Inefficacy of etanercept in a child with hyper-IgD syndrome and periodic fever

Sirs,

Hyper-IgD syndrome (HIDS) is an autosomal recessive disease caused by recessive mutations in the mevalonate kinase gene (MVK) (1, 2). HIDS is diagnosed on the basis of characteristic clinical findings (recurrent fever, limphadenopathy, diarrhea, abdominal pain, polyarthritis and macular rash) and by persistently elevated polyclonal IgD (3). Clinical signs may precede the elevated IgD levels and in patients younger than 3 years of age IgD levels are sometimes normal. Therefore for confirmation of diagnosis screening for the V377I mutations (present in > 80% of patients with HIDS) is recommended. If the result is negative and the clinical suspicion is high, sequencing of the gene to detect other mutations is possible (3).

No uniformly successful treatment of the HIDS is available. There are reports on the efficacy of steroids, which are the first choice of treatment, and anecdotal reports of efficacy of colchicine and cyclosporine in some patients. However not all patients respond to treatment (4). In a double-blind, randomized, cross-over trial, treatment with thalidomide failed to reduce the disease activity (5).

For the first time, recently Takada *et al*. (6) reported the efficacy of etanercept in the treatment of 2 girls with HIDS, with the reduction of both frequency and severity of symptoms. The authors suggest that, although abnormalities in tumor necrosis factor α (TNFα) are not the primary cause of HIDS, the elevation of the plasma TNFα levels during attacks may be considered as a therapeutic target.

We describe a 4-year-old boy with recurrent periodic fever every 10 days, starting at the age of 6 months, with concomitant important abdominal pain, lymphadenopathy (abdominal and cervical) and occasional macular skin rash and diarrhea. IgD were measured by means of an ELISA sandwich kit (Bethyl Laboratories Inc., Texas, USA). Levels of IgD were normal (45.2 mg/L) but the diagnosis of HIDS was eventually confirmed by identification of the double heterozygous T803C/G1129A missense mutations in the MKV gene, resulting in the I268T/V3771 amino acidic substitutions.

No mutations in the genes for the TNF receptor-associated periodic syndrome (TNFR SF1A) and familial Mediterranean fever (MEFV) were present. Due to the severity and duration of the attacks (about 5 days) steroid treatment was started at the beginning of the episodes of fever, with partial evidence in the reduction of symptoms but not in the recurrence of the episodes which still recurred roughly every 10-15 days. During one crisis steroid treatment failed to control symptoms with fever lasting 7 days and with the development of a severe abdominal complication, lymphadenopathy with occlusion, which required a surgical procedure. A treatment with colchicine was then attempted without any response .

Treatment with etanercept (12.5 mg/dose, two day for weeks) was then instituted taking into the account the severity of the clinical manifestations (particularly the clinical relevance of abdominal pain), the high frequency of episodes with the need for repeated doses of steroids, and a documented high level of plasmatic TNF alpha during an episode (25 pg/ml, normal value < 15 pg/ml). The levels of sTNFRSF1A (p55) and sTNFRSF1B (p75) were measured in plasma by means of ELISA sandwich kit (Hbt, Nederland). Reference intervals were 1-4 ng/ml and serum TNFRSF1A and TNFRS F1B levels were below the cutoff limits. INF gamma dosed in the same flare was strikingly high (545 pg/ml, normal value < 50 pg/ml).

Therapeutic response was assessed by comparing corticosteroid requirement, acute-phase reactants and an established scoring system over 12 weeks (number of episodes, abdominal pain, cervical lymphadenopathy, and abdominal lymphadenopathy measured by mean of ecography) both on and off etanercept.

No significant effects were reported for all parameters considered. During the 12 week period of treatment the child presented 5 episodes of fever with abdominal pain and cervical lymphadenopathy, requiring steroid treatment. The incidence (6 episodes), the characteristics of episodes, the dose of steroids required and the average acute phase reactants values did not change in the 12-week period without treatment. The echography of the abdomen during flares was repeated once in the 2 periods and showed no modification in the abdominal adenopathy. Acute phase reactants were performed during 2 flares in each period (on and off therapy with etanercept) and resulted abnormal: (a) during treatment: CPR; mean: 4.34 mg/dl; GB mean: 19.235/ mmc; ERS mean: 35mm/h; (b) after treatment: CPR, mean: 3.85 mg/L; GB: 20,900/ mmc; ERS: 38mm/h.

