Anakinra in familial Mediterranean fever: a profile of its use

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Abstract

The list of approved indications for anakinra (Kineret[®]), an anti-interleukin (IL)-1 biological, has been expanded in the EU to include Familial Mediterranean fever (FMF). The pathology of FMF is associated with excess production of IL-1, thus IL-1 blockade with anakinra was investigated as a treatment for FMF. Results from a phase 3 clinical trial and real-world experience in patients with FMF demonstrated reductions in FMF attack frequency, improvements in quality of life and reductions in serum amyloid A (SAA) and C-reactive protein (CRP) levels. Efficacy was also observed in patients with FMF and amyloidosis in the real-world setting; nevertheless, concurrent use of colchicine with anti-IL-1 biologicals is recommended to prevent and/or halt the progression of amyloidosis. Anakinra was generally well tolerated during the phase 3 clinical trial, with comparable proportions of patients with adverse reactions in the anakinra and placebo groups. Furthermore, the safety profile of anakinra in FMF was consistent with that established in other indications, based on all available evidence.

Adis evaluation of anakinra in the treatment of FMF

IL-1 receptor antagonist that blocks inflammation induced by the inappropriate production of IL-1 in patients with FMF

Decreases attack frequency, SAA and CRP levels, and improves quality of life in patients with FMF

Generally well tolerated

What is the rationale for using anakinra in familial Mediterranean fever (FMF)?

Familial Mediterranean fever (FMF) is a rare hereditary condition that is associated with self-limiting bouts of fever and serosal inflammation [1]. The underlying pathology of FMF is attributed to mutations in the *MEFV* (Mediterranean fever) gene; some *MEFV* gene mutations are associated with the abnormal production of anti-interleukin (IL)-1 β , which is

responsible for the inflammatory symptoms of FMF. FMF is most common in Mediterranean populations, where the prevalence of FMF in these populations is 1 in 1000 to 1 in 400 people [1]. Globally, the prevalence of the five founder *MEFV* mutations (V726A, M694V, M694I, M680I and E148Q) is estimated to be 0–4.4% [2].

Colchicine is the current recommended first-line therapy for FMF, with the goal of treatment being to prevent FMF attacks and to reduce acute phase reactants, serum amyloid A (SAA) in particular [3]. Minimizing SAA levels that are elevated due to chronic inflammation is important in patients with FMF, as amyloidosis is a serious consequence of uncontrolled FMF and may result in renal failure [3]. Although colchicine is effective in most patients with FMF [4], a considerable proportion of patients continue to experience FMF attacks without achieving complete disease control [5]. The criteria for colchicine resistance are yet to be formally defined [3, 4]; however, it is agreed that additional treatments are required for patients with colchicine-resistant FMF [3, 4]. Additionally, 5–10% of patients experience gastrointestinal effects, particularly diarrhoea, with therapeutic dosages of colchicine [6]. Therefore, the use of biological treatment may be required for patients with colchicine-resistant FMF or patients who are intolerant to colchicine [3].

Anakinra is an IL-1 biological treatment that has been approved in the EU for the treatment of FMF (Table 1). Discussion of the use of anakinra in other approved indications, such as rheumatoid arthritis (RA) [7, 8], cryopyrin-associated periodic syndromes (CAPS) and Still's disease [9], is outside the scope of this review.

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Table 1 Summary of the prescribing information of anakinra in the treatment of familial Mediterranean fever in the EU [10]

