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Editorial Board Member of *World Journal of Orthopedics*, Byron Chalidis, MD, PhD, Assistant Professor, The First Orthopaedic Department, Aristotle University of Thessaloniki, Thessaloniki 57010, Greece. byronchalidis@gmail.com

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WJO mainly publishes articles reporting research results and findings obtained in the field of orthopedics and covering a wide range of topics including arthroscopy, bone trauma, bone tumors, hand and foot surgery, joint surgery, orthopedic trauma, osteoarthropathy, osteoporosis, pediatric orthopedics, spinal diseases, spine surgery, and sports medicine.

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SYSTEMATIC REVIEWS

Conservative management of spinal pathology with autologous conditioned serum: A systematic review of the literature

Christian J Rajkovic, Matthew L Merckling, Alyssa W Lee, Galadu Subah, Aryan Malhotra, Zachary D Thomas, Sabrina L Zeller, John V Wainwright, Merritt D Kinon

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Christian J Rajkovic, Matthew L Merckling, Alyssa W Lee, Galadu Subah, Aryan Malhotra, Zachary D Thomas, Sabrina L Zeller, John V Wainwright, Merritt D Kinon, Department of Neurosurgery, Westchester Medical Center, Valhalla, NY 10595, United States

Co-corresponding authors: Christian J Rajkovic and Merritt D Kinon.

Corresponding author: Christian J Rajkovic, BSc, Researcher, Department of Neurosurgery, Westchester Medical Center, 40 Sunshine Cottage Road, Valhalla, NY 10595, United States. crajtkotp@gmail.com

Abstract

BACKGROUND

Chronic inflammatory pain is associated with increased expression of interleukin (IL)-1, an inflammatory cytokine, and activity on its receptor (IL-1R). In response, the body produces IL-1R antagonist (IL-1Ra) to reduce this signaling. Autologous conditioned serum (ACS) is the only biologic therapy for spinal pathologies that enhances the action of endogenous IL-1Ra reserves to improve symptoms. This systematic review investigates the effectiveness of ACS in treating pain and disability caused by spinal pathologies.

AIM

To evaluate the use of ACS as a conservative management option for spinal pathology.

METHODS

A systematic review of PubMed/Medline was performed to identify studies investigating administration of ACS for treatment of any spinal pathology.

RESULTS

Six articles were included, comprising 684 patients treated with epidural (n = 133) or transforaminal (n = 551) ACS injections. Patients had an average age of 54.0 years with slight female predominance (53.2%). The lumbar spine was most commonly treated, with 567 patients (82.9%) receiving injections for lumbar radiculopathy (n = 67), degenerative disc disease (DDD) (n = 372), or spinal stenosis (n = 128); cervical injections were performed in 109 patients (15.9%). Mean (SD) follow-up was 21.7 (4.8) weeks from first ACS injection. All studies investigating mechanical lumbar and lumbar or cervical radicular pain reported significant pain reduction at final follow-up compared to baseline. ACS achieved comparable or su-

perior results to lumbar epidural steroid injections. Adverse events were reported in 21 patients (3.1%), with no serious adverse events.

CONCLUSION
ACS injection is a safe and effective intervention for pain reduction in many spinal pathologies, including cervical and lumbar radiculopathies.

Key Words: Spine; Autologous conditioned serum; Orthokine; Regenokine; Epidural steroid injection; Interleukin-1; Interleukin-1 receptor antagonist

Core Tip: Injections of autologous conditioned serum (ACS) are an emerging conservative management strategy for reducing inflammation and pain in various osteoarthritic conditions. This therapy extracts and amplifies the novel anti-inflammatory molecule, interleukin-1 receptor antagonist, in a patient's serum for autologous treatment of inflammation. This study systematically reviews the literature for articles investigating the effectiveness of ACS in improving pain, disability, and quality of life in patients with spinal pathology.

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INTRODUCTION

Interleukin (IL)-1 is a known potentiator of osteoarthritis through biochemical enhancement of acute and chronic inflammation, thus precipitating tissue necrosis and the development of pain. Through stimulation of the IL-1 receptor (IL-1R), IL-1 induces pathological catabolic activity *via* the upregulation of cytokines, such as IL-6 and tumor necrosis factor α (TNF-α), and proteolytic enzymes, such as matrix metalloproteinases and ADAMTS-4[1]. IL-1 has also been reported to upregulate nociceptive pathways that induce hyperalgesia and neuropathic pain[2]. In pathologies of the spine, such as chronic radiculopathy, disc degeneration, and spinal stenosis, chronic inflammatory pain is associated with enhanced expression of IL-1 and activity of IL-1 on IL-1R[3-5]. To maintain balance between inflammatory stimuli and the subsequent host response, the body produces IL-1R antagonist (IL-1Ra), the only cytokine inhibitor naturally produced by the body, to reduce signaling at IL-1R[6,7]. Upregulation of IL-1Ra has been shown to inhibit necrosis of cartilage, muscle, and nervous tissue of the spine. At concentrations between ten and one thousand times in excess of normal serum, IL-1Ra can completely block IL-1R and IL-1 signaling[8,9].

