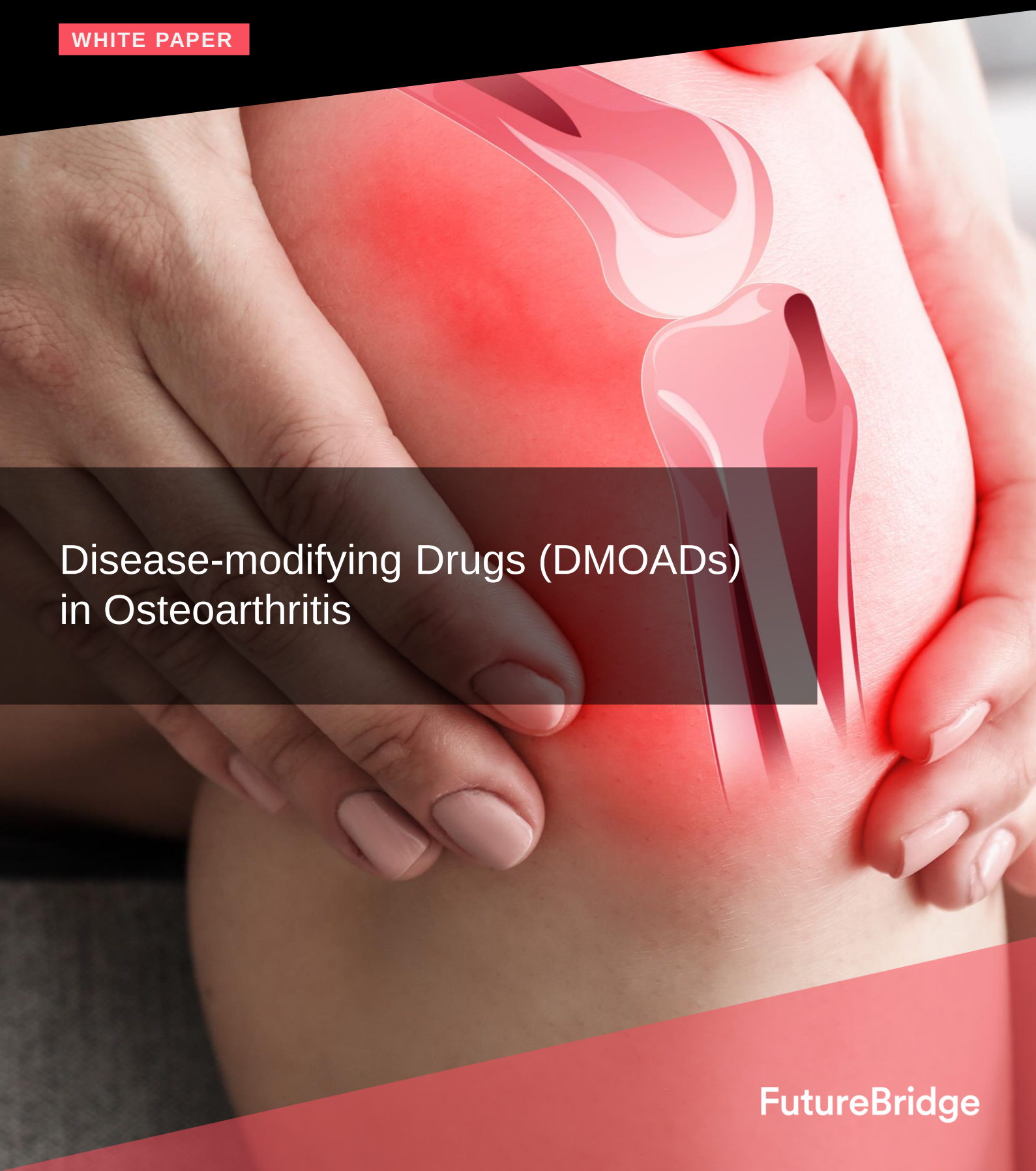




WHITE PAPER



Disease-modifying Drugs (DMOADs) in Osteoarthritis

FutureBridge



Deterioration of the cartilage in joints is the peculiar characteristic of Osteoarthritis (OA). Currently approved therapies are focused on pain reduction and functional improvement. There are no treatments available for inhibiting the structural deterioration, which is a major unmet need. Disease-modifying osteoarthritis drugs (DMOADs) are capable of inhibiting this structural deterioration in Osteoarthritis. Currently, there are no DMOADs approved in US or EU. Major challenges in development include regulatory guidelines, current assessment by conventional radiography, and lack of patient stratification in clinical trials.

