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Exploring Future Horizons in Osteoarthritis Relief: Unveiling the Potential of Slow-Acting Drugs and Innovative Medications

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Abstract

Introduction:

The existing treatment options for osteoarthritis (OA) fall short of addressing the significant challenges this disease imposes on patients in today's society. It markedly diminishes the quality of life of those affected and is one of the leading causes of disability. While conventional pharmacological interventions such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids effectively address pain, they are not intended to halt disease progression and are associated with potential health risks. Symptomatic Slow-Acting Drugs for Osteoarthritis (SYSADOA) and innovative medications, rooted in our expanding understanding of OA pathogenesis, offer promising prospects for discovering improved treatment modalities.

State of knowledge:

The evolving understanding of OA's etiology highlights the necessity for tailored treatments that consider distinct disease phenotypes. This review critically examines SYSADOA, specifically focusing on chondroitin sulfate, glucosamine, and avocado-soybean unsaponifiables, as agents designed to address the underlying pathology of OA. Chondroitin sulfate demonstrates potential disease-modifying effects, however with conflicting study results that underscore the extent of its efficacy. Glucosamine exhibits varying disease-modifying effects, with short-term trials demonstrating more promising outcomes in pain reduction. Avocado-soybean unsaponifiables show promise in alleviating knee OA pain, yet their impact on hip OA symptoms remains inconclusive. The review extends its scope to novel drugs with potential disease-modifying effects, exploring proteinase inhibitors, fibroblast growth factors, Wnt-signaling pathway inhibitors, senolytic agents, anti-nerve growth factor agents, and transforming growth factor-β.

Conclusions:

Although preliminary studies indicate potential for certain novel agents, challenges and adverse effects necessitate further investigation through rigorous, high-quality research.

Keywords: Senotherapeutics; Osteoarthritis; Anti-Inflammatory Agents, Non-Steroidal; Glucosamine; Chondroitin Sulfates; Matrix Metalloproteinase Inhibitors;

Introduction

Osteoarthritis (OA), affecting over 500 million people globally, has become a major cause of disability. This trend is likely associated with the increasing prevalence of obesity and aging populations worldwide [1]. Chronic pain linked to osteoarthritis has wide-ranging socio-economic consequences, contributing to issues such as depression [2], treatment expenditures, and disability [3], also negatively affecting the quality of life in the aspects of vitality, general health, emotional role function, and social function [4]. This disease has been the third most common cause of disability-adjusted life years in females, right after unipolar major depression and ischemic heart disease [3]. Despite its profound impact, patients often feel their concerns are overlooked, while practitioners tend to view joint replacement surgery as the only solution [5]. The most common pharmacological treatment of OA includes non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, which both have been proven to be effective in pain management, yet most probably do not slow the progression of the disease and may lead to serious health issues.

Recognizing the challenges this disease imposes on patients and considering the shortcomings of existing treatments, it's crucial to recognize the demand for new, effective treatments with improved safety profiles. This review will focus on these novel drugs and closely examine the safety and efficacy of Symptomatic Slow-Acting Drugs for Osteoarthritis (SYSADOA).

The evolving view of the etiology of osteoarthritis

The etiopathogenesis of osteoarthritis is complex and involves multiple factors such as obesity, joint injury, genetics, and aging [6]. The understanding of this condition has progressed beyond a strictly mechanical perspective, now encompassing biomechanical, immunological, and genetic considerations [7]. It is believed that various pro-inflammatory signals, such as tissue necrosis factor-α, interferon-γ, interleukin-1, interleukin-5, and many more, initiate a molecular cascade that facilitates interaction between cells in the joint, resulting in a feed-forward loop that contributes to ongoing joint degradation [7]. The triggered inflammatory response impacts all components of the joint, resulting in the

deterioration of cartilage, the formation of osteophytes, and the development of subchondral sclerosis and synovial hyperplasia [6]. Depending on the main location of structural and molecular changes, researchers have distinguished three main phenotypes of OA: cartilage-driven, synovial-driven, and bone-driven [8]. In the realm of drug development, it is rational to assume that tailored treatments are required for individual phenotypes. [9]

Challenges associated with NSAIDs and opioid treatments

While NSAIDs have traditionally been deemed the primary option for initial OA-related chronic pain management, studies have revealed that these medications can lead to severe and life-threatening side effects, including gastrointestinal bleeding, renal failure, and cardiovascular diseases [10]. Even though cyclooxygenase-2 (COX-2) selective agents exhibited fewer side effects, they were associated with a heightened cardiovascular risk. Substantial evidence emerged linking them to conditions such as heart attack (MI), stroke, hypertension, exacerbation of chronic heart failure, and cardiovascular death [11].

