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ORIGINAL RESEARCH

Real-World Experience with Canakinumab in Familial Mediterranean Fever: A Single-Center Study

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ABSTRACT

Familial Mediterranean fever (FMF) is an autoinflammatory disorder caused by mutations in the Mediterranean fever gene (MEFV), leading to excessive interleukin-1 beta (IL-1β) production. While colchicine is the primary treatment for FMF, a subset of patients exhibits resistance or intolerance, necessitating alternative therapeutic strategies. Canakinumab, a selective IL-1β inhibitor, has emerged as a potential treatment option. This study aims to evaluate canakinumab's real-world efficacy and safety in colchicine-resistant or colchicine-intolerant FMF patients. A retrospective, single-center study was conducted on FMF patients aged over 18 who initiated canakinumab treatment between January 2013 and October 2023. A total of 34 patients experiencing colchicine resistance or intolerance criteria were analyzed. Clinical and laboratory parameters, including Pras scores, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A (SAA), were assessed before and after canakinumab treatment. Statistical analyses were performed using the Wilcoxon test and paired sample t-test. Canakinumab treatment significantly reduced Pras scores ($p<0.001$), ESR ($p<0.001$), CRP ($p<0.001$), and SAA levels ($p<0.001$). A decrease was observed post-treatment among patients with proteinuria, though not statistically significant ($p=0.140$). Treatment was discontinued in three patients due to active disease or adverse effects. No serious infections were reported. In conclusion, canakinumab could be a promising treatment option in colchicine-resistant or colchicine-intolerant FMF patients.

Keywords: Canakinumab. Colchicine. Familial Mediterranean fever.

Ailevi Akdeniz Ateşinde Kanakinumab ile Gerçek Yaşam Deneyimi: Tek Merkezli Bir Çalışma

ÖZET

Ailesel Akdeniz ateşi (AAA), Mediterranean Fever (MEFV) geninde mutasyonların neden olduğu ve aşırı interlökin-1 beta (IL-1β) üretimine yol açan otoinflamatuar bir hastalıktır. Kolşisin AAA için ana tedavi olsa da, hastaların bir alt grubu direnç veya intolerans göstererek alternatif tedavi stratejilerine ihtiyaç duymaktadır. Selektif bir IL-1β inhibitörü olan kanakinumab, potansiyel bir tedavi seçeneği olarak ortaya çıkmıştır. Bu çalışma, kolşisine dirençli veya kolşisine intoleransı olan AAA hastalarında kanakinumabın gerçek yaşamdaki etkinliğini ve güvenliğini değerlendirmeyi amaçlamaktadır. Ocak 2013 ve Ekim 2023 tarihleri arasında kanakinumab tedavisine başlayan 18 yaş üstü AAA hastalarında retrospektif, tek merkezli bir çalışmadır. Kolşisin direnci veya intoleransı kriterlerini karşılayan toplam 34 hasta analiz edildi. Pras skorları, eritrosit sedimantasyon hızı (ESR), C-reaktif protein (CRP) ve serum amiloid A (SAA) dahil olmak üzere klinik ve laboratuvar parametreleri kanakinumab tedavisinden önce ve sonra değerlendirilmiştir. İstatistiksel analizler Wilcoxon testi ve eşleştirilmiş örneklem t-testi kullanılarak gerçekleştirilmiştir. Kanakinumab tedavisi Pras skorlarını ($p<0,001$), ESR ($p<0,001$), CRP ($p<0,001$) ve SAA düzeylerini ($p<0,001$) anlamlı ölçüde azaltmıştır. Proteinürisi olan hastalarda tedavi sonrasında istatistiksel olarak anlamlı olmasa da bir düşüş gözlenmiştir ($p=0,140$). Aktif hastalık veya yan etkiler nedeniyle üç hastada tedavi kesilmiştir. Hiçbir ciddi enfeksiyon bildirilmemiştir. Sonuç olarak, kanakinumab kolşisine dirençli veya kolşisine intoleranslı AAA hastalarında umut verici bir tedavi seçeneği olabilir.

Anahtar Kelimeler: Kanakinumab. Kolşisin. Ailevi Akdeniz Ateşi.