Positive evidence provided by some products (e.g. TPX-100) and the use of MRI for accurate diagnosis has reignited the pursuit of clinical trials for DMOADs. If made available DMOADs will cater to a specific unmet need in osteoarthritis - halting the progression of disease along with symptomatic improvements.

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Introduction

Osteoarthritis (OA) is defined as a heterogeneous degenerative joint disease that results from the distraction of catabolic, anabolic, and inflammatory pathways.

OA is a long-term chronic disease characterized by the deterioration of the cartilage in joints which results in bones rubbing together and creating stiffness, pain, and impaired movement. The disease normally affects the joints of the hands, feet, spine, and knees. Most of the time OA is related to aging, along with other risk factors which include obesity, non-exercise, genetic predisposition, bone density, trauma, and gender.

Most of the OA patients show disease progression over time, after symptomatic treatments. Moderate or severe class patients are treated with surgical interventions such as arthroscopy, osteotomy, joint fusions, or joint replacements. These surgical interventions further depreciate the QoL and carry a very high direct and indirect economic burden.

Prevalence

Osteoarthritis affects 7% of the global population, more than 500 million people worldwide. The estimated prevalence and incidence of OA depend on OA definition and the population under study. The pooled global prevalence of knee OA was 16.0% in individuals aged 15 and over and was 22.9% in individuals aged 40 and over. Global prevalence could be even higher due to unreported cases & limitations in data availability from developing or underdeveloped countries.

Various studies have reported the prevalence of OA in South America, Asia, and the Middle East. The prevalence of the overall OA, knee, hip, and hand OA in major markets, continents, sex, and age stratification among adults is provided in *Exhibit 1*.

EXHIBIT 1: Prevalence of knee, hip & hand OA with continent, sex & age stratification in adults

	Age of study population (yrs.)	Prevalence in Women (%)	Prevalence in Men (%)
Knee OA			
Europe	>22	14%	12%
Asia	>24 & 40-75	31% & 61%	23 & 53%
North America	>20 & 42-52	29% & 24%	32% & 44%
Hip OA			
Europe	>20 & 23	7% & 5%	7% & 11%
Hand OA			
Europe	>30	48%	44%
Asia	40-75 & >40	36% & 74%	30%
North America	>40 & 40-52	41% & 21%	42%

Source: [Hunter DJ, et al., \(2019\)](#).

Quality of Life and Economic Burden

Quality of Life

OA has a significant negative impact on Health-Related Quality of Life (HRQoL). The people with OA had an increase of 55% in all-cause mortality due to the associated comorbidities which might increase in the future. There is a high risk of death when there is an association with cardiovascular disease. OA is responsible for significant morbidity, particularly in the second half of human life, when the quality of life is of primary importance.

OA is the leading cause of disability affecting approximately 10% of the elderly population. Especially elderly OA patients with Obesity require significant surgical interventions such as Knee replacement (*refer Exhibit 2*) and cannot perform daily activities.

EXHIBIT 2: Rates of OA patients requiring knee replacement

Patient Age	Non-Obese	Obese
45-55 yrs.	1.2% / 6 years	3.5% / year
≥75 yrs.	5.1% / 6 years	9% / year

Source: [OARSI 2016](#).

Economic Burden

OA is associated with a higher direct and indirect economic burden. The United States Bone and Joint Initiative (USBJI) highlights the economic impact of OA and the all-cause cost (both direct and indirect) averaged at \$486.4 billion between 2008 and 2014. Knee Osteoarthritis itself contributes to more than \$27 billion in health care expenditure annually. A scientific study conducted in 2012, stated that OA was the biggest reason for work loss and affected more than 20 million people, which cost the US economy more than \$100 billion annually.

