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Efficacy of abatacept in a refractory case of adult-onset Still's disease

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ABSTRACT

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder, characterised by spiking fever, skin rash, and arthritis. First-line treatment consists of corticosteroids. Methotrexate is commonly used in resistant cases or as a steroid-sparing drug. The availability of biologic drugs in the rheumatic diseases, such as anti-TNFs and IL-1ra, has allowed to treat very refractory cases of AOSD and provided new clues for the pathophysiology. However, anakinra and anti-TNFs may also fail or may be contraindicated in AOSD, and other treatment strategies are then necessary. Given that T cell activation may be a relevant part of the AOSD pathophysiology, abatacept, CTLA4IgFc, was administered in a 57-year-old man with AOSD failing traditional DMARDs and to anti-IL-1 and anti-TNF therapies, with a good outcome.

Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown aetiology, characterised by daily spiking fever, evanescent skin rash, and arthritis (1). Cytokines, such as interleukin (IL)-1, IL-6, interferon (IFN)-gamma, and tumour necrosis factor (TNF)-alpha, have been found at high levels in patients with AOSD, as well as IL-18 and IL-4 (2), reflecting a T cell-oriented proinflammatory state in the pathogenesis of AOSD (1). TCR gamma delta-positive T cells have been demonstrated at very high levels in the active phase of AOSD (3), and CD4 and CD8 co-expressed T lymphocytosis was reported in a case of AOSD (4), suggesting an abnormal T cell mediated reactivity in AOSD. The availability of biologic drugs in the rheumatic diseases, such as anti-TNFs and IL-1ra, has allowed to treat very refractory cases of AOSD and provided important clues for its pathophysiology (5-8). However, anakinra and anti-TNFs may also fail in AOSD due to inefficacy or side effects, and other treatment strategies are then necessary (8). Given that T cell activation may be a relevant part of the AOSD pathophysiology (1-4), abatacept, CTLA4IgFc, may be a treatment option in such cases.

Case report

We report a 57-year-old man with clinical and laboratory findings fulfilling the classification of AOSD according to the Yamaguchi and Fautrel criteria (9-10). He presented daily early evening fever >39°C, diffuse arthromyalgias lasting longer than two weeks, with elbow, ankle and wrist arthritis, and leucocytosis (WB 14800/mm^3), but lacking a skin rash. In addition, sore throat, cervical lymphadenopathy, splenomegaly and aminotransferase elevation were found at disease onset. He also presented a markedly elevated serum ferritin concentration (1500 ng/ml, normal value 27-300 ng/ml) and C-reactive protein (CRP) (230 mg/L, normal value 0-5 mg/L), rheumatoid factor positivity (48 UI/ml, normal value <20 UI/ml), while antinuclear and anti-CCP antibodies were absent. Initially he was treated with high-dose steroids (1 mg/kg/day, slowly tapered and then suspended in six months), plus methotrexate (MTX) 20 mg/week with complete remission. After a 9-month period of remission, he experienced a relapse with arthritis and fever. Adalimumab 40 mg every other week was then started in association with MTX 15 mg/week, achieving only a partial clinical and laboratory response. After 6 months the disease further worsened with high fever, arthritis, sore throat, marked increase in serum ferritin (3600 ng/ml), CRP (260 mg/L), white blood cell count (10.300/mm^3) and aminotransferases. Anakinra 100 mg/day was started with prednisone 0.5 mg/kg/day tapered to 0.3 mg/kg/day in two weeks. Fever rapidly decreased and arthritis improved as well. However, two weeks after the first anakinra administration, the patient experienced anakinra-related thrombocytopenia, and the treatment was discontinued with platelet count recovery (11). The patient was then treated with etanercept 25 mg biweekly in association with MTX 15 mg/week, and then switched to infliximab 3 mg/kg after three months due to the persistence of arthritis and fever. Only a partial disease control, with chronic low-dose steroids and frequent short courses of high-dose steroids for disease flares was recorded under infliximab. Con-

comitantly, the patient complained of acute low back pain that was attributed to a vertebral fracture due to steroid-induced osteoporosis. Then, leflunomide was also introduced due to frequent flare of arthritis. On January 2009 the patient presented with high fever, active arthritis (6 tender joints, 7 swollen joints), prolonged morning stiffness, leucocytosis and high acute phase reactants levels (ferritin 420 ng/ml, CRP 50.5 mg/L), while aminotrasferase levels were normal. HAQ was 0.75, VAS pain was 69/100. No frank bone erosions were demonstrated by x-rays in both hands (Fig. 1). Abatacept (a soluble, fully human, recombinant fusion protein that selectively modulates the CD80/CD86:CD28 co-stimulatory signal for T-cell activation) (10 mg/kg according to weight range) by intravenous (IV) infusion on Days 1, 15 and 30, and every 4 weeks thereafter was initiated, while MTX 15 mg/week plus leflunomide 10 mg/day, and prednisone was left unchanged at 20 mg/day. Fever disappeared shortly after the first infusion, and active arthritis by the end of the third month. Response persisted at the last follow-up (month +9), with no active arthritis and morning stiffness less than 30 minutes, VAS pain reduced to 38/100, CRP reduced to 15 mg/L and serum ferritin within the normal range. HAQ was 0.8, unchanged. Steroid dose was gradually tapered to 2.5 mg/day of prednisone. Fever never relapsed, while an arthritic flare at month +2 was successfully treated with a single intra-articular steroid injection in both wrists. No serious adverse events occurred.

