Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Clinical Research

J. Exp. Clin. Med., 2021; 38(1): 27-31
doi: 10.5835/jecm.omu.38.01.006

The experience of interleukin-1 inhibition in patients with familial Mediterranean fever

Demet Yalcin Kehribar[a*], **Metin Ozgen**[b]

[a] *Department of Internal Medicine, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey*
[b] *Department of Rheumatology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey*

ARTICLE INFO

Article History
Received 07 / 09 / 2020
Accepted 25 / 09 / 2020
Online Published 26 / 01 / 2021

*** Correspondence to:**
Demet Yalçın Kehribar
Department of Internal Medicine,
Faculty of Medicine,
Ondokuz Mayıs University,
Samsun, Turkey
e-mail: kehribardemet@gmail.com

Keywords:
Anakinra
Canakinumab
Familial mediterranean fever
Interleukin-1 inhibition

ABSTRACT

This study aimed to present our single-center experience of anakinra and canakinumab treatment in patients with Familial Mediterranean fever (FMF). This study included 48 patients who were treated with anti-interleukin-1 (anti-IL-1) treatment for at least six months. Initially, all patients with colchicine-resistant or intolerant FMF were received anakinra treatment. Then those resistant to anakinra were given canakinumab treatment. Of the 48 (female/male:29/19) patients using anti-IL-1, their age was 31.2 ± 10.7 years, the duration of drug use was 15±8 months. 30 patients were already using anakinra and 18 patients were using canakinumab. Treatment was found to be switched to canakinumab in 9 patients due to non-adherence to daily injection, and inadequate response to anakinra in 9 patients. After the anti-IL-1 treatment the number of attacks, erythrocyte sedimentation rate, C-reactive protein, fibrinogen levels, colchicine dose and proteinuria (for all $p<0.001$) were decreased. Anti-IL-1 treatment is effective for controlling attacks and reducing proteinuria in patients with colchicine-resistant or intolerant FMF. In addition, canakinumab appears to be an alternative treatment option when there is a inconvenience to daily injection or resistance to anakinra treatment.

1. Introduction

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease - mainly prevalent in Eastern Mediterranean descents (i.e. Turks, Armenians, Arabs and Jews). It is characterized by recurrent fever and inflammation of the serosal membranes (Sari et al., 2014; Petrushkin et al., 2016). The attacks are self-limiting and terminate spontaneously within 1-5 days (Sohar et al., 1967).

The MEFV gene, which is responsible for the pathogenesis of the disease, encodes a protein called pyrin-an element of the NLRP3 inflamasom complex (The French FMF Consortium, 1997; Abderrazak et al., 2015). Inflammasomes are molecular platforms responsible for caspase-1 activation. The caspase-1 enzyme converts pro-interleukine (IL)-1 to IL-1 (Papin et al., 2007; Franchi et al., 2009). The mutated pyrin causes the overexpression of IL-1β and consequently leads to inflammation and increase of serum amyloid A (SAA) which is responsible for amyloidosis (Bozkurt et al., 2015).

Colchicine, which is considered as revolutionary and started being used in 1972 in the treatment of patients with FMF, reduces attacks, improves the quality of life and prevents amyloidosis. It is the first option of treatment that should be started once the

clinical diagnosis is made (Cronstein and Terkeltaub, 2006; Nuki, 2008).

While complete remission was achieved in 60-65% of the patients under the treatment of colchicine, 30-35% had a partial response, and 5-10% did not respond at all. 2-5% of the patients cannot use colchicine due to side effects such as diarrhea and hepatotoxicity (TerHaar et al., 2013).

In recent years, FMF patients with resistance or intolerance to treatment with colchicine have been reported to give very good clinical and biochemical responses when they were given treatments of anakinra (recombinant human IL-1 antagonist), canakinumab (human anti-IL-1 beta monoklonal antibody), rilonacept (a receptor fusion protein acting as IL-1 decoy receptor) many patients with FMF have been reported to have given very good clinical and biochemical responses (Van der Hilst et al., 2005; Ozen et al., 2011; Akar et al., 2015; Kucuksahin et al., 2017). We thought that our treatment experience of using anti-IL-1 agents in our FMF patients can potentially contribute the literature.