In a computer simulation study conducted by Losina L, et al., it was concluded that when approved DMOADs are likely to be cost-effective. As per the pre-evaluation of the effectiveness, costs, and cost-effectiveness of DMOAD therapy for knee OA, the drivers of cost-effectiveness might include.

- DMOADs add ~4 quality-adjusted life-years to patients
- DMOADs reduces the need for TKR by 15%
- DMOADs reduces disease progression and provides long-term pain relief

Treatment Landscape

Existing Treatment Options

The existing treatment options for OA are limited to physical therapy, drug therapy, and surgery. Physical therapy is given to patients with Mild OA and depending on the severity of OA lesions. Drug therapy and surgery are considered in Moderate and Severe forms of OA (*refer Exhibit 3*).

Physical therapy involves adjunctive treatments carried out every day

- Weight loss improves imbalanced mechanical stress, reduce joint pain and reduce the OA risk
- Daily moderated exercise strengthens muscles and delay the progression of OA

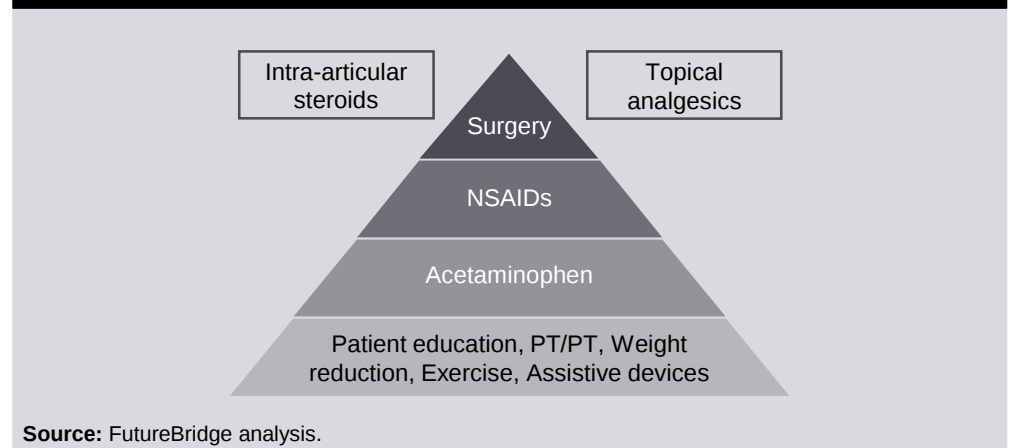
The most common option for treating OA are pharmacological agent which are mostly focused on pain relief and anti-inflammation. The current pharmacological agent of OA involves five kinds of medications (*refer Exhibit 4*):

1. Acetaminophen
2. Non-steroidal anti-inflammatory drugs (NSAIDs)
3. Opioid analgesics
4. Serotonin-norepinephrine reuptake inhibitors (SNRIs)
5. Corticosteroids

Patients with progressing OA despite the conventional therapies are considered for surgery.