Current recombinant biologics, such as Anakinra™, rilonacept, and canakinumab, manipulate the IL-1 signaling cascade for treatment of various autoimmune, inflammatory, and malignant spine and non-spine diseases[7,10]. However, autologous conditioned serum (ACS) is the only biologic therapy for spine pathology that enhances the action of patients' endogenous IL-1Ra reserves to reduce inflammation and improve symptoms[7,10]. Referred to as Orthokine™ and Regenokine™ in the United Kingdom and the United States, respectively, ACS was originally described by Dr. Peter Wehling, a German spine surgeon, in 1997 as a method of manipulating extracted patient serum to amplify production of IL-1Ra[10]. In this process, the patient's venous blood is incubated at 37 °C for several hours in the presence of borosilicate glass beads, which induce de novo production of IL-1Ra from serum monocytes and platelets to a concentration approximately ten times the serum concentration. This increased saturation of IL-1Ra functions to antagonize the inflammatory process of IL-1, thus preventing tissue destruction seen in chronic inflammation and improving the patient's pain response in a clinically meaningful manner[11]. IL-1 has been shown in the literature to sensitize affected nerve roots to hyperalgesia in cases of spinal radiculopathy[12]. In addition to IL-1Ra, other cytokines, including IL-10, IL-6, and TNF-α, and growth factors, such as fibroblast growth factor 2 (FGF-2), vascular endothelial growth factor, and hepatocyte growth factor (HGF), are also present in increased concentration following conditioning[8,10]. ACS is then either stored for later use or immediately injected into the affected area. In spinal injections, the typical dosing regimen is three injections per week over three weeks, and this regimen can be repeated as often as necessary if the therapy remains effective at relieving pain[8]. Spinal injections are typically performed twice a week over six weeks in one of two fashions, around the epidural space similar to an epidural steroid injection (ESI) or transforaminally around the spinal nerve root[13]. The purpose of this systematic review is to investigate the effectiveness of ACS in treating neurologic deficit, disability, and pain caused by spinal pathology.

MATERIALS AND METHODS

A systematic review of the literature was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Figure 1). PubMed/Medline was interrogated for clinical studies investigating the administration of ACS for the treatment of any spinal pathology. This systematic review was not prospectively registered.

Eligibility criteria

Articles included in this review met the following inclusion criteria: (1) Article discusses spinal pathology; (2) Article applies an intervention of ACS administration; and (3) Pain, disability, or quality of life outcome is reported. Studies were excluded if they met any of the following exclusion criteria: (1) Unavailable in English; (2) Abstracts and unpublished studies; (3) Reviews; (4) Articles describing non-spinal pathology; and (5) Articles describing non-ACS IL-1 therapies.

Information sources and search strategy

Using PRISMA guidelines, PubMed/Medline database was queried on November 3, 2023 using search terms inclusive for spinal pathology and anti-IL-1R therapy including: "autologous conditioned serum", "regenokine", "orthokine", "IL-1 receptor antagonist", "IL-1Ra", and "anti IL-1". No limits were imposed on the year of publication. Full search terms used can be found in Supplementary material 1. No limits were placed on the year of publication of queried articles, and all articles included were peer-reviewed, published, and accessed without requiring contact with corresponding authors.

Selection process

Articles were queried by author Rajkovic CJ, and seven authors (Rajkovic CJ, Merckling M, Lee AW, Subah G, Malhotra A, Thomas ZD, Zeller SL) independently screened each title, abstract, and manuscript for inclusion and exclusion criteria. Duplicate articles were screened and removed from the query. Bibliographies of the included articles were also screened using our inclusion and exclusion criteria for additional relevant studies. The screening results were confirmed by two additional reviewers (Rajkovic CJ and Zeller SL).

Data collection process, data items, and statistical analysis

Two authors (Rajkovic CJ and Merckling M) independently extracted and recorded all data into two separate Google spreadsheets. Source articles were used to cross-check and verify the data in each spreadsheet. The following information was extracted from each article: The spinal pathology treated, the study design, the baseline characteristics of each cohort, the dosing regimen and route of administration of the ACS treatment, and any comparable interventions for conservative management of spinal pathology. For articles where the age or sex of the ACS cohort was only reported as a pooled statistic with other cohorts, the pooled statistic was used to estimate the overall age or sex distribution of the ACS cohort. Primary outcomes investigated included patient pain, disability, and quality of life scores. Secondary outcomes investigated included reported adverse events and analgesic use. Data that was only reported graphically was extracted using webplotdigitizer (https://automeris.io/WebPlotDigitizer/) software to estimate mean and standard deviation values. All statistical comparisons for reported outcomes were extracted from individual included studies, and no meta-analysis was performed between studies. The statistical methods of this study were reviewed by Dr. Elizabeth Drugge from New York Medical College.

Study risk of bias assessment

Two reviewers (Subah G and Zeller SL) independently assessed the risk of bias of the studies included in this systematic review using the Joanna Briggs Institute critical appraisal checklist for both cohort studies and randomized control trials (RCT)[14]. This process involved considering 11 and 13 questions about cohort studies and RCT, respectively, to assess risk of bias. Studies with a score < 50% of questions answered "yes" were considered as high risk, a score between 50% and 69% as moderate risk, and a score ≥ 70% as low risk (Table 1).

