Case report

Successful treatment of familial Mediterranean fever attacks with thalidomide in a colchicine resistant patient

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ABSTRACT

Colchicine is the treatment of choice in familial Mediterranean fever (FMF) both for attacks and for prevention of secondary amyloidosis. The overall non-responder rate varies from 5-10 to 40 %. Thalidomide is known to blunt the acute phase response. We report the efficacy of the addition of thalidomide to colchicine in controlling the febrile attacks and acute phase response in a patient with FMF resistant to 2 mg col - chicine per day.

Introduction

Colchicine has no alternative in the treatment of FMF. Compliance to the treatment is the first point to investigate when the patient does not respond to the treatment. Yet a significant proportion of patients do not respond to it partially or completely. We have encountered a patient with FMF whose attacks were refractory to colchicine treatment. First we have followed him under strict control for over one year with 2 mg/d of colchicine. During this period we have witnessed that his attacks occurred 3-6 times a month. The addition of thalidomide to the colchicine treatment afterwards showed a successful result with a significant reduction of number of attacks.

Case report

A 45-year old Turkish male patient with a 26-year history of recurrent febrile attacks of abdominal pain and arthritis presented at our FMF outpatient clinic in March 2000. He had been diagnosed as having FMF and had been prescribed colchicine 4 years after the onset of his disease. Initially he experienced a partial remission on the 1.5 mg/day dose. Then for at least two years there was an increase in the frequency and severity of the attacks even though he continued to use his medication. We followed him for over one year on colchicine, first with 1.5 mg/day for 3 months and later with 2 mg/day dose for 8 months. Despite this regimen he continued to experience 3-6 attacks per month, each attack lasting 2-3 days. There was a prominent increase in the acute phase response (CRP: 48 mg/dL (0.0-0.8), ESR: 80 mm/hour, fibrinogen: 779 mg/dL (180-350), leukocyte count: 12.300/mm^3) during the attacks. This response was somewhat lower but still above normal levels during the attack free periods (CRP: 2 mg/dL, ESR: 45 mm/hour, fibrinogen: 635 mg/dL, leukocyte count: 8.700/mm^3). At this point, after receiving his consent, he was put on thalidomide at a dose of 100 mg/day in addition to colchicine 2 mg/day. Six weeks after the initiation of this treatment the number of attacks decreased significantly. The acute phase response, between the attack free periods, also returned to normal after 10 weeks of the treatment (CRP: 0.38 mg/dL, ESR: 14 mm/hour, fibrinogen: 279 mg/dL, leukocyte count: 8.500/mm^3).

Our two attempts to discontinue the drug 10 weeks and 15 weeks later resulted with an immediate reappearance of the attacks. Therefore we decided to follow him closely on continuous thalidomide and colchicine. During the first 7 months of thalidomide treatment which he received 100 mg/day he experienced approximately an attack per month. Then we increased the dose to 200 mg/day and followed him for another 8 months. He has had only 3 attacks since then. At the end of the first month of thalidomide treatment, the patient began to complain of numbness over his legs. The neurological examination and the electromyography of both extremities were found to be within normal limits. The consultant neurologist diagnosed no abnormality

so we did not discontinue the treatment. The patient's complaint resolved spontaneously after two months while he was still on the same dose of thalidomide.

Discussion

Colchicine is the sole treatment of FMF. It reduces the frequency of attacks and prevents amyloidosis (1). Complete remission is seen in about 65% of patients and partial remission is experienced in another 20-30%. Still there are 5-10% nonresponders (2). There lies a great challenge because there is no alternative to colchicine. Interferon has been tried during acute attacks to decrease the severity and the duration of the attacks (3-4). Moreover there are other difficulties with interferon like its route of delivery and its cost. Thalidomide on the other hand has never been tried in FMF attacks but seems to be promising in many inflammatory diseases (5-8).

The mechanisms responsible for the development of FMF attacks are largely unknown, withboth increased levels of tumor necrosis factor (TNF) and decreased inhibitors of complement fragment C5 a and interleukin-8 being speculated asthe probable role involved in the pathogenesis (9, 10).

Thalidomide has been shown to inhibit chemotaxis (11) and to decrease monocyte phagocytosis without apparent cytotoxicity (12). Also it has caused a highly significant drop in helper T cells and an apparent increase in suppressor T cells in healthy volunteers (13). The drug selectively inhibits TNF- production without affecting production of interleukin-1 (IL-1) and IL-6 (14). Also in human peripheral blood mononuclear cell cultures thalidomide induced specifically the inhibition of interferon-gamma (IFN-) production and enhancement of IL-4 and IL-5 production (15). So far thalidomide has shown good therapeutic effects in several inflammatory conditions (5) including Crohn and Behçet's syndrome (6, 7) and in two refractory cases of systemic onset juvenile rheumatoid arthritis (8). Nevertheless in a recent study thalidomide has been shown to have limited efficacy in controlling febrile attacks of the Hyper- Ig D and periodic fever syndrome (16).

