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REVIEW ARTICLE

# Monogenic Periodic Fever Syndromes: Treatment Options for the Pediatric Patient

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**Abstract** Autoinflammatory diseases are disorders of the innate immune system characterized by uncontrolled inflammation. The most commonly encountered autoinflammatory diseases are the hereditary periodic fever syndromes, which present with fever and other features of the skin, serosal membranes, and musculoskeletal system. The main inherited (monogenic) periodic fever syndromes are familial Mediterranean fever (FMF), cryopyrin-associated periodic syndrome (CAPS), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), and hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD). Recent advances in our understanding of the molecular and pathophysiological basis of autoinflammatory diseases have provided new treatment strategies. Patients with periodic fever syndromes have clearly benefited from anti-interleukin (IL)-1 treatment. Colchicine is still the mainstay of FMF therapy, but IL-1 blockade is also effective if colchicine fails. Early diagnosis and effective treatment can prevent irreversible organ damage. The scope of pathogenic mutations and more targeted therapy for better management of these rare diseases remains to be defined.

**Key Points**

Beneficial effects from interleukin (IL)-1-blocking agents have been reported in all monogenic autoinflammatory diseases.

Treat-to-target strategies are very important to achieve complete response, particularly in cryopyrin-associated periodic syndrome (CAPS).

Guidelines are required on how and when to use anti-IL-1 agents effectively in these autoinflammatory diseases.

The prognosis for these patients depends on early diagnosis and treatment.

## 1 Introduction

Autoinflammatory diseases are a heterogeneous group of disorders of the innate immune system that present with clinical signs of inflammation such as fevers, skin features, musculoskeletal features, and raised acute-phase inflammatory markers [1]. The most common and well-characterized group of autoinflammatory syndromes are those associated with "periodic fevers", where unprovoked sterile inflammation manifests mainly as recurrent fever and disease-specific patterns of organ inflammation. The main inherited (monogenic) periodic fever syndromes are familial Mediterranean fever (FMF), cryopyrin-associated periodic syndrome (CAPS), tumor necrosis factor (TNF)-receptor-associated periodic syndrome (TRAPS), and hyperimmunoglobulin D syndrome (HIDS)/mevalonate

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kinase deficiency (MKD). Periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome is also common. However, as it is not due to a single gene defect it is not discussed in this review, although it should be in the differential diagnosis of all four of the monogenic diseases covered here.

- Globally, FMF is the most common autoinflammatory disease, caused by mutations of the *MEFV* gene, which codes for the pyrin protein [2, 3]. Mutated pyrin causes an exaggerated inflammatory response via uncontrolled interleukin (IL)-1 secretion [4]. The typical attack will last <3 days and is characterized by fever and serositis in the form of abdominal or chest pain or arthritis. The most significant complication of FMF is amyloidosis [5]. Fortunately, the majority of cases can be treated with colchicine [6], an oral drug that is generally cheaply available in most countries. However, a minority of patients can be resistant to colchicine. Anti-IL-1 therapy is a promising second-line therapy should colchicine treatment fail [6, 7].
- CAPS is caused by gain-of-function mutations in the *NLRP3* gene encoding cryopyrin, resulting in increased IL-1 secretion [8]. CAPS is clinically characterized by fever, urticaria, musculoskeletal features, and conjunctivitis, as well as hearing loss and neurological symptoms at the more severe end of the disease spectrum. CAPS has traditionally been divided into three diseases: familial cold autoinflammatory syndrome (FCAS), representing the mildest form of the disease; Muckle–Wells syndrome (MWS), which may also cause hearing defects; and neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurological cutaneous articular syndrome (CINCA), which represents the most severe form of the disease [9]. However, a more recent approach is to consider all patients with a *CIAS1* mutation under the same heading of CAPS. This is mainly because of the overlap of the underlying mutations and the variation of symptoms with mosaicism and therapy. Diagnosis relies on clinical suspicion followed by genetic testing, but an international group of experts recently suggested classification criteria that would guide clinicians in the diagnosis of these diseases [10].
- TRAPS is caused by mutations in the *TNFRSF1A* gene encoding TNF receptor 1 (TNFR1) and is characterized by attacks of fever, serositis (chest and/or abdominal pain), migratory rash, orbital findings, and musculoskeletal symptoms such as myalgia [11]. Unlike the other three monogenic periodic fever syndromes, the duration of attacks tends to be longer than a week. FMF, TRAPS, and severe CAPS may all lead to secondary amyloidosis as a sequelae of chronic inflammation [12, 13].
- HIDS or MKD is caused by mutations of the *MVK* gene. On this basis, it is a metabolic disease; however, the defect leads to increased IL-1 production (discussed elsewhere [14]) and frank inflammation [14]. The main clinical manifestations are attacks of fever, abdominal pain, vomiting, diarrhea, lymphadenopathy, and rashes lasting 3–6 days. Attacks are provoked by immunizations, surgery, trauma, and infections [15].

