



Therapies for Osteoarthritis Today and Tomorrow – Review

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Abstract

Osteoarthritis is a common human disease with well understood pathophysiology, signs and symptoms, prevalence, risk factors, pain, and suffering with great understanding of personal, economic and social effects around the world. There are no drugs or treatments considered “disease modifying”, with symptomatic control aiming to stave off the final solution of total joint replacement. Regenerative medicine and use of mesenchymal stem cells (MSC) promised hope to change that but have so far fallen short. This review focuses on current knowledge and use of MSC in clinic, completed research, and future directions for development of this once so promising biological treatment. Powerful treatment for pain in form of monoclonal antibodies against Nerve Growth Factor (NGF) are getting close to FDA approval in the US. Wnt signalling pathway modulators that decrease inflammation, increase function and potential to regenerate cartilage should be presented to the FDA early next year.

Key words: Osteoarthritis; Mesenchymal stem cells; Wnt pathway; NGF antibodies.

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Introduction

Osteoarthritis (OA) is the most common form of joint disease worldwide. It affects 1 in 3 US adults according to Arthritis Foundation (www.arthritis.org) with radiographic evidence in more than 50 % of people over 65 years old and more than 80% at 75 years old. Symptomatic OA of the knee occurs in about 11% of people over 64 years old. By 2030, it is estimated about 20 % of the US population will be aged over 65 years.

For years, OA was labelled as “degenerative “disease; progressive loss of articular cartilage, remodelling and hypertrophy of bone, bone cysts formation and osteophyte development. Today, we have a much better understanding OA pathophysiology, explained as a “downward spiral” where cartilage degeneration is caused by injury, inflammation or metabolic defect, depletion of proteoglycans with compromised collagen ultrastructure and attempted repair by chondrocytes

with increased proteoglycan (PGs) and collagen production. At the end, an increase in matrix metalloproteinases (MMPs), cartilage degrading enzymes and inflammatory cytokines all contribute to cartilage breakdown.¹ Chondrocyte apoptosis leads to further cartilage degradation with decreased concentration and viscosity of synovial fluid. Risk factors for OA are well described and classified in major categories as: (1) demographic (age, genetics, systemic factors like obesity), (2) biomechanical (trauma/injury, overload, instability) and (3) biochemical (cytokines, MMP’s, PG’s). All play a role in OA severity.² Even today, it is difficult to explain origins of pain associated with OA, as the mechanism is unclear and its presence does not consistently correlate with imaging studies. It appears many factors contribute to pain sensation including soft tissue damage, joint capsule (stretch), synovial membrane (synovitis), periarticular bursitis, tendinitis, muscle spasm,

ligament involvement, periosteum stretching, subchondral bone, osteophytes formation, microfracture presence, increased intra-osseous pressure, etc.³

Many studies confirm that OA has profound personal, economic, and social impacts in around the world. According to the US Center for Disease Control (CDC) in 2013 the total national arthritis attributable medical care cost and earning losses among adults with OA was \$303.5 billion or 1 % of the 2013 US Gross Domestic Product (GDP).⁴ Effecting more than 32.5 million adults in US,⁵ it is also among most expensive conditions to treat when surgery is required. In fact, OA was the second most costly health condition treated at US hospitals in 2013.⁶ In that year, it accounted for \$16.5 billion or 4.3 % of the combined cost for all hospitalisations.⁶

OA management guidelines have recently been revised and adopted by the American College of Rheumatology and Clinical Consensus Group of Orthopaedic Surgeons to reflect this “New Paradigm.” After diagnosis of OA, a patient could be treated with non-pharmacologic therapy, simple analgesics or over the counter NSAID’s, Rx NSAID’s, and/or intra-articular (IA) corticosteroids all prior to surgical intervention. Even more interesting is a comparison between AAOS, ACR, OARSI⁷ for US patient and what treatments are recommended vs. inconclusive evidence vs. not recommended. American Academy of Orthopaedic surgeons (AAOS) recommends only topical NSAID’s, oral NSAIDs and Tramadol. Inconclusive evidence for acetaminophen, non-tramadol opioids and IA injections of corticosteroids (CS) and platelets rich plasma (PRP). Even IA injection of hyaluronic acid (HA) is not recommended together with Chondroitin and Glucosamine supplements.⁷ Also, there are calls for use of IA corticosteroids to be reconsidered.⁷

