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Original Article

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Effectiveness and probability of full disease control with canakinumab in familial Mediterranean fever: real-world data from the AIDA Network

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Abstract

Objectives: **To assess the effectiveness of canakinumab (CAN) in controlling clinical and laboratory inflammation by achieving complete control of cardinal disease manifestations and full normalization of laboratory inflammatory markers.**

Methods: **Data were obtained from the international AutoInflammatory Disease Alliance (AIDA) network registry, dedicated to monogenic autoinflammatory diseases. The assessment included both retrospective and prospective real-world data.**

Results: **In total, 158 FMF patients treated with CAN were enrolled. Complete clinical-laboratory response was observed in 45.6% of patients at 3 months, 58.6% at 12 months and 55.2% at the last follow-up, after a mean treatment duration of 45 months. Partial response occurred in 16.5%, 12.5% and 16.8% at the same timepoints, respectively. Complete absence of clinical manifestations was observed in more than 80% of patients at each timepoint. Inflammatory markers normalized significantly by the 3-month assessment. The probability of achieving and maintaining complete response and full laboratory control appeared higher in patients reaching these outcomes by 3 months, although it remained substantial in other patients as well. Complete response was associated with a relapsing-remitting disease course and fewer annual attacks. Nearly all patients maintained stable organ damage scores, and therapy discontinuation due to inefficacy was rare (≤6%).**

Conclusion: **CAN is effective in achieving rapid and sustained clinical and laboratory control in FMF, including stringent endpoints of complete response. Early effectiveness may favour better long-term outcomes, but delayed achievement of complete response and full laboratory control is not uncommon. This study confirms CAN as an effective, and durable therapeutic option in FMF.**

Keywords FMF, long-term remission, IL-1, autoinflammatory diseases, AIDA Registry

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Rheumatology key messages

- Canakinumab provides rapid and durable control of clinical symptoms and inflammation in FMF patients.
- Early treatment response predicts better long-term outcomes, although delayed remission remains achievable.
- Sustained disease control and stable organ damage support canakinumab as an effective long-term therapy.

Introduction

FMF is a hereditary autoinflammatory disease characterized by recurrent episodes of fever and serositis, most commonly affecting populations of Mediterranean descent. The primary treatment is colchicine, which is effective in reducing attack frequency, improving quality of life and preventing secondary amyloidosis in the majority of patients [1]. For patients who are colchicine-resistant or intolerant, alternative therapies are required. The most established options are IL-1 inhibitors, including the IL-1 receptor antagonist anakinra and the monoclonal antibody targeting IL-1β canakinumab (CAN). In particular, CAN has demonstrated efficacy in FMF patients either when refractory to colchicine or unable to continue colchicine due to adverse events. The pivotal CLUSTER trial demonstrated that 61% of FMF patients treated with CAN achieved a complete response at week 16, compared with only 6% in the placebo group [2]. Observational cohorts and meta-analyses consistently report that CAN induces rapid and sustained remission in a majority of colchicine-resistant FMF patients, including those who have failed or are intolerant to the IL-1 receptor antagonist anakinra [3–8].

Although the available data are valuable and robust, the number of FMF patients treated with CAN in individual studies remains relatively small, typically well under 100 patients. At the best of our knowledge, excluding meta-analyses, the CLUSTER trial cohort of 61 patients constitutes the largest published group of FMF patients treated with CAN to date [5].

The aim of this study is to assess the clinical and laboratory effectiveness of CAN based on real-world data from the AutoInflammatory Disease Alliance (AIDA) Network cohort.

Materials and methods

This is a cohort study based on data collected in the International AIDA Network Registry dedicated to patients with monogenic autoinflammatory diseases, registration number NCT05200715, available at https://clinicaltrials.gov [9].

Data drawn from the AIDA registry included demographic, clinical, genetic and laboratory aspects related to FMF, as well as the response to treatment in terms of clinical and laboratory inflammatory manifestations. Inclusion criteria for the patients' enrolment consisted of fulfilling the Tel Hashomer criteria and/or the Livneh criteria [10–12], while the identification of pathogenic mutations in the *MEFV* gene was supportive. When diagnostic criteria were not fulfilled, the EuroFever classification criteria were required to include the patient in the study [13]. Patients with amyloidosis were not excluded from the study.

The objective of this study was to assess the effectiveness of CAN in controlling both clinical and laboratory inflammation and in achieving *complete response*, defined as full normalization of laboratory inflammatory markers and the complete absence of fever episodes, serositis, arthritic flares, FMF-related skin involvement or abdominal pain. This stringent definition was intentionally adopted to identify patients achieving complete clinical-inflammatory control, considering the importance of suppressing both overt manifestations and subclinical inflammation in FMF. Patients presenting with a slight increase in a single inflammatory marker and/or those with persistent clinical manifestations that were reduced by at least 50% in terms of episode frequency, episode duration, arthritis attacks and both physician's and patient's global assessment were classified as having a *partial response*, according to the FMF50 score criteria [14].

Full laboratory control was defined as normalization of CRP to $<$0.5 mg/dl, ESR to $<$25 mm/h and serum amyloid A (SAA), when available, to $<$10 mg/l. Patients who did not achieve full laboratory response but reached only a partial laboratory response were required to have reductions of at least 50% from baseline in CRP, ESR and, when available, SAA. *Complete absence of disease activity* was defined as the total absence of clinical manifestations and CRP, ESR and/or SAA serum values within normal ranges.

