Case Report

Anakinra Prevents Symptoms of Familial Cold Autoinflammatory Syndrome and Raynaud's Disease

SAMY K. METYAS and HAL M. HOFFMAN

ABSTRACT. Familial cold autoinflammatory syndrome (FCAS) is a rare, hereditary disorder characterized by cold-induced inflammation. We describe the successful longterm treatment of a patient with FCAS with anakinra, an interleukin 1 receptor antagonist (IL-1Ra). The remarkable response of FCAS and associated Raynaud's disease in this patient suggests that IL-1 is an important mediator of these inflammatory diseases. Our report supports increasing evidence that anakinra plays an important role in the treatment of select chronic inflammatory diseases. (First Release Sept 15 2006; J Rheumatol 2006;33:2085–7)

Key Indexing Terms:
FAMILIAL COLD URTICARIA FAMILIAL COLD AUTOINFLAMMATORY SYNDROME
RAYNAUD'S DISEASE ANAKINRA INTERLEUKIN 1 RECEPTOR ANTAGONIST

Familial cold autoinflammatory syndrome (FCAS) is a rare autosomal-dominant inflammatory disease that presents in infancy or early childhood[1]. FCAS, also known as familial cold urticaria, is one of several disorders described as autoinflammatory diseases characterized by recurrent episodes of unprovoked inflammation in the absence of infection, autoantibodies, or antigen-specific T cells. After relatively mild cold exposure, patients develop urticarial rash, fever, and arthralgia that begin within 1 to 2 hours and usually persist for 12 to 24 hours.

FCAS is the mildest phenotype in a continuum of autoinflammatory disorders including Muckle-Wells Syndrome (MWS) and neonatal-onset multisystem inflammatory disease (NOMID) that are caused by mutations in the cold-induced autoinflammatory syndrome (*CIAS1*) gene[2]. While all 3 disorders are characterized by urticarial rash, fever, and arthralgia, patients with MWS usually develop progressive neurosensory hearing loss and have a significant risk of systemic amyloidosis, and patients with NOMID often develop severe central nervous system disease and joint and bone abnormalities.

CIAS1, also known as *NALP3*, codes for the cryopyrin protein that contains an N-terminal pyrin domain that is involved in protein-protein interactions involved in inflammatory signaling pathways. These pathways lead to the activation of caspase 1, which results in the release of inflammatory cytokines such as interleukin 1ß (IL-1ß) and IL-18[3]. Until recently, treatment of FCAS has primarily been supportive, with warming treatments and nonsteroidal antiinflammatory drugs (NSAID). Alternatively, high-dose corticosteroids have provided limited relief; however, longterm side effects have often precluded continued use of this form of therapy for patients with FCAS.

Anakinra is an IL-1 receptor antagonist (IL-1Ra) that was approved by the US Food and Drug Administration in 2001 for reducing signs and symptoms of rheumatoid arthritis (RA). Recently, anakinra has also shown efficacy in the treatment of other autoinflammatory disorders, including tumor necrosis factor-associated periodic syndrome (TRAPS), hyper-IgD syndrome (HIDS), and Schnitzler's syndrome[4-6]. We describe a patient with classic symptoms of both FCAS and Raynaud's disease who responded dramatically to anakinra.

CASE REPORT

A 58-year-old Caucasian woman presented with an intermittent generalized urticaria-like rash induced by exposure to cold. The rash was first noted at birth and was often associated with fever, chills, nausea, and arthralgia. Episodes lasted less than 24 hours with a diurnal pattern of nocturnal worsening. She had been treated with antihistamines, with no relief of rash, and with NSAID, with minimal relief of joint symptoms. She refused treatment with corticosteroids. The patient as well as her grandfather, mother, sister, niece, and multiple distant relatives were diagnosed with FCAS based on history and the presence of the common L353P founder mutation in *CIAS1*.

For several years her FCAS episodes were also associated with color changes and pain in her fingers and toes typical of Raynaud's disease. These symptoms progressively worsened, and at 56 years of age she developed gangrene and underwent amputation of the distal phalange of her left index finger. She was treated with vasodilatory therapy, but continued to experience severe Raynaud's symptoms of her hands and feet.

On examination, she had a generalized, raised, red, and pruritic rash. Joint examination was normal except for mild periarticular tenderness. She was also noted to have color changes consistent with Raynaud's phenomenon in

From the Division of Rheumatology, University of Southern California, Los Angeles, and the Division of Rheumatology, Allergy, and Immunology, University of California at San Diego, La Jolla, California, USA.