Its widespread use is hindered by its side effects. It has distinctive teratogenicity and causes peripheral neuropathy with mostly sensory symptoms and mild proximal weakness and drowsiness in the majority of patients.

This is the first case of thalidomide administered to a colchicine resistant FMF patient. It was found to be effective in this patient whose attacks and acute phase response were resistant to 2 mg/d of colchicine. The patient tolerated well the treatment with a slight transient numbness in his legs, which has disappeared despite continuing the drug. We suggest that in selected cases and pending controlled studies, thalidomide may be useful as an adjunct to colchicine treatment in FMF.

References

1. DINARELLO CA, WOLFF SM,GOLDFINGERSE *et al*.: Colchicine therapy for familial Meditterranean fever. A double blind trial. *N Eng J Med* 1974; 291: 934-7.
2. BEN-CHETRIT E, LEVY M: Familial Mediterranean fever. *Lancet* 1998; 351: 659-64.
3. TANKURT E, TUNCA M,AKBAYLAR H *et al*.: Resolving familial Mediterranean fever attacks with interferon alpha. *Br J Rheumatol* 1996; 35: 1188-9.
4. TUNCA M, TANKURT E, AKBAYLAR H *et al*.: The efficacy of Interferon alpha on colchicine-resistant familial Mediterranean fever attacks: A pilot study. *Br J Rheumatol* 1997;36:1005-8.
5. CALABRESE L, FLEISCHERAB: Thalidomide: Current and potential clinical applications. *Am J Med* 2000; 108: 487-95.
6. EHRENPREIS ED, KANE SV, COHEN LB *et al*.: Thalidomide therapy for patients with refractory Crohn's disease:An open-label trial. *Gastroenterology* 1999; 117: 1271-7.
7. HAMURYUDAN V, MAT C,SAIP S *et al*.: Thalidomide in the treatment of mucocutaneous lesions of the Behçet's syndrome. A randomized double blind placebo controlled trial. *Ann Intern Med* 1998; 128: 443-450.
8. LEHMAN TJA, STRIEGEL KH, ONEL KB: Thalidomide therapy for recalcitrant systemic onset juvenile rheumatoid arthritis. *J Pediatrics* 2002; 140: 1-5.
9. OZYILKAN E, SIMSEK H, TELATAR H: Tumor necrosis factor in familial Mediterranean fever. *Am J Med* 1992; 92: 579.
10. AYESH SK, AZAR Y, BABIOR BM *et al*.: Inactivation of interleukin-8 by the C5a-inactivating protease from serosal fluid. *Blood* 1993; 81: 1474-7.
11. FAURE M, THIOVOLET J, GAUCHERAND M: Inhibition of PMN leukocytes chemotaxis by thalidomide. *Arch Dermatol Res* 1980; 269: 275-80.
12. BARNHILL RL,DOLL NJ, MILLIKAN LE *et al*.: Studies on the anti-inflammatory properties of thalidomide:effects on polymorphonuclear cells and monocytes. *J Am Acad Dermatol* 1984;11: 814-9.
13. GAD SM, SHANNON EJ, KROTOSKI WA *et al*.: Thalidomide induces imbalances in T-lymphocyte sub-populations in the circulating blood of healthy males. *Lepr Rev* 1985; 56: 35-9.
14. SAMPAIO EP, SARNO EN, GALILLY R *et al*.: Thalidomide selectively inhibits tumor necrosis factor production by stimulated human monocytes. *J Exp Med* 1991; 173: 669-703.
15. MCHUGH SM, RIFKIN IR,DEIGHTON J *et al*.: The immunosuppressive drug thalidomide induces T helper cell type 2 (Th2) and concomitantly inhibits Th1 cytokine production in mitogen- and antigen-stimulated human peripheral blood mononuclear cell cultures. *Clin Exp Immunol* 1995; 99: 160-7.
16. DRENTH JP, VONK AG, SIMON A *et al*.:Limited efficacy of thalidomide in the treatment of febrile attacks of the hyper-IgD and periodic fever syndrome:A randomized, double-blind, placebo-controlled trial. *J Pharmacol Exp Ther* 2001; 298: 1221-6.