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Preventative and Disease-Modifying Investigations for Osteoarthritis Management Are Significantly Underrepresented in the Clinical Trial Pipeline: A 2020 Review

Nicholas N. DePhillipo, PhD, ATC, OTC[1]
Zachary S. Aman, BA[2]
Travis J. Dekker, MD[3]
Gilbert Moatshe, MD, PhD[1,4]
Jorge Chahla, MD, PhD[5]
Robert F. LaPrade, MD, PhD[6]

[1] Oslo Sports Trauma Research Center, Oslo, Norway
[2] Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, USA
[3] Eglin Air Force Base, FL, USA
[4] Ulleval University Hospital, Oslo, Norway
[5] Midwest Orthopedics at Rush, Chicago, IL, USA
[6] Twin Cities Orthopedics, Edina, MN, USA

Investigation performed at Twin Cities Orthopedics, Edina, MN, USA

Running title: Clinical Trial Pipeline for OA

Corresponding Author:

Robert F. LaPrade MD, PhD

Twin Cities Orthopedics

4010 W. 65th St, Edina, MN 55435

Laprademdphd@gmail.com

(952) 456-7000

Abstract

Purpose: to conduct a review of active U.S. based clinical trials investigating prevention, symptom resolution, and disease-modifying therapies for osteoarthritis.

Methods: A review of currently active clinical trials for OA using data obtained from ClinicalTrials.gov database as of August 2020 was conducted. Inclusion criteria were active studies registered in the U.S. that involved the prevention, symptomatic resolution, or disease-modification of OA. Descriptive statistics were recorded and summarized.

Results: 3859 clinical trials were identified and 311 were included in final analysis. Of the currently active trials, 89% (n=275) targeted symptom resolution in patients with existing OA, 6% (n=19) targeted OA disease-modifying therapeutics, and 5% (n=16) targeted the prevention of OA in high-risk patients ($P < .001$). Primary interventions included medical devices (44%, n=137), pharmaceutical drugs (14%, n=42), surgical procedures (14%, n=42), cellular biologics (13%, n=41), and behavioral therapies (13%, n=41). There was a significantly higher number of disease-modifying therapeutics for cellular biologics than pharmaceutical trials (30% vs.14%, respectively) ($P = .015$). The majority of trials targeted the knee joint (63%, $P = .042$) with 38% of all trials evaluating joint arthroplasty. There were no significant differences between private sector and government funding sources (43% and 49%, respectively) ($P = .288$), yet there was a significantly lower rate of funding from industry (8%) ($P = .026$).

Conclusion: There was a significantly higher number of clinical trials investigating symptomatic resolution therapy (89%) for existing OA in comparison to prevention (5%) and disease-modifying (6%) therapies. The most common interventions involved medical devices and joint replacement surgery with the knee joint accounting for > 60% of the current clinical trials for OA. There was a significantly higher number of disease-modifying therapeutics for cellular biologics than pharmaceutical drugs. Funding of clinical trials was split between private sector and government, with a low rate of reported funding from industry partners.

Clinical Relevance: Identifying existing needs in the current market may help increase rates of research funding or optimize current funding pathways, in this study, specifically for targeting unaddressed focus areas in OA research. Our systematic review highlights the potential need for

additional research and development regarding OA preventative and disease-modifying therapies.

Introduction

Affecting approximately 250 million individuals worldwide and accounting for 18% of all healthcare visits in the United States (U.S.), osteoarthritis (OA) is a significant source of increasing healthcare costs and patient morbidity.[1, 2] Current nonoperative treatments for noninflammatory arthritis aim to target symptom resolution through a diverse spectrum of therapies from physical exercise to injectable medications.[3, 4] While recent advances in joint-replacement techniques have resulted in improved patient satisfaction and functionality for the management of end-stage osteoarthritis, there remains a lack of approved disease-modifying therapies focusing on the delay or reversal of the structural progression of OA.[5, 6]

Current treatment for OA consists of nonoperative and operative management, including non-steroidal anti-inflammatory drugs (NSAIDs), physical therapy and bracing, therapeutic injections, activity/lifestyle modifications, and joint replacement surgery.[3, 4, 7] Although curative medicines are currently limited in the literature, recent advances in the understanding of OA pathophysiology have provided new avenues for targeted therapeutics for pain relief, disease progression, and even disease regression.[8-10] However, due to the innately slow progression of primary OA, timeline of prospective studies from inception to publication, and inherent limitations in research funding for non-urgent medical diseases[11-13], the rate of transforming the approach to OA management poses a challenge for treating clinicians at a time where the prevalence of OA is steadily increasing[1, 14]. Therefore, information regarding ongoing clinical trials is essential to better understand future directions of clinical research for OA and optimize the use of research funding. Thus, the purpose of this study was to conduct a review of active U.S. based clinical trials investigating prevention, symptom resolution, and disease-modifying therapies for osteoarthritis. It was hypothesized that there would be a significantly higher number

of clinical trials targeting symptomatic resolution of OA in comparison to prevention and disease-modification.

Methods

Study Identification and Selection Criteria

A review was conducted of currently active clinical trials for OA utilizing publicly available records. The PRISMA guidelines were followed during the study identification process to ensure a systematic and transparent method of collecting and reporting included clinical trials.[15] Data on clinical trials of OA were obtained from ClinicalTrials.gov. This database is made accessible through the U.S. National Library of Medicine of the National Institute of Health. ClinicalTrials.gov provides information on publicly and privately supported clinical studies and is the world's most comprehensive clinical trial registry. This database has been active since the year 2000 and data on the registry is maintained directly by trial sponsors. The registry includes detailed study information such as: name of trial, study description, study design, arms and interventions, outcome measures, eligibility criteria for study participants, contacts and locations, enrollment targets, recruiting status, expected start/end dates, funding type, and study results (when applicable).

