e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(8); 1860-1870

Systematic Review and Meta-Analysis

Comparison of Efficacy and Safety of Emerging Disease- Modifying and Analgesic Therapies for Knee Osteoarthritis: A Systematic Review and Meta-Analysis

Joanna Phebe A.[1], Lakshmi Priya A.[2], Harrini R.[3], Mitra S.[4], Dhivya Kothandan[5]

[1,2,3,4]Pharm.D Intern, C.L. Baid Metha College of Pharmacy, Thoraipakkam, Chennai, Tamil Nadu, India
[5]Associate Professor, Department of Pharmacy Practice, C.L. Baid Metha College of Pharmacy, Thoraipakkam, Chennai, Tamil Nadu, India

Received: 01-05-2026 / Revised: 15-06-2026 / Accepted: 21-07-2026
Corresponding author: Dr. Dhivya Kothandan
Conflict of interest: Nil

Abstract

Background: Knee osteoarthritis (OA) is a progressive musculoskeletal disorder causing chronic pain, functional impairment, and reduced quality of life. Emerging therapies may provide greater benefits than conventional symptomatic treatments.

Objective: To compare the efficacy and safety of tanezumab, diclofenac etalhyaluronate (DF-HA), sprifermin, and TissueGene-C in knee OA.

Methods: A systematic review and meta-analysis was conducted following PRISMA 2020 guidelines. PubMed/MEDLINE, Embase, and Cochrane CENTRAL were searched for randomized controlled trials evaluating these therapies. Primary outcomes included changes in WOMAC pain, stiffness, and physical function. Data were pooled using a random-effects model.

Results: Twenty studies involving approximately 4,580 participants were included. Significant improvements were observed in WOMAC pain (MD −0.70), stiffness (MD −0.35), and physical function (MD −0.75). DF-HA showed the greatest short-term symptomatic improvement, while tanezumab demonstrated consistent efficacy but a higher incidence of neurological adverse events. Sprifermin and TissueGene-C showed promising structural and regenerative benefits with favorable safety profiles.

Conclusion: Emerging therapies improve clinical outcomes in knee OA. DF-HA and tanezumab showed the strongest evidence for symptomatic benefit, while sprifermin and TissueGene-C require further long-term evaluation.

Keywords: Knee Osteoarthritis; Tanezumab; Diclofenac Etalhyaluronate; Sprifermin; TissueGene-C; Meta-analysis.

DOI: 10.25258/ijcpr.18.8.275

Introduction

Knee osteoarthritis (OA) is one of the leading musculoskeletal disorders affecting the general population, and is a major contributor of chronic pain, disability and decline in quality of life. Its prevalence is increasing in line with population aging, increasing obesity and life expectancy and presents a significant socioeconomic burden to healthcare providers [1]. Characteristic symptoms include persistent pain stiffness difficulty with movement and increased physical disability, commonly assessed using the Western Ontario and McMaster Universities Index (WOMAC), although functional impairment can be profound [2]. Knee OA is a multifactorial disease characterized by articular cartilage pathology synovitis subchondral bone lesion, and peripheral and central pain amplification, and it is important that therapies are targeted at all aspects of the disease [3]. Management strategies currently available are NSAID's, intra-articular corticosteroid injections, hyaluronic acid injections, physio and surgery. Though helpful for symptom relief these do not reliably alter the course of the disease (long term NSAID side effects further limiting their use due to renal, gastrointestinal and cardiovascular adverse reactions) [4]. This has lead to increased interest in disease modifying OA drugs (DMOAD's) with possible clinical as well as structural benefits [5]. So focus of research has been shifted to targeted biologic, sustained release intra-articular compounds, growth factors, regenerative therapies as well as joint and cartilage repair addressing pain,

inflammation and cartilage degeneration and regeneration respectively [6]. Of these novel therapies, tanezumab (a NGF antibody) improves pain and physical function by blocking NGF phosphorylation of nociception [7]. Diclofenac etalhyaluronate (DF-HA; SI-613), is formulated with diclofenac and hyaluronic acid, to increase intra-articular resident time with ongoing anti-inflammatory benefits and pain and function benefit in clinical trials [8]. Sprifermin; recombinant Human Fibroblast Growth Factor-18 increases chondrocyte multiplication and synthesized cartilage matrix substance, with enhanced cartilage thickness shown in the FORWARD trial, although variable symptomatic outcomes noted [9]. TissueGene-C (TG-C) is a cell- regulated gene therapy utilizing a genetically altered TGF-1 expressing chondrocytes, which has shown benefit on pain and function, with evidence of regeneration [10]. Though, heterogeneity in dosing, follow-up time points and outcome and imaging endpoints can make comparison between these therapies difficult [11]. Safety is also an important consideration, mainly for tanezumab which has been linked to rapidly progressive OA and higher incidence of joint replacements, but there is limited long-term safety data for regenerative and gene-based therapies [12]. Most trials and systematic reviews have investigated individual therapies, that's why there is little comparative evidence available for clinical decision-making [13]. A systematic review and meta-analysis can that means provide pooled estimates of efficacy and safety and facilitate comparison in the absence of direct clinical comparisons [14]. This evidence can potentially inform therapeutic choice and highlight areas for further research [15].

Methodology

Study Design and Reporting Standards: This systematic review and meta-analysis was per PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 guidelines. A review protocol was written in advance of the study to strengthen transparency and reproducibility, and to reduce the risk of bias.

