Long-Term Efficacy of Adalimumab in Hyper-Immunoglobulin D and Periodic Fever Syndrome

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Hyper-immunoglobulin D (HIDS) and periodic fever syndrome is an autosomal recessive autoinflammatory syndrome caused by specific mutations in the mevalonate kinase (*MVK*) gene. *MVK* is essential in the isoprenoid/cholesterol biosynthesis pathways, and *MVK* deficiency results in the accumulation of its substrate (mevalonic acid) and shortage of the end product. With regard to the pathogenesis of HIDS, it has been hypothesised that the autoinflammation is caused by a shortage of isoprenoids, which are compounds involved in the post-translational prenylation (farnesylation or geranylation) of several important intracellular signaling molecules.

Decreased apoptosis of peripheral blood mononuclear cells (PBMC) in HIDS patients may be involved in the inability to curtail the immunologic response, thus leading to generalized inflammation even after a trivial stimulus. No conventional therapy exists to prevent or cure recurrent inflammatory attacks in HIDS. Nevertheless, experimental findings on the role of several pro-inflammatory cytokines – interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNFα) and IL-6 – in the pathogenesis of the disease [1-3] support the use of anti-cytokine treatment. In this regard, anakinra, an IL-1β-blocking agent, seems to be effective, and etanercept, a soluble p75 TNFα receptor-Fc fusion protein, has been used with variable success.

To the best of our knowledge, this is the first reported case of severe HIDS successfully treated with adalimumab, a fully human monoclonal TNFα antibody. We also discuss a potential mode of action of TNFα inhibitors in this syndrome.

PATIENT DESCRIPTION

A 20 year old female reported a long history of recurrent fever attacks (39°–40°C) preceded by chills and accompanied by abdominal pain, diarrhea, headache, generalized malaise, arthromyalgia, sore throat, aphthous ulcers, and cervical lymphadenopathy. In the first few years of her clinical history, these symptoms were associated with maculopapular rash and hepatosplenomegaly. During the acute phase of the disease, she was in poor general condition but was asymptomatic between critical periods. The attacks had recurred monthly since the age of 8 months. They lasted 7–10 days and were associated with elevated acute-phase reactants. There was no consanguinity between her parents, and no other members of her family reported similar symptoms. Attacks recurred despite previous tonsillectomy, adenoidectomy and appendectomy. On admission to our clinic, she complained of the above symptoms related to fever attack. Additionally, she complained of inflammatory low back pain characterized by gradual onset over the past few months.

Laboratory data showed a significant increase in acute-phase reactants: erythrocyte sedimentation rate 35 mm/hour, C-reactive protein 205 mg/L (normal 0–5), serum amyloid A protein 120 µg/ml (normal 0–10), neutrophilic leukocytosis 14,000/µl, hemoglobin 10.2 g/dl, serum ferritin 242 ng/ml, transferrin 156 mg/dl, IgA 459 mg/dl (normal value 70–400) and total cholesterol 81 mg/dl (normal value 125–220). IgD serum levels were not tested. Proteinuria was absent, and the human leukocyte antigen (HLA) B27 test was negative.

Acute sacroiliitis on the iliac more than the sacral side of the right sacroiliac joint with no evidence of chronic changes was detected by magnetic resonance imaging (low signal intensity on T1 with enhancement after gadolinium administration, high signal intensity on short TI inversion recovery, and T2 fast short echo in the subchondral region). No vertebral involvement was detected.

A clinical response was obtained only after high dose prednisone (50 mg/day) was administered; previous treatment with low dose prednisone, non-steroidal anti-inflammatory drugs and colchicines had been ineffective.

Genetic analysis revealed a well-described missense mutation in exon 11(V377I) and a novel missense mutation in exon 8 (c.683 C>T, p.P228L) of *MVK*. The patient was also found to have the *MEFV* (Mediterranean fever) mutation in exon 2 (c. 2177 C>T, p.V726A) in a heterozygous state. The

HIDS diagnosis was confirmed by biochemical investigations of lymphocytes that revealed the markedly reduced activity of *MVK* (7 pmol/min/mg, control 142 pmol/min/mg).

