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Mevalonate kinase deficiency: therapeutic targets, treatments, and outcomes

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Article highlights.

- Mevalonate Kinase Deficiency (MKD) is a neglected disease with onset in infancy.
- MKD clinical picture is characterized by recurrent fever attacks, abdominal pain arthralgia, lymphadenopathy and, in the most severe case, neurological involvement.
- The main MKD pathogenic hypothesis is represented by a shortage of isoprenoid compounds that led to a defective geranylgeranylation of RhoA proteins and increased caspase-1-dependent inflammation.
- Mitochondrial dysfunction and altered production of 25-hydroxycholesterol represent innovative pathogenic assumptions to understand the MKD progression.
- The emerging evidences on MKD pathogenesis could widen the therapeutic approaches focused particularly on Mitochondrial-Target Antioxidants or squalene synthetase inhibitors.

ABSTRACT

Introduction: Mevalonate Kinase Deficiency (MKD) is a rare inborn disease caused by the mutation of mevalonate kinase gene.

The clinical phenotype encompasses recurrent fever episodes in combination with gastrointestinal, immunological, rheumatological and neurological complaints. No specific treatment is available, apart from the newly approved biologics (canakinumab), but MKD can be still considered an orphan-drug disease, since the identification of a reliable therapeutic target needs an improved knowledge on the pathogenesis of the disease, which is so far controversial.

Areas covered: On one hand, shortage of isoprenoid compounds downstream of mevalonate led to a defective geranylgeranylation of RhoA/Rac proteins and increased caspase-1-dependent inflammation. On the other hand, recent studies pointed the attention to the pathogenic role of the mitochondrial dysfunction and to defective production of 25-hydroxycholesterol. These mechanisms are not exclusive of each other, as they can contribute to different pathogenic features of MKD.

Expert opinion: Innovative therapeutic approaches to MKD may count upon various medicaments, such as isoprenoid compounds that can enter the metabolic pathway, specific enzyme inhibitors and mitochondria-targeted drugs. Some of these compounds have already passed the clinical phase for other uses and may be repositioned to the treatment of MKD, fostering the development of clinical trials.

Keywords: rare disease , cholesterol , immunology , inflammation

1. INTRODUCTION

Mevalonate kinase gene (*MVK*, 12q24.11, NM_000431) encodes for the mevalonate kinase (E.C. 2.7.1.36), a peroxisomal enzyme of the cholesterol pathway. Mutations in this gene have been found causative of a rare orphan disease, called Mevalonate Kinase Deficiency (MKD, OMIM #260920) [1, 2].

MKD belongs to autoinflammatory syndromes, a group of inborn errors of immunity presenting with recurrent, seemingly unprovoked, multi-organ inflammatory attacks.

MKD includes different forms of disease severity ranging from the mildest Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS, MIM # 260920) to the more severe form called mevalonic aciduria (MA, OMIM #610377), depending on the extent of the enzyme defect [3-5].

To date, *MVK* mutations associated with MKD are 204 and are present in almost all the exons without a "hot spot" area. The replacement c.1129 G> A (V377I) (1129G> A) is present in the majority of HIDS patients, especially in Northern Europe (> 80%) which was shown founder effect made which would spread to the rest of Europe and USA. The V377I was found in homozygous in a few subjects, is usually in heterozygous combined with a second mutation associated with HIDS and / or MA phenotype [2,5].

The clinical picture of MKD, as a whole, is characterized by recurrent inflammatory attacks with fever (4-5 days duration), arthralgia, rash, abdominal pain and diarrhea with early onset in infancy, subcutaneous edema and measles-like rash. Fever rises abruptly and often above 40°C, after which the temperature gradually returns to normal and, typically, recurrent febrile episodes diminish over the years. It can mimic other chronic disorders and thus many patients may remain undiagnosed for a long time and can be referred to a variety of subspecialty clinics, including neurology, gastroenterology, cardiology and genetics. Other clinical features have been associated with MKD in anecdotal reports or in small series, including retinitis pigmentosa, renal angiomyolipoma [6, 7] (**Table 1**).

The complications of the disease, occasionally present in adults, include amyloidosis [8-10], adhesions in the abdomen and, very rarely, joint contractures [11].

Patients with MA display a worse phenotype with recurrent fever attacks, developmental delay, dysmorphic features, ataxia, cerebellar atrophy. The prognosis for MA is poor: more than 50% of patients die because of an inflammatory crisis in infancy, and very few survive to adolescence [12]. During flares, acute phase reactants (ESR, CRP, and white blood cell count) and inflammatory markers (interleukin (IL)-1 β , IL-6, TNF- α) are increased in peripheral blood while high levels of mevalonic acid can be measured in urines [13]. In the periods between episodes, these exams tend to be normal, except in the most severe cases and in subjects with MA. In addition, anemia mild to moderate is usually present irrespective of the phase of disease and an increase in

transaminases and creatine phosphokinase is recorded in the most severe forms of the disease. MKD is typically associated with increased levels of IgD (and usually IgA), that is where the name of hyperglobulinemia D syndrome comes from. However, several reports highlighted that high IgD levels are not mandatory to MKD diagnosis [14, 15].

