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Review Article

Osteoarthritis

Pharmacological Therapy approaches for the treatment of Knee Osteoarthritis

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To date, no effective treatment has been able to modify the pathological progression of osteoarthritis (OA). Current therapy can be broadly categorized into pharmacological and non-pharmacological approaches before considering surgical interventions. Non-pharmacological methods address lifestyle modifications, weight reduction and physical therapy, all aiming at alleviating mechanical stress on the affected joint. In this article, we focused on pharmacological treatment options, that primarily target pain reduction by reducing joint inflammation or restoring the altered synovial environment to a normal state. In this literature review, the main focus is on approved conservative therapies and examined emerging conservative strategies. Evaluating their advantages and limitations.

Keywords: Knee, Non-Steroidal Anti-Inflammatory Drugs (NSAID), Osteoarthritis, Pain, Pharmacological Treatment

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Background

Osteoarthritis (OA) is the most common degenerative disease among geriatric patients and a major cause of significant disability in daily tasks. The degradation of articular cartilage follows the inflammation of the synovial cavity resulting in pain. Bone friction from joint space shortening, osteophyte growth, periosteum stretching, and increased intraosseous pressure also produce pain [1].

Typically the pain starts as an intense pain at heavy impact, then becomes more frequent with stiffness, and finally leads to a persistent throbbing ache with episodes of excruciating pain [2]. Joint stiffness is another clinical feature of OA, defined as perceived joint flexibility that occurs in the morning or after a long rest and improves and resolves at early OA stages with movement. Furthermore, OA can cause bone enlargement and swelling by soft tissue inflammation, blocked blood circulation, chondrocyte damage, and cyst formation, leading to bone remodelling with osteophyte formation, joint subluxation, capsular thickening, synovial hyperplasia, and synovial effusion. All factors together lead to an impairment of joint function and reduced range of motion1.OA can be divided into primary and secondary OA. Hereditary changes in type II, IX, or XI collagen in articular cartilage can cause premature OA in young people, contrary to secondary osteoarthritis that develops after a previous injury, joint deformity, or disease [3-4].

Anatomic and demographic factors, such as gender and ethnicity, also contribute to OA. Women and African American, Chinese, and Hispanic populations are at higher risk [1,5]. Various pharmaceutical treatments for OA are available, including NSAIDs in combination with other drugs such as proton pump inhibitors, opioid analgesics, cartilage active agents, and phytopharmaceuticals. Topical agents are also preferred for their limited side effects and patient acceptance. Furthermore, glucocorticoids and hyaluronic acid injections are used for intraarticular OA treatment [6]. Used treatment recommendations can vary between countries and professional societies and the results can vary between patients. In this article we discuss pharmacological methods that are already investigated and usedoff-label, considering their advantages and disadvantages.

Search Strategy

A literature search was carried out on PubMed, UpToDate and Google Scholar with the keywords “knee osteoarthritis”, “new pharmacologic agents”, and “new approaches”. Only the pertinent articles were chosen for further analysis. Articles with recently released data were given priority and articles exceeding a decade in age were excluded.

Pathological Changes in Osteoarthritis

In OA extensive matrix degradation is caused by the continuous production of proteases, stimulated by pro-inflammatory cytokines. Upregulation of interleukin (IL) 1, 6 and 8 stimulates the production of proteases, nitric acid (NA) and eicosanoids (prostaglandins and leukotrienes) in chondrocytes and macrophages. As a result, catabolic pathways are stimulated, matrix synthesis is inhibited, and cell apoptosis is promoted. Especially IL-1, which together with tumour necrosis factor (TNF) - α promotes the synthesis of metalloproteinases (MMP) -1, 3, 13 increases the promotion of cartilage matrix breakdown and reduces the synthesis of matrix components such as proteoglycans, aggrecans, and type II collagen. More precisely, the proteases MMP-1 and MMP-13 are responsible for the degradation of the collagenous framework, while stromelysin (MMP-3) and the aggrecan ADAMT-4 are responsible for proteoglycan degradation [7]. Further inflammatory mediator enzymes, such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2, are altered in OA. The upregulation of these enzymes is stimulated by increased gene expression. iNOS is responsible for the generation of NO, which contributes to cartilage degradation by upregulating MMPs and additionally inhibits the synthesis of proteoglycans and collagen. COX-2 is responsible for the production of prostaglandin E2 (PGE2) and additionally inhibits proteoglycan and collagen synthesis. Increased production of PGE2 leads to increased inflammation, apoptosis, and structural changes in OA [8]. All of these pathways together lead to the development and progression of OA. Blocking or altering either of them gives us options to target the disease.