The Cochrane report by Juni at all.⁸ generates some controversy about the use of this most common treatment for OA even with limited evidence of efficacy. Cheap to purchase and administer, and approved by all insurance companies, the risk of corticosteroids may out-weight the benefits. However, until alternate treatments are approved it will remain a first-line intra-articular therapy used by physicians. Prospective randomised clinical trials did not find evidence⁸ that IA HA is any better than IA CS despite fewer side effects. There was no evidence for AAOS to recommend IA HA for standard treatment. So, it is fair to say that there is no adequate therapy to offer once patient

goes through topical and Rx NSAIDS, injections with limited evidence of efficacy and questionable safety for the patients not ready for total joint replacement. That opened the door for more research with regenerative medicine options in last decade. Prolotherapy, PRP, APS (Autologous Protein Solution) and especially stem cell injections took centre stage in ortho research and use. Also, the search is expanding for better pain control (Anti NGF MoAb) and injectable molecules with the potential to decrease inflammation and move MSC from bone metabolism to the cartilage area and repair defect (Wnt). All of them will be presented briefly in this paper with special focus on MSC potential, research done so far, use and presented evidence to clarify what the current standpoint is and what following research should be done in order to solve the “holy grail” of orthopaedics and human locomotor system - a “disease modifying agent,” able to slow down the process of OA and potentially reverse damage of cartilage degradation, restoring new cartilage, decreasing inflammation, eliminating pain and increasing function.

Autologous Mesenchymal Stem Cell

Since a landmark MSC publication¹⁰ in 2008 highlighting their potential to facilitate musculoskeletal repair by binding to the injury site and secreting large amounts of bioactive immunomodulating and trophic factors rather than differentiating into target tissue, many physicians implemented them in clinics and data began accumulating. What is known today and what is the standpoint with the research already done and recommendations for clinical use? In order to answer that question, manuscripts of randomised clinical trials (RCT) and recent review papers were reviewed.

One of the most frequently cited works from 2014¹¹ is a proof of concept clinical trial from S. Korea (Jo at al) that enrolled 18 patients; study was dose ranging with different number of cells injected IA (low dose, mid dose and high dose) and no placebo or any control with clear conclusion that more research needs to be done with randomized clinical trials (RTC), more consistency with cell isolation (techniques, sites, preparation etc.) and use of controls.

Quickly after deploying stem cells for OA treatment, some technical issues became apparent. Different techniques of preparation and manipulation damaged the cells and caused dissemination to non-target tissues. To minimise those issues, injectors sought different injectable vehi-

cles as containment systems to provide a better microenvironment for injected cells. Roffi et al¹² reviewed 40 studies (19 preclinical and 21 clinical trials) with platelet-rich plasma (PRP), hyaluronic acid (HA) and hydrogels to help delivery and function of MSC. Even though the authors reported negligible adverse events and promising clinical outcomes, the prevalence of low-quality studies prevented demonstration of benefit, calling for studies designed to more clearly demonstrate possible improved outcomes.

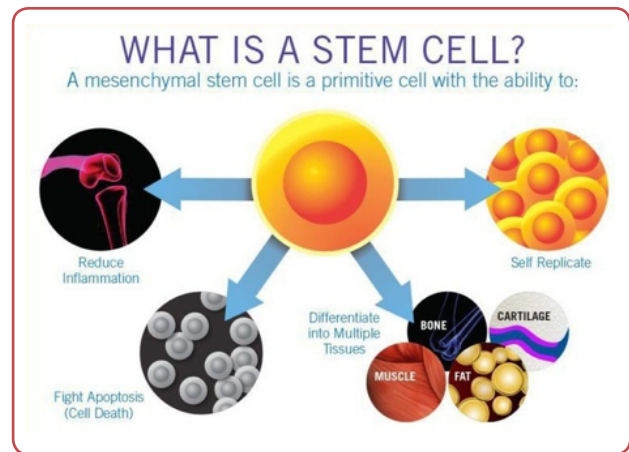
In 2019, Kim¹³ published a review article covering five RCTs with 220 total patients. This meta-analysis demonstrated that IA MSC have limited evidence of pain relief and functional improvement in knee OA. It does not support the use of intra-articular MCSs for improving cartilage repair in knee OA.