2. Materials and methods

All the patients, diagnosed with FMF between 1 February 2013 and 31 December 2018 at our rheumatology department, were included in the study. The patients were retrospectively screened. This study protocol was approved by the institutional Ethics Committee, and all the participants gave an informed consent before enrolling in the study.

This retrospective study included 48 FMF patients who can not tolerate treatment with high-dose colchicine (1.5-3.0 mg/day) and in those with uncontrolled FMF attacks, treatment of anti-IL-1 was started. In our country, anakinra and canakinumab treatments are given off-label with the permission of the Ministry of Health who permits anakinra treatment first. Therefore, anakinra 100 mg daily injection treatment was administered as the first choice of treatment.

48 out of the total 338 patients with FMF were treated with anti-IL-1 treatment. Data for a total of 48 patients were retrospectively evaluated and included the following: 1. ID information, age and gender 2. Age of onset of symptoms 3. Age at diagnosis 4. History of additional disease (hypertension, diabetes mellitus, cardiovascular diseases, chronic renal failure) 5. Family history in terms of FMF and amyloidosis 6. Patient symptom and clinic (fever, peritonitis, pleuritis, pericarditis, arthritis, myalgia, amyloidosis, erysipelas like skin rash, vasculitis) 7. Dose of colchicine used before and after treatment with anti-IL-1 treatment 8. Gene analysis 9. Laboratory values (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, proteinuria) 10. Reason for switching to anti-IL-1 treatment 11. Duration of use of anti-IL-1 treatment 12. Number of attacks before and after treatment and 13. Reasons for switching from anakinra to canakinumab 14. Screening for tuberculosis, hepatit B and C, malignancy.

The statistical method used: Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 11.0, Chicago, IL, USA). Results were given as mean ± standard deviation. Statistical differences among the groups were identified with paired-7 test. Chi-squared test was used to compare categorical variables. P values less than 0.05 were considered as significant.

Computer tomography (CT) of the pelvis showed an enlarged prostate with protrusion bladder posterior to the submucosal area. The chest CT showed diffuse lung emphysematous micro bullae. There was no bone metastasis in whole body bone scintigraphy. Other biochemical parameters were normal.

Chemotherapy and radiotherapy were planned. The daily radiotherapy dose was 1.8 Gy and the total dose was 63 Gy. In total, 35 fractions were given. Six chemotherapy cycles (carboplatin, 450 mg/AUC 5) were also administered every 21 days concomitantly and consequently to radiotherapy. The patient was asymptomatic 8 months after treatment. He died 13 months after initial diagnosis because of the metastatic lesions.

3. Results

In 48 out of 338 FMF patients, anakinra treatment was initiated because of inadequate response to colchicine in 24 patients, colchicine triggered elevated liver function test in seven patients, colchicine related diarrhea in three patients, and amyloidosis in 14 patients. Having received anakinra treatment (100 mg/day), with 18 patients (out of 48) it is switched to canakinumab treatment (150 mg/ month) due to insufficient response observed in nine patients and inconvenience to daily injection observed in another nine patients. Treatment with colchicine was also continued in patients who received anti-IL-1 treatment (Zemer et al., 1986; Ozen et al., 2016).