Better understanding of the molecular basis and pathophysiology of autoinflammatory diseases has led to new treatment targets and strategies. The common feature of the aforementioned autoinflammatory diseases (including colchicine-resistant FMF) is response to IL-1 blockade, which is a promising therapy for the management of these diseases and for the prevention of irreversible organ damage. In this review, we discuss the new treatment options for autoinflammatory diseases.

## 2 Treatment Approach to Periodic Fevers

Autoinflammatory diseases cause uncontrolled systemic inflammation, leading to irreversible organ damage. A multidisciplinary approach to early diagnosis and control of inflammation is critical in the prevention or stabilization of organ damage (hearing loss, visual loss, chronic meningitis in CAPS, or amyloidosis mostly seen in FMF and TRAPS) and to improve the patient's quality of life. In 2015, a group of experts from different countries proposed recommendations for the management of CAPS, TRAPS, and HIDS/MKD [16] (Table 1), and in 2016 an international group of experts published the European League Against Rheumatism (EULAR)-endorsed recommendations for the management of FMF [17] (Table 2), to help clinicians, pediatricians, and pediatric rheumatologists diagnose and manage these diseases. In all monogenic autoinflammatory diseases, beneficial effects from IL-1 blockade have been reported [18]. Unfortunately, these drugs are quite expensive. Three forms of anti-IL-1 medications are currently available: anakinra (a recombinant, human IL-1 receptor antagonist), canakinumab (a human immunoglobulin [Ig]-G1 monoclonal antibody directed against IL-1β), and rilonacept (a fully human dimeric fusion protein that binds the extracellular domains of IL-1α and IL-1β). The US FDA has approved anakinra, canakinumab, and rilonacept for the treatment of CAPS, and the European Medicines Agency (EMA) has approved anakinra and canakinumab for the treatment of CAPS. Recently, the FDA also approved canakinumab for the treatment of TRAPS, HIDS/MKD, and (colchicine-resistant) FMF.

**Table 1** Recommendations for the treatment of cryopyrin-associated periodic syndrome, tumor necrosis factor receptor-associated periodic syndrome, and mevalonate kinase deficiency (adapted from ter Haar et al. [16])