The timepoints for assessing response to therapy were at 3 and 12 months from the initiation of CAN (*baseline*), as well as at the last assessment for patients with a treatment duration exceeding 12 months. *Baseline* was defined as the time of initiation of CAN treatment. Clinical and laboratory variables recorded at baseline corresponded to the last available assessment prior to treatment initiation, irrespective of the presence or absence of active disease at that time. The study also included patients who initiated CAN while in clinical remission, as a result of prior effective disease control achieved with colchicine, which was subsequently discontinued due to intolerance or adverse events. In these cases, the indication for switching to CAN was not active disease at baseline, but the need for an alternative long-term therapy due to colchicine-related safety or tolerability issues. Disease activity at baseline was therefore interpreted in the context of each patient's clinical history, including prior flares and inflammatory episodes. According to the European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of FMF [15], colchicine-resistant (or non-responder) patients were defined as those experiencing one or more attacks per month despite receiving the maximum tolerated dose of colchicine; colchicine-intolerant patients were defined as those who developed adverse events that prevented the achievement or maintenance of an effective colchicine dose. Organ damage was evaluated using the Autoinflammatory Disease Damage Index (ADDI) [16] at the start of CAN treatment, at 12 months and at the last assessment.

Descriptive statistics were reported as absolute and relative frequencies, means with standard deviations, and medians with interquartile ranges. Associations between complete response

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and FMF features, as well as between colchicine use and complete response or full laboratory control, were evaluated using univariate binary logistic regression with Firth's correction. Firth's method was applied to reduce bias in the parameter estimates due to small sample sizes or rare events. Odds ratios (OR) and 95% confidence intervals (95% CIs) were derived from the regression estimates.

Differences in the proportion of patients with elevated CRP, ESR or SAA were assessed using the chi-squared test, with *post hoc* comparisons performed via the McNemar test and Bonferroni correction. Quantitative changes in laboratory markers were analysed using repeated-measures ANOVA or the repeated-measures Friedman test, depending on data distribution, followed by *post-hoc* paired t-tests or Wilcoxon signed-rank tests, as appropriate, with Bonferroni correction.

Probabilities of maintaining or achieving complete response or full laboratory control at the last assessment were calculated conditional on response status at prior time points.

Analyses were performed using an on-treatment approach, with follow-up censored at the time of CAN discontinuation. In addition, patients without sufficient follow-up to reach predefined assessment timepoints were excluded from the corresponding analyses, as these outcomes could not be reliably assessed outside periods of active treatment exposure.

As a sensitivity analysis, the main laboratory and response outcomes were re-evaluated excluding SAA from the definition of laboratory control and complete response. In this analysis, laboratory control was defined based on CRP and ESR values only. Results were compared with those obtained in the primary analysis to assess the potential impact of the limited availability of SAA measurements.

Missing data were handled using a complete-case approach; only patients with available data were included in each specific analysis.

The significance level was 95% (P-value <0.05); P-value was two-tailed. All statistical analyses were performed using RStudio software (version 4.3.0, Posit PBC, Boston, MA, USA).

The Ethics Committee of Azienda Ospedaliero-Universitaria Senese, Siena, Italy (Ref. N. 14951; NCT05200715) approved the study, which was performed according to the Good Clinical Practice guidelines and the latest Declaration of Helsinki. Written informed consents for involved patients were collected. Clinical data are kept in accordance with the EU General Data Protection Regulations (GDPR), or other counterparts, on the processing of personal data and the protection of privacy (2016/679/EU).

Results

In total, 158 FMF patients treated with CAN were enrolled (age range at the start of CAN 1.1–65.3 years). The mean treatment duration of CAN was 45.17 ± 34.45 months, for a total of 7091 months of observation, corresponding to 590.9 patients-years. In particular, 128 patients had been treated for at least 12 months at the time of the study, and 125 patients had a follow-up longer than 12 months. The median follow-up after the 12-month assessment was 34 months (range 2–202 months). Table 1 shows the demographic and clinical features of patients

Table 1 Demographic, clinical and therapeutic features of patients enrolled.

