Bone and joint disorders: screening and early clinical drug development

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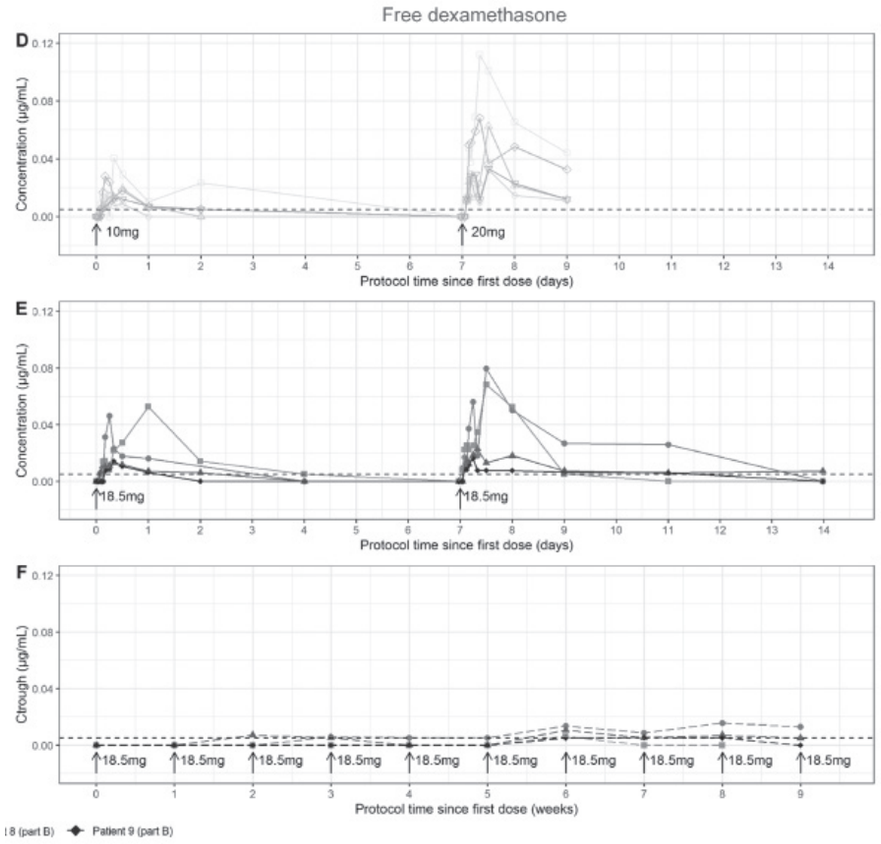

SECTION II

OSTEOARTHRITIS THERAPIES

CHAPTER 5

Challenges and opportunities of pharmacological interventions for osteoarthritis: a review of clinical trials and current developments

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ABSTRACT

OBJECTIVE Osteoarthritis (OA) is the most common cause of disability in older adults and leads to a huge unmet medical need as no registered disease modifying OA drugs (DMOADS), but only symptomatic treatments are available. New pharmacological targets, and compounds for these targets, are currently under investigation. The objective of this paper is to provide an overview of compounds under investigation for OA in phase II and III.

DESIGN We performed a review of OA trials for pharmacological interventions registered on the National Library of Medicine ClinicalTrials.gov website with a completion date in 2017 or later.

RESULTS The database search yielded 255 results, of which 184 studies were included in this review. These were structured in compounds targeting pain, immunomodulators, stem cell therapy, platelet rich plasma and DMOADS with cartilage and/or bone resorption modifying properties.

CONCLUSIONS The results provide an overview of the fields in development and may include future treatment options for OA, by which a registered DMOADS may become more than a utopic vista. Further knowledge on pathophysiology and new approaches of value-based drug development could be an opportunity for the optimization of drug development in OA.

Introduction

Clinically, osteoarthritis (OA) manifests as joint pain and/or joint dysfunction.[1] Its pathophysiology is multifactorial and depends on metabolic, genetic, and biomechanical factors.[2] The (severity of) symptoms of OA depends on the phase of the disease, and varies between patients.[3–5] Symptoms of OA and the absence of an effective disease modifying treatment contribute to patients' functional impairment and sense of illness.3,6 The incidence of OA increases with age.[3,7] Altogether, OA is the most common cause of severe long-term pain and disability in older adults, causing loss of work productivity and significant healthcare- and social support costs. Given the personal burden, the illness may result in a negative effect on mental health and may seriously impact the quality of life of patients and their relatives.[7–9]

Multiple joint tissues are involved; cartilage was long thought to play the primary role, as it lacks regenerative properties. But although cartilage is usually damaged, it is an aneural tissue and pain only appears once innervated tissues are involved.[10] Synovium and subchondral bone are also recognized to be involved in the disease process from an early stage on.[10–12]

In the last decade, studies to these aspects in pathophysiology have uncovered several different mediators that are associated with joint degeneration and OA related pain. These insights unveiled new targets for the development of disease-modifying OA drugs (DMOADS). The objective of this paper is to provide a background of OA treatments and its restrictions, upon which the pipeline of pharmacological interventions in OA is reviewed, using the clinicaltrials.gov database to get a representative, up-to-date, overview of the pharmacological interventions that are currently under investigation.