What is the approved indication for anakinra?	
Treatment of familial Mediterranean fever; in combination with colchicine, if appropriate	
How is anakinra available and how should it be stored?	
Availability	Graduated, pre-filled, single-use syringe containing 100 mg of anakinra in 0.67 mL of solution for injection (allows for doses between 20 to 100 mg)
Storage	Refrigerate, do not freeze; may be kept unrefrigerated at $\leq 25^{\circ}\text{C}$ for 12 h (dispose of syringe if not used within this period) Store in the original container to protect from light
What are the weight-based dosages of anakinra?	
Weight ≥ 50 kg	100 mg/day
Weight < 50 kg	1–2 mg/kg/day; can be $\uparrow$ to 4 mg/kg/day in children with inadequate response; not suitable in infants weighing < 10 kg
How should anakinra be administered as a subcutaneous injection?	
Preparation	Do not shake the syringe; eject excess solution from the syringe prior to administration
Injection sites	Suitable injection sites (rotate between injections): abdomen (excluding naval area), top of the thighs, upper outer areas of the buttocks and outer areas of the upper arms
To alleviate ISR	Leave at room temperature for ≈ 30 min or hold syringe gently in the hand for a few minutes; cool the injection site before and/or after injection; apply topical corticosteroids or antihistamines after injection
How should anakinra be used in special populations?	
Pts with renal impairment	Mild: no dosage adjustment required
	Moderate: use with caution
	Severe (or end-stage renal disease and dialysis pts): consider administering the prescribed dose once every 2 days ($\downarrow$ plasma clearance of anakinra with $\downarrow$ renal function)
Pts with hepatic impairment	Moderate: no dosage adjustment required
	Severe: use with caution (liver enzyme levels may $\uparrow$)
Elderly pts	Dosage adjustments are not expected to be required (based on the use of anakinra in other indications)
Pregnant or breastfeeding pts	Avoid use during pregnancy as a precautionary measure (data are limited)
	Discontinue breastfeeding during treatment (not known if anakinra is excreted in human milk)
What other special warnings/precautions pertain to the use of anakinra?	
Severe allergic reactions	Discontinue treatment and administer appropriate therapy
Infections	Pts with a history of recurring infections/predisposition to infections: use with caution
	Pts with active infections prior to initiating anakinra: do not initiate treatment
	Pts with serious infections during anakinra treatment: can continue treatment with careful monitoring
	Screen pts for latent tuberculosis prior to initiating treatment
	Screen pts for viral hepatitis before starting treatment (risk of hepatitis B reactivation)
Neutropenia ($\text{ANC} < 1.5 \times 10^9/\text{L}$)	Contraindicated in pts with neutropenia
	Measure ANC before treatment; monitor ANC monthly during the first 6 months then every 3 months; discontinue treatment and closely monitor ANC if neutropenia occurs
Immunosuppression	Pts with pre-existing malignancy: use is not recommended (lack of data)
What clinically relevant drug interactions may potentially occur with anakinra?	
TNF- α antagonists	Do not use concurrently (may $\uparrow$ rates of serious infections and neutropenia)
CYP450 substrates with a narrow TI	Consider therapeutic drug monitoring and dose adjustment of substrates ($\uparrow$ IL-1 β levels can suppress CYP450 enzymes; anakinra may normalize formation of CYP450 enzymes by $\downarrow$ IL-1 β levels)
Live vaccines	Do not administer during treatment with anakinra (insufficient data)

ANC absolute neutrophil count, IL interleukin, ISR injection-site reaction, pts patients, TI therapeutic index, TNF tumour necrosis factor, $\uparrow$ increase(d)/elevated, $\downarrow$ decreasing

What is the pathogenesis of FMF and the mechanism of action of anakinra?

Anakinra is a recombinant human IL-1 receptor antagonist that inhibits binding of IL-1 to its receptor, and thereby prevents IL-1-mediated inflammation (Fig. 1). Mutations in the *MEFV* gene cause the production of mutant pyrin,

which is associated with abnormal activation of the pyrin inflammasome [11]. Inflammasome activation results in the production of IL-1 β , and the accompanying inflammation is responsible for the clinical signs of FMF attacks. Elevated levels of SAA are a consequence of chronic inflammation, which may lead to amyloidosis and renal damage [12]. IL-1 receptor blockade by anakinra prevents the binding of IL-1 β

to its receptor, thus preventing or reducing the severity of FMF attacks [12].

What are the pharmacokinetic properties of anakinra?

The pharmacokinetics (PK) of anakinra have been established in patients with other indications and in healthy subjects; PK studies were not conducted in patients with FMF [12]. The absolute bioavailability of anakinra is 95% in healthy subjects [10]. In patients with RA, maximum plasma concentrations are reached 3–7 h after administration of clinically relevant doses (1–2 mg/kg), with no noticeable distribution phase. The terminal half-life of anakinra is 4–6 h, and clearance increases with increasing creatinine clearance [10].

What is the efficacy of anakinra in FMF?

