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Shoulder injections with autologous conditioned serum reduce pain and disability in glenohumeral osteoarthritis: longitudinal observational study

Maciej J. K. Simon ,*† Vivian E. Aartsen,†‡ Jennifer A. Coghlan,†§ André Strahl* and Simon N. Bell†§

*Department of Orthopaedics, The University Medical Center Hamburg-Eppendorf, Hamburg, Germany
†Melbourne Shoulder and Elbow Centre, Melbourne, Victoria, Australia
‡School of Medicine, The University of Groningen, Groningen, The Netherlands and
§Department of Surgery, School of Clinical Sciences, Monash Health, Monash University, Melbourne, Victoria, Australia

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Correspondence
Dr Maciej J. K. Simon, Department of Orthopaedics, The University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany.
Email: ma.simon@uke.de

M. J. K. Simon MD; **V. E. Aartsen** MD; **J. A. Coghlan** PhD; **André Strahl** MSc; **S. N. Bell** FRACS (Orth), FAOrthA, PhD.

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Abstract

Background: Currently, non-surgical treatments for glenohumeral osteoarthritis (GH-OA) mainly aim to reduce pain. Autologous conditioned serum (ACS), Orthokine, an interleukin-1 inhibitor from the patient's own blood has an anti-inflammatory effect. The objective was to determine whether intra-articular injections of this ACS improved symptoms in patients with GH-OA and delayed the need for a shoulder replacement.
Methods: A total of 36 consecutive patients, 40 shoulders, with OA received up to 6-weekly intra-articular injections of ACS were included. Imaging of GH-OA, range of motion, visual analogue scale (VAS) pain, Shoulder Pain And Disability Index (SPADI), American Shoulder and Elbow Surgeons and Constant scores were assessed pre-injection and post treatment at 3 months. At a minimum of 2 years, VAS and SPADI scores and whether anyone had progressed to a shoulder replacement were recorded.
Results: Outcomes 3 months post-ACS injections demonstrated on average statistically significant improvement ($P < 0.05$) of all measurements: SPADI (54.3 ± 21.5 vs 43.7 ± 23.7), Constant score (50.5 ± 14.1 vs 57.1 ± 17.4), VAS pain (4.8 ± 2.2 vs 3.7 ± 2.4) and range of motion. Of these, 16 shoulders progressed to a shoulder replacement, nine cases quickly (0.6 ± 0.2 years) and seven cases were delayed by 3.1 ± 1.7 years. The other 18 cases had significant improvement in pain, SPADI (58.0 ± 19.6 to 31.8 ± 21.4; $P < 0.01$) scores and no progression to a shoulder replacement at 3.6 ± 1.0 years follow-up. There was no correlation of glenoid Walch score or joint space with clinical outcome parameters.
Conclusion: ACS injections in the shoulder joint for OA can reduce pain and disability, and postpone the need for a shoulder replacement.

Introduction

Glenohumeral osteoarthritis (GH-OA) can cause pain and disability, although there is often poor correlation between shoulder symptoms and the severity of the OA.[1] Current non-surgical treatment strategies aim to reduce pain and improve the range of motion (ROM) of the shoulder joint.[2] Paracetamol, non-steroidal anti-inflammatory drugs and physiotherapy in the earlier stages of GH-OA can improve movement and reduce pain.[3] Further treatment options are an intra-articular injection with either steroids to reduce inflammation or hyaluronic acid (HA), which induces several concurrent mechanisms such as chondroprotection, increasing proteoglycan and glycosaminoglycan synthesis, and anti-inflammatory properties, and decreasing friction in the joint capsule.[4,5] Steroid injections produce only short-term improvement,[6] and HA injections have not demonstrated a significant clinical improvement of pain when compared with a placebo.[4,7] If conservative treatment fails, with increasing pain and disability from the OA, shoulder replacement is well known to give patients good pain relief.[8,9]