Variables	
Sex (females/males)	76/82
Age at disease onset in years, median (IQR)	3.8 (5.4)
Age at diagnosis in years, median (IQR)	6.85 (13.45)
Disease duration at diagnosis, median (IQR)	2.1 (5)
Age at the start of CAN in years, median ± S.D.	20.25 ± 13.9
Disease duration at the start of CAN in months, median ± S.D.	155.35 ± 132.11
Pediatrics at start of CAN, *n* (%)	58 (36.7%)
Adults at start of CAN, *n* (%)	100 (63.3%)
Number of attacks per year, *n* (IQR)	12 (10)
Mean duration of attacks (days)	3 (1)
Relapsing-remitting/chronic disease course	147 (93%)/9 (7%)
FMF manifestations at the start of CAN	***n* (%)**
Fever episodes	111 (70.3)
Serositis	73 (46.2)
Abdominal pain	69 (43.7)
Peritonitis	61 (38.6)
Pleuritis	26 (16.5)
Pericarditis	3 (1.9)
Skin rash	11 (7)
Treatment details	***n* (%)**
CAN starting dosage 150 mg/4 weeks	83 (52.5)
CAN starting dosage 300 mg/4 weeks	5 (3.2)
CAN starting dosage as mg/kg/4 weeks	70 (44.3)
Higher CAN dosage 150 mg/4 weeks	74 (46.8)
Higher CAN dosage 300 mg/4 weeks	13 (8.3)
Higher CAN dosage as mg/kg/4 weeks	71 (44.9)
Final CAN dosage 150 mg/4 weeks	71 (44.9)
Final CAN dosage 300 mg/4 weeks	8 (5.1)
Final CAN dosage as mg/kg/4 weeks	79 (50)
Concomitant colchicine at the start	130 (82.3)
Concomitant colchicine at the last assessment	115 (72.8)
Colchicine intolerance	5 (3)
Colchicine resistance	28 (17)
Previous treatments	***N* (%)**
Anakinra	91 (58)
Adalimumab	14 (8.9)
Etanercept	13 (8.2)
Certolizumab	7 (4.4)
Golimumab	1 (0.6)
Infliximab	1 (0.6)
Cause for CAN introduction	***n* (%)**
No efficacy experienced with previous treatments	68 (43)
Partial efficacy experienced with previous treatments	74 (46.8)
Loss of efficacy to previous treatments	7 (4.4)
To improve adherence to treatment	5 (3.2)
Adverse events with previous treatments	4 (2.5)

Percentages were obtained referring to the total number of patients included in the study ($n = 158$).
CAN, canakinumab; FMF, familial mediterranean fever; IQR: interquartile range; SD, standard deviation.

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enrolled, including CAN dosing at treatment initiation, the highest CAN dose administered during follow-up and the dose recorded at the last assessment. Regarding posology changes, dose escalation was observed in 10/158 (6.3%) patients, whereas dose reduction occurred in 21/158 (13.3%) patients. Supplementary Table S1 provides detailed information about the genetic *MEFV* variants identified in this cohort.

Clinical response

Complete absence of disease activity was observed in 4/158 (2.5%) cases at the start of CAN; the complete response was observed in 72/158 (45.6%) cases as soon as the 3-month assessment, in 75/128 (58.6%) cases at the 12-month assessment and in 69/125 (55.2%) patients at the last assessment. A partial disease control was reported in 26/158 (16.5%) cases at the 3-month assessment, in 16/128 (12.5%) cases at the 12-month visit and in 21/125 (16.8%) cases at the last assessment. Figure 1 shows the flow of complete response across the different timepoints; Table 2 provides data from Firth logistic regression about associations between complete response and FMF features at the different timepoints.

The complete absence of clinical manifestations was observed in 30 (19%) cases at the baseline, 136/158 (86.1%) at the 3-month assessment, 106/128 (82.8%) at the 12-month assessment and 102/125 (81.6%) at the last assessment ($P < 0.001$). Figure 2 shows the frequency of the cardinal clinical manifestations reported at the different timepoints.

Among subjects who had not achieved complete response at month 3, 32.43% attained complete response at month 12. The probability of maintaining RC at the last assessment was 80% for those with complete response at both 3 and 12 months, and 57.14% for those with complete response at month 3 but not at month 12. In contrast, only 25% of subjects who had not achieved RC at either month 3 or month 12 reached complete response at the last assessment. Figure 3 summarizes these probabilities.

There was no statistically significant evidence that concomitant use of colchicine affects the likelihood of achieving a complete response at 3 months (OR: 1.28, 95% CI: 0.37–4.45, $P = 0.70$), at 12 months (OR: 0.94, 95% CI: 0.3–2.9, $P = 0.91$) or at the last assessment (OR: 1.55, 95% CI: 0.6–4.03, $P = 0.37$).

The ADDI score increased in 2/128 patients with at least 1 year of follow-up, therefore remaining unchanged in 98.4% of cases treated with CAN.

Control of laboratory inflammation

At the start of CAN 101 patients presented increased inflammatory markers out of the 135 available data (74.8%). Increased laboratory inflammatory markers were reported in 36 out of the 113 available data (31.9%) at 3-month assessment and in 27 out of 104 available data (26%) at 12-month assessment. At the last assessment, 36/110 patients with available data (32.7%) showed increased inflammatory markers. The decrease was statistically significant overall ($P < 0.001$) as well as between baseline and the 3-month ($P < 0.001$), 12-month ($P < 0.001$) and last assessment ($P < 0.001$).

The ESR value was available in 125 patients at the start of CAN; on average, ESR decreased from 18 (IQR: 22) mm/h at the start of CAN to 12 (IQR: 11) mm/h at the 3-month assessment, 9 (IQR: 8.5) mm/h at the 12-month visit and 9 (IQR: 13) mm/h at the last assessment. The overall decrease was highly significant ($P < 0.0001$), while pairwise comparisons showed a significant decrease from baseline to 3 months ($P < 0.0001$), baseline to 12 months ($P < 0.0001$) and baseline to the last assessment ($P < 0.0001$). No significant changes were observed from the 3-month to 12-month visit ($P = 1.0$) or from the 12-month visit to the last assessment ($P = 1.0$).

