Dapsone as an Alternative Therapy in Children with Familial Mediterranean Fever

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Abstract

Objective: Familial Mediterranean Fever is an hereditary autoinflammatory disease that presents with recurrent febrile attacks and polyserositis. Colchicine is the only known treatment in this disease. However, nearly 5-10% of patients are resistant to colchicines. There are many different modalities in colchicine resistant patients, biologic and immunosupressive drugs being the known ones. We studied the efficacy of Dapsone as an anti inflammatory drug in children with FMF who did not tolerate colchicine well.

Methods: This is a case series study in 10 patients who had FMF on the base of Tel-Hashomer criteria and did not tolerate colchicine or did not respond to it well. Patients took 2mg/kg dapsone in single dose, during 6 months.

Findings In four patients episodic attacks returned after 27 days, so the drug was discontinued. One patient refused to continue the study; in five patients dapsone was taken in average for 8 months and 6 days, at least for 6 months. These five patients had no episodes of attack during the following observation.

Conclusion: Dapsone could control episodic attacks of FMF in 50% of cases. It might be considered as an alternative therapy in FMF cases not responding to colchicine.

Key Words: Dapsone; Familial Mediterranean Fever; Periodic Fever; Children

Introduction

Familial mediterranean fever (FMF) is a genetic disease characterized by recurrent painful attacks of fever and polyserositis, usually peritonitis, pleuritis and arthritis. A typical attack can be prevented with regular daily administration of colchicine in the most patients[1]. However, about ten percent of patients do not respond to colchicine or are completely resistant to the drug[2]. There is no known alternative or adjunct to colchicine therapy, although non-steroidal anti-inflammatory drugs (NSAIDs) may be of some benefit for synovial symptoms[3]. Therapeutic options for this important group of patients are unsatisfactory as proposed agents have only been studied in individual cases or in small, nonrandomized trials. Nonetheless, patients suffering frequent or disabling attacks on a maximal tolerated dose of oral colchicine, may be offered a therapeutic trial with 1 mg weekly intravenous colchicine, in addition to the regular oral regime[4]. Alternatively, efficacy of TNF inhibitors has been shown in several case reports, with significant improvement in attack parameters for both etanercept and infliximab[5,6,7]. Thalidomide, an anti-inflammatory agent with anti-TNF properties, was also

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Dapsone has been the principal drug in a multidrug regimen recommended by the World Health Organization for the treatment of leprosy [13]. As an anti-infective agent, it is also used for treating malaria [14] and for Pneumocystis carinii pneumonia in AIDS patients [15].

A considerable number of other inflammatory diseases (ITP and vasculitis) have been shown to respond in varying degrees to dapsone [16-21]. Dapsone stabilizes neutrophil lysosomes [22]. Several studies showed that dapsone may impair neutrophil chemotaxis [23]. Dapsone suppressed integrin-mediated neutrophil adherence function. It also inhibited chemoattractant-induced signal transduction and thus suppressed neutrophil recruitment and local production of toxic products in the affected skin of neutrophilic dermatoses [24]. From the above, can be concluded that neutrophils and neutrophil products are the major targets for this drug.

We observed similar therapeutic effects of dapsone with colchicines. This observation led us to try dapsone in FMF patients who could not tolerate colchicine, and/or had side effects that encouraged them to discontinue the medication.

**Subjects and Methods**

This was a descriptive study conducted in FMF and periodic fever clinic in Ardabil University of Medical Sciences. We identified 10 children among FMF patients who fulfilled Tel-Hashomer diagnostic criteria for definite FMF. We do not use routinely MEFV gene analysis in our FMF clinic, it is limited to investigational and some doubtful cases [25,26]. None of patients had any symptoms suspicious of combined and/or associated disease with FMF, like JIA and vasculitis.

They were on regular colchicine treatment. All of the patients had GI discomfort and were intolerant to colchicine and showed some degree of tendency to refuse to continue drug taking. Including criteria were having FMF on the basis of Tel-Hashomer criteria, and any side effect of colchicine, especially GI symptoms.

The patients were informed about the possible benefits and potential side-effects of dapsone, and they accepted to take the drug at least for 6 months. Informed consent approved by the ethical committee of our institute (ARUMS) was obtained from each patient’s parents.

One patient in this group disagreed to continue the study.

In all patients G6PD was checked before dapsone with 2mg/kg dosage was begun. Patients were observed closely for the side effects of dapsone, especially on GI, liver and hematological aspect.

