Effect of interleukin-1 inhibition in a cohort of patients with colchicine-resistant familial Mediterranean fever treated consecutively with anakinra and canakinumab

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ABSTRACT

Objective. *To evaluate the efficacy of IL-1 blockers in a cohort of patients with colchicine-resistant familial Mediterranean fever (crFMF) treated consecutively with anakinra and canakinumab.*

Methods. *Patients with crFMF treated with anakinra and canakinumab in any order were identified using the computerised database of Sheba Medical Center. Background characteristics of the patients, reason for switching IL-1 inhibitor, and frequency of attacks under colchicine only, anakinra, and canakinumab were extracted from the computerised patient files. Patients were then interviewed for patient-reported outcomes.*

Results. *A total of 46 patients in our clinic were prescribed canakinumab for crFMF after previous anakinra treatment, whereas no patients who switched treatment from canakinumab to anakinra were identified. Of those, 23/46 patients (50%) discontinued anakinra due to inadequate response (11 of them with secondary failure after a good initial response). Frequency of flares was significantly decreased following switch to canakinumab from anakinra treatment ($p<0.01$). After the switch to canakinumab, the median duration of flares, the severity of pain during a flare, and the patient's global assessment of disease activity were all significantly decreased ($p\leq0.01$), according to the reports from the patients.*

Conclusion. *Canakinumab is an effective treatment for FMF after failure of anakinra due to any cause.*

Introduction

Familial Mediterranean fever (FMF) is an autoinflammatory, hereditary disease characterised by recurrent attacks of fever and serositis (1, 2). When left untreated, its major long-term complication is secondary renal amyloidosis, which can lead to end-stage renal disease (2, 3) – 50% of untreated FMF patients develop signs of renal amyloidosis after 9 years of follow-up compared with less than 5% of patients treated with colchicine (4). The frequency of amyloidosis in patients clinically resistant to colchicine remains unknown, yet in our experience compliant patients treated with colchicine do not develop amyloidosis. FMF is associated with the presence of pathogenic mutations in the *MEFV* gene that lead to constitutive activation of the pyrin inflammasome and dysregulated expression of interleukin (IL)-1β, which plays a pivotal role in the pathogenesis of the disease (5, 6).

Current therapy for most patients with FMF is based on the use of colchicine, which prevents attacks, suppresses chronic subclinical inflammation, prevents amyloidosis, and improves quality of life (3, 7). However, a subset of patients with FMF fail to respond, or are intolerant to colchicine. Two biological agents that inhibit IL-1β are approved for this indication, and have proven to be effective in the treatment and prevention of flares in patients with colchicine-resistant FMF (crFMF): anakinra, a human IL-1 receptor antagonist administered as a daily subcutaneous injection (8), and canakinumab, a human anti-IL-1β monoclonal antibody administered as a monthly subcutaneous injection (9). To the best of our knowledge, there are currently no published studies comparing the two, but due to their different pharmacokinetics and pharmacodynamics, it is possible that some patients may respond differently to these two agents. There are very limited data published describing the effectiveness of anakinra or canakinumab in patients who switched from one IL-1

inhibitor to the other due to a lack of an adequate response to treatment (10, 11). Here we report the effect of anakinra and canakinumab in a cohort of patients with crFMF from the Sheba Medical Center FMF Registry (Israel) treated sequentially with anakinra and canakinumab. The Sheba Medical Center is a tertiary hospital, with the largest FMF clinic in Israel actively caring for over 3,000 FMF patients.

Patients and methods

We searched the computerised FMF registry database at the Sheba Medical Center for patients with crFMF (defined as more than 4 flares per year) who were treated sequentially with the two IL-1β inhibitors in any order. Patients treated with anakinra who switched to canakinumab were identified, but no patients were found who switched treatment from canakinumab to anakinra. Baseline characteristics at the start of treatment with anakinra, the frequency of flares for the period of treatment with each IL-1 inhibitor, and the reason for discontinuing anakinra were collected prospectively and extracted from the computerised patient files. A flare was defined as the recognition of a typical FMF attack by the patient (abdominal, pleuritic, arthritis or fever only) with symptoms recognised by the patient as an FMF flare (which may vary in severity under treatment but are symptomatically identical with and without treatment).