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Familial Mediterranean fever (FMF) is an autoinflammatory disease with autosomal recessive inheritance.[1] It is characterized by fever and recurrent episodes of serositis, usually lasting 12-72 hours.[2] FMF treatment aims to reduce the frequency of clinical attacks and suppress subclinical inflammation.[3] Inadequate treatment can lead to secondary amyloidosis, which is associated with high morbidity and mortality.[4,5] The Mediterranean fever gene (MEFV) responsible for the disease is localized in the 16p13.3 region. The MEFV gene, which consists of ten exons and 781 amino acids, encodes the pyrin protein. Mutations in the MEFV gene disrupt pyrin function and, thus, lead to uncontrolled production of interleukin-1 beta (IL-1β).[6] IL-1β is the triggering cytokine for the onset of an FMF attack.

Colchicine, the primary treatment for FMF, is highly effective in controlling attacks and preventing the development of amyloidosis.[7] However, 5–10% of patients do not respond to or resist colchicine.[8] In addition, colchicine cannot be used at adequate doses in some patients due to side effects or intolerance.[9] IL-1 inhibition is a safe and effective treatment for FMF patients who do not respond to or are intolerant to colchicine.[10,11] The IL-1 inhibitors used in Türkiye are anakinra and canakinumab. Canakinumab is a human monoclonal antibody that selectively targets IL-1β.[12] The first case report of a colchicine-resistant FMF patient who responded to treatment with canakinumab was published in 2011.[13] Later, case series with short follow-ups and small sample sizes were reported on the use of canakinumab in FMF patients.[14-17] There is limited real-life data on canakinumab's long-term efficacy and safety in FMF patients.[18-21] Our study aimed to present our experience using canakinumab in FMF patients who are colchicine-resistant or colchicine-intolerant at a single center.

Material and Method

Study Population

In our center, patients over 18 years of age who initiated canakinumab treatment between January 2013 and October 2023 with a diagnosis of FMF according to the Tel-Hashomer[22] and New Eurofever/PRINTO classification criteria[23] were evaluated using the hospital's electronic system. There were 46 patients for whom canakinumab treatment was initiated with a diagnosis of FMF. Of these patients, 12 patients who had a follow-up time of fewer than 3 months, were not regularly followed up at our center, and had missing clinical data in the hospital's electronic system were excluded from the study. The number of patients enrolled in the study was 34; all enrolled patients were either colchicine-resistant or colchicine-intolerant. Colchicine resistance was defined as having at least one attack per month despite taking the maximum tolerated dose of colchicine.[23] Colchicine intolerance was defined as the inability to increase the effective colchicine dose due to gastrointestinal side effects, especially diarrhea, nausea, and abdominal pain.[24]

Study Design and Data Collection

Patient demographics, attack characteristics at diagnosis, presence of the MEFV gene, presence of amyloidosis, family history of FMF, colchicine doses before canakinumab treatment, anakinra status prior to canakinumab treatment, the duration of disease at the start of canakinumab treatment, the follow-up period under canakinumab treatment, the duration of canakinumab treatment interval extending and the reasons for treatment discontinuation were recorded retrospectively using the hospital's electronic system. The diagnosis of patients with amyloidosis was verified by tissue biopsy. The Pras score, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A (SAA) levels at the last visit before treatment with canakinumab and at the last visit with canakinumab were used to assess the response to treatment with canakinumab. The proteinuria values of patients with proteinuria were evaluated before and after treatment. The Pras score includes age at disease onset, frequency of attacks, dose of colchicine administered to control attacks, joint involvement, erysipelas-like erythema, and presence of amyloidosis.[25] Remission was accepted as the absence of attacks in the last 6 months and normal acute phase reactant levels during the attack-free period.

Statistical Analysis

Statistical analysis was conducted using SPSS (Statistical Package for Social Sciences) version 26.0. Descriptive statistics measured the patient's sociodemographic, clinical, and laboratory parameters. The normality of variables was assessed using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Quantitative data are expressed as mean ± standard deviation for normal distribution and median (minimum-maximum) for non-normal distribution. The Wilcoxon test was used to evaluate treatment response and determine whether there was a relationship between the data Pras score, ESR, CRP, and SAA levels before and after canakinumab. A paired sample T-test was used to compare the proteinuria levels of patients with proteinuria before and after canakinumab.