CURRENT TREATMENTS

Several organizations have brought out guidelines for treatment of OA,[13–16] thorough reviews of which are published elsewhere.[17,18] Current treatments for OA are restricted to symptom relief. In short, various non-pharmacological and pharmacological interventions are available, all with modest effects. Therefore, a combination of therapeutic approaches is commonly used, the choice of which is based on individual factors such as affected joint(s), disease extensiveness, and severity, in addition to the presence of concurrent signs and symptoms.[13–16,19]

Non-pharmacological interventions consist of exercise, weight loss, education, and self-management programs, which are recommended for all

types of OA.[14,19] Among pharmacological interventions are: oral and topical non-steroidal anti-inflammatory drugs (NSAIDS), paracetamol, tramadol, duloxetine, chondroitin, intra-articular steroid administration, and topical capsaicin.[14] The advised order of steps in the treatment of OA varies between guidelines and patients.[13–15,19]

LIMITATIONS OF CURRENT TREATMENTS

The available pharmacological interventions do not have a meaningful disease modifying effect. As a result, the condition worsens over time and in some cases leads to arthroplasty. Although the cost of total hip- or knee replacement in the USA are estimated to be $22,000 to $30,000, their cost-effectiveness is well established.[20] Unfortunately, arthroplasties are commonly preceded by a long trajectory of pain and functional limitation and unsuccessful in some patients, with complications during the post-surgical trajectory.[21]

The availability of DMOADS would lead to improvement of quality of life and a vast reduction of health care costs.[22] So far, several attempts of developing DMOADS have failed, among which are sprifermin, bisphosphonates and matrix metalloproteinase (MMP)-inhibitors.[23–25] Reasons for failure include wrong assumptions in animal to human translation, side effects, structural symptom discordance, incorrect structural endpoints and a substantial placebo effect for OA related pain.[23,24,26]

Further knowledge on the pathophysiological processes in OA is imperative to enable appropriate pharmacological targeting, as the key factors that drive progressive joint destruction and pain are still only partly understood. The pain experienced by patients seems to be a combination of inflammatory (nociceptive) and/or neuropathic-like pain, and there are multiple local structures which cause pain and evolves during the progression of OA.[3,5] As a result, personalized treatment plans, considering the phase and mechanism causing symptoms, are preferable.[27] However, currently there are no well-established biomarkers to enable such profiling for clinical studies. Researchers also struggle to define and measure a valid set of endpoints.

Methods

A structured search in the clinicaltrials.gov database was performed in November 2020. For the condition or disease “Osteoarthritis” was chosen and all phase II and phase III interventional trials with a completion date in 2017 or later were selected.

Trials with pharmacotherapeutic interventions in OA patients, were included. Studies which did not aim to investigate intention to treat OA, or which aimed to investigate effects of arthroplasty, shock wave therapy or Chinese medicine therapy, were excluded. Two authors (RS and JV) reviewed all search results for inclusion independently; outcomes were compared, and disagreements were resolved by discussion.

For each trial, details of the compound (assumed mechanism of action and target cells/receptors) and trial details (target joint, randomization, blinding, inclusion of a placebo) were collected. All results were then described per category based on intended mechanism of action.

Results

The database search yielded 255 results, of which 184 studies were included in this review. Seventy-one trials were excluded based on the exclusion criteria.

Most studies included patients with knee OA (160 studies), others investigated outcomes in hip-(23 studies) shoulder-(8 studies), hand-(5 studies) or lumbar spine (1 study) OA. Six studies did not define the affected joint. Other data collected for each study were the phase of study execution and study design.

From the database search, it becomes apparent that the pipeline includes several reformulations, or combinations of existing treatment options such as NSAIDS (10 results), corticosteroids (11 results) and hyaluronic acid (10 results). In addition, new insights have already led to the identification of new treatment targets, which includes pain pathways (Table 1), DMOADS that aim to interfere with inflammation (Table 2), interventions which involve mesenchymal stromal cells (MSC) or platelet-rich plasma (PRP) (Table 3) and target cartilage- or viscosupplementation (Table 4).

PAIN MODULATION

The generation and modification of chronic pain takes place at different levels along the neuraxis.[28] The nociceptive cell bodies are in the dorsal root ganglia and can be activated and sensitized by inflammation.[29,30] Dorsal root ganglia neurons express several receptors that can be selectively targeted, including G-protein coupled receptors (GPCRS) and ion channels.[31] Compounds that interfere with GPCRS include opioid, cannabinoid, muscarinic, acetylcholine and somatostatin receptors, which are already pharmaceutically targeted for countless analgesic indications.

Placebo controlled trials for selective- and non-selective opioid receptor binding compounds Difelikefalin (NCT02944448) and Naltrexon (NCT03008590), showed a high incidence of adverse events, without improvement of OA symptoms in the active groups. A study for a combination of tramadol and celecoxib, YYC301, is to start (NCT03850587). Cannabinoids are also under investigation; pre-clinically, cannabidiol (CBD) is a promising analgetic,[32] but a study for the effects of a dermal application of cannabinoid oil was negative.[33] Several other studies for CBD and tetrahydrocannabinol (THC) in knee- and hand-OA, are ongoing (Table 1).

