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ORIGINAL ARTICLE

Effect of interleukin-1 antagonists on the quality of life in familial Mediterranean fever patients

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Abstract

Background Familial Mediterranean fever (FMF) patients suffer from chronic complications of disease such as AA amyloidosis, chronic arthritis, and spondylitis. Reduced quality of life (QoL) is a feature of chronic diseases but it is also impaired in patients with FMF. Despite the regular use of colchicine at a maximal dose, about 10% of patients do not respond well or resistant to colchicine (crFMF). IL-1 inhibitors have been shown to be effective in controlling attacks in crFMF patients. Herein, we aimed to investigate QoL changes of crFMF patients with IL-1 inhibitors.

Methods All patients were prospectively monitored for the frequency, duration, severity of attacks, patient global assessments (Visual Analog Scale; VAS), and laboratory features. Either anakinra or canakinumab was used as IL-1 antagonist treatments. Demographic information, MEFV gene mutations, attack characteristics, and previous treatments were registered. Short form-36 (SF-36) quality of life scale was implemented by the interviewer for evaluating the QoL before and 3 months after the treatment.

Results A total of 44 patients were included in this study. Striking improvements were detected in frequency, duration, and VAS severity of attacks ($p < 0.001$). In the comparison of pre- and post-treatment, SF-36 sub-components significant improvements were observed on physical function, role limitation due to physical difficulty, role limitation due to emotional problem, energy, emotional well-being, social function, pain, general health, and health change.

Conclusions In conclusion, IL-1 antagonists prevent attacks and improve QoL of crFMF.

Keywords Anakinra · Canakinumab · Familial Mediterranean fever · IL-1 antagonist · Quality of life

Introduction

Familial Mediterranean fever (FMF) is the most common autoinflammatory disease characterized by recurrent attacks of fever, peritonitis, pleuritis, arthritis, and erysipelas like erythema [1]. Although FMF attacks are self-limited and usually last in 12 to 72 h, but most of the attacks results in bed confinement due to crippling pain. Moreover, about 10% of FMF patients suffer from chronic complications of disease such as AA amyloidosis, chronic arthritis, and spondylitis [2, 3]. Reduced quality of life (QoL) is a feature of chronic diseases but it is also impaired in patients with FMF. Particularly those patients suffering from severe disease and amyloidosis have remarkably reduced QOL [3–7].

Pyrin is believed to be a regulator of inflammation. Pyrin is mainly expressed in innate immune cells and plays a major role in the regulation of inflammation. Pyrin was encoded by MEFV gene [8]. The N-terminal pyrin domain allows pyrin to interact with a CARD (ASC), an adaptor protein that mediates the proteolytic activation of caspase-1 in the inflammasomes [9]. Active caspase-1 cleaves the precursor form of IL-1β into its biologically active form [10].

Colchicine is the mainstay of FMF treatment due to its proven efficacy for reducing frequency, severity, and duration of attacks in most patients and prevention from amyloidosis in almost all patients. However, despite the regular use of colchicine at a maximal dose, about 10% of patients do not respond well or resistant to colchicine (crFMF) [11]. Besides, 5–10% of patients cannot tolerate effective doses of colchicine due to

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its side effects which prone these patients to secondary amyloidosis [3, 4]. IL-1 is the principal cytokine driving inflammation in FMF and many of the other autoinflammatory diseases. Recently, IL-1 inhibitors have been shown to be effective in controlling attacks and amyloidosis in crFMF patients [3–7].

Assessment of quality of life is a respectable method for the measurement of disease activity and the efficacy of treatments. Many studies reported reduced QoL in FMF patients and also their caregivers [12–15]. Although IL-inhibitors are effective in controlling attacks, their effects on QoL have not been studied. Herein, we aimed to investigate QoL changes of crFMF patients with IL-1 inhibitors.