| Disease | Treatment | Level of evidence[a] |
|---|---|---|
| CAPS | IL-1 inhibition is indicated for the whole spectrum of CAPS, at any age | 1B–2A |
| | To prevent organ damage, long-term IL-1 inhibition should be started as early as possible in patients with active disease | 2B |
| | There is no evidence for the efficacy of DMARDs or biological therapy other than IL-1 blockade | 4 |
| | For symptomatic adjunctive therapy, short courses of NSAIDs and corticosteroids may be used (level of evidence 3), but they should not be used for primary maintenance therapy (4) | 3, 4 |
| | Adjunctive therapy (e.g., physiotherapy, orthotic devices, hearing aids) is recommended as appropriate | 4 |
| TRAPS | NSAIDs may provide symptom relief during inflammatory attacks | 3 |
| | Short-term glucocorticoids, with or without NSAIDs, are effective for terminating inflammatory attacks | 3 |
| | The beneficial effect of corticosteroids can decline over time so that increasing doses are required to achieve an equivalent response | 3 |
| | IL-1 blockade is beneficial in the majority of patients | 2B |
| | Etanercept can be effective in some patients, but the effect might decline over time | 2B |
| | With frequent attacks and/or subclinical inflammation between attacks, maintenance therapy with IL-1 blockade or etanercept is recommended and may limit corticosteroid exposure | 2B–3 |
| | If one IL-1-blocking agent at an adequate dose is ineffective or intolerable, a switch to etanercept or another IL-1-blocking agent should be considered. Likewise, if etanercept is ineffective or intolerable, a switch to an IL-1-blocking agent should be considered | 4 |
| | Although a beneficial effect is reported in a few cases, the use of anti-TNF monoclonal antibodies is not advised because of possible detrimental effects | 3 |
| MKD | NSAIDs may provide symptom relief during inflammatory attacks | 3 |
| | Short-term glucocorticoids, with or without NSAIDs, may be effective for alleviating inflammatory attacks | 3 |
| | Colchicine or statins are not efficacious; we do not recommend them | 3 |
| | Short-term IL-1 blockade may be effective for terminating inflammatory attacks and should be considered to limit or prevent steroid side effects | 2B |
| | With frequent attacks and/or subclinical inflammation between attacks, maintenance therapy with IL-1 blockade or etanercept is recommended and may limit corticosteroid exposure | 2B–3 |
| | If one IL-1-blocking agent at an adequate dose is ineffective or intolerable, a switch to another IL-1-blocking agent or another biological agent (including TNF-α blockade or IL-6 blockade) should be considered. Likewise, if TNF-α blockade is ineffective or intolerable, a switch to another biological agent (including an IL-1- or IL-6-blocking agent) should be considered | 4 |
| | In selected cases with severe refractory disease and poor quality of life, referral to a specialist center for consideration of allogeneic hematopoietic stem cell transplantation is recommended | 3 |

*CAPS* cryopyrin-associated periodic syndromes, *DMARDs* disease-modifying antirheumatic drugs, *IL* interleukin, *MKD* mevalonate kinase deficiency, *NSAIDs* non-steroidal anti-inflammatory drugs, *TNF* tumor necrosis factor, *TRAPS* tumor necrosis factor receptor-associated periodic syndrome

[a] Level of evidence: 1B = randomized controlled study, 2A = controlled study without randomization, 2B = quasi-experimental study, 3 = descriptive study, 4 = expert opinion

### 2.1 Familial Mediterranean Fever (FMF)

FMF is the most common autoinflammatory disease. An international group of experts recently published recommendations for the management of FMF [17]. According to these recommendations, the main goal of treatment should be complete control of unprovoked attacks and minimizing subclinical inflammation between attacks. Colchicine has been the mainstay of FMF treatment since 1972 [19] and is generally safe and well-tolerated in children [20]. Colchicine can reduce the frequency and severity of attacks and suppress subclinical inflammation between attacks [21–23]. Furthermore, it prevents the development of secondary amyloidosis in patients with FMF [24]. It is recommended that colchicine should be started as soon as the patient is clinically diagnosed. Genetic diagnosis may not be enough to start colchicine treatment without clinical manifestations or subclinical inflammation. Physicians should follow-up these patients closely for clinical and subclinical signs of FMF [17]. In countries where amyloidosis is frequent, if the patient has *M694V* homozygous mutations, physicians tend to start

