The Familial Mediterranean Fever (FMF) 50 Score: Does it Work in a Controlled Clinical Trial? Re-Analysis of the Trial of Rilonacept for Patients with Colchicine-Resistant or Intolerant FMF

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ABSTRACT: **Background:** The familial Mediterranean fever 50 score (FMF50) score was recently devised to define response to treatment and as an outcome measure for clinical trials of FMF.

Objectives: To examine the performance of the FMF50 score in a previously published trial of rilonacept for patients whose FMF was resistant or intolerant to colchicine.

Methods: We re-analyzed the data from our controlled trial of rilonacept vs. placebo in 14 patients with colchicine-resistant or intolerant FMF using the FMF50 score as the primary outcome. The FMF50 score required improvement by ≥ 50 in five of six criteria (attack frequency, attack duration, global patient assessment, global physician assessment, frequency of attacks with arthritis, and levels of acute-phase reactants) without worsening of the sixth criterion.

Results: In the original trial rilonacept was considered effective according to the primary outcome measure (differences in the attack frequency) with eight analyzable patients considered responders and four as non-responders. According to the FMF50 score, only two participants would have been considered responders to rilonacept, and one to placebo. Only two participants had ≥ 50% differences between rilonacept and placebo in five criteria. The major explanation for non-response to treatment was that with rilonacept the duration of attack decreased by ≥ 50% in only 2 participants and 5 participants had no attacks of arthritis either during screening (before randomization) or during treatment with rilonacept.

Conclusions: The proposed FMF50 score did not differentiate well between responders and non-responders compared to the *a priori* defined primary outcome measure in this successful controlled study.

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KEY WORDS: familial Mediterranean fever (FMF), familial Mediterranean fever 50 score (FMF50), colchicine, rilonacept

Choosing the optimal outcome measure for a particular disease is important both for assessing the clinical response to therapy in individual patients and for designing clinical trials. This is important for clinical trials of rare diseases where the sample size is particularly small and, therefore, only one trial of a single medication can be performed.

Familial Mediterranean fever (FMF) is a genetic autoinflammatory disorder that manifests as recurrent attacks of fever, abdominal and chest pain, arthritis, and rash with late complications of amyloidosis in untreated patients [1]. The efficacy of colchicine, the standard of FMF care, was proven in several controlled trials in the 1970s that used the decrease in attack frequency as the primary outcome measure [2-5].

It is estimated that 5–10% of FMF patients do not respond adequately to, or do not tolerate, colchicine and require an alternative therapy [6-9]. However, the definition of response is controversial, with some proposing the decrease in attack frequency as the measure of responsiveness [10] and others suggesting that other criteria be included such as attack duration and severity, reduction in the level of acute-phase reactants, or global assessment scales. In 2008, Ben-Chetrit and Ozdogan [8] proposed the use of an index such as the FMF20 or FMF50 (similar to the American College of Rheumatology 20 in rheumatoid arthritis) which they defined as the decrease in the annual rate of FMF attacks, with a FMF50 response denoting a 50% decrease in attacks.

Recently Ozen et al. [11] proposed the FMF50 score as the first composite score for defining response to treatment. The score was also designed as an outcome measure for clinical trials of new medications in patients non-responsive to colchicine. The FMF50 score was defined as a ≥ 50% improvement in five of six clinical, laboratory and global assessment criteria without worsening in the sixth [Table 1].

The aim of this study was to assess the performance of these criteria in our previously published randomized, placebo-controlled trial of rilonacept for patients whose FMF was resistant or intolerant to colchicine [12].

Table 1. Response criteria included in the familial Mediterranean fever (FMF) 50 score

Responders to treatment are defined as those with at least 50% improvement in five of six criteria, without worsening in any

1. Percentage change in the frequency of attacks with treatment
2. Percentage change in the duration of attacks with treatment
3. Percentage change in the patients/parents global assessment of disease severity with treatment (10 cm visual analog scale)
4. Percentage change in the physicians' global assessment of disease severity with treatment (10 cm visual analog scale)
5. Percentage change in the frequency of arthritis attacks with treatment
6. Percentage change in levels of acute-phase reactants with treatment (the best of C-reactive protein, erythrocyte sedimentation rate, or serum amyloid A obtained at least 2 weeks after the last attack).

Adapted from Ozen S, et al. *Ann Rheum Dis* 2014; 73: 897-901 [ref 11].

