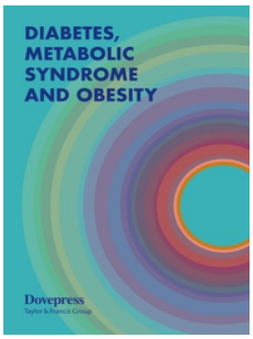

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REVIEW

Is It Time to Revisit the Role of Interleukin-1 Inhibitors in Osteoarthritis?

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Objective: There remains a huge unmet need for new osteoarthritis (OA) therapies. A putative reason for the failure of some therapies has been the absence of well-defined phenotypes, which might be more appropriate for specific targeted treatment. Interleukin-1 (IL-1) plays a key role in the development of OA, but the results of clinical trials targeting IL-1 in OA have to date been disappointing.

Methods: This narrative review is based on a literature search for publications describing interventions with direct Il-1 pathway inhibitors in patients with knee OA and substantiated by a description of key pre-clinical observations.

Results: Randomized controlled studies using IL-1 inhibition as treatment approach to knee OA have read out negatively, although trends for an improvement in pain and impact on biomarkers could be observed. However, in a post-hoc analysis of the large CANTOS trial data (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) testing an anti-IL-1 monoclonal antibody for the secondary prevention of cardiovascular events treatment arms receiving canakinumab demonstrated a substantial reduction in the incidence rate of joint replacement compared to those receiving placebo. Similar results have been reported from a post-hoc analysis of another cardiovascular risk reduction study, the low-dose colchicine 2 (LoDoCo 2) trial, raising the possibility of a beneficial effect of IL-1 inhibition in the subset of patients with metabolic phenotype.

Conclusion: Based on the above results, it seems timely to revisit the role of IL-1 in OA, its relationship with chronic low-grade inflammation and its relevance in the subset of metabolic OA.

Keywords: cytokines, inflammation, disease modifying osteoarthritis drug, drug development, metabolic syndrome, low grade inflammation

Introduction

Osteoarthritis (OA) is the most common form of arthritis,[1] with a growing prevalence, and the 14th leading cause of age-standardized years lived with disability and 7th for people aged 70 and older.[2] It is a complex disease, with diverse underlying pathologic mechanisms, and with potentially several structural and pain phenotypes.[3–9] Major risk factors for the development of OA are age, obesity, trauma, mechanical and genetic factors;[10,11] Metabolic disbalance is considered a likely contributor to OA development, although its impact is not fully elucidated,[12] treatment primarily focusses on behavioral aspects and pain management, as there are no approved disease-modifying OA drugs (DMOADs), with joint replacement remaining as the last resort.[13]

Interleukin-1 (IL-1) is a crucial and highly controlled pro-inflammatory cytokine that plays a central role in the immune system as part of the defense mechanisms of the innate immune system, but with broad implications also on specific immunity. IL-1 secretion triggers an inflammatory cascade but also influences glucose metabolism.[14] IL-1 also plays a key role in the pathogenesis of OA,[15–20] accordingly, IL-1 inhibition has been considered a potential treatment strategy. Pre-clinical studies[21–26] and a small case series[27] have suggested IL-1 inhibition to be effective but results from randomized clinical trials (RCTs) have been disappointing for knee OA.[28–31] There are several possible reasons for this incongruity, including the types of pre-clinical models[32] or patient selection in RCTs. Not all patients may benefit from IL-1 inhibition,

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and it is possible that primarily people with local or systemic inflammation are the appropriate target.[33–36] This hypothesis is supported by the post-hoc analyses of 2 trials for prevention of major cardiovascular events, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS),[37] evaluating the effect of IL-1β inhibition, and the low-dose colchichine 2 (LoDoCo 2) trial,[38] investigating the effect of the non-specific inhibitor of the inflammasome, colchicine, which is critical for production of activated IL-1. The post-hoc analyses of both studies showed a significant reduction in the incidence of joint replacements in the treatment arms,[39,40] prompting the reconsideration of the role of IL-1 inhibition in OA. We will therefore review the role of IL-1, critically examine the clinical trial experience and explore the implications of new study data.