Etanercept, a drug that binds soluble and cell-bound TNF· and decrease its biologic effects, has been effective in a small series of patients with TNF-receptor-associated periodic syndrome (TRAPS) (7). In these patients the drug does not abolish inflammatory attacks but improves disease activity allowing corticosteroid reduction (8). Etanercept has also been proven to be effective with a partial response in a patient with HIDS who had a TNFRSF1Amutation (9).

Takada and others (6) nicely demonstrated the efficacy of etanercept in 2 cases, still some aspect of their experience deserve some considerations. In one patient the efficacy of etanercept was evident after 5 months of treatment with significant side effects, increased respiratory infections, and only after such a long period a benefit was evident. There is no clear explanation for such a delayed response, while it is described that the incidence of episodes of fever may spontaneously change in time in HIDS patients. Furthermore in this patient TNFα levels were normal before treatment so a different mechanism from TNF blockade could be supposed. Actually in our case treatment was withdrawn after 12 weeks without evidence of benefits for fear of possible side effects. In their other patient a rise in the acute phase reactants was documented during treatment after a period of malaise without fever suggesting a sort of partial effect. Both their patients were heterozygous carriers of a novel mutation, and possibly different genetics may explain different patterns of response. Finally of more relevance it is the fact that steroid treatment, which is actually the more effective available treatment, is not mentioned in both these patients.

HIDS is recognised as a benign disease and both investigations and treatments may possibly be more harmful that the disease itself. Even if etanercept has a good safety record it may have rare but serious side effects (10), while intermittent steroid treatment has a well documented safety record. In our case etanercept treatment was attempted only after a severe abdominal complication needing surgery and the failure of steroid treatment to satisfactorily control the flares. On the basis of our experience, we consider the use of etanercept as experimental in patients with HIDS. More extended functional studies should be performed in HIDS patients.

Acknowledgments: We thank Dr Andrea D'Osualdo of the Molecular Genetic Laboratory of the Istituto Giannina Gaslini, Genova, for performing the genetic testing.

F. MARCHETTI, *MD* C. ORETTI, *MD*
E. BARBI, *MD* A. VENTURA, *MD*
A. TOMMASINI, *MD*

Clinica Pediatrica, IRCCS Burlo Garofolo, Università di Trieste, Italy.

Address correspondence to: Federico Marchetti, MD, Clinica Pediatrica, IRCCS Burlo Garofolo, Via dell'Istria 65/1, 34100 Trieste, Italy. E-mail: marchetti@burlo.trieste.it

References

1. DRENTH JP, CUISSET L, GRATEAU G *et al.*: Mutations in the gene encoding mevalonate kinase cause hyper-IgD and periodic fever syndrome. International Hyper-IgD Study Group. *Nature Genetics* 1999; 22(2): 178-81.
2. HOUTER SM, KUIS W, DURAN M *et al.*: Mutations in MVK, encoding mevalonate kinase, cause hyperimmunoglobulinemia D and periodic fever syndrome. *Nature Genetics* 1999; 22(2): 175-7.
3. DRENTH JP, VAN DER MEER JW: Hereditary periodic fever. *N Engl J Med* 2001; 345: 1748-57.
4. DRENTH JP, HAAGSMACJ, VAN DER MEER JW: Hyperimmunoglobulinemia D and periodic fever