The efficacy of anakinra in reducing the frequency of FMF attacks was demonstrated in a pivotal, randomized, double-blind, phase 3 clinical trial (Table 2) [13]. This trial included 25 patients aged ≥ 18 to ≤ 65 years who experienced at least one FMF attack per month in any of the four FMF sites (chest, abdomen, joints and skin). FMF in these patients was considered to be colchicine-resistant, as patients were receiving a maximum tolerated dosage of colchicine (≥ 2 to ≤ 3 mg/day), or were intolerant to colchicine ≥ 1.5 mg/day.

Subcutaneous injections of anakinra 100 mg or placebo were self-administered daily for 4 months. Colchicine and other previous treatments were continued during the trial. [13].

The primary endpoint of the trial was the difference between anakinra and placebo in the total number of FMF attacks during the study period, adjusted to participation time (number of attacks per patient per month), as well as the difference between anakinra and placebo in the number of patients with a mean of < 1 FMF attack per month [13]. Both primary endpoints were met after 4 months of treatment; the mean frequency of FMF attacks in any site was significantly lower in patients treated with anakinra than in patients receiving placebo, and significantly more anakinra-than placebo-treated patients had < 1 FMF attack per month (Table 2). The mean frequency of joint attacks per month was significantly lower in the anakinra group than in the placebo group ($p = 0.019$); however, attack frequency in other sites (abdomen, chest and skin) did not differ significantly between treatment groups. Mean levels of inflammatory proteins [C-reactive protein (CRP) and SAA] were numerically lower (both $p = 0.069$) and mean quality of life (QoL) scores were significantly higher with anakinra relative to placebo (Table 2).

In a post hoc survival analysis, the mean time to reach the target of 4 FMF attacks was 89.8 days in the anakinra group and 39.6 days in the placebo group ($p = 0.015$). In another post hoc analysis, the proportion of patients who achieved improvement according to the modified FMF 50% improvement (FMF50) score was 83% with anakinra and 31% with placebo ($p < 0.008$). Modified FMF50 was defined

Fig. 1 Pathology of familial Mediterranean fever, and mechanism of action of colchicine and anakinra [11]. *IL* interleukin, *MEFV* Mediterranean fever, *SAA* serum amyloid A

Table 2 Efficacy of anakinra 100 mg/day in patients with colchicine-resistant familial Mediterranean fever in a pivotal phase 3 study [13]

Key results at end of study (4 mo)	Anakinra (<i>n</i> = 10–12)	Placebo (<i>n</i> = 6–13)
Mean no. of FMF attacks in any site/mo ^a	1.7*	3.5
No. of pts with < 1 FMF attack/mo ^a	6**	0
Mean CRP level (mg/L)	3.9	19.9
Mean SAA level (mg/L)	11.1	110.3
QoL (VAS score, cm)	7.7*	4.2

All pts received colchicine during the study (mean baseline dosage 2.1–2.2 mg/day).

CRP C-reactive protein, *mo* months, *pts* patients, *QoL* quality of life, *SAA* serum amyloid A, *VAS* 10 cm visual analogue scale (higher scores indicate higher QoL)

* $p < 0.05$, ** $p < 0.001$ vs PL

^aPrimary endpoint

as a $\geq 50\%$ improvement in at least three of the four following categories: frequency of all FMF attacks, frequency of joint attacks, CRP or SAA levels (or normalization of these markers), and QoL score [13].

Real-world experience with anakinra and canakinumab (i.e. anti-IL-1 biological treatments) supports the efficacy results observed during the pivotal phase 3 trial (Table 3) [14–19]. Decreases in FMF attack frequency [14–18], CRP levels [14, 16, 17, 19], and/or reduction of disease activity [15–17, 19] were reported with anti-IL-1 treatment across six studies that each included ≥ 20 patients treated with anakinra (Table 3). Improvements were also reported across all 36-item short form survey (SF-36) QoL domains following anti-IL-1 treatment in one study (Table 3) [18].

Can anakinra be used in patients with FMF and amyloidosis/renal impairment?

Anakinra may be used in patients with FMF and amyloidosis or renal impairment; however, caution is recommended in patients with moderate renal impairment, and decreasing the frequency of treatment to once every 2 days should be considered in patients with severe renal impairment (Table 1) [10].

