Treatment options in colchicine resistant familial Mediterranean fever patients: Thalidomide and etanercept as adjunctive agents

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ABSTRACT

Objective. *Regular colchicine treatment cannot control the typical febrile attacks of FMF in about 5-10% of the compliant patients. Here we report the effect of thalidomide and etanercept in 5 colchicine-resistant cases.*

Methods. *Five (4M/ 1F) FMF patients between April 2005 and March 2006, who were experiencing at least 2 attacks per month, despite regular colchicine were included to the study. Four male patients were given thalidomide 100 mg/d initially. Two of these patients unresponsive to thalidomide were prescribed subcutaneous injections of etanercept 25 mg, twice a week. The female patient received etanercept as the first choice due to potential side effects. She then had to be converted to thalidomide due to a severe injection site reaction.*

Results. *The median follow up period with thalidomide and etanercept was 8 months. Both thalidomide and etanercept lowered the number of the abdominal attacks.*

Conclusion. *Thalidomide and etanercept might be effective as additional treatment in colchicine-resistant cases of FMF.*

Introduction

Familial Mediterranean fever (FMF) is characterized by recurrent attacks of fever and serositis (1). Colchicine is effective in controlling the attacks and preventing the development of amyloidosis (1-3). About 65% of patients respond to colchicine with complete remission, 20-30% experience significant improvement and 5-10% do not respond (1). Interferon (IFN) alpha, thalidomide, infliximab and intravenous colchicine were previously used to suppress or prevent the attacks in refractory cases (4-9). Infliximab was reported to be effective in two FMF patients with co-existing ankylosing spondylitis and chronic arthritis (7-8). In these patients the joint problems rather than the serosal attacks seemed preferentially respond to infliximab.

We had previously reported that thalidomide was effective in controlling colchicine resistant attacks in a FMF patient (6). We assessed prospectively, the efficacy of thalidomide and etanercept in colchicine resistant abdominal attacks in 4 further FMF patients who have no chronic joint involvement. We also give here a follow-up of the patient we had previously reported on (6) who had received thalidomide at the 200 mg/day dose.

Patients and methods

We studied 5 (4M/1F) FMF patients between April 2005 and March 2006, who were experiencing at least 2 attacks per month, despite using colchicine regularly. Patients were attending the rheumatology outpatient clinic of Cerrahpasa Medical School and all fulfilled the proposed criteria for FMF (10). None had concomitant amyloidosis, spondylitis, chronic arthritis or vasculitis. The demographic and clinical characteristics are shown in Table I. These patients were unresponsive to colchicine 2 mg/day that they had used for a median of 5 years. The actual compliance and the non-responsiveness to colchicine had been observed at least for one year before adding other agents.

All patients experienced full-blown abdominal attacks lasting 2-3 days. Patient no 5 had non-periodic leg pain, which was provoked after standing or walking for long periods. Three of the patients (no 2, 3 and 5) had acute phase responses between attacks (Table I).

All except the female patient were first given thalidomide 100 mg/day. This rather low dose was chosen because of potential side effects. In case of side effects or unresponsiveness, the therapy was converted to etanercept (twice a

Table I. Patient characteristics, the frequency of attacks before and after adjunctive treatment.