Patients who received anti-IL-1 treatment for at least six months were included in the study. The mean duration of drug use was 15 ± 8 months. All the patients treated with canakinumab neither had any side effect that required to terminate the treatment, nor remained non-responsive to the treatment. Anakinra treatment was discontinued for a short period of time in two of the patients because of allergic skin rash in one patient and streptococcal pneumonia in another patient. No further complication was observed in the follow-up of these patients and the treatment was continued successfully. None of the patients had malignancy in the follow-up period. The demographic and some clinical data of the patients were shown in Table 1. The laboratory values of the patients before and after anti-IL-1 treatment

are were shown in Table 2. When the gene analysis was investigated in 48 patients with whom anti-IL-1 treatment was initiated, 31 (64.5%) patients were M694V homozygous, 5 (10.4%) were compound heterozygous (M694V heterozygous M680I heterozygous) and M694V heterozygous mutation was detected in 5 (10.4%) patients. In addition, two patients were M694I heterozygous, two patients were M680I heterozygous, two patients were V726I heterozygous and one patient was compound heterozygous (M694I heterozygous M680I heterozygous). When the gene analyzes of the patients with amyloidosis were examined, 11 (78.5%) were found to be M694V homozygous, one (7.14%) patient was M694V heterozygote. Additionally, two (14.3%) M694V homozygote + M680I heterozygote mutation were detected. The number of attacks was 5.7 ± 1.2/six months before in the 30 patients receiving anakinra treatment and the number of attacks after anakinra treatment was 1.3 ± 0.6/six months ($p<0.001$), anakinra treatment provided complete remission in 24 patients. The number of attacks before treatment of 18 patients treated with canakinumab was 4.9 ± 0.9/six months, and the number of attacks after treatment was 1.1 ± 0.3/six months ($p<0.001$), canakinumab treatment provided complete remission in 16 patients.

Table 1. Demographic and clinical characteristics of patients with FMF included in the study.

Age	31.2 ± 10.7
Female	29 (60.4%)
Male	19 (39.6%)
Age at onset of symptom	13.4 ± 9.7
Age at diagnosis	19.9 ± 13.4
Additional diseases	16/48 (33.3%)
Family history	28/48 (58.3%)
Fever	45/48 (93.7%)
Peritonitis	45/48 (93.7%)
Pericarditis	1/48 (2.1%)
Pleuritis	24/48 (50%)
Arthritis	37/48 (77.1%)
Myalgia	24/48 (50%)
Erysipelas like rash	12/48 (25%)
Amyloidosis	14/48 (29.1%)
Vasculitis	1/48 (2.1%)

Table 2. Before and after the anti-IL-1 treatment.

	Before Anti IL-1 Treatment	After Anti IL-1 Treatment	P value
ESR (mm/h)	30.9 ± 22.4	15.8 ± 8.4	<0.001
CRP (mg/L)	22.9 ± 12.4	3.3 ± 3.9	<0.001
Fibrinogen (g/L)	5.4 ± 1.6	2.2 ± 0.9	<0.001
Proteinuria (mg/day)	69.7 ± 146.8	18.1 ± 39.1	<0.001
Attack Frequency (/six months)	5.4 ± 1.1	1.2 ± 0.5	<0.001
Colchicine Dose (mg/day)	1.8 ± 0.3	1.5 ± 0.5	<0.001

IL-1; Interleukin-1, ESR; Erythrocyte sedimentation rate, CRP; C-reactive protein

4. Discussion

The importance of this study is that the anti-IL-1 treatment is isvestigated with such high numbers of patients, yet without multiple-centers. In other words, we have carried this study out in a single center which effectively provides more homogeneity. Regarding the result of our study, it verifies the results of previous studies indicating that when the anti-IL-1 agents are used regularly, they provide remission by significantly decreasing the number of attack episodes in colchicine resistant or intolerant FMF patients (Hilst et al., 2016; Akar et al., 2018).

