Selective Serotonin Reuptake Inhibitors Reduce the Attack Frequency in Familial Mediterranean Fever

AHMET MESUT ONAT,1 MEHMET AKIF ÖZTÜRK,2 LEVENT ÖZCAKAR,3 KEMAL ÜREten,4 SEMRA ULUSOY KAYMAK,5 SEDAT KIRAZ,6 İHSAN ERTENLI6 and MERAL ÇALGÜNERI6

1Department of Rheumatology, Gaziantep University Hospitals, Gaziantep, Turkey
2Department of Rheumatology, Gazi University Hospitals, Ankara, Turkey
3Department of Physical Medicine and Rehabilitation, Hacettepe University Hospitals, Ankara, Turkey
4Department of Rheumatology, Etilik Social Security Hospital, Ankara, Turkey
5Department of Psychiatry, Hacettepe University Hospitals, Ankara, Turkey
6Department of Rheumatology, Hacettepe University Hospitals, Ankara, Turkey


Familial Mediterranean Fever (FMF) is characterized by recurrent acute attacks of fever and serositis, and colchicine is the primary treatment. The pathogenesis of the disease has not been fully understood. Resistance to colchicine remains to be a problem in up to 30% of the patients and yet there seems to be no alternative treatment. In this study our objective was to investigate whether a selective serotonin re-uptake inhibitor (SSRI) could affect the attack frequency and acute phase response in FMF patients who were unresponsive to colchicine. We retrospectively evaluated the hospital files of 11 colchicine-unresponsive FMF patients who had been treated with SSRIs. According to the records and re-evaluation of the patients, the total number of the FMF attacks was calculated before and after the SSRI, adjunct to colchicine. The laboratory values including erythrocyte sedimentation rate, C-reactive protein, fibrinogen and white blood cell counts were also noted before and after the SSRI treatment from their hospital files. The mean attack frequency before adding SSRI to colchicine was 8.09 ± 3.53 per 6 months, and at the end of this period there was a great decline in the number of mean attack frequency (0.36 ± 0.50 attacks per 6 months) (p < 0.001). Acute phase reactants were significantly decreased after SSRI treatment (p < 0.001). All of the colchicine-unresponsive patients had depression and 3 of those patients also had fibromyalgia. SSRIs appear to be useful adjuncts in the management of FMF patients who continue to have attacks despite regular colchicine treatment.

FMF; SSRI; colchicine resistance; depression; fibromyalgia

© 2007 Tohoku University Medical Press

Received September 25, 2006; revision accepted for publication November 7, 2006.
Correspondence: Ahmet Mesut Onat, Güvenevler mh, 26. cd, 57. sk, Baharkent sitesi, Mavi C 11/1, Sahinbey, Gaziantep, Turkey.
  e-mail: mesutonat@yahoo.com
Familial Mediterranean Fever (FMF) is an autosomal recessive disease characterized by recurrent acute attacks of fever, peritonitis, pleuritis, arthritis and rarely skin involvement. Acute phase response and inflammatory mediators are typically increased in these symptomatic periods that usually end within 2-4 days and are decreased in attack free intervals. However those mediators can remain higher than normal values between attacks and there is an ongoing inflammation in the asymptomatic periods (Kiraz et al. 1998; Bagci et al. 2004; Haznedaroglu et al. 2005).

Identification of the Mediterranean Fever (MEFV) gene mutations has provided great understanding for the pathogenesis of FMF. These mutations cause defects in pyrin end product, which plays key roles in apoptosis, fever and inflammation, and leads to an exaggerated response of the immune system (Richards et al. 2001). But it is still not clear what triggers the disease activity or what ends it.