Anakinra was effective in patients with amyloidosis and various stages of renal impairment (including renal transplant patients) in a real-world study of 40 patients with FMF, 36 of whom were treated with anakinra [19]. Overall, anti-IL-1 therapy improved or stabilized renal function in 79.4% of patients, and decreased CRP levels and disease activity (Table 3). However, earlier stages of renal impairment may be more receptive to anti-IL-1 therapy. The beneficial effects of anti-IL-1 therapy on renal function were

more pronounced in patients with a baseline creatinine level of < 1.5 mg/dL than in those with a baseline creatinine level of ≥ 1.5 mg/dL (Table 3) [19]. A similar trend was observed in a study of patients with colchicine-resistant FMF; only the subset of patients with a glomerular filtration rate of ≥ 60 mL/min/m² experienced a significant improvement in proteinuria (Table 3) [16]. In other studies in patients with amyloidosis and FMF treated with anti-IL-1 therapy, organ failure was not observed (Table 3) [17] and, in another study, some SF-36 QoL domain scores improved in this subset of patients (Table 3) [18].

According to the EMA, there is insufficient evidence to support the efficacy of anakinra in the prevention of amyloidosis or improvement in renal function [12]. Concurrent treatment with colchicine is recommended (if appropriate) [12], as colchicine is an established treatment for the prevention of amyloidosis in FMF patients [3, 12].

Can anakinra be used on-demand?

On-demand treatment with anakinra was suitable for some patients based on real-world experience [20]; on-demand use of anakinra is not discussed in the EU prescribing information [10]. Patients with prominent prodromal signs or triggers, such as menstruation or long travel, may benefit most from on-demand treatment, as they may administer anakinra to prevent or reduce the severity of FMF attacks [20]. This approach may not be appropriate for all patients, particularly those with persistent inflammation, as the long-term effects of on-demand treatment are unknown [20].

On-demand anakinra treatment was effective in a real-world study in 15 patients, over a median of 6 months with on-demand therapy [20]. In the study, patients who were already receiving a maximum tolerated dose of colchicine were treated with on-demand anakinra for 2–3 days after experiencing a prodromal sign, or before and during exposure to an attack trigger (e.g. 5 consecutive days during menstruation). Patients also continued to take colchicine at the highest tolerated dose. Anakinra taken on-demand provided significant improvements from baseline in attack frequency (two vs four attacks per 3 months; $p = 0.002$), attack severity (6 vs 10 on a visual analogue scale; $p = 0.001$) and attack duration (1.5 vs 3 days; $p = 0.001$) in the total population. Additionally, by the end of the study, work absenteeism (2 vs 7 days per 3 months) and presenteeism (3.5 vs 9 days per 3 months) significantly ($p = 0.002$) improved in 14 working patients. CRP levels did not significantly change from baseline; however, the effect of on-demand treatment with anakinra on CRP levels is unknown, as patients with signs of persistent inflammation, proteinuria or amyloidosis were excluded. At the end

Table 3 Efficacy of anakinra in familial Mediterranean fever in real-world studies that each included ≥ 20 patients treated with anakinra