Both in vitro and in vivo studies, particularly in animal models, analyze the molecular mechanisms of celecoxib and reveal its chondroprotective qualities, ability to prevent synovial hyperplasia, and inhibit bone destruction. These findings suggest that celecoxib, along with other coxibs, could potentially slow down the progression of osteoarthritis in humans [12]. However, the majority of available data on this topic regarding COX-2-specific NSAIDs has derived from studies involving celecoxib, and less information is available regarding the impact of other drugs within this group [13]. Some research has also provided opposite results, showing that NSAIDs could accelerate OA progression [14,15] This might occur because patients often engage in more physical activity which causes strain on joints affected by the disease [15]. Additionally, it is believed that NSAIDs, by blocking many pro-inflammatory pathways, may encourage the conversion of arachidonic acid to leukotrienes via the lipooxygenase pathway. The accumulation of various leukotrienes in body tissues through the lipoxygenase pathway could contribute to the induction of side effects typically observed in NSAIDs consumption [16]. It has been suggested that blocking both of those pathways could lead to better treatment results [17].

Slow-Acting Analgesics

The pain-relieving and disease-modifying properties of SYmptomatic Slow-Acting Drugs for OsteoArthritis (SYSADOA) have undergone extensive study over the last several decades; nevertheless, their effectiveness remains a subject of considerable debate. They have been established as safe therapeutic choices, except avocado-soybean unsaponifiables (ASUs), for which safety research remains inconclusive due to limited data [18]. It is noteworthy that EULAR still does not recommend SYSADOA in the treatment of OA except for chondroitin sulfate in hand OA [19].

Chondroitin sulfate

One of the more renowned and extensively studied SYSADOA is chondroitin sulfate (CS), a significant constituent of cartilage presumed to exert protective effects; yet research indicates conflicting results on its efficacy. A systematic review article, covering animal studies conducted between 2000 and 2021, revealed that certain studies demonstrated the positive impact of CS when administered in monotherapy. These positive effects were observed on both cartilage and the expression of biochemical osteoarthritis markers. However, it is important to highlight that in less than half of the studies analyzed, a negative impact or no effect was observed [20]. Numerous human clinical trials showed the disease-modifying potential of this compound. For instance, a double-blind placebo-controlled, two-year study demonstrated that CS reduced the loss of joint space width [21]. Another study showed no significant joint loss in the knee in patients receiving CS while the control group showed significant joint space narrowing of a mean of 0.14 ±0.61 mm after two years [22]. In a review from 2021, it was demonstrated that highly purified chondroitin sulfate effectively reduces the symptoms of OA and influences structural changes in the joints. Long-term CS treatment not only decreased the use of NSAIDs by patients but also mitigated associated side effects [23].

Glucosamine

Another well-known compound is glucosamine - a naturally occurring substance that plays a role in the formation and repair of cartilage. Animal studies have shown varying disease-modifying effects depending on the form of glucosamine. Most of them revealed the positive effect of glucosamine sulfate on the cartilage and OA biomarkers [20] with one showing a statistically significant positive effect on the synovial membrane [24]. Glucosamine hydrochloride, even though it has been more extensively studied in the past 20 years, showed

more unclear results [20]. In a large placebo-controlled clinical trial from 2008, it was found that more than twice as many patients from the placebo group underwent total knee replacement compared to those who had been receiving glucosamine, over an approximately 5-year period following drug discontinuation [25]. In a 2023 systematic review, the efficacy of glucosamine was examined, uncovering that short-term clinical trials demonstrated more encouraging pain reduction effects compared to long-term trials [26].

Animal studies investigating the effect of glucosamine-chondroitin combination therapies rarely showed inconclusively positive effects on the cartilage [20]. In a 2013 analysis of data from the Osteoarthritis Initiative Progression Cohort, it was found that the combination of chondroitin sulfate (CS) and glucosamine led to a reduction in the loss of cartilage volume in humans. The assessment, conducted using quantitative magnetic resonance imaging (qMRI), revealed changes that were not identifiable through X-rays, as suggested by the authors [27]. Another meta-analysis proved that both compounds had a statistically significant, yet minimal, effect on both joint structure and symptoms [28]. Conducting more rigorous and high-quality research is necessary to thoroughly assess the validity of such therapies.

