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Review

Disease-modifying treatments for osteoarthritis (DMOADs) of the knee and hip: lessons learned from failures and opportunities for the future

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SUMMARY

Osteoarthritis (OA) is the biggest unmet medical need among the many musculoskeletal conditions and the most common form of arthritis. It is a major cause of disability and impaired quality of life in the elderly. We review several ambitious but failed attempts to develop joint structure-modifying treatments for OA. Insights gleaned from these attempts suggest that these failures arose from unrealistic hypotheses, sub-optimal selection of patient populations or drug dose, and/or inadequate sensitivity of the trial endpoints. The long list of failures has prompted a paradigm shift in OA drug development with redirection of attention to: (1) consideration of the benefits of localized vs systemic pharmacological agents, as indicated by the increasing number of intra-articularly administered compounds entering clinical development; (2) recognition of OA as a complex disease with multiple phenotypes, that may each require somewhat different approaches for optimizing treatment; and (3) trial enhancements based on guidance regarding biomarkers provided by regulatory agencies, such as the Food and Drug Administration (FDA), that could be harnessed to help turn failures into successes.

Introduction

Osteoarthritis (OA) is the most common form of arthritis[1,2]. The incidence of OA increases with age and by 65 years approximately 80% of the population has some radiographic evidence of disease[3]. The hallmark of the disease is joint pain and progressive degeneration of articular cartilage involving remodeling of all joint tissues (bone, synovium, ligaments) with subsequent joint space narrowing (JSN)[4,5]. OA not only shortens the number of healthy years of life but also increases mortality[6,7] and comorbidities such as depression[8]. Therefore, OA and joint destruction are a serious burden to both the patient and society.

Although a number of potential disease-modifying pharmacological therapies have been investigated, a series of disappointing terminations of late-stage drug development programs suggest the need for careful reconsideration of the development process for this type of drug.

We suggest that the chance of successful OA drug development may improve in the future as a consequence of a paradigm shift informed by important developments in the field, including: (1) consideration of the benefits of localized vs systemic pharmacological treatment, indicated by increasing numbers of intra articular (IA)-administered compounds entering clinical trials; (2) greater appreciation of OA as a complex disease with multiple phenotypes, which may enable a more tailored treatment approach to address the needs of individual patients; and (3) progress toward qualifying biomarkers to implement their use as drug development tools (DDT) in OA trials based on guidance of regulatory agencies, particularly the Food and Drug Administration (FDA) in the USA and the European Medicines Agency (EMA).

In this manuscript we summarize lessons learned from failed clinical trials, review current development programs, highlight some preclinical programs with particularly promising development potential, and highlight the FDA/EMA initiatives on biomarkers to support drug development in the OA field.

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OA treatments: from systemic administration to local delivery

Failures due to unacceptable systemic toxicity, such as systemic pan-matrix metallo protease (MMP) inhibition[9] have prompted increased exploration of localized drug delivery via the IA approach. Although some OA phenotypes may have systemic manifestations[10,11], the symptoms and pathological sequelae are often localized to one or a few joints[12]. Thus, localized treatment with IA injections appears feasible for the larger joints as it potentially offers high drug concentrations, local action with limited or no systemic exposure. On the other hand, one of the main challenges with IA treatments is the invasive nature of drug delivery, requiring puncture of the joint capsule. Furthermore, IA injection is associated with a very strong placebo effect, at least for self-reported measures, posing a challenge for clinical trial design[13]. It is therefore critical to limit the number of injections required, by using drug candidates which are particularly efficacious or have a very long articular half-life, or by using suitable extended-release formulations[14].

OA: different progression rates and phenotypes

Patients with clinically diagnosed OA represent a heterogeneous population in terms of the underlying pathophysiology. In addition to cartilage, the joint is composed of different tissues including ligaments, meniscus, bone, fat, synovium and muscle. The joint therefore contains many different cell types that are capable of exhibiting pathology, resulting in many potential targets for treatment (Fig. 1). Because of this heterogeneity, there is unlikely to ever be a 'one size fits all' treatment for OA. Researchers are increasingly suggesting that there are three main phenotypes or subpopulations in OA based on pathophysiology: traumatic or cartilage-driven[15]; inflammation-driven (which to some extent overlaps with the former type)[16,17]; and bone-driven[18,19]. Each of these probably interacts with hormonal[20], genetic[21] and metabolic[22] risk factors. These three primary phenotypes and the involvement of distinct cell types and pathologies are illustrated in Fig. 2, albeit as some characteristics are commonly shared to some extent such as the bone phenotype which may demonstrate properties of the inflammation-driven group, as shown by sensitive and accurate bone scintigraphy technology[23,24]. In terms of drug development, it is reasonable to assume that each phenotype requires targeted treatment[11,25].

