Review

Challenges and opportunities of pharmacological interventions for osteoarthritis: A review of current clinical trials and 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 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.

1. 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 in OA pathophysiology: 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 for OA 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 give a representative, up-to-date, overview of the pharmacological interventions that are currently under investigation.

2. Current treatments

Several organizations have brought out guidelines for treatment of OA [13–16], thorough reviews of which are published elsewhere [17,
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 extent, 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].

3. 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 zirifluran, 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 [25,24,26].

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. There are multiple local structures which cause pain and the type of pain 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: biochemical outcomes, structural changes, pain, or all of the above?

4. 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 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 described per category, based on intended mechanism of action.

5. 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 (also) 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. Information on study phase and design are summarized in Tables 1-4.

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 stem cells or platelet-rich plasma (Table 3) and target cartilage- or viscosupplementation (Table 4).

5.1. 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 Naltrexone (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 analogetic [32], but for the effects of a dermal application of cannabidiol 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].

5.1.1. 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]. It has a long trajectory of (pre-)clinical development, with two FDA-mandated temporary holds because of rapidly progressive OA (RPOA), and sympathetic nerve system AEs [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 [42]. Nevertheless, phase III trials in knee- and hip OA are currently ongoing (Table 1).

### Table 1

| Intervention | (assumed) Mechanism | Target | N | Target joint | Randomized controlled trials N | Double blind N | Placebo controlled N | Placebo controlled |
|--------------|---------------------|--------|---|---------------|-------------------------------|---------------|---------------------|-----------------|
| Diclofenac, Ibuprofen, Ketoprofen, Naproxen | NSAIDs | COX | 10 | 9x knee, 1x lumbar spine | 10, 100% | 9, 90% | 6, 60% | NCT03081806 | NCT03110523 |
| | | | | | | | | NCT03434197 | NCT04421911 |
| Diflunisal (CB845) | GPCR – kappa opioid receptor agonist | Opioid receptor | 1 | 1x knee and hip | 1, 100% | 1, 100% | 1, 100% | NCT03978208 | NCT03199417 |
| | | | | | | | | NCT03691844 | NCT03172790 |
| | | | | | | | | NCT03277066 | NCT03691818 |
| | | | | | | | | NCT02944448 |
| Naltrexon | GPCR - Opioid receptor antagonists | Opioid receptor | 2 | 2x Not defined | 2, 100% | 2, 100% | 2, 100% | NCT03008590 | NCT04115020 |
| Tramadol, Celecoxib (YCY301) | GPCR - nonselective opioid receptor agonist, NSAID | Opoid and COX receptor | 1 | 1x knee | 1, 100% | 0, 0% | 0, 0% | NCT03850587 |
| Cannabis (CBD, THC) | GPCR - Cannabinoid receptor | Cannabisinoid receptor | 5 | 4x knee, 1x hand | 4, 80% | 4, 80% | 3, 60% | NCT03825965 | NCT04412837 |
| | | | | | | | | NCT03693833 | NCT04195269 |
| | | | | | | | | NCT02324777 |
| | | | | | | | | NCT03661996 | NCT03429049 |
| | | | | | | | | NCT03040743 | NCT04044742 |
| | | | | | | | | NCT04386980 | NCT03153813 |
| | | | | | | | | NCT03528369 | NCT02589439 |
| | | | | | | | | NCT03028870 |
| | | | | | | | | NCT03161093 | NCT03304379 |
| | | | | | | | | NCT03691974 | NCT02483329 |
| | | | | | | | | NCT03524500 | NCT03528566 |
| | | | | | | | | NCT02528188 | NCT02674386 |
| | | | | | | | | NCT02697773 | NCT02709486 |
| | | | | | | | | NCT04456686 |
| | | | | | | | | NCT04195269 |
| | | | | | | | | NCT02483329 |
| | | | | | | | | NCT03524500 |
| Fasinumab and Tanezumab | Monoclonal antibody | NGF pathway | 10 | 10x knee, 10x hip, 1x shoulder | 9, 90% | 9, 90% | 8, 80% | NCT03825965 | NCT04412837 |
| | | | | | | | | NCT03693833 | NCT04195269 |
| | | | | | | | | NCT02324777 |
| | | | | | | | | NCT03661996 | NCT03429049 |
| | | | | | | | | NCT03660943 | NCT04044742 |
| | | | | | | | | NCT04386980 | NCT03153813 |
| | | | | | | | | NCT03528369 | NCT02589439 |
| | | | | | | | | NCT03028870 |
| | | | | | | | | NCT03161093 | NCT03304379 |
| | | | | | | | | NCT03691974 | NCT02483329 |
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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, TGF transforming growth factor alpha, ACh acetylcholine, TRPM transient receptor potential melastatin.

