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Biomarkers for osteoarthritis: Current position and steps towards further validation

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A B S T R A C T

Historically disease knowledge development and treatment innovation in osteoarthritis (OA) has been considered to be slow. One of the many reasons purported as responsible for this slow pace has been the alleged lack of valid and responsive biomarkers to ascertain efficacy, which itself has been dependent upon the slow evolution of the understanding of the complex nature of joint tissue biology. This narrative review outlines the rationale for why we need OA biomarkers with regard to biomarker validation and qualification. The main biomarkers in current development for OA are biochemical and imaging markers. We describe an approach to biomarker validation and qualification for OA clinical trials that has recently commenced with the Foundation of NIH OA Biomarkers Consortium study cosponsored by the Osteoarthritis Research Society International (OARSI). With this approach we endeavor to identify, develop, and qualify biological markers (biomarkers) to support new drug development, preventive medicine, and medical diagnostics for osteoarthritis.

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Keypoints

1. Historically disease knowledge development and treatment innovation in osteoarthritis (OA) have been considered to be slow. One of the many reasons purported as responsible for this slow pace has been the alleged lack of valid and responsive biological markers (biomarkers) to ascertain efficacy, which itself has been dependent upon the slow evolution of the understanding of the complex nature of joint tissue biology.
2. With the Foundation for the National Institutes of Health OA Biomarkers Consortium, we have established and commenced a process for biomarker validation and qualification in OA that endeavours to identify, develop and qualify biomarkers to support new drug development, preventive medicine, and medical diagnostics for OA.

Introduction

Osteoarthritis (OA), the most common of all arthritides, is a heterogeneous disease characterised by the failure of the synovial joint organ. The risk of mobility disability (defined as needing help walking or climbing stairs) attributable to knee OA alone is greater than that due to any other medical condition in people aged 65 and over [1,2]. Recent estimates suggest that the global burden of knee OA affects approximately 250 million people [3]. Although ageing is a significant risk factor, the majority of those affected with OA (64%) are of working age (15–64 years) accounting for 11% of the workforce [4,5]. There are presently no therapies approved by regulatory authorities that modify the onset or progression of OA structural damage, and the available symptom-modifying (analgesic) treatments have only moderate long-term effect sizes with the majority of patients dissatisfied with their efficacy [6,7]. As a result of the failure of pharmacological approaches to manage the condition, the number of joint replacement surgeries, over 95% of which are done for OA, is increasing by ~10% annually. In the USA alone, the financial burden has been estimated to be US$81 billion in medical costs and US$128 billion in total cost, given approximately 21 million people with OA-associated limitations, 36 million outpatient visits and 750,000 hospitalizations per year [8]. This formidable individual and socioeconomic impact of OA will continue to increase as the population ages and obesity rates continue to grow, with the number of persons affected predicted to double by 2020 [4,9].

Despite the urgency driven by its frequency, individual impact of disability, and societal cost, current treatment paradigms are limited to palliative measures broadly focussed on analgesia and, when this fails, surgical knee replacement. It is clear that finding effective disease- and symptom-modifying therapies for OA is a global unmet need whose amelioration should be an international medical priority. There have been major research advances that have significantly increased our understanding of the molecular pathophysiology of joint destruction and pain in OA. Despite this pre-clinical progress, however, no new structure-modifying therapies have translated into treatments for patients. Indeed, the recent failure of a number of phase II and III clinical trials for OA structure-modifying drugs has resulted in a considerable decline in the number and size of pharmaceutical company research programmes in this area [6]. The reasons for the translational failure of anti-OA drugs are likely multifold, but include the poor relationship in individual patients between joint structural pathology (especially joint space narrowing (JSN) on radiographs) and symptomatic disease, and limited responsiveness of existing biological markers (biomarkers) [10].

This narrative chapter outlines the rationale for why we need OA biomarkers and work done in OA with regard to biomarker validation and qualification. The main biomarkers in current development for OA are biochemical and imaging markers. It then describes an approach to biomarker validation and qualification for OA clinical trials that has recently commenced with the Foundation for the National Institutes of Health (FNIH) OA Biomarkers Consortium study cosponsored by the Osteoarthritis Research Society International (OARSI).