**Table 2** The European League against rheumatism recommendations for the management of familial Mediterranean fever with grade of recommendation (adapted from Ozen et al. [17])

| | Recommendation | Grade |
|---|---|---|
| 1 | Ideally, FMF should be diagnosed and initially treated by a physician with experience in FMF | D |
| 2 | The ultimate goal of treatment in FMF is to reach complete control of unprovoked attacks and minimize subclinical inflammation between attacks | C |
| 3 | Treatment with colchicine should start as soon as a clinical diagnosis is made | A |
| 4 | Administration can be in single or divided doses, depending on tolerance and compliance | D |
| 5 | The persistence of attacks or subclinical inflammation represents an indication to increase the colchicine dose | C |
| 6 | Compliant patients not responding to the maximum tolerated dose of colchicine can be considered non-respondent or resistant; alternative biological treatments are indicated in these patients | B |
| 7 | FMF treatment needs to be intensified in amyloid A amyloidosis using the maximal tolerated dose of colchicine and supplemented with biologics as required | C |
| 8 | Periods of physical or emotional stress can trigger FMF attacks, and it may be appropriate to increase the dose of colchicine temporarily | D |
| 9 | Response, toxicity, and compliance should be monitored every 6 months | D |
| 10 | Liver enzymes should be monitored regularly in patients with FMF treated with colchicine; if liver enzymes are elevated more than twofold the upper limit of normal, colchicine should be reduced and the cause further investigated | D |
| 11 | In patients with decreased renal function, the risk of toxicity is very high, and therefore signs of colchicine toxicity, as well as CPK, should be carefully monitored and colchicine dose reduced accordingly | C |
| 12 | Colchicine toxicity is a serious complication and should be adequately suspected and prevented | C |
| 13 | When suspecting an attack, always consider other possible causes. During the attacks, continue the usual dose of colchicine and use NSAID | C |
| 14 | Colchicine should not be discontinued during conception, pregnancy, or lactation; current evidence does not justify amniocentesis | C |
| 15 | In general, men do not need to stop colchicine prior to conception; in the rare case of azoospermia or oligospermia proven to be related to colchicine, temporary dose reduction or discontinuation may be needed | C |
| 17 | Chronic arthritis in a patient with FMF might need additional medications, such as DMARDs, intra-articular steroid injections, or biologics | C |
| 17 | In protracted febrile myalgia, glucocorticoids lead to the resolution of symptoms; NSAIDs and IL-1 blockade might also be a treatment option; NSAIDs are suggested for the treatment of exertional leg pain | C |
| 18 | If a patient is stable with no attacks for more than 5 years and no elevated APR, dose reduction could be considered after expert consultation and with continued monitoring | D |

*APR* acute phase reactants, *CPK* creatinine phosphokinase, *DMARDs* disease-modifying antirheumatic drugs, *FMF* familial Mediterranean fever, *IL* interleukin, *NSAID* non-steroidal anti-inflammatory drug

[a] Grades of recommendation: A = high, B = moderate, C = low, D = very low

colchicine, since this mutation is associated with the risk of amyloidosis [25, 26].

The starting dose of colchicine has been suggested as ≤0.5 mg/day for children aged <5 years, 0.5–1 mg/day in children aged 5–10 years, and 1–1.5 mg/day in children aged >10 years and adults [17]. The optimal dosage of colchicine varies between clinical practices. Treatment is generally started at the sub-therapeutic dose of 0.5 mg/day and monitored according to disease activity and the patient's tolerance. Higher doses up to 2 mg/day in children and up to 3 mg/day in adults can be used to control ongoing disease activity and amyloidosis [17]. The side effects of colchicine are gastrointestinal, with vomiting, diarrhea, and transient elevation of transaminases occurring in up to 5% of patients with FMF. A minority of patients with FMF do not respond to colchicine or are intolerant to the drug because of its side effects [27]. These patients will experience frequent attacks and, more importantly, ongoing inflammation. The chronic inflammation may lead to many sequelae, the most frequent and worrisome being the development of secondary amyloidosis. Since the mutation in the pyrin protein has been clearly associated with increased IL-1 production, anti-IL-1 treatment has emerged as a promising option in patients with resistant disease [7, 28]. Several studies have reported successful results in colchicine-resistant patients with IL-1-blocking agents, including anakinra, canakinumab, and rilonacept [29, 30]. A literature review of anti-IL-1 treatment in FMF reported complete response in 76.5% of patients receiving anakinra treatment and 67.5% of those receiving canakinumab treatment [30]. In a small randomized controlled study, rilonacept treatment resulted in complete response in two and partial response in eight of 14 patients [31]. IL-1 blockade can also reverse proteinuria in patients with

