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Review

Osteoarthritis year 2010 in review: biochemical markers

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SUMMARY

At the 2010 Osteoarthritis Research Society International (OARSI) congress in Brussels I was asked to present on "Biochemical Markers" in the "Year in Review" session. This provided an opportunity to summarize ongoing work and consensus building in the osteoarthritis research community related to osteoarthritis biomarkers, and second, and an opportunity to briefly overview a subset of studies from the previous 12 months related to soluble biomarkers that provided novel insights in the field. This review therefore briefly summarizes the progress in 2010 of the OARSI OA Biomarkers Global Initiative and the OARSI FDA Biomarkers Working Group, and provides a summary of selected osteoarthritis biomarker studies reported over the previous 12 months based on a review of articles from seven musculoskeletal journals and a PubMed search using the terms biomarkers and osteoarthritis.

Introduction

The field of osteoarthritis (OA) biochemical markers is steadily advancing, leading to the progressive unfolding of the potential role to be played by OA biomarkers in basic research, clinical studies and clinical practice. The long-term goal is to advance, through clinical qualification, a subset of useful biomarkers from the realm of the plausible to the realm of practical application. Increasingly the OA disease process is being considered a continuum, beginning with an inciting event, such as genetic variation or injury, progressing through molecular, pre-radiographic and radiographic stages, culminating in end-stage disease[1]. With this reclassification of the disease process as a continuum of a series of stages, it is readily apparent that biomarkers could play a pivotal role in disease detection and monitoring, particularly during the critical early molecular stages when other tools could not readily identify it. These developments are occurring in parallel with efforts to harness biomarkers for applications in a wide variety of diseases and to standardize the regulatory process for biomarker qualification to accelerate development of therapies[2]. To put into perspective the progress on OA-related biochemical biomarkers in the past year, I summarize here the recent history of the networking efforts in the OA biomarkers research community, and highlight some of the biomarker studies published in the last 12 months.

OARSI OA Biomarkers Global Initiative

The OARSI OA Biomarkers Global Initiative grew out of an NIH/NIAMS sponsored biomarkers network of investigators and public biomarkers research meetings funded from 2002 through 2006. In 2008 the National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIH/NIAMS) funded support for three OA-related biomarkers workshops to continue the investigative momentum in the OA biomarker field. A first workshop was held in April, 2009 (Bethesda, MD) focusing on OA-related biochemical markers with a meeting summary published this year[3]. A second workshop, focusing on OA-related genetic markers, was held in November, 2010 (Atlanta, GA). The slides from these meetings are available through the OARSI website (http://www.oarsi.org/) and a meeting summary is in preparation. A third workshop will be held in 2012 focusing on OA-related imaging biomarkers. These workshops are serving the purpose for which they were designed, namely, to bring together a critical mass of OA biomarkers researchers to advance the knowledge, qualification, and clinical application of biomarkers in OA.

OARSI FDA Biomarkers Working Group

A second major accomplishment related to OA biomarkers, to come to fruition in 2010, has been production of a comprehensive white paper on the "Application of Biomarkers in the Development of Drugs Intended for the Treatment of Osteoarthritis" by the OARSI Food and Drug Administration (FDA) Biomarkers Working Group[4]. This group was one of seven that dealt with different aspects of OA, all part of a major initiative on the part of OARSI to assist in overcoming barriers to the development of successful disease modifying agents for

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OA. The forthcoming white papers (to be published in Osteoarthritis & Cartilage in 2011) represent responses to queries posed by the FDA in an effort to consider revision of guidelines for drug development. Action items posed in the white paper represent a summary of critical needs in the OA biomarkers field as envisioned by the 20 experts of the biomarkers working group. The white paper on biochemical markers included recommendations on biomarker qualification (defined as the evidentiary process of linking a biomarker with biological processes and clinical endpoints), and elucidated unmet needs in the field including articulating a research agenda. A few key recommendations include the need to standardize reporting of biomarker results, to find minimal meaningful differences in biomarkers in the presence and absence of a treatment, to standardize methods of sample collection for biomarker studies (the white paper provides an appendix with suggested methods of sample collection), to collect information on non-signal joints in studies measuring systemic biomarkers, to identify principal tissue sources of a biomarker, and finally, to begin epitope mapping of biomarkers using techniques such as mass spectroscopy (using the antibodies or reagents specific to the particular assay). It is hoped that this white paper will inform and facilitate the process of advancing OA biomarkers for drug development and clinical trial applications.