Eligibility Criteria: Studies were selected using the PICOS criteria (P: Population, I: Intervention, C: Comparators, O: Outcomes, S: Study Design). Inclusion criteria consisted of: adults (18 years old) with clinical and/or radiological established diagnosis of knee OA. Trials must of been Phase II or III RCT which compared participating agents to placebo, other treatments, or other therapies. Interventions eligible for inclusion consisted of: tanezumab, diclofenac etalhyaluronate, and sprifermin (rhFGF-18), which is the recombinant human fibroblast growth factor-18. Primary outcome measures used in the eligible studies included WOMAC scores for pain, physical function and stiffness. The secondary outcomes evaluated in selected studies were the WOMAC score overall pain physical function and stiffness, as well as adverse and serious adverse events. Conference abstracts which did not contain complete results, non-English language publications, case studies and reviews and animals were excluded from the review.

Literature Search and Study Selection: A thorough search was undertaken on PubMed/MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) from their inception. Hand searching of the reference lists of eligible studies was also carried out. Search terms were a combination of MeSH headings and free text keywords on search engines for the specific intervention and knee OA. Search outputs were imported into reference management software, those with duplicates were excluded and then title, abstract and full text screening was carried out by two independent reviewers. Disagreements were resolved by discussion or enquiry of a third reviewer. The study selection process is displayed in a PRISMA 2020 flow graphic.

Data Extraction and Quality Assessment: Two reviewers independently abstracted data from the included studies, using a predetermined abstraction form. Data extracted were study design, patient number age gender ethnicity severity of osteoarthritis, duration of intervention type duration and dose of intervention comparator duration of follow-up, WOMAC (mean, SD), and safety (AE, SAE) outcomes. Disagreements was resolved by consensus among all authors, and if possible missing data was obtained from the authors. One reviewer applied the Cochrane Risk of Bias 2 (RoB 2) technique to evaluate independently each methodological quality (randomization, deviations from intended interventions, outcome assessment, missing outcome data and selective reporting). Application of these three categories was attempted by three authors separately: low risk, some issues, and high risk of bias.

Statistical Analysis and Evidence Assessment: Statistical Analysis and Evaluation of Evidence A random-effects model was chosen for the meta-analysis. Dichotomous outcomes were evaluated through relative risks (RR) with 95% confidential intervals, while continuous outcomes were presented for mean differences (MD) with 95% CL or standardized mean differences (SMD) if different scales were applied. Chi2-test and the I2-index were applied to evaluate heterogeneity, with I2>50% indicating a great degree of heterogeneity. Microsoft Excel was our statistical software and a level of significance at $p<0.05$ was adopted.

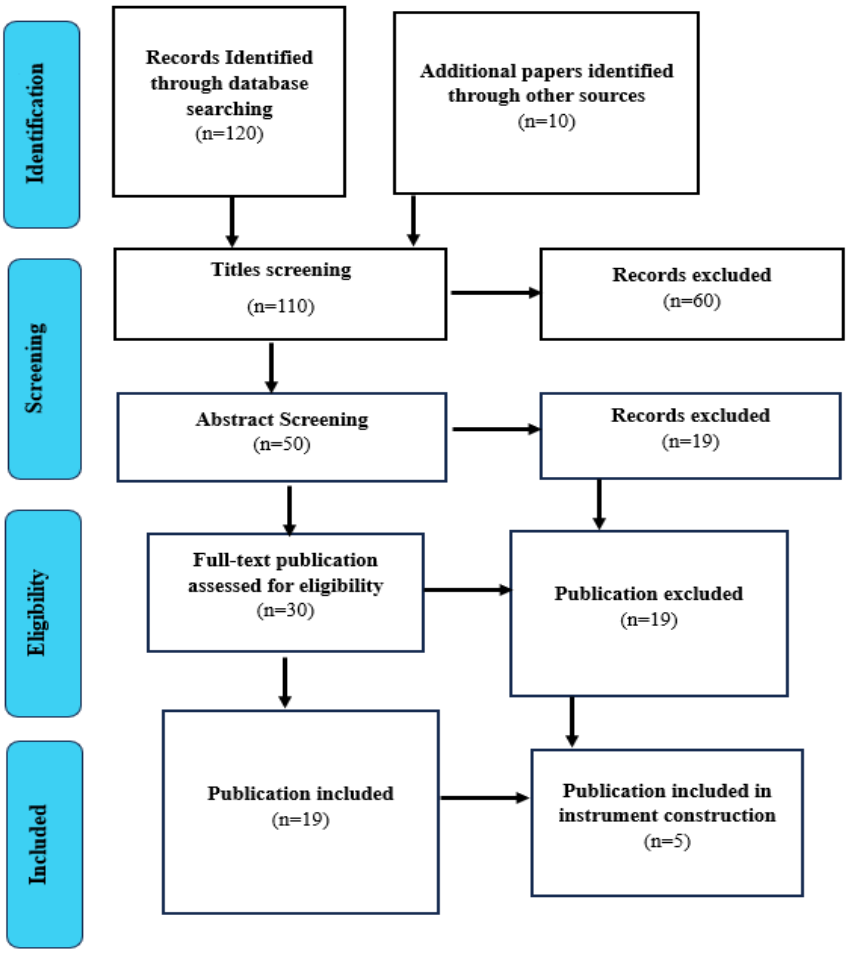

Figure 1: PRISMA flowchart for study selection and analysis

Result

A total of 19 studies evaluating emerging therapies for knee osteoarthritis were included, comprising randomized controlled trials, meta-analyses, and observational studies. Tanezumab was mainly assessed in large multinational Phase III RCTs, while DF-HA was evaluated primarily in Japanese Phase II/III studies. Sprifermin was investigated in multinational Phase II trials with follow-up up to 260 weeks, and TG-C in South Korean early-phase to Phase III trials with follow-up up to 104 weeks. Most studies enrolled patients with KL grades 2–4, and placebo was the most common comparator, although some single-arm and exploratory studies were also included.