RESULTS

Baseline characteristics of included studies

Our search query retrieved 385 articles from PubMed/Medline, and 376 articles were excluded on initial screening for the following reasons: Not spinal pathology (n = 198), no IL-1Ra treatment (n = 124), basic science study (n = 44), review article (n = 4), not English (n = 3), letter to the editor (n = 2), and retracted article (n = 1). Of the remaining nine articles, three investigated anakinra treatment and were excluded. Six articles were finally included from 2007 to 2023, comprising 684 distinct patients who were treated with ACS for spinal pathology and 72 patients who were treated with comparative steroid injections. The mean (SD) follow-up for these patients was 21.7 (4.8) weeks following their first ACS injection. All ACS injections were performed either interlaminarly (n = 61 patients) or transforaminally (n = 623 patients). The included articles consisted of two pilot studies, two prospective cohort studies, one retrospective cohort study, and one RCT. Each study's design, baseline clinical characteristics of the patient cohort, and investigated outcomes are summarized in Table 2. Among patients treated with ACS in the included articles, the average age was 54.0 years (n = 684 patients, range: 17-93), the average BMI was 26.4 kg/m^2 (n = 120 patients), and 53.2% of patients were female. Pre-existing comorbidities were only reported by Godek *et al*[13], including two patients with diabetes, four patients with peripheral vascular

Table 1 Risk of bias assessment

Manuscript type	Ref.	Related questions													Total	Risk of bias
Randomized control trial		Was true randomization used for assignment of participants to treatment groups?	Was allocation to treatment groups concealed?	Were treatment groups similar at the baseline?	Were participants blind to treatment assignment?	Were those delivering the treatment blind to treatment assignment?	Were treatment groups treated identically other than the intervention of interest?	Were outcome assessors blind to treatment assignment?	Were outcomes measured in the same way for treatment groups?	Were outcomes measured in a reliable way?	Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Were participants analyzed in the groups to which they were randomized?	Was appropriate statistical analysis used?	Was the trial design appropriate and any deviations from the standard randomized control trial design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?		
	Godek *et al* [13]	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	85%	Low
Cohort studies		Were the two groups similar and recruited from the same population?	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Was the exposure measured in a valid and reliable way?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Were the outcomes measured in a valid and reliable way?	Was the follow-up time reported and sufficient to be long enough for outcomes to occur?	Was follow-up complete, and if not, were the reasons for loss to follow-up described and explored?	Were strategies to address incomplete follow-up utilized?	Was appropriate statistical analysis used?	N/A	N/A		
	Becker *et al* [15]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	100%	Low
	Goni *et al* [16]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	N/A	N/A	73%	Low
	HS *et al*[17]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	100%	Low
	Godek *et al* [19]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N/A	N/A	82%	Low

	Godek *et al* [18]	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N/A	N/A	73%	Low

Table 2 Designs and conclusions of included studies

Ref.	Study design	Sample size	Age (mean)	BMI (mean)	Female	Pathology	Intervention (s)	Latest follow-up	Outcomes measured	Conclusion
Becker *et al* [15]	Randomized prospective cohort study	ACS: *n* = 32, 5 mg Triamcinolone: *n* = 27, 10 mg Triamcinolone: *n* = 25	53.9 (range: 29-81)	Not reported	38.10%	Lumbar radiculopathy	3 weekly transforaminal injections of ACS, 5 mg triamcinolone, or 10 mg triamcinolone	20 weeks post-final injection	VAS, ODI	Epidural ACS injection for unilateral lumbar radiculopathy significantly improved patient pain and disability compared to baseline to an extent potentially superior to ESI. No statistically significant difference in symptom improvement was observed between 5 mg and 10 mg epidural injection of triamcinolone
Goni *et al*[16]	Pilot study	ACS: *n* = 20; MPS: *n* = 20	ACS: 42.25; MPS: 46.80	Not reported	ACS: 40%; MPS: 45%	Cervical radiculopathy	A single 2-3 mL transforaminal injection of ACS or MPS	6 months post-injection	VAS, NDI, NPDS, PCS, MCS	Patients with cervical radiculopathy treated with epidural ACS injection experienced sustained improvement of pain, disability and quality of life. ACS produced as good or better improvement of symptoms with longer duration of relief compared to epidural methylprednisolone
HS *et al*[17]	Prospective study	ACS: *n* = 20	37.15	24.92 kg/m^2	Not reported	Lumbar radiculopathy	A single 2 mL transforaminal injection of ACS	6 months post-injection	VAS, SLRT, ODI, PCS, MCS	Epidural ACS injection can modify the disease course of unilateral lumbar radiculopathy by significantly improving pain, disability, and quality of life
Godek *et al* [19]	Pilot study	ACS: *n* = 15	38.8	Not reported	40%	Lumbar radiculopathy	1-2 weekly transforaminal injections of 3-4 mL ACS	6 months post-injection	VAS, ODI, SLRT, OLST, Analgesic use	ACS is a promising option for significantly improving pain and disability in patients with single-level lumbar radiculopathy. No radicular damage or sever adverse events were reported
Godek *et al* [18]	Retrospective study	ACS: *n* = 497	57.1 ± 16.5 (range: 17-93)	Not reported	57.70%	Cervical DDD (transforaminal injection): *n* = 89. Thoracic Spine DDD (transforaminal injection): *n* = 8. Lumbar Spine DDD (transforaminal injection): *n* = 271. Lumbar Spine DDD (interlaminar injection): *n* = 1. Lumbar Spine Stenosis (transforaminal injection): *n* = 118.	Cervical: 4 doses of 3-4 mL transforaminal ACS injections. Thoracic: 6 doses of 3-4 mL transforaminal ACS injections. Lumbar: 4-6 doses of 4 mL ACS injected transforaminally or interlaminarly	6 months post-final injection	Modified McNabb scale	ACS injection was well tolerated with very few and limited cases of adverse events. ACS injection produced satisfactory improvement in Modified McNabb Scale scores for patients with cervical or lumbar discopathy. Unsatisfactory results predominated in cases of lumbar spinal stenosis