The CRP value was available in 131 patients at the start of CAN; the median CRP decreased from 1.1 mg/dl (IQR: 2.5) at baseline to 0.3 mg/dl (IQR: 0.52) at the 3-month assessment, 0.2 mg/dl (IQR: 0.42) at the 12-month visit and 0.3 mg/dl (IQR: 0.75) at the last assessment. The overall decrease was highly

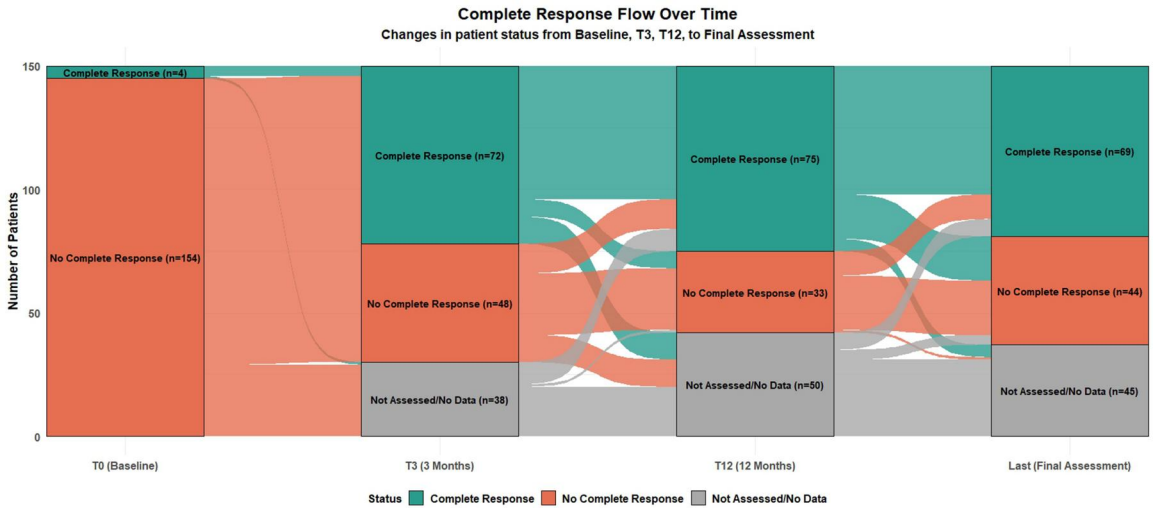


Figure 1 Flow of complete response over time in FMF patients treated with canakinumab. The Sankey diagram depicts changes in patient status from baseline (T0) through 3 months (T3), 12 months (T12), and the last available assessment by providing absolute frequency counts. Patients are categorized as achieving complete response (green), not achieving complete response (red), or not assessed/no data (grey). The figure highlights both the proportion of patients achieving complete response at each timepoint and the transitions between response categories over the course of therapy.

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Table 2 Results from univariate logistic regression with Firth penalization aimed at identifying associations between patient's demographic and clinical features and the complete response at 3-month, 6-month and last assessments.

	Complete response at 3 months	Complete response at 12 months	Complete response at last assessment
Sex (male vs female)	OR: 0.83, 95% CI: 0.4–1.7, $P = 0.61$)	OR: 0.66, 95% CI: 0.28–1.5, $P = 0.33$	OR: 0.65, 95% CI: 0.3–1.04, $P = 0.27$
Age at disease onset	OR: 0.99, 95% CI: 0.94–1.03, $P = 0.59$)	OR: 0.97, 95% CI: 0.92–1.02, $P = 0.25$	OR: 0.97, 95% CI: 0.92–1.02, $P = 0.21$
Age at the start of CAN	OR: 0.97, 95% CI: 0.93–1.007, $P = 0.12$	OR: 0.98, 95% CI: 0.94–1.01, $P = 0.23$	OR: 0.98, 95% CI: 0.94–1.007, $P = 0.13$
Pediatrics vs adults	OR: 0.95, 95% CI: 0.4–2.3, $P = 0.91$	OR: 1.13, 95% CI: 0.44–2.87, $P = 0.8$	OR: 1.96, 95% CI: 0.83–4.83, $P = 0.13$
Disease duration the start of CAN	OR: 0.997, 95% CI: 0.992–1.001, $P = 0.2$	OR: 0.999, 95% CI: 0.995–1.003, $P = 0.62$	OR: 0.999, 95% CI: 0.995–1.002, $P = 0.4$
Relapsing-remitting vs chronic disease course	OR: 6.17, 95% CI: 1.18–61.6, $P = 0.03$)	OR: 5.55, 95% CI: 0.87–59, $P = 0.07$	OR: 0.84, 95% CI: 0.14–3.99, $P = 0.83$
Number of attacks/year	OR: 0.97, 95% CI: 0.93–0.997, $P = 0.03$	OR: 0.95, 95% CI: 0.9–0.98, $P = 0.02$	OR: 0.98, 95% CI: 0.95–1.007, $P = 0.16$
Highest body temperature	OR: 0.64, 95% CI: 0.38–1.04, $P = 0.08$	OR: 1.19, 95% CI: 0.72–2.01, $P = 0.49$	OR: 0.88, 95% CI: 0.54–1.4, $P = 0.59$

Based on the output from logistic regressions, odds ratio (OR) and 95% CIs were calculated.