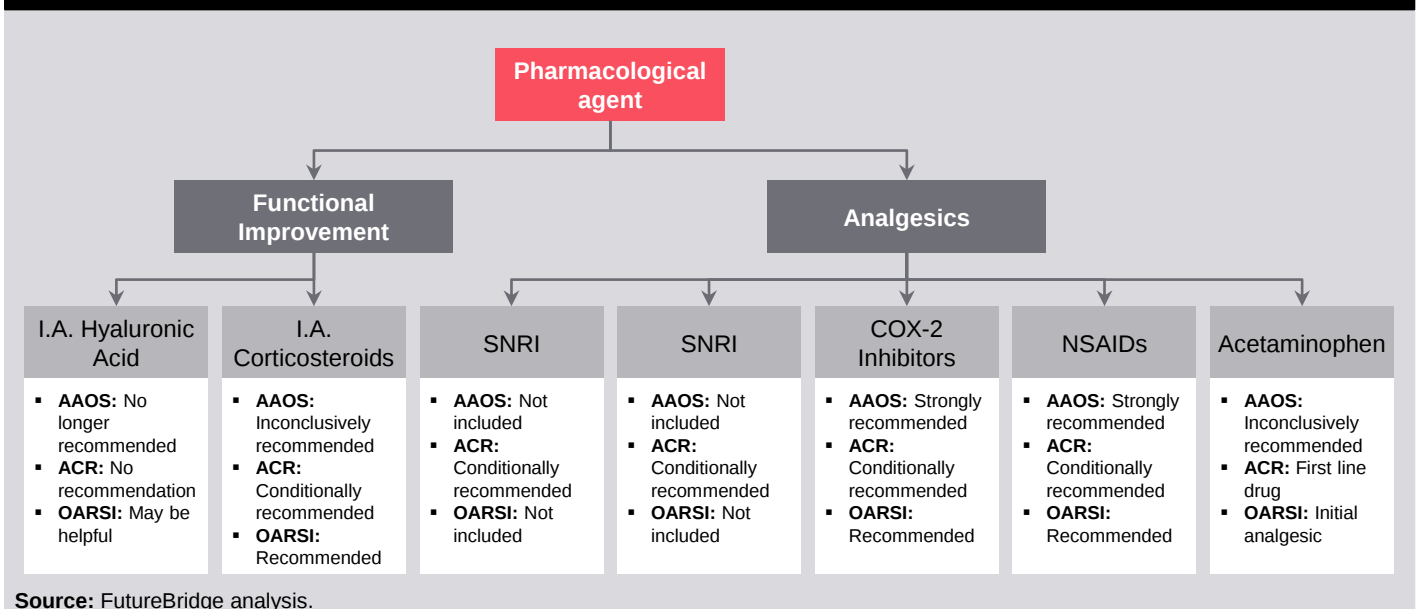
- Arthroscopic irrigation and debridement helps in reducing the pain but are not useful for long term retrieval
- Orthopedic surgeries such as total joint replacement/arthroplasty are mostly considered in severe OA which aids in recovering the joint function and reduces pain
- Arthroplasty is generally not considered for young patients as the artificial implant has a limited lifespan (10-15 years). Additionally, the long-term effects of arthroplasty also differ significantly

EXHIBIT 3: Pyramid approach to OA management



Source: FutureBridge analysis.

EXHIBIT 4: Recommendation of the AAOS, ACR & OARSI in pharmacologic management of OA



Source: FutureBridge analysis.

Limitations of Existing Pharmacologic Agents

Acetaminophen is used for short-term pain reduction in mild to moderate OA.

- The 2014 OARSI guidelines recommended conservative dosing due to safety concerns like multi-organ failure
- Additionally, US FDA has reduced the amount of acetaminophen in combination products to 325 mg per dosage unit due to risk for liver damage

NSAIDs have better efficacy over acetaminophen in terms of pain reduction but there other adverse events associated with their usage and are recommended to be used at least effective dose.

- 30% chance of adverse events in NSAIDs patients with 1-2% having GI complications
- COX-2 inhibitors are related to the risk of complication associated with the heart hence, long-term use shall be avoided

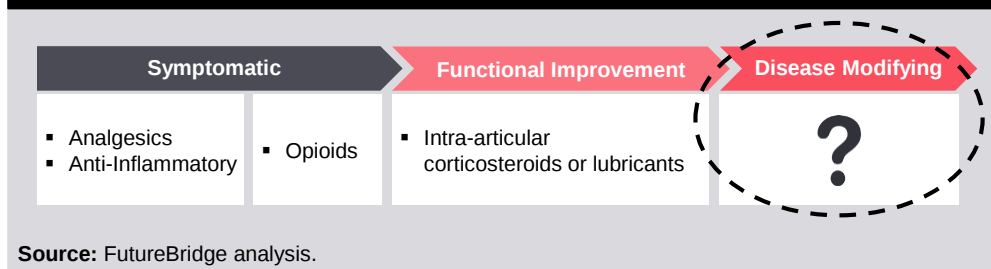
Opioids are known to offer benefits in reducing OA pain but, attribute 3 to 4 times more adverse or severe events compared to placebo hence, not recommended owing to risk-benefit assessment.