Avocado-soybean unsaponifiables

Avocado-soybean unsaponifiables (ASUs) also known by the commercial name Piascledine 300, are a natural extract made from avocado and soybean oils, which have been studied for their potential anti-inflammatory and cartilage-protective effects. A recent meta-analysis demonstrated that they reduce pain intensity associated with knee OA, but did not affect hip OA symptoms. Furthermore, there was no significant difference in side effects compared to placebo [29].

Novel drugs and their potential disease-modifying effect

To date, the primary focus in osteoarthritis treatment has been on symptom reduction and achieving optimal pain control. Despite scientific studies indicating some positive effects of current drugs on osteoarthritis progression, the observed impact has usually been minimal. Termed Disease-Modifying Osteoarthritis Drugs (DMOADs), these pharmaceutical agents represent a targeted approach poised at fundamentally altering the natural history of osteoarthritis. Certain potential DMOADs are recognized for their effectiveness against other diseases but have only recently been explored as potential causal treatments for (OA).

Table 1. presents several novel drugs alongside their respective target tissue structures in the joint. Some of them are briefly discussed below in this review.

Table 1. Novel drugs in OA [30]

Drugs targeting inflammation primarily in the synovial fluid	**Drugs targeting cartilage**	**Drugs targeting bone structure**
Interleukin-1 inhibitor	**Fibroblast growth factor 18**	**Cathepsin K inhibitors**
Gevokizumab	Sprifermin	MIV-711
AMG108	**Proteanase inhibitors**	**Parathyroid hormone**
Lutikizumab	GLPG1972/S201086	Teriparatide
Anakinra	**Wnt signaling inhibitors**	**Matrix extracellular phosphoglycoprotein**
Canakinumab	Lorecivinint	TPX-100
Diacerein	**Transforming growth factor-beta**	**Bisphosphonates**
Tumor necrosis factor-alpha inhibitors	TG-C	**Strontium ranelate**
Adalimumab	**AMPK modulator**	**Vitamin D**
Etanercept	Metformin	
Infliximab	**Platelet riched plasma**	
Senolytic therapies	Human PRP	
UBX0101		
Fisetin		
Curcuma longa extract		

Proteinase inhibitors

The only cells present in the cartilage are chondrocytes which are surrounded by an extracellular matrix composed mainly of collagen and aggrecan – the most abundant proteoglycan which drives water into the cartilage. Proteinases that destroy aggrecan and

other proteoglycans could have a pivotal role in cartilage damage associated with OA [31]. However, administering the oral drug PG-116800 which inhibits matrix metalloprotease 13 (MMP13) responsible for collagen degradation in cartilage, did not demonstrate any discernible impact on the progression of knee osteoarthritis in patients after one year of treatment. Moreover, it frequently caused musculoskeletal adverse effects such as arthralgia (35%) and led to a higher reduction in range of motion relative to the placebo group [32]. Research on another proteinase known as aggrecanase (specifically ADAMTS5) as a potential contributor to the progression of osteoarthritis (OA) led to the exploration of GLPG1972/S201086, a drug acting as an ADAMTS5 inhibitor. In a phase I clinical trial, this drug demonstrated a favorable safety profile and effectively decreased aggrecanase activity [33]. However, the results from the phase II clinical trial, published in 2023, revealed that there was no significant reduction in cartilage loss compared to the placebo group [34].

Fibroblast growth factors

Sprimerfin is a recombinant human fibroblast growth factor 18 (rhFGF18) aimed at promoting cartilage growth by increasing the production of collagen and aggrecan. It is administered intermittently by intra-articular injections every 6-12 months. A phase I study revealed no systemic adverse effects and a good safety profile [35]. Phase II trials showed thickening of the cartilage which was dose-dependent and the structural changes to the knee joint were maintained 4 years after treatment. The subgroup in the trial with a higher risk of OA progression also exhibited clinical benefits and pain reduction. These structural effects were not reflected in clinical presentation in other patient subgroups, as no pain-reduction effect was measured [36].