In order to establish “standardised” injections, an effort was made to use “minimal manipulation” methods to increase the use of MSC in orthopaedic practice. Di Matteo et al¹⁴ published a review article in 2019 to assess clinical applications of “minimally manipulated” MSC from either bone marrow (BMAC) or as stromal vascular fraction (SVF). Twenty-three papers were included in final analysis; only 4 were randomised clinical trials (RCT). They reported overall poor quality of the studies reviewed. Despite evidence of clinical safety in minimally manipulated MSC and the short term positive clinical outcomes, clinicians reported varying collection, preparation, and administration methods of MSC preventing any recommendation on the use of either product in clinical practice.

Contradictions surrounding the term “Mesenchymal Stem Cells” (MSC) are nothing new. It is fair to say since the early 2000s, various populations of these cells in the human body have been subject of controversy; origins, developmental potential, biological function, possible therapeutic uses, and even the name MSC itself¹⁶ have the subject of debate (Figure 1).

Cursory literature search reveals over 3,000 research articles in just the last 5 years with MSC derived from bone marrow, adipose and umbilical tissue with capacity for self-renewal and differentiation in the chondrocyte lineage (Figure 2).

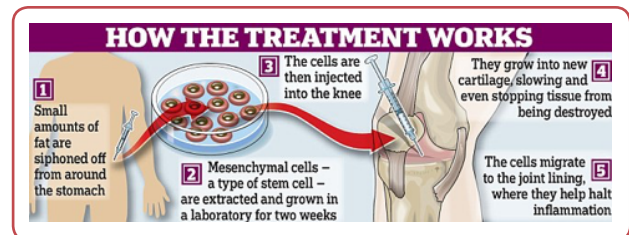
Sipp et al. 2018 explicitly asked to “clear up this stem-cell mess”, claiming that wildly varying reports have helped MSCs to acquire a near-magical “all-things-to-all-people” quality in the media



<http://www.regenorthopedics.com/wp-content/uploads/2014/09/Regen-Stem-Cell-Chart1-1200.jpg>
 Web based picture, published online, downloaded for this publication.

Figure 1: What is a stem cell?

and in the public mind. He elaborated that hype was easy to exploit, anointing it a go-to cell type for many unproven stem-cell interventions. The same authors stated “In most cases, rigorous preclinical studies of these cells are limited or non-existing.”¹⁶ In another editorial publication



<https://nsistemcell.com/wp-content/uploads/2017/06/osteoarthritis.jpg>
 Web based picture, published online, downloaded for this publication.
 Proposed mechanism of action for stem cells injected in osteoarthritic joint.

Figure 2: Explanation how the treatment with MSC works for OA of the knee

in 2018 “Emerging stem cell ethics,”¹⁷ a different array of bioethical debates and issues triggered by stem cells are reviewed. Rushing new commercial MSC products into market, off label use and direct-to-consumer marketing of unproven therapeutic benefits of MSCs are all touched upon. Other big issues include safety and efficacy of fast-tracked product and financial support for post-market efficacy data collection and testing.

How big is the stem cell market? Who is paying for these injections, and how much? In 2018 PiuZZi et al.¹⁸ published an interesting article about clinics in the US offering MSCs treatment for knee OA. All centres reported “good results” and “symptomatic improvement” in 82.2% of patients. Average cost was \$5,156 (\$1,150 - \$12,000) based on a review of 273 US based treatment centres. It is difficult to explain and understand these numbers knowing direct cost for the centre, time, people and exper-

tise needed to perform injection vary widely. For comparison, sometimes a total knee replacement surgery (involving surgery, prosthesis, anaesthesia, hospital stay etc.) is less costly than MSC based interventions. The same group of authors reviewed 420 reports, with only 6 studies offering evidence level III or lower, suggesting some positive results and modest clinical improvement that could not rule out placebo effect.