**Findings**

Four patients had recurrent episodes like before colchicine therapy after a few weeks (in average 27 days) of dapsone medication, so discontinuing it they were excluded from the study. One patient refused to take the drug and five patients took dapsone for averagely 8 months and 6 days, at least for 6 months. These five patients did not have any episode during study. The patients’ characteristics and result of treatment are summarized in Table 1.

**Discussion**

Chemotaxis, apoptosis and finally inflammasome formation has main role in FMF inflammation [10]. The most important effect of prophylactic doses of
Table 1: Characteristics of patients with Familial Mediterranean Fever and result of treatment with Dapsone

| SEX  | Age at onset of colchicine | Period of attack Before colchicine | Period of attack After colchicine | Severity | Number of severe attacks | Dosage of dapsone | Duration of dapsone therapy | Duration of fever | Result of treatment with dapsone |
|------|---------------------------|-----------------------------------|----------------------------------|----------|-------------------------|-----------------|-----------------------------|------------------|---------------------------------|
| F    | 30 - 36 years             | 1 - 3 days                         | 3 - 10 days                      | 2 - 3     | 2 times / month         | 50 mg daily     | 10 days                      | 7 - 8 days       | No attack*                        |
| M    | 30 - 36 years             | 1 - 3 days                         | 3 - 10 days                      | 2 - 3     | 2 times / month         | 50 mg daily     | 10 days                      | 7 - 8 days       | No attack*                        |
| M    | 30 - 36 years             | 1 - 3 days                         | 3 - 10 days                      | 2 - 3     | 2 times / month         | 50 mg daily     | 10 days                      | 7 - 8 days       | No attack*                        |
| M    | 30 - 36 years             | 1 - 3 days                         | 3 - 10 days                      | 2 - 3     | 2 times / month         | 50 mg daily     | 10 days                      | 7 - 8 days       | No attack*                        |
| M    | 30 - 36 years             | 1 - 3 days                         | 3 - 10 days                      | 2 - 3     | 2 times / month         | 50 mg daily     | 10 days                      | 7 - 8 days       | No attack*                        |
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| M    | 30 - 36 years             | 1 - 3 days                         | 3 - 10 days                      | 2 - 3     | 2 times / month         | 50 mg daily     | 10 days                      | 7 - 8 days       | No attack*                        |
colchicine is to prevent chemotaxis of neutrophils [11]. Moreover the anti-apoptosis effect of colchicine also has been shown [12]. In this study we used dapsone in FMF children. Dapsone is an old and famous antibacterial drug, but it has some anti-inflammatory effect [22-24], in some aspects these effects are similar to the colchicine effect in FMF. Dapsone inhibits beta2 integrin (CD11b/CD18)-mediated adherence of human neutrophils, interferes with the activation or function of the G-protein (Gi type) that initiates the signal transduction cascade common to chemo-tactic stimuli, inhibits the generation of second messengers essential to the activation of beta2 integrin molecules as well as respiratory and secretory functions of neutrophils exposed to chemoattractants [24]. In five patients we did not see FMF attacks during at least six months (mean, 8 months and 6 days) of observation. Certainly it relates to anti-inflammatory effect of dapsone, which, compared with colchicine efficacy of 80%[11], is not very high, but having 50% response, and because of similar action on immune response, it may be useful as an alternative therapy in some, especially colchicine resistant patients. We did not see any side effects of dapsone, and it has been well tolerated in children. MEFV gene analysis in these patients may be helpful and may give more information about the mutations which respond to dapsone, although it was not the scope of our study.

In the review of literature we did not find a similar study, and to our best knowledge, this seems to be the first experience on dapsone treatment of FMF particularly in children.

A limitation of this study is the lack of MEFV gene analysis. Another limitation is the short duration of the study caused by lack of long-term availability of the drug.

Conclusion

It seems that dapsone might be considered as an alternative therapy in FMF non-responding to colchicine patients.

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Conflict of Interest: There is no any conflict of interest in this study and publishing of it.