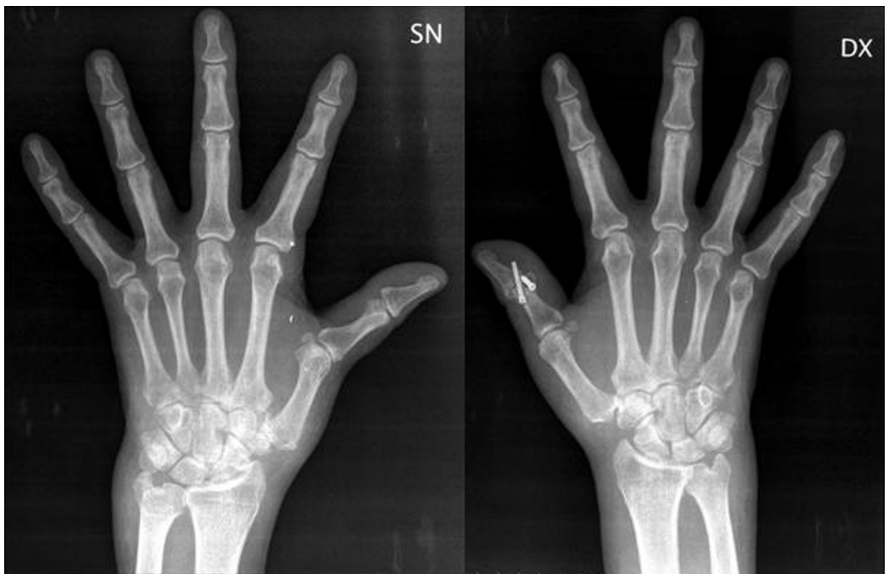

Fig. 1. Right and left x-rays of the hands were taken after 5 years of disease, characterised by articular involvement from the beginning. At both wrists, soft tissue swelling, osteopenia and sclerosis are present. Left trapeziometacarpal joint subluxation is shown. No frank bone erosions are evident.

Discussion

AOSD is an uncommon inflammatory condition of unknown origin typically characterised by spiking fever, arthralgias or arthritis, skin rash and hyperleucocytosis (1, 7). The evolution of AOSD can be monocyclic, polycyclic or chronic (1, 7). In chronic disease, joint involvement is often predominant and bone erosions are noted in one-third of patients (1, 7). Rheumatoid factor can be also positive in a minority of patients (12). Therapeutic strategies come from observational data. Corticosteroids are usually the first-line treatment, and MTX appears to be the best choice to control disease activity and to allow steroid tapering (1, 7). Biological therapy with agents blocking TNF and IL-1 are in use, and the blocking IL-6 appears promising (5-8). Anti-CD20 therapy has also been used in few cases of refractory AOSD, suggesting different subsets of the disease and a possible role of treatment approaches other than the IL-1 or TNF blockade (13).

Upstream the cytokine release, activated T-cells may play a role in the immunopathology of AOSD (4). Therefore, targeting T-cell activation represents a rational approach for the treatment of AOSD, as also suggested by the efficacy of MTX, cyclosporine A or azathioprine in this disease. Abatacept, a selective co-stimulation modulator, has been shown to be effective in treating rheumatoid arthritis (14), and recently also in all juvenile idiopathic arthritis subtypes (15), including patients with systemic manifestations. The drug was generally safe and well tolerated.

Here, we reported the first case of AOSD, to our knowledge, successfully treated with abatacept, combined with MTX and leflunomide (previously uneffective in the lack of abatacept). Abatacept allowed to control both fever and arthritis. The efficacy observed may be attributed to T-cell costimulation blockade, since all previous treatments were left unchanged.

Although IL-1 and TNF blocking agents are the biologics of choice in refractory cases of AOSD, resistance to these agents may occur in some cases of chronic AOSD, and therapeutic strategies targeting the cellular pathways upstream the cytokine release may be of value to bypass this resistance. The efficacy of anti-IL-1 therapy itself might be in part explained by an indirect effect on T-cell activation in AOSD (16). Tocilizumab, an anti-IL-6 receptor therapy, with a rapid anti-inflammatory effect observed in rheumatoid arthritis (17) and in systemic-onset juvenile idiopathic arthritis patients (18), may be effective also in AOSD (19). However, tocilizumab should be monitored for liver side effects, and AOSD-related liver disease may create difficulties for anti-IL-6 receptor therapy. .

In conclusion, although this is the first clinical information on abatacept in AOSD, this favourable experience may be helpful for refractory cases, when anti-IL-1 and anti-TNF agents failed or are contraindicated. Since T cells play a crucial role in the pathophysiology of AOSD upstream the cytokine release, abatacept deserves further investigation and might have some positioning in the treatment of AOSD in the future.

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