Corticosteroids efficacy in OA is still debated. The 2012 ACR and OARSI guidelines recommend the usage of intra-articular (IA) injection for the short term and usage of IA hyaluronic acid has not come up with any concerns.

Need of Disease-Modifying Agents

Despite the drug therapy for pain management, diseases in patients progress. All the existing pharmacologic treatment options focus on symptomatic relief but, to halt the disease progression there is a need for disease-modifying agents (*refer Exhibit 5*).

There is a high clinical unmet need in the treatment landscape of OA and there is a dire urgency of disease-modifying osteoarthritis drugs (DMOADs). Even regulatory bodies such as FDA & EMEA have advocated the development of disease-modifying agents for OA. DMOADs are expected to change the treatment paradigm of OA by improving the QoL and reducing the economic burden of OA.

EXHIBIT 5: Unmet need in OA**Pathophysiology of OA Explaining Potential of DMOADs****Cartilage Regeneration in OA**

Hyaline articular cartilage (AC) is a specialized avascular and aneural type of connective tissue which covers the articulating end of the bone surface and is the most affected AC in OA. Extracellular components of cartilage (proteoglycan and collagen type II) and chondrocytes undergo age-related metabolic changes, which result in an imbalance between matrix synthesis and degradation. Varied risk factors can concurrently change the biomechanical properties of cartilage tissue that further results in pain and joint dysfunction.

- Increased activity of catabolic signaling pathways and ECM degrading enzymes results in chondrocyte hypertrophic differentiation, matrix degradation, and vascular invasion
- Chondrocytes in OA cartilage reveal skewed TGF- β -dependent signaling from the ALK5/Smad2/3 to ALK1/Smad1/5/8 pathway which is induced through activation of the canonical Wnt pathway
- The erosion of the cartilage's superficial layer is due to overexpression of Wnts and WISP1 in synoviocytes through the up regulation of MMP and aggrecanase activities.
- The absence of the progenitor cells or their migration in cartilage defects are important factors that affect the healing

Hyaline cartilage regeneration does not occur without vasculature. So to fasten up the regenerative process, cartilage lesions should be provided with progenitor cells.

Subchondral Bone Remodeling

A vital part of OA pathology is subchondral bone remodeling and the response of which is dependent on the rest of the joint. Any deviations from normal activity in articular cartilage result in a change in subchondral bone and vice-versa.