Wnt-signaling pathway inhibitors

The Wnt signaling pathway, crucial for joint and bone development, presents a molecular target for novel therapies. Animal models have demonstrated that both inhibiting and activating the Wnt-β-catenin cascade can induce chronic arthritis [37]. Restoring the balance of these signaling routes in OA-afflicted joints is essential, potentially positively impacting joint structure. Lorecivivint, a Wnt-signaling pathway inhibitor administered intra-articularly, proved to be well-tolerated in a phase I study in 2017 [38]. A 2020 report of the phase II trial showed no pain management effect of lorecivivint at the 13-week endpoint.

However, in week 52 subjects from the UNI subgroup (showing moderate to severe, unilateral symptoms of knee OA) had a decrease in pain severity and an increase in mean joint space width (JSW) when treated with 0.07 mg of lorecivivint. The effect was even more pronounced in the UNI WP subgroup defined as having unilateral symptoms without widespread symptoms [39]. Several phase III studies have been completed or are ongoing; the preliminary results reveal that the JSW has improved in patients receiving lorecivivint while the placebo group experienced significant JSW loss [40,41].

Senolytic agents

Aging is considered a prominent factor in the progression of osteoarthritis, possibly facilitated by the accumulation of senescent cells in the cartilage. This accumulation triggers the Senescence-Associated Secretory Phenotype (SASP), characterized by the release of pro-inflammatory particles from these cells. These particles affect neighboring cells, contributing to the degradation of joint structures and driving inflammation [42]. These findings led researchers to explore potential senolytic agents that have pro-apoptotic properties leading to the death of senescent cells. One of them is UBX0101 – a drug that showed a good safety profile in phase 1 clinical trials [43]. Unfortunately, the efficacy in pain reduction was not confirmed in phase II trials where the researchers blamed the historically strong placebo effect on the group not receiving the drug [44]. Another senolytic agent, Navitoclax, already broadly studied in the treatment of hematological malignancies, has shown promising effects on cartilage during in vitro and in vivo rat models [45].

Anti-NGF agents

Emerging treatments for osteoarthritis not only focus on potential disease-modifying effects but also involve researchers exploring new approaches to pain management. Nerve growth factor (NGF) expression is found in cartilage, meniscus, and synovium, where it binds to nociceptors and is related to tissue injury and pain [46]. One of the anti-NGF agents studied in OA is tanezumab, a drug that showed high efficacy in pain management and physical function. However, clinical trials revealed cases of major adverse effects caused by tanezumab, such as rapidly progressive OA (RPOA) and osteonecrosis [47]. This has caused a hold in all anti-NGF programs which was lifted in 2017 with some additional safety requirements involving the lowering of the drug doses [46]. Phase III trials showed that among patients with moderate to severe symptoms tanezumab showed a reduction in pain

compared to the placebo group, but the effect was modest. Moreover, the incidence of RPOA was 1.4-2.8% and was dose-dependent; it was also shown that more patients receiving the drug had total joint replacement surgeries [48].

Transforming growth factor-β

Transforming growth factor-β (TGFβ) is believed to induce osteogenesis and chondrogenesis. The dysregulation of TGFβ related signaling in aging chondrocytes drives fibrosis, subchondrial bone changes and osteophyte formation in OA, by increasing pro-catabolic pathways and decreasing pro-anabolic pathways [49]. Invossa (Tissue Gene-C) is a bioproduct consisting of a combination of allogeneic human chondrocytes (GP2-293 cells) and non-irradiated allogeneic human chondrocytes, retrovirally transduced in a 1:3 ratio to enhance TGF-β1 transcription. In phase I, it did not cause serious adverse effects and was generally well tolerated [50]. Phase III studies have demonstrated the improvement in pain, sports activities, and quality of daily life in patients after a 1-year follow-up of administering a single dose of Invossa [51].

