



The Medical Therapy of Osteoarthritis: “Thinking Outside the Box”

Charles J Malemud

Department of Medicine & Anatomy, University Hospitals Case Medical Centre, Department of Medicine, Division of Rheumatic Diseases, Foley Medical Building, Ohio, USA

Corresponding author: Charles J Malemud, Department of Medicine & Anatomy, University Hospitals Case Medical Centre, Department of Medicine, Division of Rheumatic Diseases, Foley Medical Building, Ohio, USA, Tel: (216) 536-1945; E-mail: cjm4@cwru.edu

Received date: November 3, 2015; **Accepted date:** December 10, 2015; **Published date:** January 27, 2016

Copyright: © 2016 Malemud CJ. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

The Medical Therapy of Osteoarthritis

A limited number of approved United States Federal Drug Administration (US-FDA) medical therapies are presently employed for the medical therapy of osteoarthritis (OA). Why is that? And why, despite the world-wide statistical evidence which has repeatedly shown that OA is the most common type of arthritis among adults with the incidence of OA especially high among elderly individuals has there been little in the way of progress in the development of drug therapies for OA? This question appears particularly relevant if one considers that the pharmaceutical revolution over the last 20 years or so gave rise to the FDA approving a slew of innovative medical interventions for the treatment of the much less common form of arthritis, namely, rheumatoid arthritis. Is the reason for the decision to essentially curtail drug development for OA that we know so little about what the relevant targets for potential drug therapy for OA might be? I don't think so! Is it because there would be little financial reward for developing “disease-modifying-OA drugs” (DMOADs). No to that too!! So what's the reason?

The likelihood that OA will become an even more prominent musculoskeletal disease in the next two decades is a foregone conclusion. This is because for the most part, longevity is also likely to increase. OA is most commonly associated with the process of ageing. Thus, an increase in the number of aged individuals will make OA one of the most important musculoskeletal disorders among the elderly which is also going to increase the cost of caring for these patients. Thus, it is a medical certainty that OA will become more clinically relevant, in terms of health care costs alone, unless novel medical interventions are designed to retard OA pathology as OA progresses from an indolent disease process to one where it compromises the patient's quality of life to a significant extent. Therefore without a midcourse correction in the way physicians treats OA, the only “cure” for OA will be surgical intervention with joint replacement surgery playing an even more prominent role than it does today. In addition, physicians who specialize in physical medicine and rehabilitation (PM&R) will be heavily engaged in the post-surgical rehabilitation of patients (again increasing health costs). In this regard, PM&R will play a significant role in teaching the patient how to preserve the function of their “new” joint.

Make no mistake about it; the field of bioengineering has contributed to the development of improved and more durable joint prostheses which in combination with minimal invasive joint replacement surgery through the use of arthroscopy has resulted in significant advances in the right direction. However, it is also clear from some recent experiences from my laboratory that the surgical procedures employed to replace non-functioning joints stemming from end-stage OA are taking place more often. This is most likely to have resulted from the fact that there exist in today's pharmaceutical

development strategy no DMOADs capable of significantly slowing down the OA process once it ensues. So to my mind there are several steps that need to occur to improve this situation.

To begin with let's briefly review the currently available FDA-approved drugs for OA. These include corticosteroids which are generally administered by intra-articular injection, non-steroidal anti-inflammatory drug (NSAIDs) therapy employed for inhibiting Type I cyclooxygenase (COX-1) or the only COX-2 selective drug approved for OA, namely, celecoxib. From a pharmacologic perspective both COX-1 and COX-2 inhibitors having potent anti-inflammatory properties. In addition, there is acetaminophen, which is not a “coxib.” Acetaminophen is generally prescribed for treating the pain associated with OA and in our present understanding of its mechanism of action; acetaminophen does not appear to retard the progression of OA. Weak μ -opioid receptor agonists, such as tramadol, may also now be considered part of the OA armamentarium. Tramadol also acts as a serotonin and norepinephrine reuptake inhibitor where it is essentially employed in OA to reduce the moderate to moderately-severe pain associated with the disease. Another treatment modality is visco supplementation in which various formulations of hyaluronic acid and intra-articular administration of hyaluronic acid are employed. In part, visco supplementation bases its clinical efficacy for OA on ample experimental evidence from various OA animal models that indicated that hyaluronic acid has significant anti-inflammatory properties. Thus, the anti-inflammatory property of hyaluronic acid is, in all likelihood, responsible for dampening the inflammation in the OA synovial joint. Perhaps the increase in the general use of visco supplementation for the treatment of OA has also benefited from developments in ultrasound technology which can provide an ancillary technique for increasing the accuracy of where to place the injectable hyaluronic acid formulation within the affected joint. Finally, let's also not forget that many OA patients use over-the-counter “neutraceuticals” to self-treat their OA even though various clinical trials have generally shown no clinical benefit beyond the “placebo effect.”