secondary amyloidosis [30, 32]. However, there is no evidence for using anti-IL-1 treatment without colchicine to prevent amyloidosis. Thus, a maximal tolerated dose of colchicine is recommended with anti-IL-1 treatment [17]. A cluster study evaluating the efficacy and safety of canakinumab in patients with hereditary periodic fevers, including colchicine-resistant FMF, is underway (NCT02059291) [33]. Etanercept has also been used to treat FMF before administration of anti-IL-1 agents [34]. Anti-TNF treatment can be successful, especially in patients with FMF and chronic arthritis and sacroiliitis [35].

### 2.2 Cryopyrin-Associated Periodic Syndrome (CAPS)

In CAPS, corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) can be used for symptom relief [36]. However, no evidence is available relating to the efficacy and safety of disease-modifying anti-rheumatic drugs or biological therapy, except for IL-1-blocking agents [36]. Early diagnosis and initiation of treatment are very important because hearing loss, joint deformities, and neurological damage are the leading cause of morbidity and can be stabilized or improved with anti-IL-1 treatment [37–40]. Elegant research in CAPS has clearly identified the excess production of IL-1 in this disease; thus, it is no surprise that anti-IL-1 drugs have emerged as the appropriate treatment [8]. In the published series for CAPS, patients have often been defined as NOMID/CINCA or MWS or FCAS [8], and these conditions are discussed accordingly.

Anakinra was the first anti-IL-1 drug to be tried in these patients. Sibley et al. [40] showed that, in 26 patients with NOMID/CINCA (aged 8 months to 41 years), anakinra provided up to 5 years of sustained efficacy. The authors observed that anakinra not only prevented systemic inflammation but also reduced steroid use, improved patient growth, and improved or stabilized hearing and vision. However, there was no clear effect on bony lesions such as clubbing or patellar overgrowth [40]. Increasing doses of anakinra reduced the cerebrospinal fluid (CSF) leukocyte count and opening pressure, which are indicators of central nervous system (CNS) inflammation. The authors also demonstrated that cochlear enhancement on magnetic resonance imaging correlated with continued hearing loss and low optic nerve size correlated with poor visual field [40]. In another study, anakinra treatment improved not only clinical and laboratory features but also cochlear and leptomeningeal lesions [41]. In 2015, Ross et al. [42] showed the clinical and laboratory efficacy of anakinra in eight adult members of the same family with FCAS. All signs and symptoms of FCAS resolved in all patients within 24 h after the first injection of anakinra [42]. In 2015, Sibley et al. [43] demonstrated that canakinumab, a long-acting anti-IL-1 treatment, improved both symptoms and serum inflammatory markers in six patients with NOMID with appropriate dose adjustments; however, CSF pleocytosis persisted in five of six patients. Rodriguez-Smith et al. [44] recently showed that levels of IL-6, interferon γ-induced protein (IP)-10 (also known as C-X-C motif chemokine 10 [CXCL10]), and IL-18 were elevated in the CSF of patients with NOMID and could serve as markers for CNS inflammation. CSF studies showed that cytokine levels, as well as monocyte and granulocyte counts, in CSF decreased with anakinra treatment. CSF levels of IL-6, IP-10/CXCL10, and IL-18 and CSF white blood cell counts were significantly higher when patients received canakinumab than when they received anakinra, despite similar serum cytokine levels. The authors thus suggested that anakinra may be more likely to pass through the blood–brain barrier than canakinumab [44].