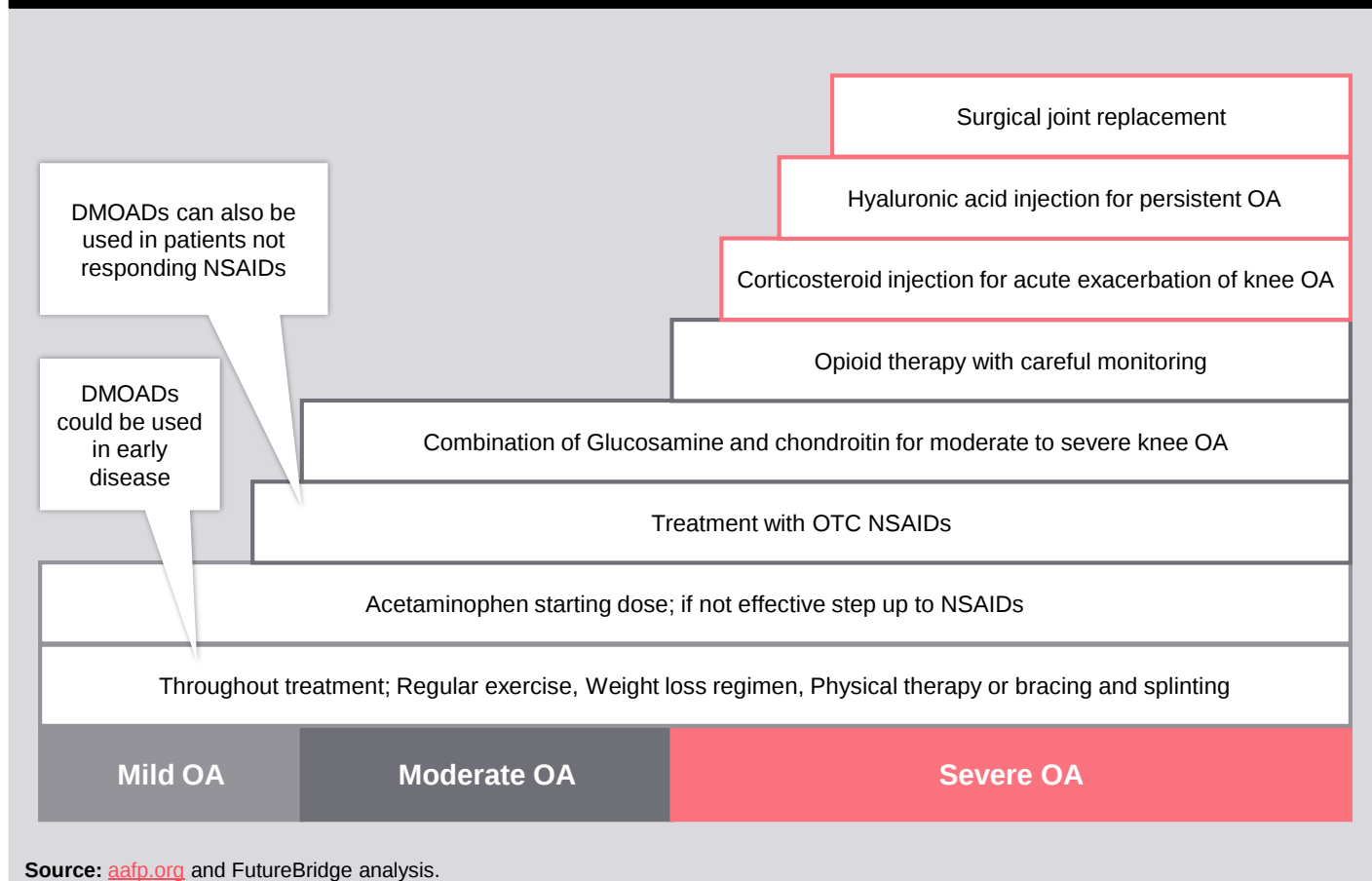
Abnormal mechanical load is the primary initiator for subchondral remodeling leading to micro-fractures. This whole process involves macrophages, MSCs forming osteoblast, and osteoclastogenesis through chemical signals. The overall

forming osteoblast and osteoclastogenesis through chemical signals. The overall effect is to increase bone tissue coupled with demineralization that results in few trabecular

- These changes can be realized as increased vascularization on MRI if, carried out in the early stages of OA
- The new blood vessels and sensory nerves move deeper inside in articular cartilage as osteoclast penetrates the osteochondral junction
- Synovial fluid and its cytokines can directly penetrate the subchondral bone and affect all the nearby cells
- The further progression to OA occurs when abnormal mechanical force enters a point where recovery is not possible. It is believed that this is the time when subchondral sclerosis may occur

Various drug regimens that affect chemical pathways are not expected to work from this point. Apart from pain relief, surgical procedures like osteotomy are more likely to be limited in further reducing the progress of the disorder (Refer Exhibit 6).

EXHIBIT 6: Potential use of DMOADs in OA treatment pyramid



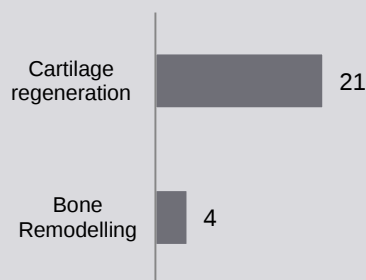
Clinical Developments in DMOADs

Globally, there are multiple DMOADs under development in various phases involving many small players & pharma giants such as Novartis, Amgen, Merck, Eli Lilly, etc. Product types include all the classes such as small molecules, biologics, mAb, cell therapy & gene therapy (refer to *Exhibit 7*, *Exhibit 8*, *Exhibit 9*). Currently, there are around 25 DMOADs underdevelopment in various developmental phases from preclinical to phase 3

