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## **Could tocilizumab be used in familial Mediterranean Fever? A systematic review**

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## **ABSTRACT**

**Introduction:** Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease characterized by recurrent fever and serosal inflammation. Although colchicine is the primary treatment, around 10% of FMF patients do not respond to it, necessitating alternative therapies. Biologic treatments, such as interleukin-1 $\beta$  (IL-1 $\beta$ ), TNF- $\alpha$ , and interleukin-6 (IL-6) inhibitors, have been considered. However, the accessibility and cost of IL-1 $\beta$  inhibitors may limit their use in certain regions. Tocilizumab (TCZ), an IL-6 receptor inhibitor, offers an alternative, but its efficacy in FMF is not well-documented.

**Objective:** To evaluate the efficacy and safety of tocilizumab in the treatment of FMF.

**Methods:** Following PRISMA guidelines, we identified 237 articles on the use of TCZ in FMF.

**Results:** After selection, 14 articles were included: 2 double-blind RCTs, 2 retrospective studies, and 10 case reports. Multicenter double-blind RCTs reported mixed results in FMF patients without AA amyloidosis due to genetic/classification heterogeneity of the available studies, possible misdiagnosed FMF patients and study design. Retrospective studies suggest that TCZ may benefit FMF patients with established renal AA amyloidosis, potentially preventing progression and managing flares more effectively. TCZ showed a safe profile with no specific adverse events, but data on its use during pregnancy or breastfeeding are lacking. There was no available data on the use of TCZ in pediatric FMF.

**Conclusion:** This review summarizes the current state of research, safety and efficacy of TCZ in FMF. While IL1 $\beta$  inhibitors remain the first choice for colchicine-resistant or intolerant FMF patients, TCZ might be of interest in some selected FMF patients with established AA amyloidosis and resistance to colchicine and interleukin 1 inhibitors.

## **KEYWORDS**

**Familial mediterranean fever, colchicine resistance, tocilizumab, AA amyloidosis**

## **KEY MESSAGES**

- IL-1 $\beta$  inhibitors remain the first choice in colchicine-resistant disease or colchicine intolerance and there is still insufficient evidence to recommend IL6 inhibition.
- Tocilizumab might be of interest in case of FMF with established AA amyloidosis who do not respond to either colchicine and IL-1 $\beta$  inhibitors.

## INTRODUCTION

Familial Mediterranean Fever (FMF) is the most common monogenic autoinflammatory disease (AID), characterized by recurrent attacks of fever and serosal inflammation. Two sets of clinical criteria, Tel Hashomer (1) and Livneh (2) criteria, were proposed for diagnosing FMF in adults before the identification of the *MEFV* gene. The pediatric clinical criteria (Yalcinkaya-Ozen) (3) were established in 2009 providing facility in diagnosis and are widely used, especially in childhood. In 2019, the Eurofever/PRINTO group introduced new classification criteria encompassing mutation status, ethnicity, and clinical parameters (4). In FMF, the abnormal activation of the pyrin inflammasome leads to excessive production of interleukin 1 $\beta$  (IL-1 $\beta$ ) and interleukin 18 (IL-18). These cytokines then trigger the synthesis of IL-6 and TNF- $\alpha$ , which activate immune cells (9). Furthermore, IL-6 is crucial for stimulating the production of C-reactive protein (CRP) and serum amyloid A (SAA). SAA could act as a trigger signal for NLRP3 inflammasome, sustaining the inflammatory activation and contributing to the development of AA amyloidosis (10,11). Colchicine is the cornerstone of FMF treatment and is effective in controlling disease manifestations of the disease in the majority of cases. In about 10% of cases (5–8), patients are resistant to colchicine (colchicine-resistant FMF, crFMF) and may require additional treatment to control the inflammatory state and prevent the development of AA amyloidosis, the most feared complication of the disease.