Current studies for compounds with affinity for ion channels, include those targeting the transient receptor potential vanilloid 1 (TRPV1), such as (trans-)capsaicin. Topical capsaicin was shown effective in knee OA but is not recommended for hip- and hand OA due to the depth of the joint, and the risk of contaminating the eyes.[14] CNTX-4975, is a highly purified, synthetic trans-capsaicin, with an analgesic effect via reversible deactivation of end terminals of primary afferent pain fibers within the joint. In a phase II study, it reduced pain and improved physical function in OA patients, up to at least 24 weeks after intra-articular administration.[34] However, (possibly dose related) procedural pain was higher than in the placebo group.[34] Still, three phase III studies with this compound are recruiting patients with knee OA (NCT03661996, NCT03429049, NCT03660943). Several other TRPV1 antagonists are studied, with results pending (NCT03528369, NCT02558439, NCT03028870). NEO6860 is a promising compound, as it showed analgesic effects in knee OA, without adverse events observed in other TRPV1 antagonists, but due to an earlier completion date, it did not come up in our search.[35]

A monoclonal antibody which is also currently studied in a phase II study, targets transforming growth factor alpha and epiregulin (LY306859, NCT04456686), which inhibits inflammatory pathways to reduce pain.

Several other mechanisms of pain modulation are explored for OA. Botulinum toxin A, effective at the neuromuscular junction, is investigated in three ongoing studies in knee- and hand-OA.36 Two studies investigate optimal doses of non-selective serotonin reuptake inhibitor Duloxetine (NCT04224584, NCT04504812). In earlier trials, Duloxetine was (positively) evaluated for its efficacy in OA pain, and guidelines already recommend the use of Duloxetine.[14,16]

The development of pan-Trk inhibitors GZ389988 and ONO-4474 and TrkA receptor antagonists ASP7962 and VM902A and the Artemin-receptor targeting REGN5069 (NCT03956550) was stopped for corporate strategy reasons.[37]

Anti-nerve growth factor antibodies

Nerve growth factor (NGF) is a member of the neurotrophin family of molecules which binds to neurotrophic tyrosine kinase receptor type 1 (tropomyosin-related kinase A, TrkA).[38] NGF is essential for the development of sympathetic- and sensory neurons, the last are responsible for nociception and temperature sensation. A systematic review concluded that reduction in pain and the improvement in function in OA may be a class effect of NGF antibodies.[39]

Anti-NGF tanezumab showed a reduction in joint pain and functional impairment.[40] After a long trajectory of (pre-)clinical development, with two FDA-mandated temporary holds because of rapidly progressive OA (RPOA), and sympathetic nerve system AEs, respectively.[41] A request for approval with the FDA was submitted, but in a vote in March 2021, the FDA decided against approval for OA, because of the observation of RPOA.[40,42] Another anti-NGF monoclonal antibody, Fanisumab, had promising results in a phase II clinical trial in OA patients, but this entire class of anti-NGFs may run into the issue of RPOA.[43] Phase III trials in knee- and hip OA are currently ongoing (Table 1).

IMMUNOMODULATION

Inflammation in OA is mostly apparent as low-grade, chronic inflammation, primarily mediated by the innate immune system.[44] Synovitis, apparent as low-grade inflammatory infiltrates, is associated with severity of symptoms, cartilage degeneration, osteophyte formation and joint dysfunction and present from an early stage of OA.[10,44,45]

Tumor necrosis factor alfa (TNF-α), interleukin (IL)-1α, IL-1β, IL-6, IL-15, IL-17, and IL-18 are considered the major mediators involved in the pathophysiology of OA.[46–48] Although their exact roles in the pathogenesis of OA is still under investigation, their antibodies are already evaluated in clinical trials (Table 2). Previous studies with several compounds targeting IL-1 (AMG 108, Anakinra and Litikizumab), did not benefit patients with hand- or knee OA.[49–52]

TNF-α blockers are highly efficacious in rheumatoid arthritis and TNF-α could also have a significant role in the pathogenesis of OA, since TNF-α expression is increased in the joint tissues.[46] However, results of hand OA-trials showed no beneficial effects on pain of TNF-α blockers adalimumab and etanercept.[53,54]

Otilimab (GSK3196165) is a fully human monoclonal antibody for granulocyte macrophage-colony stimulating factor (GM-CSF), which inhibits

macrophage proliferation, an important element in development of OA-related pain and joint swelling.[55] A 12-week study showed that treatment of patients with inflammatory hand OA was well tolerated and reduced pain (NCT02683785), but no ongoing clinical trials in OA are registered. [56]

Interleukin-6 is an inflammatory cytokine which plays a role in the upregulation of matrix metalloproteinases 3 and 13,[57] but anti-IL-6 monoclonal antibody Tocilizumab did not improve outcomes in hand OA (NCT02477059).[58]

XT-150 is an IL-10 expressing plasmid DNA gene therapy product for which a study in knee OA is currently ongoing (NCT04124042). No publications on pre-clinical studies were found.

The low-molecular-weight fraction of 5% human serum albumin (LMWF-5A) contains aspartyl-alanyl diketopiperazine (DA-DKP), which inhibits the release of TNF-α in synoviocytes.[59] In a post hoc pooled analysis of three randomized placebo (saline) controlled trials in patients with severe knee OA, LMWF-5A showed a significant decrease in pain at 12 weeks, improvements in function, and patient global assessment.[60] The long-term effects of LMWF-5A are currently investigated in an open label phase III extension study (NCT03988023).

Curcumin and ginger are polyphenols with presumed anti-inflammatory properties through cyclo-oxygenase (COX)2, prostaglandin, and leukotoxin inhibition, and are used as alternative therapies in osteoarthritis.[61] As with other supplements, daily doses vary widely, and robust evidence of its efficacy is lacking. Ongoing trials for the effects of Curcumin and Resveratrol, another polyphenol, were found (NCT02905799, NCT03715140).[62]

The development of p53 inhibitor UBX0101 was stopped, as the 12-week objective (reduction of pain) in the phase II trial (NCT04129944) was not met.[63] The development of inflammatory pathway inhibitor Piclidenoson (NCT00837291) was terminated for corporate reasons.