Methods

This narrative review is based on a non-systematic search of current literature in PubMed ® using the search terms "Interleukin 1", "IL-1" and "knee osteoarthritis" in various combinations, using different notations and wildcards to identify reports on treatment approaches for knee OA with IL-1 inhibitors. In addition, reference lists from articles were screened. Only studies using direct IL-1 inhibitors were included, while studies that evaluate substances acting via an indirect effect on IL-1 (Chondroitin Sulfate, Glucosamine, Diacerein, Avocado and Soya extracts), microRNA, or autologous preparations were not taken into account. In addition, the literature was screened for publications on IL-1 in preclinical models of OA as well as the association of pain and IL-1.

Interleukin-1 in the Pathophysiology of Osteoarthritis

Interleukin-1 is produced by chondrocytes, mononuclear cells and macrophages, osteoblasts and synoviocytes in two isoforms, IL-1α and IL-1β.[15,41] The IL-1 receptor, IL-1RI, is a transmembrane protein with an extracellular immunoglobulin-like receptor and a cytosolic TIR (Toll/interleukin-1 receptor/resistance protein) domain. Upon binding, IL-1RI recruits the co-receptor IL-1 Receptor Accessory Protein (IL-1RAP) and forms a heterodimeric receptor complex that activates the mitogen-activated protein kinase (MAPK) pathway, leading to activation of transcription factors NF-κB and AP-1.[19,20] This results in a shift towards a pro-inflammatory and catabolic state associated with a downregulation of synthesis of type II collagen and aggrecan, chondrocyte apoptosis and enhanced production of matrix degrading proteins, pro-inflammatory cytokines such as IL-6.[15,42,43] In addition, extra cellular matrix (ECM) degradation products induce a positive feedback loop that further augments production of pro-inflammatory cytokines.[43] The activity of IL-1 is modulated by two endogenous antagonists, namely a decoy receptor IL-1RII, which has no cytoplasmic domain and the IL-1 receptor antagonist (IL-1-Ra), which binds to the IL-1RI without inducing a biologic response.[20,44] A recent meta-analysis on IL-1 genetic polymorphisms identified variants that, in Caucasians especially 1RN*1/*1 and IL-1RN*1/*2 polymorphisms, were associated with an increased risk (OR, 0.50; 95% CI, 0.28–0.89; $I^2 = 84$, $p = 0.02$ and OR, 1.77; 95% CI 1.03–3.06, $I^2 = 86$, $p = 0.04$, respectively) for knee OA.[45]

IL-1 affects various cell types such as osteoblasts, osteoclasts, synoviocytes and immune cells, ultimately perpetuating inflammation. This triggers the release of matrix degrading enzymes, leads to a reduction in matrix production, drives synovitis and alters the subchondral bone potentially impacting metabolic exchange at the bone cartilage interface.

Interleukin-1 in Osteoarthritis Pain

For people living with OA, pain is the most important symptom.[5,7,46,47] IL-1 can induce pain by activating nociceptors through an intracellular kinase, enhancing the production of nitric oxide, kinins, and prostanoids such as prostaglandin E2.[46,48,49] The latter exerts its effect by binding to a variety of E prostanoid receptors present in peripheral sensory neurons and the spinal cord.[46] IL-1 induced inflammation is also responsible for the induction of angiogenesis, with vessels that penetrate the calcified cartilage from subchondral bone, and whose perivascular sensory structures are believed to play a role in pain signaling.[50] Moreover, IL-1 can induce dysregulation of the autonomic nervous system, and consequently of the anti-inflammatory effect exerted by vagal reflex, and the circadian rhythm.[51]

IL-1 has also been implicated in changes in central pain processing (see Supplemental Figure 1). In the central nervous system, IL-1 is predominantly produced by microglia, astrocytes and specific neurons, and interacts with these cell types.[52] Results from animal models suggest that in the spinal cord IL-1 associated long-term potentiation,[53]

neuronal plasticity[54] and increase in cytokine secretion occur as mechanisms involved in central pain sensitization. Changes in IL-1 expression in association with neuropathic pain have also been observed in supraspinal areas that are typically involved in pain processing.[55–57] Finally, IL-1 has been implicated in mood disturbances such as anxiety and depression[58] which associate with incident OA pain[59] and may increase the risk for chronic pain.[60]

Attur et al reported that overexpression of IL-1 was significantly associated with higher pain levels (Western Ontario and McMaster Universities (WOMAC) pain subscale and Visual Analogue Score (VAS) pain) in OA patients even after adjusting for sex, age and body mass index (BMI).[61]