Studies reporting the use of canakinumab in CAPS are increasing. In two randomized controlled trials, canakinumab induced rapid and sustained remission [45, 46]. Subcutaneous canakinumab 2 mg/kg (children) and 150 mg (adults) once per 8 weeks provided sustained remission in patients with CAPS [47, 48]. Supporting the effectiveness of canakinumab in CAPS, Kuemmerle-Deschner et al. [48] found that seven patients with CAPS treated with canakinumab achieved complete response. Furthermore, in a multicenter phase III study [47], they demonstrated that higher canakinumab doses were required to obtain complete response in younger patients and in more severe disease. Dose escalation was not associated with an increase in adverse events. The same group drew attention to the real-life effectiveness of canakinumab in CAPS. They showed that centers using a standard dose of canakinumab have fewer complete responders than centers using 'treat-to-target' strategies that adjust the canakinumab dose according to patient age and disease severity to achieve complete response [49]. Similarly, according to the Eurofever Registry, the number of patients with CAPS responding to anti-IL-1 drug therapy was lower than the literature described [35]. Yokota et al. [50] recently described 19 Japanese patients with CAPS (MWS 7; NOMID 12), who were treated with subcutaneous canakinumab 2–8 mg/kg every 8 weeks. In total, 15 (79%) patients achieved a complete response by day 15, 18 (94.7%) by week 24, and all by week 48. Thirteen (68%) patients (MWS 4; NOMID 9) required a dose increase during the trial [50].

The efficacy of rilonacept was demonstrated in two double-blind, placebo-controlled trials of 6 and 18 weeks duration in 41 patients with FCAS and three with MWS: rilonacept decreased the number of disease flare days

and levels of C-reactive protein (CRP) and serum amyloid A (SAA), improved the physician's and patient's global assessments of disease activity, and reduced limitations in patients' daily activities. The treated patients also experienced a significant reduction in mean symptom score (84%) compared with placebo (13%) [51]. During the 96-week follow-up, the effect of rilonacept was sustained [52].

### 2.3 Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS)

The treatment of TRAPS is determined by the severity of the disease. NSAIDs are usually used as on-demand therapy to relieve symptoms, but they are not effective in suppressing ongoing inflammation [36]. For patients with mild disease, corticosteroids can be an option to end attacks, but the corticosteroid doses may need to be escalated, and steroid withdrawal may be difficult [53]. Anti-TNF therapy with etanercept is effective in controlling attacks and reducing steroid requirements for some patients [53]. In the Eurofever Registry, etanercept was effective in 87% of patients with TRAPS, but a complete response was seen only in 30% [36]. Etanercept is a fusion protein containing two copies of the TNF receptor bound to the Fc region of human IgG1. Subsequent studies have shown that the responsiveness to etanercept is not usually complete and may decrease over time [54]. It has been shown that treatment with infliximab and adalimumab might trigger inflammatory attacks, and they are therefore not recommended for the treatment of TRAPS [16]. These latter two drugs are monoclonal anti-TNF antibodies. The increased proinflammatory response after infliximab administration is thought to be a result of the failure to shed infliximab-bound TNF/TNFR1 from the cell surface [55].

IL-1 blocking may be more effective than anti-TNF agents in TRAPS [36, 54, 56]. Anakinra has been a promising therapy for patients with severe disease who require long-term steroids and have an insufficient response to etanercept [56, 57]. Consistently, in the Eurofever Registry, 79% of patients experienced complete responses with anakinra [36]. However, a number of studies have shown that anakinra failed in TRAPS [36, 58]. Recent studies have shown that the efficacy of canakinumab appeared rapidly and provided long-term clinical benefits [57, 59]. The randomized phase III cluster study (NCT02059291) of canakinumab in patients with TRAPS, HIDS, or colchicine-resistant FMF also confirmed the efficacy of this drug in TRAPS [33].

Finally, three observational studies suggested tocilizumab, a humanized monoclonal antibody agent against the IL-6 receptor, was also effective for the treatment of patients with TRAPS. However, two of the three patients did not have pathogenic TRAPS mutations. Further controlled trials are necessary to assist with understanding the effect of tocilizumab on TRAPS [60–62].

