

Updated overview of molecular pathways involved in the most common monogenic autoinflammatory diseases

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Received on November 27, 2017, accepted on December, 7, 2017.

Clin Exp Rheumatol 2018; 36 (Suppl. 110): S3-S9.

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Key words: autoinflammatory diseases, hereditary periodic fever syndromes, interleukin (IL)-1, innate immunity, inflammation.

ABSTRACT

An apparently unprovoked recurrent inflammation is the quintessential hallmark of autoinflammatory diseases (AIDs), a large and heterogeneous group of disorders in which there is poor regulation of the innate immune system with no clearly demonstrated autoimmune machinery involvement. Innate immunity pathways are diverse and our understanding of their molecular composition and function is continuously expanding. The impaired immune responses we observe in monogenic AIDs, mostly in the hereditary periodic fever syndromes, is officiated by target molecules of microbial origin (pathogen-associated molecular patterns) and also host molecules (danger-associated molecular patterns). Further crucial components of innate immune mechanisms that contribute differently in the deregulated inflammatory patterns of different AIDs include Toll-like receptors, Nod-like receptors, scaffolding proteins (such as the caspase recruitment domain of proteins), cytosolic DNA-sensing molecules, inflammatory multi-protein complexes (referred to as inflammasomes), complement system, and others. In recent years, the knowledge of protean molecular pathways responsible for the most common monogenic AIDs has expanded, in parallel with very recent extraordinary technological advances, allowing the identification and characterisation of some unknown aspects of the innate immunity. This review will list and describe the most common monogenic febrile syndromes belonging to AIDs and will focus on current insights dealing with their pathologic processes.

Introduction

The term "autoinflammatory disease" (AID) was coined by Kastner *et al.* in 1999 to distinguish the more common

autoimmune diseases from the rare hereditary recurrent syndromes, familial Mediterranean fever (FMF) and tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS). FMF and TRAPS are characterised by periodically recurring episodes of systemic inflammation without any evident involvement of autoimmune pathways and no demonstrated causative infectious agents (1). Following on from this, the identification and characterisation of the genetic causes of further AIDs has allowed the depiction of *autoinflammation* as a process associated with impaired innate immunity due to abnormalities in specific mechanisms of the inflammatory response (2).

Functional studies performed on AIDs have also revealed that mutations in the genes responsible for some of these syndromes are associated with alteration of intracellular sensors, directly or indirectly related to microbial products (pathogen-associated molecular patterns [PAMPs]), and endogenous molecules acting as danger signals (danger-associated molecular patterns [DAMPs]) (3). In addition, some of these AIDs have been associated with abnormal activity of interleukin (IL)-1, interferon (IFN), or nuclear factor (NF)-κB (4). In this regard, recent *in vitro* studies on the functional characterisation of gene products causing AIDs have demonstrated the link between alteration of intracellular sensors and/or intracellular stress events and the activation of several mechanisms. These include the production of reactive oxygen species (ROS), autophagy, mitochondrial damage, and post-transcriptional events, which could play a pivotal role in the deregulation of many innate immunity responses (Fig. 1) (5). Recent findings on the pathogenesis of the most common monogenic AIDs have also provided novel control mech-

Funding and competing interests on page S-7.