The identified patients were then interviewed and asked for their assessment of global disease activity (on a scale of 1–10, where 1 was a complete absence of symptoms and 10 was very active disease to the maximal degree), the average duration of flares (in days), and the pain severity during the flares (on a scale of 1–10 from total absence of pain to pain at the maximal degree). These three patient-reported outcomes were provided retrospectively for each of the three periods of treatment: (i) without either IL-1β inhibitor, (ii) with anakinra, and (iii) with canakinumab. Patients were categorised as "anakinra inadequate responders" if the reason for switching to canakinumab was insufficient control of the disease with anakinra; patients who switched to canakinumab due to a reason other than insufficient control of disease were considered "anakinra responders". Baseline characteristics were compared between the anakinra responders and inadequate responders using a chi-square test for categorical variables and a t-test for continuous variables. We compared outcomes obtained prospectively and retrospectively in the three periods of treatment using a Wilcoxon signed-rank test. This research was approved by the Sheba Medical Center Institutional Review Board and was compliant with the Declaration of Helsinki for studies involving human participants.

Results

Patients

We analysed a cohort of 3,866 patients enrolled in the Sheba Medical Center FMF registry from January 2010 to December 2019. A total of 219 patients with crFMF were treated with IL-1 inhibitors during this period, the reason for starting this treatment was the lack of adequate control of disease activity with colchicine for all patients. Of the 219 patients, 104 were treated with anakinra as the only IL-1 inhibitor, 69 were treated with canakinumab only, and treatment was switched from anakinra to canakinumab in 46 patients. No patients were switched from canakinumab to anakinra. All patients were treated with the standard dose of 100 mg per day of anakinra and 150 mg per month of Canakinumab. Of the patients who switched from anakinra to canakinumab, 23/46 switched due to insufficient control of the disease and were considered inadequate anakinra responders, 11 of whom had an initial adequate response to anakinra but subsequently showed an inadequate response. A total of 14/46 patients switched to canakinumab due to adverse reactions when treated with anakinra: 8 patients experienced injection site reactions, 3 patients experienced systemic allergic reactions, one patient experienced headaches, one patient experienced general weakness, and one patient had thrombocytopenia and elevated liver enzymes. A further 9/46 patients switched to canakinumab for other reasons, including patient preference (convenience of dosing) and health care provider preference (canakinumab incurred lower costs than anakinra for the health care provider after it was included in the Israeli Healthcare Basket). Treatment with colchicine was continued in all patients after the introduction of the IL-1 inhibitors according to the current guidelines for the treatment of FMF (due to lack of data regarding the effect of the latter on prevention of amyloidosis), and was adjusted as per the treating physician's judgement.

The demographics and baseline characteristics of the 46 patients who switched from anakinra to canakinumab, at the start of treatment with anakinra, are shown in Table I. Most patients had a severe phenotype of FMF with a high rate of flares (a median of 24 [IQR 12–25] per 6 months) and symptoms often involving multiple sites. All patients were treated with high oral doses of colchicine (median of 2.5 mg/d), and 37.5% were also treated with intravenous colchicine before initiating biological treatment. The majority of the patients were *M694V* homozygotes (55%), 29% were *M694V* heterozygotes, and the remaining patients had other *MEFV* mutations. A statistical comparison of the baseline characteristics between anakinra responders and inadequate responders showed no significant differences for any of the parameters presented in Table I (data not shown).

Efficacy of IL-1β inhibition in patients who switched from anakinra to canakinumab

The 46 patients who switched from anakinra to canakinumab were first treated with colchicine alone for a median (first quartile, third quartile) duration of 22.5 (13, 36) years, then with anakinra for 12 (3.6, 18) months, followed by treatment with canakinumab for 7 (5.0, 12) months. The frequency of flares, their duration, the severity of pain during flares, and the patient's global assessment of disease activity were compared between three periods of time: when patients were treated only with colchicine, with colchicine plus anakinra, and with colchicine plus canakinumab (Table II, Fig. 1). Patients