Location	Treatments (no. of pts); duration (mo)	Key results (anti-IL-1 agents vs BL)
Pts with COL-resistant FMF		
Turkey [14]	Anti-IL-1 therapy + COL ^a (172) [ANA (151) or CAN (21)]; > 6 (mean 19.6)	Mean no. of FMF attacks/year: 2.3** vs 16.2 Mean CRP level: 9.3** vs 49.4 mg/L Mean 24 h urinary protein: 3557.3** vs 5458.7 mg
Turkey [15]	ANA + COL ^a (106); ≥ 1 (mean 16.0)	No FMF attacks: 75 pts (70.8%) $\geq 50\%$ $\downarrow$ in FMF attack frequency: further 16 pts (15.1%) Disease activity VAS: 3.1** vs 7.5 cm
Turkey [16]	Anti-IL-1 therapy + COL ^a (65) [ANA (41) or CAN (24)]; ≥ 3 (ANA median 6, CAN median 8)	Median FMF attack frequency/ 3 mo: 0** vs 3 Median CRP level: 2** vs 16 mg/dL Median disease activity VAS: 2** vs 10 cm (pts); 1** vs 9 cm (phys) Median proteinuria in pts ^b with GFR ≥ 60 mL/min/m ² : 890* vs 2390 mg/day Median proteinuria in pts ^b with GFR < 60 mL/min/m ² : 3960 vs 4472 mg/day
Germany [17]	Anti-IL-1 therapy + COL ^a (31) [ANA (29) or CAN (2)]; ≥ 6	FMF attack frequency: $\downarrow$ * CRP levels: $\downarrow$ ** SAA levels: $\downarrow$ ** Disease activity VAS: $\downarrow$ ** (pts); $\downarrow$ ** (phys) Organ failure in 12 pts with amyloidosis: 0% Median 24 h urinary protein in 12 pts with amyloidosis: 0.4 vs 5.0 g Serum creatinine levels in 12 pts with amyloidosis: $\downarrow$ in 4 pts; stable in 8 pts Disease activity VAS in 12 pts with amyloidosis: $\downarrow$ ** (pts); $\downarrow$ ** (phys)
Turkey [18]	Anti-IL-1 therapy (44) [ANA (33) or CAN (11)] ^a ; 3	Median FMF attack frequency/ 3 mo: 1** vs 6 Duration of FMF attack: 1** vs 3 days Severity of attack VAS: 4** vs 8 cm SF-36 QoL domains (all pts): $\uparrow$ median physical** and social** functioning, physical* and emotional** role functioning, energy**, emotional well-being**, pain** and general health** scores SF-36 QoL domains in 17 pts with amyloidosis: $\uparrow$ median energy*, emotional well-being*, social functioning* and pain* scores
Pts with amyloidosis secondary to FMF		
Turkey [19]	Anti-IL-1 therapy + COL ^a (40) [ANA (36) or CAN (4)]; > 3 (mean 25.9)	24 pts with creatinine < 1.5 mg/dL: $\uparrow$ median CL _{CR} (106* vs 95 mL/min); $\downarrow$ median proteinuria (252* vs 1525 mg/day), VAS disease activity (1* vs 8 cm) and CRP (1.6* vs 5 mg/L) 16 pts with creatinine ≥ 1.5 mg/dL: $\downarrow$ median CL _{CR} (32.4* vs 36 mL/min); $\uparrow$ median proteinuria (2595.9* vs 2362 mg/day); $\downarrow$ median VAS disease activity (2* vs 7 cm) and CRP (6* vs 25 mg/mL) 5 dialysis pts: $\downarrow$ CRP in 1 pt ($\uparrow$ in 4 pts), $\downarrow$ VAS disease activity in all pts 4 renal transplant pts: $\downarrow$ CRP and VAS disease activity in all pts

Where reported, pts generally received ANA 100 mg/day [14, 16–19], with a few pts receiving lower [14, 17] or higher [14, 17, 19] dosages; or CAN 150 mg every 4 [18, 19], 8 [14, 16, 17, 19] or 12 [14] weeks, or CAN 300 mg every 4 weeks [19]

ANA anakinra, BL baseline, CAN canakinumab, CL_{CR} creatinine clearance, COL colchicine, CRP C-reactive protein, FMF familial Mediterranean fever, GFR glomerular filtration rate, mo months, NR not reported, phys physicians, pt(s) patient(s), QoL quality of life, SAA serum amyloid A, SF-36 36-item short form survey ($\uparrow$ scores indicate $\uparrow$ QoL), VAS visual analogue scale, $\downarrow$ decrease, $\uparrow$ increase/higher

* $p < 0.05$, ** $p \leq 0.001$ vs BL

^aCOL use: 0.5–4 mg/day (in 95% of pts) [14], mean 2.34 mg/day (in 92% of pts) [15], 0.5–2.5 mg/day (in 88% of pts) [16], 0.5–3 (mean 1.5) mg/day [17], mean 1.23 mg/day [19] or NR [18]

^bPt numbers per subgroup were NR

of the study, 10 of 15 patients continued to be managed with on-demand anakinra, with five patients switching to continuous anakinra treatment [20].

On-demand anti-IL-1 therapy appeared to be effective in a study of young patients with FMF (mean age at treatment initiation 11.5 years) [21]. Of the 36 patients in this

study, six patients were treated with on-demand anti-IL-1 therapy, including four patients with menstruation-triggered FMF. Anakinra was preferred for on-demand treatment over canakinumab in this study due to its shorter response time and half-life. In the four patients with menstruation-triggered FMF attacks, who were instructed to administer

anakinra daily for 3 days from the first day of menstruation, no attacks were reported during 15 months of follow-up, and improvements in CRP levels and QoL were observed. The efficacy of on-demand treatment in the other two patients was not reported [21].