IL-1 Inhibition in Animal Models

In the 1990s, a recombinant human IL-1 receptor antagonist (RHuIL-1Ra) had a dose-dependent protective effect in vivo against both cartilage loss and osteophyte formation at 4 weeks in a canine OA model.[23] A subsequent study reported that intra-articular (IA) injection of autologous synoviocytes transduced to express IL-1Ra had a protective effect on cartilage after 4 weeks,[22] an effect confirmed by others.[24,25] In line with these protective effects related to IL-1 inhibition, reduction in OA severity has been observed in IL-1β knockout mice[62] and gene therapy approaches using IL-1Ra or IL-1RII have been successful preclinically in reducing both pain and structural damage.[63] The relevance of IL-1 for joint health may be multi-faceted though since accelerated development of OA in knockout mice for IL-1β and IL-1β converting enzyme has also been observed.[64] In contrast, no changes in synovial inflammation or in cartilage destruction were reported in IL-1 knockout mice with collagenase-induced OA.[65]

Overall, the role of IL-1 in animal models is not fully clear and may depend on the pain stimulus, the species, the behavioral endpoint and the evaluated region in the central nervous system.[66] In addition, as Vincent has argued[32] several types of bias may affect the interpretation of these preclinical results such as lack of animal randomization, lack of investigator blinding, a trend towards underpowered studies, and publication bias.

The Results of IL-1 Inhibition in Knee OA Clinical Trials

A recent systematic review by Yu et al identified 12 studies evaluating the effect of substances targeting IL-1 activity.[67] Herein, we examine the four studies (Table 1) in knee OA that evaluated specific targeting of the IL-1 pathway.[28–31]

Anakinra (Recombinant IL-1Ra)

Chevalier et al published a case series piloting a single IA injection of anakinra for knee OA[27] in 14 patients followed for 12 weeks. This patient series demonstrated anakinra to be safe. Treatment was associated with significant improvement in the VAS pain and WOMAC for the whole study period. The group subsequently performed an RCT in 170[28] comparing a single IA dose of anakinra 50 mg or 150 mg to placebo. Anakinra was safe, and although WOMAC pain scores improved with anakinra 150 mg at Day 4 ($p = 0.051$), this effect was lost subsequently and the Week 4 primary endpoint was not met.

AMG108 Fully Human Monoclonal Antibody Against IL-1R1

The IL-1R1 antibody AMG108 was studied in knee OA[29] using a two-part RCT: Part A evaluated dose-ranging, safety and pharmacokinetics in 58 patients, while Part B aimed to determine clinical efficacy in 160 patients, randomized 1:1 to receive placebo or AMG-108 300 mg sc. every 4 weeks for 12 weeks. AMG108 did not differ significantly from placebo in terms of the primary endpoint (change in WOMAC pain at Week 6), although numerical superiority for pain improvement and a reduction in need for rescue therapy were noted.

Canakinumab (Human Monoclonal Antibody to IL-1β)

Conaghan et al performed a two-part study to evaluate safety and efficacy of a single IA treatment with canakinumab in painful knee OA.[31] The first part was a double-dummy placebo-controlled, single ascending dose safety study, followed by an 18-week randomized placebo and naproxen-controlled trial, in which 136 patients were randomized to receive a single IA injection of canakinumab 600 mg or placebo at Baseline, and naproxen 500 mg twice daily or placebo until Week 12 in a double-blind, double-dummy design. The effect of canakinumab was not different from placebo or naproxen for the co-primary endpoints, change from Baseline to Day 4 in knee pain (VAS 0–100 mm) and change