The search query for active clinical trials was performed in August 2020 using a previously established systematic selection method.[16] Search engine MeSH terms of 'osteoarthritis' condition and 'United States' location were used. Data were screened and extracted by two investigators (*initials blinded for review*) independently, and any disputes on inclusion of clinical trials were reconciled by a third investigator (*initials blinded for review*). Inclusion criteria were studies registered on ClinicalTrials.gov in the U.S. that involved the

prevention, symptomatic resolution, or disease-modification of OA. All subtypes of noninflammatory OA were included. Clinical trial protocols were evaluated and screened for inclusion criterion of study participants with a current diagnosis of OA or prevention of the development of OA (e.g. posttraumatic OA). All study phases were included, consisting of early phase I, phase I, phase II, phase III, and phase IV. The status parameters of included study trials were: "Recruiting", "Not yet recruiting", "Active, not recruiting", or "Enrolling by invitation". All funder types were included: "NIH", "Other U.S. Federal agency", "Industry", and "All others (individuals, universities, organizations)."

Exclusion criteria included studies registered outside of the U.S., studies that evaluated outcome parameters as the primary endpoint that were unrelated to OA, study participants with nonosteoarthritis inflammatory joint disease (e.g. rheumatoid arthritis, lupus erythematosus, psoriatic arthritis, pseudo-gout, gout, spondyloarthropathy, polymyalgia rheumatica); recruitment classified as "suspended", "terminated", "completed", "withdrawn", or "unknown status"; use of cadaveric specimens or *in vitro* investigations. Clinical trials evaluating the effects of analgesics on opioid consumption or evaluations of postoperative pain management following joint replacement surgery were also excluded.

Clinical trials were grouped according to study focus, including OA prevention, symptom resolution, and disease-modifying therapeutics. Clinical trials regarding the prevention of OA were defined as any intervention designed to avert or avoid OA development in high-risk patient populations. Symptom resolution trials were defined as any therapy focused on reducing the symptomatology of patients with existing OA, including pain, stiffness, swelling, joint range-of-motion, muscle weakness, fatigue, joint instability, and pain-related psychological distress. Disease-modifying trials were defined as any treatment that focused on retardation of OA

(slowing the speed of progression), a complete halt in disease progression, or a reversal in disease progression (regeneration of targeted tissue).[1] Patients considered high-risk for the development of osteoarthritis are individuals who sustain a joint injury and/or repetitive joint trauma associated with recurrent instability.[17] There was no funding received for this study.

Statistical Analysis

Data from only active clinical trials were collected, including study title, study description, study design, arms and interventions, outcome measures, eligibility criteria for study participants, contacts and locations, enrollment targets, recruitment status, expected start/end dates, and funding type. Descriptive data were recorded and summarized from each trial including disease conditions, body part, intervention type, therapeutic agent, sample size, number of outcome variables, follow-up time, and phase of study. Furthermore, the main binary variables of interest were analyzed for statistical significance based on frequency distributions with an alpha level set at $P < .05$. Nonparametric testing including the Kruskal-Wallis and chi-squared tests were used for comparing differences in frequencies and included clinical trial focus area, body part, and funding sponsor type. Subanalysis was performed on cellular biologics and biopharmaceutical drugs using descriptive statistics and nonparametric one-way ANOVA testing. In addition, treatment protocol variables including the route of administration, dosage, frequency of application, and duration were recorded. When applicable, continuous numerical data were grouped for analysis and reported as mean ± standard deviation and included sample size and length of follow-up time.

Results

Clinical Trial Characteristics

There were 3859 clinical trials identified in the database search. After applying exclusion criteria, 310 were included in final analysis (Figure 1). The majority of clinical trials involved the knee joint (63%, n=195) followed by hip (14%, n=42), shoulder (8%, n=25), multiple joints (6%, n=20), foot/ankle (4%, n=13), hand/wrist (3%, n=11), spine (1%, n=3), and elbow (1%, n=1). There were significantly more clinical trials studying the knee joint than any other body part (χ^2 (7, n=195), = 6.0, P = .042). Interventional study designs accounted for 73% (n=226) of all active clinical trials while 27% (n=84) of clinical trials were observational study designs. The average sample size was 320.7 ± 994.2 patients (range, 5-10500 patients) with an average length of follow-up of 2.9 ± 3.8 years (range, 0.01-25 years).

The majority of clinical trials were reported as nonrandomized controlled trials (54%, n=167) while the remaining trials were randomized controlled trials (46%, n=143). The majority of trials involved multi-center research designs (61%, n=188), while the remaining trials were performed at a single research center (39%, n=122). Of those reporting clinical trial phases (n=93), 2% were in early phase I, 18% were in phase I, 41% were in phase II, 22% were in phase III, and 17% were in phase IV. Seventy percent (n=217) of the clinical trials were reported as 'phase not applicable'. Forty-three percent (n=133) of clinical trials were reported as privately funded (individuals, universities, organizations), 42% (n=130) were reported as funded by other U.S. federal agencies, 8% (n=24) funded by industry sponsors, and 7% (n=23) were funded by the NIH directly. No significant differences were found between the incidence of government and private funding sources (P = .288); however, the incidence of industry funding was significantly lower in comparison to government and private funding ((χ^2 (2, n=24) = 4.2, P = .026)).

Of the currently active U.S. clinical trials, 89% (n=275) targeted symptom resolution in patients with existing OA, 6% (n=19) targeted OA disease-modifying therapeutics, and 5% (n=16) targeted the prevention of OA in high-risk patient populations. There were significantly more clinical trial interventions targeting symptomatic resolution ((χ^2 (2, n=275) = 35.0, P < .001)), with no significant differences between prevention and disease-modifying interventions ((χ^2 (1, n=19) = 1.1, P = .610)). Primary interventions for clinical trials involved the study of medical devices (44%, n=137), pharmaceutical drugs (14%, n=42), surgical procedures (14%, n=42), cellular biologics (13%, n=41), behavioral therapies (13%, n=41), other (1%, n=5), and dietary supplements (1%, n=2). The majority of medical device and surgical procedural trials involved unicompartmental or total joint arthroplasty (38%, n=118). Behavioral therapies included exercise prescription, activity modification, diet and weight loss, mindfulness and meditation, and psychosocial interventions.

