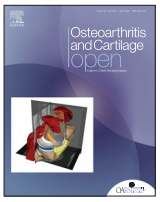
Osteoarthritis and Cartilage Open 7 (2025) 100546

Contents lists available at ScienceDirect

Osteoarthritis and Cartilage Open

journal homepage: www.elsevier.com/journals/osteoarthritis-and-cartilage-open/2665-9131



Editorial

Slow acting medications for progressive and painful knee osteoarthritis. How do we assess the benefit to risk of these potentially novel therapies?

Osteoarthritis (OA) is a common disease, affecting nearly 25 million individuals in the U.S in 2019, with nearly half of this burden being from knee osteoarthritis (OA). Often, women more often than men are affected and the direct costs of OA amount to 1–2.5 % of Gross National Product in established market economies such as the US, UK, Canada, and Australia [1–3]. In 2013 in the US, OA was the second most costly medical condition treated in hospitals, accounting for 4.3 % ($18.4 billion) of all hospitalization costs [4]. The treatment of the disease can be challenging for both the patient and the health care provider. A patient with a painful joint, e.g. knee, may appear at the physician's office for emergent knee pain while walking on flat surfaces or going up and down stairs. The knee pain may initially be intermittent and easily improved with rest and simple analgesic or anti-inflammatory medications. Conservative measures, such as weight loss and exercise are effective at this stage but are difficult for patients to maintain. Over years, depending on the age of the patient and predisposing risk factors, the disease will progress slowly but inevitably causing more pain, stiffness and, eventually severely limiting mobility. Intermittent nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) selective inhibitors, and intra-articular (IA) glucocorticoids or hyaluronic acid derivatives, can be helpful for short periods of time to reduce pain [5,6]. Due to lack of effective therapies, even unproven treatments such as IA stem cells and platelet-rich plasma are employed as part of this unsatisfactory cycle of drugs bridging patients towards the ultimate recommendation of a total joint replacement. Of note, many of the drugs used in this current paradigm of OA management also come with significant safety risks. As examples, prescription acetaminophen, NSAIDs and COX-2 inhibitors all carry Food and Drug Administration (FDA) Box warnings and prolonged IA glucocorticoid use has been known to be associated with joint damage [5,6].

Over the past 40 years NSAIDs COX-2 selective agents, IA therapies, nutraceuticals and topical agents, have been available to treat painful OA. All these medications are effective and separated from placebo (PBO) treatments to reduce pain and improve function as reported in randomized controlled clinical trials (RCTs).

Many of the NSAID randomized controlled trials (RCTs) adopted a ‘flare’ design, and nearly all approved NSAIDs demonstrate significant differences from PBO-treated subjects within 4–6 weeks of intervention. Similar results have also been reported for COX-2 inhibitors, IA glucocorticoids (both short and long-acting agents), and some IA hyaluronic acid compounds [6,7].

The trial designs for both investigator and industry sponsored studies are traditionally expected to be at least 12 weeks duration to obtain full efficacy data for treatment of a chronic disease; shorter termed trials are often used for proof of concept. The problem in demonstrating an OA drug's efficacy in RCTs is related to the not unreasonable expectation, that for a drug to be useful for treating pain, symptom improvement needs to be achieved early, perhaps within a couple of days of treatment. At the same time, it is expected that such therapies will also improve patient function. Newer pipeline drugs which can alter joint structure in addition to improve symptoms, and hence potentially slow the course of the disease, need to demonstrate improvements on joint survival. As OA pathology typically proceeds at a glacial pace, demonstrating improvement in joint survival concurrently with early symptom benefit is an unlikely outcome for these drugs. Thus, we need to alter the current paradigm expectations in to allow these slower acting drugs to become available.

Currently, there are several novel agents in development which we will refer to as “Slow acting” anti-inflammatory and/or cartilage modulating agents that we will discuss below. For these agents, their analgesic or anti-inflammatory efficacy may be delayed, and their ability to slow progression of disease will probably require multiple treatments and evaluations over two to three years. We will discuss a few of these novel therapies and raise questions regarding how the FDA might consider in evaluating their safety and efficacy.