Table 1 Comparison of Clinical Trials for IL-1 Inhibition in Knee OA

	Anakinra [a]	**AMG – 108 (part B)** [b]	**Lutikizumab** [c]	**Canakinumab** [d]
Mechanism of Action	Recombinant IL-1R antagonist	Anti-IL-1R MAb	DVD-Ig anti IL-1α and −1β	Anti-IL-1β Mab
Half-life (Hours)	4	N/D	240–336	624
Route of administration	Single IA dose	SC every 4 weeks	SC every 2 weeks	Single IA dose
Primary endpoint	WOMAC at Week 4	WOMAC pain score at Week 6	WOMAC pain score at Week 16 Synovitis (MRI) at Week 26	VAS pain at Day 4 WOMAC pain score at Week 4
Secondary endpoint	WOMAC change/ visit. WOMAC improvement >50% at W12 Pain VAS Global Activity VAS PGA by Likert Rescue analgesic use. PROs: HRPQ, EuroQol-5D, SF36 Cleavage products or pro-peptides of collagen synthesis Safety	Safety Pharmacokinetics WOMAC change Week 6 and 12. Change pain VAS Change SF36 Change EuroQol	WOMAC pain score at Week 26 and 52 OMERACT/OARSI response at Week 16, 26, and 52 Radiographic joint space narrowing at Week 52. Synovitis at Week 26 by dynamic contrast enhanced MRI	Change in Pain VAS and WOMAC subscales at every visit. Pain VAS improvement ≥50% Use of rescue medication Pharmacokinetics Pharmacodynamics
Follow-Up (months)	3	3	12	3
Control	Pbo	Pbo	Pbo	Pbo and NPX
Inclusion Criteria	Pts >18 years ACR criteria for knee OA Pain VAS > 30 mm KL 1–3	Pts >30 years ACR criteria for knee OA Pain VAS > 30 mm KL 1–3	Pts > 35 <74 years Pain VAS >40 <80 Global VAS ≥40 KL 2–3 in the medial compartment Synovitis (US or MRI)	Pts >40 <80 years ACR criteria for knee OA Pain VAS ≥40 KL 2–3 BMI ≤45
Pts included	AKN 150 mg: 67 AKN 50 mg: 34 Pbo: 69	AMG-108 300 mg SC: 80 Pbo: 79	LTZ 25 mg: 89 LTZ 100 mg: 85 LTZ 200 mg: 88 Pbo: 85	CKN 600 mg: 45 NPX 500 mg BID: 53 Pbo: 47
Age (mean)	63	60	60	61.3
Female (%)	65	68	64.9	76.2
BMI	N/D	32	29	31.4
OA duration (y)	6.1	6.1	8	N/D

(*Continued*)

Table 1 (Continued).

	Anakinra [a]	AMG – 108 (part B) [b]	Lutikizumab [c]	Canakinumab [d]
KL 1 (%)	0	AMG-108: 1 Pbo: 5	0	0
KL 2 (%)	40	AMG-108: 50 Pbo: 38	63	53.1
KL 3 (%)	58	AMG-108: 49 Pbo: 58	37	46.9
KL 4 (%)	2	0	0	0
Synovitis (%)	0	N/D	100	N/D
Mean VAS of Pain (0–100 mm)	51.9	N/D	N/D	CKN 62.2 NPX 57.1 PBO 59.8
WOMAC's Pain Scale (mean)	AKN 25.7 PBO 25.8	AMG-108 27.9 PBO 26.8	LTZ 27.5 Pbo 26.2	10.2
Concomitant medication	Slow Acting Drugs Opioids Orthotic support	Slow acting drugs Orthotic support	Not allowed before Week 26	Stable doses of Opioids
Conclusion	Primary EP not met. No improvement in knee pain, function, stiffness, or cartilage turnover No safety concerns. Trend toward pain reduction on Day 4	Non-significant but numerically greater improvement in WOMAC pain score at W6 in the AMG-108 group, especially in those with higher score at Baseline	Only LTZ 100 mg achieved significant WOMAC reduction at Week 16 and was not sustained. Structural endpoints similar between LTZ and Pbo No safety concerns	No significant difference in outcomes Patients on PBO required more rescue medication. Significant improvement in WOMAC pain at Week 12 in the subgroup of high hsCRP patients.

Notes: [a] Chevalier X et al. Intraarticular injection of anakinra in osteoarthritis of the knee: A multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2009 Mar 15;61(3):344–52. [b] Cohen et al. A randomized, double-blind study of AMG 108 (a fully human monoclonal antibody to IL-1RI) in patients with osteoarthritis of the knee. Arthritis Res Ther. 2011;13(4):R125. [c] Fleischmann RM et al. A Phase II Trial of Lutikizumab, an Anti–Interleukin-1α/β Dual Variable Domain Immunoglobulin, in Knee Osteoarthritis Patients With Synovitis. Arthritis Rheumatol. 2019 Jul 7;71(7):1056–69. [d] Conaghan P et al. Intraarticular Canakinumab (Anti-Interleukin-1β) for treatment of symptomatic knee osteoarthritis: A Randomized, Double-blind, Placebo and Naproxen-controlled Phase II study [abstract]. Arthritis Rheumatol. 2021;73(suppl9).