An alternative intra-articular injection is with autologous conditioned serum (ACS), marketed under the name of Orthokine (Orthogen AG, Düsseldorf, Germany). ACS is generated from patient's own blood and contains proinflammatory cytokines

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(interleukin-1 receptor antagonist) known to both protect cartilage from degradation and inhibit signs and symptoms of OA due to reduction of capsule and synovial inflammation.[10–13] The ACS effect has been clinically demonstrated to improve pain and function in patients with OA of the knee.[10]

ACS had not previously been studied in the shoulder joint. This study was developed to investigate the efficacy of Orthokine in the treatment of the painful osteoarthritic shoulder, both as a non-surgical option and also to possibly delay the need for shoulder replacement.

Methods

This longitudinal observational study set up in conjunction with the School of Medicine, University of Groningen, The Netherlands, was conducted to evaluate the efficacy of intra-articular GH injections of ACS in reducing the symptoms of GH-OA. Institutional research ethics approval was granted (Monash University Human Research Ethics Committee (CF10-0376, CF16/1027-2016000545)).

Patients suitable for ACS injections were offered the procedure, with discussion of the possible outcome and risks and written guidelines were given. This was a patient-driven study for those eligible patients who elected to have the ACS injections. Inclusion criteria were age greater than 30 years, radiographic evidence of GH-OA (Kellgren–Lawrence grade 2–3)[14] and clinical symptoms (e.g. pain, stiffness and disability) related to GH-OA. Exclusion criteria were a direct indication for a total shoulder replacement (TSR) (Kellgren–Lawrence grade 4), inflammatory or crystalline arthropathy, inability to receive the 6-weekly injections or unable to afford the costs of the treatment. If the patient chose to participate in the study, written informed consent was obtained.

Intervention

Blood sampling, preparation and injection were performed at two Melbourne radiology centres. All patients had 50 mL of whole blood taken using a special Orthokine syringe, containing $CrSO_4$-coated glass beads for induction of dose-dependent production Interleukin-1 receptor antagonist (IL-1Ra). During induction, syringes were rotated gently and afterwards incubated at 37°C for 24 h. After incubation, the syringes were centrifuged and the serum was filtered and divided into a minimum of six portions of 2 mL, now known as ACS, before freezing the separate tubes and portions at −20°C until use. The intra-articular injections were carried out under aseptic conditions and ultrasound guidance by a radiologist. Following subcutaneous local anaesthetic, 2 mL of ACS (one defrosted portion) was injected into the affected joint. A separate informed consent for the injections was obtained by the radiologist prior to commencing the treatment of 6-weekly injections.

Assessments

Patients completed questionnaires before the first injection and after the treatment series with ACS. These patient reported outcome measures (PROMs) included pain on visual analogue scale (VAS, 0 = no pain and 10 = the worst possible pain), Shoulder Pain And Disability Index (SPADI), American Shoulder and Elbow Surgeons (ASES) score and the Constant score (CS).[15–17] ROM (in degrees using a goniometer) was assessed both pre- and post-completion of the treatment with ACS. Specifically, active elevation in the scapular plane, passive external rotation (ER) and passive scapular-stabilized GH abduction were assessed.

All patients had imaging of the shoulder taken prior to study inclusion. GH-OA was assessed using the Kellgren–Lawrence score. The axillary view or the computed tomography scan was used to determine the glenoid wear status according to Walch[18] and the joint space width, defined as either no joint space narrowing or joint space narrowing.

Follow-up

Following signing an informed consent, pre-injection assessments were completed, and post-injection assessments were carried out with a clinical first follow-up appointment between 3 and 6 months.

A second follow-up was carried out by phone at a minimum of 2 years after the ACS series, with SPADI and VAS scores to identify whether therapeutic benefits were still present, or whether patients had progressed to a TSR. The data points were from the date of the last injection until (i) an objective time point which was the date of decision to undergo a TSR or (ii) the date of this second assessment. As a result, two groups were defined, those who had progressed to a shoulder replacement and those who had not. A SPADI and VAS pain score was performed in those who had not progressed to a TSR.

