RESEARCH PAPER

Growth Parameters of Turkish Children With an Autoinflammatory Disease Before and After Canakinumab Treatment

SIBEL BALCI[1], RABIA MIRAY KISLA EKINCI[1], DILEK DOGRUEL[2], DERYA UFUK ALTINTAS[2] AND MUSTAFA YILMAZ[1]
From [1]Department of Pediatric Rheumatology, and [2]Department of Pediatric Allergy and Immunology, Cukurova University Faculty of Medicine, Adana, Turkey.

Correspondence to: Dr Sibel Balci, Department of Pediatric Rheumatology, Cukurova University Faculty of Medicine, Adana, Turkey. drsibelbalci@hotmail.com
Received: May 27, 2019; Initial review: August 08, 2019; Accepted: December 10, 2019.

Objective: To evaluate the effect of canakinumab on growth parameters of patients with autoinflammatory diseases. **Methods:** This retrospective study included Colchicine resistant familial Mediterranean fever (FMF), Mevalonate kinase deficiency (MKD), Tumor necrosis factor receptor-associated periodic fever syndrome (TRAPS), Deficiency of adenosine deaminase 2 (DADA2) patients treated with canakinumab for at least six consecutive months. **Results:** Eleven patients with FMF, 9 with MKD, 3 with TRAPS, and 1 with DADA2 were included. The median age (range) at diagnosis and drug initiation was 6.06 (1.45-16.06) years and 9.72 (1.82-19.11) years, respectively. The mean weight, height, and BMI SD scores significantly increased after canakinumab. There were significant improvements in laboratory parameters and disease activities. However, growth parameters after the drug did not differ according to gender, the duration of diagnostic delay, and age at the diagnosis. **Conclusion:** Canakinumab seems to have a positive effect on growth in patients with autoinflammatory diseases by controlling disease activity and inflammation.

Keywords: *Familial mediterranean fever, Management, Outcome, Pyrexia of unknown origin*.

Autoinflammatory diseases are a group of disorders characterized by unprovoked, recurrent, sterile inflammation episodes [1], the various conditions reported include Familial Mediterranean fever (FMF), Tumor necrosis factor receptor associated periodic fever syndrome (TRAPS), Mevalonate kinase deficiency (MKD). FMF is the most encountered AIDs caused by mutation in *MEFV*, characterized by recurrent fever, serositis, arthralgia or arthritis [1,2]. TRAPS is caused by autosomal dominant mutations in *TNFRSF1A*. The clinical features include recurrent fever, abdominal pain, pleuritis, myalgias, arthralgias, periorbital edema, and conjunctivitis. Mevalonate kinase deficiency (MKD) is a rare disorder caused by mutations in *MVK*. The clinical features of MKD are early onset of recurrent fever episodes accompanied by lymphadenopathy, erythematous skin rashes, hepatomegaly, splenomegaly, arthritis, and gastrointestinal symptoms [3]. Auto-inflammatory diseases are disorders of the innate immune system results in overproduction of proinflammatory cytokines, including IL-1β [2]. FMF, MKD, and TRAPS are classified in IL-1–mediated diseases [1]. IL-1 blocking agents, including canakinumab, an anti-IL-1β monoclonal antibody, have been approved for the treatment of these diseases [2,4-6].

Growth parameters are well-known indicators of a child well-being that mostly affected in children with chronic inflammatory diseases or autoinflammatory [7-9]. Although, there are several reports on effect of colchicine on growth parameters of FMF [8,10,11], to our knowledge the effects of canakinumab on growth parameters of autoinflammatory diseases have not been investigated so far.

METHODS

This study had a retrospective design and included colchicine resistant FMF, MKD, TRAPS, and deficiency of ADA2 (DADA2) patients, treated with canakinumab for at least six consecutive months. All patients were diagnosed and followed by a same pediatric rheumatologist in our tertiary referral center. FMF patients were diagnosed according to Tel Hashomer Diagnostic criteria [12] and diagnosis were supported by *MEFV* analysis. Colchicine-resistant patients were defined according to Turkish FMF study group [13]. Disease activity of patients with FMF, MKD and TRAPS were calculated retrospectively before and after canakinumab by using the Autoinflammatory Diseases Activity Index (AIDAI) [14].