Conclusions

Current conservative treatment modalities for osteoarthritis (OA) predominantly center on pain management through the utilization of established agents. However, the efficacy of these agents is inconsistent, and their impact on disease progression remains questionable. Even SYSADOA, designed to address the fundamental pathology of the disease and serve as a foundation for joint regeneration, have yielded varying outcomes in numerous placebo-controlled studies and are conspicuously absent from international guidelines. These widely available treatments appear to be limited when contrasted with the significant progress made in understanding the etiopathology of osteoarthritis in recent years. Fortunately, the developmental landscape includes numerous potential disease-modifying agents targeting diverse pathogenetic factors implicated in OA. Even though some of them show promising results in phase II and III trials, more quality, placebo-controlled studies on their long-term effects should be performed. Pioneering research in the pharmaceutical treatment of OA has the potential to significantly influence the available therapeutic options for patients and provide healthcare providers with clear guidelines.

Author contributions

Conceptualization, KS and DB; methodology, MK and IM; check, KS, PP, DB and BW; formal analysis, MK, ML, PP, KS and BW; investigation, KS and IM; data curation, IM, PP, ML, BW; writing - rough preparation, KS; writing - review and editing, DB, BW, PP and ML; visualization, KS, DB and IM; supervision, KS, PP; project administration, KS. All authors have read and agreed with the published version of the manuscript.

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References:

[1] Hunter DJ, March L, Chew M. Osteoarthritis in 2020 and beyond: a Lancet Commission. Lancet 2020;396:1711–2. https://doi.org/10.1016/S0140-6736(20)32230-

3.
[2] Luong M-LN, Cleveland RJ, Nyrop KA, Callahan LF. Social determinants and osteoarthritis outcomes. Aging Health 2012;8:413–37. https://doi.org/10.2217/ahe.12.43.
[3] Brooks PM. Impact of osteoarthritis on individuals and society: how much disability? Social consequences and health economic implications. Curr Opin Rheumatol 2002;14:573–7. https://doi.org/10.1097/00002281-200209000-00017.
[4] Yan H, Guo J, Zhou W, Dong C, Liu J. Health-related quality of life in osteoarthritis patients: a systematic review and meta-analysis. Psychol Health Med 2022;27:1859–74. https://doi.org/10.1080/13548506.2021.1971725.
[5] Alami S, Boutron I, Desjeux D, Hirschhorn M, Meric G, Rannou F, et al. Patients' and practitioners' views of knee osteoarthritis and its management: a qualitative interview study. PLoS ONE 2011;6:e19634. https://doi.org/10.1371/journal.pone.0019634.
[6] Chen D, Shen J, Zhao W, Wang T, Han L, Hamilton JL, et al. Osteoarthritis: toward a comprehensive understanding of pathological mechanism. Bone Res 2017;5:16044. https://doi.org/10.1038/boneres.2016.44.
[7] Woodell-May JE, Sommerfeld SD. Role of inflammation and the immune system in the progression of osteoarthritis. J Orthop Res 2020;38:253–7. https://doi.org/10.1002/jor.24457.
[8] Oo WM, Hunter DJ. Repurposed and investigational disease-modifying drugs in osteoarthritis (DMOADs). Ther Adv Musculoskelet Dis 2022;14:1759720X221090297. https://doi.org/10.1177/1759720X221090297.
[9] Karsdal MA, Michaelis M, Ladel C, Siebuhr AS, Bihlet AR, Andersen JR, et al. Disease-modifying treatments for osteoarthritis (DMOADs) of the knee and hip: lessons learned from failures and opportunities for the future. Osteoarthr Cartil 2016;24:2013–21. https://doi.org/10.1016/j.joca.2016.07.017.
[10] McCarberg B, Tenzer P. Complexities in the pharmacologic management of osteoarthritis pain. Curr Med Res Opin 2013;29:539–48. https://doi.org/10.1185/03007995.2013.785391.
[11] Graham DJ, Campen D, Hui R, Spence M, Cheetham C, Levy G, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. Lancet 2005;365:475–81. https://doi.org/10.1016/S0140-6736(05)17864-7.
[12] de Boer TN van RJ Bijlsma JW, Lafeber FP, Mastbergen SC Zweers MC. Celecoxib considerations regarding its potential. Arthritis Res Ther 2011;13(5):239.
[13] Nakata K, Hanai T, Take Y, Osada T, Tsuchiya T, Shima D, et al. Disease-modifying effects of COX-2 selective inhibitors and non-selective NSAIDs in osteoarthritis: a systematic review. Osteoarthr Cartil 2018;26:1263–73. https://doi.org/10.1016/j.joca.2018.05.021.
[14] Perry TA, Wang X, Nevitt M, Abdelshaheed C, Arden N, Hunter DJ. Association between current medication use and progression of radiographic knee osteoarthritis: data from the osteoarthritis initiative. Rheumatology (Oxford) 2021;60:4624–32.