experienced significantly lower rates of flares during the period of anakinra treatment when compared with the previous period of treatment with colchicine only (p<0.01). However, the frequency of flares further decreased when patients were switched to canakinumab, with rates significantly lower versus anakinra for both the anakinra responder and inadequate responder groups (p<0.01 for both groups). The median duration of flares significantly decreased after initiation of treatment with anakinra (p<0.01), and the switch to canakinumab treatment resulted in a further reduction in the whole population (p=0.01), although differences did not reach statistical significance when responders and inadequate responders to anakinra were analysed separately. The reported severity of pain during flares was significantly lower after the initiation of treatment with anakinra (p<0.01), and further decreased after the switch to canakinumab (p<0.01). Finally, the patients' global assessment of disease activity was lower (*i.e.* symptoms improved) after the initiation of treatment with anakinra (p<0.01), and further decreased after the switch to canakinumab (p<0.01). Significant differences for both anakinra responders (p<0.01) and inadequate responders (p=0.03) were found.

Table I. Baseline characteristics.

	Anakinra inadequate responders (n=23)	Anakinra responders (n=23)	Total (n=46)
Age at diagnosis, median (Q1-Q3)	7 (4-16)	8 (2.5–17)	7.5 (3–16)
Age at initiating anakinra, median (Q1-Q3)*	42.5 (23–50.75)	37 (25–43.5)	39 (25–48)
Amyloidosis, n (%)	2/23 (8.6%)	4/23 (17%)	6/46 (13%)
Use of IV colchicine	8/16 (50%)	4/16 (25%)	12/32 (37.5%)
Maximal colchicine dose, median (Q1-Q3)	2.75 (2.5–3)	2.5 (2.5–3)	2.5 (2.5–3)
M694V homozygotes, n (%)	12/23 (52%)	13/23 (59%)	25/46 (55%)
M694V heterozygotes, n (%)	8/23 (34%)	5/23 (23%)	13/46 (28%)
Patients with other or unknown mutations	3/23 (13%)	3/23† (13%)	6/46† (13%)
Number of flares / 6 months, median (Q1-Q3)	24 (12-36)	24 (12-48)	24 (12-25)
Number of locations with symptoms during FMF attacks, median (Q1-Q3)	4 (3–5)	4 (3–5)	4 (3–5)

*n=18, 21 and 39 for responders, inadequate responders and total, respectively.
† Includes one patient without known mutations in the *MEFV* gene.
Q1: first quartile; Q3: third quartile.

Of note, 6 patients in our cohort were complete non-responders to anakinra, with no reduction in the frequency of flares and no improvements in any of the other parameters measured after starting anakinra treatment. Three of these patients reported clear improvements after their switch to canakinumab. The rate of flares per 6 months was decreased in two of these patients (12 and 20 flares less per 6 months, respectively), who also reported improvements in their assessment of global disease activity. The third patient did not have a reduction in the rate of flares, but reported improvements in duration of flares, in the severity of the pain associated with the flares, and in disease activity.

Discussion

IL-1 inhibitors are effective in controlling disease activity in patients with crFMF, which is essential in order to avoid complications of persistent inflammation, such as renal failure due to secondary amyloidosis (8-10, 12, 13). Both anakinra and canakinumab effectively inhibit the activity of IL-1β; however, there are no randomised controlled studies comparing their efficacy

