CHAPTER 6

ANAKINRA

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Anakinra is a recombinant, soluble, selective nonglycosylated short acting IL-1 receptor antagonist (IL-1Ra), produced by recombinant DNA technology using an Escherichiacoli (E. Coli) bacterial expression system.[1] Anakinra (Kineret; Biovitrum, Stockholm, Sweden) was approved by food and drug administration (FDA) in 2001 for the treatment of rheumatoid artiritis which is safe and well tolerated.[2,3] After that, it was approved for the treatment of patients with neonatal onset multi inflammatory diseases in 2012.[3,4] Anakinra has been used for the diseases which have IL-1-mediated pathology like monogenetic autoinflammatory disease which is a group of syndromes named cryopyrin associated periodic syndromes (CAPS). Although it has been used for monogenetic autoinflammatory disease, it has been also used for SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome); CRMO (chronic recurrent multifocal osteomyelitis); PFAPA, and PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne syndrome), Blau syndrome, Crohn's disease, Still's, Behcet's, and Schnitzler diseases which are the autoinflammatory disorders with unknown genetics. IL-1-blocking agents have been studied for the diseases of classic hereditary periodic fever syndromes including familial mediterranean fever (FMF), tumour necrosis factor receptor-associated periodic syndrome (TRAPS), hyperimmunoglobulinemia D (HIDS). Usage of anakinra in metabolic conditions associated with IL-1 pathway such as gout/pseudogout, metabolic syndrome, type 1 and type 2 diabetes mellitus, stroke, and myocardial infarction has also been reported in the literature.[4,5]

Mechanism of Action

Anakinra competitively inhibits the binding of IL-1 at the level of type I receptor (IL-1RI) which is expressed on a wide variety of tissues.[2,6,7] Interleukin 1 is a proinflammatory cytokine that regulates inflammation and immune response. IL-1 gene family consists of genes encoding IL-1α, IL-1β, and IL-1RA.[8] There are two molecular species of IL-1.[5,9] They are interleukin-1α and IL-1β which induce inflammatory responses such as fever, anorrhexia, tissue damage and remodeling. IL-1Ra is a natural antagonist that competes with IL-1α and IL-1β for the IL-1 receptor as anakinra doeS.[8] While IL-1α is present in most of the healthy tissues such as normal keratinocytes of the skin, platelets, the epithelial cells of mucosal membranes and the cells of the liver, lung and kidney, endothelium of the vessels.[4,5] IL-1β is not present in healthy tissues and its blood levels can not be detected by standard assays. Blood monocytes, tissue macrophages and dendritic cells secrete IL-1β as a product in response to a stimulus. That stimulus can be in microbial origin or other cytokines can stimulate IL-1β, the cytokines which stimulates IL-1 are tumour necrosis factor (TNF)α, IL-18, IL-1α. IL-1β can also induce IL-1β itself. IL-1 induction of itself is the cause of autoinflammation and these autoinflammatory disorders usually occur due to genetic mutations.[4,5] This group of genetic disorders have common clinical symptoms like recurrent fevers, fatigue, myalgia, arthralgia, gastrointestinal symptoms and skin rashes.[4] More recently, anakinra has also been successfully used to treat patients with neutrophilic dermatoses such as neutrophilic panniculitis, pustular psoriasis, pyoderma gangrenosum, and Sweet syndrome too.[4,9]

Recommendations for administration

Anakinra, which blocks IL-1α and -β binding to the IL-1 receptor, has a half-life of 4–6 hours and requires daily dosing self-administered via subcutaneous injection at a dose of 100 mg.[4,6,10] Anakinra is a clear, colourless to white solution for injection and is supplied ready for use in a pre-filled syringe. It may contain some translucent to white particles of protein. The presence of these particles does not affect the quality of the product. Anakinra has recently been approved for use in children aged ≥8 months. According to the literature, patients diagnosed in younger age needed higher doses of anakinra and required more frequent treatment adjustments than adults.[11]

Pack sizes of 1, 7 or 28 (multipack containing 4 packs of 7 pre-filled syringes) pre-filled syringes are available.[12] Treatment with anakinra seems to be safe in children but it is not used at neonatal age. The treatment has to be applied as earlier as possible in order to prevent secondary complications in young patients and newborns. At this age, few are known on anti-IL-1 blood concentration and distribution in the tissues. Previous reports have shown that higher doses were usually

below normal range. It is reported that intra-venous infusions of anakinra in healthy subjects at dose of 10 mg/kg did not reduce peripheral neutrophil counts. And neutropenia is not persistant, neutrophils rapidly rise with the cessation of treatment.[5] A higher rate of serious infections and two percent of neutropenia had been observed in patients treated with anakinra and etanercept combination therapy; therefore combination of anakinra with TNF blocking agents is not recommended.[15] And anakinra treatment must not be initiated in patients with neutropenia (ANC < 1.5 x 10^9/l). And neutrophil counts should be assessed prior to initiating anakinra treatment, and while receiving anakinra, monthly during the first 6 months of treatment and quarterly thereafter.[12]

Allergic reactions including anaphylactic reactions, angioedema, urticaria, rash, and pruritus have been reported infruequently and reactions were reported as maculopapular or urticarial rashes.[1,41] Anakinra is contraindicated in patients with known hypersensitivity to E. coli-derived proteins or to any components of the product.[15]

Anakinra also does not seem to cause hepatic toxicity, serious hematologic events, or serious cardiovascular events.[68]

No data are available of the effects of live vaccination or on the secondary transmission of infection by live vaccines in patients receiving anakinra. So live vaccines should not be given concurrently with anakinra treatment.[12]

Although no treatment-related risk of malignancy had been reported, four malignancies were diagnosed in the anakinra treatment group. They are melanoma, diffuse metastatic melanoma, adenocarcinoma of the cecum, uterine carcinoma, and basal cell carcinoma. Anakinra does not appear to increase the risk of death or malignancy in the broad patient group[(68)]. But the use of anakinra in patients with pre-existing malignancy is not recommended.[12]

Development of anakinra anti-drug antibodies had also been reported. This response was transient and it has not clinically significant effects on pharmacokinetics, adverse effects, efficacy, or safety.[33,68]

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