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Treatment advances in mevalonate kinase deficiency: A comprehensive review

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Abstract

Mevalonate kinase deficiency (MKD) is a rare auto-inflammatory disease caused by mutations in the mevalonate kinase gene. This leads to problems with isoprenoid production and cell function. Individuals with MKD usually experience repeated fever episodes, along with stomach issues, mouth sores, swollen neck lymph nodes, and skin rashes. In addition, the severity of MKD varies markedly among individuals. The most severe and rarest form of MKD is called mevalonic aciduria, while the most typical type is referred to as hyperimmunoglobulinemia-D syndrome. Based on new research and clinical progress, this review explores more treatment options for MKD.

Keywords: Mevalonate kinase deficiency; Hyperimmunoglobulinemia-D syndrome; Treatment; Interleukin-1; Interleukin-6

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1. Introduction

Mevalonate kinase deficiency (MKD) is a rare metabolic condition inherited in an autosomal recessive manner, characterized by periodic episodes of autoinflammation. This disorder arises due to biallelic loss-of-function mutations in the mevalonate kinase (*MVK*) gene. The *MVK* gene encodes for mevalonate kinase, an enzyme that plays a crucial role in the early stages of the isoprenoid biosynthetic pathway.[1] While MKD has been found in different populations, it seems more common in people of northern European descent, with few cases reported in Asia.[2,3]

Mutations in both copies of *MVK* reduce enzyme activity. Normally, MVK helps turn mevalonic acid into phosphomevalonic acid, a key step in isoprenoid production.[4] When the enzyme does not function properly, mevalonic acid builds up, and isoprenoid levels decrease. This causes severe, repeated inflammation.[5] In individuals with MKD, serum acute phase reactants, Immunoglobuli D, and urinary mevalonic acid levels typically rise during inflammatory episodes.[6] Moreover, symptoms typically begin before 6 months of age, with fever episodes lasting 3 – 7 days.[7] The correlation between genotype and phenotype in MKD is intricate. Although the condition is generally caused by mutations in the *MVK gene*, the clinical presentations can differ significantly.[8] This variation is not exclusively determined by the classification of genetic variants; individuals with the same genotype may still display diverse clinical symptoms. The severity of MKD can range from mild-to-severe auto-inflammatory disease (AIDs).

Common signs include high fever, mouth sores, swollen neck lymph nodes, stomach problems (nausea, vomiting, and diarrhea), rashes, and joint pain. Rare but severe complications include macrophage activation syndrome, vision loss (retinitis pigmentosa), and serum amyloid A protein (AA) amyloidosis (approximately 4% of the cases).[9] The disease varies in severity – the worst form, mevalonic aciduria (MA), exhibits almost no enzyme activity, high stillbirth risk, and severe health problems.[10] The disease trajectory of MKD appears particularly susceptible to modifiable environmental triggers. Pathogen encounters, immunological challenges from vaccinations, and physiological stress responses all demonstrate significant capacity to modulate symptom onset patterns and their subsequent progression. Moreover, additional genetic factors or modifier genes may contribute to the phenotypic expression, further complicating the genotype-phenotype relationship.[11,12] The discovery of a shared promoter region between the *MVK* gene and the metabolism of cobalamin-associated B genes implies potential regulatory crosstalk. Current diagnostic protocols recommend simultaneous analysis of both genetic markers to ensure comprehensive MKD assessment. A particular genetic variation (rs1450500) in the glutamate ionotropic receptor delta type subunit 2 gene, located in the 4q22.2 region, has been identified as potentially associated with MKD, likely acting as a phenotypic modifier.[13]

The main goal of treatment is to reduce symptoms during flare-ups and stop repeated attacks. Managing MKD remains challenging, and treatment strategies continue to evolve. Currently, a multidisciplinary approach is recommended, as reflected in several guidelines.[14-16] A comprehensive review of these treatment strategies is essential to support clinical decision-making and improve patient outcomes.

2. Results

We summarize the treatment approaches for MKD in a structured flow diagram, integrating current clinical evidence and therapeutic recommendations (Figure 1).

2.1. Inhibitors of the interleukin (IL)-1 pathway

Given IL-1t's central involvement in MKD-related inflammation, IL-1 antagonists (notably anakinra and canakinumab) have become first-line therapeutics, achieving robust treatment responses in most affected individuals.