The distinction between MA and HIDS is based on the residual enzyme activity of MK, with levels below 1% of controls in subjects with MA, while a variable enzymatic activity, estimated between 1-10%, is present in patients with HIDS. Measure of MK activity in fibroblast or in peripheral blood cells from patients is of particular importance when genetic analysis of *MVK* detects mutations without a known correlation with phenotype. This implies that the excretion of mevalonic acid in urine may differ significantly between the two phenotypes of the syndrome, ranging from 1-56 mol/mol creatinine (in MA) at 0.004-0.028 mol/mol creatinine (in HIDS) [16]. Indeed, the measure of mevalonic acid in the urines collected during 24 hours of a febrile attack can serve as reliable and noninvasive diagnostic tool. Moreover, the detection of increased urinary mevalonate between febrile crises should be regarded as a score of greater severity of the disease.

The diagnosis, indeed, must be confirmed by molecular analysis of the *MVK* gene to establish the mutations.

2. MKD PATHOGENESIS

The MKD pathogenesis is not yet completely known. The finding of pathogenic *MVK* mutations in a subject with the typical symptoms of MKD clearly confirm ~~support~~ the diagnosis of MKD. However, most of patients are in well health conditions outside the inflammatory crisis and it is not clear what mechanisms trigger the inflammation. The characteristic of seemingly unprovoked bouts of inflammation dominated by high production of the IL-1 β allows classifying MKD among autoinflammatory disease. However, unlike other autoinflammatory diseases, MKD is not due to the mutation of genes directly involved in the control of innate inflammation. Indeed, the pathogenic mutations causative of most genetic autoinflammatory disorders involve genes codifying for components of the multiprotein platform called inflammasome. The most important and studied protein for autoinflammatory diseases is NOD-like receptor (NLR) pyrin domain-containing 3 (P3), NLRP3 also indicated as NALP3 [17]. The NLRP3 is directly involved in activation of pro-caspase-1 to caspase-1, which in turn is required for processing the inflammatory cytokine, pro-IL-1 β to the active form (IL-1 β), a pyrogenic cytokine that appears to play a fundamental role in autoinflammatory disease with periodic fever, such as Cryopyrinopathies, Familial Mediterranean Fever, TNF Receptor Associated Periodic Fever and MKD itself [18, 19].

The production of IL-1 β plays a crucial role in the pathogenesis as indicated by the dysregulated secretion of this inflammatory cytokine in peripheral blood cells of patients with MKD [20-22]. There is agreement that the increased production of this cytokine in MKD can be sustained both by

activation of the transcription factor NF- κ B, which modulates the expression of inflammatory genes, and by the activation of caspase-1, which is responsible for the release of the active cytokine [23]. However, according to other evidences, a defect or delay in the phagocytosis of apoptotic leukocytes can also play a role, resulting in defective suppression of inflammation [24, 25] (Figure 1).

2.1 Mevalonate pathway in different districts of the body

To unravel the pathogenesis of MKD and to identify the best targets for therapeutic intervention, it is fundamental to take into due consideration the different regulation of the cholesterol metabolism in the different district: systemic circle, liver, immune cells and central nervous system.

Cholesterol is supplied to the organism both by diet (exogenous lipoprotein pathway), even if it accounts for a small percentage, and by endogenous biosynthesis, mostly occurring in the liver. Mainly the liver and macrophages are involved in regulating the balance of cholesterol in the organism and in tissues. To be roughly schematic, the liver produces large amounts of cholesterol to form bile acids and to load lipoproteins. The balance between uptake and synthesis of lipoproteins in liver is crucial to the maintenance of the body lipid homeostasis. Indeed, the excess cholesterol in tissues is mainly removed through High Density Lipoproteins, which are loaded with cholesterol. Alternatively, cholesterol is removed from tissues by macrophages engulfed with dead cell membranes [26].

While liver and macrophages play a major role in the metabolism of cholesterol for most tissues, brain cells have to count only on *de novo* synthesis, as the blood-brain barrier effectively prevents the passage of lipoproteins. Nonetheless, brain tissues, required in high quantities of cholesterol, as it is essential for the proper functioning of the central nervous system; neurons, in fact, need cholesterol to form the membranes of axons, dendrites, and synapses [27, 28]. Moreover, there are evidences that the homeostasis of this compound is not uniform in the different brain areas: the content [29] and the expression levels of cholesterol-specific enzymes show strong variations in the different regions of the brain [30, 31].

However, regulation of the mevalonate-cholesterol pathway in cell is not solely devoted to the production of cholesterol for cell membranes. Several intermediate products of this pathway have crucial roles in cell function and their regulation can vary hugely in different cells and tissues. This complexity makes it difficult to predict what effect a defective enzyme can have on the clinical phenotype. For this reason, appropriate animal and cellular models are necessary to understand the physiopathology of MKD and to study the pharmacologic intervention with compounds acting on this biochemical pathway.

2.2 Animal or cellular MKD models

The possibility of using an instrument that reproduces as well as possible the inflammatory phenotype characteristic of MKD is crucial to identify molecular targets useful to develop future treatments for the disease.