Cellular Biologics

Cellular biologic treatments were defined as therapeutics derived from host or donor tissues, including adipose-derived cells, autologous blood, bone marrow aspirate, amniotic fluid, and umbilical cord tissue. Of the 41 trials utilizing a total of 49 cellular biologic products, 76% (n=31) reported the use of single biologic products, 17% (n=7) reported a combination of biologic products, and 8% (n=3) reported comparisons of one or more different biologic products. The majority of cellular biologic studies evaluated adipose-derived cells (41%, n=20), followed by autologous blood (31%, n=15), bone marrow aspirate (16%, n=8), amniotic fluid (10%, n=5), and umbilical cord tissue (2%, n=1). Subanalysis of adipose-derived cells revealed the use of autologous adipose-derived cells in 80% (n=16) and allograft adipose-derived cells in

20% (n=5) of trials. Subanalysis of autologous blood cells revealed the use of leukocyte-rich platelet-rich plasma (LR-PRP) in 73% (n=11) of trials and leukocyte-poor platelet-rich plasma (LP-PRP) in 27% (n=4) of trials (Table 1).

Table 1. Cellular biologics in currently active U.S. based clinical trials for the prevention, symptomatic resolution, and disease-modification of osteoarthritis.

ClinicalTrials.gov Identifier	Biologic	Trial Sponsor	OA Focus Area	Development Phase	Sample Size	Frequency / Dosage
NCT04201743	Amniotic Allograft	Illinois Center for Orthopaedic Research and Education	Knee	IV	60	Single / 1-2 mL
NCT03441607	Amniotic Allograft	Applied Biologics, LLC	Knee	II	320	Single / 40 mg
NCT03408145	Amniotic Allograft	The Stone Research Foundation for Sports Medicine and Arthritis	Knee	N/A	88	Single / 1 mL
NCT03770546	Amniotic Allograft	University of Alabama at Birmingham	Shoulder	N/A	80	Single / NR
NCT03710005	Amniotic Allograft	StimLabs	Knee	N/A	140	Single / NR
NCT03485157	Amniotic Allograft	MiMedx Group, Inc.	Knee	II	466	Single / 40 mg
NCT03390920	Amniotic Allograft	R3 Stem Cell	Knee	III	200	Single / 0.5-1.0 mL
NCT03242707	Autologous Adipose Tissue	University of Southern California	Knee	N/A	54	Single / 5 mL
NCT02805855	Autologous Adipose Tissue	Mayo Clinic, Rochester	Knee	I	24	4 groups: -1 injection x50 million AMSCs -1 injection x100 million AMSCs -3 injections x50 million AMSCs -3 injections x100 million AMSCs
NCT02844738	Autologous Adipose Tissue + Leukocyte-Rich PRP	VivaTech International Inc.	Shoulder	II	50	Day 0: single ADSC injection + PRP Days 7 + 14: PRP injection only
NCT02844764	Autologous Adipose Tissue + Leukocyte-Rich PRP	VivaTech International Inc.	Hip	II	50	Day 0: single ADSC injection + PRP Days 7,14,30: PRP injection only
NCT02844751	Autologous Adipose Tissue + Leukocyte-Rich PRP	VivaTech International Inc.	Knee	II	50	Day 0: single ADSC injection + PRP Days 7,14,30: PRP injection only
NCT03014401	Autologous Adipose Tissue	University of Colorado, Denver	Knee	N/A	29	Single / NR
NCT03467919	Autologous Adipose Tissue	Stanford University	Knee	III	40	Single / NR
NCT03166410	Autologous Adipose Tissue	Texas Plastic Surgery	Hip, knee, ankle, thumb	N/A	500	Single / NR
NCT03513731	Autologous Adipose Tissue	InGeneron, Inc.	Lumbar spine	N/A	40	Single / 5 mL
NCT03940950	Autologous Adipose Tissue	Mayo Clinic, Rochester	Knee	I	30	Single / 6 mL
NCT04405297	Autologous Adipose Tissue	Sanford Health	Knee, hip, ankle, shoulder, wrist	N/A	250	Single / NR
NCT03503305	Autologous Adipose Tissue	InGeneron, Inc.	Wrist	N/A	40	Single / 5 mL
NCT03608579	Autologous Adipose Tissue	Mayo Clinic, Rochester	Hip	I	24	Twice 1-month intervals / 30 million AMSCs
NCT04043819	Autologous Adipose Tissue	Personalized Stem Cells, Inc.	Knee	I	125	Single / NR

NCT04440189	Autologous Adipose Tissue	GID BIO, Inc.	Knee	N/A	124	Single / NR
NCT04238143	Autologous Adipose Tissue + Leukocyte-Rich PRP	Healeon Medical Inc.	Knee, hip, shoulder, foot/ankle	N/A	100	Single / NR
NCT03579407	BMAC	Advanced Orthopaedic Specialists	Knee	N/A	30	Single / 5-6 mL
NCT03477942	BMAC	University Hospitals Cleveland Medical Center	Knee	I	16	Single / 6 mL
NCT04001361	BMAC	Endocellutions	Knee	N/A	45	Single / 1 mL
NCT03898388	BMAC	Regenexx, LLC	Knee	N/A	600	Single / NR
NCT03909139	BMAC	Massachusetts General Hospital	Hip	N/A	40	Single / NR
NCT02981394	BMAC	RUSH University Medical Center	Multiple joints	N/A	300	Single / NR
NCT04222140	BMAC	Affinity Health Research Institute	Knee	N/A	40	Single / NR
NCT03818737	1.BMAC 2.Autologous Adipose Tissue 3.Umbilical Cord Tissue	Emory University	Knee	III	480	Single / 4-6 mL
NCT04241354	Leukocyte-Poor PRP	Regenerative Orthopedics and Sports Medicine	Hip	I	84	Single / 5 mL
NCT03889925	Leukocyte-Poor PRP + Hyaluronic Acid	Andrews Research & Education Foundation	Knee	III	60	Once per week x 3 consecutive weeks / NR
NCT03201614	Leukocyte-Poor PRP + Hyaluronic Acid	Regen Lab SA	Knee	N/A	290	Twice / NR
NCT04205656	Leukocyte-Poor PRP + BMAC	Steadman Philippon Research Institute	Knee	II	99	Single / NR
NCT03491761	Leukocyte-Rich PRP	NorthShore University HealthSystem	Knee	II	100	Single / 4-6 mL
NCT03491761	Leukocyte-Rich PRP	NorthShore University HealthSystem	Knee	II	100	Single / 4-6 mL
NCT03196310	Leukocyte-Rich PRP	Kettering Health Network	Hand	N/A	150	Single / NR
NCT02984228	Leukocyte-Rich PRP	Hospital for Special Surgery, New York	Shoulder	IV	70	Single / NR
NCT03460236	Leukocyte-Rich PRP	VA Office of Research and Development	Knee	N/A	130	Single / NR
NCT02905240	Leukocyte-Rich PRP	Zimmer Biomet	Knee	N/A	332	Single / NR
NCT04351087	1. Leukocyte-Rich PRP 2.Autologous Adipose Tissue	Ohio State University	Knee	N/A	88	Single / 6 mL PRP or 5-7 mL MFAT