syndrome: the clinical spectrum in a series of 50 parients. *Medicine* (Baltimore) 1994; 73: 133-44.
5. DRENTH JP, VONK AG, SIMON A, POWELL E, VAN DER MEER JW: Limited efficacy of thalidomide in the treatment of febrile attacks of the hyper-IgD and period fever syndrome: a randomized, double blind, placebo controlled trial. *J Pharmacol Exp Ther* 2001; 298: 1221-6.
6. TAKADAK, AKSENTIJEVICH I, MAHADEVAN V, DEAN JA, KELLEY RI, KASTNER DL: Favorable preliminary experience with etanercept in two patients with the hyperimmunoglobulinemia D and periodic fever syndrome. *Arthritis Rheum* 2003; 48(9): 2645-51.
7. GALON J, AKSENTIJEVICH I, MCDERMOTT MF, O'SHEA JJ, KASTNER DL: TNFRSF1 A mutations and autoinflammatory syndromes. *Curr Opin Immunol* 2000; 12: 479-86.
8. DREWE E, MCDERMOTT EM, POWELL PT, ISAACS JD, POWELL RJ: Prospective study of anti-tumour necrosis factor receptor superfamily 1B fusion protein, and case study of anti-tumour necrosis factor receptor superfamily 1Afusion protein, in tumour necrosis factor receptor associated periodic syndrome (TRAPS): clinical and laboratory findings in a series of seven patients. *Rheumatology* 2003; 42: 235-9.
9. ARKWRIGHT PD, MCDERMOTT MF, HOOUTEN SM *et al*.: Hyper IgD syndrome (HIDS) associated with *in vitro* evidence of defective monocyte TNFR SF1Ashedding and partial response to TNF receptor blockade with etanercept. *Clin Exp Immunol* 2002; 130: 484-8.
10. LEPORE L, MARCHETTI F, FACCHINI S, LEONE V, VENTURA A: Drug-induced systemic lupus erythematosus associated with etanercept therapy in a child with juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2003; 21: 276-7.

Weber-Christian disease and pituitary dysfunction in a patient with polymyositis

Sirs,

In August 1998, a 48-year-old Chinese male was diagnosed as having polymyositis with myalgia, proximal muscle weakness, elevated muscle enzymes and electromyogram showing slow waves. He was treated with prednisone and azathioprine and became symptom-free until a fever with cough occurred in September 2001. He was given empirical antibiotic treatment and made an uneventful recovery.

In November 2001, the patient developed excessive, symmetrical painful dark erythematous nodules ranging from 1 to 5 cm^2 on his limbs, fever and chills, myalgia, arthralgia and abdominal distention. Physical examination revealed an expressionless facial appearance. Blood analysis showed neutrophilia (7.2 x 10^9/L), erythrocyte sedimentation rate 115 mm/hour, C-reactive protein 11.17 mg/dl (normal range 0-16), creatinine phosphokinase 331 u/L (20-174), lactate dehydrogenase 376 u/L (109-245), serum amylase 120 u/L (0-95), urine amylase 260 u/L(0-490), free T3 1.50 mol/L(2.30-6.36), T4 4.22 pmol/L (8.36-29.6), thyroid-stimulating hormone 0.25 mIU/L (0.4-4.0), adrenocorticotropic hormone < 1 pg/ml (0-46), morning and afternoon serum cortisol (8:00 and 14:00) 38.8 ng/ml (68.9-223.9) and 157.9 ng/ml (19.4-115) respectively, and testosterone 5.2 nmol/L (7.3-52.3). MRI showed no pituitary gland compression. Search for an underlying malignancy was negative. Biopsy of the subcutaneous nodules suggested active panniculitis (Fig. 1). No bacterial pathogens were isolated from the patient's blood, sputum or skin biopsy.

The patient was diagnosed as having Weber-Christian disease with pituitary necrosis and dysfunction, recent chest infection and underlying polymyositis. He was treated with prednisolone 40-20 mg/d for 3 months to no avail. Intravenous immunoglobulin G 10 g/day over 5 days was given, but the response was unsatisfactory with relapse of fever. Three pulses of low-dose iv cyclophosphamide (0.4 g/10-21 day) also failed to control the condition. Leflunomide (20 mg/day) (1) was added to his drug regimen and he made a full recovery after 2 months. Our patient fulfilled all of the following 3 criteria for Weber-Christian disease: (1) fever, arthralgia, myalgia and relapsing painful subcutaneous nodules; (2) scar lipoatrophy of the nodules; (3) pathological evidence with characteristic panniculitis (2, 3). The diagnosis of hypopituitarism was based on his abnormal facial appearance and the low serum levels of thyroxin, adrenocortisol, testosterone and pituitary hormones.