Regular colchicine treatment is effective in most of the patients (65%) for controlling the attacks completely. On the other hand 20-30% of FMF patients have partial resistance and 10% of the patients have complete resistance to colchicine (Ben-Chetrit and Levy 1998; Drenth and Van Der Meer 2001). Different agents have been tried in those non-responders for controlling the burden of the disease. Tunca et al. (2004) showed some beneficial effects of interferon alpha (IFN-α) when given in the first hours of an attack. Calguneri et al. (2004) used IFN-α 2-3 times a week regularly and demonstrated a definite decline in the attacks of the colchicine resistant group. However, the patients had additional diseases including spondylitis and/or vasculitis. In a recent study Ozdogan et al. (2006) used thalidomide and etanercept in five colchicine-resistant FMF patients. There are also limited data regarding infliximab (Ozgocmen et al. 2006) and azathioprine (Sayarlioglu et al. 2006). Important limitations for the use of the above mentioned alternative agents could be the treatment cost and potential side effects. Hence colchicine unresponsiveness is still an important issue; safer and cheaper alternatives in those patients are awaited.

In clinical practice it is a common observation that FMF patients may have uncontrolled attacks especially when they come across with intensive distress, cold or fatigue. Besides, depression may be important for FMF patients to control their disease activity. However, there are no data available in this regard. We noticed are our clinic that one of our FMF patients, who had been diagnosed according to the Tel-Hashomer criteria (Livneh et al. 1997), had no FMF attack for one year without using colchicine but only paroxetine, a selective serotonin re-uptake inhibitor (SSRI) (Ozcakar et al. 2005). Before paroxetine the patient had had 4-5 attacks per month despite regular 2 g/day colchicine. We hypothesized that the depression might have triggered the attacks, and with the treatment of the depression attacks were suppressed.

In this study, we therefore tried to find out whether SSRIs did affect the attack frequency and acute phase response in FMF patients who have been resistant to colchicine.

**MATERIALS AND METHODS**

The hospital files of the patients with FMF were retrospectively evaluated. We found 11 colchicine-resistant FMF patients who had been treated with SSRIs (Table 1). All of the patients were female (mean age: 31 ± 10.3 years) with uncontrolled recurrent fever, serositis or arthritis attacks despite regular and maximum tolerated dosage of colchicine treatment for more than 6 months. They had no concomitant systemic inflammatory disorders. Mean duration of the disease was 125.54 ± 53 months, and the mean duration of medical care was 47.1 ± 34.31 months. All patients fulfilled the Tel-Hashomer diagnostic criteria for FMF (Livneh et al. 1997) and they were also taking colchicine 1-2.5 mg/day. They had no concomitant systemic inflammatory disorders. Mean duration of the disease was 125.54 ± 53 months, and the mean duration of medical care was 47.1 ± 34.31 months. All patients fulfilled the Tel-Hashomer diagnostic criteria for FMF (Livneh et al. 1997) and they were also taking colchicine 1-2.5 mg/day. The total number of the FMF attacks was recorded according to the patients’ reports before and after the SSRI treatment, adjunct to colchicine (Table 1). Blood samples were not taken during attack. The attack frequencies were re-evaluated by phone calls for each patient and corrected with re-examinations in the clinic. The laboratory values including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen and white blood cell counts were also noted before and after the SSRI treatment from their hospital files. Eight of those patients were diagnosed as having depression in the psy-
A.M. Onat et al.

SSRIs in FMF

A psychiatry department according to DSM-IV criteria (American Psychiatric Association 1994) and they were treated by the psychiatrists with appropriate antidepressants (4 of them with paroxetine and 4 of them with fluoxetine). Three patients were diagnosed as fibromyalgia (FM) in our rheumatology clinic according to the American College of Rheumatology (Wolfe et al. 1990) and were treated with SSRIs (two of them with paroxetine and one of them with fluoxetine). There was no medical history of depression for the 3 patients with FM in their hospital files. However, psychiatric examinations were done after re-evaluation of the patients and they were also diagnosed to have depression and kept on with SSRI.

Statistical evaluations

Wilcoxon and paired t-tests were used to analyze the data. A p value < 0.05 was considered statistically significant.