Summary of selected biomarkers publications (2009–2010)

To identify OA biomarker studies for this year in review presentation, I reviewed the OA biomarker studies of the past 12 months in seven musculoskeletal journals (Osteoarthritis & Cartilage, Arthritis & Rheumatism, Arthritis Care & Research, Arthritis Research & Therapy, Annals of Rheumatic Disease, J Rheumatology, and J Orthopaedic Research), performed a PubMed search using the query terms of biomarkers and OA with the search limited to the prior 12 months, and reviewed the abstracts of the 2010 World Congress on Osteoarthritis OARSI (Brussels). A summary of selected studies is provided in Table I. In brief, this Table summarizes: a recent major review of human OA biomarker studies fulfilling the need for a means of comparing and contrasting various trials and biomarkers using some specific reporting criteria[5]; two trials (one clinical in humans and one preclinical animal study) addressing the need for greater inclusion of biomarkers in OA clinical trials in order to potentiate the effective clinical use of biomarkers in the future; five studies related to advances with aggrecanase-generated neoepitopes providing excellent examples of efforts to develop biomarker tools to facilitate dose setting in early clinical studies and to increase confidence in drug mechanism; two studies related to prediction of incident OA addressing the need to identify biomarkers that recognize the early molecular stages of OA that may be most susceptible to disease modification[6,7]; four studies related to various OA disease subsets addressing the need to study a wide variety of patient types with varied clinical characteristics and joint-site involvement; and three studies related to identifying the joint tissue source of a biomarker addressing the need to understand the principle tissue source(s) of a given biomarker as accurately as possible so that the origin(s) of the epitope(s) is/are clearly understood.

I would like to highlight a few particulars from several of these studies. The paper on OA biomarkers by van Spil *et al.*[5] represents a seminal review on the current qualification status of OA biomarkers for structure and pain outcomes. van Spil summarized biomarker results from knee and hip OA studies (84 in all), and classified them according to the BIPED classification scheme[8] (denoting Burden of disease, Investigative, Prognostic, Efficacy of intervention and Diagnostic biomarkers). Of note, the OARSI FDA initiative Biomarkers Working Group recently expanded the acronym to BIPEDS with the addition of a Safety biomarker category, to be able to categorize this additional essential use and capability of biomarkers, anticipated to be of increasing importance as the armamentarium of biomarkers expands and becomes more sophisticated. The van Spil review was elegantly organized, and included two monumental supplementary tables that provide a succinct and comprehensive summary of the vast majority of biomarker studies performed to date. The strength (or lack thereof) of evidence for a biomarker to be classified into a BIPED category was scored on a 1–2+ scale. In addition, the precise details were provided regarding the particular assay used (e.g., manufacturer, antibodies, additional references, *etc.*), thus providing a strong paradigm for a method of reporting biomarker results and an example of the level of detail that is not only useful, but increasingly necessary, as we endeavor to further refine our understanding OA-related biomarkers and seek to apply them clinically.

Two papers provided data showing baseline biomarkers predicting incident knee OA ~7–10 years later[6,7]. I look upon these studies as providing particularly exciting evidence to support the capability of selecting biomarkers to detect the molecular stage of the disease and to pave the way for gaining insights into the early molecular stages of OA. The first, by Ling, is a case-control study nested within the Baltimore Longitudinal Study of Aging that included 22 incident cases of radiographic OA (both hand and knee together) and 66 age, sex and body mass index matched controls without radiographic hand or knee OA[6]. The samples that were tested were obtained at the time of radiographic classification as either case or control and they had a second sample that was obtained up to 10 years earlier at a time when the participants were free of radiographic hand and knee OA, representing pre-radiographic or molecular earlier stages of the disease. Antibody-based microarrays, requiring only 20 μL of serum, were used to screen 169 proteins. Overall, there were 10 differentially expressed proteins predictive of incident OA and 16 proteins that were significantly different between cases and controls at the time of classification at follow-up diagnosis of OA. There were a total of six 'disease initiating event' biomarkers that were elevated and differentially expressed prior to radiographic OA but that were not differentially expressed at the time of prevalent OA. There were a total of four 'disease sustaining event' biomarkers that were elevated both before and at the time of radiographic OA. There were several 'take-home messages' from this study: that altered extracellular matrix catabolism plays a central role in OA initiation; that increased expression of inflammatory cytokines and chemokines is associated with prevalent OA, lending additional support to the notion of OA as an inflammatory disease; and that prevalent OA is associated with ongoing attempts at repair based on the observation of increased expression of TIMPs and growth factors.

The second study by Golightly[7], presented as a poster at OARSI (Brussels), evaluated the predictive ability of biomarkers for incident knee OA. There were no statistically significant biomarker associations with incident knee OA based on using Kellgren–Lawrence (KL) grading, however, serum Cartilage Oligomeric Matrix Protein (COMP) was highly predictive of incident osteophytes, and both COMP and serum hyaluronan (HA) were predictive of incident joint space narrowing. It was also notable that osteophyte and joint space narrowing were detected by different biomarkers, and as presented in the Year in Review session by Wim van den Berg (his own work and that of Chris Little's), these two processes appear to involve different pathways, and different pathophysiologies. This suggests that these two aspects of radiographic OA are inappropriately conflated by KL grade, and in biomarker studies, analyses of these features should ideally, be looked at individually.

Three studies addressed the effects of immobilization and activity on biomarkers[9–11] and are remarkable for their novelty and rigor. The first, a crossover trial of five individuals, studied the effects of 14 days of enforced immobilization in a 6 degree 'head-down-tilt-bed-rest' position, with and without two brief treatments (5 min) of whole body vibration[9]. The 2-week periods of