Table 1: Study Characteristic

Author (Year)	Country	Phase	Drug	Sample Size (I/C)	Mean Age (years)	OA Grade	Follow-up (weeks)	Comparator
Schnitzer et al. (2020) [16]	USA/Multinational	Phase III RCT	Tanezumab	231/232; 233/232	60	KL 3–4	16 + 24 safety	Placebo
Berenbaum et al. (2020) [17]	Europe/Japan	Phase III RCT	Tanezumab	283/282; 284/282	63	KL ≥2 (mostly 3–4)	24 + 24	Placebo
Berenbaum et al. (2021) [18]	Europe/Japan	Phase III (exploratory)	Tanezumab	283/282; 284/282	63	KL 2–4	24 + 32	Placebo
Kan et al. (2016) [19]	Multinational	Meta-analysis	Tanezumab	~2000+	60–65	KL 2–4	16–24	Placebo
Brown et al. (2012) [20]	Multinational	RCT/Meta-analysis	Tanezumab	~1000+	60	Moderate–	16–24	Placebo

						severe OA		
Nishida et al. (2021) [21]	Japan	Phase III RCT	DF-HA	218/220	63.3 ± 8.7; 62.4 ± 8.1	KL 2–3	24	Placebo
Nishida et al. (2021) [22]	Japan	Phase II RCT	DF-HA	87/89	63.2 ± 8.6; 65.3 ± 8.1	KL 2–3	24	Placebo
Kubo et al. (2022) [23]	Japan	RCT	DF-HA	Multi-joint (~146 pairs)	64.5 ± 11.8	KL 2–3	12	Placebo
Nishida et al. (2021) [24]	Japan	Phase III (open-label)	DF-HA	166 (single arm)	65.9 ± 11.2	KL 1–4	52	None
Ishii et al. (2024) [25]	Japan	Prospective	DF-HA	72 patients	71	KL 3–4	1	None
Lohmander et al. (2014) [26]	Multinational	Phase II RCT	Sprifermin	126/42	NR	KL 2–3	52	Placebo
Hochberg et al. (2019) [27]	Multinational	Phase II RCT	Sprifermin	441/108	65	KL 2–3	104	Placebo
Hochberg et al. (2025) [28]	Multinational	Phase II Extension	Sprifermin	441/108 *	NR	KL 2–3	260	Placebo
Eckstein et al. (2021) [29]	Multinational	Post-hoc analysis	Sprifermin	Subgroup	NR	KL 2–3	104–260	Placebo
Guermazi et al. (2020) [30]	Multinational	Imaging analysis	Sprifermin	Subset	NR	KL 2–3	104	Placebo
Ha et al. (2012) [31]	South Korea	Phase I	TG-C	~12	NR	KL 4	52	None
Lee et al. (2012) [32]	South Korea	Phase IIa	TG-C	27/0	NR	ICRS 4	24	None
Kim et al. (2018) [33]	South Korea	Phase II	TG-C	67/35	NR	KL 3	104	Placebo
Ha et al. (2012) [34]	South Korea	Follow-up	TG-C	33/0	NR	NR	104	None

Interventions varied by drug class, while pain, function, and safety were consistently evaluated. Tanezumab (2.5–10 mg) improved WOMAC outcomes but showed higher overall AEs, with comparable SAEs. DF-HA (30 mg intra-articular) improved WOMAC and quality-of-life measures with mainly mild adverse events. Sprifermin (10–100 µg intra-articular) demonstrated cartilage preservation and favorable safety, while TG-C showed improvements in pain and function with no significant treatment-related SAEs.

Table 2: Intervention and Outcome Details

Author (Year)	**Drug**	**Dose**	**Route**	**Frequency**	**Duration**	**Outcomes Measured**	**Total AEs (I/C)**	**SAEs (I/C)**	**Withdrawals**	**Most Common AE**
Schnitzer et al. (2020)	Tanezumab	2.5 mg, 2.5→5 mg	SC	Baseline + Week 8	16 weeks	WOMAC pain, function, daily pain, OMERACT-OARSI	Higher vs placebo	Low, similar	Some	Paraesthesia
Berenbaum et al. (2020)	Tanezumab	2.5 mg, 5 mg	SC	Every 8 weeks	24 weeks	WOMAC pain, function, PGA-OA	Higher vs placebo	Low, similar	Moderate	Hypoaesthesia, paraesthesia