RESULTS

All of the patients had febrile abdominal attacks (100%), 4 had pleuritic chest pain (36%) and two had arthritis (18%) before SSRI treatment. Two of the patients had severe diarrhea (patients 1 and 4) with higher than 1.5 mg colchicine and one of the patients (patient 3) could have not tolerated the higher than 1 mg/day because of leukopenia and also severe diarrhea. After SSRI, they could have tolerated 1.5 mg/day colchicine without any problem. Their mean attack frequency before adding SSRI to colchicine was 8.09 ± 3.53 per 6 months. At the end of the six months there was a great decline in mean attack frequency (0.36 ± 0.50 attacks per 6 months [p < 0.001] [Table 1]). No patient suffered from a side effect of paroxetine or fluoxetine and they all continued to colchicine treatment. The type of the attacks did not change. The patients who were suffering from diarrhea had no ongoing symptoms after SSRIs, despite using the same colchicine dosage.

We compared the differences of acute phase response before and after SSRI addition to colchicine. ESR, CRP and fibrinogen levels were significantly decreased after six months of SSRIs. ESR, CRP and fibrinogen levels were 69.36 ± 9.31 mm/hr, 7.80 ± 5.50 g/dl, and 588.54 ± 55.21 mg/dl, respectively before SSRI, and were 18.8 ± 5.3 mm/hr, 0.66 ± 0.49 g/dl, and 293.90 ± 89.12 mg/dl, respectively after SSRI (p < 0.001 for each comparison) (Table 2). The difference for leukocyte counts was not significant (p > 0.05).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Disease duration (years)</th>
<th>Colchicine dosage (mg/day)</th>
<th>Attack features</th>
<th>Prescribed SSRI</th>
<th>SSRI indication</th>
<th>Attack frequency /month (before SSRI)</th>
<th>Total number of attacks for 6 months (before SSRI)</th>
<th>Attack frequency /6 months (after SSRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>23</td>
<td>1-1.5</td>
<td>1,2,3</td>
<td>Paroxetine</td>
<td>Depression</td>
<td>3</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>6</td>
<td>2</td>
<td>1,3,4</td>
<td>Paroxetine</td>
<td>Fibromyalgia</td>
<td>1</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>13</td>
<td>1</td>
<td>1,2</td>
<td>Fluoxetine</td>
<td>Fibromyalgia</td>
<td>1-2</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>7</td>
<td>1-1.5</td>
<td>1,2,3</td>
<td>Paroxetine</td>
<td>Depression</td>
<td>2</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>5</td>
<td>2</td>
<td>1,3,4</td>
<td>Fluoxetine</td>
<td>Depression</td>
<td>1-2</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>4</td>
<td>1.5</td>
<td>1,3</td>
<td>Fluoxetine</td>
<td>Depression</td>
<td>1</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>5</td>
<td>2.5</td>
<td>1,2,3</td>
<td>Fluoxetine</td>
<td>Depression</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>46</td>
<td>22</td>
<td>1.5</td>
<td>1,3</td>
<td>Paroxetine</td>
<td>Fibromyalgia</td>
<td>1</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>26</td>
<td>7</td>
<td>2</td>
<td>1,3</td>
<td>Paroxetine</td>
<td>Depression</td>
<td>1-2</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>37</td>
<td>16</td>
<td>1.5</td>
<td>1,3</td>
<td>Paroxetine</td>
<td>Depression</td>
<td>1</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>31</td>
<td>8</td>
<td>1.5</td>
<td>1,3</td>
<td>Fluoxetine</td>
<td>Depression</td>
<td>1</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1. Clinical features of FMF patients unresponsive to colchicine.

DISCUSSION

In this study we demonstrated that adding a SSRI to colchicine significantly decreased the number of acute attacks in colchicine resistant FMF patients in their six-month follow-up and this result was in accordance with our previous observation (Ozcakar et al. 2005). Moreover, acute phase reactants of those patients significantly improved after SSRIs. Interestingly all of the 11 patients had the diagnosis of depression and three of them also had FM.

We know today that there is some evidence for the cytokine network which is activated in depression (Leonard 2001) and that cytokines also play important roles in the pathogenesis of depressive disorders (Maes 1999; Pollak and Yirmiya 2002). Treatment with antidepressants such as SSRIs reduces the pro-inflammatory cytokine levels, on the contrary they increase the anti-inflammatory ones (Kubera et al. 2001). Stressors (environmental factors, diminished self-care) are also known to be potent antecedents of depression, and such events may also promote elevated cytokine levels (Kubera and Maes 2000). In daily practice FMF patients are sensitive to such stressors and in these conditions they might be prone to attacks. All of our patients were treated with SSRIs because of their depression/FM and we hypothesized that their environmental stressors and depression might have activated the inflammatory cytokine network additionally.