Diagnosis of MKD was confirmed by genetic analysis

and the patients with bi-allelic mutations in *MVK* were considered as MKD. TRAPS patients were diagnosed according to the genetic analyzes of *TNFRSF1A*. The diagnosis of DADA2 was confirmed by mutations in *CECR1*. We utilized the *MEFV, MVK, TNFRSF1A*, and *CECR1* analysis as molecular diagnostics tools by using a next-generation sequencing platform (MiSeq System, Illumina, San Diego, CA, USA).

Demographic parameters, including age, gender, clinical manifestations, medical data of the patients were retrospectively obtained from medical files. Complete blood count, acute phase reactants (APRs), including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), studied before and after canakinumab administration were also collected from medical files.

Growth parameters, including weight, height, and BMI were recorded. Height (cm) and weight (kg) were preferentially measured in the morning at each visit by the same operator with the same type of stadiometer (Harpender). Standard deviation (SD) scores of growth parameters were calculated by anthropometric references in Turkish children [15]. The study protocol was approved by local Ethics Committee. Written informed consent was obtained from legal guardians of each patient before the study.

Statistical analysis: The SPSS 20.0 statistical software (IBM SPSS Statistics) was utilized. Kolmogorov-Smirnov test, stem-and-leaf diagram, and the histogram was utilized for the confirming the normality of distribution of growth indices. Paired-sample t-test was used for comparing two dependent variables in the same study group and Wilcoxon signed rank test was used for two independent variables. The statistical level of significance for all tests was considered to be 0.05.

RESULTS

Totally 24 patients (13 males) with auto-inflammatory diseases were included to the study. Eleven (45.8%) patients had diagnosis of FMF, 9 had MKD, 3 had TRAPS, and one had DADA2. Present study also contains the data of 10 patients reported in the previous study [16], whose growth parameters were available. A girl patient had a Met694Val/null mutation in *MEFV* besides the diagnosis of DADA2, which was reported previously, elsewhere [3]. The median age at diagnosis was 6.06 (range, 1.45-16.06) years. The mean age at study time was 11.29±5.21 years. The median diagnostic delay was 2.67 years (0.24-15.56). The median age at canakinumab initiation was 9.72 (range, 1.82-19.11) years, and median follow-up during treatment was 1.59 (range, 0.56-4.33) years; and the median dose used was 10 (4-27) doses.

Patients with FMF had recurrent fever attacks accompanying with abdominal pain, increased APRs and were given colchicine together with canakinumab. One of the FMF patients also had polyarticular chronic arthritis which were treated unsuccessfully with etanercept before canakinumab. HIDS patients showed recurrent fever attacks together with gastrointestinal symptoms and enlarged lymphadenopathies. They were given colchicine before the diagnosis of HIDS. All three TRAPS patients had recurrent fever attacks and were given colchicine before canakinumab. One of the patients with TRAPS also had IgA nephropathy and was given methylprednisolone and cyclosporine before canakinumab [17]. The DADA2 patient had hepatosplenomegaly, nephrotic range proteinuria, low serum immunoglobulin G, and immunoglobulin M levels and was diagnosed with renal amyloidosis. He was given methylprednisolone, cyclosporine, and colchicine before canakinumab [2], colchicine treatment was continued thereafter with canakinumab.

Disease activities of the patients were evaluated, except for the DADA2 patient because of the unavailability of activity score. Only one FMF patient with chronic arthritis was not in remission according to the AIDAI score after CAN. White blood cell and platelet counts, ESR, and CRP levels significantly decreased after canakinumab (***Table* I**).

