Colchicine Failure in Familial Mediterranean Fever and Potential Alternatives: Embarking on the Anakinra Trial

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ABSTRACT: Familial Mediterranean fever (FMF) is a genetic auto-inflammatory disease characterized by spontaneous short attacks of fever, elevated acute-phase reactants, and serositis. Approximately 5–10% of FMF patients do not respond to colchicine treatment and another 5% are intolerant to colchicine because of side effects. Recently, following the discovery of the inflammasome and recognition of the importance of interleukin-1β (IL-1β) as the major cytokine involved in the pathogenesis of FMF, IL-1β blockade has been suggested and tried sporadically to treat FMF, with good results. To date, case reports and small case series involving colchicine-resistant FMF patients and showing high efficacy of IL-1β blockade have been reported. At the Israel Center for FMF at the Sheba Medical Center the first double-blind randomized placebo-controlled trial of anakinra in FMF patients who are resistant or intolerant to colchicines is underway. In this report we discuss the mechanism of colchicine resistance in FMF patients, the data in the literature on IL1β blockade in these patients, and the anakinra trial inclusion criteria and study protocol.

KEY WORDS: familial Mediterranean fever (FMF), colchicine, anakinra, inflammasome, interleukin-1β (IL-1β)

Familial Mediterranean fever (FMF) is a genetic auto-inflammatory disease that affects mainly people from the Mediterranean basin, including Turks, Armenians, North-African Jews and Arabs [1]. The disease is characterized by spontaneous short attacks of fever, elevated acute-phase reactants, and serositis (mostly peritonitis, but pericarditis, pleuritis and synovitis may also occur). FMF is caused by mutations in the MEDITerranean Fever (MEFV) gene, located on the short arm of chromosome 16 and encoding the pyrin protein. Longstanding untreated FMF might result in chronic complications, including anemia of chronic disease, growth retardation in children, and reactive amyloidosis [2]. The treatment of FMF relies mainly on continuous colchicine treatment, which prevents the acute attacks and chronic complications, including the development of amyloidosis [3,4].

Approximately 5–10% of FMF patients do not respond to colchicine treatment and another 5% are intolerant to colchicine because of side effects [5]. The mechanism of colchicine resistance is not clear; one study showed that colchicine-resistant patients had inadequate colchicine concentration in their mononuclear cells, probably resulting from a genetic defect unrelated to the underlying FMF [6]. Clinically, colchicine unresponsiveness is defined as the occurrence of at least one attack per month despite daily treatment with 2 mg of colchicine or more [7,8]. Some of the patients who do not respond to standard colchicine treatment may respond to higher doses of daily colchicine or to the addition of a weekly intravenous infusion of colchicine [9]. Nevertheless, a substantial number of patients continue to suffer from frequent attacks and chronic complications of FMF despite these measures. For many decades, colchicine was the only treatment option available for FMF patients. Recently, following the discovery of the inflammasome and recognition of the importance of interleukin-1β as the major cytokine involved in the pathogenesis of FMF, IL-1β blockade has been suggested and tried sporadically for the treatment of FMF [10].

Currently, there are three different IL-1β antagonists in the market: an IL-1β receptor antagonist (anakinra), a soluble human IL-1β receptor fused with an Fc portion of immunoglobulin G1 (rilonacept), and a human monoclonal antibody to IL-1β (canakinumab). These drugs are all given subcutaneously but differ in their half-life, hence in the frequency of administration. To date, case reports and small case series involving colchicine-resistant FMF patients and demonstrating high efficacy of IL1β blockade have been published. Rilonacept was the only drug shown to be effective in a small randomized placebo-controlled trial of 12 FMF patients resistant or intolerant to colchicine [11]. Canakinumab was also shown to be effective, although no randomized controlled trials have been performed [12,13]. Regarding anakinra, a few case reports [14-17] and one
case series [18] have shown its efficacy in FMF patients who are colchicine resistant. Anakinra was also shown to be effective in FMF patients who developed amyloidosis secondary to their disease, with regression of the deleterious outcomes of amyloidosis such as proteinuria and renal failure [19,20]. To date, no controlled study has thoroughly evaluated the efficacy and safety of anakinra in colchicine-resistant FMF patients.

Other biological treatments reported to be effective in FMF include anti-interleukin 6 (tocilizumab) and tumor necrosis factor inhibitors. Tocilizumab was shown to be effective in a case reported from Japan [21]. Although FMF is an IL-1 mediated disease, IL-6 blockade may be relevant since IL-1 induces IL-6 transcription and raises IL-6 levels [22]. Anti-TNF agents were also reported in case reports and case series to be effective in colchicine-resistant FMF patients [23-25]. To date, no controlled clinical trials with these agents have been performed in FMF patients.