According to the current EULAR recommendations (12), treatment with colchicine should be initiated as soon as a clinical diagnosis of FMF is made. Compliant patients who do not respond to the maximum tolerated dose of colchicine can be considered non-respondent or resistant, and alternative biologic therapies are indicated for these patients. These alternative biologic therapies should be prescribed alongside colchicine, as colchicine is the only treatment that has significantly reduced the risk of amyloidosis. Biologic therapies that may be indicated in these cases are IL-1 $\beta$ , TNF- $\alpha$  and IL6 inhibitors. IL-1 inhibitors are very effective therapies in FMF (13–16), but their cost (several thousands of euros per injection for canakinumab), administration schedule (subcutaneous for both, daily for anakinra) and availability may make their prescription difficult in some countries. On the other hand, IL-6 receptor inhibitors therapies such as tocilizumab (TCZ) may be an interesting alternative due to their lower cost and more acceptable administration regimen (monthly for intra-venous regimen, weekly for subcutaneous regimen), or in case of inefficacy of IL-1 inhibitors; but there is limited data on the efficacy of TCZ in FMF.

Here, we conducted a systematic review of the literature to assess the efficacy and safety of TCZ in the treatment of FMF. **Table 1** summarizes the objectives of this systematic review according to PRISMA guidelines.

## **METHODS**

A systematic review of the literature was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (17), searching for articles reporting on the use of TCZ in FMF.

### ***Search strategy***

We searched three different databases using the appropriate MESH terms from inception to December 2023: MEDLINE via PubMed ("*Familial Mediterranean Fever*"[Mesh]) AND "*tocilizumab*" [Supplementary Concept]; Embase (*'familial mediterranean fever'/exp OR 'familial mediterranean fever'*) AND (*'tocilizumab'/exp OR tocilizumab*) and Cochrane (*[Familial Mediterranean Fever] explode all trees AND [Interleukin-6 Inhibitors] explode all trees*).

### ***Eligibility criteria***

Randomized controlled trials (RCTs) and their extension trials, prospective case series and retrospective studies were included regardless of the FMF definition used in the studies. Due to the rarity of the disease and the potential paucity of literature on the use of TCZ in FMF, we also decided to report separately available case reports. Whenever articles reported pooled data from different AID (e.g. data from AID registries), papers were excluded to avoid confusion with other AID. Articles in English, French, German or Spanish were included.

### ***Study Selection***

Two investigators (S.G-L. and P.M.) independently selected the articles on the basis of the title and abstract and, if necessary, the full texts. If publications were not available through open or institutional access, we contacted the authors of the studies. Additional articles were identified by checking the references of the selected articles. If articles reported duplicate patient data (e.g. same patient cohort at different time points), the most recent and complete article was selected.

### ***Questions addressed in this systematic review and extracted data***

Questions addressed in this systematic review aimed to assess the efficacy and safety of TCZ in the treatment of FMF (see **Table 1**):

1. What is the efficacy of TCZ in reducing the frequency and severity of FMF attacks?
2. What is the safety profile of TCZ in patients with FMF?
3. What is the optimal administration regimen of TCZ in FMF patients, and how does it affect treatment outcomes?

4. What are the gaps in the current evidence regarding the use of TCZ in FMF, and what further research is needed in this area?
5. Are there any particularities in pediatric patients compared to adult FMF patients regarding the indication, efficacy and safety of TCZ?

For RCTs and retrospective studies, we retrieved information on inclusion and exclusion criteria and primary and secondary endpoints. For all studies, we retrieved data on the number of patients, their geographical origin, *MEFV* variants, the criteria used to establish FMF diagnosis, coexisting diseases, amyloidosis, indication/ dosage/ route of administration and mean duration of tocilizumab therapy, the previous use of other biologics, and main outcomes (efficacy and safety). For case reports, we retrieved any additional data that might be of interest in assessing the efficacy and safety of TCZ.

### ***Analysis and interpretation of reported data***

Reported data was summarized in a descriptive way. For interpretation of the reported data, we chose to use Eurofever/PRINTO classification criteria for FMF (4). Interpretation of the different degree of pathogenicity of different *MEFV* variants was made based on the INFEVERS (<https://infevers.umai-montpellier.fr/web/>) registry.

For case reports, we defined three different levels of response to TCZ : complete response (CR) was defined as normalization of the inflammatory markers and absence of recurrent attacks, partial response (PR) was defined if only one of these was achieved, and no response (NR) was defined as persistently elevated inflammatory markers and no change in attacks.

## **RESULTS**

### **Literature search**

The extensive literature search identified 237 articles. After selection, 14 articles were included in the study: 2 double-blind randomized controlled trials (RCTs), 2 retrospective studies and 10 case reports. The flowchart is presented in figure 1.

### **Data available from the double-blind randomized controlled trials**

Two recent double-blind RCTs were identified (see **Table 2**).