Methods

Study design and patients

FMF patients receiving IL-1 inhibitor treatment were enrolled into the study. This study was conducted between 2015 and 2018. FMF diagnosis was established according to Tel-Hasmoher criteria [16]. Demographic features, comorbidities, clinical manifestations, detailed attack characteristics, treatment responses, disease complications, family history, laboratory features, and *MEFV* mutations were recorded. All patients were prospectively monitored for the frequency, duration, severity of attacks, patient global assessments (Visual Analog Scale; VAS), and laboratory features. Complete response to colchicine was defined as less than one attack per 6 months. Colchicine resistant was defined as more than one attack per month [11]. Before and after IL-1 antagonist treatment SF-36 parameters were compared. Pre-treatment SF-36 parameters were compared with the standard norm values of Turkish population reported by Demiral et al. [17]. SF-36 parameters were compared in two groups as colchicine responsive and resistant. Either anakinra or canakinumab was used as IL-1 antagonist treatments. Anakinra was given 100 mg daily and canakinumab was given 150 mg monthly. Complications such as amyloidosis were registered. Comorbidities, such as hypertension and diabetes mellitus, were registered. For use of IL-1 antagonists, off-label permission was obtained from regulatory authority and local ethics committee approved the study.

Quality of life assessment

Short form-36 (SF-36) quality of life scale was implemented by the interviewer for evaluating the QoL before and 3 months after the treatment. SF-36 was developed by Ware et al. and has been validated for Turkish language [18, 19]. SF-36 form has various domains, namely, physical function, role limitation due to physical health, role limitation due to emotional problem, energy, emotional well-being, social function, pain, general health, and health change. Changes in these domains were compared before and after IL-1 antagonist therapies.

Statistical analysis

All statistical analyzes were performed with the Statistical Package for the Social Sciences (SPSS) 15.0 software (SPSS Inc., Chicago, IL, USA). Descriptive values were presented by mean (standard deviation, SD), median (minimum-maximum), and categorical variables as percentages. One sample *t* test was used to assess differences between the standard norm values of Turkish population and IL-1 group. Wilcoxon and Mann-Whitney U tests were used to assess differences between groups and two time periods. A p value equal or less than 0.05 is considered statistically significant.

Results

A total of 44 patients were included in this study. Twenty-five (56.8%) were female, 19 (43.2%) were male, and the median age was 35.6 ± 12.1 years. The clinical characteristics of the patients are presented in Table 1. Thirty patients (68.2%) had M694V and three patients had M680I homozygous mutations. Remainder had other single or compound heterozygous mutations. Seventeen patients (38.6%) had AA amyloidosis.

Thirty-three patients were treated with anakinra and 11 were with canakinumab. Striking improvements were detected in frequency, duration, and VAS severity of attacks ($p < 0.001$ for each, Table 2). Pre-treatment SF-36 parameters were compared with the standard norm values of Turkish population reported by Demiral et al. [17]. All sub-components of SF-36 were found to be worse in FMF patients compared to healthy subjects (Table 2). We compared two groups with colchicine response and resistant. No significant difference was found in the energy components. All other sub-components of SF-36 were found to be worse in colchicine-

Table 1 Clinical characteristics of study population

Clinical features	*N* (%)
Fever	35 (79.5)
Peritonitis	37 (84.1)
Pleuritis	23 (52.3)
Arthritis	34 (77.3)
Myalgia	23 (52.3)
Skin rash	19 (43.2)
Amyloidosis	17 (38.6)
Age at disease onset, years, (mean ± SD)	13.0 (± 11.7)
Age at FMF diagnosis, years, (mean ± SD)	22.4 (± 14.7)

Table 2 SF-36 domains of crFMF patients and norm values detected in healthy population

	crFMF N:44	Norm values* N:1279	*p* value
Physical functioning	55.3 (± 26.2)	83.8 (± 20)	< 0.001
Role limitations due to physical health	28.9 (± 39.2)	86.3 (± 24.9)	< 0.001
Role limitations due to emotional problems	25.5 (± 38.3)	90.1 (± 19.4)	< 0.001
Energy	43.7 (± 23.8)	64.5 (± 12.9)	< 0.001
Emotional well-being	49.4 (± 17.9)	71.0 (± 11.0)	< 0.001
Social functioning	47.9 (± 28.8)	91.0 (± 12.9)	< 0.001
Pain	42.4 (± 27.9)	82.9 (± 18.9)	< 0.001
General health	32.2 (± 21.9)	71.6 (± 16.1)	< 0.001

All values are presented as mean ± standard deviation. *Norm values were retrieved from Demiral et al. (16). *crFMF*, colchicine resistant FMF

resistant FMF patients compared to colchicine responsive FMF patients (Table 3).

In the comparison of pre- and post- treatment SF-36 sub-components, significant improvements were observed on physical function, role limitation due to physical difficulty, role limitation due to emotional problem, energy, emotional well-being, social function, pain, general health, and health change (Table 4 and Fig. 1).