Most published articles share a commonality; IA injections of MSC resuspended in saline (2.5 ml up to 8 ml of saline and different number of cells). Reviewing literature regarding saline injections for knee OA finds 2 reviews published by Altman et al²³ in 2016 and Saltzman et al²⁴ reporting all investigators have long suspected saline is not really “placebo,” but rather a “comparator” due to respectable efficacy as a stand-alone intervention. Altman reported that a review of 38 eligible RCTs, IA saline was able to provide significant improvement in short-term knee pain (3 months) in 32 studies totalling 1,705 patients. Even long-term (6-12 months) knee pain was significantly reduced following IA injection of saline in 19 studies (1,445 patients) with no SAE’s (serious adverse events) related to saline. Similar results are published by Saltzman et al.²⁴ in September 2017. 14 cohorts in 13 studies totalling 1,076 patients with KL grade 1 - 4, VAS and WOMAC met all inclusion criteria for enrolment. At 3 months there was significant improvement in VAS score, WOMAC approached that but did not reach statistical significance. At 6 months, both VAS and WOMAC total scores were significantly improved (statistically and clinically significant) in comparison to pre-injection values. The hypothesis that these “placebo” injections have therapeutic effect has been quantified in RCTs with active treatment group like HA (hyaluronic acid). Since almost all stem cells are resuspended in saline, it is not a surprise to see decreases in VAS and WOMAC at short and long duration follow-up.

Presented articles and reviews are from 2000 to 2019. Efforts were made to research 2020 publications to find more better designed studies for knee OA. Unfortunately, Vasiliadis et al²² reported a review of 8 articles with varying OA grades and different scales of assessment (KL grading, IKDC). In KL grading studies, all grades were involved from KL 1 to KL 4, two studies have control without treatment, but received analgesia, weight management, exercise and injection of saline. Two studies used SVFT (stromal vascular fraction, 19 patients total) and 6 used cultured AD-MSC involving 96 patients. AD-MSC studies

required culturing the cells before IA injection and reports are very different about the length of cultures (1 week, 3 weeks up to 6 weeks). The number of cells injected IA differed too, ranging from 5 million to 100 million per injection. Half of the studies used ultrasound for injection, half did not. Four studies reported using adipose tissue from the abdomen, while 2 studies used tissue from the thigh, flanks and abdomen and 2 studies did not even report where they obtain adipose tissue.

Arshi et al¹⁵ published an interesting review article including a brief scientific stem cell overview, preclinical data and animal research, use of implantable scaffolds to enhance chondrogenesis and incorporation in cartilage defect of MSCs. They ultimately concluded that “extreme diversity in methodologies and therapeutics used in these studies obviates the need to higher quality study design to have reliable external validity into clinical application.” Future directions are clean and clear: calling for RCT with control group, well powered, with long follow up, specific primary and secondary endpoints and adequate imaging (x-rays and MRIs). Also of note, regulatory efforts in this field are not easy to establish and enforce.^{20,21} The American Academy of Orthopaedic Surgeons (AAOS) and National Institute of Health (NIH) had issued a statement of minimal standards for product development and clinical research for valid safety and efficacy data collection and ethical responsibility to patients.¹⁹ Their great concern was that “misrepresentation of uncharacterised and unproven minimally manipulated products as stem cells may erode public trust and compromise development of legitimate cell therapies.” Many professional organizations like the National Academy for Science, International Society for Cellular Therapy, the American Association for the Advancement of Science together with AAOS and NIH joined the consensus statement recognising the potential value of the cell therapies and the risk that current environment may erode public trust and investment needed to bring legitimate cellular and biological therapies to the patients. Recommendations include: define terminology to clearly distinguish uncharacterised minimally manipulated autologous cell products from rigorously characterised and culture-expanded and purified stem cell and progenitor cell population, standardise reporting requirements, establish registries for post-market monitoring and quality assessments of biologic therapies, and four additional tasks.¹⁹ When implemented, these recommendations can create difference in designing and reporting results from RCT.