PATIENTS AND METHODS

In brief, this was a multicenter, randomized, double-blind, single-subject, alternating treatment study [12]. After a 1 month screening phase to determine eligibility and the frequency of FMF attacks, the 14 participants were randomized to one of four treatment sequences that included two treatment courses, 3 months each, with subcutaneous injections of rilonacept (2.2 mg/kg/week, max 160 mg) and two with placebo. Colchicine was continued at the participants' pre-study dose. Participants who experienced at least two attacks during any treatment course (rilonacept or placebo) were allowed to "escape" to the other treatment arm until the end of that course (blinding was maintained) and then resume their assigned sequence. The Institutional Review Boards at all participating centers approved the study protocol. Informed consent was obtained from all adult subjects or parents/legal guardians for subjects under age 18 (ClinicalTrials.gov Identifier NCT00582907).

The primary efficacy outcome was the difference in the rate of FMF attacks between treatment arms. Responders were *a priori* defined as participants with a > 40% difference in attacks between treatment arms. We found a 76% decrease in the attack rate with rilonacept vs. 39% with placebo (risk ratio by Bayesian statistics of 0.45, SD = 0.13, 95% confidence interval 0.26–0.77). There were 8 responders and 4 non-responders among 12 analyzable participants who received both rilonacept and placebo.

Among the data we collected were all the elements needed for calculation of the FMF50 score, including attack frequency, attack duration, acute-phase reactant levels (erythrocyte sedimentation rate, C-reactive protein and serum amyloid A; in each patient we chose the test that yielded the greatest response to treatment), the character of the attacks, i.e., if they included arthritis and global assessment of disease activity on a 0–10 visual analog scale (10 being worst). Using these data we calculated how many patients attained the FMF50 level of response during treatment with rilonacept or placebo vs. the screening month. We also examined how many patients attained a FMF50 difference between rilonacept and placebo.

RESULTS

After re-analysis of the data using the FMF50 score we found that only two participants (#2 and #6 in Table 2) would have been considered responders to rilonacept and one (#11) to placebo. Only two participants (# 4 and #5) exhibited ≥ 50% differences between rilonacept and placebo in five criteria. The major reason for non-response to treatment was that with rilonacept the duration of attack decreased by ≥ 50% in only 2 participants and 5 participants had no attacks of arthritis either during screening (before randomization) or during treatment with rilonacept. The response of individual participants to each of the criteria and summary data on the performance of each criterion are detailed in Tables 2 and 3, respectively.

If the requirement for response was a 50% improvement in at least four criteria, two additional participants (and four overall) would have been considered responders to rilonacept (two other participants improved in four criteria but worsened in at least one criterion), and one more to placebo (two overall). Two additional participants (four overall) showed ≥ 50% differences between rilonacept and placebo in four criteria (one other participant improved in four criteria but worsened in at least one criterion).

If the requirement for response was at least three criteria overall, six patients would have been considered responders to rilonacept (two other participants improved in at least three criteria but worsened in at least one criterion) and two to placebo (two other participants improved in three criteria but worsened in at least one). No additional participants (remaining four overall) would have had ≥ 50% difference between rilonacept and placebo (four additional participants improved in at least three criteria but worsened in at least one).

DISCUSSION

We found that the FMF50 score did not differentiate well between responders and non-responders in a controlled clinical trial of rilonacept for colchicine-resistant patients. The trial, considered a success in the primary outcome and many secondary outcomes, would have been considered a failure by the proposed FMF50 score. There are several reasons why the FMF50 score may not have worked in our study:

- There is substantial evidence from our trial and colchicine studies that treatment does not shorten attack duration, even among responders, thus this criterion may lack external validity [12-14]. In addition, duration cannot be used as a criterion in patients with no attacks
- Many patients with FMF do not develop arthritis. Furthermore, there may be regional differences, as more patients

Table 2. Performance of criteria items of the familial Mediterranean fever (FMF) 50 score in individual participants in the controlled trial of rilonacept for colchicine-resistant/intolerant patients