Rates of structural progression and selection of populations for clinical trials

To prove the efficacy of a drug in reducing OA progression, a patient population with disease progression is needed. Data from the Osteoarthritis Initiative (OAI) show that 4% of OA patients with stable disease and up to 14% with incident OA experience measurable progression over a 1-year period[26]. This suggests that OA disease activity may vary between periods of inertia and periods of faster progression[26]. Consequently, it is essential to identify the drivers of disease progression in order to test effective interventions; biomarkers able to predict OA progression are vital to efforts to appropriately power clinical trials and understand mechanisms of progression.

The use of unselected patient populations in clinical trials has the potential to obscure efficacy signals that may be apparent in smaller patient subgroups. For example, although early research into the use of bisphosphonates for treating OA showed promising results[27], a phase III trial in a broad, near-all-comer population demonstrated no significant effects[28]. This failure may partly be explained by the fact that only those patients with the bone-driven OA phenotypes benefitted from this bone anti-resorptive

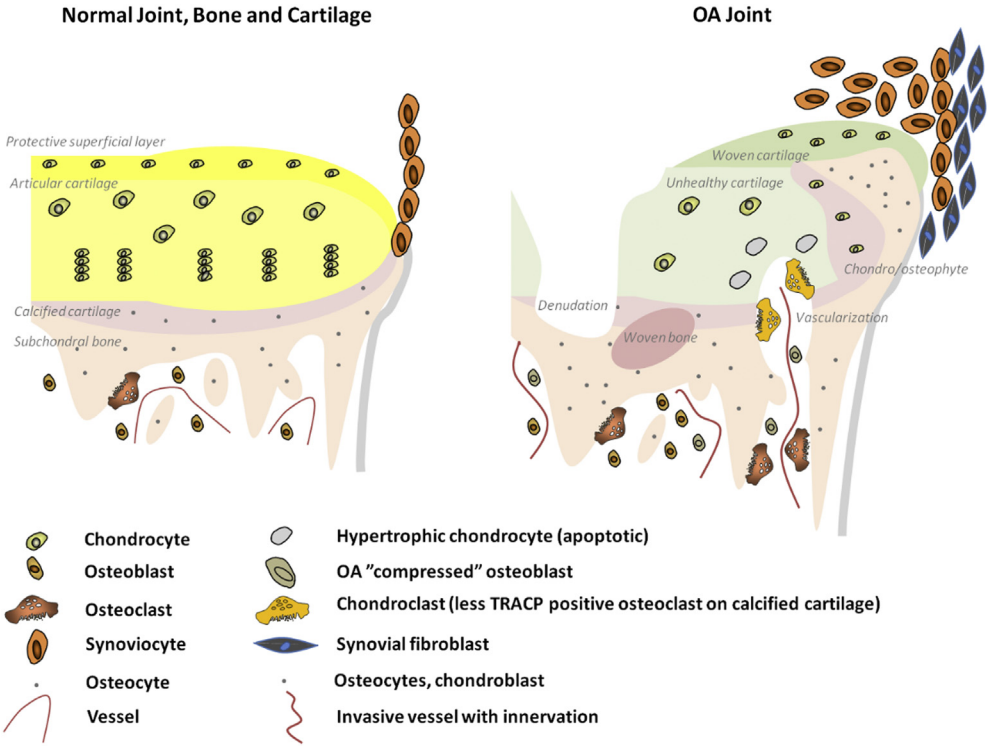

Fig. 1. Schematic representation of a healthy joint and an OA-affected joint. Compared with the healthy joint, the OA joint is damaged as follows: cartilage loss (up to denudation of bone); hypertrophic chondrocytes and cloning of chondrocytes (local proliferation); vascularization of the subchondral bone and vascular penetration into the calcified matrix; presence of nerve endings in the osteophytes, meniscus, posterior cruciate ligament and synovium itself; altered phenotypes of osteoblasts and osteoclasts (chondroclasts); subchondral bone sclerosis; under-mineralized areas consequent to hyper-remodeling (woven bone); bone marrow lesions; trabecular thinning; and synovial inflammation. Reprinted with permission from Karsdal *et al.*[18].