Aktaş *et al.*[17] described a 15-year-old female patient who presented to their clinic with recurrent fever and abdominal pain since the age of four. Initially, she was diagnosed with familial Mediterranean fever (FMF) based on clinical symptoms consistent with FMF, a history of consanguineous marriage, and the fact that Turkey is a region where FMF is endemic. However, subsequent genetic analysis, including whole-exome sequencing, identified pathogenic variants in the *MVK* gene. As a result, anakinra was incorporated into her treatment regimen. The patient experienced a positive response to anti-IL-1 therapy, with the cessation of disease flare-ups and a reduction in acute-phase reactants. In addition, a case report involving two Moroccan patients with MKD evaluated the efficacy of anakinra. In these cases, anakinra achieved complete clinical remission in one patient, while the other showed mild residual inflammation but experienced normalized growth.[18] The Eurofever Registry's retrospective analysis found that eight patients received anakinra only during flare-ups, with three achieving a complete response and five experiencing a partial response. Among 19 patients receiving anakinra as maintenance therapy, three attained complete remission, 13 had a partial response, and three showed no response; all of these latter patients had recurrent disease patterns. An individual with severe disease progression exhibited cerebellar ataxia, cognitive impairment, and retinitis pigmentosa, whereas the two mildly affected subjects displayed no significant complications. In a subset of seven patients who showed inadequate or incomplete response to initial anakinra therapy, dose escalation was attempted but failed to achieve full disease control. Of these, four transitioned to alternative treatments, while three remained on anakinra despite suboptimal outcomes. Six other patients with partial therapeutic response did not undergo dose adjustments; half continued anakinra without further intervention.[7] In addition, a non-interventional prospective study involving 11 patients with MKD reported on the use of anakinra.[19] Two patients with MA began continuous anakinra treatment (1 – 2 mg/kg/day), whereas nine patients with hyperimmunoglobulinemia-D syndrome (HIDS) chose between continuous and on-demand treatment (100 mg/day or 1 mg/kg/day for 5 – 7 days at first symptoms). Anakinra induced partial remission in one MA patient but no response in the other. One HIDS patient achieved complete remission for 7 months with continuous treatment but stopped due to side effects. Eight HIDS patients opted for on-demand treatment, which reduced fever attack duration and severity in eight of 12 treated episodes without changing attack frequency. In summary, on-demand anakinra treatment in HIDS effectively decreases fever attack duration and severity.

While anakinra has demonstrated benefits for numerous patients, the long-acting IL-1 antagonist canakinumab has been studied more extensively. Several international observational registries and studies have demonstrated