MULTIPOTENT MESENCHYMAL STROMAL CELLS

Multiple clinical trials with MSC were initiated during the last decade. MSC are stromal cells that can differentiate into a variety of connective tissue lineages, including bone-forming osteoblasts and cartilage-forming chondrocytes.[64] MSC can be isolated from a variety of tissues, such as placenta, umbilical cord, bone marrow, and adipose tissue. In the joints MSC contribute to the maintenance of healthy cartilage and the response to injury. Amongst other tissues, they reside in the di-arthrodial joints, where they act as a reservoir for other cells.[65] MSC also have paracrine and immunomodulatory effects, reducing local inflammation through inhibition of T-cell and B-cell proliferation, when exposed to certain cytokines like TNF-α and IL-1.[66] The MSC of patients with end-stage OA have substantially reduced proliferative and chondrogenic capacity, which may contribute to OA progression.[65,67] As such, MSC may have the potential to halt inflammation and regeneration of tissues.[65]

The regenerative properties of MSC intends to work through intra-articular injection of MSC after *ex-vivo* culture-expanding preparation. In a goat-model of post-traumatic OA, this was successfully tested: a meniscal repair response and clinical improvement of the treated joints, as well as paracrine effects, were confirmed.[68]

We found 51 interventional clinical trials with MSC-based therapy in OA, the majority of which investigate knee OA (Table 3). The source of these cells is variable and includes bone marrow-derived, adipose tissue-derived, and umbilical cord/placenta/Wharton's jelly derived MSC. Most of these studies are RCTs (65%), but only 45% are blinded, and (24%) are placebo controlled.

The effects of previous MSC-based therapies for knee OA were investigated in reviews and meta-analyses of randomized controlled clinical trials.[61,69,70] Some studies showed a dose-response relationship and short term improvement in pain and function, but there was little to no evidence for DMOAD activity.[61,69,70] In literature, the potential of MSC-based therapy for OA is recognized, but origin and preparation lack standardization.[14,61,64] In order to draw firm conclusions about the efficacy of MSC, and to recommend MSC-based therapies in guidelines, well-described, standardized preparation methods must still be conducted.

Despite the current lack of proven efficacy, minimally manipulated adipose tissue injections are widely available at clinics.[71]

PLATELET-RICH PLASMA

PRP contains an elevated concentration of platelets, growth factors, cytokines, adhesive proteins and plasma proteins and leucocytes.[72] These constitutes, influence the innate immune response in many ways. The growth factors, also mediate the proliferation and differentiation of MSC, which could contribute to cartilage repair.[73] In a meta-analysis of 74 RCTS, symptomatic outcome effects of PRP in knee OA were compared with those of hyaluronic acid and corticosteroids. Most included studies (87%) were blinded and showed superior outcomes of PRP injections compared to hyaluronic acid and corticosteroids; this positive effect on WOMAC score and VAS faded

after one year follow-up.[74] These outcomes may be affected by publication bias and the designs of the included studies (randomized, blinded) is not representative for the studies registered in clintrials.gov (Table 3). Finally, few studies for the efficacy of PRP treatment of OA in other joints have been performed, precluding conclusions on its efficacy.[75,76]

Our search yielded 15 studies investigating platelet-rich plasma in knee- (11 studies), hip- (2 studies), and shoulder- (1 study) OA. Similarities are observed between the study designs of these studies and those investigating MSC: 80% of the studies are randomized, 40% are blinded and 20% are placebo controlled. A review for PRP preparation techniques and its relation to patient reported outcomes also found wide variations.[77] Clearly this field is upcoming, but the applied preparation, dose, and dose interval vary widely, precluding conclusions on effectiveness. Consequently, the efficacy of PRP in OA is yet to be confirmed in high-quality, long-term follow-up studies.[73,75,76]

CARTILAGE METABOLISM AND BONE RESORPTION

Table 4 captures pharmacological interventions which aim to restore or maintain cartilage and the subchondral bone.

The progressive destruction of cartilage in OA involves degradation of its matrix constituents (collagen and aggrecan) by matrix metalloproteinases (MMPS) and/or proteinases 'A Disintegrin and Metalloproteinases with Thrombospondin' (ADAMTS) motifs 4 and 5, in combination with the failure to repair the tissue.[78,79] Blocking ADAMTS and MMPS, may inhibit the degradation of collagen and aggrecan degradation and preserve cartilage.

Inhibitors for MMP have been evaluated as OA treatments, but their efficacy was poor and local safety profile unfavorable, possibly due to lack of specificity.[78,80] Indeed, no results for MMP inhibitors were found (Table 4).