Perhaps the most promising of the novel ideas for non-surgical treatment of OA is the use of human bone marrow or adipose tissue-derived chondroprogenitor cells for transplantation. This technique is designed to repair variously sized but mostly small surface lesions of articular cartilage that are detected in early OA [1]. This procedure has also benefited from experimental and clinical evidence indicating that non-invasive imaging can be useful not only to accurately pinpoint the location of these articular cartilage lesions but also to determine the extent to which cartilage repair ensures as a measure of the clinical efficacy derived from the transplanted cells.

Although a few of these advances have improved the clinical outcomes of patients with OA, identifying novel targets for medical

intervention is also called for at this time. In that regard, we and other laboratories have recently focused on the emerging concept that as OA progresses; pro-inflammatory cytokine-induced inflammation drives the process of articular cartilage destruction [2]. Inflammation is also likely to alter the structure and function of ligaments, tendons and subchondral bone as these tissues are altered and typically found in OA joints. Moreover, these changes are thought to be progressive and, in many cases, considered to be irreversible endpoints of the OA process. Importantly, bone marrow edema has also been recognized as a component of OA pathology.

Our research group has provided compelling evidence, at the molecular level, that several of the relevant targets which were identified for intervention in the medical therapy of RA were also prominently found in OA joints [2]. More recently, I reviewed the biological evidence which strongly indicated that immune-mediated inflammation, involving T- and B-lymphocytes as well as activated macrophages, should now be considered as critical components in the development of inflammation during the OA process [3]. Thus, activated immune cells as well as the important role played by the aberrant activities of these cells as they affect articular chondrocytes and bone cells provide additional drivers of OA disease progression that could be specifically targeted for intervention in the OA process.

So what should we be considering as future novel targets for the development of DMOADs? To begin with, we previously identified that the mitogen-activated protein kinase signaling (MAPK) pathway and signal transducers and activators of transcription protein-3 (STAT3) was activated by treating human chondrocytes derived from normal and OA knee cartilage with recombinant human tumor necrosis factor- α (rhTNF- α) [4], a pro-inflammatory cytokine found to be significantly elevated in OA synovial fluid [2]. More recently, we also showed that recombinant human interleukin-6, (rhIL-6), another of the pro-inflammatory cytokines involved in OA [2], activated the MAPK pathway [5], in addition to its better known role as an activator of the Janus kinase/Signal Transducers and Activators of Transcription

pathway. Therefore, I would like to propose that researchers design experimental studies to evaluate in pre-clinical in vitro model systems the extent to which rhTNF- α or rhIL-6 blockade (perhaps using biological drugs already approved for treating RA) alters chondrocyte gene expression and in particular, matrix metalloproteinase (MMP) gene expression, the latter target constituting a known significant molecular driver of OA pathology [6]. In that regard, we have recently shown that rhIL-6 blockade with tocilizumab suppressed the production of MMP-9 in the C-28/I2 immortalized line of human juvenile chondrocytes. I also propose that we should consider studying in greater detail the role played by the adipokines 3, 5 (e.g., adiponectin) in OA. In that regard, I propose that we examine the interaction between adiponectin and the immune cells found in OA synovial joints and concomitantly employ well-validated animal models of OA to test the hypothesis that blockade of adipokine activity ameliorates the progression of OA.

References

1. Malemud CJ (2014) CORR Insights®: A novel system improves preservation of osteochondral grafts. *Clin Orthop Relat Res* 472: 3514-3516.
2. Malemud CJ, Schulte ME (2008) Is there a final common pathway for arthritis? *Future Rheumatol* 3: 253-268.
3. Malemud CJ (2015) The biological basis of osteoarthritis: State of the evidence. *Curr Opin Rheumatol* 27: 289-294.
4. Malemud CJ, Sun Y, Pearlman E, Ginley NM, Awadallah A, et al. (2012) Monosodium urate and tumor necrosis factor- α increase apoptosis in human chondrocyte cultures. *Rheumatology (Sunnyvale)* 2: 113.
5. Wylie MA, Meszaros EC, Malemud CJ (2015) The effect of interleukin-6-type cytokines and adiponectin on MAPK activation in the immortalized human chondrocyte C28/I2 line and normal human chondrocytes. *J Cell Biol Histol* 1: 101.
6. Meszaros E, Malemud CJ (2012) Prospects for treating osteoarthritis: enzyme-protein interactions regulating matrix metalloproteinase activity. *Therapeut Adv Chronic Dis* 3: 219-229.