At the Israel Center for FMF at the Sheba Medical Center we are conducting the first double-blind randomized placebo-controlled trial of anakinra in FMF patients who are resistant or intolerant to colchicine. The inclusion criteria for the study are adult FMF patients who meet the Tel Hashomer criteria for the diagnosis of FMF [26], age 18–65 years, with verified mutations in both alleles of the MEFV gene, thus including homozygous and compound heterozygous patients who continue to have at least one febrile attack per month despite the maximum tolerable dose of colchicine. Fifty patients will be recruited and will undergo randomization to treatment with either anakinra 100 mg/day or placebo for 4 months. The primary endpoint of the study is the total number of abdominal, thoracic, skin or joint attacks during the observational period (4 months), as recorded in the patient diary. Secondary endpoints include the total number of attacks during the first, second and third months, the number of attacks per site (joint, chest, skin or abdomen), the level of serum acute-phase reactants, C-reactive protein or serum amyloid A protein, safety of anakinra in treating FMF, patient quality of life (Visual Analogue Scale rating), and the use of non-steroidal anti-inflammatory drugs or other pain relievers during FMF attacks. In addition to the administration of the study drug, patients are required to keep a diary recording every injection of the study drug as well as every side effect or FMF attack. A study nurse will telephone all participating patients once a week to monitor patient compliance as well as ask patients about any symptoms or attacks. The patients will be followed for another 2 months after drug cessation.

Currently, as of April 2014, 24 patients were recruited, 12 of whom demonstrated a remarkable response with few side effects, mostly injection-site reaction. The other 12 either continued to suffer FMF attacks or withdrew from the study, feeling that the drug was not effective. It is assumed that beneficial effect is associated with the real medication while failure implies the use of placebo. The answer will be available only at the end of the study. However, an interim analysis by an independent party is planned for the near future to decide whether further exploration is warranted. We hope that this study will raise the curtain on a new era in FMF treatment and radically reduce the suffering associated with refractory FMF.

References

A Crohn’s disease variant in ATG16L1 enhances its degradation by caspase 3

Crohn’s disease is a debilitating inflammatory bowel disease (IBD) that can involve the entire digestive tract. A single-nucleotide polymorphism (SNP) encoding a missense variant in the autophagy gene ATG16L1 (rs2241880, Thr300Ala) is strongly associated with the incidence of Crohn’s disease. Numerous studies have demonstrated the effect of ATG16L1 deletion or deficiency; however, the molecular consequences of the Thr300Ala (T300A) variant remains unknown. Murthy et al. show that amino acids 296–299 constitute a caspase cleavage motif in ATG16L1 and that the T300A variant (T316A in mice) significantly increases ATG16L1 sensitization to caspase-3-mediated processing. The authors observed that death-receptor activation or starvation-induced metabolic stress in human and murine macrophages increased degradation of the T300A or T316A variants of ATG16L1, respectively, resulting in diminished autophagy. Knock-in mice harboring the T316A variant showed defective clearance of the ileal pathogen Yersinia enterocolitica and an elevated inflammatory cytokine response. In turn, deletion of the caspase-3-encoding gene, Casp3, or elimination of the caspase cleavage site by site-directed mutagenesis rescued starvation-induced autophagy and pathogen clearance, respectively. These findings demonstrate that caspase 3 activation in the presence of a common risk allele leads to accelerated degradation of ATG16L1, placing cellular stress, apoptotic stimuli and impaired autophagy in a unified pathway that predisposes to Crohn’s disease.

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Vitamin D and multiple health outcomes: umbrella review

Theodoratou et al. evaluated the breadth, validity, and presence of biases of the associations of vitamin D with diverse outcomes. The authors performed an umbrella review of the evidence across systematic reviews and meta-analyses of observational studies of plasma 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D concentrations and randomized controlled trials of vitamin D supplementation. The identified 107 systematic literature reviews and 74 meta-analyses of observational studies of plasma vitamin D concentrations and 87 meta-analyses of randomized controlled trials of vitamin D supplementation. The relation between vitamin D and 137 outcomes was explored, covering a wide range of skeletal, malignant, cardiovascular, autoimmune, infectious, metabolic, and other diseases. Ten outcomes were examined by both meta-analyses of observational studies and meta-analyses of randomized controlled trials, but the direction of the effect and level of statistical significance was concordant only for birth weight (maternal vitamin D status or supplementation). On the basis of the available evidence, an association between vitamin D concentrations and birth weight, dental caries in children, maternal vitamin D concentrations at term, and parathyroid hormone concentrations in patients with chronic kidney disease requiring dialysis is probable, but further studies and better designed trials are needed to draw firmer conclusions. In contrast to previous reports, evidence does not support the argument that vitamin D-only supplementation increases bone mineral density or reduces the risk of fractures or falls in older people. The authors conclude that despite a few hundred systematic reviews and meta-analyses, highly convincing evidence of a clear role of vitamin D does not exist for any outcome, but associations with a selection of outcomes are probable.

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“I don’t need time. What I need is a deadline”
Duke Ellington (1899-1974), American composer, pianist and bandleader of jazz orchestras