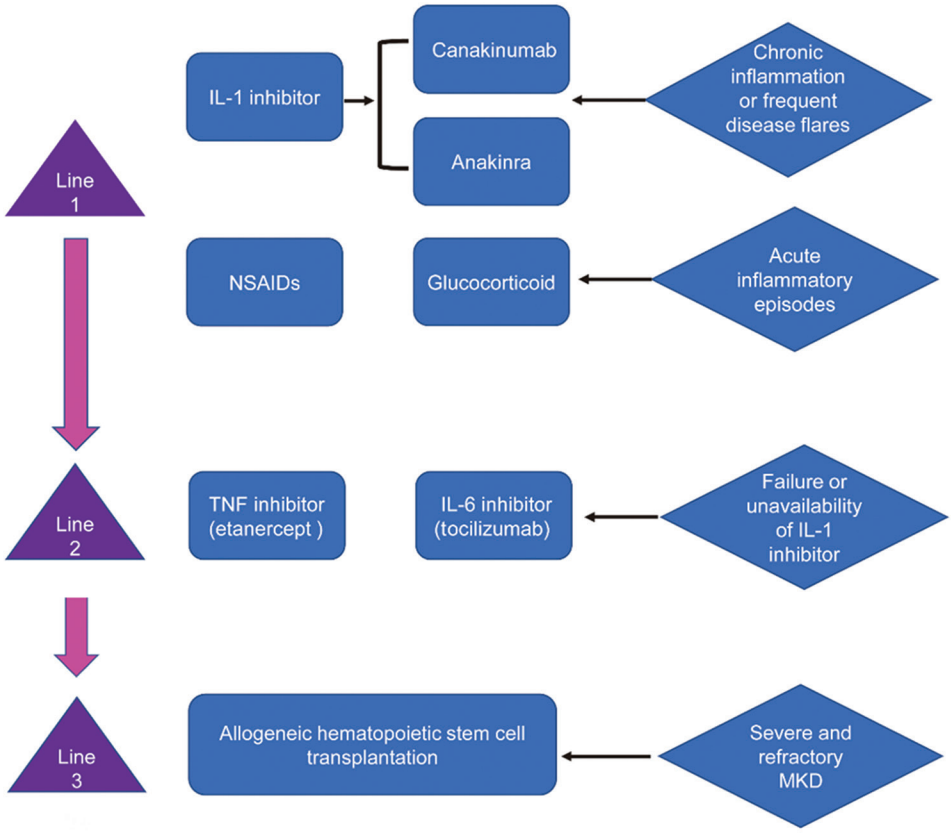

Figure 1. Recommended therapeutic approach for patients with MKD
Abbreviations: MKD: Mevalonate kinase deficiency; NSAIDs: Non-steroidal anti-inflammatory drugs; IL-1: Interleukin 1; TNF: Tumor necrosis factor.

encouraging outcomes with a particular treatment.[20,21] The cluster randomized controlled trial stands as a methodological benchmark in MKD research, employing rigorous randomization and control protocols that have since become referential.[22] It rigorously assessed the efficacy of canakinumab in MKD patients. The study randomized molecularly diagnosed MKD subjects to 4-week regimens of placebo versus two canakinumab dose tiers (150 mg or 300 mg, subcutaneously). Complete therapeutic response, characterized by durable disease flare abatement through the 16-week assessment period, served as the primary outcome measure. The results favored canakinumab, which achieved a six-fold higher complete response rate to placebo (35% vs. 6%), underscoring its therapeutic value in MKD. Despite higher infection rates observed with IL-1 inhibition, the substantial clinical improvement positions canakinumab as a viable treatment option with an acceptable safety profile. The extended open-label phase 3 cluster trial evaluated canakinumab's efficacy and safety over 72 weeks in MKD patients.[23] Canakinumab administration (150 – 300 mg every 4 – 8 weeks) demonstrated significant flare reduction efficacy, with 64% of patients achieving complete flare cessation compared to their pre-treatment median of 12 flares/year. Remarkably, >90% of the cohort attained minimal disease activity by study conclusion, with parallel reductions in C-reactive protein (CRP) and serum AA (SAA) levels. The observed adverse event profile aligned with IL-1 inhibition expectations, corroborating its suitability for chronic MKD management. Furthermore, Koné-Paut *et al.*[24] conducted a retrospective analysis of data from the French juvenile inflammatory rheumatism cohort of patients with MKD. During the study period, 26 MKD patients were administered canakinumab, most starting at the recommended dose of either 2 mg/kg or 150 mg. After 2 years of treatment, the retention rate for canakinumab was 73.7% among MKD patients. This analysis demonstrated the effective maintenance of canakinumab therapy over 2 years and reaffirmed its safety profile in real-world clinical practice in France for individuals with MKD.

An ongoing non-interventional prospective cohort study involving eight MKD cases at multiple German centers is documenting canakinumab's real-world efficacy and safety parameters through systematic longitudinal observation.[25] The cohort included five children (<18 years) and three