						Lumbar Spine Stenosis (interlaminar injection): n = 10				
Godek *et al* [13]	Randomized control trial	ACS: n = 100	46.29 + 13.61	26.67 ± 4.49	51%	Lumbar Radiculopathy due to DDD (interlaminar injection): n = 50. Lumbar Radiculopathy due to DDD (transforaminal injection): n = 50	2 weekly interlaminar or transforaminal injections of 8 mL ACS	24 weeks post-final injection	NRS, ODI, RMQ, EQ-5D-5 L mobility, EQ-5D-5 L self-care, EQ-5D-5 L usual activities, EQ-5D-5 L pain/discomfort, EQ-5D-5 L anxiety/depression, EQ-5D-5 L-based LSS, EQ-5D-5 L VAS, EQ-5D-5 L Index	Epidural and transforaminal ACS injections both significantly improve patient outcomes compared to baseline. Treatment with transforaminal ACS injection produced statistically superior improvement in EQ-5D-5 L scores compared to epidural ACS injection

BMI: Body mass index; ACS: Autologous conditioned serum; VAS: Visual acuity scale; ODI: Oswestry disability index; ESI: Epidural steroid injection; MPS: Methylprednisolone; NDI: Neck disability index; NPDS: Neck pain disability scale; PCS: Physical component score; MCS: Mental component score; SLRT: Straight leg raise test; OLST: One leg standing test; DDD: Degenerative disk disease; RMQ: Roland Morris questionnaire; EQ-5D-5 L: Euro quality of life-five dimensions-five levels; LSS: Level sum score.

disease, and two patients with bone metabolism disorders in the RCT of 100 subjects. At baseline, patients were described to have moderate-severe pain of at least six weeks duration in three studies[15–17] and any chronic radicular symptoms in the remaining three studies[13,18,19]. Patients were opioid or steroid-naive for at least six months in three of the six included studies[15,17,19], and oral nonsteroidal anti-inflammatory drugs were allowed during the treatment period for four of the six included studies[15–17,19]. The lumbar spine was the most common spinal segment treated, with 567 patients (82.9%) receiving ACS injections for either lumbar radiculopathy (n = 67 patients), lumbar DDD (n = 372 patients), or lumbar stenosis (n = 128 patients). Cervical ACS injections were performed in 109 patients (15.9%) for either cervical radiculopathy (n = 20 patients) or DDD (n = 89 patients), and only eight patients received thoracic ACS injections (1.2%) in our systematic review, exclusively for thoracic DDD. Radiographic severity at presentation was only evaluated in one study with Godek *et al*[19] reporting an average disc herniation size of 5.3 ± 2.4 mm. Risk of bias assessment was low for all included studies.

Efficacy in pain management

All included articles investigated pain relief following injection with ACS as a primary outcome. Specific metrics used to report pain included the visual acuity scale (VAS; four studies; Figure 2), numerical ranking scale (NRS; one study), and modified McNab scores (one study). All studies investigating ACS treatment of lumbar pathology reported significant pain reduction at final follow-up compared to baseline. Godek *et al*[19] reported a significant reduction in VAS score compared to baseline at both one month and three months (P = 0.002 and P < 0.0001, respectively) following transforaminal ACS injection for lumbar radiculopathy. Similarly, Becker *et al*[15] and HS *et al*[17] reported a significant reduction in baseline VAS scores at the end of 22 weeks and 24 weeks, respectively, for patients receiving transforaminal ACS injections for lumbar radiculopathy (P < 0.001 for both studies). Godek *et al*[13] observed a significant reduction in NRS scores at 24 weeks post-injection compared to baseline for both interlaminar and transforaminal injections in their RCT (6.1 *vs* 2.8, P < 0.0001 for interlaminar ACS injection; 6.1 *vs* 2.8, P < 0.0001 for transforaminal ACS injection). Among patients who received transforaminal ACS injections for cervical radiculopathy in a study by Goni *et al*[16], a 73.24% improvement (71.0 mm to 19.0 mm) in reported VAS scores was observed at six months following injection (P-value not reported).

Comparing ACS injection with ESI for treatment of lumbar pain, Becker *et al*[15] observed no significant difference in reported VAS scores between patients receiving ACS or 10 mg triamcinolone ESI at 22 weeks following their first injection (95%CI: -23.5, 4.9). When comparing ACS injection to a 5 mg triamcinolone ESI, the authors found that patients receiving