no	Age (years) / Sex	Disease duration (years)	Colch. duration (years)	Adjunctive drug, duration	Frequency and duration of attacks Before (n/month)	After Total duration (n/month)	After Last 3 months (n)	Acute phase reactants in between attacks Before	After	Side effects	Comment
1	29 y /M	22	7	Thalidomide 11 month	2 / month 3 days	0.18 / month 2-3 days	0	CRP*: N ESR: 4 mm/hr	CRP: N ESR: 7 mm/hr	No complaint EMG: mild axonal polyneuropathy	Effective
2	27 y/ M	21	9	Thalidomide 8 month	3 / month 2 days	0.38 / month 2 days	0	CRP: 25 mg/L ESR: 26 mm/h Fibrinogen†: 455 mg/dL	CRP: 21 mg/L ESR: 21 mm/h Fibrinogen: 665 mg/dL	No complaint EMG normal	Effective
3	35 y/ F	30	8	Etanercept 2 weeks	2-3/ month 2 days	1 / week 2- 3 days	-	CRP: 7 mg/L ESR: 25 mm/hr Fibrinogen:	Not assessed	Injection site reaction (3rd injection)	Caused side effects
				Thalidomide 8.5 month		0.70 / month 2 days	1	525 mg/dL	CRP: 9 mg/L ESR: 28 mm/h Fibrinogen: 700 mg/dL	Drowsiness EMG normal	Moderately effective
4	42 y/ M	40	18	Thalidomide 2 months	2-3/ month 3 days	4 / month 2 days	-	CRP: N ESR: 10 mm/h Fibrinogen: N	CRP: N ESR: 42 mm/h Fibrinogen: N	Drowsiness EMG: normal	Ineffective
				Etanercept 8 month	2 days	0.75 / month	0		CRP: N ESR: 5 mm/h Fibrinogen: N	None	Effective
5	49 y/ M	37	20	Thalidomide 7 months	2-3/ month 3 days	2-3 / month 3 days	6	CRP: 22 mg/L ESR: 40 Fibrinogen: 711 mg/dL	Not available	Pain and numbness in the legs EMG: normal	Ineffective and caused side effects
				Etanercept 8 month		1.25 / month 1-2 days	2		CRP: 18 mg/L ESR: 27 mm/ h Fibrinogen: 560 mg/dL	None	Effective

Colch: colchicine; *the range for CRP: 0 - 5 mg/L; N: normal †: the range for fibrinogen: 180-350 mg/dL.

week 25 mg, subcutaneous injections). The female patient was first administered etanercept but then had to be switched to thalidomide because of side effects.

A calendar and a questionnaire were given to each patient to note the frequency and the characteristics of the attacks. All patients gave written informed consent after being fully informed about the side effects of the drugs. Colchicine 2 mg/day was continued in all patients. Patients were followed prospectively mostly at 2 month intervals with history taking, physical examinations and laboratory tests. Patients who were kept on thalidomide underwent neurological examination every 3 months. An electromyogram (EMG) was performed at the end of the sixth month.

Results

The frequency of the attacks before and after additional treatment and the duration and side effects of the treatment can be seen in Table I. All 5 (4M, 1F) patients were given thalidomide, 3 (2 M, 1F) also received etanercept.

a) Thalidomide

Thalidomide, 100 mg/day, was effective in controlling the febrile attacks in 3 (2 M/ 1 F) (no 1-3, in Table I) out of 5 patients. The duration for thalidomide use was 11, 8 and 8.5 months, respectively. The frequency of abdominal attacks decreased significantly especially after the 3rd month. Two patients did not have any attacks during that period, and the other had only one. During the first 3 months of thalidomide therapy, all three patients (no 1-3) experienced one episode of lower leg pain, swelling and erysipelas-like erythema, which recurred after 7 and 9 years in the first 2 patients and occurred for the first time in the third. Venous Doppler USG did not detect any abnormality in the superficial or deep veins. These episodes lasted for 4-5 days, disappeared spontaneously and did not repeat during the rest of the therapy. One patient (no 3) complained of drowsiness for the first 2 months while using thalidomide. EMG detected a mild sensorial polyneuropathy in another patient (no 1) at the sixth month although his neurological examination was normal. The dose of thalidomide was lowered to 50 mg/day, when the repeated EMG after an interval of 14 weeks showed similar findings, while he did not have any parestesia and his neurological examination was still normal. The neurological evaluations were normal in the remaining 2 patients.

Thalidomide 100 mg/d was not effective in other two patients (no 4 and 5 in Table I). Patient no 4 experienced an increase in the frequency of attacks and reported drowsiness interfering with his daily life. Patient no 5 who was reported previously in detail (6) had used thalidomide successfully at a dose of 200 mg/day for 1.5 years, however he complained of numbness and lower leg pain. His neurological examination and EMG were within normal limits. Following this, thalidomide had to be stopped due to unavailability. The attacks resumed at a rate of around 2 per month. When thalidomide became available after a year he was given this medication for an additional 7 months, this time at a reduced dose of 100 mg/d. With this regimen, however, he did not observe a change in the frequency of attacks and was prescribed etanercept as explained below.

b) Etanercept

Etanercept was given to two patients who failed to respond to thalidomide and to another as the first alternative (Table I). The treatment had to be stopped in the last patient due to a severe injection site reaction in the second week.