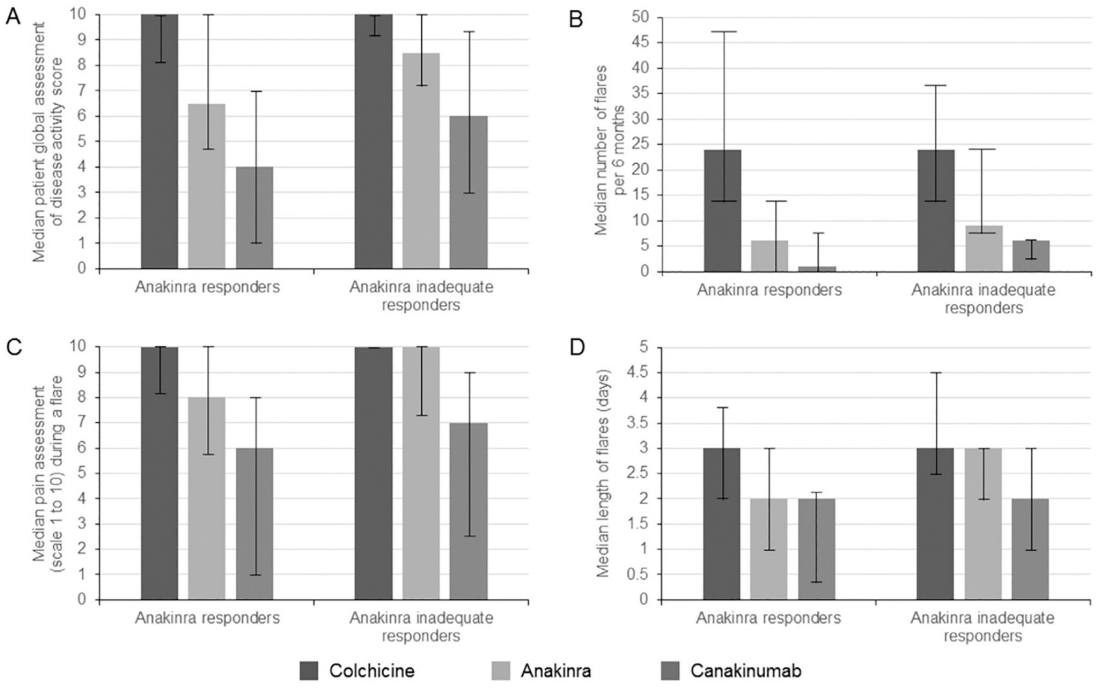

Fig. 1. Results for patients receiving colchicine only, anakinra, and canakinumab.
A: median patients' global assessment of disease activity score;
B: median number of flares per six months;
C: median pain assessment during a flare;
D: median length of flares (days).
Error bars represent interquartile ranges.

Table II. Patient-reported outcomes during periods of treatment with colchicine only, anakinra, and canakinumab.

Outcome	Treatment	Parameter	Patient group		Total
			Anakinra responders (n=23)	Anakinra inadequate responders (n=23)	(N=46)
Number of flares per 6 months	Colchicine only	Median (Q1–Q3)	24 (12–48) n=23	24 (12–36) n=21	24 (12–45) n=44
	Anakinra	Median (Q1–Q3)	6.0 (0–12) n=21	9.0 (6.0–24) n=21	6 (3.0–13.5) n=42
		Median change *vs*. colchicine only (%)	-18 (-75%) *p*<0.0001	-6 (-25%) *p*<0.0001	-12 (-50%) *p*<0.0001
	Canakinumab	Median (Q1–Q3)	1.0 (0–6.0) n=19	6.0 (3.0–6.0) n=14	3.0 (0–6.0) n =33
		Median change *vs*. colchicine only (%)	-22 (-91%) *p*<0.0001	-18 (-75%) *p*=0.0002	-18 (-75%) *p*<0.0001
		Median change *vs*. anakinra (%)	-3.0 (-50%) *p*=0.0093	-5.0 (-55%) *p*=0.0049	-3.5 (-58%) *p*<0.0001
Duration of flares (days)	Colchicine only	Median (Q1–Q3)	3 (2–3.8) n=16	3 (2.5–4.5) n=15	3 (2–4) n=31
	Anakinra	Median (Q1–Q3)	2 (1–3) n=14	3.0 (2.0–3.0) n=15	2.5 (2–3) n=29
		Median change *vs*. colchicine only (%)	-0.5 (-16.6%) *p*=0.0078	0 (0%) *p*=0.125	0 (0%) *p*=0.001
	Canakinumab	Median (Q1–Q3)	2 (0.38–2.13) n=14	2 (1–3) n=8	2 (0.88–3) n=22
		Median change *vs*. colchicine only (%)	-1.0 (-33%) *p*=0.0005	-0.5 (-16%) *p*=0.0625	-1.0 (-33%) *p*<0.0001
		Median change *vs*. anakinra (%)	-1 (-50%) *p*=0.07	-0.5 (-17%) *p*=0.0625	-1.0 (-50%) *p*=0.01
Pain severity during a flare (on a scale 1 to 10)	Colchicine only (n=16 and 16)*	Median (Q1–Q3)	10 (8.25–10) n=16	10 (10–10) n=16	10 (9.12–10) n=32
	Anakinra (n=14 and 16)*	Median (Q1–Q3)	8 (5.75–10) n=14	10 (7.25–10) n=16	8 (6.75–10) n=30
		Median change *vs*. colchicine only (%)	-1.5 (15%) *p*=0.0039	0 (0%) *p*=0.0859	0 (0%) *p*=0.001
	Canakinumab	Median (Q1–Q3)	6 (1–8) n=14	7 (2.5–9) n=9	6 (2–8) n=23
		Median change *vs*. colchicine only (%)	-3.5 (35%) *p*=0.001	-3 (30%) *p*=0.0469	-3 (30%) *p*=0.0002
		Median change *vs*. anakinra (%)	-2 (25%) *p*=0.0078	-2 (20%) *p*=0.0625	-2 (25%) *p*=0.001
Patient global assessment of disease activity	Colchicine only	Median (Q1–Q3)	10 (8.25–10) n=16	10 (9.25–10) n=16	10 (9–10) n=32
	Anakinra	Median (Q1–Q3)	6.5 (5–10) n=15	8.5 (7.25–10) n=16	8 (6–10) n=31
		Median change *vs*. colchicine only (%)	-1.5 (15%) *p*=0.002	-0.5 (5%) *p*=0.041	-1 (10%) *p*=0.0002
	Canakinumab	Median (Q1–Q3)	4 (1–7) n=15	6 (2–7.5) n=9	5 (2–7) n=24
		Median change *vs*. colchicine only (%)	-4 (40%) *p*=0.0002	-3 (30%) *p*=0.0273	-4 (40%) *p*<0.0001
		Median change *vs*. anakinra (%)	-2.75 (42%) *p*=0.0049	-3 (35%) *p*=0.0313	-3 (37.5%) *p*=0.0002