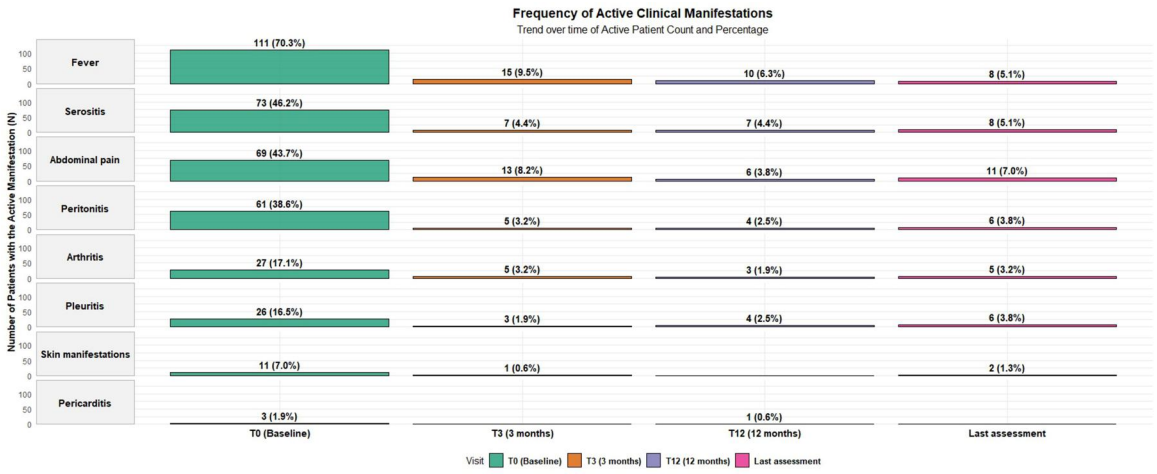


Figure 2 Frequency of the cardinal clinical manifestations of familial Mediterranean fever in patients across the different study timepoints. The bars represent the number of patients with each manifestation (absolute values shown above the bars, with percentages in parentheses) at Baseline (T0), 3 months (T3), 12 months (T12), and at the last assessment. The results show that some manifestations, such as fever and serositis, tend to decrease over time, while others, less frequent at baseline, remain stable or appear in only a few patient

significant ($P < 0.0001$), with pairwise comparisons showing a significant decrease from baseline to 3 months ($P < 0.0001$), baseline to 12 months ($P < 0.0001$) and baseline to the last assessment ($P = 0.0002$). No significant changes were observed from the 3-month to 12-month visit ($P = 1.0$) or from the 12-month visit to the last assessment ($P = 0.15$).

The SAA value was available in 29 patients at the start of CAN; the median SAA decreased from 12 mg/l (IQR: 24.66) at the start of CAN to 5 mg/l (IQR: 10) at the 3-month assessment, 2.96 mg/l (IQR: 6.15) at the 12-month visit and 3 mg/l (IQR: 7.28) at the last assessment. The overall decrease was significant ($P = 0.003$), but pairwise comparisons showed no significant change from baseline to 3 months ($P = 0.54$) or baseline to 12 months ($P = 0.22$), from 3 to 12 months ($P = 1.0$) or from 12 months to the last assessment ($P = 0.13$). Figure 4 shows the frequency of patients with increased laboratory inflammatory markers at baseline and between different follow-up assessments, with the corresponding *P*-value.

Among patients who still showed laboratory inflammation at 3 months after CAN introduction, the median CRP decreased from 4.68 mg/dl (IQR: 4.14) at baseline to 0.95 mg/dl (IQR: 1.3) after 3 months of CAN therapy ($P = 0.03$). The median ESR was 22 mm/h (IQR: 32) at baseline and 13 mm/h (IQR: 19) at 3 months ($P = 0.07$). Analyses for SAA were not performed due to the limited number of available measurements.

The probability that a patient achieves full laboratory control of inflammation at 12 months, if it was not achieved at the 3-month