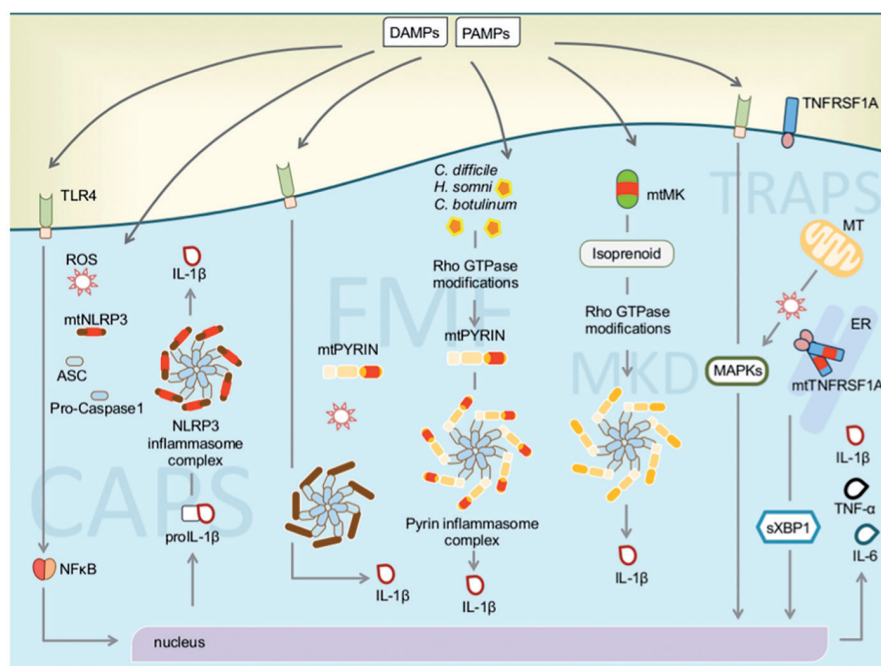


Fig. 1. Schematic representation of the pathophysiology of hereditary periodic fever syndromes belonging to the family of monogenic autoinflammatory diseases.

Mutations in genes related to autoinflammatory diseases undermine the innate immune response triggered by both endogenous and exogenous ligands. In particular, CAPS-causing mutations impair NLRP3-inflammasome activation, resulting in exaggerated IL-1 β production. Depending on the exogenous stimuli (including lipopolysaccharide and/or Rho-modifying bacterial toxins), pyrin mutations causing FMF lead to enhanced IL-1 β secretion by NLRP3 or pyrin-inflammasome complex activation. Abnormalities in the isoprenoid pathways due to MKD-causing mutations trigger a shortage of intermediate compounds associated with alteration of rho GTPase, recently linked to the pyrin-inflammasome activation. In TRAPS, intracellular accumulation of mutated TNFRSF1A leads to increased inflammatory responses involving ER stress (represented by enhanced splicing of the X-box binding protein 1, sXBP1) and MAPK activation (due to increased levels of mitochondrial ROS).

CAPS: cryopyrin-associated periodic syndrome; DAMPs: danger-associated molecular patterns; ER: endoplasmic reticulum; FMF: familial Mediterranean fever; MAPK: mitogen-activated protein kinase; MKD: mevalonate kinase deficiency; MT: mitochondria; PAMPs: pathogen-associated molecular patterns; ROS: reactive oxygen species; TNF: tumour necrosis factor; TRAPS: TNF receptor-associated periodic syndrome.

animals of the innate immune response, prompting us to outline some of these pathogenetic aspects with a special focus on the latest findings related to the hereditary periodic fever syndromes (Table I).

Cryopyrin-associated periodic syndrome

Cryopyrin-associated periodic syndrome (CAPS) encompasses a group of disorders including, in order of increasing severity, familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and chronic infantile neurological cutaneous articular (CINCA) syndrome. These disorders are caused by gain-of-function mutations in the gene, NOD-like receptor 3 (*NLRP3*), which is also known as cold-induced autoinflammatory syndrome 1 (*CIAS1*).

NLRP3 is located on chromosome 1q44 and encodes the NLRP3 protein, also known as cryopyrin (6). Molecular genetic analysis in patients with CAPS has identified more than 180 *NLRP3* variants (<http://fmf.igh.cnrs.fr/infevers/>) (7), all characterised by autosomal dominant inheritance and mostly localised in exon 3. In addition, somatic *NLRP3* mosaicism has also been reported in patients with clinical features of CAPS who are negative for germline mutations (8).

The NLRP3 protein is mainly expressed in monocytes, macrophages, and neutrophils, and is directly involved in the regulation of the inflammatory response, as it represents a key-component of the NLRP3-inflammasome complex belonging to the NLR-proteins. These consist of 22 members ac-

cording to different N-terminal effector domains that are classified into three subfamilies: caspase-recruitment domain (CARD), pyrin domain (PYD), and baculoviral inhibitors of apoptosis repeat (BIR-like). In addition, NLRP3 has other functionally active domains that include the central nucleotide-binding and oligomerisation (NACHT) domain, and a carboxy-terminal leucine-rich repeat domain, which is involved in the recognition of any microbial components.