Statistical analyses

Data management and analyses were conducted using Statistical Package for the Social Sciences, SPSS, version 25 (SPSS Inc., Chicago, IL, USA). The values of descriptive statistics are expressed as mean ± standard deviation. In addition to standard descriptive statistics of variables, parametric (independent *t*-test and dependent *t*-test) and non-parametric (Fisher's exact test, chi-squared test and Wilcoxon test) methods were used to assess associations between variables. The Kolmogorov-Smirnov (K–S) test was performed to examine the normal distribution of variables. The evaluation of change in outcome was performed using last observation carried forward (LOCF) to deal with missing data and to minimize the number of the patients unavailable for final analysis. The LOCF method is a conservative estimator for missing values. As this study assumes an improvement in pain and functional ability, the use of LOCF does not overestimate the effects of the intra-articular injections of ACS. Statistical significance was set to a two-tailed *P*-value of 0.05 and Bonferroni's correction for multiples analyses was applied.

Results

There were 36 patients with 40 shoulder joints with symptomatic and radiographic GH-OA (Fig. 1), with a mean age of 61.5 ± 10.8 years (range 40–79) (Table 1) and 26 males and

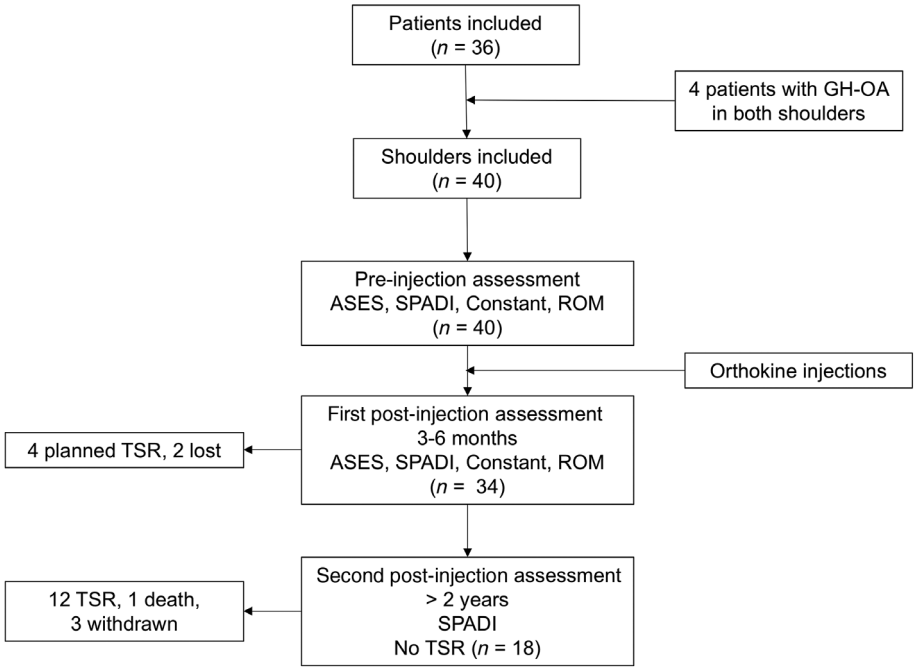

Fig 1. Flow chart demonstrating the total amount of shoulders including the three assessment points and tests (ASES, American Shoulder and Elbow Surgeons; GH-OA, glenohumeral osteoarthritis; ROM, range of motion; SPADI, Shoulder Pain and Disability Index; TSR, total shoulder replacement).

14 females with the majority being right handed (37/40), but with an equal distribution of right and left shoulders injected. The majority of cases demonstrated a Walch score radiological assessment of A1 (n = 27) or a B2 (n = 9) glenoid formation. There was no joint space narrowing in 23 of 40 shoulder joints.

The first post-treatment outcome assessment was at an average of 3.7 ± 3.0 months. At that data point, two patients were lost to follow-up and four chose not to participate deciding to progress to a TSR (Fig. 1). Three patients chose not to complete the entire set of six injections (range 1–4 injections).