https://doi.org/10.1093/rheumatology/keab059.
[15] Reijman M, Bierma-Zeinstra SMA, Pols HAP, Koes BW, Stricker BHC, Hazes JMW. Is there an association between the use of different types of nonsteroidal antiinflammatory drugs and radiologic progression of osteoarthritis? The Rotterdam Study. Arthritis Rheum 2005;52:3137–42. https://doi.org/10.1002/art.21357.
[16] Burnett BP, Levy RM. 5-Lipoxygenase metabolic contributions to NSAID-induced organ toxicity. Adv Ther 2012;29:79–98. https://doi.org/10.1007/s12325-011-0100-7.
[17] Anderson GD, Keys KL, De Ciechi PA, Masferrer JL. Combination therapies that inhibit cyclooxygenase-2 and leukotriene synthesis prevent disease in murine collagen induced arthritis. Inflamm Res 2009;58:109–17. https://doi.org/10.1007/s00011-009-8149-3.
[18] Honvo G, Reginster J-Y, Rabenda V, Geerinck A, Mkinsi O, Charles A, et al. Safety of Symptomatic Slow-Acting Drugs for Osteoarthritis: Outcomes of a Systematic Review and Meta-Analysis. Drugs Aging 2019;36:65–99. https://doi.org/10.1007/s40266-019-00662-z.
[19] Kwaśniewska A, Chudala M, Romanowski W. Recommendations for the use of imaging and management of osteoarthritis in the light of current guidelines. Rheumatology Forum 2022;8:1–5. https://doi.org/10.5603/RF.2022.0001.
[20] Fernández-Martín S, González-Cantalapiedra A, Muñoz F, García-González M, Permuy M, López-Peña M. Glucosamine and Chondroitin Sulfate: Is There Any Scientific Evidence for Their Effectiveness as Disease-Modifying Drugs in Knee Osteoarthritis Preclinical Studies?-A Systematic Review from 2000 to 2021. Animals (Basel) 2021;11. https://doi.org/10.3390/ani11061608.
[21] Kahan A, Uebelhart D, De Vathaire F, Delmas PD, Reginster J-Y. Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: the study on osteoarthritis progression prevention, a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2009;60:524–33. https://doi.org/10.1002/art.24255.
[22] Michel BA, Stucki G, Frey D, De Vathaire F, Vignon E, Bruehlmann P, et al. Chondroitins 4 and 6 sulfate in osteoarthritis of the knee: a randomized, controlled trial. Arthritis Rheum 2005;52:779–86. https://doi.org/10.1002/art.20867.
[23] Reginster J-Y, Veronese N. Highly purified chondroitin sulfate: a literature review on clinical efficacy and pharmacoeconomic aspects in osteoarthritis treatment. Aging Clin Exp Res 2021;33:37–47. https://doi.org/10.1007/s40520-020-01643-8.
[24] Wen ZH, Tang CC, Chang YC, Huang SY, Hsieh SP, Lee CH, et al. Glucosamine sulfate reduces experimental osteoarthritis and nociception in rats: association with changes of mitogen-activated protein kinase in chondrocytes. Osteoarthr Cartil 2010;18:1192–202. https://doi.org/10.1016/j.joca.2010.05.012.
[25] Bruyere O, Pavelka K, Rovati LC, Gatterová J, Giacovelli G, Olejarová M, et al. Total joint replacement after glucosamine sulphate treatment in knee osteoarthritis: results of a mean 8-year observation of patients from two previous 3-year, randomised, placebo-controlled trials. Osteoarthr Cartil 2008;16:254–60. https://doi.org/10.1016/j.joca.2007.06.011.
[26] Vo NX, Le NNH, Chu TDP, Pham HL, Dinh KXA, Che UTT, et al. Effectiveness and

safety of glucosamine in osteoarthritis: A systematic review. Pharmacy (Basel) 2023;11. https://doi.org/10.3390/pharmacy11040117.

[27] Martel-Pelletier J, Roubille C, Abram F, Hochberg MC, Dorais M, Delorme P, et al. First-line analysis of the effects of treatment on progression of structural changes in knee osteoarthritis over 24 months: data from the osteoarthritis initiative progression cohort. Ann Rheum Dis 2015;74:547–56. https://doi.org/10.1136/annrheumdis-2013-203906.