Abbreviations: AKN, Anakinra; BMI, Body Mass Index; CKN, Canakinumab; DVDIg, Dual Variable Domain Immunoglobulin; EP, Endpoint; HRPQ, Health Related Productivity Questionnaire; IA, intraarticular; IL-1, Interleukin-1; IL-1R, IL-1 receptor; KL, Kellgren Lawrence; LTZ, Lutikizumab; Mab, Monoclonal Antibody; N/D, No data; NPX, Naproxen; NSAIDS, Non-Steroidal Anti-inflammatory Drugs; OA, Osteoarthritis; PBO, Placebo; PGA, Physician Global Assessment; PROs, Patient Reported Outcomes; SC, Subcutaneous; SF-36, Short Form 36;Slow Acting Drugs, Chondroitin Sulfate, Glucosamine, Diacerein, Avocado and Soya extracts.

from Baseline to Day 29 in WOMAC pain. An effect of canakinumab on pain was observed in a subpopulation with elevated Baseline hsCRP levels.[31]

Lutikizumab (Human Dual Variable Domain Immunoglobulin Inhibiting IL-1α and IL-1β)

After demonstration of safety and target engagement, evidenced by significant reduction in the serum concentration of hsCRP and MMP-1,[68] the efficacy of the IL-1α and -β inhibitor lutikizumab was evaluated in an RCT enrolling 350 patients with radiographic knee OA and MRI/ultrasound synovitis.[30] Patients received lutikizumab 25, 100 or 200 mg, or matching placebo SC every 2 weeks for 52 weeks. The co-primary endpoints were the change in WOMAC pain from Baseline to Week 16 and the change in synovitis at Week 26. Lutikizumab showed significant WOMAC pain improvement for the 100 mg dose only at Week 16, and there was no significant change in synovitis for any dose.

What Can We Learn from Cardiovascular Trials?

The value of anti-inflammatory treatments for cardiovascular risk reduction is increasingly recognized.[69] Since often in cardiovascular drug development large outcome trials are required, other therapeutic areas have started leveraging the wealth of data. Especially for osteoarthritis research, this can be relevant since the target populations are overlapping,[70] and anti-inflammatory treatments are a cornerstone of OA treatment. In this context, CANTOS evaluated 10,061 patients with prior myocardial infarction and elevated hsCRP, (≥2 mg/l) a known risk factor for future cardiac events and a surrogate for systemic low-grade inflammation. Patients were treated with canakinumab 50 mg, 150 mg, 300 mg or placebo subcutaneously every 3 months and followed up to a maximum of 5 years (mean 3.7 years) for the occurrence of a major cardiovascular event. Canakinumab 150 mg significantly reduced the occurrence major cardiovascular events, and all dose levels led to a reduction in hsCRP.[37] The large patient number and long follow-up period offered the opportunity to evaluate the effect of IL-1β inhibition on the incidence of knee joint replacement, analyzed using reporting of intercurrent surgery or adverse events including narratives and case notes.[40] This post-hoc analysis compared the pooled canakinumab patients to those receiving placebo and revealed incidence rates for total hip and total knee replacement of 0.31 and 0.54 events, respectively, per 100 person-years (HR, 0.58 [CI, 0.42 to 0.80]; P = 0.001), with similar benefits seen in the subgroup of 1369 patients who had a medical history of peripheral (i.e., non-spinal) OA (HR, 0.57 [CI, 0.39 to 0.83]).[40] These OA patients differed from the overall CANTOS population by being older, more likely female, and having a higher BMI and waist circumference than those without OA, suggesting a metabolic syndrome-like phenotype.[40]

Some confirmation of these results comes from another recent post-hoc analysis of a large cardiovascular trial on low-dose colchicine. The low-dose colchicine 2 (LoDoCo 2) trial,[38] an investigator initiated randomized controlled trial, enrolled 6528 patients with stable coronary disease for a one-month open label run-in phase, after which 9.4% discontinued for perceived side effects (mostly gastro-intestinal), 6.1% for other reasons, and 5522 patients were randomized to receive daily 0.5 mg of colchicine or placebo. Over the average observation time of 28.55 months, colchicine (on top of standard of care) was shown to reduce the rate of cardiovascular events compared to placebo treatment. In these patients, a post-hoc analysis demonstrated a substantial reduction in total hip and knee joint replacements in the treatment arm (HR, 0.69 [CI, 0.51 to 0.95]). These results were similar in a sensitivity analysis excluding patients with a medical history of gout (HR, 0.68 [CI, 0.49 to 0.94]).[39]