Two completed studies for ADAMTS-5 inhibitors in knee OA were found: anti-ADAMTS-5 nanobody M6495 (NCT03583346) and ADAMTS-5 inhibitor GLPG1972 (NCT03595618). In a phase I trial in healthy volunteers, GLPG1972 was well tolerated and prevented the release of aggrecan fragments, which can be a signal of joint protection.[81,82] However, the compound failed to reduce cartilage loss in the phase II efficacy study.[83]

Cathepsin K is a lysosomal cysteine protease, expressed in osteoclasts and chondrocytes, which also cleaves aggrecan and collagen.[78] MIV-711 is a cathepsin-K inhibitor that showed structure modifying properties in preclinical models and reduced crosslaps levels pre-clinically and in healthy volunteers.[84] A phase II trial showed that MIV-711 significantly reduced progression of bone and cartilage loss, with a tolerable safety profile, but it did affect pain.[85]

TPX-100 and LRX712 target chondroprogenitor cells, which aim for regeneration and repair of cartilage by inducing chondroprogenitor cell differentiation and production of new extracellular matrix. A placebo-controlled phase II study for TPX-100, showed that treatment was safe and improved knee function, with reduction in pain and disease burden, but no follow up study is registered.[86]

In the joint, the Wnt pathway helps to control tissue homeostasis through regulation of MSC differentiation into chondrocytes and osteoblasts. Increased Wnt signaling stimulates production of pro-inflammatory cytokines and catabolic enzymes like MMP.[87] Wnt pathway inhibitor, Lorecivivint (SM04690) preclinically showed potential to improve symptoms of knee OA.[88] Inflammatory cytokines and cartilage degradative enzymes were inhibited, resulting in increased cartilage and functionality and decreased pain.[88] In a phase II study, a single administration with Lorecivivint, did not yet lead to statistically significant improvement of knee OA pain, physical function, or improved medial joint space width compared to placebo.[89] Other phase II and III studies in knee OA are currently ongoing.

Several studies for Invossa™ (TissueGeneC) are ongoing; it consists of chondrocytes which are retrovirally transduced to overexpress transforming growth factor-β1. In a double-blind, placebo-controlled phase III trial in patients with knee OA, Invossa™ was found safe and improved pain and patient reported functional outcomes compared to a placebo group. No significant change was observed in cartilage thickness.[90]

As the condition of the subchondral bone contributes to OA progression, it may be a target for pharmacological interventions.[11] A randomized, placebo controlled trial with zoledronic acid in knee OA patients with bone marrow lesions, improved pain and bone marrow lesion size after one year.[91] However, efficacy of bisphosphonates was not confirmed in a study with two-year follow-up.[25] In a meta-analysis for the efficacy of bisphosphonates on improvement of pain and radiological progression, an effect failed to materialize too.[92] Nevertheless, two studies are currently recruiting knee- and hip OA patients (NCT043030, NCT02746068). Studies for calcium-regulating compounds Denosumab and Teriparatide in knee- and hand OA, are currently ongoing (NCT02771860, NCT03072147).

Viscosupplementation intends to lubricate the joint and relief pain by doing so. Studies investigating viscosupplements are either new formula-

tions of hyaluronic acid alone, or a combination of hyaluronic acid and corticosteroids/NSAIDS. Ongoing studies investigate compounds with the dual aim of viscosupplementation and cartilage repair (SB-061, collagen-PVP, and MM-II), but no (pre-)clinical results of these compounds were found published.

Finally, glucosamine and chondroitin sulphate are popular food supplements which intend to treat pain and loss of function in OA. Several systematic reviews and meta-analyses have analyzed their efficacy, with various outcomes. Some find a positive effect on pain and/or function,[93] whereas others are inconclusive or do not find a positive effect on function compared to placebo.[94] New formulations of glucosamine (NCT02830919), and combination with NSAIDS (NCT03936192) are under investigation.

Discussion

The understanding of mechanisms that lead to chronic pain in OA has evolved. As a result, therapies for OA pain are transforming from classic analgesics towards more mechanism-based interventions on different levels, such as pain modulation, inflammation, and cartilage regeneration. These new insights may be beneficial for patient- and societal burden.[22]

In this paper, the pipeline of treatments in development for OA was reviewed. We used the clinicaltrials.gov database to get a representative, up-to-date, overview of the pharmacological interventions under investigation. The use of the clinical trial registry gives up-to-date outcomes and to some extend prevents publication bias, in contrast to a search of published data. The international committee of medical journal editors requires prospective clinical trial registration with the aim of transparency,[95] but it remains unknown which studies are not registered or registered elsewhere.[96] Clinicaltrials.gov is a well-recognized clinical trial registry, which leads to representative search results.

A potential limitation of this search strategy is that we chose not to include phase I and phase IV trials in our results. This may have led to missing potential new candidates that are in a very early stage of clinical development (phase I), and studies with registered compounds, for new indications. Although both categories potentially yield new treatments for OA. We aimed to create an overview of new candidate compounds for OA, which have passed the first phase of development, hence phase I and phase IV trials were not in the scope of this paper.

Information from 184 studies for pharmacological interventions for osteoarthritis was collected, giving a good impression of the study designs in the field. In the categories of pain, immunomodulation and cartilage metabolism, high percentages of blinded, randomized, placebo-controlled trials were found (Tables 1, 2 and 4). This was less so for studies investigating the effects of MSC and platelet rich plasma. A blinded, randomized, placebo-controlled trial is generally assessed to be the most valuable study design for interventional studies.[97] Therefore, study designs are an opportunity in the fields of MSC and platelet rich plasma. Those studies would enable drawing firmer conclusions on MSC and PRP efficacy.

Overall, success is still elusive. One of the great challenges is the translation of preclinical animal models to the patient situation.[98] Many compounds with promising results in preclinical and early clinical studies, fail in phase I or II clinical trials. This might be explained by the fact that OA is such a complex heterogeneous disease in which multiple pathways lead to pain and functional failure of joints. Although research on the mechanisms involved is active at this moment and continually provides new insights and therapeutic targets to treat OA, it seems that important outcome parameters may be absent or missed in pre-clinical and early phase clinical drug development.