Common Pharmacological Treatment Options

Topical NSAID Applications: Currently, only a few medications are approved for the treatment of knee OA. First-line therapy for mild to moderate knee OA is the use of topical NSAIDs.

Especially, ibuprofen is recommended because it is comparatively safe, cost-efficient, and clinically effective. The benefit of topical applications compared to oral prescriptions is that the first pass (liver metabolism) is skipped. Higher local plasma concentrations can be achieved with a relatively low dosage. For oral prescriptions, a higher dosage with a resulting higher systemic exposure is needed to achieve the same local dose. Therefore, topical applications have side effects associated with local skin reactions such as itching or rashes, whereas oral administrations have a higher risk of systemic reactions, overdosing, and drug-drug interactions. The mechanism of action for topical or oral applications is that pain in patients with OA is, as discussed above, a direct result of inflammatory processes. The metabolism of arachidonic acid potentiates the effects of histamine over two pathways: It increases the permeability of blood vessel walls and decreases the pain threshold in peripheral neurons by nociceptor sensitization. NSAIDs such as ibuprofen inhibit prostanoids and thereby the release of histamines and bradykinins, reducing local inflammation and nociceptive transmission. Although topical administration has a lower risk of systemic adverse effects, the relatively low plasma concentration and slow absorption are the biggest disadvantages. Only moderate results of pain reduction can be achieved[9,10]. Taking this into account, topical application of NSAIDs such as ibuprofen or diclofenac is beneficial for short-term pain reduction in mild cases of OA but cannot be used in advanced cases.

Oral NSAIDs: Other already approved options for pain treatment in OA are oral NSAIDs. They work by inhibiting the COX-1 and/or COX-2 signalling pathway in that way inhibiting prostaglandin synthesis and nociceptive transmission as described above. The advantage of oral administration is that higher plasma concentrations and therefore greater pain reduction can be achieved. The disadvantage involves that the mechanisms of COX-1 and COX-2 are not only involved in inflammatory processes at the site of OA but are also important in gastric protection and renal perfusion processes [9, 10]. Inhibition of these enzymes leads to many side effects, such as gastric ulcers or renal hypoperfusion. Therefore, usage should be limited to the lowest dosage and the shortest time possible. At the moment, mainly diclofenac or ibuprofen is used as a standard over-the-counter NSAID [11]. Alternative NSAIDs include Etodolac or Lornoxicam, which reduce pain in cases of knee OA and produce significantly fewer gastrointestinal (GI) side effects [12]. The mechanism of action is the same but with different intensities. Another approach is to use eterocoxibum, as an elective inhibitor of the COX-2 pathway, which has a lower risk of unwanted GI side effects, but a greater risk for patients with cardiovascular diseases [13].To conclude, the use of oral NSAIDs in the treatment of knee OA is only beneficial for symptomatic pain relief and does not influence the disease progression. So other approaches, such as intraarticular injections of glucocorticoids, are also recommended, and their benefits and mechanism of action are discussed in the next chapter [13,14].

Intraarticular Corticosteroid Injections (IACI)

Injections such as triamcinolone acetonide act on disease progression in knee OA by modulating synovial inflammation with their potent anti-inflammatory properties. Their mode of action is that by binding to glucocorticoid receptors on cartilage cells, anti-inflammatory responses are activated, leading to downregulation of pro-inflammatory cytokines, prostaglandins, arachidonic acid, lipocortin and leukotriene expression. As a drawback these beneficial effects are only for a brief time, achieving meaningful pain reduction only for 1 to 5 months, depending on the administered glucocorticoid [15]. The short action interval and systemic side effects are the biggest problems in the use of IACI. Furthermore, close monitoring of time intervals and dosage must be performed, as many studies have shown that beneficial effects are only achieved at low doses, while prolonged exposure and high dosage lead to detrimental effects [15,16]. Therefore, careful administration should be performed, and more approaches must be investigated. Theside effects of IACI administration can be significantly reduced when using extended-release polylactic co-glycolic acid (PLGA) microsphere-based formulations of 32mg triamcinolone acetonide. Significantly reducing the risk of blood glucose elevation with the same pain-relieving effects as corticosteroid formulations and a longer effective period without worsening the progression of OA [17]. The use of IACI has shown that, despite the benefits of low cost and easy access, there are many backfires, such as systemic side effects the possibility of damage to the joints and an eruption of the OA process.

