Allogeneic Umbilical Cord Mesenchymal Stromal Cells for Knee Osteoarthritis: Systematic Review and Meta-Analysis of Controlled Injection Trials

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Systematic Review

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Abstract

Background

Knee osteoarthritis is a leading cause of chronic pain and reduced mobility worldwide. Intra-articular corticosteroids and hyaluronic acid injections are commonly used, but many patients experience limited durability of symptom improvement. Allogeneic umbilical cord derived mesenchymal stromal cells (UC-MSCs) have emerged as a regenerative medicine strategy intended to modulate inflammation and improve clinical outcomes.

Objective

To evaluate controlled clinical trial evidence for intra-articular allogeneic UC-MSC therapy in symptomatic knee osteoarthritis, with emphasis on durability of pain improvement at 12 months.

Methods

A systematic review was conducted to identify controlled clinical trials evaluating intra-articular allogeneic UC-MSCs for knee osteoarthritis with comparator injection arms. The primary endpoint was WOMAC pain at 12 months. Secondary outcomes included WOMAC total at 12 months. When trials did not provide numeric endpoint values in tables, values were extracted from published figures as estimated mean and dispersion measures. Outcomes were synthesized under a random effects framework with consideration of comparator type (hyaluronic acid vs corticosteroid).

Results

Two controlled trials met criteria for quantitative synthesis at 12 months. Across comparator subgroups, UC-MSC therapy demonstrated lower WOMAC pain scores at 12 months compared with control injections. UC-MSC therapy also demonstrated lower WOMAC total scores at 12 months relative to comparator injection arms. One phase I single-arm study was included in qualitative synthesis for feasibility and safety interpretation but was not eligible for pooled analysis.

Conclusion

Controlled clinical trial evidence suggests intra-articular allogeneic UC-MSC therapy may provide durable improvements in knee osteoarthritis pain at 12 months compared with standard injection-based comparators. Larger randomized trials with standardized reporting are needed to further define efficacy, durability, and safety across broader populations.

INTRODUCTION

Knee osteoarthritis is among the most prevalent causes of chronic pain, impaired mobility, and functional decline. Symptom burden often progresses over time, contributing to reduced activity tolerance and loss of quality of life.

Standard injection-based therapies such as intra-articular corticosteroids and hyaluronic acid are commonly used for symptom management. While these approaches can provide benefit in some patients, durability is frequently limited and patients often seek strategies associated with longer-lasting improvements in pain and function.

Allogeneic umbilical cord derived mesenchymal stromal cells (UC-MSCs) have gained increased attention in regenerative medicine due to proposed immunomodulatory, anti-inflammatory, and tissue homeostasis effects within the osteoarthritic joint environment. Controlled clinical trials comparing UC-MSC therapy with standard injection approaches offer clinically relevant insight into relative durability and symptom improvement.

The objective of this study was to systematically evaluate controlled clinical trial evidence for intra-articular allogeneic UC-MSC therapy in symptomatic knee osteoarthritis, with emphasis on WOMAC pain outcomes at 12 months. Secondary evaluation of WOMAC total outcomes was also performed to support interpretation of overall symptom and functional improvement.

METHODS

Reporting Standards

This systematic review and meta-analysis was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Study Design

This study was conducted as a systematic review and meta-analysis of controlled clinical trials evaluating intra-articular allogeneic UC-MSC therapy for knee osteoarthritis.

Eligibility Criteria

Studies were eligible if they met the following criteria: human clinical trials enrolling adult patients with symptomatic knee osteoarthritis; intra-articular administration of allogeneic umbilical cord derived or umbilical cord tissue derived MSCs; inclusion of a comparator injection arm (placebo, sham, or active comparator); and reporting of WOMAC pain outcomes with follow-up available at, or near, 12 months.

Studies were excluded if they were reviews or meta-analyses, preclinical investigations, extracellular vesicle or secretome-only therapies without live MSC administration, or lacked a controlled comparator arm. Single-arm early-phase studies were retained for qualitative synthesis of feasibility and safety where appropriate.

Outcomes

Primary outcome: WOMAC pain at 12 months.

Secondary outcome: WOMAC total at 12 months.

Additional outcomes included adverse events and supportive imaging findings when reported.

Data Extraction

Study characteristics, comparator type, sample sizes, intervention protocols, and outcomes were extracted. When numeric outcome values were not provided in table format, values were extracted from published figures based on graphical presentation of mean values and dispersion measures. Extracted figure-based values were treated as approximations and were transparently described.

Risk of Bias

Risk of bias was assessed using structured domains aligned with randomized trial methodology, including randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting.

Statistical Analysis

Outcomes were interpreted using a random effects synthesis framework due to expected clinical and methodological heterogeneity. Comparator type was evaluated as a clinical subgroup (hyaluronic acid vs corticosteroid). Given the limited number of controlled studies, quantitative findings were interpreted cautiously as an early synthesis of controlled evidence.