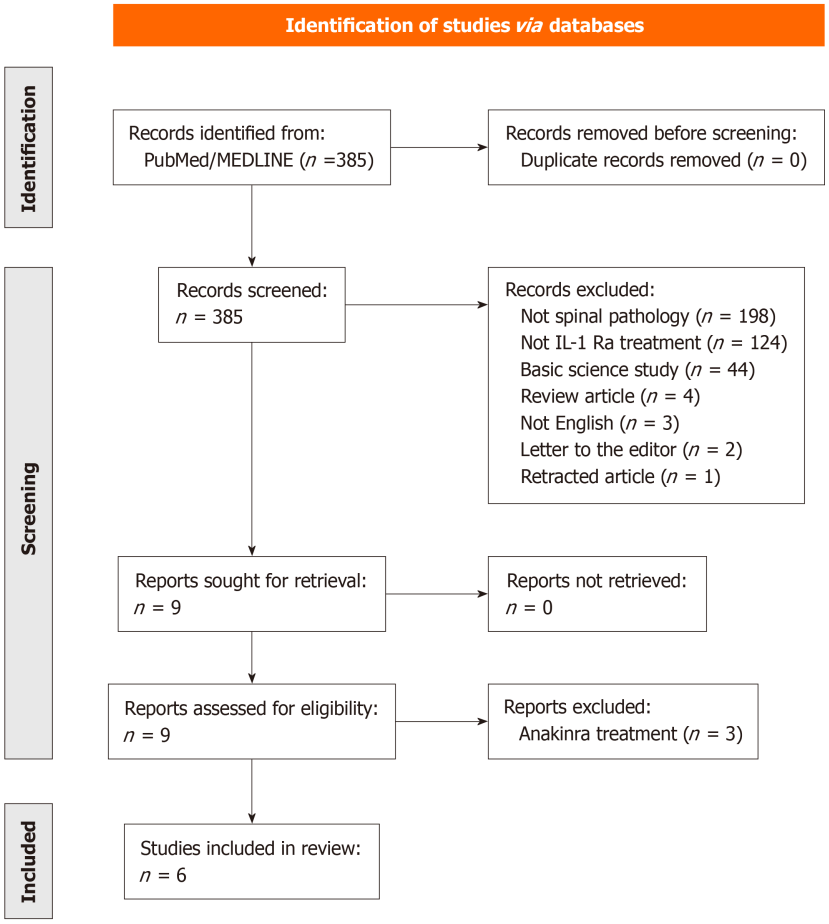

Figure 1 The preferred reporting items for systematic reviews and meta-analyses flowchart of search results.

ACS injection reported significantly lower mean (SD) VAS scores [23.3 (24.8) mm *vs* 36.8 (28.3) mm; $P = 0.046$]. Goni *et al* [16] reached a similar conclusion observing that patients receiving epidural ACS for cervical radiculopathy reported significantly lower VAS scores at their six-month follow-up than patients receiving methylprednisolone ESI (19.0 mm *vs* 27.5 mm; $P = 0.027$).

The modified McNab scores used by Godek *et al*[18] assessed both pain and disability using the following scoring system: (1) Excellent (no pain or mobility restriction and full level of activity); (2) Good (occasional pain and return to previous activity level); (3) Fair (improvement of pain with continued disability and reduced activity level); and (4) Poor (no pain improvement with continued disability and/or necessitated surgical intervention)[18]. For ease of comparison between different spinal pathologies, the authors defined a score of A or B as a satisfactory outcome. In cases of cervical and lumbar DDD, a satisfactory outcome at six-month follow-up was achieved in 61.8% and 56.5% of patients, respectively. These patients also had remarkably low rates of deterioration following initial improvement, with only 4.07% and 3.69% of patients showing a worsening of symptoms for cervical and lumbar DDD, respectively. In cases of thoracic DDD and lumbar spinal stenosis treated with transforaminal ACS injection, outcomes were less favorable with only 37.5% and 33.9% of patients achieving a satisfactory outcome. Patients with lumbar stenosis who were treated with interlaminar ACS injection fared better than those treated with transforaminal injection, achieving a 90% satisfactory outcome rate at six-month follow-up. However, this result was not statistically significant from baseline McNab scores because of a ten-patient cohort size.

Improvement of disability

All included studies investigated disability following injection with ACS as a primary outcome. Disability metrics included the Oswestry Disability Index (ODI; four studies; Figure 3), the Roland Morris Questionnaire (one study), the neck disability index (NDI; one study), and the neck pain and disability scale (NPDS; one study). Similar to pain response following ACS injection, Godek *et al*[19], Godek *et al*[13], Becker *et al*[15], and HS *et al*[17] reported significantly improved ODI scores at 12 weeks ($P = 0.005$), 24 weeks ($P < 0.0001$), 22 weeks ($P < 0.001$), and 24 weeks ($P < 0.001$), respectively. To assess patient disability due to cervical radiculopathy, Goni *et al*[16] documented both NDI and NPDS scores at baseline and 24 weeks following cervical transforaminal ACS injection and demonstrated a 74.47% and 73.76% improvement in average scores, respectively (*P*-value not reported).

The efficacy of ACS injection compared to ESI was less conclusive regarding disability outcomes. While Goni *et al*[16] observed that patients receiving cervical ACS injection reported significantly lower NDI and NPDS scores (NDI 15.9 *vs* 30.4, $P < 0.001$; NPDS 18.55 *vs* 31.1, $P < 0.001$) than patients receiving methylprednisolone ESI at 24 weeks, Becker *et al*[15]