	Participant #	**#1**	**#1**	**#2**	**#2**	**#3**	**#3**	**#4**	**#4**	**#5**	**#5**	**#6**	**#6**	**#7**	**#7**
	Responded in trial	Yes		Yes		Yes		Yes		Yes		Yes		Yes	
		% change	FMF 50 response	% change	FMF 50 response	% change	FMF 50 response	% change	FMF 50 response	% change	FMF 50 response	% change	FMF 50 response	% change	FMF 50 response
Rilonacept	Frequency	-63	Yes	-77	Yes	-91	Yes	-100	Yes	-83	Yes	-83	Yes	-83	Yes
	Duration	600	No	-56	Yes	-25	No	NA		0	No	-67	Yes	220	No
	Patient global	75	No	25	No	-57	Yes	-100	Yes	-100	Yes	-71	Yes	17	No
	Physician global	-58	Yes	0	No	-100	Yes	-100	Yes	-100	Yes	-94	Yes	-50	Yes
	Arthritis*	-100	Yes	-50	Yes	-100	Yes	NA		NA		NA		NA	
	APR	-67	Yes	-100	Yes	-91	Yes	-28	No	-100	Yes	-96	Yes	-35	No
Rilonacept summary	Responders by FMF 50; response to individual criteria (Yes/No/NA)	No, 4/2		No, 4/2		Yes, 5/1		No, 3/1/2		No^, 4/1/1		Yes, 5/0/1		No, 2/3/1	
Placebo	Frequency	-44	No	-30	No	46	No	-66	Yes	110	No	-50	Yes	-32	No
	Duration	290	No	-14	No	163	No	25	No	29	No	100	No	142	No
	Patient global	175	No	0	No	-64	Yes	-42	No	25	No	-14	No	67	No
	Physician global	-8	No	400	No	-67	Yes	-33	No	25	No	-81	Yes	50	No
	Arthritis*	-80	Yes	0	No	-50	Yes	~	No	NA		NA		NA	
	APR	30	No	-100	Yes	NA		44	No	-71	Yes	-100	Yes	NA	
Placebo summary	Responders by FMF 50; response to individual criteria (Yes/No/NA)	No, 1/5		No, 1/5		No, 3/2/1		No, 1/5		No, 1/4/1		No, 3/2/1		No, 0/4/2	

	Participant #	**#8**	**#8**	**#9**	**#9**	**#10**	**#10**	**#11**	**#11**	**#12**	**#12**	**#13**	**#13**	**#14**	**#14**
	Responder in trial	Yes		No		No		No		No		NA		NA	
		% change	FMF 50 response	% change	FMF 50 response	% change	FMF 50 response	% change	FMF 50 response	% change	FMF 50 response	% change	FMF 50 response	% change	FMF 50 response
Rilonacept	Frequency	-100	Yes	-4	No	-4	No	-66	Yes	-16	No	59	No	NA	
	Duration	NA		25	No	-6	No	-29	No	10	No	-18	No	NA	
	Patient global	-100	Yes	-8	No	150	No	-57	Yes	-20	No	0	No	NA	
	Physician global	-78	Yes	250	No	70	No	-81	Yes	0	No	-16	No	NA	
	Arthritis*	NA		-84	Yes	100	No	-45	No	133	No	NA		NA	
	APR	-98	Yes	-52	Yes	NA		-47	No	-56	Yes	NA		NA	
Rilonacept summary	Responders by FMF 50; response to individual criteria (Yes/No/NA)	No^, 4/0/2		No, 2/4		No, 0/5/1		No, 3/3		No, 1/5		No, 0/4/2		NA	
Placebo	Frequency	69	No	-9	No	-74	Yes	-57	Yes	-35	No	-59	Yes	NA	
	Duration	1350	No	-20	No	13	No	-40	No	110	No	9	No	-60	Yes
	Patient global	-25	No	-17	No	-83	Yes	-57	Yes	0	No	NA		-100	Yes
	Physician global	-56	Yes	100	No	-90	Yes	-75	Yes	67	No	NA		-100	Yes
	Arthritis*	~	No	-100	Yes	-90	Yes	-75	Yes	67	No	NA		NA	
	APR	NA		50	No	120	No	-57	Yes	112	No	117	No	-89	Yes
Placebo summary	Responders by FMF 50; response to individual criteria (Yes/No/NA)	No, 1/4/1		No, 1/5		No, 4/2		Yes, 5/1		No, 0/6		No, 1/2/3		No^, 4/0/2	

All results are compared to the screening period prior to treatment or the baseline visit (the latter for measurement of acute-phase reactants)

Frequency refers to the changes in attack frequency per month. Duration refers to changes in the mean length of individual attacks. Patients and physician global assessments were measured on a 0–10 scale (10 is worst). Arthritis refers to the change in the percentage of attacks that included arthritis. Acute-phase reactants refer to the greatest improvement in measurement of erythrocyte sedimentation rate, C-reactive protein or serum amyloid A

*Five of the participants did not develop arthritis throughout the trial

^Not considered responder because of lack of arthritis

~Infinity (divided by 0)

FMF = familial Mediterranean fever, NA = Not applicable/not available or unknown, APR = acute-phase reactants

Table 3. Overall performance of the familial Mediterranean fever (FMF) 50 score in the controlled trial of rilonacept for colchicine-resistant/intolerant patients (n=14)

	Criterion	No. of patients ≥50 responders (yes/no/unable to determine)
Rilonacept	Frequency of attacks	9/4/1
	Duration of attacks	2/9/3
	Patient global assessment	6/7/1
	Physician global assessment	8/5/1
	Attacks with arthritis	4/3/7*
	Acute-phase reactants	8/3/3
Overall rilonacept responders		2/11/1
Placebo	Frequency of attacks	5/8/1
	Duration of attacks	1/13
	Patient global assessment	4/9/1
	Physician global assessment	6/7/1
	Attacks with arthritis	5/4/5*
	Acute-phase reactants	5/6/3
Overall placebo responders		1/13

*Five patients did not have attacks that included arthritis

living in Turkey develop arthritis than in Western Europe (< 20%) [15].