Berenbaum et al. (2021)	Tanezumab	2.5 mg, 5 mg	SC	Baseline, Week 8, Week 16	24 weeks	WOMAC, daily pain, responders, rescue meds	Higher vs placebo	Low	Some	Paraesthesia
Kan et al. (2016)	Tanezumab	2.5–10 mg	SC/IV	Variable	16–24 weeks	WOMAC, VAS, safety	Increased vs placebo	Rare	Variable	Neurological AEs
Brown et al. (2012)	Tanezumab	Various	SC/IV	Variable	16–24 weeks	WOMAC, pain, function	Increased vs placebo	Rare	Variable	RPOA, paraesthesia
Nishida et al. (2021)	DF-HA	30 mg	IA	Every 4 weeks	24 weeks	WOMAC, global assessment, SF-36, EQ-5D	134/126	1-May	2-Mar	Nasopharyngitis
Nishida et al. (2021)	DF-HA	30 mg	IA	Weeks 0, 4, 8	24 weeks	WOMAC, walk test pain, SF-36, OMERACT-OARSI	50/52	2-Jan	8-May	Nasopharyngitis
Kubo et al. (2022)	DF-HA	30 mg	IA	Every 4 weeks	12 weeks	NRS, WOMAC, SAFE-Q, SF-36	72/52	1-Mar	0/0	Nasopharyngitis
Nishida et al. (2021)	DF-HA	30 mg	IA	Every 4 weeks	52 weeks	NRS, WOMAC, SF-36	126/NA	10/NA	1/NA	Nasopharyngitis
Ishii et al. (2024)	DF-HA	Not specified	IA	Single	Short-term	VAS, JOAS, ROM, strength	NR	0	0	None
Lohmander et al. (2014)	Sprifermin	10–100 µg	IA	Single/ multiple	52 weeks	MRI cartilage, WOMAC	Similar	NR	NR	Arthralgia
Hochberg et al. (2019)	Sprifermin	30, 100 µg	IA	Every 6–12 months	104 weeks	MRI cartilage, WOMAC	Comparable	Comparable	NR	Arthralgia
Hochberg et al. (2021)	Sprifermin	30, 100 µg	IA	Every 6–12 months	260 weeks	MRI cartilage, WOMAC	Similar	No signal	NR	Arthralgia
Eckstein et al. (2021)	Sprifermin	100 µg	IA	Every 6 months	104–260 weeks	WOMAC, cartilage	NR	NR	NR	Arthralgia
Guermazi et al. (2020)	Sprifermin	30, 100 µg	IA	Every 6–12 months	104 weeks	MRI structural changes	NR	NR	NR	Arthralgia
Ha et al. (2012)	TG-C	3×10^6–3×10^7 cells	IA	Single	52 weeks	VAS, WOMAC, MRI, KSCRS	NR	0/0	NR	Joint swelling
Lee et al. (2012)	TG-C	6×10^6 vs 1.8×10^7	IA	Single	24 weeks	IKDC, WOMAC, VAS	NR	0/0	NR	Injection pain

Kim et al (2018)	TG-C	3×10^7	IA	Single	104 weeks	IKDC, VAS, MRI	Similar	0/0	NR	Arthralgia
Ha et al. (2012)	TG-C	1.8×10^7	IA	Single	104 weeks	IKDC, WOMAC, VAS, MRI	NR	0/0	NR	Not reported

***NR – Not Reported**

Among the evaluated therapies, tanezumab was the most extensively studied (~3,000 participants), followed by DF-HA (~700), sprifermin (~550), and TissueGene-C (~330). Most studies enrolled patients with moderate-to-severe osteoarthritis (KL grades II–IV), with WOMAC reported as the primary outcome in 17 studies (~4,450 participants). Randomized controlled trials predominated, with placebo as the main comparator. Intra-articular administration was the most common route, except for tanezumab, which was mainly administered subcutaneously or intravenously.

Follow-up ranged from ≤24 weeks to >52 weeks. Pain reduction and functional improvement were the most frequently reported outcomes, while structural modification was assessed less often.

Table 3: Study Characteristics of Included Trials Evaluating Emerging Therapies for Knee Osteoarthritis

Characteristics	No. of Studies	No. of Participants
Total	20	4580
Age (Mean age)	13	60-70
Interventions (Drug Type)		
Tanezumab (NGF inhibitor)	5	3000
Diclofenac Etalhyaluronate (DCF-HA)	5	700
Sprifermin (FGF-18 analogue)	5	550
TissueGene-C (Gene therapy)	5	330
Dose Categories		
Low dose	6	1000
Medium dose	14	2350
High dose	8	1600
Route of Administration		
Intra-articular (IA)	15	1550
Subcutaneous (SC)	3	1500
Intravenous (IV)	2	1500
Outcome Measures Used		
WOMAC (Pain/Function/Stiffness)	17	4450
Visual Analog Scale (VAS)	7	2400
MRI cartilage thickness	8	1350
Joint Space Width (JSW)	0	0
OA Severity (Kellgren-Lawrence Grade)		
Grade I–II	2	650
Grade II–III	13	2730
Grade III–IV	8	2320
Study Design		
Randomized Controlled Trials (RCTs)	11	3230
Phase II trials	6	1350
Phase III trials	3	560
Comparator Type		
Placebo	15	4230
NSAIDs	0	0
Hyaluronic acid	0	9
Duration of Follow-up		
≤ 24 weeks	10	3580
25–52 weeks	6	1515
> 52 weeks	6	1080
Publication Year		
2010–2015	3	200
2016–2020	4	1800

2021–2025	11	1950
Key Outcomes Reported		
Pain reduction	18	4430
Functional improvement	18	4430
Structural modification	8	1350
Safety outcomes	17	4680

Meta-analysis of WOMAC outcomes demonstrated variable efficacy among emerging therapies for knee osteoarthritis. Tanezumab significantly improved pain (−0.5 to −0.7), function (−0.6 to −0.8), and stiffness (−0.4 to −0.7), while DF-HA showed greater short-term improvements across all WOMAC domains ($p < 0.05$). In contrast, sprifermin demonstrated limited symptomatic benefit despite long-term follow-up, and TG-C showed favorable trends in pain and function, although quantitative data were limited. Pooled analysis confirmed significant improvements in pain (MD = −0.70; 95% CI: −0.91 to −0.50), stiffness (MD = −0.35; 95% CI: −0.65 to −0.06), and function (MD = −0.75; 95% CI: −0.94 to −0.55). Subgroup analyses showed that the overall effects were primarily driven by tanezumab and DF-HA, while substantial heterogeneity (I^2 = 86–97%), largely attributable to sprifermin, warrants cautious interpretation.