females, with a median age of 8.0 years (range 2.0 – 39.0). All patients had previously received canakinumab before enrollment. The study demonstrated sustained therapeutic efficacy, with >50% of patients maintaining continuous disease remission through the 24-month observation period. Inflammatory markers (CRP and SAA) consistently normalized throughout the follow-up period. Notably, most patients required canakinumab dosing exceeding initial protocol recommendations, yet demonstrated favorable long-term safety outcomes, supporting its use in MKD/HIDS management. In addition, the prospective cluster study enrolled 70 patients with MKD to assess the impact of canakinumab on health-related quality of life, work or school attendance, and social life.[26] Participants had a confirmed genetic or biochemical diagnosis and a history of ≥3 flares in the prior 6 months. Patients received canakinumab (150 mg or 300 mg) every 4 weeks. Quality of life was evaluated using the 12-item short-form health survey for adults (≥18 years) and the child health questionnaire-parent form 50 for children aged 5 – 18 years. Results indicated that canakinumab significantly improved the physical, psychological, social, and functional aspects of quality of life, with sustained benefits over the 41-week study period. Despite low baseline quality of life scores, patients experienced significant improvements following canakinumab treatment, reflecting effective disease control and reduced symptom burden. Isik *et al.*[27] reported a case of recurrent fever and arthritis attacks that did not respond to anakinra but were successfully managed with canakinumab. Balci *et al.*[28] investigated the impact of canakinumab on growth parameters in children with AIDs, including nine patients with MKD among a cohort of 24. Following canakinumab treatment, significant improvements were observed in mean height, weight, and body mass index standard deviation scores. These positive outcomes were linked to canakinumab's effective control of disease activity and suppression of chronic inflammation. Notably, improvements in growth parameters following treatment were not influenced by gender, diagnostic age, or time to diagnosis. These findings highlight canakinumab's efficacy in promoting growth in children with autoinflammatory conditions, particularly MKD.

No direct head-to-head comparison has been made between anakinra and canakinumab. A retrospective cohort study of 13 adult MKD patients treated with IL-1 blockade demonstrated variable therapeutic outcomes: anakinra induced complete remission in 30% (3/10) of cases, partial response in 50% (5/10), and no clinical benefit in the remaining 20% (2/10). However, switching to canakinumab resulted in partial remission for those who did not respond to anakinra. Canakinumab achieved complete remission in 3 out of 7 patients and partial remission in 4 out of 7. These findings suggest that canakinumab generally elicits a better response, with frequent partial remissions noted.[21] For on-demand treatment, initiating anakinra at the earliest signs of an episode is essential, as this can help shorten MKD's duration. However, due to the limited availability of robust evidence, on-demand anakinra should primarily be used for patients with infrequent episodes[29] provided that there is clear documentation of no acute phase response between attacks. Clinical evidence indicates anakinra therapy effectively mitigates acute inflammatory markers (median CRP reduction of 85%), shortens febrile episodes (mean duration decrease from 5.2 to 1.8 days), and improves symptom severity scores ($p < 0.01$). However, its lack of prophylactic efficacy against disease flares necessitates treatment intensification to daily subcutaneous administration for patients with high disease activity (>1 episode monthly) to achieve adequate inflammatory control.[21] Anakinra is typically administered via daily subcutaneous injections, though some patients may require more frequent dosing. However, the injection frequency can be challenging for some patients due to the pain associated with both the injection and the medication itself. The primary adverse events linked to anakinra treatment are injection site reactions, especially in children.[30] While these reactions are generally mild and may resolve over time, they can still be a source of concern for families. Therefore, engaging in thorough communication with the patients and addressing their fears and preferences is vital to optimizing treatment adherence.

2.2. Inhibitors of the IL-6 pathway

For patients who do not respond to IL-1 inhibitors, IL-6 receptor antagonists might be a good second choice. Tocilizumab, a humanized monoclonal antibody that targets the IL-6 receptor and binds to both membrane-bound and soluble IL-6R, thereby inhibiting IL-6 signaling, appears effective for treating MKD. However, the evidence supporting its use is limited to a few case reports and small-scale studies. In one retrospective study, Lane *et al.*[31] investigated two MKD patients who did not respond to other treatments such as anakinra or etanercept. After using tocilizumab, their disease reached complete remission. However, one of them needed a kidney transplant because of complications from AA amyloidosis and later got a *Staphylococcus aureus* infection. The tocilizumab dose had to be lowered until the infection was gone. A case report describes the use of tocilizumab in a 12-year-old girl with MKD who had severe autoinflammation that was refractory to both IL-1 and TNF-α blockade.[32] She began receiving intravenous tocilizumab at a dosage of 8 mg/kg every 2 weeks. Following the first infusion, she experienced

