Adalimumab (anti-TNF-alpha) therapy to improve the clinical course of adult-onset Still's disease: the first case report

Sirs,

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown etiology which affects young adults during the second or third decade of life, either as a primary disease or as a relapse of childhood Still's disease (1). Clinical features are characterized by initial pharyngitis, with prolonged fever, polyarthritis and maculopapular rash; moreover, liver and pericardium involvement are commonly observed (2). Biological data show an increase in all inflammatory proteins and leukocytosis (usually > 20,000 cells/mm^3). The poor prognosis of AOSD is due to its slow evolution, frequent relapses and serious complications such as thrombotic thrombocytopenic purpura (3) and amyloidosis (4). The levels of tumor necrosis factor (TNF-α) and IL6 and other inflammatory markers (C-reactive protein, Ferritin) increase dramatically in patients with AOSD. TNF-α seems to play a role in the pathogenesis of AOSD and therefore some anti-TNF-α drugs, such as infliximab (5) and etanercept (6) have been used with success in the treatment of AOSD. Therefore, we tested adalimumab, a fully human anti-TNF-α therapy, in a case of refractory AOSD.

A 48 year-old non-smoking, non-drinking woman with regular menstrual cycles was referred with high fever and with flu characteristics in December 1999. Remote anamnesis did not show relevant pathologies. She showed clinical improvement after ten days. A second episode of high fever (38-39.5°C) started on 4th January, reaching a maximum of 40.2°C in a couple of days. In the following week the symptoms worsened with appearance of pain, swollen wrist joints and metacarpalphalanges with subsequent engagement of the knees, ankles and shoulders. The fever persisted intermittently so cetriaxone 1g/day and antipyretic drugs were prescribed by her doctor.

On 22nd January 2000 the patient was admitted to hospital due to the persistence of her symptoms. The results of the tests were: ESR 123 mm/h, CRP8.5 mg/dl, leucocytes 18.750 mm^3, (N 78%, L12%, M 6%, B 0%, and E 4%), platelets 578,000 mm/^{3}, ferritin 980 ng, LDH 678 UI/L, Rheumatoid factor and autoantibodies (ANA, ENA, DNA) negative. The thorax and abdomen CT showed slight splenomegaly (diameter 13 cm), but no lymphoadenopathy. X-rays of the segment joints showed osteoporosis in the iuxtarticular area with reduction of the joint spaces of the right hand carpal. During a febrile episode (39.6°C) evanescent intense rose-coloured lesions appeared on the forearms. AOSD was established according to Yamaguchi criteria (7). She started therapy with prednisone 50 mg/day with good response in respect of pain, but fever persisted irregularly, reaching a maximum of 38° C. Due to the persistence of symptoms she started therapy in March 2000 with 6 cycles of methylprednisolone 2 g + cyclophosphamide 1 g/day for 3 days/one month. Reduction of the inflammation parameters (ESR 32 mm/h CRP 1.2 mg dl), ferritin 201 ng and number of leucocytes (10.300 mm^3) was observed. Moreover, the painful symptoms and fever disappeared.

In January 2001 tests showed: ESR 16 mm/h, ferritin 32 ng, leucocytes 6.700 mm^3. The therapy with methylprednisolone was reduced to 4 mg/day. In March 2003 fever (39.4°C) at night and painful symptoms appeared again. Tests showed: ESR 84 mm/h, CPR 7.6 mg/dl, ferritin 658 ng, leucocytes 15,800 mm^3. She started therapy with methylprednisolone 32 mg/day and methotrexate 10 mg/week up to 15 mg/week in May 2003. In June 2003 sinovitis of the right wrist and fever (37.4°C) persisted. Tests showed: ESR 46mm/h, CRP 4.15 mg/dl, ferritin 424ng, leucoytes 13.600 mm^3. It was also possible to measure the serum circulating levels of cytokines by QUANTIKINE Human TNF-α and Human IL6 Immunoassay (RD Systems): TNF-α 22.6 pg/ml (v.n < 15.6 pg/ml) and IL-6 38.5 pg/ml (v.n <12.5 pg/ml). When methylprednisolone therapy was reduced to 16 mg/day a cutaneous rash appeared. Therefore the patient started additional therapy with adalimumab 40 mg/2 weeks. A rapid improvement in her symptoms with no more fever or sinovitis of the right wrist was observed. In September 2003 tests showed: ESR 13 mm^3, leucocytes 7.100 mm^3 , CRPnegative, TNF-α < 15.6 pg/ml and IL-6 < 12.5 pg/ml. We reduced methylprednisolone therapy to 8 mg/day and methotrexate therapy to 10 mg/week. In October 2003 tests showed: ESR 11mm/h, ferritin 28 ng, leucocytes 6,700 mm^3, CRP negative, TNF-α < 15.6 pg/ml and IL-6 <12.5 pg/ml. In January 2004 methotrexate therapy was stopped. Complete remission was noted in March 2004. The patient then took only methylprednisolone 4 mg/ day and adalimumab 40 mg/2 weeks. From September 2004 the patient has taken only adalimumab with good control of clinical symptoms up to now.

AOSD first line treatment includes non steroidal anti-inflammatory drugs and corticosteroids but in refractory cases, or when a high dose of corticosteroids is unacceptable, additional immunosuppressive therapy has been used (8-9). A recent study showed the efficacy of infliximab (5) and etanercept (6) anti-TNF-α therapy in AOSD refractory to conventional therapy. Recent papers showed a good prognosis also in a series of cases (10). The pivotal role of anti-TNF-α therapy has been shown in a paper underlining the role of some cytokines such as TNF-α and IL-6 showing high circulating levels in peripheral blood (11). Also our patient showed high serum cytokine levels during the AOSD relapse, decreasing to normal range after 2 months of adalimumab therapy. To the best of our knowledge this is the first case report of AOSD treated with adalimumab therapy. Because of the long life of adalimumab, very good control over the serum circulating cytokine levels is expected, leading to the complete remission of symptoms. Although further studies confirming the long-term efficacy and safety of Adalimumab therapy in a larger number of patients are needed and although all anti-TNF-α agents can be used in the treatment of AOSD refractory to conventional therapy, the use of Adalimumab could be recommended for its better compliance.

M. BENUCCI[1], *MD*
F. LI GOBBI[1], *MD*
A. DEL ROSSO[2], *MD*
M. MANFREDI[3], *BD*

[1]Section of Rheumatology and [3]Unit of Immunology and Allergology, Nuovo Ospedale di S. Giovanni di Dio, ASL10, Florence;
[2]Division of Rheumatology, Department of Internal Medicine, University of Florence, Florence, Italy.

Address correspondence to: Maurizio Benucci, MD, Section of Rheumatology, Nuovo Ospedale S.Giovanni di Dio, Via di Torregalli 3, 50143 Florence, Italy.
E-mail: maubenucci@tiscali.it maurizio.benucci@asf.toscana.it

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