***Intraarticular Hyaluronic Acid*:** Other approaches to intraarticular medications (IA), such as hyaluronic acid (HA) or platelet-rich plasma (PRP), are still not included in the recommended treatment plan for knee OA.HA is a high molecular weight glucosamine synthesized by fibroblasts, chondrocytes, and synoviocytes. These are responsible for the viscoelastic and lubricant features of the synovial fluid, protecting the cartilage from mechanical degradation. In the case of OA, the amount and molecular weight of endogenous HA decreases due to abnormal synoviocyte production and molecular fragmentation, but the exact mechanism of symptom improvement is not yet fully understood [18,19]. Many studies have proven the safety and short-term efficacy of HA (<6 months) [20], but there are different results on the severity of side effects and long-term efficacy.

Intraarticular Growth Factor and Platelet-Rich Plasma Injections

Growth factors (GF) are known to be beneficial in chemotaxis, mesenchymal stem cell differentiation, chondrocyte proliferation, and osseous and cartilaginous cell synthetic activities, thus playing a key role in remodelling processes of cartilaginous tissues19.In the autologous biological treatment of patients with their platelet-enriched plasma (PRP), the release of GF from platelets and the endogenous fibrin scaffold is used. Supraphysiological release of platelet-derived factors directly at the desired location, stimulates chondrocyte and mesenchymal stem cell proliferation, thus promoting the synthesis of type II collagen. Furthermore, suppression of inflammatory mediators such as IL-1 leads to analgesic and anti-inflammatory properties. The study by H. Bansal et al. [21] showed that inactivated PRP has significant chondroprotective and symptom-alleviating properties. Other studies also state that the right number of cells in the injection is crucial to its efficacy and that a therapeutic injection of PRP should contain a plasma concentration of 200,000 mm3 cells, with higher or lower concentrations being ineffective or even having suppressive effects on the healing process [22].

***Activated Plasma IA injections*:** The use of activated plasma, plasma that is enriched in leucocytes (L-PRP) or enriched with fibrin (P-PRF) can lead to a higher release of signalling elements.

The use of leukocyte platelet-rich plasma (L-PRP) is still under discussion since animal models have given both positive and negative results. The idea behind the use of L-PRP is that leukocytes, which are involved in the inflammatory phase, can release both inflammatory and anti-inflammatory molecules. After injection of L-PRP, activated platelets release arachidonic acid that, in the next step, neutrophils pick up and then convert into inflammatory mediators (prostaglandins and leukotrienes). The leukotrienes can be picked up by platelets and converted into lipoxin, an anti-inflammatory protein that limits neutrophil activation and promotes the resolution phase in the healing process, in this way, reducing tissue degradation due to prolonged inflammation [23]. A study on cultivated OA synoviocytes showed that an L-PRP preparation compared to a P-PRP and PPP preparation led to long-term upregulation of pro-inflammatory factors (IL-1ß, IL-8 and FGF-2) and additionally, to down-regulation of human growth factor (HGF) and TIMP-4 expression, which are known to be anticatabolic mediators. Thereby supporting the theory that L-PRP, at least until the environment is changed, leads to a proinflammatory reaction. P-PRP and PPP, compared to this, did not cause pro-inflammatory reactions and did not show significant differences in gene activation. The benefit of either of these injections is immense rapid results with pain reduction in less than an hour and the result can last for almost 2 months [24]. Still, there are many potential risks: optimal dosage, sterile injection application, and high expenses [23,24]. In the next chapter conservative therapy methods, which are still under investigation, will be evaluated.