S.K. Metyas, MD, Division of Rheumatology, University of Southern California; H.M. Hoffman, MD, Division of Rheumatology, Allergy, and Immunology, University of California at San Diego.

Address reprint requests to Dr. S.K. Metyas, Division of Rheumatology, University of Southern California, Los Angeles, CA 90033, USA. E-mail: metyas@usc.edu

Accepted for publication May 8, 2006.

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Figure 1. Urticarial rash before (A, C) and after treatment with anakinra (B, D).

both hands and feet. She had no ocular findings or thyromegaly, and the remainder of her examination was normal. Laboratory evaluation showed a C-reactive protein (CRP) of 1.9 mg/dl (normal 0–0.8 mg/dl, platelet count of 400×10^3 cells/ml (normal $150–450 \times 10^3$ cells/ml), and white blood cell (WBC) count of 10.9×10^3 cells/ml (normal 4.3 to 10.8×10^3 cells/ml). She had a positive antinuclear antigen (ANA) of 1:160 with a speckled pattern, with a normal lupus panel. Antithyroid peroxidase antibody (anti-TPO) level was 421.1 IU/ml (normal < 35 IU/ml) and thyroid stimulating hormone (TSH) was 1.03 mU/l (normal 0.3–3.0 mU/l).

After providing informed consent, the patient began taking anakinra 100 mg subcutaneously (SC) daily. She improved significantly within 24–48 hours of the first dose, with complete resolution of the rash, arthralgia, and fever. Surprisingly, she also noticed resolution of her Raynaud's disease symptoms within 1 week of beginning anakinra therapy. A few weeks later, her anakinra was discontinued briefly during an upper respiratory infection and her rash recurred within 48 hours, with significant rash present on the back and forearms (Figures 1A, 1C). After 15 months of anakinra treatment she continues to have no FCAS symptoms, and her Raynaud's symptoms are also completely controlled (Figures 1B, 1D). A trial of every other day anakinra therapy was attempted, which has been successful in a number of FCAS patients, but was not tolerated by our patient due to recurrence of symptoms between doses. Repeat laboratory evaluation showed improvement of CRP to < 0.6 mg/dl, platelet count to 288×10^3 cells/ml, and WBC count at 6.3×10^3 cells/ml.

DISCUSSION

We describe a patient who showed a remarkable clinical response to anakinra treatment with resolution of rash and arthralgia within 48 hours and complete resolution of Raynaud's disease symptoms within 1 week of beginning therapy. Similar rapid therapeutic responses have been observed in FCAS in a cold-challenge model and in MWS and NOMID, 2 other primarily IL-1 mediated diseases[3]. This is the first report of successful maintenance anakinra therapy in FCAS.

Raynaud's disease or phenomenon has been recognized in 4 of 114 patients with FCAS (not seen in any of 14 patients with MWS or NOMID) in the UCSD database. This incidence is not significantly different from that of the general population. However, FCAS and Raynaud's are both characterized by cold-induced inflammation and may share common pathophysiology. This is the first case report to our knowledge of successful use of anakinra in Raynaud's disease, a common inflammatory disorder with poorly understood etiology. The effectiveness of this therapy may also suggest a role for IL-1 in this disease. This is supported by findings of an association of polymorphisms in IL-1 related genes with Raynaud's disease in patients with Sjögren's disease[7].

Autoinflammatory diseases are characterized by inflammation in the absence of autoantibodies. ANA and antithrombopoietin were present in our patient, but she had no clinical signs of lupus and had normal thyroid levels. It is possible that

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these are false-positive tests (ANA is false-positive in up to 32% of the general population) or that she has Hashimoto's thyroiditis, a common condition in women (anti-TPO is present in up to 20% of women).

The potential of anakinra to ameliorate clinical symptoms and effect hematological and biochemical changes in patients with FCAS indicates a central role for IL-1 in this syndrome. This is supported by *ex vivo* data with mononuclear cells from patients with FCAS[8]. IL-1ß is a key proinflammatory cytokine promulgating inflammatory responses. Further, involvement of cryopyrin in activation of caspase 1 signaling suggests a possible role in several chronic inflammatory diseases[3]. Most recently, anakinra has been used to successfully treat other autoinflammatory syndromes such as TRAPS and HIDS[5,6]. Although FCAS is rare (estimated at 1 in 1,000,000) it has provided yet another model in which targeted anticytokine therapy may mediate safe and effective longterm relief of symptoms without the damaging effects of corticosteroids.

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