These 2 patients used etanercept for 8 months, during which, the frequency of the abdominal attacks, although less severe, did not change for the first 3 months then disappeared gradually. During the last 3 months of etanercept therapy, one patient did not have any attack, while the other had only two. The lower leg and foot pain, which was a constant complaint of the last patient, that had not respond to thalidomide, disappeared in the first month of etanercept. No other side effect was observed in these two patients during the follow-up.

The increased acute phase response in between attacks observed in 3 patients did not return to normal levels after the addition of thalidomide or etanercept.

Discussion

In this observational study with a limited number of patients, thalidomide and etanercept were tried as adjunctive therapy to colchicine in five FMF patients whose attacks were refractory to colchicine. Both drugs seemed to be effective.

Thalidomide has been used in the treatment of many inflammatory conditions including cutaneous lupus erythematosus and Behçet's syndrome (11-14). The inhibition of TNF-α is reported to be the main mechanism of action of thalidomide (15). Etanercept, on the other hand, is a soluble TNF receptor that binds specifically to TNF and blocks its interaction with cell surface receptors (16). It is used effectively to treat many inflammatory diseases, some vasculitic disorders and few autoinflammatory diseases (17). Although IL-1β seems to be the target cytokine in FMF attacks (18), it has also been shown that TNF-α may act synergistically with IL-1 in promoting the inflammation cascade (19).

Thalidomide is a potent drug but with serious side effects like teratogenity and polyneuropathy. The latter is dose-related, can be detected in up to 40 % of the patients and may be irreversible (11-14). Thalidomide 50-400 mg /day has been shown to be effective in SLE and BS (11-14). Higher doses (200-800 mg/d) are used in multiple myeloma (20) with an increase in the frequency of side effects. All the patients in this study received 100 mg/d. The only patient who had used 200 mg/d was described in detail previously (6) had responded favorably to this dose but had developed numbness of the lower extremities. Even if thalidomide is more effective in higher doses, we cannot recommend its routine use due to the potential and dose-related side effects especially in the light of the, of necessity, life-long treatment of FMF. The potential neuromyotoxic side effects of concomitantly used colchicine are a further consideration (21).

We also observed that 3 out of 5 pa-

tients who used thalidomide had episodes of lower leg pain, swelling and erysipelas-like erythema. These manifestations, typical of FMF, were quite rare before the use of thalidomide among these patients. Thalidomide is also known to cause pretibial edema or deep venous thrombosis of lower extremities (22), however venous Doppler USG were normal among our patients. These episodes may have occurred incidentally or could have been related to thalidomide.

Etanercept was as effective as thalidomide, but with less side effects. The only side effect was the injection site reactions serious enough to stop the treatment. The efficacy of thalidomide and etanercept became apparent only after the third and forth month of treatment. We had previously reported that etanercept was ineffective in controlling the febrile attacks of FMF (23) in 2 patients who were treated for 3 months, however after a longer period of follow-up we suggest that the patients should receive treatment longer than 4 months before assessing efficacy of either thalidomide or etanercept. Rather a limited response with etanercept in Crohn's disease (24) and systemic onset juvenile rheumatoid arthritis (soJRA) also has been shown (25). TNF blockade with infliximab rather than etanercept is reported to be efficacious in Crohn's disease (26), suggesting that some differences in molecular structure and binding specificities may account for the different effects of two biological agents. Whereas, in soJRA, the limited efficacy of etanercept is explained by the evidence of the different driving pro-inflammatory cytokines such as IL-6 and IL-1 rather than TNF-α (27). Another interesting observation was that the acute phase response in between attacks was above normal even though there was a clinical response. Maybe it will take some more time before the acute phase return to normal, similar to that observed in the late initiation of clinical efficacy. The question exists whether thalidomide or etanercept can prevent amyloidosis on the long term, therefore it is of utmost importance that the patients are informed that they must continue colchicine under any condition, together with any other drug, and for life-long. High cost and limited availability in countries where FMF is prevalent are other drawbacks of these drugs.

Conclusions

Colchicine is still the anchor drug to treat FMF patients. Thalidomide and etanercept seem to be effective as additional treatments, in controlling the febrile attacks in colchicine-resistant cases. Serious side effects of thalidomide limit its usefulness, especially in a disease like FMF that needs a life long treatment. The long-term efficacy of etanercept on the other hand should be tested in a larger group of colchicine resistant FMF patients.

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