Autologous Conditioned Serum

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KEYWORDS

• Interleukin-1 receptor antagonist • Osteoarthritis • Radicular compression
• Intra-articular therapy • Anterior cruciate ligament • Tendinopathy • Muscle injury
• Pain

KEY POINTS

- Autologous conditioned serum is prepared by the incubation of whole blood with surface-treated glass beads within a special syringe.
- During incubation, the serum is enriched in products synthesized and released by peripheral blood platelets and leukocytes including, but not limited to, the interleukin-1 receptor antagonist.
- Randomized, controlled trials find that locally injected autologous conditioned serum is effective in treating osteoarthritis, radicular compression, and tunnel widening after reconstruction of the anterior cruciate ligament.
- Additional studies suggest utility in treating tendinopathies and muscle injuries.
- Further studies are required to confirm clinical effectiveness in specific indications, to determine the composition of autologous conditioned serum, to determine its mode of action, to understand individual responses to therapy, and to explore potential synergies with other therapeutic agents.

INTRODUCTION

Autologous conditioned serum (ACS) is an autologous blood product enriched in the interleukin-1 receptor antagonist (IL-1Ra), a naturally occurring inhibitor of interleukin-1 (IL-1).[1–4] ACS is administered locally to treat conditions in which IL-1 is thought to be an important agent of pathologic conditions. Several reviews have been written on this topic.[5–8]

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IL-1Ra has been produced in *Escherichia coli* as the recombinant molecule anakinra, marketed as Kineret. Anakinra, in combination with methotrexate, is approved by the US Food and Drug Administration for the treatment of rheumatoid arthritis (RA), self-administered subcutaneously at a daily dose of 100 mg. However, the therapeutic efficacy of anakinra in RA has generally been disappointing, and it is not widely used in this context. Clinical responses in sepsis have also been weak. However, systemic anakinra is effective in systemic juvenile idiopathic arthritis and a variety of rare autoinflammatory disorders; it is also of benefit in gout and pseudogout.[9]

There is considerable interest in using anakinra intra-articularly in the treatment of osteoarthritis (OA) and injured joints. An initial, open-label clinical trial in patients with OA of the knee provided highly encouraging results with sustained clinical improvement after intra-articular injection of 100 mg of anakinra.[10] However, a subsequent multicenter, randomized controlled trial (RCT) showed no sustained benefit of intra-articular Anakinra.[11] Nevertheless, there was transient improvement, observed at day 4, in certain parameters, notably pain. The temporary nature of the beneficial effects probably reflects the rapidity with which proteins are removed from joints.[12] An additional clinical trial administered anakinra intra-articularly to patients after rupture of the anterior cruciate ligament (ACL) and again found improvement in certain parameters during the 2-week study period.[13] In a further small, uncontrolled, unblinded study of 6 patients with persistent postsurgical knee effusions, a single 200-mg injection of anakinra decreased pain and swelling, improved range of motion, and permitted return to sporting activities.[14]

There is, thus, optimism that IL-1Ra could prove efficacious in injured and arthritic joints if there were a way to maintain therapeutic concentrations intra-articularly. Gene delivery provides one technology for achieving this, and proof of principle has been established in animal models and human clinical trials for RA.[15–17] Genetic delivery of IL-1Ra into human knee joints with OA is at an advanced preclinical stage of development.[18]

AUTOLOGOUS CONDITIONED SERUM

Background

Wehling and colleagues developed ACS in the mid-1990s as an expeditious, practical, and relatively inexpensive means of generating IL-1Ra for local, therapeutic application in musculoskeletal diseases. ACS is based on studies that found that macrophages and monocytes are major endogenous sources of IL-1Ra.[19,20] Production of IL-1Ra can be enhanced by a variety of stimuli, including adhesion to certain surfaces. Based on this information, Meijer and colleagues[21] developed a method for stimulating IL-1Ra synthesis by whole human blood. According to their method, peripheral blood is drawn into a syringe containing treated glass beads to which blood monocytes and other adherent cells have the opportunity to attach. The syringe and its contents are then incubated at 37° for several hours, during which time platelets degranulate and mononuclear cells synthesize and secrete IL-1Ra along with a variety of additional anti-inflammatory products. During this period, synthesis of the inflammatory cytokines IL-1β and tumor necrosis factor-α (TNF-α) does not increase greatly. After incubation, the ACS is recovered and sterilized by filtration. ACS is then injected locally into sites of injury or disease.

Stimulation of blood cells by the glass beads is not specific to IL-1Ra, and ACS contains a variety of growth factors and cytokines (**Table 1**). Indeed, it has not been formally demonstrated that IL-1Ra is responsible for the therapeutic properties of ACS. The composition of ACS shown in **Table 1** is in rough agreement with that reported by Darabos and colleagues[22] and Rutgers and colleagues[23]; the only major discrepancy is the