In a systemic review published by Van der Hilst et al., complete remission was achieved in 76.5% of patients treated with anakinra and in 67.5% of patients treated with canakinumab (Van der Hilst et al., 2016) In 2017, the data obtained by Akar et al., have shown a remission of 40% and 65%, respectively (Akar et al., 2018). In our country, anakinra and canakinumab treatments are used off-label with the permission of the Ministry of Health. Anakinra treatment is preferred for the transition to anti-IL-1 treatment because of the lower cost, and then canakinumab treatment is started in case of insufficient response to anakinra treatment or inconvenience to daily injection It has been considered that canakinumab maybe more effective than anakinra with a longer half-life, canakinumab can block IL-1 action for a longer time and it has higher patient compliance. In this respect, the comparison of the response rates of these two treatments in our study would not be appropriate. Of those 48 patients who were already under anti-IL-1 treatment, 30 are receiving anakinra treatment. While %80 of patients receiving anakinra treatment had complete remission, the remaining %20 has still experienced FMF attacks. However, it should be recalled that nine patients using anakinra underwent canakinumab treatment due to treatment failure. Current status in terms of treatment with canakinumab, 16 patients out of 18 patients had complete remission, and two patients had one episode in three months. The success rate of remission achieved in patients using canakinumab was 88.8%, supporting the view that the treatment efficacy increases as a result of high compliance to treatment and stable plasma concentration. In conclusion, canakinumab treatment is considered to be an effective alternative treatment for patients who do not comply or respond to anakinra treatment.

In our study, when the gene analysis of the patients who could not achieve remission with anti-IL-1 treatment was investigated, of the six patients who could not be remedied with anakinra, five of them were M694V homozygous, one was M694V heterozygote and according to the gene analysis of nine patients who were treated with canakinumab due to anakinra resistance, five patient were M694V homozygote, three

patients were M694V heterozygote one was M694V heterozygote.

Homozygosity for the M694V mutation is generally thought to be associated with a more severe FMF phenotype (Cazeneuve et al., 2000), as well as with amyloidosis and colchicine resistance (Soylemezoglu et al., 2010). In a study conducted by Küçükşahin et al (Kucuksahin et al., 2017) the non-responsiveness to anti-IL-1 treatment was connected to presence of additional chronic multiple diseases in patients. In our study, there was no relationship between additional chronic disease and treatment non-responsiveness. In our country, Turkey, anakinra and canakinumab treatments are used off-label. There are occasional difficulties in patient's access, and the attacks are usually seen when patients cannot get regular treatment.

The results of our study support the results of other studies (Urieli-Shoval et al., 2000; Hilst et al., 2005; Chae et al., 2009; Stankovic et al., 2012; Kucuksahin et al., 2017; Ozdogan and Ugurlu, 2017) reporting that anti-IL-1 treatment used in colchicine resistant FMF patients prevented FMF attacks and decreased proteinuria. In previous studies, colchicine resistance was reported as 30-35% (Cerquaglia et al., 2005; Seyahi et al., 2006). In our study, 48 (14.2%) out of 338 patients had anti-IL-1 treatment. The reason for such a difference, we think, is due to the patients who are considered resistant to the treatment of the colchicine but refused the transition to anti-IL-1 treatment.

This study has some limitations. There was a significant decrease in proteinuria in the follow-up of patients but we did not perform a biopsy to prove the regression of amyloidosis. In addition, serum amyloid A level could not be evaluated in our patients. Although anti-IL-1 treatment decreased the number of attacks and the acute phases in the follow-up of our patients, we did not standardize the effects of these drugs on quality of life by measuring with any scale. In fact, despite the fact that they did not report an attack, the patients with persistent elevation in their acute phase reported an increase in performance after anti-IL-1 treatment and stated that they no longer get tired easily. Evaluating what with the quality of life scale could have revealed this situation. Patients using anti-IL-1 treatment reported that they had difficulty in accessing drugs and were unable to use their medication at regular intervals and, therefore, experienced attacks. Since our patients were evaluated retrospectively, we could not determine the frequency of this condition. Therefore, when evaluating the data of patients with anti-IL-1 treatment, this situation should be taken into consideration.

As a result; anti-IL-1 treatment appear to be effective and safe in the treatment of patients who are resistant to the treatment of the colchicine and cannot tolerate the treatment of the colchicine. On the other hand, in patients resistant to anakinra treatment, canakinumab treatment controlled the attacks and achieved high treatment compliance in patients with inconvenience to daily injection. Anti-IL-1 treatment under an acceptable safety profile is an effective alternative not only to control exacerbations but also to reduce proteinuria in patients with colchicine-resistant FMF in routine clinical practice. In addition, canakinumab may be considered as a good alternative in case of resistance to anakinra treatment and non-compliance.

