The Use of Anakinra in Juvenile Arthritis

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Interleukin-1 (IL-1), one of the major pro-inflammatory cytokines, plays an important role in the pathophysiology and progression of adult and pediatric arthritis. Inhibiting IL-1 activity by using a recombinant human IL-1 receptor antagonist (anakinra) given alone or in combination with methotrexate, moderately reduced the signs and symptoms of active arthritis in adults and slowed the rate of radiographic destruction. Preliminary results from an open label portion of a trial in children with polyarticular arthritis show similar outcomes with 58% of children exhibiting clinical improvements based on the Juvenile Arthritis 30% Core Set Criteria. The drug has an overall favorable safety profile and injection-site reactions are the most commonly reported adverse event in both groups. However despite its rather disappointing effect in polyarticular arthritis, anakinra is being discovered as an effective treatment of systemic arthritis and children with mutations in the NALP3/CIAS1/PYPAF1 genes leading to autoimmune inflammatory disorders such as neonatal-onset multisystem inflammatory disease.

Introduction

Interleukin-1 (IL-1) is one of the major pro-inflammatory cytokines involved in various autoimmune diseases and plays a key role in the pathogenesis of arthritis. Its endogenous counterpart IL-1 receptor antagonist (IL-1Ra), a member of the IL-1 family, competitively inhibits the binding of IL-1 to its cell surface receptors and thus, acts as an anti-inflammatory mediator. Anakinra is identical to the naturally occurring nonglycosylated human form of IL-1Ra with the exception of its N-terminal methionine. Despite its initial rather disappointing performance in rheumatoid arthritis trials, anakinra has experienced a renaissance in the treatment of other autoimmune diseases such as systemic arthritis, neonatal-onset multisystem inflammatory disease (NOMID), arthritis in systemic lupus, or ankylosing spondylitis.

This paper briefly summarizes the science of IL-1 and its inhibitor IL-1Ra and describes the clinical experience with anakinra focusing on juvenile arthritis (JA).

The Biology of IL-1 and IL-1Ra

Extensive evidence from in vivo and in vitro experiments indicates that IL-1, a prototypic cytokine, is one of the major pro-inflammatory cytokines involved in various autoimmune diseases including arthritis where it plays a major role in progressive joint destruction. In the synovium IL-1 is mainly synthesized by fibroblast and macrophages but is also secreted by neutrophils [1–3].

Interleukin-1 possesses several biologic properties including increased gene expression of pro-inflammatory mediators such as cyclooxygenase type 2 (COX-2) as well as the induction of nitric oxide synthase (iNOS) and prostaglandin-E2 (PGE2). Another important pro-inflammatory property of IL-1 is its ability to increase the expression of adhesion molecules such as the intercellular adhesion molecule-1 (ICAM-1) on endothelial and other cell surfaces, which promotes the infiltration of inflammatory and immunocompetent cells into the extravascular space [4–7]. Moreover IL-1 stimulates the production of and acts synergistically with other pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and IL-6 [8–10]. On the vascular endothelium these cytokines induce the activation of platelet activating factor (PAF), PGE2, nitric oxide, and the chemokine IL-8, which by itself is involved in chemotaxis [11•].

There are three members of the IL-1 gene family: IL-1α, and IL-1β, which are receptor agonists and IL-1Ra a specific, naturally occurring receptor antagonist.

On the binding side are two IL-1 receptors (IL-1R): IL-1RI which is capable of signal transduction, whereas IL-1RII binds IL-1 but does not transduce a signal, and rather acts as a decoy receptor for IL-1α [12–15]. After binding of IL-1 to IL-1RI, a complex is formed that involves the IL-1R accessory protein (IL-1R AcP), resulting in high-affinity binding and signal transduction (Fig. 1) [16,17]. Soluble portions of the IL-1RI and IL-1RII are part of the regular immune homeostasis and function as natural buffers for IL-1α, IL-1β, and IL-1Ra [18–20].