Genetic Model

To date, an early issue in assessing the MKD pathogenesis is represented by the lack of a reliable genetic model. Knockout of MK in animals is not compatible with life, highlighting the importance of cholesterol and intermediate compounds for several vital cell functions. Unfortunately, in mice, the homozygous knock-in of mutations associated with human MKD was also unsuccessful. Thus, the only genetic mouse model of MKD has been obtained by the heterozygous deletion of one MVK allele; however, this model only partially reproduces the MKD-like inflammatory phenotype and does not show the features of neurological dysfunction [32].

Similarly, there have been difficulties in developing an *in vitro* genetic model. Recently a report showed that the knockdown of mevalonate kinase, using the silencing RNA (siRNA) technology, in a murine microglial cellular model (BV-2 cells) is not a suitable MKD model, because the NLRP3 expression and the apoptosis does not correspond to the expression obtained from MKD patients [33].

Biochemical Model

To overcome these limitations, in recent years, our and other groups have set an MKD model, both *in vitro* and *in vivo*, using pharmacological inhibitors to induce a biochemical imbalance mimicking the genetic deficiency of MK. Indeed, compounds such as statins or amino-bisphosphonates block the synthetic pathway of cholesterol and provoke an inflammatory dysregulation similar to that characteristic of MKD. On this substrate, the inflammatory attacks were triggered by the addition of a bacterial compound (lipopolysaccharide or muramyl-dipeptide) stimulating natural immunity activation. In this way, this model tried to reproduce the condition of patients with MKD, where the febrile attacks are often associated with minor external stimuli such as vaccination, infection or physical exertion [34].

The results obtained from both monocytes and neuronal cell lines treated with such inhibitors show that the shortage of intermediate compounds downstream of mevalonate can induce an inflammatory phenotype. Using the same experimental approach, mice with impaired biosynthesis of mevalonate-derived isoprenoid, displayed an increased inflammatory reactivity to the inflammatory stimulus muramyl-dipeptide [35]. This model appears to be particularly consistent with MKD, since it reproduces the molecular markers typical of the disease in humans (SAA Serum

amyloid A, inflammasome activation, biosynthesis of inflammatory cytokines), regardless of the mouse strain used [36].

The availability of these models, even with their weaknesses and limitations arising from a biochemical system, offers a valuable opportunity to address the study of the pathogenesis of MKD.

This is particularly important to investigate the neurological features in MA [37, 38]. In fact, whilst peripheral blood cells obtained from patients can allow studies relevant to systemic inflammation, no neurological tissues can obviously be available for *ex vivo* researches.

Moreover, the establishment of accurate *in vitro* and *in vivo* models for MA can represent a first step towards a better understanding the neuroinflammatory events occurring not only in MA, but also in other neurodegenerative disorders in which the cholesterol pathway is involved, including Alzheimer's disease, Huntington's disease, Parkinson's disease, Niemann-Pick type C disease and Smith-Lemli Opitz syndrome [39].

2.3 Shortage of isoprenoids underlies MKD inflammation

The defects in MK, logically could suggest that an accumulation of upstream intermediates, like mevalonate, occurs in MKD and related diseases and that this accumulation could be responsible for the pathological features of the diseases. On the contrary, the experiences with statins and the evidences that these drugs can block the pathway without resulting in inflammatory processes, suggest that the pathogenesis arises likely from a shortage of downstream products, rather than the accumulation of upstream intermediates [40].

Indeed, it was shown that the decrease of the intermediate isoprenoid levels, is responsible for the increased secretion of inflammatory cytokine IL-1 β in MKD [21]. However, literature data demonstrated that even though MK enzyme activity is reduced and the residual MK levels are below detection levels in cultured skin fibroblasts from MA patients, the *de novo* biosynthesis of cholesterol and non-sterol isoprenoids can be sufficient [40, 41]. This paradox is probably due to the compensatory induction of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase leading to increased concentration of mevalonate. Indeed, the increased substrate of MK may allow the production of sufficient amount of the product [41, 42]. However, albeit sufficient in most physiological condition, this mechanism may be overcome in stress conditions, when the organism may needs higher synthesis of mevalonate-derived isoprenoids and cholesterol. Several studies highlight that the inflammatory phenotype associated with MKD is attributable to the inability of this system to compensate an instant further decrease in the MK residual activity or an increased usage of some isoprenoid compound. For example, it was suggested that the regulation of the immune response may require and extra-use of isoprenoid intermediates [18, 43].

2.4 Crucial role of defective geranylgeranylation of Rho and Rac in inflammation

The complex mechanism activated by mevalonate block and supported by NLRP3 implies a shortage of isoprenoids and in particular non-sterols isoprenoids, such as geranylgeranyl-PP (GGPP). Isoprenylation with GGPP modulates the function of some membrane-bound proteins involved in the control of inflammatory response, proliferation, and apoptosis, such as the small GTPases of the Ras homolog gene family (RhoA) [44, 45]. Thus, depletion of GGPP can lead to impaired prenylation of such GTPases, resulting in an unbalanced control of inflammation. Furthermore, isoprenoids and sterols derived from mevalonate can also play a direct role in DNA transcription, enzymatic regulation and response to oxidative stress [46-48].

Notably, environmental factors can act on this scenario in different ways: nutritional factors can influence the availability of substrates and the regulation of various enzymes; immune stimuli such as infections and vaccinations can trigger an inflammatory response that involves several prenylated proteins [49]; oxidative stress of various natures can exceed the antioxidant capacity of a defective mevalonate pathway [50, 51].

