently [12] in a randomized study in which ACS was compared to standard of care (hyaluronic acid) and placebo on 376 patients. Results were in both cases in favor of ACS, being responses superior and longer-lasting.

The same results were confirmed in a randomized study by Yang et al. [13] on 176 patients with OA of the knee, and by Baselga and Hernandez in a non-blinded 2-year prospective study [10].

In more recent times, the use of ACS was successfully extended to OA of the hip [14], and other orthopedic disorders in witch inflammation plays a major pathogenic role, such as lumbar radicular compression [15,16] and stress lesions of muscles/tendons [17].

Following this encouraging results, a collaboration was stated with the Immunohematology and Transfusion Medicine Service (SIMT) in San Raffaele Hospital (OSR) for the production of ACS-Ortokine.

This work is a preliminary retrospective report of the first 28 patients with OA of the knee and the hip, treated from November 2013 to February 2016.

According to a Legal Decree of the Italian Estate, from November 2015 blood products for non-transfusion use can be administered only in the context of clinical trials; since then, therefore, patients have been enrolled in a prospective trial.

2. Materials and methods

All patients were treated between November 2013 and February 2016.

X-ray based grading for OA was performed before treatment, according to Kellgren-Lawrence Classification System [18].

All patients were proposed to receive intra-articular injection of ACS in case of symptomatic AO of the knee or hip with clinical indication for treatment: (a) in case they preferred conservative treatment to surgery or (b) were not candidate to surgery due to medical problems. They were adequately informed about possible alternative therapies and agreed for treatment with ACS.

Written informed consent was obtained for blood uptake and ACS preparation, and for intra-articular injection.

2.1. ACS preparation

ACS was prepared at the Immunohematology and Transfusion Medicine Unit of OSR, according to the product instruction manual (Orthogen Lab Services GmbH).

A total amount of 40 ml full-blood was taken from a venous puncture with a standard winged pick-up needle and drawn into 2 EOT II syringes (Orthogen Lab Services GmbH), adequately labeled with name and Unique Patient Number (UPN) barcode.

In the Cell Manipulation Laboratory (CML), the EOT II were incubated for 6 h at 37° in a controlled incubator (Forma Scientific 3165 S/N), and subsequently centrifuged at 5000 rpm for 10 min. The resulting surnatant (ACS) was therefore divided in 4 aliquots of 2 ml, each in a 5 ml-syringe under a sterile laminar-flow cabinet and conserved at the controlled temperature of −20° until use.

2.2. ACS administration

The adopted schedule was 4 consecutive weekly intra-articular injections of 2 ml of ACS [13].

An expert orthopedic performed the injection with sterile instruments and materials, in an adequate outpatient environment according to the standards of good clinical practice. A barrier filter 022 μM (Millex GP, Merck Millipore) was applied to the injection syringe.

In case of hip OA the injection was performed under echo guide.

2.3. Clinical evaluationsand follow-up

According to standard practice, the same expert orthopedic evaluated patients before any ACS infusion (Timepoints 1–4), one month (Timepoint 5) and 6 months (Timepoint 6) after the last infusion.

At any visit, all patients were asked to describe the intensity of their pain using the universally recognized VAS (visual analog scale) psychometric scale [19,20] as a measurement of their subjective symptoms.

The objective parameter ROM (Range Of Motion) -expressed in degrees- was recorded in case of injection in the knee.

Any adverse event (persistent pain in the site of injection, bleeding or intra-articular hematoma, local infection etc.) was reported.

2.4. Data collection

This study was approved by the local Ethical Committee (CE).

Clinical data were retrospectively collected from the patients' files and reported on a Case Report Form (CRF) before analysis.

The CRF reported VAS and ROM for all the Timepoints.

In some cases, patients had been asked to indicate the intensity of their pain on a VAS template, and the clinician had reported only the numeric values. As these data were no longer reproducible, and some of the values could have been approximated to the nearest multiple of 10 mm, it was decided approximate all VAS values in the same way for the retrospective data collection.

The chronic use non-steroidal anti-inflammatory drugs (NSAIDs), steroids and other painkillers was recorded in the patient's file, and reported in the CRF.

For some patients the on-demand use of drugs had not been prospectively recorded, therefore this information was omitted on the CRF.

2.5. Inclusion and exclusion criteria

All patients who agreed for the treatment with ACS before November 2015 could be included, given that the therapy had been completed (4 total injections) and the VAS before treatment was 50 mm or more.

Of note, all patients should have been aged 18 or more and should not have been pregnant or childbearing women for receiving ACS treatment. Moreover, were initially excluded from treatment with ACS patients with serious neurologic/psychiatric diseases, peripheral vascular diseases, positive serology for Hepatitis B or C or HIV, or documented infection of the joint.

2.6. Primary and secondary endpoints

Primary endpoint was VAS reduction from Timepoint 1 to Timepoint 6

Secondary endpoints were:

- VAS reduction at one months after the end of treatment (Timepoint 5).
- Increase of ROM from Timepoint 1 to Timepoint 6
- Treatment safety, measured as number of adverse events connected to ACS therapy in the period of treatment.