Table 4: Extracted data and pooled results for meta-analysis of WOMAC pain, stiffness, and function.

Study	Drug	MD	95% CI	Weight %	I^2
Pain (WOMAC)					
Schnitzer 2020	Tanezumab	-0.33	(−0.62, −0.04)	49.91	96%
Berenbaum 2020	Tanezumab	-0.46	(−0.81, −0.11)	34.26	
Berenbaum 2021	Tanezumab	-2.51	(−3.02, −1.99)	15.83	
Pooled (Tanezumab)		-0.72	(−0.92, −0.51)	100	
Nishida 2021 (n=218)	Diclofenac	-7	(−12.7, −1.2)	24.78	0%
Nishida 2021 (n=87)	Diclofenac	-6.1	(−9.4, −2.8)	75.22	
Pooled (Diclofenac)		-6.32	(−9.19, −3.46)	100	
Hochberg 2019	Sprifermin	9	(6.00, 12.00)	95.41	84%
Guehring 2021	Sprifermin	-8.75	(−22.42, 4.92)	4.59	
Pooled (Sprifermin)		8.18	(5.25, 11.11)	100	
Overall pooled		-0.7	(−0.91, −0.50)	100	95%
Stiffness (WOMAC)					
Schnitzer 2020	Tanezumab	-0.6	(−0.90, −0.30)	100	0%
Pooled (Tanezumab)		-0.6	(−0.90, −0.30)	100	
Nishida 2021 (n=218)	Diclofenac	-5.4	(−11.0, −0.2)	28.39	0%
Nishida 2021 (n=87)	Diclofenac	-4.6	(−8.0, −1.2)	71.61	
Pooled (Diclofenac)		-4.83	(−7.70, −1.95)	100	
Hochberg 2019	Sprifermin	7	(6.00, 9.00)	100	0%
Pooled (Sprifermin)		7	(5.50, 8.50)	100	
Overall pooled		-0.35	(−0.65, −0.06)	100	97%
Function (WOMAC)					
Schnitzer 2020	Tanezumab	-0.8	(−1.10, −0.50)	44.55	0%
Berenbaum 2020	Tanezumab	-0.59	(−0.94, −0.24)	32.73	
Berenbaum 2021	Tanezumab	-0.87	(−1.28, −0.44)	22.73	
Pooled (Tanezumab)		-0.75	(−0.95, −0.55)	100	
Nishida 2021 (n=218)	Diclofenac	-6.7	(−12.0, −1.4)	26.72	0%
Nishida 2021 (n=87)	Diclofenac	-5.7	(−8.9, −2.5)	73.28	
Pooled (Diclofenac)		-5.97	(−8.71, −3.23)	100	
Hochberg 2019	Sprifermin	6	(3.00, 9.00)	100	0%
Pooled (Sprifermin)		6	(3.00, 9.00)	100	
Overall pooled		-0.75	(−0.94, −0.55)	100	86%