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.
5.2. 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, osteocyte formation and joint dysfunction and present from an early stage of OA [10,44,45].

Clinically relevant inflammation is predominantly mediated by Toll-like receptors (TLRs) and the inflammasome through NLRP3 and NLRP12, the inflammasome [46,47]. However, results of hand OA-trials showed no beneficial effects on pain of TNF-α blockers adalimumab and etanercept [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 its expression is increased in osteoarthritic joint tissues [46]. However, results of hand OA-trials showed no beneficial effects on pain of TNF-α blockers adalimumab and etanercept [49–52].

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 osteoarthritis and joint dysfunction and present from an early stage of OA [10,44,45]. Previous studies with several compounds targeting IL-1 (AMG 108, Anakinra and Litikizumab), did not benefit patients with hand- or knee OA [49–52].

5.3. Pharmacological interventions

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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 in the literature, but generally range from 1-4 g per day.

For ongoing studies, NCT numbers are in bold.

Table 2

| Intervention | (assumed) Mechanism | Target | N | Target joint | Randomized controlled trials N, % | Double blind N, % | Placebo controlled N, % | NCT nrs. |
|-------------|---------------------|--------|---|--------------|-------------------------------|-----------------|----------------------|---------|
| Corticosteroids (Fluticasone, Dexamethasone) | Corticosteroid | Glucocorticoid receptor | 11 | 7x knee, 3x hip, 2x shoulder | 8, 73% | 4, 36% | 5, 45% | NCT04120402, NCT0123561 |
| Diacerein | Antraquinolone derivate | IL-1 | 2 | 2x knee | 2, 100% | 2, 100% | 2, 100% | NCT03750409, NCT04065074 |
| Adalimumab | TNF-α antibody | TNF-α | 2 | 2x knee | 2, 100% | 2, 100% | 2, 100% | NCT04160991, NCT03795010 |
| Otilimab (GSK3196165, MOR103) | Granulocyt macrophage-colony stimulating factor antibody (GM-CSF) | GM-CSF | 1 | hand | 1, 100% | 1, 100% | 1, 100% | NCT03046446, NCT03382262 |
| Tocilizumab | Anti-IL-6-receptor monoclonal antibody | IL-6 | 1 | hand | 1, 100% | 1, 100% | 1, 100% | NCT03378076, NCT03529942 |
| 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 |
| LMWF-5A, DMI9523 | Immunomodulation | TNF-α, IL-6 and IL-7 among others | 3 | 3x knee | 2, 67% | 2, 67% | 2, 67% | NCT03988023, NCT03182686 |
| Curcumin | Presumed inhibition to the release of inflammatory through NLRP3 | NLRP3 | 1 | Not defined | 1, 100% | 1, 100% | 1, 100% | NCT03349645 |
| Resveratrol | Immunomodulation | Several targets (T- and B-lymphocytes) | 1 | Knee | 1, 100% | 1, 100% | 1, 100% | NCT02905799 |
| UBX0101 | p53, MDM2 interaction inhibitor modulation of the nuclear factor-κB (NF-κB) and the Wnt signal transduction pathways | A3 adenosine receptor (A3AR) agonist IL17, IL23 | 1 | Knee | 1, 100% | 1, 100% | 1, 100% | NCT00837291 |

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, MDM2 mouse double minute 2 homolog.