[28] Yang W, Sun C, He SQ, Chen JY, Wang Y, Zhuo Q. The Efficacy and Safety of Disease-Modifying Osteoarthritis Drugs for Knee and Hip Osteoarthritis-a Systematic Review and Network Meta-Analysis. J Gen Intern Med 2021;36:2085–93. https://doi.org/10.1007/s11606-021-06755-z.

[29] Simental-Mendía M, Sánchez-García A, Acosta-Olivo CA, Vilchez-Cavazos F, Osuna-Garate J, Peña-Martínez VM, et al. Efficacy and safety of avocado-soybean unsaponifiables for the treatment of hip and knee osteoarthritis: A systematic review and meta-analysis of randomized placebo-controlled trials. Int J Rheum Dis 2019;22:1607–15. https://doi.org/10.1111/1756-185X.13658.

[30] Li S, Cao P, Chen T, Ding C. Latest insights in disease-modifying osteoarthritis drugs development. Ther Adv Musculoskelet Dis 2023;15:1759720X231169839. https://doi.org/10.1177/1759720X231169839.

[31] Troeberg L, Nagase H. Proteases involved in cartilage matrix degradation in osteoarthritis. Biochim Biophys Acta 2012;1824:133–45. https://doi.org/10.1016/j.bbapap.2011.06.020.

[32] Krzeski P, Buckland-Wright C, Bálint G, Cline GA, Stoner K, Lyon R, et al. Development of musculoskeletal toxicity without clear benefit after administration of PG-116800, a matrix metalloproteinase inhibitor, to patients with knee osteoarthritis: a randomized, 12-month, double-blind, placebo-controlled study. Arthritis Res Ther 2007;9:R109. https://doi.org/10.1186/ar2315.

[33] van der Aar E, Deckx H, Dupont S, Fieuw A, Delage S, Larsson S, et al. Safety, Pharmacokinetics, and Pharmacodynamics of the ADAMTS-5 Inhibitor GLPG1972/S201086 in Healthy Volunteers and Participants With Osteoarthritis of the Knee or Hip. Clin Pharmacol Drug Dev 2022;11:112–22. https://doi.org/10.1002/cpdd.1042.

[34] Schnitzer T, Pueyo M, Deckx H, van der Aar E, Bernard K, Hatch S, et al. Evaluation of S201086/GLPG1972, an ADAMTS-5 inhibitor, for the treatment of knee osteoarthritis in ROCCELLA: a phase 2 randomized clinical trial. Osteoarthr Cartil 2023;31:985–94. https://doi.org/10.1016/j.joca.2023.04.001.

[35] Dahlberg LE, Aydemir A, Muurahainen N, Gühring H, Edebo HF, Krarup-Jensen N, et al. A first-in-human, double-blind, randomised, placebo-controlled, dose ascending study of intra-articular rhFGF18 (sprifermin) in patients with advanced knee osteoarthritis First-in-human study of sprifermin in knee OA / L.E. Dahlberg et al 2016;34:443–50.

[36] Guehring H, Moreau F, Daelken B, Ladel C, Guenther O, Bihlet AR, et al. The effects of sprifermin on symptoms and structure in a subgroup at risk of progression in the

FORWARD knee osteoarthritis trial. Semin Arthritis Rheum 2021;51:450–6. https://doi.org/10.1016/j.semarthrit.2021.03.005.

[37] Lories RJ, Corr M, Lane NE. To Wnt or not to Wnt: the bone and joint health dilemma. Nat Rev Rheumatol 2013;9:328–39. https://doi.org/10.1038/nrrheum.2013.25.

[38] Yazici Y, McAlindon TE, Fleischmann R, Gibofsky A, Lane NE, Kivitz AJ, et al. A novel Wnt pathway inhibitor, SM04690, for the treatment of moderate to severe osteoarthritis of the knee: results of a 24-week, randomized, controlled, phase 1 study. Osteoarthr Cartil 2017;25:1598–606. https://doi.org/10.1016/j.joca.2017.07.006.