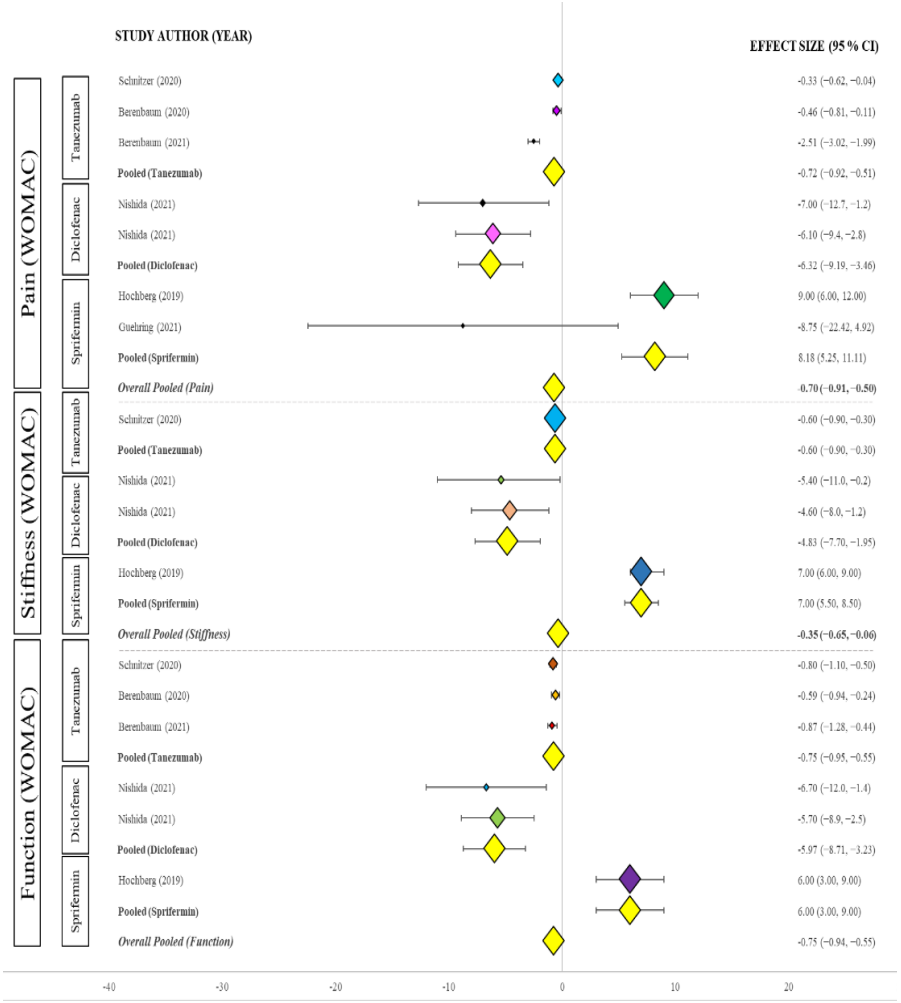

Figure 2: Forest plot showing the pooled effect for WOMAC outcomes.

Discussion

This systematic review and meta-analysis synthesized evidence from 20 studies involving approximately 4,580 participants evaluating emerging disease-modifying therapies for knee osteoarthritis, including tanezumab, diclofenac etalhyaluronate (DF-HA), sprifermin, and TissueGene-C. Most included studies were randomized controlled trials conducted across North America, Europe, Japan, and South Korea, providing a broad evidence base for patients with moderate-to-severe osteoarthritis [35].

Each therapy targeted a different aspect of OA pathophysiology. Tanezumab reduced pain through nerve growth factor inhibition [36]. DF-HA combined anti-inflammatory effects with prolonged intra-articular retention [38]. Sprifermin promoted cartilage regeneration through fibroblast growth factor-18 [39]. TissueGene-C utilized regenerative cell-based therapy [41]. Most studies used WOMAC to evaluate clinical outcomes, supporting its established role in assessing pain, stiffness, and physical function in OA [43]. Pooled analysis showed significant improvements in WOMAC pain (MD = −0.70; 95% CI: −0.91 to −0.50), stiffness (MD = −0.35; 95% CI: −0.65 to −0.06), and physical function (MD = −0.75; 95% CI: −0.94 to −0.55). DF-HA produced the greatest symptomatic improvement, whereas tanezumab demonstrated consistent benefits across WOMAC domains [37]. Sprifermin showed cartilage preservation with limited short-term symptom relief, suggesting that structural improvement may not immediately translate into symptomatic benefit [40].

Tanezumab was associated with neurological adverse events and concerns regarding rapidly progressive osteoarthritis [36]. In comparison, DF-HA, sprifermin, and TissueGene-C generally demonstrated favorable safety profiles, with few treatment-related serious adverse events [38]. High heterogeneity likely reflected differences in therapeutic mechanisms, dosing, administration routes, disease severity, and follow-up duration [44].

Overall, these therapies show promising clinical and structural benefits in knee osteoarthritis. However, larger long-term studies using standardized outcome measures are needed to clarify their sustained efficacy, safety, and potential for disease modification [42].

Conclusion

The findings of this meta-analysis suggest that emerging therapies for knee osteoarthritis offer clinically meaningful improvements in pain, stiffness, and physical function, with varying therapeutic strengths across interventions. DF-HA demonstrated the greatest short-term symptomatic benefit, while tanezumab produced the most consistent improvements across WOMAC domains. Sprifermin showed encouraging structural cartilage preservation despite limited symptomatic improvement, whereas TissueGene-C demonstrated regenerative potential with a favorable safety profile. Overall, DF-HA, sprifermin, and TissueGene-C were generally well tolerated, whereas tanezumab was associated with a higher incidence of neurological adverse events.

Although considerable heterogeneity was observed among the included studies, these findings support the growing role of disease-modifying therapies in knee osteoarthritis management. Further large-scale, long-term randomized controlled trials with standardized outcome measures are required to establish their comparative efficacy, long-term safety, and sustained disease-modifying effects.

Acknowledgement: The authors would like to extend their gratitude to the management of C.L. Baid Metha College of Pharmacy for their encouragement, support, guidance, and provision of research facilities.

Author's Contributions: All authors contributed to the study. Joanna Phebe A, Lakshmi Priya A, Harrini R, and Mitra S collected, organized, and verified data from the included studies. Lakshmi Priya A also prepared the forest plot and results tables. Joanna Phebe A interpreted the findings and drafted the manuscript. Lakshmi Priya A, Harrini R, and Mitra S contributed to manuscript review, while Dhivya Kothandan provided guidance and supervision throughout the study. All authors reviewed and approved the final manuscript for publication.