Acknowledgements:
The authors would like to thank Enago (www.enago.com) for English language review.

REFERENCES

Abderrazak, A., Syrovets, T., Couchie, D., El Hadri, K., Friguet, B., Simmet, T., Rouis, M., 2015. NLRP3 inflammasome: From a danger signal sensor to a regulatory node of oxidative stress and inflammatory diseases. Redox. Biol. 4, 296-307.

Akar, S., Cetin, P., Kalyoncu, U., Karadag, O., Sari, I., Cınar, M., Yilmaz, S., Onat A.M., Kisacik, B., Erden, A., Balkarli, A., Kucuksahin, O., Oner, S.Y., Senel, S., Tufan, A., Direskeneli, H., Oksuz, F., Pehlivan, Y., Bayindir, O., Keser, G., Aksu, K., Omma, A., Kasifoglu, T., Unal, A.U., Yildiz, F., Balci, M.A., Yavuz, S., Erten, S., Ozgen, M., Sayarlıoglu, M., Dogru, A., Yildirim, G., Oner, F.A., Tezcan, M.E., Pamuk, O.N., Onen, F., 2018. Nationwide experience with off-label use of interleukin-1 targeting treatment in familial mediterranean fever patients. Arthritis Care Res. 70, 1090-1094.

Bozkurt, Y., Demir, A., Erman, B., Gul, A., 2015. Unified modeling of familial Mediterranean fever and cryopyrin associated periodic syndromes. Comput. Math. Methods Med. 2015, 893507.

Cazeneuve, C., Ajrapetyan, H., Papin, S., Roudot-Thoraval, F., Genevieve, D., Mndjoyan, E., Papazian, M., Sarkisian, A., Babloyan, A., Boissier, B., Duquesnoy, P., Kouyoumdjian, J.C., Girodon-Boulandet, E., Grateau, G., Sarkisian, T., Amselem, S., 2000. Identification of MEFV-independent modifying genetic factors for familial Mediterranean fever. Am. J. Hum. Genet. 67, 1136-1143.

Cerquaglia, C., Diaco, M., Nucera, G., La Regina, M., Montalto, M., Manna, R., 2005. Pharmacological and clinical basis of treatment of familial Mediterranean fever (FMF) with colchicine or analogues: An update. Curr. Drug. Targets Inflamm. Allergy. 4, 117-124.

Chae, J.J., Aksentijevich, I., Kastner, D.L., 2009. Advances in the understanding of familial Mediterranean fever and possibilities for targeted treatment. Br. J. Haematol. 146, 467-478.

Cronstein, B.N., Terkeltaub, R., 2006. The inflammatory process of gout and its treatment. Arthritis Res. Ther. 8, S3.

Franchi, L., Eigenbröd, T., Munoz-Planillo, R., Nurez, G., 2009. The inflammasome; A caspase-1-activation platform that regulates immune response and disease pathogenesis. Nat. Immunol. 10, 241-247.

Kucuksahin, O., Yildizgoren, M.T., Ilgen, U., Ates, A., Kinikli, G., Turgay, M., Erten, S., 2017. Anti-interleukin-1 treatment in 26 patients with refractory familial Mediterranean fever. Mod. Rheumatol. 27, 350-355.

Nuki, G., 2008. Colchicine: its mechanism of action and efficacy in crystal-induced inflammation. Curr. Rheumatol. Rep. 10, 218-227.

Ozdogan, H., Ugurlu, S., 2017. Canakinumab for the treatment of familial Mediterranean fever. Expert. Rev. Clin. Immunol. 13, 393-404.