2.5 Mitochondrial dysfunction in the pathogenesis of inflammation

Recent evidences of the literature point out that to understand the pathogenesis of MKD is necessary to focus on the role of the mevalonate pathway on the modulation of autophagy.

Autophagy can be triggered by mitochondrial dysfunctions, when the energy produced is reduced and the cell activates a saving mode to preserve its integrity. This program can lead to reduced performances of the cells, metabolism, and reuse of macromolecules and digestion of damaged mitochondria.

Recent literature evidence emphasizes that mitochondrial damage and induction of apoptosis can be due to various intracellular stress conditions, including DNA damage, cytotoxic insult, oxidative stress, infections. These various stimuli act by inhibiting or activating a particular anti- and pro-apoptotic Bcl-2 family member [52]. The Bcl-2-associated X protein (Bax) is known to be a very important pro-apoptotic protein promoting the formation of channels into the mitochondria. The Bax-induced channels formed in the mitochondria are important for the dissipation of the mitochondrial transmembrane potential ($\Delta\psi_m$), the inhibition of the respiratory chain and the interruption of the production of reactive oxygen species (ROS) [53]. Similar mitochondrial dysfunctions also represent a central causal factor in the pathogenesis of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease and many others [54].

Recent studies on the action of genistein, an isoflavonoid compound acting on the mevalonate pathway, established a link between this pathway and oxidative stress in neurons. In particular,

genistein is able to recover the ROS production, to favor an anti-apoptotic Bcl-2/Bax ratio and contrast the NF- κ B and MAPK inflammatory pathways. The potential neuroprotective and antiinflammatory action of this natural compound may indirectly support the role of mitochondrial stress in MA [55].

2.6 Defective 25-hydroxycholesterol may underlie hyperimmunoglobulinemia D and inflammation

About 10 years ago, a pioneering work of Goldstein [56] described the hydrophobic molecule 25-hydroxycholesterol (25-HC) within the metabolic pathway of cholesterol. Since then, many studies have followed with the aim of establishing a biological role for this molecule [57-59]. In particular, 25-HC is a lipid with immunoregulatory potential, produced by macrophages to downregulate the adaptive immune response [60]. Of note, the lack of 25-HC can be responsible for an increased production of Immunoglobulin A, which is typical of the most severe forms of MKD (such as MA) (**Table 1**). Furthermore, other studies showed that 25-HC could suppress the activation of NLRP3 and consequently the production of inflammatory cytokines such as IL-1 β [60]. Based on this data, it could be logical to hypothesize that a shortage of 25-HC may play a role in the pathogenesis of inflammation and hyperimmunoglobulinemia in MKD [61]. However, recent data showed that 25-HC could have as well inflammatory effects, as in the case of cerebral inflammation associated with X-linked adrenoleukodystrophy [62]. Thus, the role of 25-HC in MKD remains controversial.

3. DRUGS ACTING ON THE MEVALONATE PATHWAY AND POTENTIAL ROLE IN MKD

Drugs acting on the mevalonate pathway may have variable effects on inflammation, with sometimes-unpredictable consequences in relation to dosage. In fact, the enzymes in the mevalonate pathway are highly regulated according to the availability of substrates and products. Such drugs have the ability to interfere with the metabolic pathway and are described in the following paragraphs (3.1 to 3.5), while in Chapter 4 actual and future therapeutic options for MKD will be discussed.

3.1 Statins

Statins, also known as HMG-CoA-reductase inhibitors, are a class of lipid-lowering drugs, acting on the rate-limiting step in the cholesterol pathway. The statins, indeed, act upstream of the mevalonate pathway by reducing the availability of mevalonate and the production of endogenous cholesterol [63-66].

Statins have been considered to treat MKD, with the aim of inducing a compensatory effect on the residual mevalonate kinase activity. In a small group of HIDS patients, continuous treatment with simvastatin seemed associated with a lowered number of inflammatory crisis [67]. Nevertheless, the treatment with lovastatin in patients with MA led to a severe worsening of the clinical symptoms [68]. Taken together, these data suggest that statins can allow some improvement in subjects with milder diseases, like HIDS phenotype, while they will worsen the defect in subjects with more severe deficiency, such as MA. Thus, the use of statins in MKD remains controversial. Of note, several studies showed that statins could exert either anti- or pro-inflammatory effects in slightly different conditions [69].

3.2 Amino-bisphosphonates

The amino-bisphosphonates are nitrogenous bisphosphonates with a strong effect in preventing bone resorption. Thanks to their chemical structure with two phosphate groups, these drugs are highly concentrated in bones where they act by inhibiting the function of osteoclasts. The high concentration of the drug reached in bones makes the amino-bisphosphonates particularly useful to prevent and treat osteoporosis, but also to contrast bone inflammation or bone metastasis. In particular, the amino-bisphosphonates such as alendronate, pamidronate, zoledronate, act on farnesyl diphosphate synthase (FPPS), just downstream of mevalonate kinase and or on other enzymes in the pathway to cholesterol, reducing in a variable manner the availability of isoprenoid intermediates. Inhibition of mevalonate pathway enzymes leads to various biological effects, including inhibition of osteoclast or tumor metastatic cells [70-72]. Alike occurs in MKD, the action of the amino-bisphosphonates leads to an accumulation of mevalonate and at the same time the reduction of downstream compounds of FPPS.

