Successful Therapy with Canakinumab and Mepolizumab for Familial Mediterranean Fever and Eosinophilic Pneumonia

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Biological therapies with monoclonal antibodies have revolutionized the management of many inflammatory and autoimmune diseases. Combining biological treatments is very rarely indicated and may theoretically result in severe adverse effects, specifically, an increased tendency toward infectious diseases. We present the case of a woman in whom combination therapy with canakinumab for familial Mediterranean fever (FMF) and mepolizumab for chronic eosinophilic pneumonia was successfully employed.

PATIENT DESCRIPTION

A 63-year-old woman who never smoked had been diagnosed with FMF during childhood. FMF presented as typical recurrent episodes of abdominal pain and fever (abdominal attacks), monoarthritis, and arthralgia. The diagnosis was later supported by homozygous Met694Val mutations in the MEFV gene. She was treated with colchicine 2 mg/day, which prevented the inflammatory attacks, yet arthralgia remained. There was no proteinuria. During 2019 she began to present with chronic diarrhea and abdominal pain that led to significant weight loss. A thorough gastrointestinal evaluation was negative, and eventually the diarrhea resolved with complete discontinuation of colchicine. Therapy with 150 mg subcutaneous canakinumab every 4 weeks was initiated on January 2020 for colchicine intolerant FMF with excellent control of symptoms.

Additional medical history was significant for idiopathic chronic eosinophilic pneumonia (CEP) diagnosed in 1993 (at age 35 years) and treated with long-term corticosteroids. Previous attempts for steroid-sparing therapy with methotrexate failed. She required 20 mg of prednisone daily. Lower doses resulted in worsening dyspnea, cough, and radiographic consolidations. Chronic steroid therapy, however, can cause serious complications. Our patient developed osteoporosis, which led to vertebral compression fractures and severe kyphoscoliosis as well as fractures of the ramus pubis and of the right ribs cage following minor trauma. Bilateral cataract surgeries were required in 2008 (at age 50 years). On August 2018 she was hospitalized for respiratory deterioration and was diagnosed with Pneumocystis jirovecii pneumonia (PCP), another complication of chronic steroid treatment. She was referred to the pulmonary clinic for evaluation for possible steroid-sparing agents in late 2020.

At that time, she was being treated with prednisone 20 mg/day. Pulmonary functions tests revealed a very severe restrictive pathology, a combination of parenchymal disease, and severe kyphoscoliosis. The peripheral blood eosinophil count was 200 cells/μL. Investigations for alternative causes of eosinophilic lung disease were unrevealing. Attempts to gradually taper down the steroid dose, including the addition of high-dose inhaled corticosteroids, were unsuccessful and resulted in clinical and radiological worsening [Figure 1A].

We initiated treatment with monthly subcutaneous mepolizumab 100 mg in February 2021. During the following 9 months, dyspnea improved, and the prednisone dose was gradually decreased to 5 mg/day. Regarding pulmonary function tests, FVC and FEV1 improved by 200 ml each, from 760 ml to 960 ml and from 600 ml to 800 ml, respectively (relative improvement of over 25%). Peripheral blood eosinophils count was suppressed at 70 cells/μL, and the chest X-ray remained clear of consolidations [Figure 1B]. No adverse events of the therapy are evident.

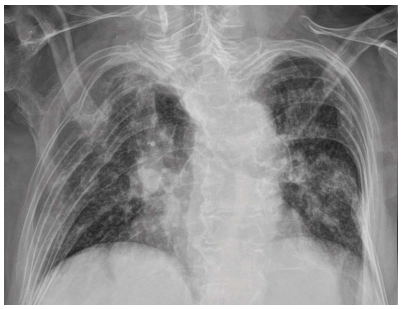
COMMENT

FMF is an inherited autoinflammatory disease that typically manifests with recurrent episodes of fever and serositis attacks. A serious complication is AA amyloidosis, which presents as proteinuria and can result in nephrotic syndrome and end stage kidney disease. FMF is associated with mutations in the gene MEFV, which codes for the protein pyrin. The Met694Val mutation is associated with more severe forms of the disease and an increased risk for amyloidosis. Colchicine, the mainstay