[39] Yazici Y, McAlindon TE, Gibofsky A, Lane NE, Clauw D, Jones M, et al. Lorecivivint, a Novel Intraarticular CDC-like Kinase 2 and Dual-Specificity Tyrosine Phosphorylation-Regulated Kinase 1A Inhibitor and Wnt Pathway Modulator for the Treatment of Knee Osteoarthritis: A Phase II Randomized Trial. Arthritis Rheumatol 2020;72:1694–706. https://doi.org/10.1002/art.41315.

[40] Yazici Y, Swearingen C, Ghandehari H, Simsek I, Kennedy S, Tambiah J, et al. Pos1365 structural severity in knee osteoarthritis impacts treatment response: a post hoc pooled analysis of lorecivivint clinical trials. Scientific Abstracts, BMJ Publishing Group Ltd and European League Against Rheumatism; 2023, p. 1035.1-1035. https://doi.org/10.1136/annrheumdis-2023-eular.2791.

[41] Yazici Y, Swearingen C, Lopez V, Britt J, Kennedy S, Tambiah J, et al. Op0074 radiographic and pain outcomes from a phase 3 extension study evaluating the safety and efficacy of lorecivivint in subjects with severe osteoarthritis of the knee (oa-07): single blind and crossover results. Scientific Abstracts, BMJ Publishing Group Ltd and European League Against Rheumatism; 2023, p. 50.2-51. https://doi.org/10.1136/annrheumdis-2023-eular.2833.

[42] Coryell PR, Diekman BO, Loeser RF. Mechanisms and therapeutic implications of cellular senescence in osteoarthritis. Nat Rev Rheumatol 2021;17:47–57. https://doi.org/10.1038/s41584-020-00533-7.

[43] Hsu B, Visich J, Lane NE, Li L, Mittal J, An M, et al. Safety, tolerability, pharmacokinetics, and clinical outcomes following treatment of painful knee osteoarthritis with senolytic molecule UBX0101. Osteoarthr Cartil 2020;28:S479–80. https://doi.org/10.1016/j.joca.2020.02.752.

[44] Lane N, Hsu B, Visich J, Xie B, Khan A, Dananberg J. A phase 2, randomized, double-blind, placebo-controlled study of senolytic molecule UBX0101 in the treatment of painful knee osteoarthritis. Osteoarthr Cartil 2021;29:S52–3. https://doi.org/10.1016/j.joca.2021.02.077.

[45] Yang H, Chen C, Chen H, Duan X, Li J, Zhou Y, et al. Navitoclax (ABT263) reduces inflammation and promotes chondrogenic phenotype by clearing senescent osteoarthritic chondrocytes in osteoarthritis. Aging (Albany NY) 2020;12:12750–70. https://doi.org/10.18632/aging.103177.

[46] Latourte A, Kloppenburg M, Richette P. Emerging pharmaceutical therapies for osteoarthritis. Nat Rev Rheumatol 2020;16:673–88. https://doi.org/10.1038/s41584-020-00518-6.

[47] Miller RE, Block JA, Malfait A-M. Nerve growth factor blockade for the management

of osteoarthritis pain: what can we learn from clinical trials and preclinical models? Curr Opin Rheumatol 2017;29:110–8. https://doi.org/10.1097/BOR.0000000000000354.

[48] Schnitzer TJ, Easton R, Pang S, Levinson DJ, Pixton G, Viktrup L, et al. Effect of tanezumab on joint pain, physical function, and patient global assessment of osteoarthritis among patients with osteoarthritis of the hip or knee: A randomized clinical trial. JAMA 2019;322:37–48. https://doi.org/10.1001/jama.2019.8044.

[49] van der Kraan PM. The changing role of TGFβ in healthy, ageing and osteoarthritic joints. Nat Rev Rheumatol 2017;13:155–63. https://doi.org/10.1038/nrrheum.2016.219.

[50] Ha C-W, Noh MJ, Choi KB, Lee KH. Initial phase I safety of retrovirally transduced human chondrocytes expressing transforming growth factor-beta-1 in degenerative arthritis patients. Cytotherapy 2012;14:247–56. https://doi.org/10.3109/14653249.2011.629645.

[51] Cho J, Kim T, Park Y, Shin J, Kang S, Lee B. Invossa^{TM}(Tissuegene-C) in patients with osteoarthritis: A phase III trial. Osteoarthr Cartil 2016;24:S190. https://doi.org/10.1016/j.joca.2016.01.374.