***Koga et al. conducted a multicenter, double-blind, randomized, placebo-controlled phase III trial in Japan. This study is registered on the University Hospital Medical Information Network Clinical Trials Registry as UMIN000028010 (18).*** Twenty-two Japanese adults labelled “FMF” patients who met the Tel Hashomer criteria were enrolled. Of the 17 patients for whom *MEFV* testing was available, none of the patients bore two pathogenic *MEFV* variants, 4 patients bore one pathogenic *MEFV* variant, 2 patients bore a pathogenic *MEFV* variant and a variant of unknown significance (VUS), 2 patients bore 2 VUS and 6 patients bore an isolated VUS. Three patients did not bore any pathologic *MEFV* variant. Data on the *MEFV* variants are shown in supplementary **table 2**. None of the patients had coexisting inflammatory diseases or inflammatory (AA) amyloidosis. Patients were biologic naïve and received TCZ SC 162 mg/week for 24 weeks due to colchicine

resistance or intolerance as defined by Ozen et al. (6). All patients received concomitant colchicine therapy (unless colchicine intolerance, n=1 in the TCZ arm and n=2 in the placebo arm) at a mean daily dose of 0.63 mg/ day. The study was followed by an open-label phase until week 48. The primary endpoint of the study was the number of fever attacks due to FMF during 24 weeks of treatment. No significant difference ( $p=0.58$ ) was observed between the TCZ arm (0.37 attacks) and the placebo arm (0.53 attacks).

The secondary endpoints were the frequency of accompanying symptoms during attacks; the time between fever attacks; duration of fever attacks; the serum CRP and SAA levels; patient score on the 36-item Short Form Health Survey (SF-36) questionnaire; physician global assessment (100 mm visual analogue scale [VAS]); body temperature; and the percentage of achievement of FMF 50 score (improvement of 50% or more in at least five out of six items) at 12 weeks and 24 weeks during the double-blind phase. The recurrence of attacks was significantly lower in the TCZ arm (hazard ratio = 0.457; 95% CI, 0.240–0.869). Fever attacks, associated symptoms, serum CRP and SAA levels were controlled in most of the patients receiving long-term TCZ. The number of fever attacks tended to decrease with increasing duration of TCZ treatment.

The most common reported adverse events were hypofibrinogenemia (n=8), injection site reaction (n=2), headache (n=2) and neutrophilic myocarditis (n=1). The latter was excluded from the study after discontinuation of TCZ and treatment with steroids.

**Henes et al. conducted a multicenter, double-blind, randomized, placebo-controlled phase II trial in Germany, the TOFFIFE study (19). This study is registered with ClinicalTrials.gov (NCT03446209).** Twenty-five German adult FMF patients (n=25) who met the Tel Hashomer criteria were enrolled. Of these, 18 patients bore two pathogenic *MEFV* variants, 5 bore a single pathogenic *MEFV* variant and 2 bore 2 VUS. Data on the variants are shown in supplementary **table 1**. None of the patients had coexisting inflammatory diseases or inflammatory (AA) amyloidosis. Three of them had previously received anakinra and one canakinumab, both of which were discontinued prior to study entry with an adequate wash-out period. Patients received TCZ 8 mg/kg monthly for 12 weeks for colchicine resistance or intolerance, which were defined as “disease activity despite colchicine with at least 2 x 0.5 mg/day or intolerance to colchicine”. All patients received concomitant colchicine therapy at a median daily dose of 1.6 mg/ day. Patients with an inadequate response at week 12, as determined by the treating physician, had the option to receive open label TCZ at weeks 16, 20, and 24.

The primary endpoint was the number of patients achieving complete remission at week 16, defined as a Physician Global Assessment (PGA) score of  $\leq 2$ , a normalized ESR or CRP (whichever led to inclusion had to normalize), and a normalized SAA. At week 16, 2/16 (15.4%) patients in the TCZ arm achieved the primary endpoint, compared to none in the placebo arm. This resulted in a significant difference in favor of the TCZ arm ( $p = 0.089$ ). In addition, two patients in the TCZ arm discontinued treatment before week 16 because of complete inefficacy and one due to adverse events.