Anakinra, a member of the IL-1 family, binds to both IL-1 receptors but does not induce any cellular responses. IL-1Ra competitively inhibits the binding of IL-1 to its cell surface receptors and thus, acts as an endogenous anti-inflammatory mediator. IL-1Ra is partly responsible for the regulation of IL-1α and IL-1β by competitively binding with high avidity to the type 1 IL-1R [21–23,24••]. Anakinra is identical to the naturally occurring nonglycosylated human form of IL-1Ra with the exception of its N-terminal methionine [11•]. Anakinra blocks the biologic activity of IL-1 by competitively inhibiting IL-1 binding to...
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the IL-1 receptor, preventing docking of the accessory protein and subsequent intracellular signaling events (Fig. 1).

Consequently anakinra has a number of anti-inflammatory effects, including suppression of pro-inflammatory cytokine production such as TNF-α and IL-6, decreased production of collagenases by chondrocytes, decreased production of adhesion molecules by endothelial cells, fibroblasts, and osteoclast precursors [20,24••,25–27].

IL-1Ra—From the Animal Model to the Bedside

Proof of principle for the anti-inflammatory role of IL-1Ra has been established in numerous experimental animal arthritis models by systemic administration or local delivery of IL-1Ra into the joint by gene therapy, which attenuated the severity of the inflammatory response and reduced articular destruction [28–30]. Interestingly IL–1Ra-deficient mice have elevated basal concentrations of plasma IL-6, manifest a hepatic acute phase protein response, and have low litter numbers as well as growth retardation in adult life [31]. Moreover, several studies in rheumatoid arthritis synovium suggest that a relatively deficient production in IL-1Ra and imbalance to IL-1 may lead to the perpetuation of chronic inflammation [18,27,32].

Krane et al. [33] and Dayer et al. [34] were among the first to describe the role of IL-1 in rheumatoid arthritis in humans and found that there was a significant overlap of its biologic effects with TNF-α in regards to inflammation, systemic properties such as fevers, and tissue remodeling [9]. Furthermore, Eastgate et al. [35] showed that resident macrophages in rheumatoid synovium constitutively expressed IL-1 and TNF-α and that circulating levels of IL-1α correlated with disease exacerbation in patients with rheumatoid arthritis.

Similar to rheumatoid arthritis, joints in children with JA are infiltrated by various cell populations releasing inflammatory mediators, including cytokines such as TNF, lymphotoxin-α (LT-α), IL-1, prostaglandins, and matrix metalloproteinases, facilitating systemic symptoms and joint damage. In particular, TNF, IL-1, and IL-6 are present at high levels in synovial fluid and tissue in JA and juvenile spondyloarthropathies [36–41]. Even though TNF plays a dominant role in most subforms of JA, IL-1, IL-6, and IL-18 may be the more dominant cytokines in systemic onset JA [42,43,44••,45,46].

The correlation of IL-1 with disease activity in JA has been examined in three studies. In the first study the production of IL-1α, IL-1β, and IL-1Ra by blood mononuclear cells (MNC) was compared with corresponding serum levels of IL-1Ra in umbilical cord blood samples (n = 11), a cohort of control children (n = 40), adults (n = 20), and 42 patients with chronic JA of pauci- or polyarticular onset type. IL-1Ra serum levels were found to differ significantly between the three age groups, being higher in neonates (569 pg/mL) than in children (70 pg/mL) and adults (177 pg/mL). IL-1Ra levels in the sera of both subgroups of JA patients were significantly elevated (median 257 pg/mL), but did not correlate with clinical disease parameters. Furthermore, in synovial fluid samples IL-1Ra levels tended to be fairly high, (up to approximately 2 ng/mL), but again did not correlate with the serum levels of IL-1Ra. The authors concluded that an insufficient production of IL-1Ra was unlikely to contribute to the pathogenesis of JA [47].

In the second study circulating IL-1β, IL-6, TNF-α, osteocalcin, and conventional parameters of inflammation were serially examined in 14 children with JA. While serum IL-1β was undetectable in all JA patients, IL-6, and conventional parameters of inflammation were significantly elevated in the active phase of JA, whereas hemoglobin levels were significantly lower [48].

In a third study, acute phase proteins, synovial fluid (SF) cellular infiltrates, pro-inflammatory (TNF-α, IL-1α, IL-6),