The mean weight, height, and BMI SD scores after therapy were significantly higher than before (***Table* I**). The growth parameters after canakinumab did not differ significantly with gender and age-group at diagnosis (<6 year and ≥6 year) or follow-up duration (less than or more than 3 years).

DISCUSSION

In the present study, mean height, weight, and BMI SD scores of the patients with autoinflammatory diseases significantly increased after canakinumab treatment. Growth parameters after canakinumab did not differ according to gender, the duration of diagnostic delay and age at diagnosis. Controlling disease activity with the drug in these patients suppressed ongoing inflammation, which may explain the significant improvements in growth parameters.

We recently reported the canakinumab experience in 14 colchicine-unresponsive FMF patients. Attack frequency, proteinuria, and acute phase reactants, including ESR and CRP, were significantly decreased after the drug [16]. In the present study, depicting improvement in growth parameters, acute phase reactants and disease activity in patients with AIDs on

WHAT THIS STUDY ADDS?

- Canakinumab treatment has positive effects on growth parameters in children with autoinflammatory diseases.

Table I Growth and Laboratory Parameters of Patients With an Autoinflammatory Disease Before and After Canakinumab Treatment (*N*=13)

Parameters	*Before treatment*	*After treatment*	*P*
White blood cell per mm^3, median (range)	8665 (4730-74200)	6350 (4300-12200)	0.003
Hematocrit (%), mean (SD)	34.7 (4.78)	36.9 (3.96)	0.1
Platelet count per mm^3, mean (SD)	406000 (123900)	269000 (73550)	0.01
Erythrocyte sedimentation rate (mm/h), median (range)	41 (22-120)	10.50 (2-36)	0.001
C-reactive protein (mg/dL), median (range)	4.1 (1.1-29.2)	0.1 (0.1-1.6)	0.001
AIDAI score, median (range)	26 (15-54)	0 (0-35)	0.001
Weight SD score, mean (SD)	-0.80 (1.13)	-0.25 (1.18)	0.002
Height SD score, mean (SD)	-0.35 (1.09)	0.04 (1.10)	0.006
Body mass index SD score, mean (SD)	-0.74 (1.20)	-0.14 (1.10)	0.005

AIDAI; Autoinflammatory Diseases Activity Index.

canakinumab further suggests its effectiveness in those patients.

The effect of anti-interleukin 1 blocking agents, either anakinra or canakinumab, were also presented in eight colchicine-unresponsive FMF patients in a previous report [18]. Moreover, the effectiveness of canakinumab for the treatment of autoinflammatory diseases has been investigated in another study, in where colchicine resistant FMF, MKD and TRAPS patients were included. It was efficacious in controlling and preventing flares in those patients [5].

Even though, the heterogeneity of the study population, small number of patients, retrospective design and data collection are the limitations, the rarity of the autoinflammatory diseases and having no data on growth parameters in those treated with canakinumab make the present study valuable. Another limitation of the study is the lack of investigation about environmental factors, including diet and physical activity. Therefore, prospective and even multicenter studies conducted on a large number of AIDs patients are needed to clarify the effect of canakinumab on growth in patients with autoinflammatory disease.

Contributors: SB, MY: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; RMKE,DD: collected data, carried out the initial analyses, and reviewed and revised the manuscript; DUA, DD: designed the data collection instruments, and coordinated and supervised data collection, and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. *Funding*: None; *Competing interest*: None stated.