### 2.4 Hyperimmunoglobulin D Syndrome (HIDS)/ Mevalonate Kinase Deficiency (MKD)

NSAIDs can be effective in HIDS/MKD, and corticosteroids have been tried for HIDS attacks. In the Eurofever Registry, NSAIDs were mostly used as on-demand therapy for attacks, with five (13%) of the 39 patients experiencing complete response and 25 (64%) experiencing a partial response [36]. NSAIDs can relieve symptoms in most patients but may not end the attacks and inflammation [16]. High-dose corticosteroids administered at the onset of an attack can reduce the severity and duration of febrile episodes. In the Eurofever Registry, treatment with corticosteroids resulted in a complete response in eight (24%) and a partial response in 22 (67%) of the 33 patients [36]. Colchicine is not an effective therapy in patients with HIDS/MKD. In the Eurofever Registry, colchicine was used in 17 patients, but 65% experienced no response [36]. As the mutant enzyme in HIDS/MKD is a member of the cholesterol and isoprene pathway, statins have been used for treatment, but results were poor [53]. Moreover, there might be a detrimental effect on attack severity [63]. Because of the increased IL-1β secretion in patients with HIDS/MKD, IL-1 blockade has emerged as a therapeutic option [64]. In the Eurofever Registry, 89% of 27 patients receiving anakinra and 65% of 17 patients receiving etanercept experienced a response. Complete remission was observed in 22% of patients receiving anakinra and in 6% of those receiving etanercept [36]. A small prospective study found a ≥50% reduction in the severity and duration of febrile episodes in patients with HIDS/MKD using on-demand therapy with anakinra when administered in the first 24 h of an attack [65].

Continuous therapy with IL-1-blocking agents or anti-TNF drugs should be preferred in patients with HIDS/MKD with frequent attacks and those with ongoing subclinical inflammation between attacks and long-term complications [16, 65]. Ter Haar et al. [16] found that neither anakinra nor etanercept were superior to each other as first-line biological therapies in HIDS/MKD. For anti-IL-1 treatment, dose escalation should be tried first before switching to other biological therapies. In a recent literature review [66] of the treatment of pediatric patients with HIDS/MKD, 21 patients were treated with anakinra, 16 with etanercept, and five with canakinumab; response rates were 90%, 50%, and 100%, respectively. Galeotti et al. [67] treated six patients with HIDS with canakinumab; three patients achieved a complete response and the remaining three achieved a partial response. If anti-IL-1

and anti TNF therapy do not provide significant improvement, tocilizumab may be a treatment option. Shendi et al. [68] reported on a patient with HIDS/MKD resistant to colchicine, corticosteroids, etanercept, and anakinra who was treated successfully with tocilizumab. In very severe cases, hematopoietic stem cell transplantation may be indicated, and suppression of systemic inflammation and improvement of neurologic symptoms has been observed in such patients [69–71]. Again, canakinumab was also shown to be effective in the treatment of patients with HIDS in the cluster study (NCT02059291) [33].

## 3 Conclusions

Autoinflammatory diseases are rare, chronic disorders characterized by high inflammatory states. The scope of pathogenic mutations and more targeted therapy for better management of these rare diseases remains to be defined. The prognosis for these patients depends on early diagnosis and early treatment. Colchicine is still the main therapy in FMF, but if colchicine fails, IL-1 blockade is a promising second-line therapy. In CAPS, the effect of anti-IL-1 agents is clear cut. In TRAPS and HIDS/MKD, IL-1 blockade seems more effective than other biologics. We can now offer patients with CAPS, TRAPS, HIDS/MKD, or colchicine-resistant FMF a much better quality of life while protecting them from irreversible organ damage.

**Compliance with Ethical Standards**

**Conflict of interest** Seza Ozen has previously received consultancy and speaker fees from Novartis, Sobi, and R-Pharma. Selcan Demir has no conflicts of interest.

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