BMAC: bone marrow aspirate concentrate. PRP: platelet-rich plasma. LP: leukocyte-poor. LR: leukocyte-rich. ADSC: adipose-derived stromal cell. AMSC: adipose-derived mesenchymal stem cell. MFAT: microfragmented adipose tissue. NR: not reported. N/A: not applicable.

Sixty-three percent (n=26) of clinical trials utilizing biologics targeted symptom resolution in existing OA patients, 30% (n=12) targeted OA disease-modifying therapeutics, and 7% (n=3) targeted prevention of OA in high-risk patients. All 41 clinical trials reported the use of intra-articular injections for delivery of each cellular biologic product. Eighty-three percent (n=34) of interventions reported a single dose and 17% (n=7) of interventions reported ≥ 2 doses

for clinical trials evaluating cellular biologics. Less than half (43%, n=18) of the clinical trials reported specific dosage concentrations for the biologics being administered. The majority of biologic clinical trials (54%, n=22) were classified as 'phase not applicable'. Of the remaining clinical trials reporting development phases, 32% (n=6) were in phase I, 37% (n=7) were in phase II, 21% (n=4) were in phase III, and 10% (n=2) were in phase IV. Of the biologic trials targeting disease-modification, only one (8%) was reported in later phase development (phases III or IV). For clinical trials targeting disease-modifying therapies, there was a significantly higher number of cellular biologics in comparison to pharmaceutical drugs ((χ^2 (1, n=12) = 2.0, P = .015)).

Pharmaceutical Drugs

Pharmaceutical drug treatments were defined as therapeutics utilizing recombinant proteins, small molecules, monoclonal antibodies, and gene therapies which modify host protein expression, including adenovirus vectors. Of the 42 trials utilizing pharmaceutical drugs, 79% (n=33) targeted symptom resolution in existing OA patients, 14% (n=6) targeted OA disease-modifying therapeutics, and 7% (n=3) targeted prevention of OA in high-risk patients. There were 27 different pharmaceutical products identified from the currently active 42 clinical trials. The majority of clinical trials reported unique pharmaceuticals derived from small molecule drugs (21.5%, n=9), followed by monoclonal antibodies (19.5%, n=8), recombinant proteins (7%, n=3), and gene therapy drugs (7%, n=3). Remaining trials reported the use of existing pharmaceutical agents for the treatment of OA, including corticosteroids (17%, n=7), hormone

drugs (7%, n=3), synthetic capsaicin (7%, n=3), cannabinoids (5%, n=2), NSAIDs (2%, n=1), anti-gout (2%, n=1), anti-hypertension (2%, n=1), and bisphosphonates (2%, n=1) (Table 2).

Table 2. Pharmaceutical drugs in currently active U.S. based clinical trials for the prevention, symptomatic resolution, and disease-modification of osteoarthritis.

ClinicalTrials.gov Identifier	Drug	Drug Type/Mechanism	Trial Sponsor(s)	OA Focus Area	Phase	Sample Size	Route of Administration	Frequency/Dosage
NCT03968913	Anakinra (Kineret®)	Recombinant protein / IL-1Ra	University of California, Los Angeles	Knee	0*	48	IA Injection	Two / 150 mg
NCT04412837	CBD	Cannabinoid / anti-inflammatory	Solace Brands, Inc.	Knee	II	74	Topical	24 hours x 4 weeks / 35mg
NCT04195269	CBD / THC	Cannabinoid / anti-inflammatory	Pure Green, LLC	Knee	II	30	Sublingual	2 tablets daily x 30 days / 10mg THC, 10mg CBD
NCT03660943	CNTX-4975-05	Synthetic capsaicin / TRVP-1Ra	Centrexion Therapeutics	Knee	III	332	IA Injection	Twice / 1.0 mg
NCT03661996	CNTX-4975-05	Synthetic capsaicin / TRVP-1Ra	Centrexion Therapeutics	Knee	III	857	IA Injection	Single / 1.0 mg
NCT03913442	Colchicine	Anti-Gout / anti-inflammatory	NYU Langone Health	Knee	IV	120	Oral	Once daily x 3 months / 0.8 mg
NCT04123561	Dexamethasone (BioSeizer®)	Corticosteroid / anti-inflammatory	Taiwan Liposome Company	Knee	III	500	IA Injection	Single / 1 mL
NCT03754049	Dexamethasone (BioSeizer®)	Corticosteroid / anti-inflammatory	Taiwan Liposome Company	Knee	II	90	IA Injection	Single / 6mg-12 mg
NCT02746068	Disodium zoledronate tetrahydrate (AXS-02)	Bisphosphonate / antiresorptive	Axsome Therapeutics, Inc.	Knee	III	346	Oral	Once per day x6 weeks / NR
NCT03491904	Fasinumab	Monoclonal antibody / NGF inhibitor	Regeneron Pharmaceuticals	Knee / Hip	I	100	SubQ Injection	Multiple / NR
NCT03161093	Fasinumab	Monoclonal antibody / NGF inhibitor	Regeneron Pharmaceuticals	Knee / Hip	III	3307	SubQ Injection	Multiple / NR
NCT03304379	Fasinumab	Monoclonal antibody / NGF inhibitor	Regeneron Pharmaceuticals	Knee / Hip	III	1650	SubQ Injection	Multiple / NR
NCT02683239	Fasinumab	Monoclonal antibody / NGF inhibitor	Regeneron Pharmaceuticals	Knee / Hip	III	5331	SubQ Injection	Multiple / NR
NCT03691974	Fasinumab	Monoclonal antibody / NGF inhibitor	Regeneron Pharmaceuticals	Knee / Hip	II	180	SubQ Injection	Repeat every 4 weeks / NR
NCT03949673	Fasinumab	Monoclonal antibody / NGF inhibitor	Regeneron Pharmaceuticals	Knee / Hip	II	50	SubQ Injection	Multiple / NR
NCT03988023	Human Serum Albumin (Ampion™)	Small molecule / anti-inflammatory	Ampio Pharmaceuticals Inc.	Knee	III	1034	IA Injection	Single / 4 mL
NCT04119687	Humantakinogene hadenovec (FX201)	Gene therapy / IL-1Ra	Flexion Therapeutics, Inc.	Knee	I	24	IA Injection	Single / NR
NCT04082533	Hydrocortisone	Corticosteroid / anti-inflammatory	Hospital for Special Surgery, New York	Knee	IV	132	Intravenous	Single / 100 mg
NCT03275064	LNA043	Recombinant protein / ANGPTL3 agonist	Novartis Pharmaceuticals	Knee	II	60	IA Injection	Once weekly x 4 weeks / 20 mg
NCT03706521	Lorecivivint (SM04690)	Small molecule/ anti-inflammatory	Samumed LLC	Knee	II	15	IA Injection	Single / 0.07 mg
NCT03727022	Lorecivivint (SM04690)	Small molecule / anti-inflammatory	Samumed LLC	Knee	II	100	IA Injection	Single / 0.07 mg
NCT04385303	Lorecivivint (SM04690)	Small molecule / anti-inflammatory	Samumed LLC	Knee	III	726	IA Injection	Single / 0.07 mg