Amino-bisphosphonates can be either anti- or pro-inflammatory, depending on the experimental context, similarly to what occurs for statins [73, 74]. The different effects may be related to their different ability to be metabolized by the cells [75].

3.3 Plant-derived isoprenoids

Isoprene (also called isoprene units) is the common name for 2-methyl-1,3-butadiene, a compound that contains five carbon atoms, characterized by a branched "head" and a "tail". These ends of each isoprene unit can be joined "head-to-head", "head-to-tail" or "tail-to-tail" to form different terpenes. Terpenes are a class of lipids: they can be hydrocarbons or alcohols containing oxygen, aldehydes or ketones.

To date, there are more than 20,000 known terpenes. Many plants, particularly conifers, produce a huge variety of them and some insects. Terpenes are the main components of resins and essential

oils of plants, mixtures of substances that give each flower or plant a distinctive odor or flavor. They, also, are the biosynthetic precursors of steroids and cholesterol. Many flavorings used in foods and fragrances were derived from natural terpenes or terpenoids, as well as many perfumes and flavors found in plants and known as essential oils.

Moreover, isoprenoids can be found as intermediate compounds of the mevalonate pathway, so that while some of the plant isoprenoids can enter the metabolic pathway in humans (i.e. geraniol, farnesol, geranylgeraniol, etc.), or can act as enzyme inhibitors (i.e. menthol, limonene, etc).

The geraniol (GOH) for example, is a terpene alcohol extracted from certain types of plant (geranium, orange, vervain, myrtle, lemon balm) and commonly used in perfumery and food industry. The geraniol, relatively abundant in nature, is readily soluble in alcohol and in ether, with excellent good chemical stability and fat solubility, appearance that makes it ideal for a good absorption through different routes of administration. Some authors have already described the use of geraniol for topical use [76] or as an adjunct to anti-cancer drugs [77]. Likewise, menthol (MOH) is also a monoterpene, the active ingredient in the essential oil content of mint. Strongly aromatic and bitter, menthol is particularly known for its antiseptic, antispasmodic and local anesthetic action. The inhalation of the vapors that developed by placing a few drops of alcoholic solution of menthol in boiling water is famous for its ability to relieve the bronchial disorders and nasal congestion; menthol in fact can act as expectorant and disinfectant. Taken orally, the menthol is also used as anti-fermentative, antiseptic (facilitates the excretion of bile and runoff), refreshing and spasmolytic (reduces intestinal motility), which is useful in the presence of colics of the upper gastrointestinal tract, biliary tract and colon irritations, such as irritable bowel syndrome [78, 79].

What is also very interesting from the medical aspect is the antiinflammatory properties highlighted in studies on geranylgeraniol (GGOH), a diterpene soluble in organic solvents such as alcohol and acetone.

Moreover, some of these compounds are already used as adjuvants in cancer therapies and as anti-metastatic agents [77, 80].

3.4 Inhibitors of prenylation

Prenylation inhibitors act individually on the enzymes farnesyltransferase (FT) and geranylgeranyltransferase (GGT), which catalyze the transfer of isoprenoid "activated" groups (FPP or GGPP) on polypeptide chains.

The characterization and the role of farnesylation and geranylgeranylation protein have been made possible by using specific inhibitors: inhibitors of farnesyltransferase (FTI) and geranylgeranyltransferase (GGTI).

The FTI act on different mechanisms of inhibition: some of them, such as manumycin A (ManA), a natural compound derived from *Streptomyces*, belong to the class of isoprenoid derivatives, in this case of the FPP analogs, while others, to the class of peptidomimetic.

The inhibitors of GGT act similarly to FTI as competitors. The discovery that some geranylgeranylated proteins are involved in pathological processes such as cancer, inflammation, and viral infections, has led to a growing interest in the study of GGT as a possible therapeutic targets. They have been described several peptidomimetic GGTI, such as GGTI-298 and GGTI-2154, both amino benzoic acid derivatives [81]. Recently it has been observed that some inhibitors belonging to the class of FTI can also inhibit GGT-type 2, also known as Rab-GGT since it is specific for Rab proteins [82].

The RAS family of proteins must be prenylated to properly perform their function and therefore are the main targets of such inhibitors. In particular, the FTI can inhibit RAS, while the GGTI-type 1 inhibit Rho and Rac [82, 83].

3.5 Zaragozic acid

Noteworthy is the effect of the zaragozic acid (ZAA), an inhibitor of squalene synthase. ZAA can reduce the synthesis of cholesterol, redirecting the flux throughout the cholesterol pathway to isoprenoids biosynthesis and functioning as a potential new cholesterol lowering agent [83-85].

ZAA is an inhibition of the competitive type, because it mimics the enzyme substrate presqualene-PP, which typically forms during the reaction leading to the synthesis of squalene [86].

Recently ZAA has been proven to inhibit the hyper-inflammatory response in cellular models of MKD, by diverting mevalonate intermediates toward geranylgeranylation rather than to the synthesis of squalene.