Several studies have demonstrated that a number of PAMPs and DAMPs can activate NLRP3. These include viral or bacterial nucleic acids, muramyl dipeptide, lipopolysaccharide (LPS), ROS, intracellular Ca²⁺ release, K⁺ flux, and monosodium urate crystals. Interaction with these inciting factors causes the activation of NLRP3 and final assembly of the NLRP3-inflammasome complex, which orchestrates IL-1 β production through the recruitment and activation of caspase-1 (9-11). The activation of this protease by the NLRP3-inflammasome complex is finely regulated by two consecutive distinct signals: a priming signal initially required to activate NF- κ B leading to enhanced transcription of several NLRP3-inflammasome complex components as well as the inactive IL-1 β precursor, and a second PAMP- or DAMP-induced signal that triggers caspase-1 activation, ultimately resulting in enhanced release of IL-1 β .

Early *in vitro* studies performed on peripheral blood mononuclear cells (PBMCs) of CAPS patients have shown that disease-causing mutations lead to increased production of IL-1 β in both LPS stimulated and unstimulated samples when compared with healthy controls. Furthermore, PBMCs from CINCA patients, the most severe CAPS phenotype, display LPS induced hypersecretion of IL-1 β without ATP stimulation (12, 13). In addition, NLRP3-inflammasome activation also appears to be related to pre-existing redox alterations associated with elevated ROS levels and overexpression of antioxidant systems in CAPS monocytes (14). Together, these data suggest that the most commonly observed CAPS-related mutations, which are located in

Table I. General identifying items and most relevant clinical features of hereditary periodic fever syndromes belonging to the family of monogenic autoinflammatory diseases.

Disease	Inheritance	Gene	Protein	Main clinical features of each disease
CAPS	AD	NLRP3	NLRP3	Variable patterns of fever, urticaria-like rashes, joint involvement, irregular ossification in the long bones and chronic meningitis in CINCA syndrome, eye involvement, potential sensorineural deafness, risk of amyloidosis
FMF	AR	MEFV	Pyrin	Febrile attacks, serositis, arthralgias or arthritis, erysipela-like eruption on the extremities, amyloidosis in the untreated or noncompliant patients
MKD/HIDS	AR	MVK	Mevalonate kinase	Febrile attacks, heterogeneous rashes, arthralgias, abdominal pain, diarrhoea, lymph node enlargement, splenomegaly, mucosal aphthosis
TRAPS	AD	TNFRSF1A	TNFRSF1A	Febrile attacks, migrating muscle and joint involvement, conjunctivitis, periorbital oedema, arthralgias or arthritis, variable serosal involvement, risk of amyloidosis

AD: autosomal dominant; AR: autosomal recessive; CAPS: cryopyrin-associated periodic syndrome; CINCA: chronic infantile neurological cutaneous articular; FMF: familial Mediterranean fever; HIDS: hyper-IgD syndrome; MKD: mevalonate kinase deficiency; TRAPS: tumour necrosis factor receptor-associated periodic syndrome.

the oligomerisation NACHT domain, render NLRP3 more susceptible to inflammasome activation.

Despite the discovery of somatic *NLRP3* mosaicism, which could partially explain the most typical CAPS clinical features observed in subjects without germline mutations, the genotype-phenotype correlations remain poorly characterised (8). This could suggest the potential involvement of additional disease-amplifying mechanisms. Vento-Tormo and colleagues, who recently investigated the role of DNA demethylation in inflammasome-related genes, showed that several genes were rapidly demethylated in both monocyte-to-macrophage differentiation and in the process of monocyte activation after stimulation with LPS, IL-1, and granulocyte-macrophage colony-stimulating factor (15). In particular, untreated CAPS patients showed an increased demethylation of the inflammasome-related genes compared with healthy controls or with CAPS patients treated with IL-1 inhibitors (15).

Interestingly, a recent study demonstrated that activated macrophages could release inflammasome particles into the extracellular compartment (16). Notably, an enhanced release of IL-1 β

has been observed when transferring oligomeric particles of recombinant NLRP3 (p.D303N)-YFP to wild-type or *Nlrp3*^{-/-} macrophages. These functional oligomeric inflammasome particles, containing both NLRP3 and apoptosis-associated speck-like protein with a CARD (ASC), were also identified in the sera of patients with active CAPS as well as in CAPS mosaic patients, but not in patients with other AIDs (16). These results highlight a potential disease-amplifying mechanism that might explain the severe multi-systemic phenotype observed in some CAPS patients and provide additional potential biomarkers of CAPS activity.