RESULTS

Study Selection (PRISMA Flow Counts)
Records identified through database searching: 36
Records screened (title/abstract): 36
Records excluded after title/abstract screening: 30
Full-text articles assessed for eligibility: 6
Full-text articles excluded: 3
Studies included in qualitative synthesis: 3
Studies included in quantitative synthesis (meta-analysis): 2

Reasons for full-text exclusion included review articles, non-controlled designs, or non-eligible interventions.

Included Studies
Two controlled trials were eligible for pooled quantitative synthesis at 12 months, with active comparator injection arms including hyaluronic acid and intra-articular corticosteroid. One phase I single-arm study evaluating repeated UC-MSC injections was included in qualitative synthesis for feasibility and safety interpretation only.

Risk of Bias Summary

Overall risk of bias across the included controlled trials was considered low to moderate. Primary limitations were related to modest sample sizes and incomplete numeric reporting of follow-up outcomes in one trial, requiring figure-based data extraction for quantitative synthesis. No evidence of selective reporting within the primary pain outcome domain was identified.

Primary Outcome: WOMAC Pain at 12 Months

Across controlled trials, UC-MSC therapy demonstrated lower WOMAC pain scores at 12 months compared with standard comparator injections. In the hyaluronic acid comparator trial, repeated UC-MSC dosing resulted in substantially lower WOMAC pain at 12 months relative to hyaluronic acid control. In the corticosteroid comparator trial, UC-MSC therapy demonstrated sustained improvement through 12 months compared with triamcinolone, supporting a durability advantage relative to intra-articular corticosteroid. Random effects synthesis favored UC-MSC therapy at 12 months for WOMAC pain, with consistent directionality across comparator subgroups. The characteristics of the included studies are summarized in Table 1.

Secondary Outcome: WOMAC Total at 12 Months

Two controlled trials reported 12-month WOMAC total outcomes comparing UC-MSC therapy with active comparator injections. Across both comparator subgroups, UC-MSC therapy was associated with lower WOMAC total scores at 12 months compared with control injections, supporting broader improvement in symptom severity and function in addition to pain reduction. Extracted outcome data for WOMAC pain and WOMAC total at 12 months are shown in Table 2.

Safety and Tolerability

No clear signal of severe treatment-related adverse events was identified across controlled trials included in the quantitative synthesis. The phase I qualitative study further supported feasibility and tolerability of repeated UC-MSC administration, though larger controlled trials are required to characterize rare risks and refine optimal dosing strategies.

Table 1. Included studies and design characteristics

Study	Design	Intervention	Comparator	Follow-up	Included in meta-analysis
Matas et al., 2019	Randomized controlled phase I/II	UC-MSC intra-articular injection (single vs repeated dosing)	Hyaluronic acid	12 months	Yes
Pico et al., 2025	Randomized, controlled, double-blind pilot trial	Cryopreserved UC-MSC intra-articular injection	Triamcinolone	12 months	Yes
Ao et al., 2023	Phase I, single-arm	Weekly repeated UC-MSC intra-articular injections	None	3 months	Qualitative only

Table 2. Primary and secondary endpoints at 12 months (extraction dataset)

Study	Comparator	UC-MSC group (n)	Control group (n)	WOMAC pain 12 mo UC-MSC (mean ± SD)	WOMAC pain 12 mo control (mean ± SD)	WOMAC total 12 mo UC-MSC (mean ± SD)	WOMAC total 12 mo control (mean ± SD)	Notes
Matas 2019	Hyaluronic acid	9	8	1.1 ± 1.3	4.3 ± 3.5	4.2 ± 3.9	15.2 ± 11	Numeric table reported
Pico 2025	Triamcinolone	15	15	3.5 ± 2.5	6.5 ± 3.5	16 ± 14	30 ± 13	Estimated from published figure

Supplementary Table S1. Baseline and clinical improvement support (controlled steroid comparator trial) This table summarizes baseline WOMAC values and baseline-to-12-month percent improvement reported in the trial results, supporting durability interpretation.

Study	Arm	Baseline WOMAC pain (mean ± SD)	Baseline WOMAC total (mean ± SD)	WOMAC pain percent improvement at 12 months	WOMAC total percent improvement at 12 months	Notes
Pico 2025	UC-MSC	7.57 ± 2.40	30.07 ± 14.82	53.77%	47.26%	Percent change reported in trial table
Pico 2025	Triamcinolone	7.93 ± 3.69	29.80 ± 17.88	19.3%	-0.2%	Percent change reported in trial table

DISCUSSION

This systematic review and meta-analysis evaluates controlled clinical trial evidence for intra-articular allogeneic UC-MSC therapy in symptomatic knee osteoarthritis, with emphasis on durability of pain improvement at 12 months. Across controlled trials with active comparator injection arms, UC-MSC therapy demonstrated consistently favorable WOMAC pain outcomes relative to comparator injections including hyaluronic acid and intra-articular corticosteroid.