immediate cessation of fever and significant improvement in her energy levels. After the fifth dose, she achieved complete clinical and serological remission, which has been sustained for 24 months. This case represents one of the first successful uses of tocilizumab in a child with MKD, further expanding the limited experience with this treatment modality for MKD. Moreover, Li *et al.*[33] reported three children with genetically confirmed HIDS who showed typical symptoms. All three improved after receiving tocilizumab, with decreased inflammatory flares. The researchers found that starting treatment early leads to better outcomes for HIDS patients. A 13-year-old girl who did not respond to anakinra or etanercept improved significantly after tocilizumab treatment.[34] Her HIDS episodes ceased completely, and her inflammatory markers, including erythrocyte sedimentation rate (ESR) and CRP, normalized. However, she later developed frequent colds with a runny nose, sore throat, and muscle aches, even though her blood test result was nearly normal. A study from China reported two young boys with MKD.[35] They received tocilizumab treatment because IL-1 antagonists were unavailable. Before treatment, their ESR, CRP, and IL-6 levels were high. After tocilizumab treatment, their ESR and CRP levels became normal, although IL-6 levels elevated occasionally. Both kids recovered and showed no adverse side effects after 6 months. Tocilizumab treatment was initiated alongside methylprednisolone, as tocilizumab was considered experimental at the time. This combination therapy led to remission, allowing for the gradual tapering of methylprednisolone. While tocilizumab is not commonly used to treat MKD, these cases suggest that tocilizumab could be a second-line option. Further research is needed to confirm its safety and effectiveness.

2.3. Tumor necrosis factor-α (TNF-α) blockers

TNF-α is believed to play a role in the pathophysiology of MKD, and TNF-α antagonists have been employed in patients' treatment. Similar to tocilizumab, TNF blockers have become potential second-line therapeutic options.

Etanercept, a TNF-α receptor fusion protein, has shown its therapeutic effect in several patients with MKD/HIDS. A retrospective case series involving 38 MKD/HIDS patients reported that 71% initially received anti-IL-1 therapy, with 68% using anakinra.[36] In contrast, anti-TNF (etanercept) and anti-IL-6 (tocilizumab) were used in only 26% and 3% of patients, respectively. The study reported no significant difference in complete clinical response between anakinra and etanercept (52% vs. 88%). Treatment was discontinued in 15 patients, with lack of efficacy being the reason for all four patients receiving etanercept. In another study of 33 pediatric HIDS patients treated with biologics, 16 received etanercept. Complete response was observed in three patients (19%), partial response in five (31%), and no response in four (25%).[37] An international, multicenter registry has examined the clinical and genetic features of 114 MKD patients, representing the largest cohort studied to date. Etanercept was administered to 27 patients, resulting in a beneficial effect in 16 individuals, with two achieving a complete response. However, the disease did not respond to etanercept in 11 patients.[7] Inflammatory AA amyloidosis, a rare but severe complication of MKD, may lead to mortality or the need for kidney transplantation. Rodrigues *et al.*[10] documented the occurrence of amyloidosis in 20 MKD patients, among whom 7 were treated with etanercept. The outcomes included four successful cases, one partial response, and two failures. However, another retrospective study reported that etanercept failed in five out of nine patients.[5] While etanercept's role in modulating inflammation suggests potential benefits in managing MKD symptoms, more extensive clinical data are needed. It may be effective when anakinra therapy fails and vice versa.[38] Due to the more robust evidence base for IL-1 inhibition, etanercept is no longer considered a first-line therapy. It is typically reserved for patients with contraindications, inadequate response, or limited access to IL-1 blockers.

Infliximab and adalimumab, both TNF-α inhibitors, are widely utilized in managing chronic ulcerative colitis.[39] Their application in MKD has also been documented in several case reports. Çakan *et al.*[40] described a 15-year-old girl who visited a pediatric rheumatology outpatient clinic due to joint swelling over the past 2 months. Whole-exome sequencing revealed that she carried a compound heterozygous mutation (G18R/V377I) in the *MVK* gene. She underwent adalimumab therapy for 36 months (40 mg, subcutaneous, every 2 weeks). As a result, she experienced a remarkable improvement, with a resolution of arthritis, fever attacks, and pulmonary symptoms from the first dose of adalimumab. Kousa *et al.*[41] investigated a 10-year-old Syrian boy with concurrent mutations in the Mediterranean fever and *MVK* genes. This child had been dependent on corticosteroids and showed a limited response to colchicine. However, after switching from tocilizumab to infliximab, significant improvement was observed, with no fever, joint swelling, or lymphadenopathy noted in the latest follow-up.