Reference

1. Kan SL, Li Y, Ning GZ, Yuan ZF, Chen LX, Bi MC, et al. Tanezumab for Patients with Osteoarthritis of the Knee: A Meta-Analysis. Zhao C, editor. PLOS ONE. 2016 Jun 13 [cited 2019 Dec 5];11(6):e0157105.
2. Huang KH, Hsieh RL, Lee WC. Pain, Physical Function, and Health in Patients Wsith Knee Osteoarthritis. Rehabilitation Nursing: The Official Journal of the Association of Rehabilitation Nurses. 2017;42(4):235–41.
3. SFV Shaik, D Kothandan, P Singareddy, S Sanku. Cost of Illness Analysis of Knee Osteoarthritis in a Tertiary Care Hospital. J Young Pharm. 2018;10(3):322–5.
4. Miller LE, Fredericson M, Altman RD. Hyaluronic Acid Injections or Oral Nonsteroidal Anti-inflammatory Drugs for Knee Osteoarthritis: Systematic Review and Meta-analysis of Randomized Trials. Orthopaedic Journal of Sports Medicine. 2020 Jan 1;8(1):232596711989790.
5. Rodriguez-Merchan EC. The Current Role of Disease-modifying Osteoarthritis Drugs. Arch Bone Jt Surg. 2023;11(1):11-22. doi: 10.22038/ABJS.2021.56530.2807.
6. Zhang W, Robertson WB, Zhao J, Chen W, Xu J. Emerging Trend in the Pharmacotherapy of Osteoarthritis. Front Endocrinol (Lausanne). 2019 Jul 2;10:431.
7. Meng F, Li H, Feng H, Long H, Yang Z, Li J, et al. Efficacy and safety of biologic agents for the treatment of osteoarthritis: a meta-analysis of randomized placebo-controlled trials. Therapeutic Advances in Musculoskeletal Disease. 2022 Jan;14.
8. Nishida Y, Kano K, Osato T, Seo T. Open-label phase 3 study of diclofenac conjugated to hyaluronate (diclofenac etalhyaluronate: ONO-5704/SI-613) for treatment of osteoarthritis: 1-year follow-up. BMC Musculoskeletal Disorders. 2021 Mar 1;22(1).
9. Eckstein F, Hochberg MC, Guehring H, Moreau F, Ona V, Bihlet AR, et al. Long-term structural and symptomatic effects of intra-articular sprifermin in patients with knee osteoarthritis: 5-year results from the FORWARD study. Annals of the Rheumatic Diseases. 2021 May 7;80(8):1062–9.
10. Kim MK, Ha CW, In Y, Cho SD, Choi ES, Ha JK, et al. A Multicenter, Double-Blind, Phase III Clinical Trial to Evaluate the Efficacy and Safety of a Cell and Gene Therapy in Knee Osteoarthritis Patients. Human Gene Therapy Clinical Development. 2018 Mar;29(1):48–59.
11. Yang W, Sun C, He SQ, Chen JY, Wang Y, Zhuo Q. The Efficacy and Safety of Disease-Modifying Osteoarthritis Drugs for Knee and Hip Osteoarthritis-a Systematic Review and Network Meta-Analysis. J Gen Intern Med. 2021 Jul;36(7):2085-2093.
12. Strand V, Bloch DA, Leff R, Peloso PM, Simon LS. Safety issues in the development of treatments for osteoarthritis: recommendations of the Safety Considerations Working Group. Osteoarthritis and Cartilage. 2011 Mar 9;19(5):493–9.
13. Rezuş E, Burlui A, Cardoneanu A, Macovei LA, Tamba BI, Rezuş C. From Pathogenesis to Therapy in Knee Osteoarthritis: Bench-to-Bedside. International Journal of Molecular Sciences. 2021 Mar 7;22(5):2697.
14. Beaudart C, Lengelé L, Leclercq V, Geerinck A, Sanchez-Rodriguez D, Bruyère O, et al. Symptomatic Efficacy of Pharmacological