Durability of symptom improvement is a key clinical priority in knee osteoarthritis. Conventional injection-based therapies may provide temporary symptom relief, whereas UC-MSC therapy in controlled trial settings has demonstrated sustained improvements through 12 months. The consistent direction of benefit across comparator subgroups supports clinical relevance and justifies continued evaluation in larger randomized trials.

The observed clinical improvements may reflect joint microenvironment modulation through immunoregulatory and anti-inflammatory effects that influence pain signaling and functional limitation. Osteoarthritis pain is multifactorial and may improve through reductions in synovial inflammation and inflammatory signaling even when structural imaging endpoints do not uniformly demonstrate change over intermediate follow-up. This dissociation between symptomatic outcomes and imaging findings is consistent with broader osteoarthritis research and regenerative medicine trial experience.

Secondary analyses supported the primary findings. Across controlled trials, UC-MSC therapy was associated with lower WOMAC total scores at 12 months compared with comparator injection arms, suggesting broader improvement in overall symptoms and function in addition to pain reduction.

Safety remains essential in allogeneic cell therapy. Across the controlled evidence included here, no clear signal of severe treatment-related adverse events was identified. Early-phase repeated dosing data further support feasibility and tolerability, though larger controlled trials are required to establish rare risk profiles and confirm optimal dosing strategies.

Limitations

This analysis is limited by the small number of controlled trials currently available for quantitative synthesis, variability in comparator injection type, and differences in dosing strategies across studies. Additionally, complete numeric endpoint values were not uniformly reported in all included trials, requiring figure-based extraction for at least one 12-month outcome. Despite these limitations, the controlled study designs and consistent directionality of outcomes across comparator subgroups support a meaningful durability signal warranting further controlled investigation.

Clinical Relevance

Intra-articular corticosteroids and hyaluronic acid are commonly used for knee osteoarthritis symptom management, but many patients experience limited durability of improvement. Controlled trial evidence synthesized here suggests allogeneic UC-MSC therapy may provide greater long-term symptom improvement at 12 months compared with standard injection approaches, supporting potential clinical value for patients seeking longer-lasting outcomes.

Certainty of Evidence (GRADE)

Certainty of evidence for WOMAC pain at 12 months was considered low to moderate due to the limited number of controlled trials, modest sample sizes, and comparator heterogeneity. Despite these limitations, directionality of benefit was consistent across comparator subgroups.

CONCLUSION

Controlled clinical trial evidence suggests intra-articular allogeneic UC-MSC therapy may provide durable improvements in knee osteoarthritis pain at 12 months compared with standard injection-based comparators. While the controlled evidence base remains limited, consistent directionality of benefit supports continued evaluation in larger randomized trials designed to define durability, comparative efficacy, and safety in broader patient populations.

Declarations

AUTHOR CONTRIBUTIONS

Kirk Sanford conceptualized the study, supervised project execution, and contributed to manuscript drafting and final review.
Félix Porras contributed to clinical interpretation, regenerative medicine context, and critical revision of the manuscript.
Fergie Martínez contributed to regenerative protocol interpretation, clinical relevance of outcome measures, and manuscript review and editing.
Hugo Ramos contributed to imaging and diagnostic interpretation and reviewed the manuscript for clinical accuracy.
Janine Zamitiz contributed to patient-centered clinical framing, manuscript review, and editorial refinement.
Carlos Green contributed to technical evaluation of treatment protocols and data organization supporting the analysis.
Edward Ramsay contributed to scientific review, interpretation of clinical lab and biomarker relevance, and manuscript review and editing.
All authors reviewed and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest related to this work.

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No external funding was received for this study.

DATA AVAILABILITY

All data included in this study were derived from published clinical trials and publicly available materials.

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

References

1. Matas J, Orrego M, Amenabar D et al (2019) Umbilical Cord-Derived Mesenchymal Stromal Cells (MSCs) for Knee Osteoarthritis: Repeated MSC Dosing Is Superior to a Single MSC Dose and to Hyaluronic Acid in a Controlled Randomized Phase I/II Trial. Stem Cells Transl Med 8(3):215–224. 10.1002/sctm.18-0053PMID:30592390
2. Pico N et al (2025) Efficacy of a single dose of cryopreserved human umbilical cord mesenchymal stromal cells for the treatment of knee osteoarthritis: a randomized, controlled, double-blind pilot study. Cytotherapy. 10.1016/j.jcyt.2024.09.005

3. Ao Y et al (2023) Repeated intra-articular injections of umbilical cord-derived mesenchymal stem cells for knee osteoarthritis: a phase I, single-arm study. BMC Musculoskelet Disord. 10.1186/s12891-023-06555-y