SF-36 sub-components significant improvements were observed on energy, emotional well-being, social function, and pain in amyloidosis patients after IL-1 antagonist treatment (Table 5).

Post-treatment SF-36 parameters were compared with the standard norm values of Turkish population. SF-36 components were found to be statistically worse in the post-treatment group than the norm values, except for pain and energy. Although pain and energy components were worse than norm values, no statistically significant difference was found (Fig. 1).

Discussion

In this study, we evaluated the effect of the IL-1 inhibitor treatments on quality of life of crFMF. We demonstrated that IL-1 antagonist treatment improves the quality of life by reducing number, duration, and severity of attacks.

Pyrin is a regulator of inflammation. Pyrin domain allows pyrin to interact with a CARD, an adaptor protein that mediates the proteolytic activation of caspase-1 in the inflammasomes. Active caspase-1 cleaves the precursor form of IL-1β into its biologically active form. IL-1 is the principal cytokine driving inflammation in FMF and many of the other autoinflammatory diseases.

It has been reported that quality of life is impaired in FMF patients [3–7, 20]. Consistently, we found worse SF-36 scores in crFMF patients than norm values for Turkish population. Sahin et al. reported lower QoL scores in all domains of SF-36 except for energy. In their study, crFMF patients had a lower physical function, physical role limitation, and emotional role limitation components; however, they found no relationship between number of attack and quality of life [15]. Giese et al. reported impaired QoL in both German and Turkish FMF patients, evaluated with WHOQOL-BREF questionnaire [13]. Deger et al. have found that SF-36 physical components were lower in FMF patients, but no differences were found in mental components of SF-36.However, depression and anxiety score in hospital anxiety depression scale was found to be higher in FMF patients [12].

Some patients were not completely responsive to IL-1 treatment, especially in patients with musculoskeletal attacks. This situation may be related to some patients not taking drug

Table 3 SF-36 domains of crFMF patients and colchicine responsive FMF patients

	crFMF N:44	Colchicine responsive N:41	*p* value
Physical functioning	55 (0–100)	87.5 (15–100)	< 0.001
Role limitations due to physical health	0 (0–100)	100 (0–100)	< 0.001
Role limitations due to emotional problems	0 (0–100)	100 (0–100)	< 0.001
Energy	40 (0–95)	52.5 (15–95)	0.14
Emotional well-being	48 (20–96)	56 (16–84)	0.002
Social functioning	50 (0–100)	75 (25–100)	< 0.001
Pain	32.5 (0–100)	67.5 (10–100)	< 0.001
General health	25 (0–90)	42.5 (10–85)	0.008

All values are presented as median (minimum-maximum)

Table 4 SF-36 domains of crFMF patients before and after IL-1 inhibitor treatments

	Before IL-1 treatment	After IL-1 treatment	*p* value
Number of attacks per 3 months	6 (0–30)	1 (0–11)	< 0.001
Duration day of attack	3 (0–10)	1 (0–5)	< 0.001
Severity of attack, VAS	8 (0–10)	4 (0–10)	< 0.001
Patient global assessment, VAS	6 (1–10)	3 (0–8)	< 0.001
Physical functioning	55 (0–100)	75 (15–100)	0.001
Role limitations due to physical health	0 (0–100)	62.5 (0–100)	0.007
Role limitations due to emotional problems	0 (0–100)	66.6 (0–100)	0.001
Energy	40 (0–95)	60 (5–100)	0.001
Emotional well-being	48 (20–96)	60 (20–96)	< 0.001
Social functioning	50 (0–100)	75 (0–100)	< 0.001
Pain	32.5 (0–100)	78.7 (10–100)	< 0.001
General health	25 (0–90)	40 (5–95)	0.001

All values are presented as median (minimum-maximum)

doses, especially anakinra. Low drug compliance can be seen in patients using anakinra.

Most of the tools used in the activity assessment of rheumatic diseases are largely based on more objective signs and symptoms of disease, such as tender and swollen joint counts. Efficacy of treatments is assessed by these tools most of the time. Although this approach is suitable in the past, increasing demand of patients about their life standards, necessitated use of QoL tools in recent studies. There are a few tools for the assessment of activity of FMF and efficacy of treatments. Most widely used tools in the assessment of efficacy of IL-1 inhibitors are number of attacks, time span to the first attack, and FMF50 [5, 6, 21]. All these methods ignored QoL aspect in FMF which is an indispensable part of accurate evaluation.