Although these post-hoc analyses have methodological limitations, the results provided valuable information on a possible role of IL-1 inhibition in the subgroup of patients with metabolic syndrome and merits further evaluation.[40]

How Should We Interpret the Previous Clinical Trials in Light of CANTOS and LoDoCo 2?

The meta-analysis of Yu et al demonstrated a benefit on both pain and function in OA patients; however, this benefit was primarily driven by their included studies on diacerein and autologous preparations.[67] There is therefore a discordance between the results from the CANTOS and LoDoCO 2 post-hoc analyses[39,40] and the results of the four knee OA RCTs, included in Yu et al, and discussed above. While none of these RCTs achieved their pre-specified primary endpoints, all of them demonstrated that IL-1 inhibition lowered levels of some biomarkers including hsCRP and IL-6.[28–31] In all these trials, IL-1 inhibition was safe and well tolerated.

The comparison of clinical trials is generally challenging due to different pharmacodynamics and pharmacokinetic properties of the treatments, routes of administration, and the heterogeneity of patients, especially regarding the presence of systemic or local inflammation (ie, synovitis) which could be the most crucial differentiator for demonstrating benefits of IL-1 inhibition in OA.[28–31]

While pain is associated with synovitis, and the prevalence of synovitis differs greatly based on the clinical or imaging tools employed,[71] none of those trials met their primary symptomatic endpoint independent of enrichment for synovitis or effusion. On the other hand, the CANTOS and LoDoCo 2 post-hoc analyses, both studies not enriched for OA patients, demonstrated a benefit in terms of joint replacement, an endpoint presumably driven by patient

symptoms.[39,40] This interesting observation suggests that the efficacy of IL-1 inhibition in OA may depend more on systemic inflammatory status than local joint inflammation.

When trying to understand the discordance, another potential confounder, also raised by Vincent's critical review,[32] is the role of crystals. Although the previously cited clinical trials excluded patients with any non-OA arthritis, the prevalence of sub-clinical crystals in OA is known to range between 10% (using imaging) and up to 90% (based on cartilage histology).[48,72–75] Since IL-1 inhibition has been proven as a valid strategy for the treatment of crystal-induced arthritis,[76–78] it may be possible that the responses in CANTOS and LoDoCO 2 were biased by un-diagnosed crystal arthropathy, although sensitivity analyses excluding formally diagnosed gout or other types of inflammatory arthritis still demonstrated the substantial reduction in joint replacement.

Baseline pain-levels have an impact on the possibility of detecting a change from baseline,[79,80] and lower pain levels than seen in recent OA trials may have contributed to the negative findings in some of the above studies. This is supported by the fact that numerically greater improvement in WOMAC pain score at Week 6 in the AMG-108 group was observed in patients with higher pain score at Baseline.[29] In addition to slight differences in the pain eligibility criteria in the above studies, pain as an outcome is vulnerable to confounders[48,80–84] such as analgesic medication that were not controlled in all studies. Finally, the striking magnitude of the placebo effect in two studies, with up to 65%[28] and 70.6%[30] of patients on placebo achieving the OARSI/OMERACT response criteria,[85] raises concerns about the methods to control for placebo effects.[86]

Osteoarthritis and the Metabolic Phenotype

Finally, the heterogeneity of the included patients in the previous RCTs may partly explain the inconsistent response to IL-1 inhibition.[5] Osteoarthritis is comprised of multiple phenotypic subgroups that are assumed to be associated to specific endotypes.[3,8,11] The "metabolic phenotype" is one of the most extensively studied subgroups.[87] Knoop et al identified an "obese – weak muscle phenotype" which is associated with worse pain and activity outcomes than the "minimal joint disease", "strong muscle" and "non-obese and weak muscle" subgroups.[6] Others have defined the metabolic phenotype as obese with metabolic abnormalities,[11] or more specifically by the presence of metabolic syndrome with obesity, hypertension, diabetes and dyslipidemia as well as high levels of biomarkers such as hsCRP or leptin.[3] Although as pointed out by Berenbaum et al, the differential impact from metabolic alterations vs obesity is not fully clear yet.[12] Applying unsupervised machine learning algorithms to the Osteoarthritis Initiative database, a "comorbid" cluster of patients, defined by higher BMI and burden of comorbidity showed a higher burden of pain, structural damage, and risk of knee replacement versus the other clusters, and this effect was more pronounced in a cluster with effusion as sign of local inflammation.[8,88]