Proinflammatory cytokines (PICs) are central to joint degeneration of OA, as well as to sensitization of pain neurons that innervate the joint capsule and other soft tissues [8,9]. Produced by chondrocytes and synoviocytes (fibroblasts and macrophages), PICs promote the cartilage-damaging activities of these same chondrocytes and synoviocytes. Therefore, inhibition of such PIC molecules may be important targets for pharmaceutical intervention. Interleukin-1 (IL-1) is known to be an inflammatory cytokine that can increase the production of metalloproteinases that degrade cartilage in OA joints. A natural inhibitor of IL-1, the IL-1 receptor antagonist (IL1RA), is currently being evaluated as a gene therapy in which an adeno-associated virus (AAV) vector containing an IL-1RA gene is injected into the knee joint. The goal of the consequent IL-1RA gene transfection of cells, is to produce IL-RA that circulates in the joint, and over time may reduce inflammation, pain and possibly slow progression of the disease. Pre-clinical studies have demonstrated efficacy [10,11], and two Phase I trials in participants with knee OA have been completed with no safety signals reported [12] [Genescense data on file]. Phase 2 studies are planned to determine efficacy and if there are signals of IL-1RA slowing cartilage loss in knee OA subjects.

Interleukin-10 (IL-10) is an anti-inflammatory cytokine, that can potently and broadly suppress proinflammatory cytokine activity. A key natural counter-regulator of cytokine-mediated inflammation, IL-10 inhibits the production and function of key proinflammatory cytokines that

https://doi.org/10.1016/j.ocarto.2024.100546
Received 11 November 2024; Accepted 20 November 2024

are active in OA including IL-1β, IL-6 and tumor necrosis factor-α (TNF-α). Also, IL-10 has been found to be reduced in knee OA synovial fluid. IL-10 in vitro appears to downregulate pro-inflammatory cytokines by inhibiting their transcription, translation and post-translational processing as well as promoting upregulation of IL-1RA [13]. In preclinical studies the administration of IL-10 into inflammatory joints resulted in a reduction in joint inflammation and improved joint motion [13]. At the time of this writing, phase 1 and phase2a clinical trials are being conducted to determine if the introduction of an IL-10 plasmid into the knee joint causes cells to produce IL-10 and potentially reduce pain/improve function in knee OA subjects [NCT04124042] [14]. Following the study subjects over time for safety and evaluating imaging, either radiographs or MRI will determine if this mode of administration of this anti-inflammatory therapy will prevent progression of the disease.

Lorecivivint (LOR) is an intra-articular agent thought to have anti-inflammatory and Wnt pathway modulating properties. LOR has a dual mechanism of action through inhibition of intra-nuclear kinases known as dual-specificity Tyrosine-phosphorylation regulated kinases (DYRKs), and CDC2-like kinases (CLKs), that leads to downregulation of pro-inflammatory and cartilage catabolic pathways. In vitro and in vivo preclinical studies have demonstrated that compared to controls, LOR reduced inflammatory cartilage destruction and preserved cartilage in OA-induced animal models [15]. Over the past 7 years, LOR has been studied in man as a disease-modifying OA drug (DMOAD) for the treatment of painful knee OA, and the results have been inconsistent. Overall, the compound has shown no major safety signals when injected into knee joints. An initial phase 2a trial identified a responder population with unilateral symptomatic knee OA and with comorbid pain excluded. A large phase 2b trial, (OA-04, NCT03122860) tested this target population *a priori*, and found demonstration of LOR efficacy in reducing signs and symptoms in treated knee OA subjects compared to PBO for two doses [16–18]. However, two later phase 3 LOR trials (OA-10, NCT04385303; OA-11, NCT03928184) for treatment of painful knee OA did not show a difference from the PBO-treated subjects 3 months after study initiation [19,20]. Of note, the phase 3 trials enrolled subjects with more structurally advanced knee OA than previous trials and were conducted during the COVID pandemic – both potentially confounding factors. Interestingly, a post-hoc analysis of OA-10 did show that subjects with Kellgren-Lawrence Grade 2 radiographic disease (definite OA but not severe radiographic disease) did show efficacy compared to the PBO treated group. This subgroup was radiographically like the trial population from the previously successful OA-04 trial (Biosplice data on file). A phase 3 extension of OA-11 study (OA-07, NCT04520607) continued to follow up OA-11 completers, who remained blinded and randomized to their original treatment. Subjects were given an additional two annual injections and the study subjects that continued to receive LOR, over time showed reduced knee joint pain, improved function and reduced radiographic joint space width loss compared to the PBO arm [21]. These data suggest the hypothesis that either reducing the inflammation or preventing cartilage deterioration may not be immediate in this novel therapy.