Applied interventions and primary outcomes of trials with patients who have different underlying pathophysiology, or different phases of disease progression, must be different.[27] The pathophysiological processes, contribution of sensitization of nociceptive pathways and psychosocial factors vary depending on the origin and stage of the disease. Currently, there is insufficient information about these phenotypes, to enable adequate patient selection efficient translation from pre- and early clinical drugs to a successfully registered DMOAD.

Rational starting points to optimize early development, would be to focus on the pathophysiology of early-stage OA in preclinical and clinical experiments. The feasibility of trials in phenotypically well-characterized patient populations, using validated (wet-, digital-, or imaging-) biomarkers, is currently under investigation.[99] Furthermore, follow-up during the progression of OA requires more accurate and adequate endpoints examples of which are structural (quantitative) imaging and information gained from wearables.[100]

Conclusion

High-quality research for compounds with potential disease modifying activity is ongoing. Meanwhile, a more complete understanding of the development of OA and a set of clinically valid and responsive biomarkers are thought essential players in the success of (clinical studies for) pharmacological interventions in OA.

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Table 1 Phase II and phase III OA trials investigating efficacy of pharmacological interventions with a completion date in 2017 or later that interfere with pain pathways

Intervention	Mechanism (assumed)	Target	N	Target joint	Randomized controlled trials N, %	Double blind N, %	Placebo controlled N, %	Placebo controlled
Diclofenac, Ibuprofen, Ketoprofen, Multiprofen, Naproxen	NSAIDs	COX	10	9× knee, 1× lumbar spine	10,100	9,90	6,60	**NCT03081806[a]** **NCT03110523[a]** **NCT03434197[b]** **NCT04421911[b]** **NCT03978208[b]** NCT03199417[d] NCT03691844[c] NCT03172780[c] NCT03277066[c] NCT03691818[c]
Difelikefalin (CR845)	GPCR – kappa opioid receptor agonist	Opioid receptor	1	1× knee and hip	1,100	1,100	1,100	NCT02944448c
Naltrexon	GPCR – Opioid receptor antagonists	Opioid receptor	2	2× Not defined	2,100	2,100	2,100	NCT03008590c NCT04115020d
Tramadol, Celecoxib (YYC301)	GPCR – nonselective opioid receptor agonist, NSAID	Opiod -and COX receptor	1	1× knee	1,100	0,0	0,0	**NCT03850587[a]**
Cannabidiol (CBD, THC)	GPCR – Cannabinoid receptor	Cannabinoid receptor	5	4× knee, 1× hand	4,80	4,80	3,60	**NCT03825965[a]** **NCT04412837[a]** **NCT03693833[b]** **NCT04195269[b]** NCT02324777[e]
Capsaicin, Transcapsaicin, Resiniferatoxin	Ion channels	TRPV1 receptor	9	9× knee	9,100	8,89	8,89	**NCT03661996[b]** **NCT03429049[b]** **NCT03660943[b]** **NCT04044742[a]** **NCT04386980[a]** NCT03153813[d] NCT03528369[c] NCT02558439[c] NCT03028870[c]
Fasinumab and Tanezumab	Monoclonal antibody	NGF pathway	10	10× knee, 10× hip, 1× shoulder	9,90	9,90	8,80	**NCT03161093[b]** **NCT03304379[b]** **NCT03691974[b]** **NCT02683239[b]** **NCT03245008[b]** NCT03285646[c] NCT02528188[c] NCT02674386[c] NCT02697773[c] NCT02709486[c]
LY3016859	Monoclonal antibody	EGF inhibitor, TGFα inhibitor	1	1× knee	1,100	1,100	1,100	**NCT04456686[b]**
GZ389988, ASP7962, ONO-4474	Tropomyosin receptor kinase inhibitors	NGF pathway	3	3× knee	3,100	3,100	3,100	NCT02845271[c] NCT02611466[c] NCT02997696d
REGN5069,	Monoclonal antibody	GFRalpha3	1	1× knee	1,100	1,100	1,100	**NCT03956550[d]**
Botulinum toxin A	ACh inhibitors; Glutamate antagonists; Membrane transport protein modulators; Neuromuscular blocking agents	Neuromuscular junction and noncholinergic neurons	3	2× knee, 1× hand	3,100	2,67	1,33	**NCT03726788[a]** **NCT03187626[b]** **NCT02832713[b]**
Duloxetine	non-selective serotonin reuptake inhibitor	Serotonin-receptor	2	2× knee	2,100	1,50	1,50	**NCT04224584[b]** **NCT04504812[a]**
Oxytocin	Oxytocin agonist	Parasympatic stimulation	2	2× knee	0,0	0,0	0,0	**NCT04429880[a]** **NCT04431193[a]**
Biofreeze 4 Topical Gel	TRPM8 channels, vasodilatation	TRPM8 channel	1	1× knee	1,100	1,100	1,100	**NCT04351594[a]**
Oxygen-ozone therapy	prostaglandine synthese inhibitor	Prostaglandine synthese inhibitor	1	1× knee	1,100	1,100	0,0	**NCT04426721[b]**
3VM1001 copper cream	Unknown	Unknown	1	1× knee	1,100	1,100	1,100	NCT03142178[c]