Six patients (n = 6/40) found the treatment successful and chose to have a second series of ACS 1.5 ± 0.7 years after the first series, to further delay the progression to TSR. Four of these patients had not progressed to TSR at the second follow-up assessment (3.3 ± 1.7 years). The remaining two did progress to TSR 1.0 ± 0.3 years after the second series of ACS.

The second follow-up at a minimum of 24 months following completion of the ACS treatment (56 ± 15 months) included a SPADI and VAS on those who had not progressed to a TSR (n = 18). At this data point, none of these 18 patients, except the six who had the second series of ACS, had chosen or required any other intervention.

Table 1 Biometrical data of the cases including the radiographic assessment (Walch score and joint space narrowing)

	Total	TSR	No TSR
Shoulders (n)	40	16	18
Age (years)	61.5 ± 10.8 (40–79)	62.3 ± 9.7 (43–79)	62.8 ± 11.4 (40–78)
Sex (n)			
Male	26	9	14
Female	14	7	4
Dominant arm (n)			
Right	37	14	18
Left	3	2	0
Injected arm (n)			
Right	20	8	9
Left	20	8	9
BMI (%)	28.6 ± 4.7 (24–38)	28.1 ± 4.7 (25–31)	29.4 ± 5.1 (24–38)
Walch score (n)			
A1	27	11	12
A2	1	0	1
B1	3	3	0
B2	9	2	5
Joint space narrowing (n)			
No	23	7	11
Yes	17	9	7

BMI, body mass index; TSR, total shoulder replacement.

Measurements

The imputation method LOCF was applied in eight cases for SPADI and ASES, in nine cases for CS and in six cases for ROM. The analyses demonstrated a statistically significant improvement in the SPADI (54.3 ± 21.5 versus 43.7 ± 23.7; $P < 0.01$), CS (50.5 ± 14.1 versus 57.1 ± 17.4; $P < 0.05$) and ASES (51.8 ± 14.1 versus 58.9 ± 17.6; $P < 0.05$) assessments for all patients (n = 34) at the first follow-up after the ACS series (Table 2). Pain levels decreased significantly from 4.8 ± 2.2 to 3.7 ± 2.4 on the VAS ($P < 0.05$). The overall scores for ROM improved significantly for passive ER ($P < 0.001$), passive GH abduction ($P < 0.01$) and active elevation ($P < 0.01$). To validate the results, all analyses were additionally performed without the LOCF method. Both LOCF (Table 2) and non-LOCF analysis (Table S1) showed significant results. A total of 10 patients had deteriorated in some PROMs (SPADI (three), CS (four), ASES (five) and pain (six)) at this first follow-up.

Table 2 Clinical scores, pain and range of motion for the overall group and break down into cases needing and not needing a shoulder replacement using last observation carried forward imputation method