Sprifermin is a recombinant human fibroblast growth factor 18 (rhFGF18) which has been shown in preclinical models of OA to stimulate chondrocyte proliferation and cartilage matrix growth [22]. Based on the preclinical findings, a large, randomized PBO-controlled study phase II study was performed. Sprifermin, administered at a dose of 100 μg 3 weekly injections every 6 months or 12 months for 2 years found study subjects that had received intra-articular administration of 100 μg of sprifermin every 6- or 12-months vs placebo had significant improvement in total femorotibial joint cartilage thickness, compared to placebo treated subjects. However, there was no significant difference between sprifermin and placebo in joint pain or function assessed by the WOMAC [23]. Five-year assessments of the Sprifermin efficacy have also shown prevention structural progression [24].

In addition to intra-articular therapies, preclinical studies have now shown that skeletal stem cells can be introduced into the knee joint of mice through inducing an injury that transects the cartilage and the subchondral bone. At the site of the lesion, introduction of anti-VEGF and BMP2, directed the skeletal stem cells to differentiate into chondrocytes and heal the cartilage lesions [25]. This regenerative therapy and many others like it are rapidly advancing toward clinical trials. Clearly, there will most likely be a delay from the time of the procedure until there are measurable effects on joint structure, and clinical outcomes. It is also possible that this treatment to augment joint structure may not change clinical outcomes. Regulatory agencies will have new challenges with the assessment of efficacy with these novel treatments.

We have reviewed a few of the new therapies in development for the treatment of knee OA pain and their potential to slow the progression of the disease. Their proposed mechanisms of action include either introduction of a gene into joint tissues generating a molecule which reduces inflammation (Il-1RA, Il-10), or causing reduction of cartilage deterioration (LOR), or causing augmentation of cartilage matrix formation (sprifermin). Most of these therapies do not appear to work rapidly such that symptoms of knee pain would differ from PBO before 12 weeks. For structural changes, such as measuring an increase, or a reduced rate of loss in cartilage thickness by radiographic or MRI quantification could take up to 2 years to quantify, or to translate into reduced knee pain.

Given the challenges of assessing the efficacy of these novel therapies in development for knee OA, other study designs could be considered. Studies of longer duration to assess potential structure modifying therapies for knee OA will be significantly more expensive to perform. In addition, it would be difficult to maintain study subjects on PBO medication for several years given the anticipated long duration of RCTs which would explore structure modification as a goal, there would be need for use of background therapies to modify the pain signal, which in turn could confound interpretation of pain efficacy. Another ethical consideration is potential condemnation of the PBO arm towards OA disease progression. The study drug would be added to one arm with dose posology understood. The comparator arm would not receive study drug and thus would be the PBO control arm. All patients should receive the same dose of background therapy.