Secondary endpoints were the efficacy of TCZ as a rescue therapy as measured by the PGA score at week 28, the proportion of patients with a serological remission (defined as CRP <0.5 mg/dL or normalized SAA level) at weeks 16 and 28, patient improvement and physician global assessment of FMF activity on a visual analogue scale (VAS) of 0–10, the ability to reduce the use of non-steroidal anti-inflammatory drugs (NSAIDs) or the impact of the disease on health-related quality of life, as assessed by the German “Funktionsfragebogen Hannover” (FFbH) scale and the overall safety assessed by adverse events of TCZ in patients with crFMF. Patients were asked to complete a patient diary to record signs and symptoms and NSAIDs use to help the investigators assess the PGA.

This difference between TCZ and PBO was very clear for SAA ( $p < 0.015$ ) and for CRP ( $p < 0.011$ ), whereas no significant difference was observed for the PGA, reduction in NSAID use, reduction in VAS or the FFbH score.

Regarding safety, one case of ileitis and one case of elevated liver enzymes were reported in the TCZ arm.

### **Data available from the retrospective trials**

Two retrospective studies were identified, both from Turkey (see **Table 2**).

**Colak et al.** (20) reported on 15 adult FMF patients who met the Tel Hashomer criteria, of whom 10 bore 2 pathogenic *MEFV* variants, one bore 1 pathogenic variant and one had no known *MEFV* variant. One patient had a history of IgA vasculitis. All patients were receiving TCZ for renal amyloidosis and were biologic naïve. Patients received TCZ IV 8 mg/kg per month. All patients received concomitant colchicine therapy at a mean daily dose of 1.23 mg/ day. Eight patients had a complete response with no attacks after 12 months of treatment, 6 had a partial response with a clear reduction in the number of attacks, and one had no response and had to be switched to anakinra after 3 months of TCZ treatment. Interestingly, this patient was homozygous for M694V. There were no adverse events reported.

**Ugurlu et al.** (21) reported on 12 adult FMF patients who also met the Tel Hashomer criteria of whom 6 bore 2 pathogenic *MEFV* variants, 4 bore 1 pathogenic *MEFV* variant and 1 bore no pathogenic *MEFV* variant. One patient had no known variant on the *MEFV* gene, and the last patient had no genetic testing. Three patients had a history of spondyloarthritis and another had both spondyloarthritis and Crohn’s disease. Most of the patients had already received biologic therapies: 5 patients had received anakinra, 3 had received canakinumab, 3 had received infliximab and 1 had received etanercept. All biologic therapies had been discontinued due to lack of efficacy or allergic reactions. All patients received TCZ IV 8 mg/kg per month for renal amyloidosis. All patients received concomitant colchicine therapy at a median daily dose of 1.9 mg/ day. Ten patients had a GFR > 50 ml/min which remained stable during treatment, with improvement of the mean 24-hour urine protein level and reduction in CRP and ESR levels. Two patients had a GFR < 50 ml/min which improved over time with TCZ treatment, while mean 24-hour urine protein level and CRP/ ESR levels decreased. No FMF attack were observed in 10 of the 12 patients,



while one patient, who was also diagnosed with spondyloarthritis, experienced less frequent and mild attacks. Only one patient had recurrent attacks of erysipelas-like erythema on TCZ and was therefore switched to canakinumab.

In terms of safety, one patient experienced transient diplopia after the 6th dose which resolved after therapy discontinuation, and another had an increase in blood pressure after the 13th dose and was switched to canakinumab. An interesting observation was that renal function deteriorated rapidly in two patients after temporary discontinuation due to side effects and in one patient after the infusion interval was increased from one to two months due to a good response.

### **Data available from case reports**

Ten case reports or case series of 25 adult FMF patients from different geographical origins were captured by our search equation (22–31). Detailed data is available on **Table 3**.

Only 10/ 25 patients met the Eurofever/ PRINTO classification criteria and could be considered as having FMF as defined in our systematic review. Interestingly, two of the patients who did not meet the Eurofever/ PRINTO classification criteria met the Tel Hashomer criteria and were diagnosed with adult-onset Still's disease in one case and rheumatoid arthritis in the other. The indication for TCZ was crFMF complicated by AA amyloidosis in most cases (14/25), followed by crFMF without AA amyloidosis (9/25) and protracted febrile myalgia with colchicine intolerance in one case (1/25). TCZ was given monthly by intravenous infusion at a dose of 8 mg/kg in most cases. A global response is difficult to assess due to the heterogeneity of the cases (heterogeneous genetic background, patients not fulfilling the Eurofever/PRINTO classification criteria in most cases, different indications, dosing regimens and different treatment durations). Of interest, authors reported a diminution of amyloid fibrils in kidney and intestinal biopsies of patients treated with TCZ for amyloidosis (23,25,27). Slightly elevated liver enzymes (n=1) and mild thrombocytopenia 110.000/mm<sup>3</sup> (n=1) were the only reported adverse effects, with no discontinuation of TCZ in neither of both cases.