The Arthroscopy Association of Canada also issued a position statement on intra-articular injections for knee osteoarthritis in 2019, as follows.²⁵

Corticosteroids (CS)

After a detailed literature review, recognising that AAOS found inconclusive evidence to recommend for or against IA steroid for knee OA, this Canadian association recommends their use based on short term moderate pain relief and restoration of function with good cost efficacy in patients with early OA. Grade A.

Hyaluronic acid (HA)

Numerous RCTs were reviewed with significant heterogeneity in trial designs, preparations, data collection and analysis of outcomes measured. However, a recommendation was given stating improved pain relief after IA HMW HA (high molecular weight HA) and restoration of function compared with placebo and can be helpful in patients with mild to moderate OA of the knee. Grade A.

Platelet Rich Plasma (PRP)

PRP received grade C, meaning conflicting or poor-quality evidence (level 4 or 5) not allowing a clean recommendation for or against an intervention. Studies did show the potential to relieve pain and improved physical function up to 1 year after injection in the knee with mild to moderate OA. There is no evidence of efficacy in more advanced OA like KL grade 4. Until further high-quality studies become available it is not possible to recommend for or against.

Cellular based BMAC

Grade I – insufficient evidence to support use of MSCs or BMAC in the treatment of OA of the knee and recommended that they should be limited to registered controlled clinical trials and did not recommend their use in routine medical practice until further evidence becomes available.

Search for new therapies

It is obvious that well evidenced non-surgical interventions are not possible currently to offer to patients suffering from osteoarthritis. Only topical and oral NSAIDs and Tramadol are recommended by AAOS. No recommendation for or against Acetaminophen, non-tramadol opioids and IA-corticosteroids or IA PRP. IA HA is not recommended, neither are glucosamine or chondroitin. Once a patient stops responding to above mentioned treatments, surgery is the final solution. Since many patients cannot take NSAIDs (bleeding issues and other side effects), acetamin-

phen has potential liver toxicity with high dose and long-term use, opioids are not recommended for long-term use in chronic diseases like OA, surgery is often the only options. However, some help may appear relatively soon for pain control and via the first “disease modifying” agent.

Anti NGF monoclonal antibodies (MoAb)

Nerve Growth Factor (NGF), a member of the neurotrophin family was discovered in the 1950's²⁶ and plays a critical role in normal development of sympathetic neurons as well as sensory neurons responsible for nociception and temperature sensation. There are many studies with additional evidence that NGF receptors play a role in pain propagation.²⁷⁻³⁰ The mechanism by which NGF may impact pain remains under investigation (Figures 3 and 4).²⁹⁻³²

One of the first publications about fasinumab Tiseo et al was published in 2014 with a double-blind, placebo-controlled exploratory study in the OA of the knee.³³ All 3 doses of fasinumab significantly decreased pain in the study knee and WOMAC total and subscale scores.

In 2015, Schnitzer et al³⁴ published a systematic review of the efficacy and safety of antibodies to NGF in the treatment of OA of the hip and knee.

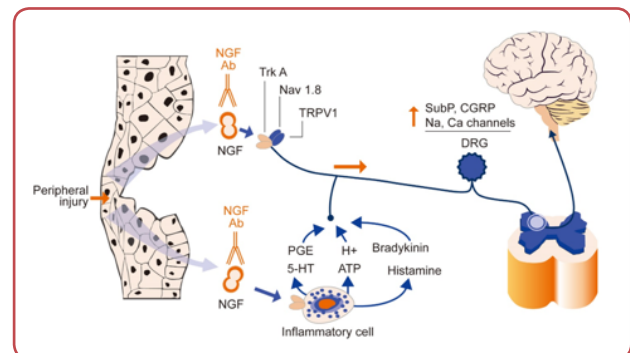
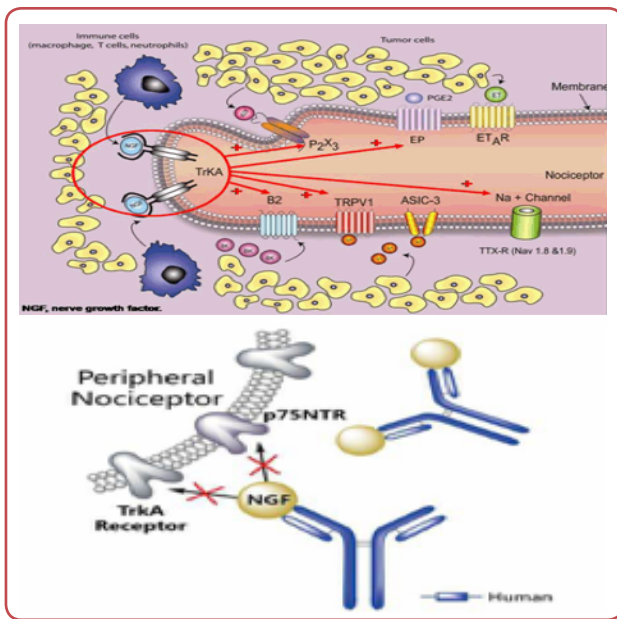