Combined therapy targeting TNF-α and IL-1 has demonstrated promising outcomes in patients with refractory MKD. Martin *et al.*[42] described a severe case of MKD resulting from a rare homozygous mutation in the *MVK* gene. The patient developed severe inflammatory bowel disease at a very early age, which persisted despite standard targeted treatments. Upon initiating combined therapy using IL-1 and TNF-α blockade, the child achieved

long-term control of systemic inflammation and colitis, as evidenced by normalization of fecal calprotectin levels.

2.4. Allogeneic hematopoietic stem cell transplantation (HSCT)

MVK is an enzyme found in various cell types. However, the inflammation observed in MKD is likely caused by dysfunction in immune cells known as phagocytes. Given this, allogeneic stem cell transplantation, a procedure that replaces faulty immune cells with healthy ones, may offer a potential cure for severe cases of MKD that do not respond to other treatments.

The initial case report detailed a 3-year-old child with MA who did not respond to anakinra and etanercept therapy. The patient underwent allogeneic bone marrow transplantation from a human leukocyte antigen (HLA)-identical sibling. Follow-up assessments 15 months post-transplantation revealed complete remission, with normalized inflammatory markers, although the patient still exhibited mild neurological symptoms (persistent ataxic gait).[43] Neven *et al.*[44] described a case of a 3-year-old boy with MA who did not respond to anti-inflammatory treatment and subsequently underwent allogeneic bone marrow transplantation from an HLA-identical sister. The patient experienced sustained remission of febrile attacks and inflammation over the 15-month follow-up period. In another case, two children with severe MKD received haploidentical α/β T-cell and B-cell-depleted stem cell transplantation. Both patients achieved stable full donor engraftment, complete resolution of clinical and biochemical signs of inflammation, and showed no acute organ toxicity or graft-versus-host disease (GvHD). Notably, despite the absence of inflammatory signs, urinary excretion of mevalonic acid remained high post-transplant.[45] However, Erdol *et al.*[46] reported a case of a 7.5-month-old boy with MA who underwent allogeneic bone marrow transplantation from an HLA-identical sibling but failed to improve, ultimately dying of septicemia 3.5 months post-transplant. In a multicenter retrospective analysis by Jeyaratnam *et al.*,[47] the outcomes of allogeneic HSCT were evaluated in nine patients with MKD. Engraftment was achieved in all except one case. Two individuals underwent secondary transplantation due to either partial engraftment or initial graft failure. Complete remission was attained in seven recipients. Adverse outcomes included grade II – IV acute GvHD in four patients and transplantation-associated mortality in two cases during follow-up.

HSCT represents a potentially curative intervention for severely affected MKD patients, though its use is generally limited to refractory cases due to substantial treatment-associated risks. While demonstrating clinical efficacy, the procedure carries significant morbidity and mortality, necessitating careful patient selection. HSCT should be contemplated primarily for individuals with life-threatening disease manifestations unresponsive to conventional therapies.

2.5. Other therapies

Non-steroidal anti-inflammatory drugs (NSAIDs) serve as first-line therapy for acute inflammatory flares in MKD, with both the Single Hub and Access Point for Pediatric Rheumatology in Europe (SHARE) consensus recommendations and German treatment guidelines supporting their use as a primary pharmacological intervention.[22] As reported by Ter Haar *et al.*,[7] NSAIDs were given to 66 patients, primarily to manage symptoms during attacks, and were effective in 48 cases. Among these, seven patients had a complete response to NSAIDs. Five of these individuals used NSAIDs only during flare-ups rather than as continuous therapy. Two patients received NSAIDs as monotherapy, while the remaining five used NSAIDs in combination with corticosteroids. The response to corticosteroids was complete in four patients and partial in one. The Eurofever Registry shows that NSAIDs were primarily used on-demand during attacks, with complete response in 13% (five out of 39) of patients and partial response in 64% (25 out of 39).[48] However, NSAIDs alone often fail to provide sufficient relief for severe inflammatory attacks.[14]

For MKD patients exhibiting suboptimal responses to NSAIDs or experiencing moderate-to-severe manifestations, corticosteroids represent a viable therapeutic alternative. Early intervention with brief, high-dose corticosteroid regimens during acute attacks may reduce febrile intensity and episode duration. Three guidelines supported this approach,[15,16] which cautions against the side effects of prolonged corticosteroid use and emphasizes the need for careful monitoring. In a retrospective study,[7] corticosteroids were administered to 49 patients to manage fever attacks. Among them, 19 patients achieved complete suppression of inflammatory episodes (16 of them had not received biologic agents). Some improvement was observed in 21 patients. Among the seven patients who received maintenance corticosteroids, five experienced some benefit, while the remaining two did not respond. In the Eurofever Registry, corticosteroid treatment led to a complete response in 24% (eight out of 33) and a partial response in 67% (22 out of 33) of patients.[48] In summary, NSAIDs and corticosteroids can provide symptomatic relief for mild disease flares.