	Total		TSR			No TSR		
	Pre-Orthokine ($n = 40$)	Post-Orthokine ($n = 34$)	Pre-Orthokine ($n = 16$)	Post-Orthokine ($n = 16$)	Follow-up ($n = 18$)	Pre-Orthokine ($n = 18$)	Post-Orthokine ($n = 18$)	Follow-up ($n = 18$)
Time (months)	0	3.7 ± 3.0 (1–10)	0	3.7 ± 3.6 (1–10)	52.7 ± 17.0 (35–84)	0	3.5 ± 2.6 (1–9)	52.7 ± 17.0 (35–84)
SPADI pain (%)	62.2 ± 18.7 (26–88)	51.0 ± 23.7 (12–92)**	62.2 ± 22.7 (26–88)	48.6 ± 24.1 (22–88)	36.5 ± 19.3 (6–66)**	63.8 ± 16.3 (38–88)	54.2 ± 25.5 (12–92)	36.5 ± 19.3 (6–66)**
SPADI disability (%)	49.3 ± 24.1 (10–86)	40.3 ± 23.7 (5–86)*	46.3 ± 27.5 (10–86)	38.5 ± 23.5 (10–86)	33.3 ± 23.9 (6–71)*	54.3 ± 22.5 (14–83)	42.5 ± 26.3 (5–79)*	33.3 ± 23.9 (6–71)*
SPADI total (%)	54.3 ± 21.5 (16–87)	43.7 ± 23.7 (8–87)**	52.4 ± 25.3 (16–87)	40.6 ± 24.2 (16–87)	31.8 ± 21.4 (2–69)**	58.0 ± 19.6 (23–80)	47.0 ± 25.6 (8–84)	31.8 ± 21.4 (2–69)**
ASES total (%)	51.8 ± 14.5 (30–80)	58.9 ± 17.6 (22–90)	54.2 ± 16.7 (30–80)	59.0 ± 16.4 (35–80)		49.2 ± 13.8 (32–68)	58.5 ± 20.1 (22–90)	
Constant score	50.5 ± 14.1 (15–77)	57.1 ± 17.4 (15–92)*	49.0 ± 12.2 (23–64)	54.8 ± 12.1 (42–64)		49.4 ± 15.1 (15–71)	56.5 ± 19.9 (15–88)	
VAS (0–10)	4.8 ± 2.2 (2–10)	3.7 ± 2.4 (0–10)*	4.7 ± 2.6 (2–10)	4.3 ± 2.9 (0;10)	3.5 ± 1.6 (1–6)	5.2 ± 1.9 (2–9)	3.2 ± 2.3 (0–8)*	
Passive external rotation (°)	31.0 ± 19.0 (0–80)	44.0 ± 20.7 (10–80)**	34.6 ± 20.8 (10–80)	42.5 ± 22.5 (15–80)*		28.8 ± 18.4 (0–70)	45.3 ± 19.5 (10–80)**	
Passive glenohumeral abduction (°)	68.3 ± 16.3 (40–110)	75.4 ± 20.2 (20–100)**	68.6 ± 19.9 (40–110)	68.6 ± 25.3 (20–100)		67.8 ± 14.1 (45–90)	81.3 ± 13.5 (45–100)**	
Active elevation (°)	100.9 ± 26.2 (60–150)	117.0 ± 28.6 (60–170)**	97.3 ± 23.9 (60–140)	109.2 ± 28.4 (60–160)		101.7 ± 27.5 (60–150)	125.0 ± 27.3 (60–170)*	

Significance: * $P < 0.05$; ** $P < 0.01$.

ASES, American Shoulder and Elbow Surgeons; SPADI, Shoulder Pain And Disability Index; TSR, total shoulder replacement; VAS, visual analogue scale.

At the second follow-up, 16 of 40 shoulder joints had progressed to a TSR. Seven of the 16 (TSR) cases reported that the injection helped for a time and delayed the TSR by 2.5 ± 1.6 years (Table 3). Nine of the 16 (TSR) cases said subjectively the injections did not help. Eight of these nine cases progressed quickly (0.6 ± 0.2 years) to a TSR, and one had a TSR 5.5 years later. Eighteen of 40 patients had not required a TSR at this time and they believed this was due to the effect of the ACS. Six cases did not participate (Fig. 1). The data were analysed separately for the two groups of TSR and no-TSR. There were no significant differences in demographic data but a tendency towards males reporting more benefit from the ACS injections than females in the longer term was present (Table 1). No correlation of a specific predisposing factor with clinical improvement was found (e.g. age, arm dominance, gender or radiographic changes).

In the group who progressed to TSR, whilst at first follow-up the ER improved significantly ($P < 0.05$), the other collected data pre- and post-ACS injection showed minimal improvement only (Table 2). In the no-TSR group, SPADI disability and pain, and ROM demonstrated significant improvements at the first follow-up ($P < 0.05$) (Table 2). This significant trend persisted in the second follow-up (52.7 ± 17.0 months) for both pain ($P < 0.05$) and disability ($P < 0.01$) sections of the SPADI scores including the total score ($P < 0.01$).