New Inflammatory Pathway-Altering Drugs

Interleukin 1 Antagonists: As described above, proinflammatory molecules play an important role in pain and progression of OA; therefore, their inhibition could give us one possible pathway to treat OA. Interleukin 1 (IL-1) is a proinflammatory cytokine and pain mediator. IL-1 has two subclasses: IL-1ß, secreted by innate immune cells after caspase-1 cleavage and IL-1a, which is stored intracellular or in membranes and is secreted after cell damage. Both bind to the IL-1R1 receptor and induce inflammatory and pain responses, but both IL-1a and IL-1ß are increased in the synovial fluid of patients with knee OA and thereby promote tissue destruction in knee OA.

The mechanism is that by activation of enzymes involved in cartilage destruction, inhibition of collagen synthesis, promotion of osteoclast genesis, and pain mediation in the peripheral and central nervous system is achieved. Therefore, antagonists to IL-1ß are important to reduce the progression of cartilage lesions. One of these antagonists is the human monoclonal antibody IL-1R1 AMG 10825,26. Injection of AMG 108 can reduce CRP and neutrophil counts in patients with knee OA but gives only minor clinical improvement. Resembling results were found with another investigated IL-1 inhibitor lutikizumab, which inhibits IL-1a and IL-1ß simultaneously, leading to a reduction in pain. Additionally, no changes in cartilage thickness or other structural endpoints were detectable, leading to the conclusion that IL-1 inhibition is not effective as a disease-modifying therapy [25].

Tumour Necrosis Factor Antagonists

Other cytokines involved in tissue destruction in knee OA are tumour necrosis factors (TNFs). Approaches to inhibit these mediators by TNF rec 1 antagonist (TNF α) showed that this can inhibit type II collagen cleavage and increase glycosaminoglycan release in OA cartilage cultures[26]. Furthermore, the down-regulation of genes of MMP1, MMP3, and MMP13 could be held responsible for the degradation of the extracellular matrix in the synovial cleft, promoting pain in patients with knee OA. Investigated IA injections of adalimumab showed effectiveness in reducing signs and symptoms of inflammation in knee OA and improving functionality [27]. Another investigated TNF α inhibitor is etanercept, which shows an improvement in pain, measured by the Western Ontario and McMaster Universities Arthritis Index (WOMAC) [28].

Nuclear Factor Kappa B Inhibitors

The proinflammatory mediators IL-1ß and TNF α, are increasingly synthesized in the case of OA and are activating the transcription factor nuclear factor kappa B (NFxB), which is responsible for the transcription of genes encoding pro-inflammatory cytokines, enzymes like COX-2 or metalloproteinases (MMP-1,3,13) and thereby promotes inflammation and cartilage degradation. By inhibiting IxB kinase, which is a key enzyme in the NFxB pathway, the inflammatory process is believed to be altered and reduced.

Some studies have already been conducted where IkB kinase-inhibiting compounds were used systemically to treat systemic inflammatory diseases. These showed high liver toxicity and were not further investigated. K.Grthe et al. [29] started a trial with IA SAR113945- an IkB kinase inhibitor in patients with knee OA. With a slow-release formulation and local administration, it was possible to prevent systemic toxicity. The results showed a reduction in the number of pro-inflammatory markers and significantly reduced effusion. Further research is needed to prove the concept, but especially for patients with effusions, inflammatory episodes, and flares, the drug seems promising.

Microsomal PGE Synthase 1 Inhibition

Selective inhibition of microsomal PGE synthase 1 (mPGES1) catalyzes the production of PGE2. In vitro studies in human articular cartilage from OA patients with the MF63 drug showed effective enchanting of the production of metallothionein 1 (MT1), an antagonist of IL-1 and IL-36. Furthermore, the expression of IL-6 was downregulated. By these mechanisms, promising anti-inflammatory and disease-modifying results could be achieved in OA treatment [30].

Toll-Like Receptor Inhibitors

In OA toll-like receptors (TLRs) are upregulated and promote cartilage breakdown by activating pro-inflammatory pathways. Multiple trials have been conducted with hydroxychloroquine (HCQ) injections (a medication that blocks TLR) but without any reduction in pain or improvement in functionality [31].