The pyrin inflammasome is the key mediator in FMF pathogenesis, another disorder characterized by autoinflammatory features. While colchicine demonstrates

remarkable efficacy in FMF management, its therapeutic potential for MKD remains formally unstudied. Nevertheless, some clinicians empirically administer colchicine for mild MKD presentations, supported by anecdotal evidence. Ter Haar *et al.*[7] reported that colchicine was administered to 21 patients, with 13 showing no response to the treatment. Only one patient, who was heterozygous for p.V377I and p.S135L, experienced a complete response. This patient, of Caucasian descent from Italy, had not undergone screening for FMF. In addition, the patient did not receive NSAIDs, corticosteroids, or biologic agents. A documented instance involved an 8-month-old patient exhibiting non-classical MKD symptoms who received this treatment.[49] This infant experienced recurrent fever episodes, diarrhea, and lethargy. After being treated with colchicine for 8 months, no further fever episodes were observed. It is important to note that mevalonic acid excretion may not be detectable in urine in mild MKD cases. However, according to the Eurofever Registry, colchicine is generally ineffective in patients with HIDS/MKD. Among the 17 patients treated with colchicine, 65% showed no response.[48] To summarize, although colchicine might provide minimal advantages to limited patients, the evidence in its favor is not robust. Other inflammasomes, such as those involving nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3), may play a role in MKD, suggesting potential therapeutic benefits from specific NLRP3 inhibitors. A preclinical investigation examined the connection between the NLRP3 inflammasome and MKD utilizing peripheral blood mononuclear cells (PBMCs) obtained from a patient with a mild form of MKD.[50] Upon stimulation with the NLRP3-specific stimulant nigericin, these cells produced significantly higher levels of IL-1β compared to PBMCs from either parent. However, this heightened response was eliminated when the NLRP3 inflammasome was blocked using its inhibitor, MCC950. This finding indicates that targeting the NLRP3 inflammasome may be a promising strategy for treating MKD. Four additional NLRP3 inhibitors—CY-09, OLT1177, Tranilast, and Ordinonin—have recently been identified as pharmacological inhibitors of the NLRP3 inflammasome. These compounds have not yet been tested in MKD patients or relevant models. Two inhibitors (OLT1177 and Tranilast) have demonstrated relative safety in humans treated for other conditions.[51] However, further research is necessary to explore their safety and therapeutic potential specifically for MKD.

Statins, with simvastatin being the most studied, have been evaluated as potential therapeutic agents for attenuating MKD exacerbations. A pilot clinical study employing a randomized, double-blind, placebo-controlled crossover design was conducted with six participants to assess whether oral administration could effectively decrease pathological mevalonate buildup.[52] The study observed a modest but significant improvement in the treatment group, with five out of six patients reporting benefits while using simvastatin. Nevertheless, previous studies have demonstrated that culturing fibroblasts from patients with MKD-HIDS in the presence of simvastatin can enhance *MVK* gene transcription and MVK enzyme activity. However, this treatment also disrupts the flux through the isoprenoid biosynthesis pathway, rendering the potential therapeutic benefits uncertain.[53] The most comprehensive retrospective analysis demonstrated limited efficacy of statin therapy, with 11 of 15 treated patients showing no clinical improvement. Notably, symptom progression occurred in three cases, while only four individuals exhibited partial therapeutic response.[7] Statins have been employed in treating MKD patients, yet they have proven ineffective for the majority of individuals and, in some cases, have exacerbated symptoms. In light of this evidence and the potential for aggravating isoprenoid deficiency, current SHARE recommendations explicitly advise against statin administration for MKD management.[14]