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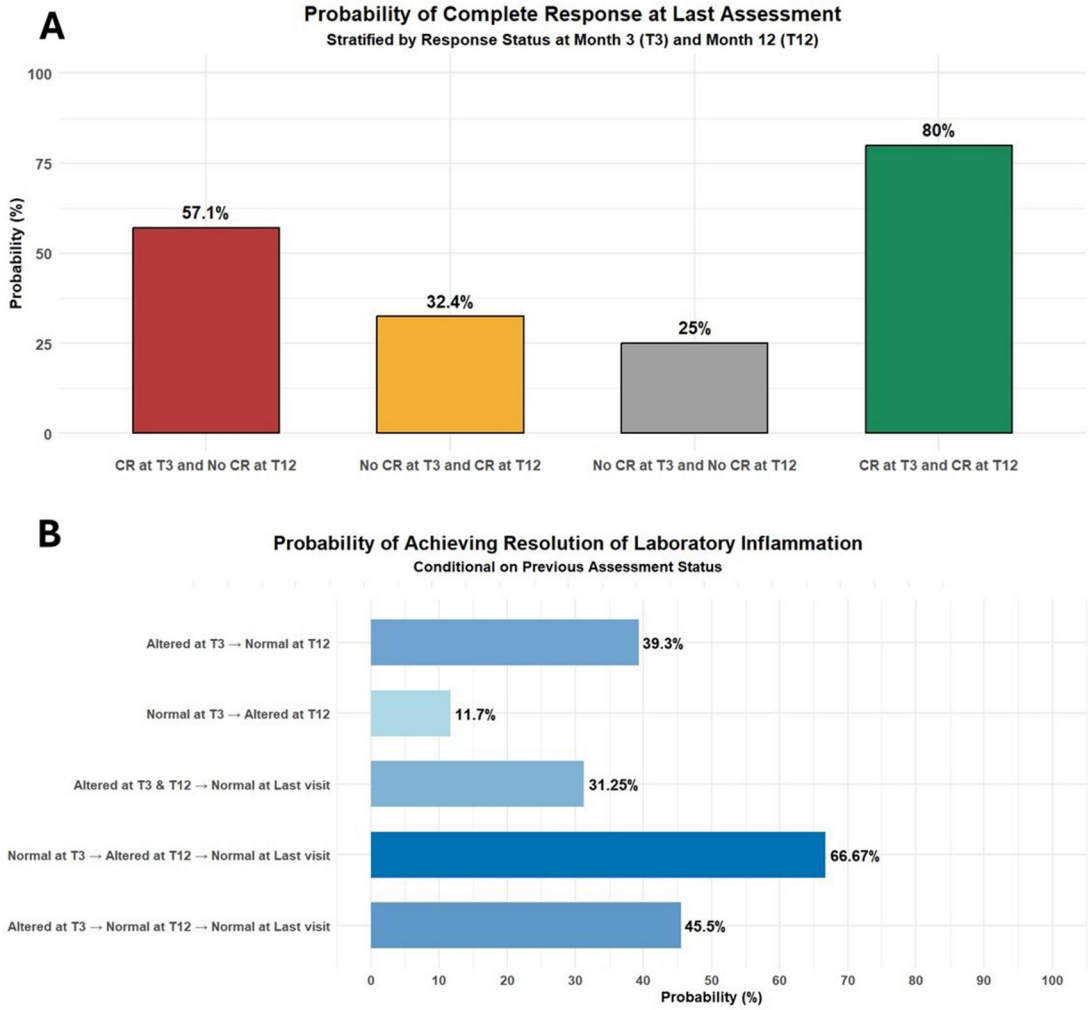


Figure 3 Conditional probability analysis of achieving (A) the Complete Response (CR) at last assessment and (B) the full resolution of laboratory inflammation at the different timepoint conditioned to previous outcome. CR is strictly correlated with the response kinetics observed during the first 12 months. The optimal prognostic profile is characterized by achieving remission at both 3 and 12 months (CR at T3 & T12), which provides an 80.0% conditional probability of final clinical stability. Patients with an early response followed by an intermediate relapse (CR at T3, No CR at T12) maintain a 57.1% probability of recovering CR, while persistent non-response (No CR at T3 &T12) identifies the subgroup with the poorest prognosis, with a probability of success remaining at 25.0%. Regarding full control of laboratory manifestations, early achievement appears to favour sustained maintenance of this outcome over time. However, failure to achieve inflammatory control within the first 3 months of therapy does not preclude the possibility of reaching this target at a later stage. Specifically, among patients who achieved full laboratory control at month 12, the probability of maintaining this status beyond month 12 was 45.5%. Conversely, in patients who had not achieved full control of laboratory inflammation by month 12, the probability of attaining this outcome after month 12 was 31.25%

assessment, was 39.3%. The probability that inflammatory markers normalized at the last assessment was 31.25% if they remained abnormal at both the 3- and 12-month assessments. If markers were normal at 3 months but abnormal at 12 months, the probability of normalization at the last assessment was 66.67%.

Among patients without full laboratory control at 3 months, 39.3% achieved control at 12 months. At the last assessment, normalization of laboratory markers was observed in 31.25% of patients with persistent abnormalities at both 3 and 12 months. In contrast, among patients with normal markers at 3 months but abnormal values at 12 months, 66.67% achieved normalization at the last assessment.

Colchicine use did not influence the persistence of laboratory inflammation at 3 months (1 mg/day: OR 0.14, 95% CI 0.0009–3.0, $P = 0.2$; 1.5 mg: OR: 0.19, 95% CI 0.001–3.8, $P = 0.28$; 2 mg/day: OR 0.1, 95% CI 0.0007–2.25, $P = 0.15$), 12 months (1 mg/day: OR 0.4, 95% CI 0.03–5.25, $P = 0.49$; 1.5 mg/day: OR 0.15, 95% CI 0.01–1.98; 2 mg/day: OR 0.14, 95% CI 0.01–1.74, $P = 0.13$) or at the last assessment (1 mg/day: OR 2.54, 95% CI 0.23–27.7, $P = 0.44$; 1.5 mg/day: OR 1.87, 95% CI 0.17–19.9, $P = 0.61$; 2 mg/day: OR 2.1, 95% CI 0.21–20.2, $P = 0.53$).

Sensitivity analyses excluding SAA from the definition of laboratory control and complete response yielded results consistent with the primary analysis, supporting the robustness of the findings despite the limited availability of SAA measurements, as reported in Supplementary Table S2.