4. PHARMACOLOGIC OPTIONS IN MKD

Although in recent years treatments for these rare diseases have been developed, it is worthy highlighting that, to date, there is no pathway-oriented treatment available for MKD. Indeed, current options are primarily intended to prevent or alleviate inflammatory symptoms, while future pharmacological treatments have the goal to be more close to the pathogenesis of the disease and more effective for patients with severe MKD (**Figure 2**).

4.1 Current MKD treatments and biological drugs

Several drugs have been used in MKD, but few of them still maintain a role in the treatment of the disease. In particular, the disease usually shows a good response to corticosteroids, but the adverse effects of these drugs can soon overcome the benefits, in particular when there is a need

for prolonged treatment. The major side effects associated with the traditional MKD treatments are a headache, stomach ulcers and kidney damage [4].

While antiinflammatory drugs and steroids on demand provide acceptable control of symptoms in patients with milder forms of the disease, lifelong treatment with biological drugs (such as Anakinra or Canakinumab) [87, 88] is usually required for patients with high recurrence of severe inflammatory attacks. The response to anti-IL-1 biologics confirms once more the autoinflammatory nature of MKD.

Anakinra is a recombinant, non-glycosylated, IL-1Ra, an endogenous antagonist that binds to IL-1 receptors and inhibits the inflammatory effects of IL-1: it is administered subcutaneously and present a high bioavailability (95%). Other anti-IL-1 biologics include Riloncept, a fully human fusion protein that incorporates the extracellular domains of the IL-1 receptor linked to the Fc portion of IgG1 and Canakinumab, a monoclonal antibody specific for IL-1 β . Canakinumab, approved both in Europe and USA, has been studied for the treatment of rheumatologic diseases such as rheumatoid arthritis and systemic juvenile idiopathic arthritis, and for autoinflammatory diseases such as cryopyrin-associated periodic syndrome (CAPS). Very recently, Canakinumab has been approved by US Food and Drug Administration (September 2016) and by European Medicines Agency (December 2016) as treatment for MKD after the substantial results obtained in a Phase III Study (www.clinicaltrials.gov, NCT02059291).

These biologics have been shown effective in controlling MKD-related inflammation in clinical reports. However, the use of Anakinra is hindered by the need of daily painful injections, even if some patients well tolerate this treatment and then get good improvements [65, 66]. Canakinumab seem to be more effective, but it is not always able to completely control the disease, in particular in cases with severe disease. Moreover, biologics, especially Canakinumab, are very expensive and, at today, the dosing is still a matter of investigation. To date, the only valuable therapeutic option for patients with MA is hematopoietic stem cell transplantation, which however is burdened with a series of risks and complications [89, 90].

4.2 Future directions

The aim of the innovative pharmacological strategies is to obtain a more complete control of the disease than what can be achieved with cytokine inhibitors. An ideal causal therapy is expected to control all the different signs of the disease, including the neurologic and the lymphoproliferative signs, which are not completely targeted by current treatments. Furthermore, anti-cytokine biologics have just a theoretical risk of infections: on a particular ground it is recommended to pay attention to the risk of the infection in patients treated with anti-IL1, and this may make difficult to discriminate if the inflammatory events during the therapy are due to this is flare of infections.

The easier therapeutic approach would be to exploit the supplementation with plant isoprenoids that can enter the mevalonate pathway compensating for the shortage of endogenous isoprenoids. This approach is based on the experimental evidence of the role of the shortage of isoprenoids in MKD inflammation. Moreover, several plant isoprenoids have been reported to have anti-inflammatory properties and could represent an attractive therapeutic opportunity thanks to their commercial availability, low cost, oral bioavailability and low toxicity. Moreover, recent literature data have showed that these natural products can also regulate in central nervous system, in particular, controlling motor and cognitive function [91].

Nevertheless, a limit to the translational of plant isoprenoids to the therapeutics of MKD can be represented by the amount of substance needed to have the anti-inflammatory benefit *in vivo*, which could be above the tolerated doses.

Another approach is based on the use of inhibitor enzymes that can diverge the flux of isoprenoids toward anti-inflammatory molecules. This is the case for FTIs, like the such as Tipifarnib (R115777, Zarnestra™) and Lonafarnib (SCH66336, Sarasar™), which showed their potential use as antiparasitic, antifungal, antiviral and anticancer like, thanks to their effects exerted on oncoproteins such as RAS [92]. Preliminary *in vitro* studies on MKD monocytes treated with Tipifarnib and geraniol showed a significative reduction of IL-1 β production, supporting the idea that an effective therapy for MKD may need combinatory approaches.

Another attractive therapeutic possibility is represented by Lapaquistat (TAK-475, Takeda) [93, 94], an analogue inhibitor of zaragozic acid, a squalene synthetase inhibitor, which is a drug that underwent extensive clinical trials as cholesterol lowering agent 10 years ago with a good safety profile [95-98]. The possibile advantages for this compound are that it has already passed all the clinical stages and that could be evaluated in clinical trials and it can be administerly orally.