Alendronate, a commonly prescribed medication for osteoporosis and disorders involving elevated bone turnover, inhibits mevalonate metabolism and disrupts protein prenylation. A clinical case study documented the administration of bisphosphonates, particularly alendronate, in an adolescent male (aged 14) diagnosed with MKD.[54] Following the initiation of therapy, the patient exhibited complete resolution of both symptomatic and biochemical manifestations of MKD. However, this finding remains puzzling, as alendronate would theoretically exacerbate the underlying metabolic impairment in MKD. In addition, a recent *in vitro* investigation failed to demonstrate any anti-inflammatory effects of alendronate in murine models or monocytes isolated from two MKD patients.[4] Consequently, current data do not justify the therapeutic use of alendronate in MKD management.

The squalene synthase inhibitor, Lapaquistat, initially developed as a cholesterol-lowering agent, modulates the mevalonate cholesterol pathway, thereby increasing the availability of anti-inflammatory isoprenoid intermediates. Research conducted by Rimondi *et al.*[55] demonstrated that Lapaquistat exhibits anti-inflammatory effects when associated with a low blockade of the metabolic pathway. However, these effects were not sustained with a more stringent blockade. Based on these findings, Lapaquistat may be considered a potential therapeutic option for mild forms of MKD, where residual enzymatic activity is diminished but not nearly absent as in severe forms.

Tofacitinib, a Janus kinase (JAK) inhibitor, is an orally administered non-biologic disease-modifying anti-rheumatic drug primarily used for treating rheumatoid arthritis. Its efficacy in inhibiting JAK has been documented in a few cases of FMF.[56] For instance, Gök *et al.*[57] reported a female patient with both rheumatoid arthritis and colchicine-resistant FMF, whose FMF attacks and disease activity were fully controlled following treatment with tofacitinib. However, there is insufficient data on using JAK inhibitors for MKD treatment to provide definitive guidance.

IL-18, a pro-inflammatory cytokine belonging to the IL-1 superfamily, has recently emerged as a potential biomarker for AIDs.[58] A retrospective analysis in France revealed that the highest levels of IL-18 were observed in diseases associated with the pyrin inflammasome, such as MKD.[59] Receiver operating characteristic curve analysis demonstrated that IL-18 effectively differentiates pyrin inflammasome-related diseases from other monogenic inflammatory conditions. These findings highlight the potential use of total serum IL-18 as a diagnostic tool, particularly for pyrin inflammasome-related AIDs, and may aid in developing personalized therapeutic strategies in the future.

In patients with severe, persistent inflammation, MKD can progress to AA amyloidosis and eventually cause kidney failure. The Eurofever cohort identified five patients with AA amyloidosis out of 114 individuals studied. Four of these patients required kidney transplantation due to end-stage renal failure, while one patient succumbed to complications related to dialysis.[7] Biological therapies can be continued during the pre-transplantation period, even when patients are on hemodialysis.

Supportive measures are integral to the comprehensive management of MKD. The guidelines emphasize addressing potential triggers, educating patients, monitoring disease progression, and implementing lifestyle modifications. The 2013 SHARE guideline, in particular, highlights the significance of patient education and identifying potential triggers.

3. Conclusion

MKD is a congenital metabolic disorder that results in recurrent inflammatory episodes. Further research is needed to elucidate the spectrum of pathogenic mutations and develop more targeted therapeutic approaches for improved management of MKD. The prognosis for affected individuals hinges on prompt diagnosis and timely intervention. There is substantial evidence supporting the use of IL-1 pathway inhibitors, such as canakinumab, as primary treatment options for MKD. However, the high cost of canakinumab limits its accessibility for many patients. In cases where canakinumab is unavailable, anakinra is a viable and more affordable alternative. In addition, if IL-1 inhibitor therapy proves ineffective, TNF-α inhibitors (etanercept) or IL-6 blockers (tocilizumab) can be considered potential second-line treatments, with proven success in managing the condition. For patients experiencing acute inflammatory episodes, NSAIDs or corticosteroids are typically the preferred treatments to alleviate symptoms of mild disease flares. The use of statins or colchicine for treating MKD is not advised based on current evidence due to the risk of severe complications. In patients with severe refractory MKD, HSCT may be considered as a last resort, although it is associated with a significant increase in treatment-related morbidity and mortality.

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Conflict of interest

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