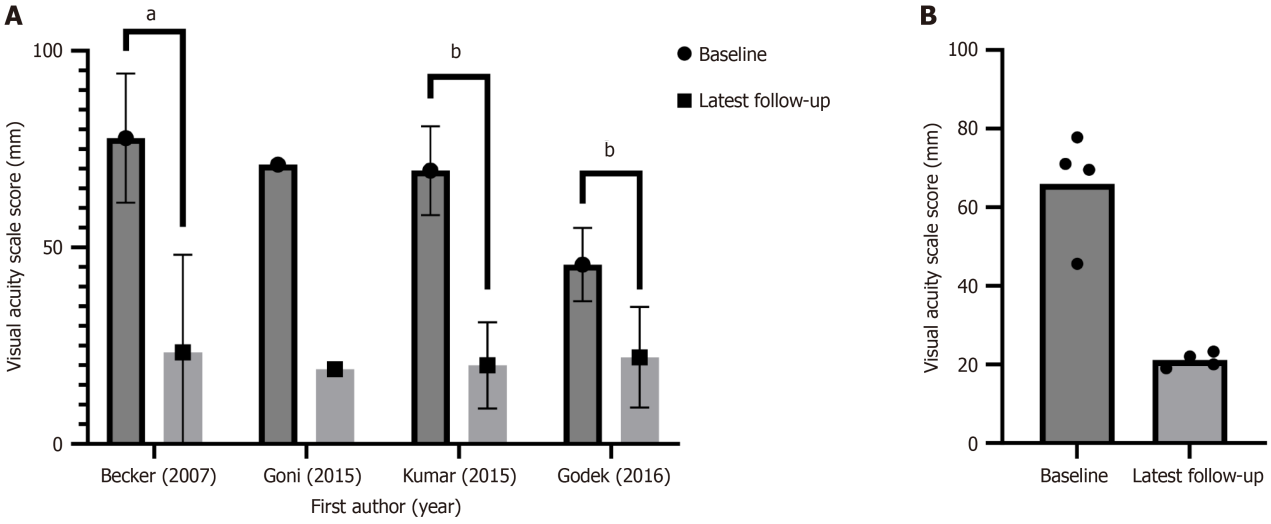

Figure 2 Patient visual acuity scale scores at baseline and at latest follow-up. A: The mean and standard deviation visual acuity scale (VAS) scores are depicted at baseline and latest follow-up after autologous conditioned serum injection for each of four included studies Becker *et al*[15]: n = 32, Goni *et al*[16]: n = 20, HS *et al*[17]: n = 20, Godek *et al*[19]: n = 15. Goni *et al*[16] did not report standard deviations for reported VAS scores or conduct pairwise comparison between baseline and follow-up VAS scores; B: The combined mean VAS scores are depicted at baseline and follow-up as reported by Becker *et al*[15], Goni *et al*[16], HS *et al*[17], and Godek *et al*[19]. $^{a}P < 0.05$; $^{b}P < 0.01$.

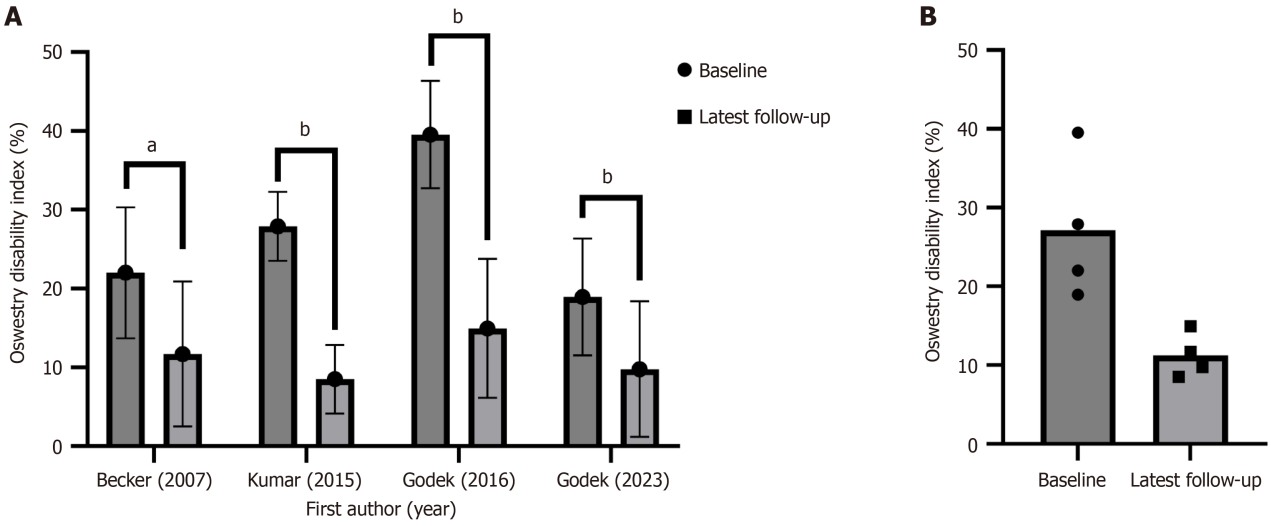

Figure 3 Patient Oswestry disability index at baseline and at latest follow-up. A: The mean and standard deviation Oswestry disability index (ODI) are depicted at baseline and latest follow-up after autologous conditioned serum injection for each of four included studies Becker *et al*[15]: n = 32, HS *et al*[17]: n = 20, Godek *et al*[19]: n = 15. Godek *et al*[13]: n = 100; B: The combined mean ODI scores are depicted at baseline and follow-up as reported by Becker *et al*[15], HS *et al*[17], Godek *et al*[19], and Godek *et al*[13]. $^{a}P < 0.05$; $^{b}P < 0.01$.

found no significant difference between ODI scores (P = 0.95) of patients receiving epidural ACS, 5 mg triamcinolone ESI, or 10 mg triamcinolone ESI for lumbar radiculopathy at 22 weeks.

Quality of life improvement

Quality of life was assessed using the Euro quality of life-five dimensions-five levels (EQ-5D-5 L) index (one study), the EQ-5D-5 L VAS (one study), the physical health component score (PCS) of the short form-36 (SF-36) questionnaire (two studies), and the mental health component score (MCS) of the SF-36 questionnaire (two studies). Comparing scores at baseline and 24 weeks post-injection, the RCT by Godek *et al*[13] observed a significantly improved EQ-5D-5 L index for patients receiving interlaminar (0.805 *vs* 0.913, P = 0.0001) and transforaminal (0.754 *vs* 0.895, P = 0.0001) ACS injections. Similarly, improvement from baseline to 24 weeks was also observed in EQ-5D-5 L VAS scores for interlaminar (66.14 *vs* 74.25, P = 0.0474) and transforaminal (60.14 *vs* 77.62, P < 0.0001) ACS injections. ACS injections were also shown to improve the average PCS of patients with cervical radiculopathy (27.35 at baseline to 49.08 at 24 weeks, P-value not reported) and lumbar radiculopathy (27.25 at baseline to 49.32 at 24 weeks, P < 0.001) in studies by Goni *et al*[16] and HS *et al*[17], respectively. Similarly, these two studies reported an improvement in MCS at 24 weeks for cases of cervical radiculopathy (36.22 at baseline to 47.12 at 24 weeks, P-value not reported) and lumbar radiculopathy (36.59 at baseline to

47.51 at 24 weeks, $P < 0.001$). Epidural ACS injections were also shown to outperform methylprednisolone ESI in improving PCS (49.08 *vs* 44.39, $P = 0.004$) and MCS (47.12 *vs* 42.42, $P < 0.001$) at 24 weeks following injection for cervical radiculopathy.