The data which suggest that antidepressants may attenuate cytokine-induced depressive symptoms by exerting negative immunoregulatory effects are limited. Some in vitro studies with human whole blood have reported that SSRIs are able to inhibit the production of pro-inflammatory cytokines (IL-1, IL-2, IL-6) while stimulating the negative immunoregulatory cytokine IL-10 (Kubera et al. 2000, 2001). However the efficacy of antidepressant treatment may also reflect indirect immunomodulatory effects rather than a direct down-regulation of inflammatory cytokine activation which occurred during depression (Schepers et al. 2005). All of our patients used these SSRIs for depression. On the other hand 3 had also FM. SSRI treatment significantly decreased the symptoms in both subgroups. Therefore we concluded that the SSRIs might have beneficial effects on the inflammatory process in FMF. Moreover, the acute phase reactants (ESR, CRP, fibrinogen) of our patients were elevated even in the attack-free periods, supporting previous observations of ongoing subclinical disease activity in FMF between acute attacks (Bagci et al. 2004; Haznedaroglu et al. 2005) and in keeping with our hypothesis, all those markers significantly improved after SSRI addition. Besides the acute phase response of the patients were too high for symptom free intervals of FMF and should be reduced to normal values in attack free periods. We concluded that either the patients might have suffered more frequent attacks than they had pronounced or the samples had been obtained in acute attacks despite the files and/or patient reports.

Lidar et al. (2004) demonstrated that mononuclear cell colchicine concentrations in FMF patients, who responded well to this drug were 2 fold higher than colchicine concentrations in the mononuclear cells of nonresponders. Adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1) is a cellular efflux transporter and extrudes a variety of drugs including colchicine out of cells (Kim 2002). This protein is expressed

| Laboratory findings of the patients before adding SSRI to colchicine and after 6 months. |
|---------------------------------------------|----------------|----------------|
|                | Before SSRI  | On the 6 month’s control | p value   |
| ESR (mm/1 hr)  | 69.36 ± 9.31 | 18.8 ± 5.3                | < 0.001      |
| CRP (g/dl)     | 7.80 ± 5.50  | 0.66 ± 0.49                | < 0.001      |
| Fibrinogen (mg/dl) | 588.54 ± 55.21 | 293.90 ± 89.12 | < 0.001 |
| WBC (10⁶/μl)   | 7,463.63 ± 3,262.29 | 6,336.36 ± 1,546.13 | > 0.05 |
on mononuclear cell surface. Therefore, the amount of ABCB1 expressed on mononuclear cells might alter colchicine response in FMF patients. ABCB1 gene 3435CT polymorphism has been demonstrated to alter ABCB1 expression in mononuclear cells. Recent data suggest that FMF patients with 3435TT genotype had better response to colchicine treatment both in terms of clinical efficacy and colchicine dose requirements (Tufan et al. 2006). Paroxetine and fluoxetine can inhibit the ABCB1 function (Marzolini et al. 2004; Balayssac et al. 2005), therefore an alternative hypothesis to explain our results would be the inhibition of ABCB1 which in turn increases intracellular concentrations of colchicine after SSRI treatment.

It is difficult to explain such a clear difference in the mean attack frequency after six months of adding SSRI to colchicine in FMF. Until today there are no data in the literature about the incidence of depression in FMF patients. Depression might be aggravating the disease activity and as it is treated, FMF attack frequency may be decreasing. Besides, SSRIs may be exerting yet uncovered effects in FMF through serotonin (5-HT). Toubi et al. (2003) reported increased serum 5-HT during FMF attacks despite regular colchicine. We also advocate that depression should reasonably be evaluated in patients who are resistant to colchicine therapy. The major limitation of our study is the retrospective design and the limited number of subjects. Hence further prospective studies with larger number of patients are warranted and whether different SSRIs have similar effects on FMF attacks remains to be clarified. Better management of colchicine-resistant FMF patients could then be launched with alternative drugs.

References