Wnt Signalling Pathway Alteration

The Wnt pathway is responsible for progenitor cell differentiation and cartilage/bone metabolism. It is up-regulated in OA joints. Lorecivivint (LOR) inhibits the intranuclear kinase CLK2/DRRK1A and therefore modulates the Wnt pathway and inflammatory responses. Improvement in WOMAC pain score has been detected, but more studies must be conducted with an evaluation of radiographic effects and long-term studies [32].

Mesenchymal Stem Cell Injections

Mesenchymal stem cells (MSCs) have shown effects over two different pathways: First the ability of these cells to differentiate into tissue-specific cell

Types and rebuild cartilage is considered beneficial and additionally the ability to alter paracrine activity in OA, thereby turning off the inflammatory pathway, limiting stress responses and apoptosis, and recruiting immune cells and reparative cells, is of benefit.

Studies with MSCs showed that after injection, a resolution of symptoms was detectable in most patients, but the results lasted only 1-2 years, without complete resolution of the disease. Compared to PRP treatment, MSCs survive longer in the joint cavity and release microenvironment-changing substrates over a longer period [33].

Medications Targeting Articular Cartilage and Proliferative Processes

***MicroRNAs (miRNAs)*:** Are known to play a key role in cellular proliferation and cell apoptosis through the tissue growth factor 1ß (TGF-1ß) pathway. A study by Zihilin et al.[34] showed that in an IL-1ß induced cell model, miR-296-5p was significantly down-regulated.MiR-296-5p inhibits IL-1ß induced chondrocyte apoptosis and cartilage degradation by negative feedback of TGF-ß1. However, overexpression of TGF-1ß leads to proteoglycan degradation and the appearance of OA.

Alteration of the Epidermal Growth Factor Pathway

Destruction of articular cartilage is one of the main characteristics of OA. In mouse models, cartilage-specific epidermal growth factor (EGFR) deficiency was a reason that led to an accelerated development of knee OA. The study of Wei et al. [35] investigate modification of the EGFR pathway by activating it through an overexpression of heparin-binding EGF-like growth factor ligand, specifically in cartilage (Col2-Cre HBEGFR). The result was an expanded pool of chondroprogenitors with increased proliferative capacity, higher survival rate, and higher lubricant production. The second investigated pathway was through Mig6, a negative feedback inhibitor of EGFR. Lack of this molecule leads to thickened articular cartilage with a larger number of superficial chondrocytes. A hypothesis was that EGFR is critical for maintaining homeostasis of the superficial layer of articular cartilage. The results of the study were that overexpression of HBEGF in chondrocytes leads to cartilage enlargement and that overactivation of EGFR can expand the pool of chondroprogenitors.

***Bisphosphonates*:** This group of drugs is commonly used in osteoporosis therapy but could also be beneficial for some OA phenotypes. An annual infusion of zoledronic acid is beneficial in reducing knee pain and bone marrow lesions(BML) in patients with knee OA, thus delaying the need for joint replacement surgeries and improving the quality of life for the patient. The flaws are that during infusion, acute phase reactions are common and combinations with methylprednisolone should be used for the infusion [36]. Risedronate is another commonly used bisphosphonate, and the effects were studied in a rabbit model. The results were that long-term use was unable to reduce trabecular bone loss by inhibiting osteoarthritic hypertrophic cartilage responses. But compared to other chondroprotective medications, it showed better results [37].

Calcitonin Gene-Related Peptide (CGRP) Inhibition

CGRP has crucial functions in shock absorption by supplementing cartilage with nutrients and removing metabolic waste products. In OA, bone turnover increases dramatically, leading to a disorganised bone architecture and decreased mineralisation that influences the integrity of the overlying cartilage. By blocking CGRP, which is associated with inflammatory pain and blood vessel dilation, regulation of bone integrity, osteoclast genesis, and osteoblast differentiation, sclerotic changes in the subchondral bone can be inhibited, cartilage degradation prevented, and pain reduced. The CGRP receptor antagonist Olcegepant in a mouse model showed inhibition of these sclerotic changes. Therefore, the use of CGRP receptor antagonists in the early stages of OA could prevent the progression of OA and attenuate articular cartilage degeneration [38,39].