Figure 3: NGF mechanism of action after tissue injury, inflammation and chronic pain conditions

Neurotransmitters, receptors and ion channels get modulated and upregulated by nerve growth factor (NGF) binding to Tropomyosin-related kinase A receptor (TrkA) primary afferent sensory nerve fibers with their cell body in the dorsal root ganglia (DRG), transmitting sensory information from the periphery to the spinal cord and brain. During inflammation or injury, inflammatory cells (eosinophils, lymphocytes, macrophages, mast cells, schwann cells) release NGF that binds to TrkA directly activating nociceptors and triggering synthesis of neuropeptides (Substance P, ion channels like Na and Ca, calcitonine gene-related peptide (CGRP) etc.). Also, inflammatory cells release inflammatory mediators like histamine, serotonin (5HT), prostaglandins (PGE) and protons (H+). Binding of NGF to TrkA activates intracellular signaling pathways which results in increased expression or modulation at the membrane surface of number of receptors including bradykinin, transient receptor potential vanilloid 1 (TRPV1), voltage-gated sodium (Na), calcium (Ca) etc. These rapid changes in the afferent terminal modify the sensory fiber's response to sensory stimuli and propagation of sensory impulses to the dorsal horn.

Schematic and explanation adapted from Bélanger et al. *J Toxicol Sci.* 2018;43(1):1-10 and Mantyh PW et al.³⁰



Adopted from Hefti at all. Web based pictures, published online, downloaded for this publication.

Figure 4: NGF receptors are highly involved in pain propagation. Blocking receptors with MoAb developed against NGF receptors, pain propagation is slowed down and diminished

Nerve growth factor (NGF) regulates multiple receptors/ion channels expressed by sensory nerve fibers that innervate bone and skin. There are differences in the percentage of tropomyosin-related kinase A receptors (TrkA) that innervate bone vs skin. The skin is mostly innervated by thickly myelinated A-beta fibers (TrkA-). The bone appears to be predominantly innervated with thinly myelinated A-delta fibers (mostly TrkA+) and peptide rich C-fibers (mostly TrkA+). According to published data, more than 80% of all sensory nerve fibers that innervate the bone are TrkA+ and only 30% that innervate the skin are TrkA+. This data may help explain why blocking NGF or TrkA is highly efficacious in diminishing skeletal pain. Modified from Mantyh et al.³⁰

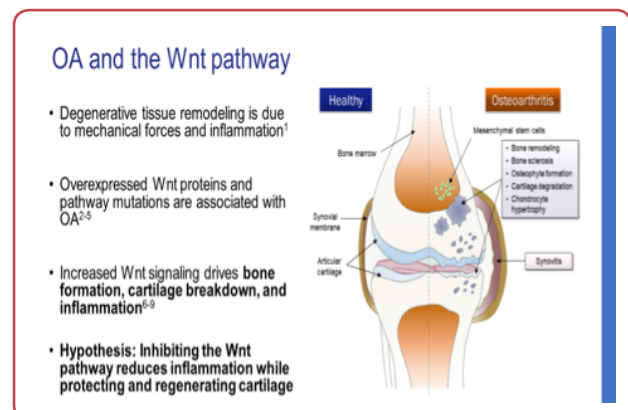
Tanezumab (Pfizer) and fasinumab (Regeneron) demonstrated superiority in efficacy compared to placebo and general safety was established in all RCT Phase II. Those results initiated clinical trials Phase III, some of the largest ever with 10,000 enrolled across the world. Regeneron announced in May 2016 positive topline results from Phase 2/3 fasinumab study in patients with OA pain. Pfizer and Lilly received FDA fast track designation for Tanezumab, was announced June 2017, and complete results from ongoing Phase 3 program for Tanezumab were published in Press Releases in October 2018 demonstrating significant improvement in pain and function in OA patients. In January 2019 Pfizer and Lilly announced top-line results from second Phase 3 study that this humanised monoclonal antibody acting as nerve growth factor (NGF) inhibitor demonstrated statistically significant improvement in pain and physical function over placebo. Regeneron just announced in a new press release in early August 2020 that all three Phase III RCT's for OA (knee and hip) met primary and secondary endpoints with clinical and statistical significance.