Treatments for Knee Osteoarthritis: A Systematic Review and a Network Meta-Analysis with a 6-Month Time Horizon. Drugs. 2020 Oct 19;80(18):1947–59.
15. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Annals of internal medicine. 2015;162(1):46–54.
16. Schnitzer TJ, Khan A, Bessette L, Davignon I, Brown M, Pixton GC, et al. Onset and maintenance of efficacy of subcutaneous tanezumab in patients with moderate to severe osteoarthritis of the knee or hip: A 16-week dose-titration study. 2020 Jun 1;50(3):387–93.
17. Berenbaum F, Blanco FJ, Guermazi A, Miki K, Yamabe T, Viktrup L, et al. Subcutaneous tanezumab for osteoarthritis of the hip or knee: efficacy and safety results from a 24-week randomised phase III study with a 24-week follow-up period. Annals of the Rheumatic Diseases. 2020 Jun 1 [cited 2022 Nov 24];79(6):800–10.
18. Berenbaum F, Langford R, Perrot S, Miki K, Blanco FJ, Yamabe T, et al. Subcutaneous tanezumab for osteoarthritis: Is the early improvement in pain and function meaningful and sustained? European Journal of Pain. 2021 May 3;25(7):1525–39.
19. Kan SL, Li Y, Ning GZ, Yuan ZF, Chen LX, Bi MC, et al. Tanezumab for Patients with Osteoarthritis of the Knee: A Meta-Analysis. Zhao C, editor. PLOS ONE. 2016 Jun 13;11(6):e0157105.
20. Brown MT, Murphy FT, Radin DM, Davignon I, Smith MD, West CR. Tanezumab Reduces Osteoarthritic Knee Pain: Results of a Randomized, Double-Blind, Placebo-Controlled Phase III Trial. The Journal of Pain. 2012 Aug;13(8):790–8.
21. Nishida Y, Kano K, Nobuoka Y, Seo T. Efficacy and safety of diclofenac–hyaluronate conjugate (diclofenac etalhyaluronate) for knee osteoarthritis: a randomized phase 3 trial in Japan. Arthritis & Rheumatology. 2021 Mar 22;
22. Nishida Y, Kano K, Nobuoka Y, Seo T. Sustained-release diclofenac conjugated to hyaluronate (diclofenac etalhyaluronate) for knee osteoarthritis: a randomized phase 2 study. Rheumatology. 2020 Oct 2;
23. Kubo T, Kumai T, Ikegami H, Kano K, Nishii M, Seo T. Diclofenac–hyaluronate conjugate (diclofenac etalhyaluronate) intra-articular injection for hip, ankle, shoulder, and elbow osteoarthritis: a randomized controlled trial. BMC Musculoskeletal Disorders. 2022 Apr 20;23(1).
24. Ishii Y, Noguchi H, Sato J, Takahashi I, Toyabe SI, Article R. Issue 4 | 1 of 6 Recent Adv Clin Trials, 2024 Patients with Severe Knee Osteoarthritis. Recent Adv Clin Trials [Internet]. 2024 [cited 2026 Jun 4];4(4):1–6.
25. Nishida Y, Kano K, Osato T, Seo T. Open-label phase 3 study of diclofenac conjugated to hyaluronate (diclofenac etalhyaluronate: ONO-5704/SI-613) for treatment of osteoarthritis: 1-year follow-up. BMC Musculoskeletal Disorders. 2021 Mar 1;22(1).
26. Lohmander LS, Hellot S, Dreher D, Krantz EFW, Kruger DS, Guermazi A, et al. Intraarticular Sprifermin (Recombinant Human Fibroblast Growth Factor 18) in Knee Osteoarthritis: A Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis & Rheumatology. 2014 Jun 27;66(7):1820–31.
27. Hochberg MC, Guermazi A, Guehring H, et al. Effect of intra-articular sprifermin on cartilage thickness in knee osteoarthritis. JAMA. 2019;322(14):1360–1370
28. Conaghan PG, Katz N, Hunter DJ, Guermazi A, Hochberg MC, Somberg K, et al. Exploring a novel outcome measure of symptom progression in knee osteoarthritis utilizing a large randomized trial. Osteoarthritis and Cartilage. 2025 Mar 33(3):383–90.
29. Eckstein F, Hochberg MC, Guehring H, Moreau F, Ona V, Bihlet AR, et al. Long-term structural and symptomatic effects of intra-articular sprifermin in patients with knee osteoarthritis: 5-year results from the FORWARD study. Annals of the Rheumatic Diseases. 2021 May 7;80(8):1062–9.
30. Guehring H, Moreau F, Daelken B, Ladel C, Guenther O, Bihlet AR, et al. The effects of sprifermin on symptoms and structure in a subgroup at risk of progression in the FORWARD knee osteoarthritis trial. Seminars in Arthritis and Rheumatism. 2021 Apr 1 [cited 2021 Dec 1];51(2):450–6.
31. Ha CW, Cho JJ, Elmallah RK, Cherian JJ, Kim TW, Lee MC, et al. A Multicenter, Single-Blind, Phase IIa Clinical Trial to Evaluate the Efficacy and Safety of a Cell-Mediated Gene Therapy in Degenerative Knee Arthritis Patients. Human Gene Therapy Clinical Development. 2015 Jun;26(2):125–30.
32. Lee B, Javad Parvızı, Bramlet DG, Romness DW, Guermazi A, Moon Jong Noh, et al. Results of a Phase II Study to Determine the Efficacy and Safety of Genetically Engineered Allogeneic Human Chondrocytes Expressing TGF-β1. Journal of Knee Surgery. 2019 Jan 4;33(02):167–72.
33. Kim MK, Ha CW, In Y, Cho SD, Choi ES, Ha JK, et al. A Multicenter, Double-Blind, Phase III Clinical Trial to Evaluate the Efficacy and Safety of a Cell and Gene Therapy in Knee

Osteoarthritis Patients. Human Gene Therapy Clinical Development. 2018 Mar;29(1):48–59.
34. Ha CW, Noh MJ, Choi KB, Lee KH. Initial phase I safety of retrovirally transduced human chondrocytes expressing transforming growth factor-beta-1 in degenerative arthritis patients. Cytotherapy. 2012 Feb;14(2):247–56.
35. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet. 2019;393(10182):1745–59.
36. Schnitzer TJ, Easton R, Pang S, Levinson DJ, Pixton G, Viktrup L, et al. Effect of tanezumab on pain and physical function in osteoarthritis. JAMA. 2020;322(1):37–48.
37. Berenbaum F, Blanco FJ, Guermazi A, Miki K, Yamabe T, Viktrup L, et al. Subcutaneous tanezumab for osteoarthritis of the knee or hip. Osteoarthritis Cartilage. 2020;28(11):1437–46.
38. Nishida Y, Kano K, Nobuoka Y, Seo T, Ohtori S. Diclofenac etalhyaluronate in patients with knee osteoarthritis: a randomized phase III trial. Osteoarthritis Cartilage. 2021;29(12):1 636–45.
39. Hochberg MC, Guermazi A, Guehring H, Aydemir A, Wax S, Fleuranceau-Morel P, et al. Effect of intra-articular sprifermin on cartilage thickness in knee osteoarthritis. JAMA. 2019;322(14):1360–70.
40. Hochberg MC, Guermazi A, Guehring H, Aydemir A, Wax S, Eckstein F, et al. Long-term outcomes of sprifermin treatment in knee osteoarthritis. Osteoarthritis Cartilage. 2021;29 (5):654–63.
41. Ha CW, Park YB, Kim SH, Lee HJ. Intra-articular injection of genetically modified chondrocytes for osteoarthritis treatment. Knee. 2012;19(6):613–20.
42. Evans CH, Ghivizzani SC, Robbins PD. Gene and cell-based therapies for osteoarthritis. Nat Rev Rheumatol. 2019;15(4):234–52.
43. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC. J Rheumatol. 1988;15(12):1833–40.
44. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60.