- The highest activity of DMOADs development has been observed in the phase 2 stage of development
- DMOADs under development are majorly new molecular entities (NMEs) with more focus on cartilage regeneration
- Of the 25 entities, 21 have the potential of cartilage regeneration, and 4 for subchondral bone remodeling.
- 2 products under development can be used for both
- Marketed Products for other indications, such as Denosumab, Teriparatide, etc., are being tried as DMOADs for bone regeneration
- All the different classes of pharmacologic therapies under development include:
 - 8 small molecules
 - 7 Stem Cell therapy
 - 6 Biologics
 - 3 gene therapy

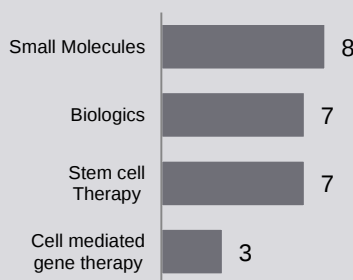
The major focus in DMOADs design is in the direction of using it as an intra-articular (IA) injection, as opposed to other therapies, and this can be seen with the current trend of clinical trials. As IA treatments are directed towards the pathophysiology of OA within the joint, there are higher chances for drugs with a new mechanism of action to be more efficacious than the traditional systemic treatments.

EXHIBIT 7: Number of products on basis of activity



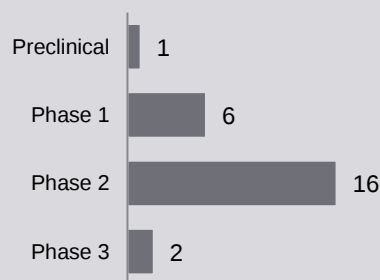
Source: FutureBridge analysis

EXHIBIT 8: Number of products by molecule type



Source: FutureBridge analysis

EXHIBIT 9: Number of products by phase of development



Source: FutureBridge analysis

Gene Therapy

INVOSSA which is developed by Kolon Life Sciences has completed the phase 3 stage of development and is used as an intra-articular injection (Sales suspended in South Korea).

Various studies have identified that the re-differentiated status of chondrocytes and induced cartilage regeneration could be maintained by providing a continuous supply of TGF- β 1. Additionally, they have also found that chondrocytes supplemented with TGF- β 1 producing cell help in cartilage regeneration. Their preclinical studies showed the production of hyaline cartilage using a mixture (TG-C) of human chondrocytes (hChonJ) and irradiated TGF- β 1 producing chondrocytes (hChonJb#7).

Stem Cell Therapy

In Stem cell therapy, mesenchymal stem cells (MSCs) are most commonly been sought after in regenerative medicine because of their multi-potency and immune-modulatory properties. They can exert tissue regenerative activity by being pro-angiogenic, anti-apoptotic, and anti-fibrotic.

MSCs can divide into adipocytes, chondroblasts, osteoblasts which are defined by the presence of various cell surface markers. One of the most attractive properties of MSCs which warrant their need in regenerative medicine is their immunomodulatory and anti-inflammatory properties.

MSCs have been proven to provide protection against apoptosis induced by oxidative stress, trauma, and different type of injuries by secretion of varied growth factors like IGF-1, TGF- β 1, IL-6, and anti-oxidative molecule-like erythropoietin and heme oxygenase (OH)-1.

MSCs have also been found to release extracellular vesicles (EVs) which are mediators of paracrine action in regenerative medicine. The EVs exhibit an immunosuppressive role in the B-lymphocytes and T-cell population and are also known to suppress the inflammatory function of monocytes and macrophages.

7 stem cell therapies are under development at the clinical and pre-clinical stage and all of them use mesenchymal stem cells. Out of this pool, one product Caristem is marketed by Medipost and it had received approval for commercialization by the Ministry of Food and Drug Safety in Jan 2012.