As of today, there is no FDA approval for tanezumab or fasinumab, but with overwhelming evidence of pain reduction, improved function and good safety profile, there will likely soon be possible to have "once a month, sub-cutaneous injection" of anti-NGF monoclonal antibodies for OA of the knee and hip. This Mo-Ab has a potential to replace use of other pain medication with multiple side effects. It is a pain killer, far superior to current options.

Wnt signaling pathway

As noted previously, current OA treatments are limited. They provide temporary symptomatic relief. No "disease modifying osteoarthritis drugs" (DMOADs) exist. Looking closely at the cellular level, many mesenchymal stem cells (MSC) are present in the synovial space and subchondral bone, fully capable of differentiation into cartilage forming chondrocytes, bone forming osteoblasts and adipose tissue.^{35, 36} Joints affected with OA are rich with stem cells, especially synovium,^{37, 38} clearly pointing that failure to regenerate articular cartilage is not a lack of supply but rather a failure to differentiate. The next logical question is why? Understanding the Wnt signalling pathway and the central role it plays in cell differentiation and tissue remodeling,³⁹ especially in the joint, provides some insight. It helps control tissue homeostasis through regulation of MSC differentiation in chondrocytes and osteoblasts^{40, 41} (Figure 5).

Many publications indicate increased Wnt activity in OA joint drives MSC to osteogenic differentiation and stimulates metalloproteinase production, resulting in cartilage destruction.^{42, 43} Downregulating Wnt activity locally could promote restoration of articular cartilage.⁴⁴ Pre-clinical studies demonstrated that Wnt inhibition results in reduced cartilage degradation and improved cartilage health (Figures 6 and 7). Figure 7



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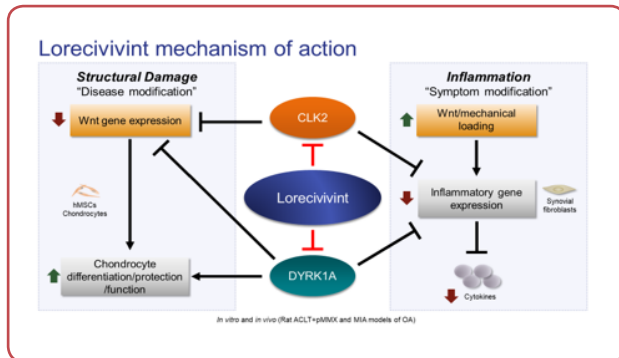
Figure 5: Osteoarthritis and role of Wnt pathway

The first human Phase I RCT to assess the safety, tolerability, PK, dose limiting toxicities and exploratory efficacy of a single IA knee injection in patients with moderate to severe OA of the knee. Yazici et al⁴⁵ reported that molecule SM04690 appeared safe and well tolerated with no evidence of systemic exposure and exploratory efficacy analyses suggested positive trends for pain control and function, opening the door for addition-