NCT03928184	Lorecivivint (SM04690)	Small molecule / anti-inflammatory	Samumed LLC	Knee	III	725	IA Injection	Single / 0.07 mg
NCT04212650	Losartan®	Angiotensin receptor blocker / TGF-B1	Steadman Philippon Research Institute	Hip	II	60	Oral	Twice daily x 30 days / 12.5 mg
NCT04456686	LY3016859	Monoclonal antibody / TGFA inhibitor	Eli Lilly and Company	Multiple Joints	II	125	Intravenous	Single / NR
NCT03878589	Pitocin®	Hormone / oxytocin receptor	National Institute of Aging	Knee	II	210	Intranasal	Twice daily x 4 weeks / 24 IUs
NCT04493229	Pitocin®	Hormone / oxytocin receptor	Wake Forest University Health Sciences	Knee	II	50	IM Injection	Single / NR
NCT03956550	REGN5069	Monoclonal antibody / GRFa3 agonist	Regeneron Pharmaceuticals	Knee	II	259	Intravenous	Every 4 weeks x 12 weeks / NR
NCT03542838	Resiniferatoxin	Synthetic capsaicin / TRVP-1Ra	Sorrento Therapeutics, Inc.	Knee	I	94	IA Injection	Single / 5-30 ug
NCT02790723	sc-rAAV2.5IL-1Ra	Gene therapy / IL-1Ra	Mayo Clinic, Rochester	Knee	I	9	IA Injection	Single / 10 mL
NCT03072147	Teriparatide (Forteo®)	Hormone / antiresorptive	Eli Lilly and Company; University of Rochester	Knee	II	76	SubQ Injection	Once per day x 24 weeks / 20 mcg
NCT03203330	TissueGene-C (INVOSSA™)	Gene therapy / TGF-B1 agonist	Kolon TissueGene, Inc.	Knee	III	510	IA Injection	Single / 2 mL
NCT03552705	Tranexamic Acid	Small molecule / antifibrinolytic	Stanford University	Knee	II	50	Oral	3 tablets per day x5 days / 3900 mg/day
NCT04278833	Triamcinolone	Corticosteroid / anti-inflammatory	Stanford University	Multiple Joints	IV	198	IA Injection	Max 3 times in 6 months / 10-80 mg
NCT03586687	Triamcinolone	Corticosteroid/ anti-inflammatory	Milton S. Hershey Medical Center	Shoulder	IV	171	IA Injection	Single / 20-80mg
NCT03895840	Triamcinolone (Zilretta®)	Corticosteroid / anti-inflammatory	University of Kansas Medical Center	Knee	IV	70	IA Injection	Single / 32mg
NCT04261049	Triamcinolone (Zilretta®)	Corticosteroid / anti-inflammatory	Flexion Therapeutics, Inc.	Knee	I	35	IA Injection	Single / 32mg
NCT02700451	Toradol	NSAID / anti-inflammatory	Hospital for Special Surgery, New York	Lumbar Spine	N/A	300	Intravenous	Single / 15-30 mg
NCT04349956	UBX0101	Small molecule / senolytic inhibitor	Unity Biotechnology, Inc.	Knee	N/A	180	IA Injection	Single / NR
NCT04229225	UBX0101	Small molecule / senolytic inhibitor	Unity Biotechnology, Inc.	Knee	I	35	IA Injection	Twice / 4.0 mg
NCT04129944	UBX0101	Small molecule / senolytic inhibitor	Unity Biotechnology, Inc.	Knee	II	183	IA Injection	Single / 0.5-4.0 mg
NCT04124042	XT-150	Recombinant protein / IL-10	Xalud Therapeutics, Inc.	Knee	II	270	IA Injection	Single / 1 mL

IL-1Ra: interleukin-1 receptor antagonist. IL-10: interleukin-10. TRVP-1Ra: transient receptor potential cation channel subfamily V member 1 receptor antagonist. THC: tetrahydrocannabinol. CBD: cannabidiol. NSAID: non-steroidal anti-inflammatory drug. TGFA: transforming growth factor alpha. NGF: nerve growth factor. TGF-B1: transforming growth factor beta-1. GRFa3: GDNF family receptor alpha-3. ANGPTL3: angiopoietin-like 3. IA: intra-articular. IM: intra-muscular. SubQ: subcutaneous. NR: not reported. N/A: not applicable.