Thirteen patients (38%) subjectively reported that they did not respond to the ACS injection (Table 3). In a subgroup analysis, these 13 (non-responders) were compared with those 21 who reported a subjective good response. There were statistically significant improvements in all examined outcome parameters in the responder group ($P < 0.01$), but not in the non-responder group (Table 2).

Discussion

The primary aim of this study was to determine whether intra-articular injections in the shoulder joint with ACS reduced pain and disability in patients with GH-OA in both the short and medium term, and thereby delayed or reduced the need for a later TSR. To the authors' knowledge, the current study is the first study investigating the efficacy of ACS injections in the GH joint for GH-OA. Decrease in pain levels with ACS would be related to decreased capsule and synovial inflammation resulting in reduced pain scores, and improvement in active and passive ROM.[13,19,20]

We have demonstrated promising clinical improvement in 62% of patients ($n = 21$) with an average improvement duration of 3.2 ± 1.3 years. There were 13 patients (38%) considered to have little clinical improvement, but only nine of these cases (27%) required a TSR with an average time of 1.2 ± 1.8 years after injections. An additional seven patients (21%) of the group with initial good improvements ($n = 21$; 62%) after ACS injections went on to have a TSR. Overall, the 21 patients with good clinical results reported significantly less need for TSR compared with patients with little improvement ($P = 0.042$) with the TSR on average 2.5 ± 1.6 years after the injection series. Ultimately, 16 patients (47%) had a TSR at an average of 1.8 years after the completion of injection series. It is encouraging that 18 (53%) patients had

Table 3 Postponed times to radiographic assessments, the need of a shoulder replacement and patients' satisfaction

	Total		TSR		No TSR	
	n	Postponement, years (minimum–maximum)	*n*	Postponement, years (minimum–maximum)	*n*	Postponement, years (minimum–maximum)
Total	34	2.8 ± 1.7 (0.3–5.5)	16	1.8 ± 1.7 (0.3–5.5)	18	3.6 ± 1.0 (2.3–5.5)**
Missing	6		n/a		n/a	
Walch score						
A1	23	3.2 ± 1.6 (0.5–5.5)	11	2.4 ± 1.9 (0.5–5.5)	12	3.8 ± 1.0 (2.5–5.5)*
A2	1	3.5	0		1	3.5
B1	3	0.7 ± 0.1 (0.5–0.8)	3	0.7 ± 0.5 (0.5–0.8)	0	
B2	7	2.4 ± 1.5 (0.3–4.5)	2	0.5 ± 0.3 (0.3–0.8)	5	3.1 ± 1.1 (2.3–4.5)**
Joint space narrowing						
No	18	3.5 ± 1.5 (0.8–5.5)	7	2.9 ± 2.2 (0.8–5.5)	11	3.8 ± 1.0 (2.5–5.5)
Yes	16	2.0 ± 1.5 (0.3–4.5)	9	1.0 ± 0.8 (0.3–2.5)	7	3.4 ± 1.0 (2.3–4.5)
Did the injection help?						
Yes	21	3.2 ± 1.3 (0.8–5)	7	2.5 ± 1.6 (0.8–4.7)	14	3.5 ± 1.0 (2.3–5)
No	13	2.2 ± 2.1 (0.3–5.5)	9	1.2 ± 1.8 (0.3–5.5)	4	4.1 ± 1.1 (3–5.5)*

Significance: *$P < 0.05$; **$P < 0.01$.

TSR, total shoulder replacement.

benefited significantly from the injections and did not require a TSR even after an average time of 3.6 ± 1.0 years. It was also demonstrated in four patients that a second ACS injection was effective again in further delaying the need for a TSR.