Adverse events

Adverse events of any kind were reported in 21 of the 684 patients (3.1%) included in this systematic review following ACS injection. No serious adverse events directly attributable to ACS injection, including infection, muscle atrophy, or hematoma, occurred in any of the patients in this review. The most severe adverse events reported were due to natural progression of disease, specifically four patients who eventually required emergency surgery due to persistent pain and foot paresis while receiving ACS therapy[18,19]. Further, three of the six studies included protocols for the treatment of persistent pain with over-the-counter analgesics taken as needed. The remaining adverse events were self-limited and resolved within 48 hours. These included headache ($n = 4$), dizziness ($n = 4$), syncope ($n = 1$), sweating ($n = 3$), tachycardia ($n = 2$), back stiffness ($n = 1$), and neck stiffness ($n = 2$). Godek *et al*[18] reported a mild complication rate of approximately 10% in its pooled cohort of osteoarthritis treatment, limited to mild myalgia, chills, weakness, and fevers resolving within 48 hours of injection[18]. In studies that compared ACS to ESI, the adverse event rates were similar between groups, with Becker *et al*[15] reporting one adverse event in each of its ACS and triamcinolone ESI treatment groups, and Goni *et al*[16] reporting 8 adverse events in its ACS treatment group and 11 adverse events in its methylprednisolone ESI treatment group ($P = 0.53$).

DISCUSSION

Despite the 200 billion dollars spent annually on its management, spine pain remains a leading cause of disability and the most common cause to seek emergency care[20]. Therefore, the need for continued advancements in managing chronic spine symptomatology is clear. While surgical intervention may be indicated in select patients depending on the nature and severity of their conditions, nonoperative treatment remains the first-line management for most mechanical and radicular pain generated by the spine[21]. In this review, all studies investigating ACS for mechanical lumbar, lumbar radicular, and cervical radicular pain unanimously reported significant pain reduction compared to baseline. Pain relief was sustained through final follow-up, ranging between 3 and 6 months from treatment.

Disrupting the inflammation-pain cycle of chronic spine pathologies is a mainstay of nonoperative treatment strategies, and ACS represents a particularly intriguing option for the treatment of spine-related pain due to its anti-inflammatory properties. ACS has been widely marketed for the treatment of knee osteoarthritis as Orthokine™ in Europe and Regenokine™ in the United States, and several clinical trials have demonstrated its effectiveness in relieving arthritic pain through the anti-inflammatory effects of IL-1Ra, its active ingredient[22–24]. Further, ACS contains several other anti-inflammatory factors such as IL-4, IL-10, IL-13, FGF-2, HGF, and TGF-β1, which may further inhibit inflammation-induced hyperalgesia[25,26]. In cases of radiculopathy, standard injection protocol for ACS is done *via* fluoroscopic guidance to the nerve root for transforaminal injections or following an interlaminar approach for epidural injections[8]. The proposed physiologic mechanism by which ACS is thought to relieve symptoms of radiculopathy concerns the inflammatory pathogenesis of back pain. In particular, several studies have correlated significant differences in pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α with severity of presentation of lower back pain[27]. Therefore, the antagonism of these factors with IL-1Ra and the previously described anti-inflammatory contents of ACS show promise as therapeutic components to alleviate the symptoms of spinal radiculopathy[17]. The sustained pain relief noted by several studies suggests the efficacy of ACS for these conditions, especially when considering these results in studies that used ESI as a comparator therapy[23].

ESIs serve both diagnostic and therapeutic purposes in spinal pain management, including identifying the anatomic locus of pain, providing short- or long-term pain relief, or delaying the need for surgical intervention; however, there is no definitive consensus on the exact indications of ESI treatment[28]. Further, patients experience variable responses with regard to the extent and duration of pain relief following ESI[29]. Patients are also limited to 2-3 ESIs annually to avoid the complication of increased degenerative changes secondary to increased osteoclast-driven bone turnover seen with repetitive corticosteroid treatment. Despite these limitations, ESI is a mainstay in the nonoperative management of many spine conditions and served as a comparison to ACS in several of the reviewed studies. ACS produced better long-term reduction in lumbar radicular symptoms when compared to 5 mg triamcinolone ESI, although no significant difference was appreciated compared to the 10 mg triamcinolone dose[15]. In the context of cervical radiculopathy, ACS treatment outperformed the methylprednisolone ESI regarding pain relief, further suggesting the comparable if not superior efficacy of ACS injection compared to ESI for pain relief[16]. In addition, ACS injections do not have the same limitation on dosing frequency that is observed with ESI and can be repeated as many times as necessary if symptom relief continues[8]. The only contraindications to receiving ACS therapy are ongoing infections, fever, diarrhea, vaccinations within the last 4 weeks, and comorbid cancer due to the altered cytokine profile of blood samples of patients with these conditions[18]. Cost is also an important factor when comparing ACS to ESI with a complete regiment of ACS therapy costing between $1000 and $3000 often out-of-pocket compared to a lumbar ESI costing an average of $601[30,31].