REFERENCES

1. Oda H, Kastner DL. Genomics, Biology, and Human Illness: Advances in the monogenic autoinflammatory diseases. Rheum Dis Clin North Am. 2017;43:327-45.
2. Kisla Ekinci RM, Balci S, Bisgin A, Hershfield M, Atmis B, Dogruel D, *et al*. Renal Amyloidosis in Deficiency of Adenosine Deaminase 2: Successful Experience with Canakinumab. Pediatrics. 2018;142:e20180948..
3. van der Burgh R, Ter Haar NM, Boes ML, Frenkel J. Mevalonate kinase deficiency, a metabolic autoinflammatory disease. Clin Immunol. 2013;147:197-206.
4. ter Haar NM, Oswald M, Jeyaratnam J, Anton J, Barron KS, Brogan PA, *et al*. Recommendations for the management of autoinflammatory diseases. Ann Rheum Dis. 2015; 74:1636-44.
5. de Benedetti F, Gattorno M, Anton J, Ben-Chetrit E, Frenkel J, Hoffman HM, *et al*. Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. N Engl J Med. 2018;378:1908-19.
6. Ozen S, Kone-Paut I, Gül A. Colchicine resistance and intolerance in familial mediterranean fever: Definition, causes, and alternative treatments. Semin Arthritis Rheum. 2017;47:115-20.
7. Balci S, Ekinci RMK, Bayazit AK, Melek E, Dogruel D, Altintas DU, *et al*. Juvenile systemic lupus erythematosus: A single-center experience from southern Turkey. Clin Rheumatol. 2019;38:1459-68.

8. Kisla Ekinci RM, Balci S, Akay E, Dogruel D, Altintas DU, Yilmaz M. Disease severity and genotype affect physical growth in children with familial mediterranean fever. Arch Rheumatol. 2019;34:i-vi. [Epub ahead of print]
9. Gutierrez-Suarez R, Ruperto N, Gastaldi R, Pistorio A, Felici E, Burgos-Vargas R, *et al*. A proposal for a pediatric version of the systemic lupus international collaborating clinics/american college of rheumatology damage index based on the analysis of 1,015 patients with juvenile-onset systemic lupus erythematosus. Arthritis Rheum. 2006;54: 2989-96.
10. Zung A, Barash G, Zadik Z, Barash J. Familial mediterranean fever and growth: Effect of disease severity and colchicine treatment. J Pediatr Endocrinol Metab. 2006;19:155-60.
11. Yoldas TC, Cakar N, Basaran O, Acar B, Uncu N, Caycý FS. The effect of colchicine and disease severity on physical growth in children with familial mediterranean fever. Clin Rheumatol. 2016;35:1603-07.
12. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, *et al*. Criteria for the diagnosis of familial mediterranean fever. Arthritis Rheum. 1997;40:1879-85.
13. Ozen S, Demirkaya E, Duzova A, Erdogan O, Erken E, Gul A, *et al*. FMF50: A score for assessing outcome in familial mediterranean fever. Ann Rheum Dis. 2014;73:897-901.
14. Piram M, Koné-Paut I, Lachmann HJ, Frenkel J, Ozen S, Kuemmerle-Deschner J, *et al*. Validation of the auto-inflammatory diseases activity index (AIDAI) for hereditary recurrent fever syndromes. Ann Rheum Dis. 2014;73: 2168-73.
15. Neyzi O, Gunoz A, Furman A, Bundak R, Gökçay G, Darendeliler F, *et al*. Weight, height, head circumference and body mass index references for Turkish children. Cocuk Sagligi ve Hastaliklari Derg. 2008;51:1-14. [article in Turkish]
16. Kisla Ekinci RM, Balci S, Dogruel D, Altintas DU, Yilmaz M. Canakinumab in children with familial mediterranean fever: A single-center, retrospective analysis. Paediatr Drugs. 2019;21:389-95.
17. Balci S, Kisla Ekinci RM, Melek E, Atmýþ B, Bisgin A, Yilmaz M. Phenotypic variability in two patients with tumor necrosis factor receptor associated periodic fever syndrome emphasizes a rare manifestation: Immuno-globulin a nephropathy. Eur J Med Genet. 2019; Oct 3:103780. [Epub ahead of print]
18. Basaran O, Uncu N, Celikel BA, Taktak A, Gur G, Cakar N. Interleukin-1 targeting treatment in familial Mediterranean fever: an experience of pediatric patients. Mod Rheumatol. 2015; 25: 621-4.