Because of the patient's clinical dependence on high dose steroids and the presence of sacroiliitis, she was treated with subcutaneous adalimumab (40 mg every 2 weeks). Treatment was immediately successful in aborting the inflammatory attacks and inflammatory low back pain. Clinical remission and normalization of acute-phase reactants were maintained until her last visit, one year after the start of treatment. One year follow-up of the sacroiliac joints revealed resolution of acute sacroiliitis on MRI. No side effects were observed with adalimumab therapy. Adalimumab was continued while steroid therapy was gradually tapered and eventually stopped. The patient's quality of life improved markedly.

COMMENT

We report a sustained clinical remission in a young patient with HIDS treated with adalimumab. Several features of the present case report are noteworthy.

The patient was a compound heterozygote for two *MVK* mutations (common V377I mutation and a novel P228L substitution) with distinctly diminished MK activity in combination with the common V726A *MEFV* variant. It is not known if the concomitant heterozygosity of the *MEFV* mutation results in a more severe HIDS phenotype. With the notable exception of sacroiliitis in our patient, there were no other clinical differences between the phenotypic presentation of her disease and what is generally observed in the usual variant of the HIDS with no *MEFV* mutation.

The presence of sacroiliitis in HIDS patients has not been previously reported in the medical literature. A few case reports describe the coexistence of familial Mediterranean fever (FMF) and ankylosing spondylitis [4,5] without pointing to a clear ethiopathogenetic relationship. Alternatively, other authors have described seronegative spondyloarthropathy, with no vertebral involvement and negativity of HLA B-27, as a rheumatologic manifestation of FMF [6,7]. In our patient vertebral involvement was absent and the HLA B-27 test was negative. We also report an excellent response to adalimumab in aborting laboratory and clinical HIDS features and the resolution of bone edema in the sacroiliac joint.

Various studies highlight the activation of the cytokine network (IL-1β, IL-6 and TNFα) during inflammatory attacks in HIDS [1,2]. Unstimulated peripheral blood mononuclear cells from patients with inactive HIDS produce a complex network of cytokines capable of inducing the synthesis of pentraxine and serum amyloid A [3]. Cytokine activation may represent the endpoint of an inflammatory process, where the triggering events are still not fully understood. Cytokine activation suggests the use of anti-cytokines as a therapeutic option in HIDS patients. IL-1 receptor antagonists (e.g., anakinra) have been used with success in vaccine-induced models of HIDS and in other HIDS patients. In our patient, anakinra was not used since it has not been reported to be effective in patients with sacroiliitis.

Three anti-TNFα agents are effective in rheumatoid arthritis; two of them (infliximab and adalimumab, both anti-TNF monoclonal antibodies) are also effective in Crohn's disease, while etanercept, which is derived from a soluble form of TNF receptor type II, is not. A possible explanation may reside in their different biologic activities on transmembrane TNFα, which is a precursor form of TNFα expressed as a 26 kD cell surface type II polypeptide on activated macrophages and lymphocytes. In a recent study [8] on Jurkat T cells that were stably expressing an uncleavable form of transmembrane TNFα, infliximab and adalimumab exerted almost equal complement-dependent cytotoxicity while etanercept showed considerably lower activity. Adalimumab and infliximab also induced apoptosis and cell cycle arrest in Jurkat T cells, reflecting an outside-to-inside signal transduction through transmembrane TNFα. A recent study [9] showed decreased apoptosis after stimulation with anisomycin in lymphocytes from fever-free patients with HIDS, but not in lymphocytes derived from TRAPS (TNF receptor-associated periodic syndrome) or FMF patients. The authors hypothesize that the defective regulation of apoptosis and the attendant increased lifespan of activated lymphocytes may be the cause of the exaggerated inflammatory response in HIDS patients.

Thus, TNFα monoclonal antibodies, which are able to induce apoptosis of lymphocytes, may be a more valid therapeutic option than soluble TNFα receptor. Notably, etanercept has been the anti-TNFα more frequently used in HIDS patients, but it has been found to be either ineffective or only partially effective. A single case report is available where infliximab dramatically improved nummular keratopathy; however, its effect on the frequency of HIDS flares was not well defined [10].

To the best of our knowledge, this is the first report of a patient with a long-term remission (1 year) of severe HIDS after adalimumab therapy, suggesting that adalimumab could be a therapeutic option in refractory HIDS patients. Further investigation on the use of TNFα monoclonal antibodies in HIDS therapy is warranted.

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