However, there may be a missed opportunity to take advantage of resources that can reduce the cost of these longer duration knee OA studies. The Osteoarthritis Initiative recruited 4796 participants, and the inclusion criteria included men or Women ages 45–79 years, with or without symptomatic knee OA, of all ethnic minorities with a focus on Afro-Americans [26]. The study participants were divided into three cohorts: 1) Progression cohort: that included symptomatic tibial-femoral knee OA (n = 1389–29 %), presence of both osteophytes and frequent symptoms in 1 or both knees (Definite Tibial - Femoral osteophyte (OARSI atlas grade 1–3) at baseline (clinic interpretation and Symptoms: Pain, aching or stiffness on most days of a month in past year); 2) an incidence cohort: no symptomatic tibial-femoral OA in either knee (n = 3285–68 %), at increased risk for symptomatic OA in 1 or both knees: Frequent knee symptoms without x-ray OA, could have osteophytes in one or both knees, but not osteophytes and frequent symptoms in the same knee, with two or more other eligibility risk factors and 3) A control cohort that had no symptoms and no radiographic tibial-femoral or patello-femoral OA in either knee, or no risk factors (n = 122–3 %)]. These study subjects obtained xrays and MRIs of their knees at baseline, 12 m, 24 m, 36 m, 48 m, 72 m, 96 m of the study. These datasets are available to the public and provide validated data on quantitative and semi-quantitative cartilage changes over a 96-month period in knee OA subjects with symptoms. Utilization of these data could allow for companies to recruit knee OA subjects that are equivalent to the OAI population with symptomatic knee OA and use the OAI group as a control or PBO treated group. This concept could reduce the cost of the longer-term clinical trials. Another important aspect of the OAI cohort is that the study subjects were allowed to have the standard of care for the knee pain during the trial, which would also equipoise long-term clinical trial intervention.

Another factor to consider is if the current endpoints are adequate for determining if an experimental agent for OA affects pain and function.

How can a reduction in pain at a single timepoint be valid for a DMOAD which takes years to act? We might need to consider outcomes with cumulative integration of benefit over a certain timeframe such as long-term pain dairies, daily or weekly texts to get information via cell phone technology or incorporate wearable technology rather than rely on patient reported outcomes.

So, a new pathway for the potential approval of these slow acting agents is needed for OA. OA is a slowly progressive disease, and for the most part signs and symptoms of the disease that include knee pain and reduced function can be treated with NSAIDs, glucocorticoid injections or topical NSAIDs. To date, we have no approved therapies for OA that may over time prevent cartilage destruction or increase cartilage thickness, studies that evaluate structure modification will take several years to complete.

We need to think about how best to evaluate the safety and efficacy of these new potentially slow acting agents as they are presented to the regulatory agencies. It is a new day, and early days for these new slow acting agents that may slow the progression of the slow-moving osteoarthritis.

This work was supported by NIH grant R01AG070647 to N.E.L.

Author contributions

Conceptualization: Nancy E Lane, Jeyanesh Tambiah.

Writing- Original draft preparation: Nancy E Lane, Lee S. Simon, Jeyanesh Tambiah.

Writing- Reviewing and Editing, Nancy E. Lane, Lee S. Simon, Jeyanesh Tambiah. No other contributors.

Funding source

NIH grant R01AG070647. The funding source will pay the publishing fees.

Declaration of competing interest

None.

References

[1] H. Long, Q. Liu, H. Yin, N. Diao, Y. Zhang, J. Lin, et al., Prevalence trends of site-specific osteoarthritis from 1990 to 2019: findings from the global burden of disease study 2019, Arthritis Rheumatol. 74 (7) (2022) 1172–1183.

[2] United States Bone and Joint Initiative. The Burden of Musculoskeletal Diseases in the United States (BMUS). In: In. fourth ed. Rosemont, IL. 2018: Available at: https://www.boneandjointburden.org/fourth-edition. Accessed June 12, 2019.

[3] M. Cross, E. Smith, D. Hoy, S. Nolte, I. Ackerman, M. Fransen, L. Bridgett, S. Williams, F. Guillemin, C.L. Hill, L.L. Laslett, G. Jones, F. Cicuttini, R. Osborne, T. Vos, R. Buchbinder, A. Woolf, L. March, The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study, Ann. Rheum. Dis. 73 (7) (2014 Jul) 1323–1330.

[4] M Torio Celeste, BJM, National Inpatient Hospital Costs: the Most Expensive Conditions by Payer, 2013: Statistical Brief #205. Healthcare Costs and Utilization Project (HCUP) Statistical Briefs [Internet], Agency for Healthcare Research and Quality (US), Rockville (MD), 2016.