The majority of pharmaceutical trials reported the use of intra-articular injections (55%, n=24) as the delivery method; 17% (n=7) reported subcutaneous injection delivery, 10% (n=4) reported intravenous delivery, 10% (n=4) reported oral delivery, 2% (n=1) intranasal delivery,

2% (n=1) sublingual delivery, 2% (n=1) topical delivery, and 2% (n=1) intramuscular injection delivery. Fifty-two percent (n=22) of interventions reported a single dose and 48% (n=20) of interventions reported ≥ 2 doses for clinical trials evaluating pharmaceuticals. The majority (71%, n=30) of the clinical trials reported specific dosage concentrations for the pharmaceuticals being administered. Only 5% (n=2) of clinical trials were classified as 'phase not applicable'. Of the remaining clinical trials reporting development phases, 2% (n=1) were in early phase I, 15% (n=6) were in phase I, 42% (n=17) were in phase II, 28% (n=11) were in phase III, and 13% (n=5) were in phase IV. Of the pharmaceutical trials targeting disease-modification, 50% (n=3) were reported in later phase development (phases III or IV) (Figure 2).

Discussion

The most important findings of this review were that there was a high number of clinical trials investigating symptom resolution therapy for existing OA with a low number of clinical trials investigating OA disease-modifying therapies. The most common interventions involved medical devices and joint replacement surgery, both largely focused on the knee joint. There was a higher number of disease-modifying therapeutics for cellular biologics than pharmaceutical drugs. Funding of clinical trials was split between private sector and government, with a low rate of reported funding from industry partners.

Primary OA is characterized as a chronic, degenerative disease affecting the cartilage, bone, and related synovium and soft tissues.[1, 18, 19] Clinically, patients with OA typically present with significant pain, joint stiffness, or feelings of instability and often have a history of increased age, obesity, malalignment, and/or previous joint injury.[20] Coinciding with an aging population, increasing obesity rates[21], and increased early participation and specialization in competitive sports[22-24], the global prevalence of OA in the U.S. is projected to reach 25% by

2030[25]. Inevitably, the projected increase in OA prevalence has pertinent implications on rates of future disability[26, 27], national healthcare costs[2], and personal loss of income[28]. Furthermore, progressive and debilitating OA has been reported to be associated with significant co-morbidities such as higher rates of cardiovascular disease, diabetes, and depression.[29-33] Therefore, studies focused on early recognition and implementation of preventative and disease-modifying therapies are essential to reduce the burden of OA on both the healthcare system and patient quality of life.[34]

Based on this review, the clinical trial pipeline for OA therapies are concentrated on medical devices and joint arthroplasty procedures focused on the symptomatic treatment of existing knee OA. Knee OA has been reported to account for approximately 85% of the burden of OA worldwide.[35] Current research and drug development initiatives are aligned with this predominance, with 63% of current clinical trials for OA targeting the knee joint. However, there are currently a low number of clinical trials evaluating therapies to implement for the prevention of posttraumatic OA. Posttraumatic OA comprises a large burden of younger patients living with this disease, responsible for approximately 12% of all patients with symptomatic OA in the U.S.[36] Posttraumatic OA is extremely prevalent following anterior cruciate ligament (ACL) injuries.[37] With an average age of 17 years old for ACL tears and estimated 50% prevalence of knee joint OA within 10 to 20 years from injury[38-40], this depicts the proverbial 'young patient, with old knee' clinical scenario. Since joint arthroplasty is reserved for older patients with end-stage OA, there is currently a gap in the available treatment options for younger patients with posttraumatic OA. Thus, there is a dire need for the development of posttraumatic OA therapies to treat this high-risk patient population. However, due to the complex pathogenesis of OA and

varying causes of posttraumatic OA[41, 42], further basic science research is needed in the area of posttraumatic OA disease prevention prior to clinical implementation[14].

The use of cellular biologics is currently more prevalent than the use of pharmaceutical drugs for the development of disease-modifying OA therapies in the clinical trial pipeline. Cellular biologics may be more popular based on their proposed advantages for reversing or halting OA structural damage that occurs following a traumatic injury.[43, 44] It has been well described that the presence of blood in the joint and the resultant inflammatory process that occur after a traumatic joint injury can be deleterious to chondrocyte regeneration and survival.[45, 46] There are numerous inflammatory degenerative cytokines, activated macrophages, and other degenerative products which can lead to early chondrocyte death, chondrocyte loss over time, and ultimately OA progression.[9, 41, 47] Being able to target symptom resolution by neutralizing inflammatory cytokines while also promoting chondrocyte repair makes cellular biologics a promising area for future clinical therapy.[8, 48]

Combined government funding (i.e., NIH and other federal agencies) represented 48% of current funding sources for active U.S. clinical trials for OA, with the other majority (44%) of sourced funding reported was from the private sector (i.e., individuals, universities, organizations). The medical cost of OA has been estimated to account for 1% of the gross domestic product in the U.S., with knee and hip replacements representing the major proportion of these healthcare related costs.[26] In an effort to reduce costs associated with treating OA, increased government funding for developing OA disease therapies is essential. Prior investment models regarding drug discovery for Alzheimer's disease suggest a governmental funding 'portfolio approach' to increase the efficiency of parallel drug discovery and reduce overall investment risk in unsuccessful disease-modifying therapeutics.[49, 50] Similarly, prediction models

have been proposed to reduce investment risk throughout varying stages of drug development. The ability to predict clinical outcomes for patients with OA using big data is central to the future of precision medicine and the future design of successful clinical trials.[51] Developing predictive models may allow for targeted research designs towards therapeutics that have a higher likelihood of success and thus FDA approval, effectively reducing the time and expenses towards unsuccessful trials and thereby reducing financial risk and improving research funding allocation.[52, 53] Additional research is recommended to evaluate the potential future cost-savings of effective OA therapies using a similar financial government funding model.[49]

Limitations

This study is not without limitations. First, not all currently active clinical trials being conducted in the U.S. are registered on ClinicalTrials.gov and thus missing data on currently active clinical trials for OA is unknown. Second, this review attempted to summarize the clinical trial pipeline in the U.S. and provide a snapshot of pending clinical investigations; thus, this review is limited by the exclusion of international research initiatives which may limit the global perspective of existing disease-modifying therapies for OA. Third, this review does not encompass prior completed clinical trials or inactive clinical trials which limit the scope of evaluating all pre-existing devices and therapeutics for prevention and management of OA.