Familial Mediterranean fever

FMF is the most common monogenic AID, mainly affecting populations of Mediterranean origin living in Arabic or Turkish coasts, South Europe, and North Africa. The disease is caused by mutations in the *MEFV* gene, which is located on the short arm of chromosome 16 (16p13.3), and consists of 10 exons encoding a protein of 781 amino acids, called pyrin (also named marenostin or TRIM20) (17-19). More than 300 variants, located mainly in exons 2, 3, 5, and 10, have been

listed (<http://fmf.igh.cnrs.fr/infevers/>) and associated with the FMF phenotype. There have also been reports of rare mutations in the less frequently involved exons 1, 7, and 9 (7, 20). FMF is characterised by protean genotype as well as phenotype heterogeneity. Previous genetic studies conducted in various populations, including Jews, Armenians, Turks, and Arabs and later extended to other ethnic groups (Italians, Greeks, Spanish, and French), have suggested that the most common *MEFV* variants are M694V, V726A, M694I, and M680I. Over the years, several studies have tried to clarify FMF genotype-phenotype correlations underscoring some interesting results; patients homozygous for the M694V, M680I, and M694I mutations have a more severe clinical expression, while compound heterozygotes may display a milder disease course (20-22).

Pyrin is primarily expressed in several cell types, including neutrophils, eosinophils, monocytes, dendritic cells, and fibroblasts. In particular, its expression is regulated by many proinflammatory stimuli variably involving IFN- γ , TNF- α , and LPS (23). This protein is composed of five functionally active domains, known to exert a critical role in the inflammatory response and in programmed cell death: the N-terminal PYD, bZIP transcription factor basic, zinc-finger domain B-box, coiled-coil, and B30.2/ca/SPRY domains (24). Despite the genetic cause of FMF, the exact link between FMF-associated mutations and the molecular basis of FMF is still unknown. Omenetti *et al.* recently observed that monocytes obtained from FMF patients have an enhanced production of IL-1 β after LPS stimulation as well as increased ROS production compared with healthy controls; this enhanced IL-1 β release has been associated with both number and penetrance of *MEFV* mutations (25). IL-1 β overproduction is also dependent on the NLRP3-inflammasome complex activation. Indeed, silencing of NLRP3 inhibits IL-1 β hypersecretion, suggesting that the expression of mutant pyrin induces production of IL-1 β in a NLRP3-inflammasome dependent manner (25). In addition, py-

rin is also capable of regulating IL-1 β activation in an ASC-dependent and NLRP3-independent manner. Indeed, macrophages obtained from mice carrying missense mutations related to the pyrin C-terminal domain (FMF-knock-in mice) and ASC-deficient mice display reduced production of IL-1 β after LPS stimulation if compared with NLRP3-deficient FMF-knock-in mice (26). More recently, pyrin was shown to have intracellular sensor features towards Rho-modifying bacterial toxins, leading to the activation of caspase-1 (27, 28). Downstream molecules of RhoA pathways, such as serine-threonine kinases PKN1 and PKN2, regulate pyrin phosphorylated inactive state promoting the interaction with 14-3-3 proteins. Rho GTPase inactivation by Rho-modifying bacterial toxins leads to pyrin-inflammasome complex activation, and ultimately to IL-1 β processing and secretion. Accordingly, PBMCs obtained from FMF patients have shown reduced IL-1 β release when there is co-treatment with PKN activators, including bryostatin 1 and arachidonic acid, after LPS stimulation (28).

Mevalonate kinase deficiency

van der Meer *et al.* first described mevalonate kinase deficiency (MKD), also known as hyper-IgD syndrome, in 1984 (29). In 1999, MKD was defined genetically as an autosomal recessive metabolic disorder caused by loss-of-function mutations in the *MVK* gene. MKD is located on chromosome 12q24 encoding the enzyme mevalonate kinase (MK), which is involved in the early stage of the metabolic pathway of isoprenoid and cholesterol biosynthesis (30, 31).

The *MVK* gene was already known as the cause of the most severe expression of MKD, called mevalonic aciduria due to peculiar mutations associated with very limited residual MK activity (below the detection limit): this condition is characterised by psychomotor retardation, failure to thrive, cataracts, hepatosplenomegaly, lymphadenopathy, chronic diarrhoea, myopathy, progressive ataxia, and recurring fevers (32). On the other hand, MKD-causing mutations lead to variably reduced ac-

tivity of MK and subsequent different abnormalities in the isoprenoid pathway, leading to post-translational modifications of several proteins involved in the regulation of a wide variety of cellular functions, including inflammatory pathways (33).