## **DISCUSSION**

TCZ is an IL6 receptor inhibitor biologic that has been shown to be effective in other rheumatic diseases such as rheumatoid arthritis (32), Still's disease (33), Takayasu arteritis (34) or non-HIV multicentric Castleman's disease (35).

Here, we performed a systematic review of the literature to assess the efficacy and safety of TCZ in FMF, as IL-6 inhibition could be an interesting therapeutic approach due to the pathogenesis of the disease and AA amyloidosis. The summary of evidence and responses to the questions addressed in this systematic review are presented in **Table 4**.

Our search yielded two different multicenter double-blind RCTs, one Japanese and one German, with mixed results.

The Japanese trial did not meet its primary endpoint of the study which was a reduction in the number of fever attacks due to FMF during 24 weeks of TCZ SC 162 mg/week. This may have been due to a specific genetic background, as none of the 22 patients enrolled in the study bore two pathogenic *MEFV* variants. Without the presence of these variants, it seems difficult to classify Japanese patients as having a classical FMF according to the Eurofever/PRINTO classification criteria (36), and proper diagnosis may have been syndrome of undifferentiated recurrent fever (SURF) or undefined systemic autoinflammatory disease (USAID) (37–41). All patients received concomitant colchicine therapy, but at a mean daily dose of 0.6 mg/day, which is close to pediatric doses. Higher doses of colchicine (1.5 – 2 mg/day) may have improved the efficacy of TCZ. In addition, SC treatment may be less effective than IV treatment. The number of fever attacks tended to decrease with increasing duration of TCZ treatment, which may indicate that significance may have been reached with a longer duration. Altogether, as those patients are more likely to be SURF than classical FMF patients, this study may finally not be retained in the analysis.

The German trial: firstly, it should be noted that 2 patients in this study had no *MEFV* mutation and 5 were heterozygous, which in practice means that 7 patients had non-classical FMF. Secondly, the trial did meet its primary endpoint, which was the number of patients achieving complete remission (defined as a PGA score of  $\leq 2$ , a normalized ESR or CRP and a normalized SAA) at week 16, with a significant statistical difference in favor of the TCZ arm ( $p = 0.089$ ) which should be interpreted with caution as only 2/12 patients achieved remission and 2 patients had to discontinue treatment due to complete inefficacy. Regarding the secondary endpoints, a clear difference between TCZ and PBO was observed for the reduction of SAA ( $p < 0.015$ ) and CRP ( $p < 0.011$ ) levels, which was logically expected given the mechanism of action of the drug, but no significant difference was observed for the PGA, reduction in NSAID use, reduction in VAS or the FFbH score.

Our search equation also retrieved 2 Turkish retrospective studies in which TCZ was indicated for 27 different adult patients with renal AA amyloidosis. In most cases, TCZ appeared to be effective against progression of renal disease and to control the disease. This may suggest that the role of IL6 may be different in FMF patients without and with established renal amyloidosis, as TCZ seemed to be more effective on disease activity in the case of renal amyloidosis. TCZ targets the IL-6 receptor and inhibits its interaction with IL-6, which logically leads to the inhibition of SAA production by the liver and the progression of AA amyloidosis. Clinical symptoms observed during FMF attacks result from inflammasome activation and are mostly mediated by IL-1 and IL-18. This may explain why TCZ is not effective in preventing attacks in FMF patients without AA amyloidosis. On the other hand, it has been shown that SAA may activate the NLRP3 inflammasome (10,11). Therefore, it is possible that in cases of established AA amyloidosis, SAA itself may trigger NLRP3 inflammasome activation in addition to pyrin pathology. In this case, TCZ may help limit stimulation of the NLRP3 inflammasome and be more effective in preventing attacks or decreasing the intensity of FMF flares (see figure 2). Interestingly, some case reports also included in our search equation reported the improvement or complete resolution of amyloid deposition in biopsies of patients treated with TCZ.