Pathologically Weber-Christian disease may be divided into three stages: early stage: inflammatory nodosa with neutrophil infiltration and fat cell degeneration; middle stage: histiocyte phagocytosis of necrotic fat cells and foam cells, and mononuclear cell infiltration; late stage: fibrosis and atrophy (3). Fat necrosis is a particular clinical manifestation of Weber-Christian disease which may involve all organs (4). We believe that our patient's hypopituitary state was secondary to fat necrosis of the pituitary gland. This extremely rare complication has been reported previously (5).

The cause of Weber-Christian disease is unknown but etiological factors include fat metabolic disorders, infection, autoimmunity, and drugs. In our patient, most of the known secondary causes of Weber-Christian disease were excluded. Potentially, however, the patient had contracted bronchopneumonia 2 months earlier and his condition could perhaps be linked to this or to his underlying polymyositis (6).

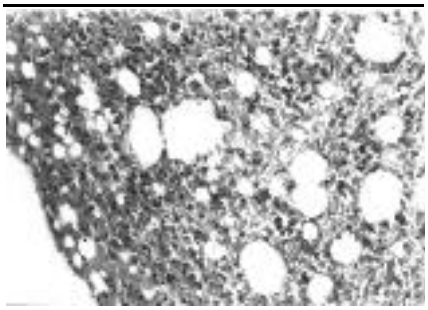

Fig. 1. Pathological section of subcutaneous nodule showing obvious fat denaturalization and necrosis in fat tissue, with intense histiocyte (mainly macrophage) infiltration and some lymphocyte infiltration (x200).

The conventional treatment for Weber-Christian disease includes the use of steroid and immunosuppressive agents such as cyclophosphamide, azathioprine and cyclosporine A (7), but when our patient did not respond to these we added leflunomide, an inhibitor of pyrimidine synthesis in activated immune cells (1). This is the first report of the successful use of cyclophosphamide and leflunomide combination treatment for Weber-Christian disease.

In conclusion, we have reported the case of a patient with Weber-Christian disease complicated by hypopituitarism. The Weber-Christian disease was probably secondary to a recent infection, although a possible casual relationship with polymyositis cannot be ruled out. This is the first time that such a combination of syndromes has been reported. Additionally, we show that leflunomide may be considered in the treatment of Weber-Christian disease.

O. JIN, *MD, Rheumatology Fellow*
L.-Y. SUN, *MD, Professor*
C.-S. LAU[1], *MD, Professor*

Division of Rheumatology, Affiliated Drum Tower Hospital of Nanjing University, Nanjing; [1]Division of Rheumatology, Department of Medicine, The University of Hong Kong, Hong Kong, P.R. China.

Address correspondence to: Dr. Ou Jin, Division of Rheumatology, University Department of Medicine, Queen Mary Hospital, Pokfulam Road, Hong Kong SAR, P.R. China. E-mail: jinouwishugood@hotmail.com

Reference

1. HERRMANN ML, SCHLEYERBACH R, KIRSCHBAUM BJ: Leflunomide: an immunomodulatory drug for the treatment of rheumatoid arthritis and other autoimmune diseases. *Immunopharmacology* 2002; 47: 273-89.
2. VALENTINI F: Weber-Christian disease with systemic involvement. Apropos of a case of histiocytic cytophagous panniculitis. *Minerva Med* 1985; 76: 865-72.
3. FRIEDENBERG R: Weber-Christian's disease: A report of two cases. *Ann Intern Med* 1953; 38: 528-32.
4. TER POORTEN MA, THIERS BH: Systemic Weber-Christian disease. *J Cutan Med Surg* 2000; 4: 110-12
5. KAWAI K, KUGAI N, KIMURA S *et al*.: A case of chronic relapsing febrile nodular panniculitis (Weber-Christian disease) associated with pituitary dysfunction. *Nippon Naika Gakkai Zasshi* 1980; 69: 954-9.
6. RAIMER SS, SOLOMON AR, DANIELS JC: Polymyositis presenting with panniculitis. *J Am Acad Dermatol* 1985; 13: 366-9.
7. IWASAKI T, HAMANO T, OGATA A *et al*.: Successful treatment of a patient with febrile, lobular panniculitis (Weber-Christian disease) with oral cyclosporin A: implications for pathogenesis and therapy. *Intern Med* 1999; 38: 612-14.