[5] J.N. Katz, K.R. Arant, R.F. Loeser, Diagnosis and treatment of hip and knee osteoarthritis: a review, JAMA 325 (6) (2021 Feb 9) 568–578.

[6] W. Zhang, G. Nuki, R.W. Moskowitz, et al., OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through January 2009, Osteoarthritis Cartilage 18 (4) (2010) 476–499.

[7] American Academy of Orthopaedic Surgeons Management of Osteoarthritis of the Knee (NonArthroplasty) Evidence-Based Clinical Practice Guideline. https://www.aaos.org/oak3cpg Published August/31/2021.

[8] M. Kapoor, J. Martel-Pelletier, D. Lajeunesse, J.P. Pelletier, H. Fahmi, Role of proinflammatory cytokines in the pathophysiology of osteoarthritis, Nat. Rev. Rheumatol. 7 (1) (2011 Jan) 33–42.

[9] R.E. Miller, R.J. Miller, A.M. Malfait, Osteoarthritis joint pain: the cytokine connection, Cytokine 70 (2) (2014 Dec) 185–193.

[10] C. Evans, Editorial: arthritis gene therapy using interleukin-1 receptor antagonist, Arthritis Rheumatol. 70 (11) (2018) 1699–1701.

[11] R.S. Watson Levings, A.D. Smith, T.A. Broome, B.L. Rice, E.P. Gibbs, D.A. Myara, E.V. Hyddmark, E. Nasri, A. Zarezadeh, P.P. Levings, Y. Lu, M.E. White, E.A. Dacanay, G.B. Foremny, C.H. Evans, A.J. Morton, M. Winter, M.J. Dark, D.M. Nickerson, P.T. Colahan, S.C. Ghivizzani, Self-complementary adeno-associated virus-mediated interleukin-1 receptor antagonist gene delivery for the treatment of osteoarthritis: test of efficacy in an equine model, Hum Gene Ther Clin Dev 29 (2) (2018 Jun) 101–112.

[12] Conaghan P, Hochberg M, Cohen S, Nakazawa M, DiGiorgi M, Slonin J, Sustained Clinical effects after a single intra-articular injection of PCRX201 for moderate to severe osteoarthritis of the knee. Osteoarthritis Cartilage, Volume 32, Issue 6, 785.

[13] E.M. van Helvoort, E. van der Heijden, J.A.G. van Roon, N. Eijkelkamp, S.C. Mastbergen, The role of interleukin-4 and interleukin-10 in osteoarthritic joint disease: a systematic narrative review, Cartilage 13 (2) (2022 Apr-Jun) 19476035221098167.

[14] L.R. Watkins, R.A. Chavez, R. Landry, M. Fry, S.M. Green-Fulgham, J.D. Coulson, S.D. Collins, D.K. Glover, J. Rieger, J.R. Forsayeth, Targeted interleukin-10 plasmid DNA therapy in the treatment of osteoarthritis: toxicology and pain efficacy assessments, Brain Behav. Immun. 90 (2020 Nov) 155–166.

[15] E. Grigsby, S. Collins, L. Kapural, M. McBride, J. Rieger, M. Stokes, H. Rutman, F. Cicuttini, Efficacy of XT-150, a novel non-viral gene therapy delivering IL-10v, on moderate to severe pain Due to osteoarthritis of the knee: results of a phase 2 trial [abstract], Arthritis Rheumatol. 75 (suppl 9) (2023).

[16] Y. Sun, T. Hu, M. Zhang, J. Song, Z. Qin, M. Liu, J. Ji, Z. Li, Z. Qiu, J. Bian, Structure-guided discovery of potent and selective CLK2 inhibitors for the treatment of knee osteoarthritis, J. Med. Chem. 67 (6) (2024) 4603–4623.

[17] Y. Yazici, T.E. McAlindon, A. Gibofsky, 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. 72 (10) (2020) 1694–1706.