Biologics

The best biologic agent for OA should be a product that would be able to reduce pain, relieve symptoms and re-establish the normal structure of joints. In Biologics

there are six products that can be used as DMOADs in OA which are further grouped below:

Platelet Rich Plasma

Platelets are composed of alpha granules with numerous growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor- β (TGF- β), etc. as well as certain cytokines, chemokine, and mediators which play vital roles in tissue regeneration and regenerative mechanism. PDGF and TGF- β may also possibly direct the local MSCs to migrate, divide, and increase collagen and matrix synthesis.

There are more than a dozen clinical trials, and all of them have reported symptomatic relief after PRP injection. But the trials which are examining the structural benefits are missing. In a review, Bennell, et.al, stated that “no conclusive statements can be made regarding the effect of PRP in OA given the procedure modalities and heterogeneity between the studies.

Fibroblast Growth Factors

A clinical trial was conducted to assess the safety and efficacy of intra-articular sprifermin (recombinant human fibroblast growth factor) in 180 patients for the treatment of symptomatic knee OA. In a dose-dependent manner, sprifermin was able to reduce the loss of total and lateral femoro-tibial cartilage thickness and volume along with the joint space. No adverse events were recorded between the groups. There is a need to perform more clinical studies for a full investigation of this new biologic drug.

Other Inhibitors

There are also other proteins like M-6495 and LNA-043, having active roles in inflammation and rheumatics. These proteins are in Phase-1 development for Osteoarthritis in Denmark and the USA and results are awaited.

Small Molecules

In the small molecule bucket, there are 8 molecules which have the potential to be used as Disease-modifying OA drug. Of the 8 molecules, 50% of them are small players and are targeting signaling pathways that are involved in the degeneration of cartilage.

Out of 8 small molecules, GLPG1972 is developed by Galapagos and has the potential to become a first in class disease-modifying osteoarthritis drug (DMOAD). They have also received the Fast Track designation from FDA in recognition of the high unmet medical need in OA.

- It is a DMOAD candidate targeting a cartilage-degrading enzyme called ADAMTS-5, as confirmed in two animal models.

- A Phase 1 trial in healthy volunteers met all its safety and pharmacokinetic targets.
- Demonstrated that within two weeks, GLPG1972/S201086 reduced the blood level of ARGS neo-epitope, a biomarker for cartilage breakdown, by approximately 50%.

Small molecule SM04690, is a potent inhibitor of the Wnt/ β -catenin pathway has shown encouraging results by intra-articular injection in a phase-I study. A phase-II study described a reduction in pain and function with a tendency of maintaining mJSW with adverse effects only in 3.7% of participants (n=455).

Matrix Metalloproteinase (MMP) are zinc-dependent proteolytic enzymes are required for maintaining the extracellular matrix. The development of MMP inhibitors is important; as MMP is believed to be involved in physiological remodeling and destruction of joint tissue. In a clinical trial of knee OA; the MMP inhibitor, PG-116,800, showed a significant change in JSW of the knee.

Other small molecules like MIV-711, LRX – 712, TPX-100, Teriparatide, and Balicatib are in Phase-II trials.

Conclusion

OA is a progressive disease with a structural change where policymakers and healthcare workers understand that the prevalence of OA is going to increase in the coming years to a point where it will be classified as the most frequent disease.

Considering the increasing prevalence, impact on QoL, and economic burden of OA there is a need for products that could look beyond existing treatment options of symptomatic therapies. This unmet need has generated interest in developing DMOADs which could completely change the treatment paradigm, especially in moderate and severe OA cases.

To prove a drug as a DMOAD, it should not only demonstrate structure modifying effects but also a symptomatic relief. Even if it satisfies one of the conditions, the lack of the other will lead to disapproval from regulatory bodies. Recent advancements in the diagnosis of cartilage degeneration by MRI have improved the chances of detection of DMOADs effectiveness clearly.

Comparing to the past experience with DMARDs, the DMOADs will be given for a long duration, hence proving its safety in elderly patients who already have various co-morbidities will be a challenge.

Furthermore, DMOADs probably will find their usage in disease stages before irreversible molecular and biomechanical pathology is established. This highlights that the need for early diagnosis in OA is equally important as developing disease-modifying agents.

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