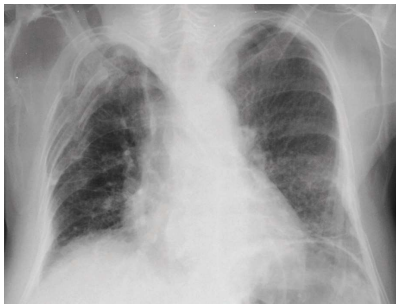
Figure 1. Posterior-anterior chest X-ray of the patient

Severe kyphoscoliosis and old rib fractures on the right side are evident on both figures. The alveolar consolidations significantly improved following mepolizumab treatment despite significant reduction in the steroid dose.

[A] Before mepolizumab therapy



[B] After 3 months of mepolizumab therapy



of FMF therapy, reduces the number of attacks and prevents amyloidosis. Interleukin (IL)-1 blockers are second-line treatments in cases of colchicine resistance or intolerance. Canakinumab, an IL-1β blocker, is effective and safe in preventing attacks when administered to subjects with colchicine-resistant FMF. A systematic literature review demonstrated the efficacy and safety of canakinumab in FMF, although the risk for infections is increased [1]. A moderately increased risk for mild and moderate infections was noted in a review of canakinumab for various indications (including FMF); opportunistic infections, however, are very uncommon [2].

CEP usually responds well to systemic corticosteroids, yet some patients require prolonged and even lifelong treatment. There are no approved steroid-sparing agents for CEP. Mepolizumab is an anti-IL-5 monoclonal antibody, which has demonstrated improved disease control and a significant steroid-sparing effect in severe eosinophilic asthma. It is also indicated for the treatment of eosinophilic granulomatosis and angiitis, chronic rhinosinusitis with nasal polyps, and hypereosinophilic syndrome. It is evaluated for various other eosinophilic diseases. Several case reports and a case series indicated highly successful treatment of CEP with off-label mepolizumab, leading to improved clinical outcomes and reduced corticosteroid doses [3]. The safety profile of mepolizumab is reassuring. A theoretically increased risk of helminthic infections was not evident in asthma studies [2,4]. Both canakinumab and mepolizumab are not associated with increased risk for malignancy [4].

To the best of our knowledge, this is the first report of combination therapy with canakinumab and mepolizumab for any indication. In addition to a literature search, we contacted the manufacturers of both agents, yet were unable to find such cases.

Our primary consideration when contemplating the therapeutic combination was increased risk of infections from the intensified immunosuppression. Nevertheless, experience with IL-5 inhibition has not been shown to increase the risk for infections or malignancy. We think that the already established perils of chronic steroid therapy in our patient, which included recurrent osteoporotic fractures, cataract, and opportunistic infection (PCP), outweigh the theoretical risk of adding mepolizumab to canakinumab, expecting the steroid dose would be significantly reduced.

Another concern was the possibility that the inhibition of one cytokine pathway would diminish the efficacy of the second inhibitor. However, the IL-5 pathway is relatively specific to eosinophilic inflammation and theoretically should not interfere with canakinumab mechanism of action. In addition, there is evidence that IL-1β may induce eosinophilic inflammation by stimulating the production of IL-5 and IL-13 from innate lymphoid cells [5]. Thus, the combination of inhibitors is not speculated to counteract each other.

While our patient's clinical status and radiological findings significantly improved following mepolizumab therapy, pulmonary function tests improved only modestly. We believe that the patient's lung volume was essentially limited by severe kyphoscoliosis, resulting in a severe restriction even with complete resolution of the parenchymal disease. Courses of high-dose steroids also failed to improve the pulmonary function tests further in the past. Previous reports of patients with CEP (in the absence of other limiting conditions); however, described normalization of lung function following mepolizumab therapy [3].

CONCLUSIONS

Long-term combination therapy with canakinumab and mepolizumab for FMF and chronic eosinophilic pneumonia, respectively, is safe, while the efficacy of individual medication was maintained.

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