More than 200 variants in the *MVK* gene (<http://fmf.igh.cnrs.fr/infervers/>) have been related to MKD; these are mostly missense mutations, broadly distributed throughout the coding sequence region of the gene. In particular, the most common variants are the V377I and I268T substitutions, which can be variably found in heterozygote compounds. In addition, *MVK* deletions and insertions have also been reported (34). Many studies mimicking the characteristic genetic block of this disease through the inhibition of components of the isoprenoid pathway have elucidated the link between this metabolic disorder and the observation of enhanced inflammatory responses, which are typical of the disease. In particular, PBMCs from healthy controls stimulated with LPS showed elevated caspase-1 activation as well as IL-1 β production when pre-treated with specific inhibitors of geranylgeranyl pyrophosphate (35).

A complicated network of molecular interactions hallmarks the complex pathogenetic pathways of MKD. Kuijk *et al.* have partially shed light on this field by investigating the molecular mechanisms responsible for an increased IL-1 β secretion in MKD. Their studies demonstrated that caspase-1 activation follows small GTPase Rac1/PI3K/protein kinase B-dependent pathways (36). Accordingly, inhibition of Rac1 decreased IL-1 β release from PBMCs of MKD patients (36). These findings suggest that MK functional abnormalities result in isoprenoid shortage and decrease of Rho GTPase activity, which in turn induces Rac1 activation and IL-1 β hypersecretion.

Impaired isoprenoid biosynthesis leads to monocyte IL-1 β overproduction in MKD, due to decreased mitochondrial stability, higher ROS production, and attenuated autophagosome degradation (37). Although IL-1 β is considered a major cytokine in MKD pathogenesis, the partial response to anti-IL-1 therapy

observed in some patients suggests that a substantial contribution to the pathogenesis of MKD inflammatory attacks could derive from other cytokines. Accordingly, PBMC obtained from MKD patients and stimulated with different PRR ligands for TLR2 (Pam3Cys), TLR4 (LPS) and NOD2 (MDP), displayed, along with an increased basal activation of caspase-1 and enhanced levels of IL-1 β , a hyperproduction of other important inflammatory mediators, including IL-1 α , TNF- α , and IL-6 (38).

Park *et al.* have recently described a pyrin-mediated inflammasome activation in a RhoA-dependent manner, showing an unexpected link between pyrin activation and MKD inflammatory attacks (28). Indeed, the authors observed that isoprenoid shortage induced by simvastatin triggers pyrin-inflammasome activation by inactivation of RhoA in LPS-stimulated bone-marrow-derived macrophages. Interestingly, pyrin-inflammasome inhibitors blocked IL-1 β production after LPS stimulation in PBMCs of MKD patients (28). These data provide additional proof concerning the still partially understood pathogenesis of MKD.

TNF receptor-associated periodic syndrome (TRAPS)

TRAPS, initially named “familial Hibernian fever”, is the most common among AIDs with autosomal dominant inheritance, and is caused by mutations in the *TNFRSF1A* gene encoding the TNFRSF1A protein, *i.e.* the p55 TNF receptor, also known as TNFR p55 (1). TNFRSF1A is a member of the TNF receptor superfamily, which are a group of proteins with homology in their extracellular domain that are involved in various cell functions, including survival and inflammation (39). In particular, TNFRSF1A represents a transmembrane protein ubiquitously expressed on most cell types, and is characterised by three functionally distinct portions: an extracellular domain consisting of the tandem repeat of four cysteine-rich subdomains (CRD1-4), a transmembrane region, and an intracellular death domain involved in signal transduction (40).

At least 150 variants in the *TNFRSF1A* gene, mainly missense mutations, (<http://fmf.igh.cnrs.fr/infevers/>) have been identified: most of these are located in exons 2, 3, 4, and 6, and are responsible for encoding the extracellular portion of the receptor (7). TRAPS-associated mutations can be distinguished into two subgroups: high penetrance variants (also named “structural” mutations), which are principally associated with cysteine substitutions that alter the secondary structure of the receptor, and low penetrance variants. Subjects with high penetrance variants show early disease onset, severe phenotype, and higher risk of developing secondary amyloidosis. In contrast, low penetrance variants are associated with late development of clinical manifestations, milder phenotype, and lower risk of amyloidosis (41–46). In addition to germline mutations, the description of *TNFRSF1A* somatic mosaicism has also been reported (47).