What is the tolerability profile of anakinra in FMF?

The safety profile of anakinra in FMF is consistent with its established safety profile in other indications, such as RA, Still's disease and CAPS [10]. Overall, the most common (frequency $\geq 10\%$) adverse reactions associated with anakinra (regardless of indication) are increased blood cholesterol, headache and injection site reactions (ISRs) [10].

Anakinra 100 mg/day for 3 months was generally well tolerated in the pivotal phase 3 trial in 25 patients with colchicine-resistant FMF [13]. Drug-related adverse events (ISRs, headache, presyncope, dyspnoea and itching) were reported in 16.7% of patients in the anakinra group and 30.8% of patients in the placebo group. The proportion of patients with local ISRs was comparable between the anakinra and placebo groups (41.7% and 46.2%). Serious adverse events were not reported during the trial. All adverse events were mild or moderate in severity in both the anakinra and placebo groups [13].

Anti-IL-1 biologicals (including anakinra) had an acceptable safety profile in real-world studies in patients with FMF [14, 16, 17, 19]. In the largest dataset of patients receiving only anakinra ($n = 106$), ten patients discontinued treatment due to adverse events, including skin reactions ($n = 5$), leukopenia ($n = 4$), increased liver enzymes ($n = 3$) or ISRs ($n = 2$). All adverse events were reversible and resolved after discontinuation of treatment [15].

Anakinra may be associated with ISRs, which typically present as erythema, ecchymosis, inflammation and/or pain that develops within 2 weeks of initiating treatment and resolves within 4–6 weeks [10]. Recommendations should be followed to alleviate ISRs (Table 1). Other precautions should also be followed with regard to the risk of allergic reactions, infections and neutropenia (Table 1) [10].

What is the current clinical role of anakinra in FMF?

Anakinra is an effective treatment option in FMF, with reductions in frequency and severity of FMF attacks reported in patients with colchicine-resistant FMF in a phase 3 clinical trial (Table 2) and in the real-world setting (Table 3). The safety profile of anakinra has been established in other

indications [10], and treatment was generally well tolerated in patients with FMF [13].

The two overarching objectives in EULAR guidelines for the treatment of FMF are to prevent FMF attacks and to minimize subclinical inflammation between attacks to prevent the progression of amyloidosis [3]. Guidelines recommend initiating treatment with colchicine as soon as FMF is diagnosed, and the addition of a biological treatment is recommended in patients who experience ≥ 1 attack per month for 6 months while receiving a maximally tolerated dosage of colchicine. While no particular biological treatment is recommended over others, EULAR guidelines suggest anti-IL-1 therapies in combination with colchicine are promising second-line treatment options [3]. As the most recent EULAR recommendations were published prior to the EU approvals of anakinra [10] and canakinumab [22], updated guidelines are awaited with interest.

First-line treatment with anakinra and colchicine may be justified in some patients, despite recommendations in current EULAR guidelines [3]. Colchicine is often ineffective in FMF patients with amyloidosis, and starting treatment with anti-IL-1 biologicals after colchicine failure may result in patients irreversibly losing the opportunity to benefit from biological therapy [23]. Real-world experience with anakinra supports this viewpoint, as the efficacy of anakinra was less pronounced in patients with renal insufficiency and/or amyloidosis (Table 3) [19].

To date, no randomized trials have directly compared the efficacy of anakinra with that of canakinumab, another biological anti-IL-1 therapy, in the treatment of FMF. In the absence of such trials, a preference for one treatment over another can only be based on indirect data. Economic factors may dictate treatment preference [24]. Differences in dosing frequency between anakinra and canakinumab may also influence treatment preference, as anakinra is administered daily [10], while canakinumab is administered once every 4 weeks [22]. Although the less frequent dosing of canakinumab is potentially more convenient to patients, the shorter duration of action of anakinra has been preferred for on-demand treatment [20]. Although data are limited, on-demand therapy with anakinra may be considered in patients with prominent prodromal signs or triggers and without signs of sustained inflammation [20]. Further research is required to determine the efficacy of on-demand anakinra treatment of FMF attacks.

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