Conclusions

There was a significantly higher number of clinical trials investigating symptomatic resolution therapy (89%) for existing OA in comparison to prevention (5%) and disease-modifying (6%) therapies. The most common interventions involved medical devices and joint replacement

surgery with the knee joint accounting for > 60% of the current clinical trials for OA. There was a significantly higher number of disease-modifying therapeutics for cellular biologics than pharmaceutical drugs. Funding of clinical trials was split between private sector and government, with a low rate of reported funding from industry partners.

References

1. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet.* 2019;393:1745-1759.
2. Centers for Disease C, Prevention. National and state medical expenditures and lost earnings attributable to arthritis and other rheumatic conditions--United States, 2003. *MMWR Morb Mortal Wkly Rep.* 2007;56:4-7.
3. Kon E, Filardo G, Drobnic M, et al. Non-surgical management of early knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc.* 2012;20:436-449.
4. Watterson JR, Esdaile JM. Viscosupplementation: therapeutic mechanisms and clinical potential in osteoarthritis of the knee. *J Am Acad Orthop Surg.* 2000;8:277-284.
5. Markatos K, Savvidou OD, Foteinou A, et al. Hallmarks in the History and Development of Total Hip Arthroplasty. *Surg Innov.* 2020:1553350620947209.
6. Mahoney O, Kinsey T, Sodhi N, et al. Improved Component Placement Accuracy with Robotic-Arm Assisted Total Knee Arthroplasty. *J Knee Surg.* 2020.
7. Whitney KE, Liebowitz A, Bolia IK, et al. Current perspectives on biological approaches for osteoarthritis. *Ann N Y Acad Sci.* 2017;1410:26-43.
8. Sherman BJ, Chahla J, Glowney J, Frank RM. The Role of Orthobiologics in the Management of Osteoarthritis and Focal Cartilage Defects. *Orthopedics.* 2019;42:66-73.
9. Mobasheri A, Batt M. An update on the pathophysiology of osteoarthritis. *Ann Phys Rehabil Med.* 2016;59:333-339.
10. Maheshwer B, Polce EM, Paul K, et al. Regenerative Potential of Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis and Chondral Defects: A Systematic Review and Meta-Analysis. *Arthroscopy.* 2020.
11. Challa S, Wu HH, Cunningham BP, et al. Orthopaedic Trauma in the Developing World: Where Are the Gaps in Research and What Can Be Done? *J Orthop Trauma.* 2018;32 Suppl 7:S43-S46.
12. Bessman SC, Agada NO, Ding R, Chiang W, Bernstein SL, McCarthy ML. Comparing National Institutes of Health funding of emergency medicine to four medical specialties. *Acad Emerg Med.* 2011;18:1001-1004.
13. Bernstein M, Desy NM, Matache BA, McKinley TO, Harvey EJ. A ten-year analysis of the research funding program of the orthopaedic trauma association. *J Bone Joint Surg Am.* 2013;95:e1421-1426.
14. Little CB, Hunter DJ. Post-traumatic osteoarthritis: from mouse models to clinical trials. *Nat Rev Rheumatol.* 2013;9:485-497.
15. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 2009;339:b2535.
16. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* 2009;151:264-269, W264.
17. Thomas AC, Hubbard-Turner T, Wikstrom EA, Palmieri-Smith RM. Epidemiology of Posttraumatic Osteoarthritis. *J Athl Train.* 2017;52:491-496.
18. Martel-Pelletier J, Barr AJ, Cicuttini FM, et al. Osteoarthritis. *Nat Rev Dis Primers.* 2016;2:16072.
19. Kon E, Filardo G, Marcacci M. Early osteoarthritis. *Knee Surg Sports Traumatol Arthrosc.* 2012;20:399-400.
20. Hunter DJ, McDougall JJ, Keefe FJ. The symptoms of osteoarthritis and the genesis of pain. *Med Clin North Am.* 2009;93:83-100, xi.