N Number of studies, NSAID nonsteroidal anti-inflammatory drugs, GPCR G-protein coupled receptor, COX cyclooxygenase enzymes, CBD cannabidiol, THC tetrahydrocannabinol, TRPV1 transient receptor potential vanilloid 1, NGF nerve growth factor, EGF epidermal growth factor, TGFα transforming growth factor, ACh acetylcholine, TRPM transient receptor potential ion channels.
Study status in clinicaltrials.gov November 2020 indicated in superscript:
a Not yet recruiting
b Recruiting or active, not recruiting
c Completed with- or without results
d Terminated or withdrawn
e Unknown
NCT numbers of ongoing studies, are in bold font

Table 2 Phase II and III OA trials investigating efficacy of pharmacological interventions with a completion date in 2017 or later that intend to interfere with inflammation

Intervention	Mechanism (assumed)	Target	N	Target joint	Randomized controlled trials N, %	Double blind N, %	Placebo controlled N, %	NCT nrs
Corticosteroid (Fluticason, Zilretta, sustained release Dexamethasone)	Corticosteroid	Glucocorticoid receptor	11	7x knee, 3x hip, 2x shoulder	8, 73	4, 36	5, 45	**NCT04120402[a]** **NCT04123561[b]** **NCT03754049[b]** NCT04065074[c] NCT04160091[d] NCT03793010[d] NCT03046446[c] NCT03382262[c] NCT03378076[c] NCT03529942[c] NCT03005873[c]
Diacerein	Anthraquinolone dervivate	IL-1	2	2x knee	2, 100	2, 100	2, 100	**NCT04318041[a]** **NCT02688400[a]**
Adalimumab	TNF-α antibody	TNF-α	2	2x knee	2, 100	2, 100	1, 50	**NCT02471118[b]** **NCT02893098[b]**
Otilimab (GSK3196165, MOR103)	Granulocyt macrophage-colony stimulating factor antibody (GM-CSF)	GM-CSF	1	hand	1, 100	1, 100	1, 100	NCT02683785[c]
Tocilizumab	Anti-IL-6-receptor monoclonal antibody	IL-6	1	hand	1, 100	1, 100	1, 100	**NCT02477059[b]**
XT-150: gene therapy expressing IL-10	Immunomodulation	IFN-γ, IL-2, IL-3, TNF-α, GM-CSF inhibition	1	Knee	1, 100	1, 100	1, 100	**NCT04124042[b]**
LMWF-5A, DMI9523	Immunomodulation	TNF-α, IL-6 and IL-7 among others	3	3x knee	2, 67	2, 67	2, 67	**NCT03988023[b]** NCT03182686[c] NCT03349645[d]
Curcumin	Presumed inhibition to the release of inflammasome through NLRP3	NLRP3	1	1x Not defined	1, 100	1, 100	1, 100	**NCT03715140[b]**
Resveratrol	Immunomodulation	Several targets (T- and B-lymphocytes)	1	Knee	1, 100	1, 100	1, 100	**NCT02905799[b]**
UBX0101	p53, MDM2 interaction inhibitor	p53, MDM2	1	knee	1, 100	1, 100	1, 100	NCT04129944[c]
Piclidenoson (CF101, IB-MECA.	modulation of the nuclear factor-κB (NF-κB. and the Wnt signal transduction pathways	A3 adenosine receptor (A3AR) agonist IL-17, IL-23	1	Knee	1, 100	1, 100	1, 100	NCT00837291[d]

n Number of studies, TNF-α tumor necrosis factor alpha, LMWF-5A low-molecular-weight fraction of 5% human serum albumin, IL interleukin, NLRP3 NLR family pyrin domain containing 3, GM-CSF granulocyte macrophage-colony stimulating factor, ADORA3 Adenosine A3 receptor agonist, MDM2 mouse double minute 2 homolog.
Study status in clinicaltrials.gov November 2020 indicated in superscript:
a Not yet recruiting,
b Recruiting or active, not recruiting
c Completed with- or without results
d Terminated or withdrawn
e Unknown.
NCT numbers of ongoing studies are in bold

Table 3 Phase II and III OA trials investigating efficacy of pharmacological interventions with a completion date in 2017 or later which investigate interventions with mesenchymal stem cells

Intervention	Mechanism (assumed)	Target	N	Target joint	Randomized controlled trials N, %	Double blind N, %	Placebo controlled N, %	NCT numbers
Mesenchymal Stem Cells (adipose tissue-derived)	Regenerative capacity	Several targets	26	23x knee 3x shoulder 3x hip 1x not defined	15, 58	10,39	7, 28	**NCT04368806**[a] **NCT03984461**[b] **NCT04351932**[a] **NCT04230902**[b] **NCT04208646**[a] **NCT03990805**[b] **NCT04050111**[a] **NCT04448106**[a] **NCT04427930**[b] **NCT03955497**[b] **NCT04321629**[b] **NCT03509025**[b] **NCT03308006**[a] **NCT02838069**[b] **NCT02784964**[b] **NCT02844738**[b] **NCT02844764**[b] **NCT02844751**[b] NCT03467919[b] NCT03869229[b] NCT02846675[c] NCT03164083[d] NCT02674399[c] NCT02351011[c] NCT02967874[c] NCT02827851[e]
Mesenchymal Stem Cells (placenta, umbilical cord, Wharton's jelly derived)	Regenerative capacity	Several targets	15	14x knee 1x hip 1x shoulder 1x not defined	10, 67	6, 40	3, 20	**NCT03383081**[b] **NCT04520945**[a] **NCT04453111**[b] **NCT04314661**[b] **NCT04313894**[b] **NCT03485157**[b] **NCT03866330**[b] **NCT03390920**[b] NCT03166865[e] NCT02580695[c] NCT02237846[d] NCT03441607[e] NCT02776943[e] NCT03028428[e] NCT01733186[c]
Mesenchymal Stem Cells (bone-marrow derived)	Regenerative capacity	Several targets	9	9x knee	7, 78	7, 78	2, 22	**NCT04351932**[a] **NCT04240873**[b] **NCT04205656**[b] **NCT03818737**[b] **NCT03589287**[b] **NCT03876795**[b] **NCT02848027**[b] NCT03271229[d] NCT02958267[c]
Mesenchymal Stem Cells (unknown origin)	Regenerative capacity	Several targets	1	1x knee	1, 100	0, 0	0, 0	NCT03975101[d]
Platelet-rich plasma	Regenerative capacity	Several targets	15	11x knee 2x hip 1x shoulder 1x not defined	12, 80	6, 40	3, 20	**NCT03984461**[b] **NCT03477630**[b] **NCT02776514**[b] **NCT02844738**[b] **NCT02844764**[b] **NCT02844751**[b] **NCT04333160**[b] **NCT04205656**[b] **NCT03491761**[b] **NCT03889925**[b] NCT04352075[c] NCT04331327[c] NCT03138317[e] NCT01697423[e] NCT02694146[c]
Autologous continued serum	Regenerative capacity	Several targets	1	1x knee	0, 0	0, 0	0, 0	NCT03850080[c]

