α_2-Macroglobulin
Autologous Protease Inhibition Technology

Jason M. Cuéllar, MD, PhD[a], Vanessa Gabrovsky Cuéllar, MD[b], Gaetano J. Scuderi, MD[c,*]

KEYWORDS

• α_2-macroglobulin (A2M) • Inflammation • Anti-inflammatory • Cytokines • Arthritis • Osteoarthritis • Discogenic back pain • Autologous

KEY POINTS

- A2M has emerged as a potential treatment of cartilage-based pathology and inflammatory arthritis because of its ability to bait and trap inflammatory mediators.
- A2M has been successfully applied to musculoskeletal pathology to decrease pain and modulate cartilage degeneration.
- Autologous A2M can be concentrated from plasma using a unique filtration process.
- New recombinant formulations of A2M can even more precisely target molecular pathways of intra-articular and extra-articular and intervertebral disk disease.

INTRODUCTION

Musculoskeletal conditions causing pain are ubiquitous, making up a large percentage of physician visits each year. Etiology and treatment range widely, and it is not necessarily appropriate to discuss the application of a particular treatment of all aspects of musculoskeletal pain. Musculoskeletal pathology, however, can be generally divided into the following categories:

1. Intra-articular joint pain
2. Extra-articular pain
3. Spinal intervertebral (discogenic) pain

Intra-articular joint pain is most commonly attributed to idiopathic osteoarthritis (OA), posttraumatic OA (PTOA), and other systemic inflammatory arthropathies,

[a] Department of Orthopaedic Surgery, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Los Angeles, CA 90048, USA; [b] 450 North Roxbury Boulevard, Suite 602, Beverly Hills, CA 90210, USA; [c] 210 Jupiter Lakes Boulevard, Suite 3102, Jupiter, FL 33458, USA
* Corresponding author.
E-mail address: scuderimd@aol.com

Phys Med Rehabil Clin N Am 27 (2016) 909–918
http://dx.doi.org/10.1016/j.pmr.2016.06.008
pmr.theclinics.com

such as rheumatoid arthritis (RA). In recent decades the development of tumor necrosis factor α (TNF-α) inhibitors have been a significant clinical impact on the treatment of RA, providing many patients with significant pain relief and disease progression modification. Unfortunately, no such treatment has been adopted for OA or PTOA. OA is a common problem affecting a large proportion of the population and can affect many joints, including but not limited to the spine, knee, shoulder, hip, fingers, and ankle. It is characterized by progressive cartilage degeneration and loss. Current treatment of OA is limited to physical therapy in attempts to improve joint stabilization, weight loss to reduce joint reactive forces, systemic anti-inflammatory medications (ie, nonsteroidal anti-inflammatory drugs [NSAIDS]) and intra-articular injections of substances, such as steroids or so-called joint lubricants like hyaluronic acid. Physical therapy often has limited benefit, especially as disease progresses, and patients often have difficulty losing weight if physical activity is painful. Systemic NSAIDS can have serious side effects, including gastrointestinal bleeding, and have recently been implicated in cardiac side effects, thus limiting their use. Intra-articular injections of steroids have been demonstrated to have no additional benefit compared with an exercise program alone in a randomized controlled trial[1] and may double the infection rate after total knee or hip replacement.[2] Furthermore, multiple studies have recently brought into question the efficacy of hyaluronic acid injections, leading the American Academy of Orthopaedic Surgeons (AAOS) to withdraw their recommendation of its clinical use.[3] Perhaps most importantly, none of these potential therapies can successfully prevent cartilage degeneration and osteoarthritis.

Distinct from cartilage pathology and osteoarthritis, extra-articular joint pain most commonly involves inflammation of tendons inserting at or near a joint. The most common examples of such enthesopathies are Achilles tendonitis, subacromial bursitis of the rotator cuff, and lateral epicondylitis of the elbow (tennis elbow). These often resolve with activity modification or with a short course of NSAIDS. Persistent enthesopathies can be difficult to treat, however, and have led to many attempts to treat with various types of platelet-rich plasma injections. Several studies have failed to demonstrate a significant benefit, however, with the possible exception of Achilles tendonitis,[4] although this too has been called into question in randomized studies.[5]

Spinal intervertebral discogenic pain is possibly the most controversial musculoskeletal pain etiology — invoking some physicians to question even its existence as a pain generator, whereas others advocate invasive surgical procedures, such as spinal fusion or total disk replacement surgery. The authors believe that discogenic pain does exist but that determining with certainty which particular disk(s) is(are) the source of back pain can be challenging. Nonsurgical treatments for this clinical entity have been limited until recently.[6] There is growing evidence that discogenic pain may be an inflammatory process, without any discrete mechanical pathology.[7] In contrast, spinal radiculopathic pain is caused by compression and/or inflammation of a spinal exiting nerve root, usually by a herniated intervertebral disc. Although this clinical entity most often resolves without surgical treatment approximately 80% to 90% of the time, the remaining cases can be treated successfully by surgical decompression.[8] This pathophysiology of radiculopathic pain should be differentiated from spinal intervertebral discogenic pain, because they are 2 distinct clinical problems.

In the setting of advanced cartilage disease and osteoarthritis, there is little that can be offered patients short of joint replacement. Even in early stages of disease, however, historically there have not been disease-modifying agents that are clinically effective. Discogenic back pain and enthesopathies present a similar challenge, because there has not been any clear effective clinical intervention to mediate the course of