Metabolic syndrome (MetS) is a constellation of clinical and biochemical characteristics associated with an increased CVD (cardiovascular disease) risk. Although there is no universally accepted definition, there is consensus on its components: Abdominal obesity, elevated blood pressure, impaired fasting glucose levels, increased triglycerides, and decreased high-density lipoprotein cholesterol levels.[89] A relationship between CVD risk factors and an augmented prevalence of OA has been observed.[90] For years, the main hypothesis linking metabolic syndrome and OA was the increase in mechanical loading on weight-bearing joints in obesity. However, increasing work suggests systemic effects beyond biomechanical loading: a cohort study from Norway with a 10-year-long follow-up found an association of obesity with knee and hand OA, but not with hip OA.[91] Similarly, a Japanese study demonstrated an impact of the individual components of MetS on the incidence and progression of OA, as well as an additive effect of individual components.[92] Since then, several studies demonstrated an increased risk for OA in MetS, independent of weight.[93] Additionally, there is growing evidence of an association of metabolic syndrome and chronic low-grade inflammation, with associated dysregulation of CNS and pain tolerance.[48,94] The link between MetS and OA could be adipokines as comprehensively reviewed by Zhang et al.[95]

Several physio-pathological alterations lead to this chronic low-grade systemic inflammatory state. First, the chronic excess of nutrients present in the MetS induces impairment of the cellular energy and nutrient sensors, inducing an altered mitochondrial function, DNA damage, premature senescence, and reduced organelle autophagy, which leads to chondrocyte apoptosis, and in consequence, increased oxidative stress and inflammation.[93,96] Second, the expansion of

visceral white adipose tissue induces the expression of adipokines such as leptin and adiponectin, resulting in an enhanced release of IL-1β, IL-6 and matrix degrading proteins.[97,98]

A study by Francisco et al found that patients with OA have higher levels of leptin in serum, synovial tissue and cartilage compared to healthy controls.[97] Furthermore, the knee's infrapatellar fat pad can produce adipokines and exert an amplified paracrine effect.[99] Third, high fat diets can activate the NLRP3 inflammasome, either directly through the recognition of elevated concentrations of saturated fatty acids by the toll like receptors, or indirectly by inducing the impairment of the gut mucosal barrier, and consequently, an increase of circulating lipopolysaccharides.[93] High levels of oxidized cholesterol can induce mitochondrial dysfunction and lead to oxidative stress within the chondrocyte.[96] Finally, vascular pathology caused by MetS can lead to subchondral ischemia, and thereby induce metabolic stress on the avascular cartilage, and apoptosis of osteocytes and chondrocytes.[96,100]

Conclusion

OA is a complex disease, with different phenotypes and pathophysiologic pathways involved. Chronic low-grade systemic inflammation associated with metabolic OA phenotype may be a treatable cause of OA pain. Based on the various insights described in this review, IL-1 inhibition remains a potential treatment for OA, but in a selected subset of patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Martin Brom is employee and shareholder of Novartis. Franziska Saxer is employee and shareholder of Novartis, she is affiliated to the University Basel and member of the European Union Medical Devices – Expert Panel section Orthopaedics, traumatology, rehabilitation, rheumatology. Linda Mindeholm is consultant to Novartis and Versanis Bio, employee and shareholder of Novartis. In addition, she reports a pending patent WO2019215484A1. Matthias Schieker is employee and shareholder of Novartis, he is owner of LivImplant GmbH. In addition, he reports a pending patent WO2019215484A1. Philip G Conaghan reports consultancies or speakers bureaus for AbbVie, EliLilly, FormationBio, Genascense, GlaxoSmithKline, Grunenthal, Janssen, Kolon TissueGene, Levicept, Merck, Moebius, Novartis, Stryker, Takeda and TrialSpark. The authors report no other conflicts of interest in this work.

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