Several *in vitro* studies on TRAPS-causing mutations have shown heterogeneous mechanisms related to the function of TNFRSF1A. It has been demonstrated that patients carrying high penetrance variants display low levels of TNFRSF1A cell-surface expression, impaired TNF- α binding, alteration in TNF-induced apoptosis, and also defective receptor shedding or trafficking (48–53).

Simon *et al.* reported that a full expression of the TRAPS phenotype depends on the interaction between wild-type and mutant TNFRSF1A proteins (54). Indeed, LPS-stimulated *TNFRSF1A* mutant mice display enhanced and prolonged activation of mitogen-activated protein kinases (MAPKs) as well as high secretion of different proinflammatory cytokines (54). Subsequently, Bulua *et al.* demonstrated that MAPKs activation was a consequence of altered mitochondrial function with enhanced oxidative capacity and mitochondrial ROS generation (55). These studies suggest that cellular stress, due to intracellular accumulation of the mutated receptor, might play a relevant role on the proinflammatory state of TRAPS patients' cells. Accordingly, Dickie *et al.* showed that the intracellular accu-

mulation of mutant TNFRSF1A leads to enhanced ROS levels as well as induction of endoplasmic reticulum stress, as shown by the activation of an important component of the unfolded protein response, named X-box binding protein 1 (XBP1) (56). In particular, LPS-stimulated PBMCs of patients with TRAPS have revealed hyperactivation of XBP1 compared with healthy controls, which can be lessened by the administration of antioxidants (56). Moreover, aberrant mechanisms of autophagy might be a substantial contribution to cellular stress as well as IL-1 β hypersecretion after LPS stimulation (57).

Furthermore, with respect to specific T cell subpopulations, Pucino *et al.* found that the *TNFRSF1A* mutations strongly affect the adaptive immune compartment, suggesting a key-role for T cells in the pathogenesis of TRAPS (58). Notably, hyperactivation of many intracellular pathways was observed, including ERK1/2, STAT1/3/5, mTOR, and NF- κ B in conventional CD4⁺CD25⁻ T cells, with disadvantage of regulatory CD4⁺CD25⁺ T cells, which were less frequently found in TRAPS patients carrying high penetrance variants, irrespective of treatment with IL-1 inhibitors (58).

A non-negligible role has also been ascribed to a potential epigenetic control in TRAPS pathogenesis and, indeed, altered levels of circulating miRNA have been detected in the sera of patients with TRAPS (59). More recently, LPS-stimulated monocytes from TRAPS patients have shown upregulation of several miRNA involved in the regulation of inflammatory response and in NF- κ B activation (60). Together, these results may provide new insights into the protean mechanisms of TRAPS. However, the translation of these discoveries into everyday clinical practice with the final aim to develop potential novel targets for a more effective and personalised therapy has yet to come.

Concluding remarks

AIDs are a complex group of systemic disorders characterised by abnormalities in several pathways involved in the regulation of inflammatory responses.

According to current advances, the pathogenetic pathways involved in the development of different AIDs phenotypes appears directly or indirectly linked to impaired intracellular sensor function. Despite the growing awareness of subverted signalling mechanisms and dysregulated proinflammatory reactions in AIDs, genotype/phenotype correlations remain poorly defined or understood.

In conclusion, the increasing interest in the pathogenesis of these rare but underdiagnosed syndromes will expand our knowledge of mechanisms existing in both cellular and humoral components of innate immunity, may identify new biomarkers that provide improved disease control from a therapeutic viewpoint, and ideally, will improve the overall clinical outcome of patients with AIDs.

Acknowledgments

The authors acknowledge Dr Melanie Gatt for Health Publishing & Services Srl, for her English language assistance.

Funding

This paper is part of a supplemental issue supported by an unrestricted grant from Novartis Farma, Italy, through a service agreement with Health Publishing & Services Srl. Health Publishing & Services Srl provide editorial assistance. Article processing charges were also funded by Novartis Farma, Italy.

Competing interests

L. Obici has received speaker's fees and support from Novartis for travelling to meetings; M. Cattalini has received honoraria and speaker's fees from AbbVie, Novartis and SOBI; M. Gattorno has received consultancies, speaker's fees and unrestricted grants from Novartis and SOBI; L. Cantarini has received consultancies and speaker fees from Novartis and SOBI. All the other authors declare no competing interests.

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