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Efficacy of thalidomide in refractory adult Still's disease: A new case report

Sirs,

Adult Still's disease is a febrile disorder of unknown etiology which affects young adults during the second or third decade, presenting either as a primary disease or as a relapse of childhood onset Still's disease (1). Clinical features are characterized by an initial pharyngitis with prolonged fever, polyarthritis and maculopapular rash; liver and pericardium involvement are commonly observed (2). The biological data comprise a major increase in all inflammatory proteins and leukocytosis usually >20,000 cells/mm^3. The poor prognosis of Still's disease is determined by the long time course of its evolution, the frequent relapses, and serious complications [thrombotic thrombocytopenic purpura (3), amyloidosis (4)].

Levels of tumor necrosis factor α (TNFα), like the levels of other inflammatory markers (C reactive protein, ferritine), increase dramatically in patients with Still's disease. TNFα seems to play a role in the pathogenesis of Still's disease and therefore some anti-TNFα drugs, such as infliximab (5) and etanercept (6), have been used with success in the treatement of adult Still's disease. Thalidomide is also known to inhibit the production of TNFα and has consequently been tested in other inflammatory diseases (7-9). Taken together, these facts led us to test thalidomide in a case of refractory adult Still's disease.

A 23-year-old male presented in April 2000 with hyperthermia (39.5ºC), polyarthritis, rash and pericarditis. He had a history of childhood onset Still's disease diagnosed at the age of 9 years and treated with corticosteroids for 12 years. The disease was considered to be in remission since 1998. The relapse of Still's disease was established according to the Yamaguchi criteria (10). Corticotherapy (prednisone) was started at 60 mg/day and remission occurred within 1 month; prednisone was progressively tapered to 10 mg/day and the patient remained well for one year. In April 2001 fever, arthritis and rash relapsed. Prednisone was increased to 50 mg/day. One month later the disease was still evolving and treatment was complemented with i.v. immunoglobulin (400 mg/kg/day over 5 days each month), methotrexate (20 mg/week *per os*) and colchicine 1 mg/day.

Two months later, despite this quadritherapy, the disease was still clinically and biologically progressing. The C-reactive protein level was 112 mg/l. Therefore methotrexate and colchicine were stopped and thalidomide was started (150 mg/day). One month later the disease was in total remission, with a CRP level at 2 mg/l despite a reduction in the daily prednisone dosage to 30 mg/day. Nine months after the beginning of thalidomide treatment, remission was maintained with a CRP level at 9 mg/L, and a prednisone dosage of 15 mg/day. Throughout the follow-up the neurological examination was normal and electroneurograms performed after 3 and 9 months of treatment showed no sign of peripheral neuropathy.

Teratogenic effects led to the withdrawal of thalidomide from the world market in 1961. However, the recent discovery of the anti-inflammatory, immunomodulatory and anti-angiogenesis properties of thalidomide has increased interest in this molecule, especially in the field of inflammatory and immune-mediated diseases. Thalidomide is able to inhibit TNFα production in human monocytes by stimulating mRNA degradation in a dose-dependent fashion and to reduce the half-life of TNFα mRNA by 50% (11). Stambe *et al*. (12) reported the efficacy of thalidomide in a 44-year-old woman with adult onset Still's disease refractory to other treatments. The patient was therefore given thalidomide (200 mg/day, then 100 mg/day). Improvement was observed after 2 weeks of treatment (thalidomide + prednisone) and the disease was in remission during a 6-month follow-up period. During the study, the percentage of monocytes producing TNFα decreased from 42.7% before thalidomide to 1.4% during the treatment.

Our results confirm the efficacy of thalidomide in adult Still's disease, even at a dosage of 150 mg/day. This efficacy is particularly remarkable when one considers the cost-effectiveness of this drug in comparison to other anti-TNFα drugs. Moreover, no significant side effects were observed.

In conclusion, thalidomide seems to offer a new approach for the treatment inflammatory diseases linked to the overproduction of TNFα. Refractory adult Still's disease might be a new indication for thalidomide as long as careful monitoring of peripheral nerve conduction with electroneurograms every 6 months is conducted to detect asymptomatic neuropathy. In fertile women the use of thalidomide should be authorized only in women taking the birth control pill.

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