In terms of safety, the number of adverse events reported was low, and TCZ appears to be a safe biotherapy overall. A total of 61 patients received TCZ treatment, and mild adverse events were reported in 14 cases. These included hypofibrinogenemia (n = 8), injection site reactions (n = 2), headaches (n = 2), and elevated liver enzymes (n = 2). Treatment discontinuation due to major adverse events was reported in a case of neutrophilic myocarditis (n = 1), ileitis (n = 1), transient diplopia (n = 1), and increased blood pressure (n = 1). Notably, no cases of hypertriglyceridemia (the most common adverse effect of TCZ) were reported. Due to the study design, no data were available on the use of TCZ during pregnancy or lactation, and no case reports have been published on this topic.

This systematic review has several limitations due to the rarity of the disease studied and the rarity of the use of TCZ in FMF. The most important limitation is that only two RCTs are available, and they use different primary endpoints to assess the efficacy of TCZ, and therefore the results could not be pooled and analyzed. Furthermore, and independently from the design of our study, it should be noted that one of the two available worldwide RCTs may not have included patients with classical FMF, but rather patients with SURF/USAID. This highlights the importance of using the recent Eurofever/PRINTO classification criteria (36) for FMF in future trials, which take into account mutation status, ethnicity, and clinical parameters. This is important because with the advances of genetic testing and the description of new autoinflammatory diseases, there is a high probability that patients who meet the Tel Hashomer criteria and are resistant to colchicine do not have classical FMF, but are more likely to have another autoinflammatory disease. Furthermore, our findings also emphasize the need for homogeneous endpoint definitions, based on official definitions of colchicine-resistance, intolerance and clinical and biological disease complete and partial remission for future RCTs. The definitions of colchicine-resistance and intolerance by Ozen et al. (6) are a first step in homogenizing important definitions that are mandatory to better assess treatment efficacy and safety in such a complex disease and to help derivate specific disease activity scores. Further research is also needed to better assess quality of life measures, adherence and patient satisfaction. Finally, there was no available data on the use of TCZ in pediatric FMF.

In conclusion, we conducted a systematic review of the efficacy and safety of TCZ in FMF. Finally, only one multicenter double-blind RCTs concerned authentic FMF as defined by actual classification criteria and *MEFV* genotyping concerning only 18 patients and showed mixed results in FMF patients without AA amyloidosis, probably due to the study design and the heterogeneous genetic background. On the other hand, retrospective studies show that TCZ may be of interest in FMF patients with established renal AA amyloidosis with resistance to colchicine and to IL-1 inhibitors in order to prevent progression of renal disease and may even be more effective in controlling disease attacks in case of established AA amyloidosis. The effect appears to be suspensive, as indicated by the renal AA amyloidosis progression or relapse after discontinuing TCZ. TCZ has a very safe profile and no specific adverse events were observed. Of note, there is no available data on TCZ among pediatric, pregnant or breastfeeding patients.

IL1 $\beta$  inhibitors agents remain the first choice in case of colchicine resistant disease or colchicine intolerance and there is still insufficient evidence to recommend IL6 inhibition. Nevertheless tocilizumab might be of interest among some selected FMF patients with established AA amyloidosis, resistance to colchicine and to IL-1 inhibitors but further studies are needed to confirm this.

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**Data availability:** The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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## **FIGURES**

**Figure 1: Flowchart of the selection process**



**Figure 2: Proposed mechanisms of IL-1 $\beta$  and IL-18 activation in FMF, both with and without established AA amyloidosis, to hypothesize the different efficacy of tocilizumab in these two different cases (FMF with or without AA amyloidosis).**

FMF leads to the activation of the pyrin inflammasome pathway, with increased levels of IL-1 $\beta$  and IL-18. These cytokines are responsible for most of the symptoms during FMF attacks. Other pro-inflammatory cytokines such as IL-6 are also elevated, which induces the production of C-reactive protein (CRP) and serum amyloid A (SAA) by the liver. When inflammatory markers are chronically elevated, SAA can lead to AA amyloidosis. SAA fibrils may activate the NLRP3 inflammasome, leading to increased secretion of IL-1 $\beta$  and IL-18 through activation of both pyrin and the NLRP3 inflammasome. In these cases, inhibition of the IL-6 axis by tocilizumab (TCZ) may help to reduce NLRP3 activation and thus better control the inflammatory state in FMF patients.