[18] Y. Yazici, T.E. McAlindon, A. Gibofsky, N.E. Lane, C. Lattermann, N. Skrepnik, C.J. Swearingen, I. Simsek, H. Ghandehari, A. DiFrancesco, J. Gibbs, J.R.S. Tambiah, M.C. Hochberg, A Phase 2b randomized trial of lorecivivint, a novel intra-articular CLK2/DYRK1A inhibitor and Wnt pathway modulator for knee osteoarthritis, Osteoarthritis Cartilage 29 (5) (2021 May) 654–666.

[19] Y. Yazici, C. Swearingen, H. Ghandehari, V. Lopez, I. Simsek, M. Fineman, S. Kennedy, J. Tambiah, T. McAlindon, A phase 3, 28-week, multicenter, randomized, double-blind, placebo-controlled trial (OA-10) to evaluate the efficacy and safety of a single injection of lorecivivint injected in the target knee joint of moderately to severely symptomatic osteoarthritis subjects [abstract], Arthritis Rheumatol. 74 (suppl 9) (2022).

[20] Y. Yazici, C. Swearingen, H. Ghandehari, J. Britt, I. Simsek, M. Fineman, S. Kennedy, J. Tambiah, T. McAlindon, A phase 3, 56-week, multicenter, randomized, double-blind, placebo controlled trial (OA-11) to evaluate the efficacy and safety of a single injection of lorecivivint injected in the target knee joint of moderate to severe osteoarthritis participants [abstract], Arthritis Rheumatol. 74 (suppl 9) (2022).

[21] Y. Yazici, C. Swearingen, J.R.S. Tambiah, et al., Radiographic and pain outcomes from a phase 3 extension study (OA-07) evaluating the safety and efficacy of repeat Lorecivivint injections over 3 years in subjects with severe knee osteoarthritis, Ann. Rheum. Dis. 83 (2024) 194.

[22] N.N. DePhillipo, H. Hendesi, Z.S. Aman, D.R.G. Lind, J. Smith, G.R. Dodge, Preclinical use of FGF-18 augmentation for improving cartilage healing following surgical repair: a systematic review, Cartilage 14 (1) (2023 Mar) 59–66.

[23] M.C. Hochberg, A. Guermazi, H. Guehring, et al., Effect of intra-articular sprifermin vs placebo on femorotibial joint cartilage thickness in patients with osteoarthritis: the FORWARD randomized clinical trial, JAMA 322 (14) (2019) 1360–1370.

[24] F. Eckstein, M.C. Hochberg, H. Guehring, et al., Long-term structural and symptomatic effects of intra-articular sprifermin in patients with knee osteoarthritis: 5-year results from the FORWARD study, Ann. Rheum. Dis. 80 (8) (2021) 1062–1069.

[25] M.P. Murphy, L.S. Koepke, M.T. Lopez, X. Tong, T.H. Ambrosi, G.S. Gulati, O. Marecic, Y. Wang, R.C. Ransom, M.Y. Hoover, H. Steininger, L. Zhao, M.P. Walkiewicz, N. Quarto, B. Levi, D.C. Wan, I.L. Weissman, S.B. Goodman, F. Yang, M.T. Longaker, C.K.F. Chan, Articular cartilage regeneration by activated skeletal stem cells, Nat. Med. 26 (10) (2020 Oct) 1583–1592.

[26] G. Lester, The osteoarthritis initiative: a NIH public-private partnership, HSS J. 8 (1) (2012 Feb) 62–63.

Nancy E. Lane*
Department of Medicine, U.C. Davis Health, Sacramento, CA, 95817, USA

Lee S. Simon
SDG, LLC, One Mifflin Place, Suite 400, Cambridge, MA, 02138, USA.

Jeyanesh Tambiah
Biosplice Therapeutics, 9360 Towne Center Dr., San Diego, CA, 92121, USA.

* Corresponding author. Division of Rheumatology and Clinical Immunology, Department of Medicine, U.C. Davis Health, USA.
E-mail addresses: nelane@ucdavis.edu (N.E. Lane), leesimon@sdgllc.com (L.S.Simon), jeymi.tambiah@biosplice.com (J. Tambiah).