Methylene Blue: The commonly used reagent, methylene blue (MB), has a strong affinity to nerve endings, therefore having long-term inhibitory effects on peripheral nerve axons and acting as an antioxidant and anti-inflammatory agent. Pain relief and joint protective effects can be achieved by the regulation of reactive oxygen species (ROS) scavenging systems. MB upregulates the cellular redox regulator nuclear factor (erythroid-derived 2) (Nrf2) that is involved in the recognition and clearance of damaged organelles and proteins.

The other intracellular antioxidant peroxiredoxin (PRDX 1) regulated by methylene blue is important for cellular survival and metastasis. In OA, excessive oxidative stress leads to changes in microenvironment homeostasis with abnormal ROS release, accumulation of MMP and impaired cell functioning. A study by Li et al.confirms MB cartilage protective, osteophyte preventive, anti-inflammatory and antioxidative effects [40].

Medications Altering Pain Pathways

Nerve Growth Factor (NGF) Inhibitors**:** *Tanezumab and fasinumab are known NGF inhibitors, commonly used to treat chronic pain. A study by Tian et al. [41] showed in a rat model, that the effective dose of NGF antibody needed to achieve pain relief and improvement in weight-bearing performance, in weekly intra-articular injections (100µg) is much lower than in systemic administrations and has no systemic side effects. In systemic administration, side effects of paranesthesia, arthralgia, pain in the extremities, and headache were observed.*

Methotrexate (MTX): MTX competitively inhibits dihydrofolate reductase, thus acting as a folic acid antagonist and inhibiting the central sensitization pathway in neuropathic pain. In a study by Yamanashi et al.[42], an oral administration of 3mg/kg/week of MTX in a rat model was able to improve pain by suppressing pain-related mRNA expression of TRPV-1 and BDNF in DRG significantly. No improvement in cartilage degeneration was observed and no effects in suppression of MMP-3 expression were detected, therefore it can only be used for pain reduction.

Humanized Monoclonal Antibody Galcanezumab**:** Other pathways involved in the generation and transmission of pain in OA include the calcitonin gene-related peptide (CGRP). It acts as a local facilitator of pain and inflammatory processes in OA. The investigation by Jin et al.[43] showed that the administration of 300 mg of Galcanezumab every 4 weeks was unable to provide important clinical improvements in knee OA, resulting in no efficacy in the treatment of chronic OA pain.

I2 Receptor Agonists: I2 receptors are a group of proteins that allosterically modulate the activity of enzymes required for brain energy generation and monoaminergic pathways for pain control. A 14-day clinical trial showed clinically significant results in analgesia in people with chronic knee OA pain [44].

Targeting Metabolic Syndrome

Metformin: In OA, reduced activity of adenosine monophosphate-activated protein kinase (AMPK) is observed in the cartilage of a knee with OA, resulting in increased catabolic events. Therefore, the administration of metformin could be beneficial in maintaining cartilage homeostasis. Metformin, a commonly used medication for the treatment of diabetes mellitus type 2 (DM 2) is known to activate AMPK. Studies in animal models showed that the administration of metformin was able to significantly reduce cartilage degradation, osteophyte formation and synovial hyperplasia. Metformin was also able to reduce the TNF α and IL-1ß induced expression of MMP-3, MMP-13, Adamts 4 and 5 and showed an upregulation of anabolic genes through AMPK-dependant mechanisms, thereby producing chondroprotective effects. Furthermore, the study showed that metformin was able to inhibit pain-related signalling in cartilage tissues and therefore reduce pain in the OA model [45]

Additionally, a novel human study showed promising results. People with diabetes received metformin treatment, resulting in a significant reduction in the risk of developing OA [46,47].

Conclusion

Osteoarthritis is considered a complex condition that affects the entire joint. Therefore, an effective treatment approach should be comprehensive and focus on multiple pathways and joint components simultaneously.

Currently, therapeutic efforts have progressed to a point where we can effectively manage the pain and discomfort associated with OA. However, the goal of altering the progression of the disease or achieving a complete cure remains a distant prospect. Given the increasing occurrence of OA in the ageing population, it is crucial to enhance research efforts and address not only pain management but also disease modification and potentially curative approaches to improve the quality of life of affected people. These strategies should be tailored to the individual clinical presentation of each patient, recognizing that OA manifests differently in various individuals.

This underlines the importance of exploring treatment options encompassing the entire spectrum of the disease, considering its diverse manifestations and the unique characteristics of each patient's condition

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