Ozen, S., Bilginer, Y., Aktay Ayaz, N., Calguneri, M., 2011. Anti-interleukin treatment for patients with familial Mediterranean fever resistant to colchicine. J. Rheumatol. 38, 516-518.

Ozen, S., Demirkaya, E., Erer, B., Livneh, A., Ben-Chetrit, E., Giancane, G., Ozdogan, H., Abu, I., Gattorno, M., Hawkins, P.N., Yuce, S., Kallinich, T., Bilginer, Y., Kastner, D., Carmona, L., 2016. EULAR recommendation for the management of familial Mediterranean fever. Ann. Rheum. Dis. 75, 644-651.

Papin, S., Cuenin, S., Agostini, L., Martinon, F., Werner, S., Beer, H.D., Grütter C., Grütter, M., Tschopp, J., 2007. The SPRY domain of pyrin, mutated in familial Mediterranean fever patients, interacts with inflammasome components and inhibits proIL-1 beta processing. Cell Death Differ. 14, 1457-1466.

Petrushkin, H., Stanford, M., Fortune, F., Jawad, A.S., 2016. Clinical review: Familial Mediterranean Fever-An overview of pathogenesis, symptoms, ocular Manifestations, and treatment. Ocul. Immunol. Inflamm. 24, 422-430.

Sari, I., Birlik, M., Kasifoğlu, T., 2014. Familial Mediterranean fever: An updated review. Eur. J. Rheumatol. 1, 21-33.

Seyahi, E., Ozdogan, H., Celik, S., Ugurlu, S., Yazici, H., 2006. Treatment options in colchicine resistant familial Mediterranean fever patients: Thalidomide and etanercept as adjunctive agents. Clin. Exp. Rheumatol. 24, 99-103.

Sohar, E., Gafni, J., Pras, M., Heller, H., 1967. Familial Mediterranean fever a survey of 470 cases and review of the literature. Am. J. Med. 43, 227-253.

Soylemezoglu, O., Arga, M., Fidan, K., Gonen, S., Emeksiz, H.C., Hasanoglu, E., Buyan, E., 2010. Unresponsiveness to colchicine treatment in patients with familial Mediterranean fever homozygous for the M694V mutation. J. Rheumatol. 37, 182-189.

Stankovic, S.K., Delmas, Y., Torres, P.U., Peltier, J., Pelle, G., Jéru, I., Colombat, M., Grateau, G., 2012. Dramatic beneficial effect of interleukin-1 inhibitor treatment in patients with familial Mediterranean fever complicated with amyloidosis and renal failure. Nephrol. Dial Transplant. 27, 1898-1901.

TerHaar, N., Lachmann, H., Özen, S., Woo, P., Uziel, Y., Modesto, C., Kone-Paut, I., Cantarini, L., Insalaco, A., Neven, B., Hofer, M., Rigante, D., Al-Mayouf, S., Touitou, I., Gallizzi, R., Papadopoulou-Alataki, E., Martino, S., Kuemmerle-Deschner, J., Obici, L., Iagaru, N., Simon, A., Nielsen, S., Martini, A., Ruperto, N., Gattorno, M., Frenkel, J., 2013. Treatment of autoinflammatory disease: Result from the euro fever registry and a literatüre review. Ann. Rheum. Dis. 72, 678-685.

The French FMF Consortium, 1997. A candidate gene for familial Mediterranean fever. Nat. Genet. 17, 25-31.

The International FMF Consortium. 1997. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. Cell. 90, 797-807.

Urieli-Shoval, S., Linke, R.P., Matzner, Y., 2000. Expression and function of serum amyloid A, a major acute phase protein, in normal and disease states. Curr. Opin. Hematol. 7, 64-69.

Van der Hilst, J.C., Simon, A., Drenth, J.P., 2005. Herediaty periodic fever and reactive amyloidosis. Clin. Exp. Med. 5, 87-98.

Zemer, D., Pras, M., Sohar, E., Modan, M., Cabili, S., Gafni, J., 1986. Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. N. Engl. J Med. 314, 1001-1005.