in FMF or other indications, nor are guidelines available to help physicians and patients decide which IL-1 inhibitor should be used in each case, and in which situations treatment should be switched from one inhibitor to the other.

In this study we describe the sequential effectiveness of anakinra and canakinumab, based on rate of flares and patient-reported outcomes. We describe a relatively large cohort of patients with crFMF who switched from anakinra to canakinumab. All patients were initially started on anakinra due to suboptimal control of disease with colchicine with a significant decrease in the median rate of flares. The decrease in the median rate of flares was significant in all patients, regardless to the reason they switched from anakinra to canakinumab, suggesting that anakinra was at least partially effective in the majority of patients, even those defined as "inadequate responders". However, both the rate of flares and the patient-reported disease activity further improved with treatment with canakinumab in both the anakinra responders and inadequate responder groups, suggesting that canakinumab was an effective therapeutic option for this patient population. These results are aligned with previous publications reporting the efficacy of canakinumab after discontinuation of anakinra in isolated cases and small case series (10, 11, 14-16). Moreover, in Epoch 4 of the Phase 3 CLUSTER trial, the long-term efficacy of canakinumab was studied in 60 patients with crFMF, including 15 who had been previously treated with anakinra (15 of whom during the year prior to baseline) (13). During the 72-week period, one patient reported two flares, 8 patients reported one flare, and 6 patients reported no flares, as compared with a median rate of 24 flares reported in the year before baseline. These data suggest that optimal disease control was achieved with canakinumab in these patients (Dekker, personal communication of unpublished data).

The results of our study suggest suboptimal efficacy of anakinra in certain patients with crFMF. Secondary failure of other biologics, such as TNF blockers, is a well-known phenomenon in certain diseases, including rheumatoid arthritis, where it has been shown that switching from a TNF blocker to an alternative biologic therapy may be an effective treatment strategy (17). In contrast, secondary failure of IL-1 inhibitors has not yet been described or studied in patients with crFMF, or other autoinflammatory conditions, and may present an important challenge in the management of patients with crFMF. No patients switched treatment from canakinumab to anakinra in our registry, and the efficacy of anakinra in patients who discontinued canakinumab remains largely unknown.

As the use of these drugs to treat patients with crFMF is increasing, large-scale studies would be beneficial in order to better characterise the patients at risk for failure of treatment with IL-1 inhibitors. In our cohort we did not find any baseline differences between anakinra "responders" and "inadequate responders", suggesting that the maintained response to Anakinra is unrelated to the baseline disease activity. Limitations of this study include the observational nature of the study design, and the fact that the patient-reported outcomes were obtained retrospectively at a time when patients were being treated with canakinumab.

In summary, the results of this study show that canakinumab is clinically effective in patients with crFMF who discontinued anakinra for a number of different reasons, including suboptimal control of disease.

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