Results

The demographic and clinical characteristics of 34 patients with FMF treated with canakinumab are shown in Table I. The mean FMF diagnosis age of the

patients was 19.7±11.1 years, and 19 (55.8%) were male. The median time between diagnosis and initiation of treatment with canakinumab was 15 (1.8-50.6) years. The most common symptom at diagnosis was abdominal pain (n=30, 80.2%). MEFV mutation was analyzed in 29 patients. Of these patients, 10 were M694V homozygous, 6 M680I heterozygous, 3 M694V heterozygous, 3 M694V/V726A positive, 2 M680I homozygous and 1 E148Q heterozygous. The MEFV mutation was negative in 4 patients. Amyloidosis was present in 4 patients. A kidney biopsy was performed in two patients, a rectal biopsy in one patient, and a colon biopsy in one patient to determine the presence of amyloidosis. The most common comorbidity was hypertension (n=6, 17.6%). All patients had been treated with colchicine before treatment with canakinumab, and the median colchicine dose was 1.5 (1-2) mg. Twenty-one (61.8%) patients had received anakinra before treatment with canakinumab. Among patients receiving anakinra treatment, 14 had active disease with anakinra, and 7 had side effects with anakinra.

The mean follow-up time under canakinumab treatment was 49.1±35.1 months. Treatment with canakinumab was started at 150 mg once a month in all patients. A complete remission was achieved in 23 patients (67.6 %) and a partial response in 8 patients (23.5 %). The dosing interval for canakinumab was extended in 5 patients in remission during treatment. The median duration of the extending of the canakinumab dosing interval was 14.1 (7.9-104.2) months. The canakinumab doses of the patients in whom the dosing interval was extended were initially adjusted to 150 mg every 6 weeks. No activation was observed in the patients with extended dosing intervals during a follow-up period of 51.4±26.5 months. In two patients with extended dose intervals, the canakinumab dose was adjusted to 150 mg every 8 weeks.

Efficacy and Side Effects

Pras score, ESR, CRP, and SAA values were analyzed before and after treatment with canakinumab to evaluate the efficacy of canakinumab treatment. Statistically significant differences in Pras score, ESR, CRP, and SAA values were found after treatment with canakinumab compared to before treatment ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, respectively). The creatinine value before canakinumab was 0.78 (0.55-5.85), the creatinine value after canakinumab was 0.76 (0.52-5.92) and there was no statistically significant difference ($p=0.092$). In 7 patients with proteinuria, proteinuria was 4698±4691 mg/day before treatment with canakinumab and decreased to 2084±1390 mg/day after treatment with canakinumab. However, no statistically significant difference was found between the proteinuria values before and after treatment with canakinumab ($p=0.140$). Treatment was discontinued in 3 patients. In 2 patients, treatment with canakinumab was discontinued after 4.3 and 8.4 months due to active disease during canakinumab treatment. In one patient, treatment with canakinumab was discontinued after 4.2 months due to dizziness.

Table I. Demographic and clinical features of FMF patients treated with canakinumab (n=34)

Age, years, median (min.-max.)	37.6 (25.4-74.9)
Gender (F/M)	15/19
FMF diagnosis age, years, mean ± std deviation	19.7±11.1
Age at onset of canakinumab therapy, years, median (min.-max.)	33.4 (21.8-72.4)
Time between diagnosis and canakinumab therapy, years, median (min.-max.)	15 (1.8-50.6)
Family history FMF n (%)	14 (41.2)
Fever n (%)	24 (70.6)
Abdominal pain n (%)	30 (80.2)
Chest pain n (%)	7 (20.6)
Arthralgia/Arthritis n (%)	15 (44.1)
Myalgia n (%)	9 (26.5)
Erysipelas-like erythema n (%)	2 (5.9)
Hepatomegaly n (%)	3 (8.8)
Splenomegaly n (%)	6 (17.6)
Amyloidosis n (%)	4 (11.8)
Comorbidities n (%)	16 (47.1)
Hypertension n (%)	6 (17.6)
Chronic renal failure n (%)	5 (14.7)
Spondyloarthropathies n (%)	4 (11.8)
Coronary artery disease n (%)	3 (8.8)
Hyperlipidemia n (%)	2 (5.9)
Pulmonary disease n (%)	2 (5.9)
Diabetes mellitus n (%)	1 (2.9)
Anakinra treatment before canakinumab n (%)	21 (61.8)
Colchicine dose before canakinumab, mg, median (min.-max.)	1.5 (1-2)
Colchicine dose after canakinumab, mg, median (min.-max.)	1.5 (1-2)
Duration of canakinumab, months, mean ± std deviation	49.1±35.1

Min: Minimum, Max: Maximum, F: Female, M: Male. Std: Standard, FMF: Familial Mediterranean Fever

Table II. Comparison of treatment responses before and after canakinumab

	Before canakinumab	After canakinumab	p
PRAS, median (min.-max.)	6 (3-12)	2 (0-5)	<0.001
ESR, mm/h, median (min.-max.)	10.5 (2-80)	4.5 (2-32)	<0.001
CRP, mg/L, median (min.-max.)	10 (2-289)	2 (2-82)	<0.001
SAA mg/L, median (min.-max.)	43.5 (2-1370)	9.5 (2-60)	<0.001

PRAS: Disease Severity Score, Min: Minimum, Max: Maximum, ESR: Erythrocyte Sedimentation Rate, CRP: C-reactive protein, SAA: Serum Amyloid A.