N Number of studies.
Study status in clinicaltrials.gov November 2020 indicated in superscript:
a Not yet recruiting
b Recruiting or active, not recruiting
c Completed with- or without results
d Terminated or withdrawn
e Unknown
For ongoing studies, NCT numbers are in bold

Table 4 Phase II and III OA trials investigating efficacy of pharmacological interventions with a completion date in 2017 or later, which interfere with cartilage regeneration or bone resorption or involve viscosupplementation

Intervention	Mechanism (assumed)	Target	N	Target joint	Randomized controlled trials N, %	Double blind N, %	Placebo controlled N, %	NCT nr.
GLPG*1972, M6495*	ADAMTS-5 inhibitors	ADAMTS-5	2	2x Knee	2,100	2,100	2,100	NCT03595618[c] NCT03583346[c]
MIV-*711*	Selective cathEPsin-K inhibitor	CathEPsin K	2	2x Knee	1,50	1,50	1,50	NCT02705625[c], NCT03037489[c]
LRX*712*, TPX-*100*	Regeneration and rEPair of cartilage	Chondroprogenitor cells	2	2x Knee	2,100	2,100	2,100	**NCT04097379[b]** NCT02837900[c]
Lorecivivint (SM04690)	DYRK kinase inhibitors; Wnt signalling pathway inhibitors	Wnt signalling	7	7x Knee	6,86	6,86	6,86	**NCT04520607[b]** **NCT04385303[b]** **NCT03706521[b]** **NCT03727022[b]** **NCT03928184[b]** NCT03122860[c] NCT02536833[c]
TissueGene-C (Invossa K),	TGF-overexpressing Chondrocyte suppletion	Chondrocytes	3	3x knee	3,75	3,75	3,75	**NCT03383471[b]** **NCT03291470[a]** **NCT03203330[b]**
CartiLife	Chondrocyte suppletion	Chondrocytes	1	1x knee	1,100	0,0	0,0	NCT03545269[c]
Zolendronic acid	Bisphosphonates	Osteoclasts	2	1x knee, 1x hip	2,100	2,100	2,100	**NCT04303026[b]** **NCT02746068[b]**
Denosumab, Teriparatide	Calcium regulating compounds	Osteoclasts, osteoblasts	2	1x knee, 1x hand	2,100	2,100	2,100	**NCT02771860[b]** **NCT03072147[b]**
Alfacalcidol	Osteocyte/ chondrocyte hypertrophy by Vit. D substitution	Osteoclasts	1	1x knee	1,100	1,100	1,100	NCT04405960[c]
Losartan	Enhanced articular cartilage rEPair after microfracturing	Chondrocytes	1	1x hip	1,100	1,100	1,100	**NCT04212650[b]**
Hyaluronic acid, some with supplements of triamcinolon, mannitol or diclofenac	Visco-supplementation	-	10	9x knee, 1x hip	10,100	9,90	6,60	**NCT04231318[b]** NCT03561779[e] NCT03209362[c] NCT04315103[c] NCT03190369[c] NCT03191903[c] NCT03390036[c] NCT03200288[c] NCT02698865[d] NCT03636971[c]
SB-*061*	Aggrecan mimic	-	2	2x knee	2,100	2,100	2,100	NCT02802709[c] NCT03231280[c]
MM-*II*	Visco-supplementation	-	1	1x knee	1,100	1,100	1,100	**NCT04506463[a]**
Collagen-PVP	Visco-supplementation	-	1	1x Knee	1,100	1,100	0,100	**NCT04019782[b]**
Glucosamine with Chondroitin, glucosamine with Meloxicam	Synthesis of synovial fluid	-	2	2x knee	2,100	2,100	1,50	**NCT03936192[a]** NCT02830919[c]

N Number of studies, ADAMTS metalloproteinase with a thrombospondin type 1 motif, DYRK dual-specificity tyrosine phosphorylation-regulated kinase, Wnt wingless-related integration site
Study status in clinicaltrials.gov November 2020 indicated in superscript:
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c Completed with- or without results
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For ongoing studies, NCT numbers are in bold