Of note, not all etiologies of spinal pain achieved significant relief with ACS. Godek *et al*[18] reported an improvement of radicular symptoms when DDD was the underlying pathology, but significant relief was not achieved in those with radicular pain secondary to spinal stenosis. This limitation has also been observed in ESI for lumbar stenosis and is thought to be due to the addition of fluid volume to an already compressed spinal canal along with a lipomatosis effect stimulated by the steroid[32]. In the remainder of our review, three studies only investigated radiculopathy due to DDD,

and two studies did not clarify underlying pathology, making the evaluation of ACS for the treatment of spinal stenosis difficult to assess.

In addition to pain relief, all included studies assessed improvement in disability. All studies reported significant improvement in disability when compared to baseline as measured by various disability indices; however, there were variable findings across studies when comparing ACS to ESI. In patients with cervical radiculopathy, NDI and NPDS scores were significantly less following ACS injections than following methylprednisolone ESI injections[16]; however, no significant difference in ODI scores was observed between ACS and either 5 or 10 mg triamcinolone ESI for lumbar radiculopathy at 22 weeks[15]. The comparison of disability reduction after ACS *vs* ESI is inconclusive as the studies utilized variable ESI medications and different disability measures. Thus, additional studies are needed to make this comparison.

All studies reporting quality of life measures demonstrated significant improvement following ACS injections when assessed by several different subjective tools. This benefit was seen specifically for patients suffering from cervical or lumbar radiculopathy. The improvement in MCS is particularly relevant considering the well documented association between radicular pain and declining mental health outcomes[33]. The inclusion of this outcome was an important factor in assessing the utility of ACS treatment for patients living with chronic radicular pain.

Another potential benefit of ACS is the minimization of steroid treatment in diabetic patients concerned with blood glucose management. While long-term diabetes management assessed through hemoglobin A1C levels has been shown to be unaffected by ESI treatment, a transient increase in blood glucose levels for several days following ESI has been well-documented[34]. ACS represents an alternative treatment option for chronic spine conditions in this patient population, who may benefit from the avoidance of hyperglycemia in the days following treatment.

Finally, ACS has a favorable safety profile, with an overall adverse event rate of 3.1%, and no serious adverse events attributable to ACS were identified in this review. Self-limited adverse events reported in the studies, such as headache, dizziness, and syncope, have also been well documented among ESIs[35] and are most likely related to the penetrating nature of injections rather than the injectate. The safety of ACS was shown to be comparable to that of ESI, and this review derived no indication of ACS injection carrying a higher risk profile than other forms of epidural injections.

This study is a systematic review and is thus limited by the heterogeneity of data in the included articles and the lack of compatibility between cohorts at baseline. As a result, a meta-analysis was not performed to compare data given the different pathologies and outcomes reported by each study. One limitation of this study is the limited reporting of pre-existing comorbidities that may have influenced outcomes of treatment with only one cited study including this information. Future studies may benefit from analyzing the effect of comorbidities on response to ACS. Various metrics were used across studies to evaluate pain, disability, and quality of life changes to treatment which precluded a meta-analysis of the outcomes. Further, some studies included the use of oral analgesics and variable injection sites, both of which may have played a role in outcomes. Large scale, multi-center clinical trials are needed to supplement the current literature on the effectiveness of ACS for the treatment of spinal pathology with significant follow-up and comparison to controls and standard of care conservative treatments such as ESI. Currently, a prospective protocol has been published for ultrasound-guided injection of ACS for the treatment of cervical pain with anticipated completion of the trial in early 2025[36].

CONCLUSION

While further research is needed for the evaluation of ACS in various spinal conditions and its comparison to ESI, its risk to benefit profile has shown promise for nonoperative management of spine conditions. ACS therapy for mechanical and radicular symptoms has demonstrated value when compared to ESI. Examined studies showed improved long term relief, ability to repeat treatments without risk of bone destruction, and elimination of excessive corticosteroid treatments in diabetic patients. ESI continues to be a useful treatment option due to its cost effectiveness relative to ACS and its ability to serve as a diagnostic tool, however the future of spine care can benefit from the inclusion of ACS in the treatment algorithm of nonoperative management. Future research is needed to compare and recommend specific ACS treatment protocols with long term outcome data focused on clinical outcomes. Examination of cost effectiveness, avoidance of surgical intervention, and subjective quality of life measures should be included in these future studies.

FOOTNOTES

Author contributions: Rajkovic CJ was responsible for designing the review protocol, writing the protocol and report, conducting the search, screening potentially eligible studies, extracting and analyzing data, interpreting results, writing the manuscript, updating reference lists, and creating figures and tables; Merckling ML was responsible for screening potentially eligible studies, extracting and analyzing data, interpreting results, and writing the manuscript; Lee AW was responsible for screening potentially eligible studies and creating the PRISMA figure; Malhotra A, Thomas ZD was responsible for screening potentially eligible studies; Subah G, Zeller SL, Wainwright JV and Kinon MD was responsible for designing the review protocol, screening potentially eligible studies, assessing bias in included studies, writing the manuscript, and providing feedback.

Conflict-of-interest statement: Dr. Merritt Kinon reports stock and honorarium with Globus Medical, Inc and is a consultant for Sanara MedTech. The remaining authors have no conflicts of interest to disclose.

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ORCID number: Christian J Rajkovic 0000-0003-3559-2766.

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