Discussion and Conclusion

In this study, we evaluated the real-life efficacy and safety of canakinumab in FMF patients who were colchicine-resistant or colchicine-intolerant. Treatment with canakinumab resulted in a statistically significant reduction in Pras score, ESR, CRP, and SAA levels.

In FMF patients, colchicine is a treatment that prevents attacks and suppresses subclinical inflammation.[26,27] However, a group of patients do not respond to colchicine or develop intolerance to colchicine.[28] Several studies have shown the efficacy of canakinumab in colchicine-resistant FMF patients.[29-32] In a systematic review of eight studies, including 40 colchicine-resistant FMF patients, the complete and partial response rates to canakinumab were 68% and 32%, respectively.[31] In the study conducted by Ataş et al. with 27 FMF patients receiving canakinumab, disease activity was improved.[33] Similar to other studies, our study observed a significant decrease in disease activity scores and inflammatory markers with canakinumab treatment.

The aim of treatment in FMF patients is to prevent attacks and suppress inflammation. The most serious complication in FMF patients is amyloidosis. Controlling inflammation can prevent the development and progression of amyloidosis. Colchicine, the primary treatment for FMF, can reduce proteinuria. Sevillano et al. showed that IL-1 inhibitors reduce proteinuria.[34] In the study conducted by Ataş et al., 8 patients treated with canakinumab had proteinuria.[33] No decrease in proteinuria was observed in 6 of the patients. A decrease in proteinuria was observed in 2 patients previously treated with anakinra and in whom anakinra was discontinued due to side effects.[33] In our study, a decrease in proteinuria was observed after treatment with canakinumab in patients who had proteinuria at the start of treatment with canakinumab. However, this decrease was not statistically significant. This may be due to the small number of patients. Canakinumab could have a positive effect on renal involvement in FMF. However, more extensive studies with extended follow-up periods are needed to reduce proteinuria and prevent complications associated with amyloidosis. Data on the use of IL-1 inhibitors as monotherapy in amyloidosis are limited.[35-37] The standard approach is to use IL-1 inhibitors in combination with colchicine. In our study, treatment with colchicine was continued in all patients, along with treatment with canakinumab.

Canakinumab is administered at 150 mg every 4 weeks. There is no clear consensus on the optimal dose, the extension of the dosing interval, and the duration of treatment with canakinumab; in the study conducted by Akarcan et al., a standard tapering protocol was used in 9 pediatric FMF patients.[38] Four of the patients experienced a seizure 9.0±2.9 (6-12) months after discontinuation of treatment.[38] However, in practice, factors such as concomitant diseases and varying numbers and types of attacks during treatment may complicate the application of standard protocols for dose reduction or discontinuation of therapy. In our study, treatment with canakinumab was started every 4 weeks in all patients. In 5 patients in remission during treatment, the dose interval was extended. In the patients with prolonged dose intervals, no activation was observed during the 51.4±26.5-month follow-up period after prolongation of the dose interval. It may be appropriate to extend the canakinumab dosing intervals and duration of tapering depending on patient characteristics.

In terms of safety, canakinumab was generally well tolerated. However, two patients experienced active disease during treatment with canakinumab, and therapy was discontinued. No severe infection was observed during the follow-up. In a review of 40 colchicine-resistant FMF patients, no side effects related to canakinumab were observed in any patient. Two patients reported serious infections in a randomized controlled trial of 63 colchicine-resistant FMF patients.[32] In our study, no severe infection was observed during follow-up. Treatment with canakinumab was discontinued after 4.23 months in only one patient because he felt dizzy after the injection and did not want to continue treatment. In a 3-year interim analysis postmarketing of canakinumab in cryopyrin-associated periodic syndromes, dizziness was also reported among the side effects.[39] The rare occurrence of dizziness during treatment with canakinumab should be considered in patients' follow-ups.

The main limitations of our study are that it is a retrospective study involving a limited number of patients and evaluating the clinical characteristics of patients using data stored in the hospital's electronic system.

In conclusion, our study provides real-world data demonstrating the efficacy and safety of canakinumab in FMF patients. Canakinumab has been shown to reduce disease activity and inflammatory markers. Canakinumab could be a good treatment option for this patient group.

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