Study status in clinicaltrials.gov November 2020 indicated in superscript.

For ongoing studies, NCT numbers are in bold.

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.

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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.

5.2.1. Multipotent mesenchymal stromal cells

Multiple clinical trials were initiated with mesenchymal stromal cells (MSC) 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 recovery from injury. Amongst other tissues, they reside in the diarthrodial 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 could have the potential to halt inflammation and regeneration of tissues [65].

The therapeutic regenerative effect 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 intra-articular injection of MSC after culture-expanding preparation lack standardization [14,61,64]. In order to draw conclusions about the efficacy of MSC, and to recommend MSC-based therapy for 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%), 45% of which 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 trials. 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 for knee OA, 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%), 45% of which 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 therapy for knee OA, 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%), 45% of which are blinded, and 24% are placebo controlled.

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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].

5.2.2. Platelet-rich plasma

Platelet-rich plasma (PRP) contains an elevated concentration of platelets, growth factors, cytokines, adhesive proteins and plasma proteins and leucocytes [72]. These constitute, 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 randomized studies, 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 clinicaltrials.gov (Table 3). Finally, few studies for the efficacy of PRP treatment of OA in joints other than knees 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 (1 undefined). Similarities are observed between the study designs of these studies and those investigating MSC: 80% of the studies are randomized, recruiting or Active, not recruiting. Study status in clinicaltrials.gov November 2020 indicated in superscript. 

### 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 | (assumed) Mechanism | Target | N | Target joint | Randomized controlled trials N, % | Double blind N, % | Placebo controlled N, % | NCT nr. |
|--------------|---------------------|--------|---|--------------|----------------------------------|-------------------|------------------------|---------|
| GLPG1972, M6495 | ADAMTS-5 inhibitors | ADAMTS-5 | 2 | 2x Knee | 2, 100% | 2, 100% | 2, 100% | NCT03595618 |
| MIV-711 | Selective cathepsin-K inhibitor | Cathepsin K | 2 | 2x Knee | 1, 50% | 1, 50% | 1, 50% | NCT02706265 |
| LRX712,TPX-100 | Regeneration and repair of cartilage | Chondrogenic progenitor cells | 2 | 2x Knee | 2, 100% | 2, 100% | 2, 100% | NCT04097379 |
| Lorecivivint(SMO4690) | DMRK kinase inhibitors; Wnt signalling pathway inhibitors | Wnt signalling | 7 | 7x Knee | 6, 86% | 6, 86% | 6, 86% | NCT04520607 |

**Table 4 continued...**
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 up-and-coming, but the applied preparation, dose, and dose interval vary, 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].

5.3. Cartilage metabolism and bone resorption

Table 4 captures pharmacological interventions which aim to restore or maintain cartilage and 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, and preserve cartilage.

Inhibitors for MMP have been evaluated as OA treatments, but their efficacy was poor and their 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].

Cathespin K is a lysosomal cysteine protease, expressed in osteoclasts and chondrocytes, which 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 LXR712 target chondroprogenitor cells, with the aim of 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 further 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 signalling stimulates production of pro-inflammatory cytokines and catabolic enzymes like MMP [87]. Wnt pathway inhibitor, Lorecivitvin (SMO4690) 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 Lorecivitvin 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 chondrocyte and chondroprogenitor cell populations, which have passed the preclinical stage and are evaluated in early phase I trials in knee OA patients (NCT043030, NCT02746068). And 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 formulations 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-I), 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 varying 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.

6. 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 analogies 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 obtain 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 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 design is 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, 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.

A 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 under investigation [99]. Furthermore, follow-up during the patient populations, using validated (wet-, digital-, or imaging-) biomarkers are thought essential players in the success of (clinical studies the development of OA and a set of clinically valid and responsive bio-
experiments. The feasibility of trials in phenotypically well-characterized samples of which are structural quantitative imaging and information gained from wearables [100].

7. Conclusion

High-quality research for compounds with potential disease modi-

fying 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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