21. Wall KC, Politzer CS, Chahla J, Garrigues GE. Obesity is Associated with an Increased Prevalence of Glenohumeral Osteoarthritis and Arthroplasty: A Cohort Study. *Orthop Clin North Am.* 2020;51:259-264.
22. Jayanthi NA, LaBella CR, Fischer D, Pasulka J, Dugas LR. Sports-specialized intensive training and the risk of injury in young athletes: a clinical case-control study. *Am J Sports Med.* 2015;43:794-801.
23. Hall R, Barber Foss K, Hewett TE, Myer GD. Sport specialization's association with an increased risk of developing anterior knee pain in adolescent female athletes. *J Sport Rehabil.* 2015;24:31-35.
24. DePhillipo NN, Cinque ME, Kennedy NI, Chahla J, Moatshe G, LaPrade RF. Patellofemoral Chondral Defect in a Preadolescent Skier: A Case Report in Early Sport Specialization. *Int J Sports Phys Ther.* 2018;13:131-136.
25. Turkiewicz A, Petersson IF, Bjork J, et al. Current and future impact of osteoarthritis on health care: a population-based study with projections to year 2032. *Osteoarthritis Cartilage.* 2014;22:1826-1832.
26. Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. *Nat Rev Rheumatol.* 2014;10:437-441.
27. Gupta S, Hawker GA, Laporte A, Croxford R, Coyte PC. The economic burden of disabling hip and knee osteoarthritis (OA) from the perspective of individuals living with this condition. *Rheumatology (Oxford).* 2005;44:1531-1537.
28. Schofield DJ, Shrestha RN, Percival R, Passey ME, Callander EJ, Kelly SJ. The personal and national costs of lost labour force participation due to arthritis: an economic study. *BMC Public Health.* 2013;13:188.
29. Wang H, Bai J, He B, Hu X, Liu D. Osteoarthritis and the risk of cardiovascular disease: a meta-analysis of observational studies. *Sci Rep.* 2016;6:39672.
30. Hsu PS, Lin HH, Li CR, Chung WS. Increased risk of stroke in patients with osteoarthritis: a population-based cohort study. *Osteoarthritis Cartilage.* 2017;25:1026-1031.
31. Hall AJ, Stubbs B, Mamas MA, Myint PK, Smith TO. Association between osteoarthritis and cardiovascular disease: Systematic review and meta-analysis. *Eur J Prev Cardiol.* 2016;23:938-946.
32. Brandt KD, Radin EL, Dieppe PA, van de Putte L. Yet more evidence that osteoarthritis is not a cartilage disease. *Ann Rheum Dis.* 2006;65:1261-1264.
33. Bierma-Zeinstra SMA, Waarsing JH. The role of atherosclerosis in osteoarthritis. *Best Pract Res Clin Rheumatol.* 2017;31:613-633.
34. Hootman JM, Helmick CG. Projections of US prevalence of arthritis and associated activity limitations. *Arthritis Rheum.* 2006;54:226-229.
35. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet.* 2016;388:1545-1602.
36. Brown TD, Johnston RC, Saltzman CL, Marsh JL, Buckwalter JA. Posttraumatic osteoarthritis: a first estimate of incidence, prevalence, and burden of disease. *J Orthop Trauma.* 2006;20:739-744.
37. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. *Am J Sports Med.* 2007;35:1756-1769.

38. von Porat A, Roos EM, Roos H. High prevalence of osteoarthritis 14 years after an anterior cruciate ligament tear in male soccer players: a study of radiographic and patient relevant outcomes. *Ann Rheum Dis.* 2004;63:269-273.
39. Lohmander LS, Ostenberg A, Englund M, Roos H. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. *Arthritis Rheum.* 2004;50:3145-3152.
40. Cinque ME, Dornan GJ, Chahla J, Moatshe G, LaPrade RF. High Rates of Osteoarthritis Develop After Anterior Cruciate Ligament Surgery: An Analysis of 4108 Patients. *Am J Sports Med.* 2018;46:2011-2019.
41. Koh SM, Chan CK, Teo SH, et al. Elevated plasma and synovial fluid interleukin-8 and interleukin-18 may be associated with the pathogenesis of knee osteoarthritis. *Knee.* 2020;27:26-35.
42. He Y, Li Z, Alexander PG, et al. Pathogenesis of Osteoarthritis: Risk Factors, Regulatory Pathways in Chondrocytes, and Experimental Models. *Biology (Basel).* 2020;9.
43. Chahla J, Piuzzi NS, Mitchell JJ, et al. Intra-Articular Cellular Therapy for Osteoarthritis and Focal Cartilage Defects of the Knee: A Systematic Review of the Literature and Study Quality Analysis. *J Bone Joint Surg Am.* 2016;98:1511-1521.
44. Chahla J, Dean CS, Moatshe G, Pascual-Garrido C, Serra Cruz R, LaPrade RF. Concentrated Bone Marrow Aspirate for the Treatment of Chondral Injuries and Osteoarthritis of the Knee: A Systematic Review of Outcomes. *Orthop J Sports Med.* 2016;4:2325967115625481.
45. Sivasubramaniyan K, Koevoet W, Hakimiyan AA, et al. Cell-surface markers identify tissue resident multipotential stem/stromal cell subsets in synovial intimal and sub-intimal compartments with distinct chondrogenic properties. *Osteoarthritis Cartilage.* 2019;27:1831-1840.
46. van Meegeren ME, Roosendaal G, Jansen NW, Lafeber FP, Mastbergen SC. Blood-Induced Joint Damage: The Devastating Effects of Acute Joint Bleeds versus Micro-Bleeds. *Cartilage.* 2013;4:313-320.
47. Rahmati M, Mobasheri A, Mozafari M. Inflammatory mediators in osteoarthritis: A critical review of the state-of-the-art, current prospects, and future challenges. *Bone.* 2016;85:81-90.
48. Ziegler CG, Van Sloun R, Gonzalez S, et al. Characterization of Growth Factors, Cytokines, and Chemokines in Bone Marrow Concentrate and Platelet-Rich Plasma: A Prospective Analysis. *Am J Sports Med.* 2019;47:2174-2187.
49. Lo AW, Ho C, Cummings J, Kosik KS. Parallel discovery of Alzheimer's therapeutics. *Sci Transl Med.* 2014;6:241cm245.
50. Fernandez JM, Stein RM, Lo AW. Commercializing biomedical research through securitization techniques. *Nat Biotechnol.* 2012;30:964-975.
51. Sawitzke AD. Personalized medicine for osteoarthritis: where are we now? *Ther Adv Musculoskelet Dis.* 2013;5:67-75.
52. Beaver JA, Tzou A, Blumenthal GM, et al. An FDA Perspective on the Regulatory Implications of Complex Signatures to Predict Response to Targeted Therapies. *Clin Cancer Res.* 2017;23:1368-1372.
53. Siah KW, Khozin S, Wong CH, Lo AW. Machine-Learning and Stochastic Tumor Growth Models for Predicting Outcomes in Patients With Advanced Non-Small-Cell Lung Cancer. *JCO Clin Cancer Inform.* 2019;3:1-11.

Figure Legends

Figure 1. Flowchart for the systematic selection of currently active U.S. based clinical trials for the treatment and prevention of osteoarthritis (as of August 2020). All studies were identified using publicly available database (ClinicalTrials.gov) with search terms of 'osteoarthritis' and 'United States' location.

Figure 2. Clustered bar chart demonstrating the number of pharmaceuticals in corresponding phases of development for prevention, symptom resolution, and disease-modifying osteoarthritis drugs (n=42).