Reasons for CAN discontinuation

Twenty-one (13.3%) patients discontinued CAN, nine (5.7%) due to primary inefficacy, six (3.8%) because of only partial benefit,

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two (1.3%) due to the presence of a second inflammatory comorbidity requiring TNF inhibition. One patient discontinued due to recurrent infections and additional four patients interrupted CAN for poor compliance. A further patient interrupted CAN because of other non-medical reasons.

Discussion

Both clinical trials and real-world studies have demonstrated the efficacy of CAN in FMF patients, particularly in subjects resistant or intolerant to colchicine [2–4]. Accordingly, systematic reviews have confirmed that anti-IL-1 agents, including CAN, achieve high rates of complete remission and have a favourable safety profile in both adult and paediatric populations [17]. In particular, systematic reviews and meta-analyses report that 61–81% of FMF patients achieve complete remission with anti-IL-1 therapy, including CAN [18], while real-world registries and multicentre cohorts show that 42–79% of colchicine-resistant FMF patients attain attack-free status, alongside significant reductions in inflammatory markers [3, 4, 19].

The present study further confirms the effectiveness of CAN in FMF, considering stringent response endpoints, such as the complete absence of clinical and laboratory manifestations and the full normalization of inflammatory markers. This stringent definition of complete response was intentionally selected because less restrictive criteria may underestimate persistent subclinical inflammation despite apparent clinical improvement. Since sustained inflammatory activity is considered a major driver of long-term complications such as AA amyloidosis, we considered complete normalization of inflammatory markers together with absence of clinical manifestations as a clinically meaningful therapeutic target, although not a formally validated end point. Even when considering only complete clinical-laboratory control, aprroximately 45% of patients responded to CAN after just three months of therapy. To this proportion, an additional 16.5% of patients achieved a partial response, defined as a slight increase in at least a single inflammatory marker and/or persistent, but substantially improved, clinical manifestations.

These responses not only persisted over time but further improved at month 12, when nearly 60% of patients reached complete response; at the last follow-up, after a mean treatment duration of 4 years, a complete response rate was still observed in 55% of patients. These results highlight both the rapid onset and sustained efficacy of CAN in FMF, confirming previous real-world observations drawn from smaller populations [3, 4, 17, 18].

The present study further provides a detailed analysis of FMF patients treated with CAN, distinguishing between clinical and laboratory outcomes. Indeed, to prevent AA amyloidosis as a long-term complication, it is essential to achieve optimal control of both clinical manifestations and laboratory markers [18]. More in details, the absence of clinical manifestations exceeded 80% at all three time points following the start of CAN, despite being only 19% at baseline. From a laboratory perspective, the proportion of patients with raised inflammatory markers decreased sharply within the first 3 months of therapy, from 75% to 32%, and further declined to 26% at month 12. The reduction in inflammatory markers involved CRP, ESR and SAA across the entire cohort, as well as in the subgroup of patients who still exhibited elevated levels. Actually, even among patients who did not achieve full normalization of inflammatory markers within three months, a quantitative reduction relative to baseline was evident, demonstrating CAN's capacity to attenuate systemic inflammation even in patients defined as partial responders during the early phase of treatment. This effect was particularly pronounced for CRP, for which the reduction reached statistical significance, whereas ESR showed a trend towards significance. Noteworthy, the reduction in SAA, while significant when considering the overall data collected across follow-ups, did not reach statistical significance at individual time points. This should be interpreted in light of the limited number of patients for whom SAA values were available.

Of particular interest is the conditional probability of achieving complete disease control based on prior time points. As shown in Fig. 3A, among patients not in complete remission at three months, about 33% reached it by month 12. The probability of maintaining remission at the last assessment was 80% for those who achieved it at 3 months and maintained it at month 12, compared with 32.4% for patients who reached remission only at month 12. Patients who lost remission at month 12 after initially achieving it at three months still had a 57% chance of regaining it in subsequent follow-ups, emphasizing the benefit of an early response. Complete remission at the last assessment was still possible in patients who had not achieved it at either 3 or 6 months, with a probability of 25%.

Regarding the probability of achieving complete control of laboratory inflammation, reported in Fig. 3B, patients with normalized markers by 3 months showed over a 65% chance of maintaining this status at the last assessment, even though inflammatory signs were present at month 12. Patients with persistent laboratory abnormalities at both 3 and 12 months still had nearly a one-third probability of reaching full laboratory control by the last assessment. Overall, these clinical and laboratory findings emphasize that early remission facilitates both the maintenance and recovery of complete response and full inflammatory control over time.

Further supporting the excellent disease control observed across the entire patient cohort, nearly all patients showed no increase in the index of organ damage ADDI [16] throughout the observation period during ongoing CAN therapy.

An additional indirect end point supporting the efficacy of CAN is the relatively low proportion of patients requiring CAN discontinuation due to primary inefficacy or inadequate response.

The outcomes were not significantly influenced by concomitant colchicine use. This finding reinforces recent observations [20], which reported that among 55 patients, 31 receiving CAN plus colchicine and 24 receiving CAN monotherapy, colchicine did not significantly affect the efficacy of CAN in FMF patients. The authors concluded that CAN can be continued as monotherapy when colchicine cannot be used, a position that we also adopt.