The potential use of Lapaquistat seem to be in contrast with data showing a role for defective 25-HC in MKD, as squalene synthase inhibition is expected to lower even more the levels of 25-HC [34]. However, the role of 25-HC remains controversial, as in adrenoleukodystrophy this molecule seem to be responsible for activation of NLRP3 and neuroinflammation [62]. Due to the complex regulation of the mevalonate pathway, only pre-clinical studies in animals and pilot studies in human will clarify this controversy indicating the correct direction for innovative treatments of MKD. Drugs belonging to the Mitochondrial-Target Anti-oxidants (MTAs) family, such as MitoQ, Mitotempo, represent as well a promising pharmacological approach and MitoVitE could potentially be effective in tackling the disease. MTAs, which are well known and well characterized for their anti-oxidant and mitochondrial protective activity in response to Bax, could indeed be potential candidate molecules to improve MA treatment. Moreover, MTAs are mitochondria-targeted drugs, several hundred folds more potent at in preventing mitochondrial oxidative damage than an

untargeted antioxidant [99] and, once accumulated into mitochondria, MTAs are able to inhibit step by step the activation of programmed cell death pathways [100].

5. EXPERT OPINION

MKD is still a rare orphan drug disease with onset in infancy. Only drugs able to reduce the inflammatory symptoms are used in clinical practice, often with incomplete control of symptoms. Thus, patients with severe MKD still tend to have a poor quality of life.

Patients with mevalonic aciduria, indeed, have high morbidity and reduced life expectancy in spite of current treatments. In some cases, while attenuating the flares, the treatments (especially with glucocorticoids) can lead to a chronic course of disease with weaker but constant symptoms.

Furthermore, recent data indicate that MKD often remains misdiagnosed for years and the burden of MKD may be even greater than expected. Thus, the development of an effective drug to cure classical MKD might provide novel options for a larger number of patients than those suffering from diagnosed MKD.

Moreover, the development of new models, both *in vitro* and *in vivo*, that can reproduce the neurological involvement in MA, is crucial to improve the knowledge on its pathogenesis, which is still unknown, and to develop new therapies able to improve the pathological conditions of patients. The dietary approaches have not yet considered. Even if MKD may be associated with low cholesterol, reducing the intake of cholesterol with diet may have a beneficial effect in MKD, by inducing an upregulation of the endogenous biosynthetic machinery.

In general, it is important to emphasize that MKD belongs to the family of the autoinflammatory syndromes (AIS), a group of rare disorders, often underestimated or misdiagnosed and characterized by difficult therapeutic issues.

From a scientific point of view, the AIS provide a clear model to understand the mechanisms involved in controlling inflammation and to study how combined mutations in functionally related genes may condition these pathologies as well as more common inflammatory disorders.

Furthermore, in-depth knowledge on autoinflammatory disease may allow identifying novel targets for antiinflammatory therapies, both for AIS and AIS-like disorders. In particular, studying the potential impact of manipulation of the mevalonate pathway on inflammation may open novel avenues for antiinflammatory therapies. The identification, also, of epigenetic signatures associated with the development of AIS in genetically predisposed individuals may provide new tools to trace how environment and medical treatments influence the course of the disease.

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Declaration of Interest

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TABLES LEGENDS

Table 1. Mevalonate kinase deficiency clinical phenotype based on the typical signs and symptoms observed in the patients.

FIGURES LEGENDS

Figure 1.

Pathogenesis of inflammatory processes in Mevalonate Kinase Deficiency (MKD). BisP: bisphosphonates; CH25H: cholesterol 25-hydroxylase; FTI: farnesyltransferase inhibitors; GGTI: geranylgeranyl transferase inhibitors; HMGCR: 3-hydroxy-3-methylglutaryl-CoA reductase; MK: mevalonate kinase; S Synth: squalene synthase; ZAA: zaragozig acid.