Conclusion

All aspects of osteoarthritis: prevalence, pathophysiology, symptoms, oeconomic impact and current treatments are summarised in this paper. Pain control (paracetamol, tramadol, opioids) and NSAIDs as anti-inflammatory tablets or creams/gels, physical therapy, weight loss, IA articular injections of corticosteroids and hyaluronic acid have been the mainstream treatments for decades. Short acting, temporary relief and numerous side effects are limiting their use and pushing many patients to consider total knee replacement. Regenerative medicine was extremely promising in describing potential of mesenchymal stem cells to the point that after decades of use with aggressive marketing many patients are willing to pay a high price to prolong the use of their own joint. After reviewing literature in last 20 years with a focus on more recent robust articles, Level 1 evidence to justify hype and enthusiasm sold to patients does not exist. The most common conclusion in each review is similar; more good research needs to be done. Comparing modest results MSC produced from published data with role of saline, commonly used as “placebo” in ortho trials, most recently as comparator group since saline efficacy was established during last 10-15 years for short (3 months) and even longer (6 months) period of time. Since MSC are, after being harvested, from different places of the body, resuspended in saline (2.5 to 8 mL) there is definitely that “effect” of saline, explained as “therapeutic lavage” of the joint, simple dilution of what is left from synovial fluid in inflamed and arthritic joint and appears that saline “resets” synovium for a while and patient are reporting decreased pain and increased mobility. In the near future better options will be present, more objective parameters to follow patient mobility in real time, using already available trackers to count steps, calories spent, general activity^{47, 48} etc. These should be complementary or better than metrics used today such as very subjective like VAS pain score, WOMAC and KOOS scores.

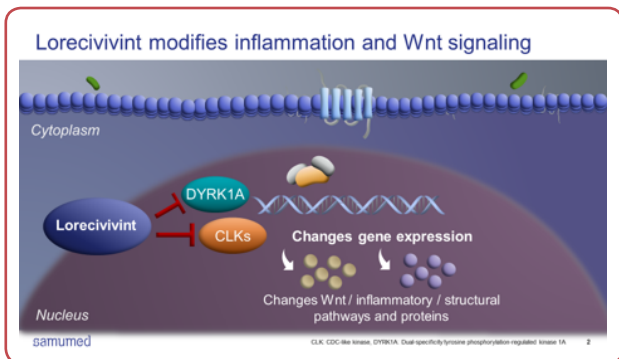
In the near future we hope to have at least two new, exciting drugs added to therapeutic arsenal. Based on my personal experience with both molecules (NGF antibodies since 2008 and Wnt blocking agent since 2012) and many studies from Phase I up to late Phase III with few hundred patients enrolled just at our research centre, I am very optimistic to see both therapies approaching date for FDA submission for approval.



Approved by Summed for publication. Presented and published before. Yazici Y. et al. Arthritis & Rheumatology, Vol.0, No 0, Month 2020, pp1-13.

Figure 6: Lorecivivint is the first Wnt inhibitor for treatment of OA of the knee

Lorecivivint affects Wnt pathway activity via inhibition of two intranuclear targets, CDC-like kinase 2 (CLK2) and dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A), through which it acts both independently and in combination to improve chondrocyte health and function while inhibiting inflammation.



Approved by Summed for publication. Presented and published before. Yazici Y. et al. Arthritis & Rheumatology, Vol.0, No 0, Month 2020, pp1-13.

Figure 7: Lorecivivint mechanism of action in modifying inflammation in knee joint

The Wnt is integral pathway for tissue homeostasis and regeneration and is a key regulator of progenitor cell differentiation in the knee joint. Cartilage homeostasis requires a balance of Wnt activity. While necessary for chondrocyte differentiation and function, aberrant Wnt activity in OA directs progenitor cell differentiation in the joint toward development of osteoblasts instead of chondrocytes. Increased activation of Wnt pathway is known to increase OA development in humans whereas excessive inhibition of the Wnt pathway can cause cartilage and bone destruction. Potential DMOAD (disease modifying OA drug) approach would need to maintain signaling within an optimal range. CLKs = CDC-like kinase 2 (CLK2) and dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A).

al phases to further assess the disease modifying properties.⁴⁶ Results of Phase III are already presented at a few international meetings and a manuscript with data is submitted for publication. FDA submission of this potential treatment for OA of the knee is anticipated in 2021.

Acknowledgements

None.

Conflict of interest

Dr Skrepnik is currently consultant for Sanofi, Regeneron, Samumed, Orthofix and was consultant for Zimmer, DePuy Johnson@Johnson, Chiltern International and 17 other companies and CRO's.

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