The main reasons for treating GH-OA are pain and disability.[2] VAS pain scores portray the current level of pain, whereas clinical scores, such as the pain section of the SPADI, focus on a broader spectrum of pain and identify disability.[21] There was an overall statistical improvement in all scores, ROM, pain, CS, SPADI and ASES, at the initial follow-up. Very few patients deteriorated. The significant improvement in the SPADI score for the entire group persisted with significant improvement more than 2 years after the injections.

Studies of an alternative injection treatment of the shoulder for GH-OA with HA demonstrate similar pain reduction on the VAS and improved function; however, the follow-up in these studies was only up to 6 months.[22,23] Intra-articular corticosteroid injections can also be used to reduce inflammation of the synovium and surrounding tissues.[24] However, a comparison study of injections of HA and 6-methylprednisolone acetate in the GH joint showed that pain reduction and functional outcome score improvement with corticosteroid injections lasted only for 1 month.[6]

Despite the clinical improvements in many patients from ACS injections, no predisposing factor was found, such as the glenoid morphology or the radiographic severity of the arthritis, in particular if it had progressed to bone on bone, which suggested an increased likelihood of improvement with the ACS injections. These results also support the suggestion that the degree of pain in patients with GH-OA is not correlated with the severity of radiological findings, but that it is more likely related to the degree of inflammation within the joint[25] and that ACS injections can produce some short-term clinical benefit in almost all patients and can postpone a TSR in 75%.

Similar positive outcomes in clinical signs and symptoms were demonstrated by Baltzer *et al*. for ACS injections for OA of the knee.[10] They identified that patients benefitted significantly from ACS injections when compared with HA or saline injections. In the shoulder, Damjanov *et al*. showed in a 24-week trial that patients with supraspinatus tendinopathy benefited from ACS injections under sonographic guidance in the supraspinatus paratendon.[26] These patients improved significantly in VAS and CS. Another shoulder study reported the effect of autologous conditioned plasma in the subacromial space versus cortisone treatment in cases of partial rotator cuff tears.[27] These results showed good clinical improvement in the first weeks after injections for patients with autologous conditioned plasma; however, the results did not differ significantly from the cortisone group, with an observation time of 6 months.

Statistical analyses used the LOCF imputation method to examine longitudinal data. This conservative calculation method assumes that in the case of missing data no changes of the outcome measures occur over time. Hence, the true effects of interventions are usually underestimated. Therefore, all data were additionally analysed without LOCF, which led to similar results (Table S1).

This study has some limitations, in particular there is no comparison/control group. As there have been previous studies[10,27] assessing the benefit of ACS in the knee and shoulder subacromial space, the aim of this study was to focus on the GH joint, which has not previously been studied. There was no clinical evaluation of the patients at the more than 2-year follow-up, but a telephone SPADI and pain (VAS) assessment determined the degree of improvement, and whether the patient had required a TSR. All patients were offered a clinical assessment if desired, but no patient was so inclined. Six cases were not available for follow-up and their results remain unknown.

Conclusion

This longitudinal study demonstrates that in patients with GH-OA, ACS injections into the shoulder joint can improve clinical function and decrease pain in many cases and delay the need for TSA. Insufficient symptoms were present in 53% to require a TSR with an

average follow-up of 3.6 years. These results demonstrate that ACS injections may have a role in the conservative management of GH-OA, particularly in patients who wish to delay surgery or are at increased risk with a surgical procedure.

Conflicts of interest

None declared.

Author Contributions

Maciej Simon: Data curation; formal analysis; investigation; writing-original draft; writing-review and editing. **Vivian Aartsen:** Data curation; formal analysis; methodology; writing-review and editing. **André Strahl:** Formal analysis; methodology; writing-review and editing. **Jennifer Coghlan:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; supervision; writing-original draft; writing-review and editing. **Simon Bell:** Data curation; formal analysis; investigation; methodology; project administration; supervision; validation; visualization; writing-original draft; writing-review and editing.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Demonstration of the clinical scores, pain and range of motion for the overall group and break down into cases needing and not needing a shoulder replacement without last observation carried forward imputation method.