As shown in Table 2, complete response to CAN was significantly associated with a relapsing-remitting rather than chronic disease course and inversely related to the annual number of FMF attacks. These relationships were maintained at month 12 but not at the last assessment, suggesting that early complete

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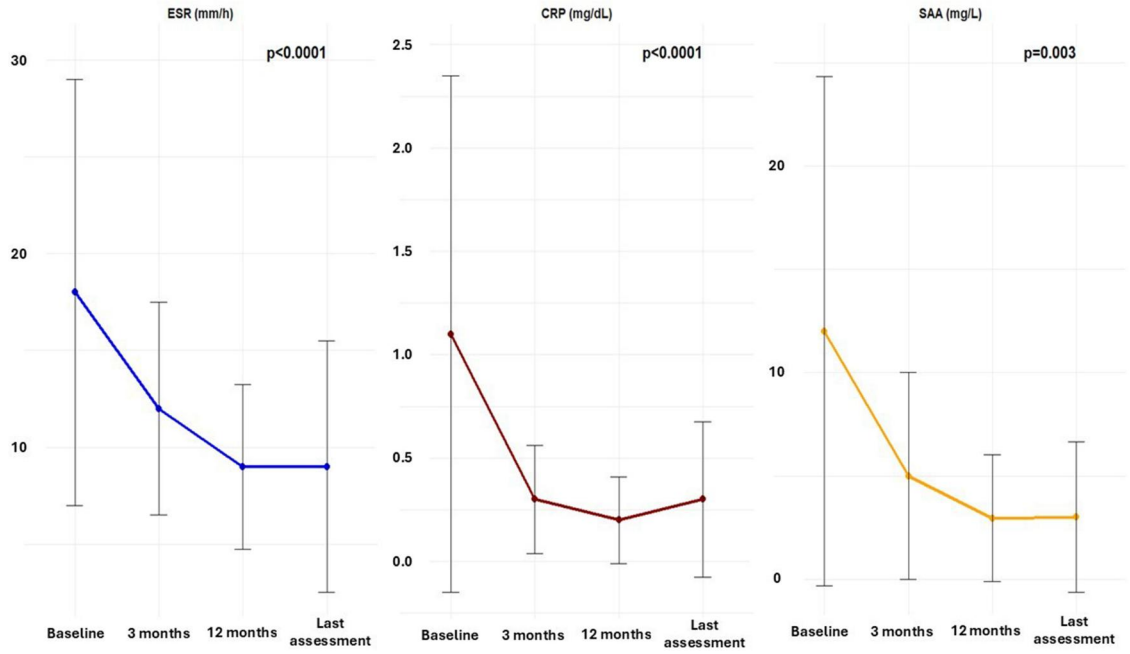


Figure 4 Trends in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A (SAA) at the different study time points

response is more likely in patients with a relapsing-remitting course and fewer attacks prior to CAN initiation.

This study has several limitations that should be acknowledged. First, the observational and retrospective design precludes causal inferences and may be subject to selection and reporting biases. Although the overall cohort included 158 patients, subgroup analyses, particularly those involving SAA, were limited by small sample sizes. Data completeness was another limitation, as not all patients had laboratory or clinical assessments available at every timepoint, which restricted the applicability of repeated-measures analyses and may have introduced attrition bias. Finally, patients who discontinued therapy were excluded from certain analyses, potentially introducing survival bias. Despite these limitations, the study provides valuable real-world evidence on the effectiveness of CAN in the largest cohort of FMF patients treated with this biotechnological agent reported to date. By corroborating previously published findings and carefully evaluating both clinical and laboratory parameters of treatment response, the results confirm that CAN is effective in a substantial proportion of patients, even when stringent response criteria are applied. Importantly, despite the adoption of highly stringent response criteria, CAN achieved sustained complete response in more than half of patients during long-term follow-up. Also, although SAA measurements were available only in a subset of patients, sensitivity analyses excluding SAA from the composite laboratory end point yielded results consistent with the primary analysis, supporting the robustness of the study findings.

In conclusion, CAN is effective in controlling both clinical and laboratory manifestations of FMF patients, inducing complete response in a substantial proportion of patients. Therapeutic benefits are observed early, within the first 3 months of treatment, and are generally sustained at 12 months and longer-term follow-up, with significant reductions in laboratory inflammatory markers. Concomitant colchicine use does not appear to significantly influence treatment response in this cohort, although residual confounding cannot be excluded given the observational study design, suggesting that CAN effectiveness is not substantially modified by concomitant colchicine treatment. Overall, these findings are consistent with previously published real-world and clinical trial data, supporting CAN as an effective, and sustainable therapeutic option even when stringent response criteria are applied.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. Requests to access these datasets should be directed to the corresponding author: Luca Cantarini, MD, PhD, Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinics, Department of Medical Sciences, Surgery and Neurosciences, University of Siena (cantariniluca@hotmail.com).

Author contributions

All the authors substantially contributed to the conception or design of the work, the acquisition and interpretation of data and critically revised the article. All the authors approved the final version and agreed to be responsible for all the aspects of the work. In addition, A.V. wrote the first draft of the article and performed the preliminary data analysis and interpretation. V.C., J.S., A.T., G.R., G.L., P.P., D.R., S.A.M.A., A.S., N.T., E.V., L.F.,

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