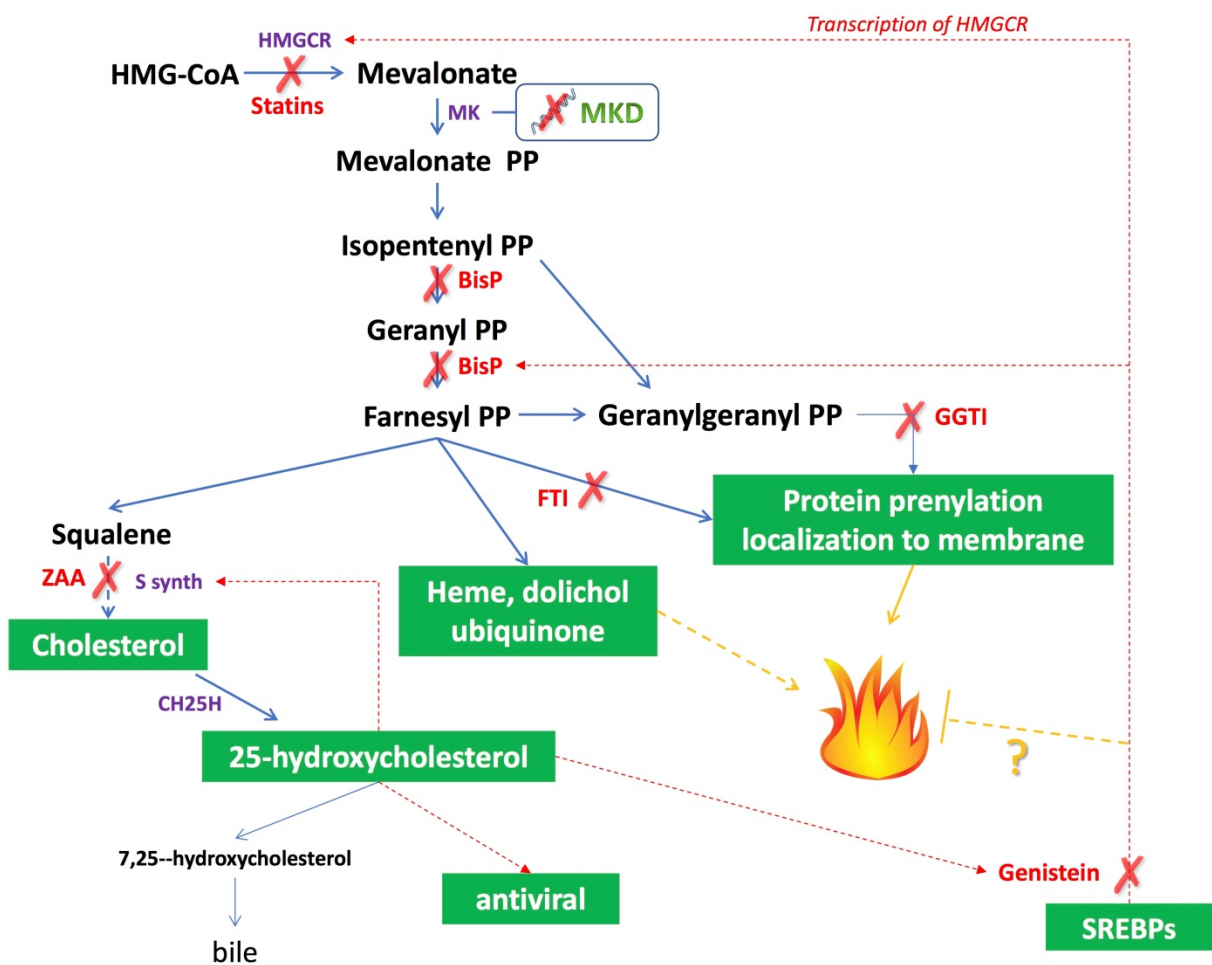
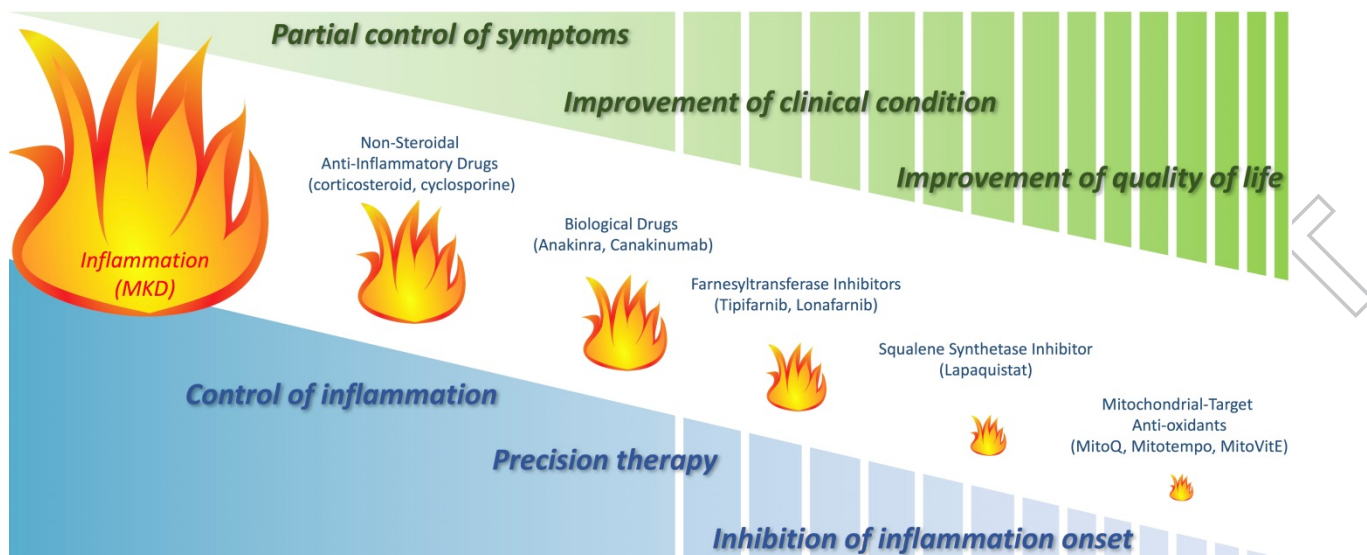


Figure 2.
Therapeutic options in Mevalonate Kinase Deficiency.

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	Typical	Others (may be associated with most severe disease)
Clinical symptoms	Recurrent episodes of fever Arthralgia/arthritis Abdominal pain Diarrhea Lymphadenopathy Enlarged spleen	Hepatopathy Retinitis pigmentosa Renal angiomyolipoma Cataract Nephritis Diabetes insipidus CNS involvement Amyloidosis
Laboratory features	Increased neutrophils, Raised CRP, Anemia, Increased urinary mevalonic acid, High IgD levels	Increased immunoglobulins of various classes (IgA, IgM) In some cases, hypogammaglobulinemia

Table 1. Mevalonate kinase deficiency clinical phenotypes based on the typical signs and symptoms observed in the patients.