Two very small and short-term studies evaluated QoL in crFMF by treatment. In one of these, Gul et al. were the first to report a significant improvement in both physical and mental component scores of SF-36 at day 8 [22]. In a similar short-term study, HRQoL physical scores of crFMF patients were found to be lower than the social norms, while the psychosocial scores are similar. Rilonacept treatment significantly improved HRQoL scores [23]. Our study evaluated QoL improvement by IL-1 antagonists in a relatively large number of patients. We found significant improvements in all domains of SF-36 by IL-1 inhibitors. Although there are improvements in quality of life after IL-1 inhibitors treatment, it has been determined that the normal values of Turkish population were still not reached.

We have a couple of limitations in our study. First, QoL was evaluated at baseline and 3 months after the treatment; however, the duration of IL-1 antagonist treatment is very long. Whether QoL improvement is lost or more enhanced

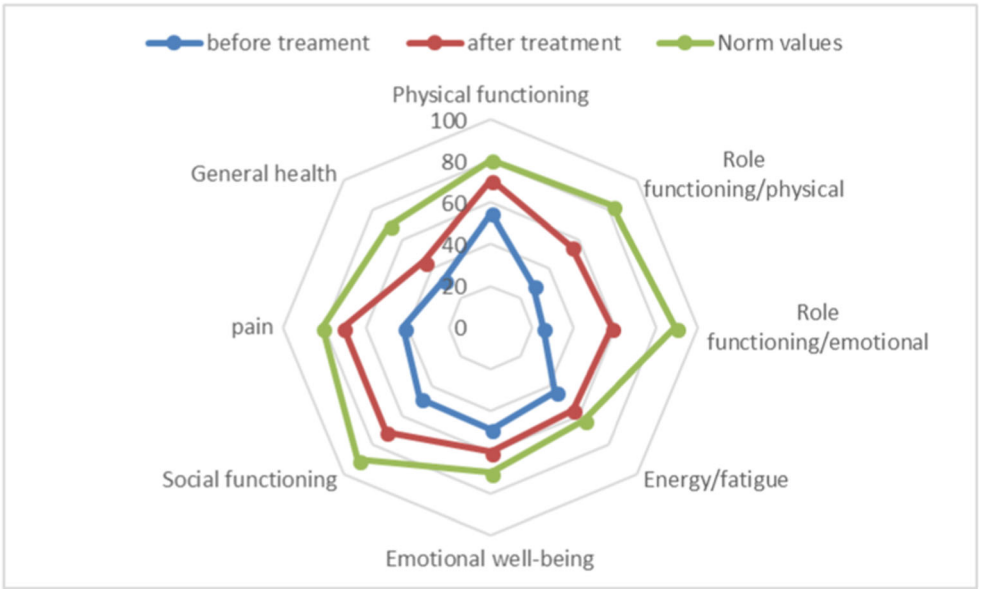

Fig. 1 Changes in SF-36 domains before and after IL-1 inhibitor treatments. Norm values were retrieved from Demiral et al. (16)

Table 5 SF-36 domains of amyloidosis patients before and after IL-1 inhibitor treatments

	Before IL-1 treatment	After IL-1 treatment	*p* value
Physical functioning	65 (5–100)	85 (40–100)	0.12
Role limitations due to physical health	25 (0–100)	50 (0–100)	0.3
Role limitations due to emotional problems	33.3 (0–100)	66.6 (0–100)	0.13
Energy	52.5 (5–95)	65 (20–100)	0.026
Emotional well-being	46 (36–96)	64 (36–96)	0.009
Social functioning	56.2 (0–100)	75 (25–100)	0.023
Pain	61.2 (10–100)	90 (32.5–100)	0.025
General health	37.5 (0–75)	40 (5–85)	0.34

All values are presented as median (minimum-maximum)

by time could not be assessed. Second, we did not assess depression and anxiety in our study. It has been reported that depression and anxiety are problems encountered in FMF patients as many other chronic conditions which may have a significant effect on QoL [12]. Moreover, attack frequency is related to anxiety and depression [24, 25].

Conclusion

In conclusion, IL-1 antagonists prevent attacks and improve QoL of crFMF. More studies are needed to assess temporal change in the QoL by prolonged treatments.

Compliance with ethical standards

For use of IL-1 antagonists, off-label permission was obtained from regulatory authority and local ethics committee approved the study.

Disclosures None.

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