References

1. Tunca M, Akar S, Onen F, et al. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine (Baltimore) 2005; 84(1):1-11.
2. Lidar M, Livneh A. Familial Mediterranean fever: clinical, molecular and management advancements. Neth J Med. 2007; 65(9):318-24.
3. Tunca M, Akar S, Soytürk M, et al. The effect of interferon alpha administration on acute attacks of familial Mediterranean fever: A double-blind, placebo-controlled trial. Clin Exp Rheumatol 2004;22(4 Suppl 34):S37-40.
4. Lidar M, Kedem R, Langevitz P, et al. Intravenous colchicine for treatment of patients with familial Mediterranean fever unresponsive to oral colchicine. J Rheumatol 2003;30(12):2620-3.
5. Mor A, Pillinger MH, Kishimoto M, et al. Familial Mediterranean fever successfully treated with etanercept. J Clin Rheumatol 2007;13(1):38-40.
6. Ozgocmen S, Ozczakar L, Ardigoglu O, et al. Familial Mediterranean fever responds well to infliximab: single case experience. Clin Exp Rheumatol 2006;25(1):83-7.
7. Sakallioğlu O, Duzova A, Ozen S. Etanercept in the treatment of arthritis in a patient with familial Mediterranean fever. Clin Exp Rheumatol 2006;24(4):435-7.
8. Seyahi E, Ozdogan H, Celik S, et al. Treatment options in colchicine resistant familial Mediterranean fever patients: Thalidomide and etanercept as adjunctive agents. Clin Exp Rheumatol 2006;24(Suppl 42):S99-103.
9. Tunca M, Tankurt E, Akbaylar Akpınar H, et al. The efficacy of interferon alpha on colchicine-resistant familial Mediterranean fever attacks: a pilot study. Br J Rheumatol 1997;36(9):1005-8.
10. Matzner Y, Abedat S, Shapiro E, et al. Expression of the familial Mediterranean fever gene and activity of the CSa inhibitor in human primary fibroblast cultures. Blood 2000;96(2):727-31.
11. Cerquaglia M, Diaco G, Nucera M, et al. Pharmacological and clinical basis of treatment of familial Mediterranean fever (FMF) with
1. Colchicine or analogues: an update. Current drug targets. *Inflammation & Allergy* 2005; 4:117-24.

2. The effect of colchicine on apoptosis of neutrophils from healthy donors & patients with familial Mediterranean fever. www.rheumatology.org.il/2004oral.pdf

3. Shepard CC. Leprosy today. *N Engl J Med* 1982; 307(26):1640-1.

4. Chiodini PL. The chemoprophylaxis of malaria. *J Antimicrob Chemother* 1987;20(3):297-302.

5. Hughes WT, Smith BL. Efficacy of dexamethasone and other drugs in murine pneumocystis carinii pneumonia. *Antimicrob Agents Chemother* 1984;26(4):436-40.

6. Bernstein J, Lorincz A. Sulfonamides and sulfones in dermatologic therapy. *Int J Dermatol* 1981; 20(2):81-8.

7. Vancine-Califani SM, De Paula EV, Ozelo MC, et al. Efficacy and safety of dapsone as a second-line treatment in non-splenectomized adults with immune thrombocytopenic purpura. *Platelets* 2008;19(7):489-95.

8. Sunderkötter C, de Groot K. Therapy of vasculitides and vasculopathies. *Hautarzt* 2008; 59(5):382-93.

9. Smith LC, Cox NH. Dapsone treatment for eosinophilic fasciitis. *Arch Dermatol* 2008; 144(7):845-7.

10. Diaz-Ruiz A, Zavala C, Montes S, et al. Antioxidant, antiinflammatory and antiapoptotic effects of dapsone in a model of brain ischemia/reperfusion in rats. *J Neurosci Res* 2008; 86(15):3410-9.

11. Ludgate MW, Greig DE. Bullous systemic lupus erythematosus responding to dapsone. *Austral J Dermatol* 2008;49(2):91-3.

12. Williams K, Capstick RB, Lewis DA, et al. Antiinflammatory actions of dapsone and its related biochemistry. *J Pharm Pharmacol* 1976;28(7):555-8.

13. Booth SA, Moody CE, Dahl MV, et al. Dapsone suppresses integrin-mediated neutrophil adherence function. *J Invest Dermatol* 1992; 98(2):135-40.

14. Debol SM, Herron MJ, Nelson RD. Anti-inflammatory action of dapsone: inhibition of neutrophil adherence is associated with inhibition of chemoattractant-induced signal transduction. *J Leukoc Biol* 1997;62(6):827-36.

15. Touitou I, Koné-Paut I. Best practice and research. *Clinical Rheumatology* 2008;22(5):811–29.

16. Lidar M, Livneh A. Familial Mediterranean fever: clinical, molecular and management advancements. *Netherland J Med* 2007; 65(9):318-24.