- The FMF50 score was developed in FMF patients initiating first-line therapy with colchicine [11] and may not be valid for colchicine non-responders in trials of new medications and biologic agents
- It is technically difficult in a regimented clinical trial with prescheduled visits to assure that acute-phase reactant testing will always occur ≥ 2 weeks after an attack
- The requirements of ≥ 50% improvement in at least five of six criteria without worsening in any other criteria appear to be too restrictive and are more stringent than composite outcome scores for other rheumatic diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, dermatomyositis, and systemic lupus erythematosus.

It may be important to include other criteria in a composite score, in particular the physical aspects of health-related quality of life, which is an important outcome especially for patients with this life-long disease. With regard to secondary outcome measures we indeed found a significant improvement in the physical health-related quality of life when participants were treated with rilonacept vs. placebo [12,16].

In summary, in this controlled clinical trial of rilonacept for colchicine-resistant patients the proposed FMF50 score did not differentiate well between responders and non-responders. While the proposed score may be adequate in clinical practice and perhaps in regional trials, these criteria should be revisited before being adopted as a primary outcome measure in multinational FMF trials.

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References

1. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. *Am J Med* 1967; 43: 227-53.
2. Goldfinger SE. Colchicine for familial Mediterranean fever. *N Engl J Med* 1972; 287: 1302.
3. Zemer D, Revach M, Pras M, et al. A controlled trial of colchicine in preventing attacks of familial Mediterranean fever. *N Engl J Med* 1974; 291: 932-4.
4. Dinarello CA, Wolff SM, Goldfinger SE, Dale DC, Alling DW. Colchicine therapy for familial Mediterranean fever. *N Engl J Med* 1974; 291: 934-7.
5. Goldstein RC, Schwabe AD. Prophylactic colchicine therapy for familial Mediterranean fever. A controlled-double blind study. *Ann Intern Med* 1974; 81: 792-4.
6. Ben-Zvi I, Livneh A. Colchicine failure and potential alternatives in FMF: embarking on the anakinra trial. *IMAJ* 2014; 14: 271-3.
7. Lidar M, Scherrmann JM, Shinar Y, et al. Colchicine nonresponsiveness in familial Mediterranean fever: clinical, genetic, pharmacokinetic, and socioeconomic characterization. *Semin Arthritis Rheum* 2004: 33: 273-82.
8. Ben-Chetrit E, Ozdogan H. Non-response to colchicine in FMF definition, causes and suggested solutions. *Clin Exp Rheumatol* 2008; 26 (Suppl 50): S49-51.
9. Gul A. Treatment of familial Mediterranean fever: colchicine and beyond. *IMAJ* 2014; 14: 281-4.
10. Hentgen V, Grateau G, Kone-Paut I, et al. Evidence-based recommendations for the practical management of Familial Mediterranean Fever. *Semin Arthritis Rheum* 2013; 43: 387-91.
11. Ozen S, Demirkaya E, Duzova A, et al. FMF50: a score for assessing outcome in familial Mediterranean fever. *Ann Rheum Dis* 2014; 73: 897-901.
12. Hashkes PJ, Spalding SJ, Giannini EH, et al. Rilonacept for colchicine-resistant or -intolerant familial Mediterranean fever: a randomized trial. *Ann Intern Med* 2012; 157: 533-41.
13. Wright DG, Wolff SM, Fauci AS, et al. Efficacy of intermittent colchicine therapy in familial Mediterranean fever. *Ann Intern Med* 1977; 86: 162-5.
14. Schwabe AD, Peters RS. Familial Mediterranean fever in Armenians. Analysis of 100 cases. *Medicine (Baltimore)* 1974; 53: 453-62.
15. Ozen S, Demirkaya E, Amaryan G, et al. Results from a multicentre international registry of familial Mediterranean fever: impact of environment on the expression of a monogenic disease in children. *Ann Rheum Dis* 2014; 73: 662-7.
16. Hashkes PJ, Spalding SJ, Giannini EH, et al. The effect of rilonacept versus placebo on health-related quality of life in patients with poorly controlled familial Mediterranean fever. *Biomed Res Int* 2014: 854842.

"We hang the petty thieves and appoint the great ones to public office"

Aesop (620-564 BCE), Ancient Greek fabulist or story teller credited with a number of fables now collectively known as *Aesop's Fables*. Many of the tales are characterized by animals and inanimate objects that speak, solve problems, and generally have human characteristics