The most recent advances in pathophysiology and management of tumour necrosis factor receptor-associated periodic syndrome (TRAPS): personal experience and literature review

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ABSTRACT

Tumour necrosis factor-receptor associated periodic syndrome (TRAPS) is a rare autosomal dominant autoinflammatory disorder characterised by recurrent episodes of long-lasting fever and inflammation in different regions of the body, as musculo-skeletal system, skin, gastrointestinal tube, serosal membranes and eye. Inflammatory attacks usually start in paediatric age with initial corticosteroid-responsiveness. Most reported cases of TRAPS involve patients of European ancestry and diagnosis can be formulated by the combination of genetic analysis and a compatible phenotype. Its prognosis is strictly dependent on the appearance of amyloidosis, secondary to uncontrolled relapsing inflammation. Thanks to a better understanding of its pathogenesis, the disease is now managed with anti-interleukin (IL)-1 antagonists, rather than corticosteroids or tumour necrosis factor (TNF) inhibitors. The aim of this review is to describe the current understanding and advances of TRAPS genetic basis, pathogenesis and management options by integrating the most recent data in the medical literature.

Introduction

Hereditary periodic fever syndromes represent an expanding list of diseases characterised by unprovoked recurrent attacks of systemic inflammation with lack of autoantibodies or autoreactive T-cells (1). In each of these rare syndromes a specific genetic defect, which involves the regulation of innate immunity, has been demonstrated, and the vast majority of these conditions is related to the activation of the interleukin-1 (IL-1) pathway, which results in a common unifying pathogenetic mechanism (2). Although rare, tumour necrosis factor-receptor associated periodic syndrome (TRAPS) is the most common autosomal dominant autoinflammatory disorder and is caused by mutations in the *TNFRSF1A* gene (12p13) encoding the 55-kD receptor for tumour necrosis factor-α (TNF-α) (TNFRSF1A) (3). The disease is characterised by recurrent fever attacks, typically lasting from 1 to 3 weeks; in addition to fever, common clinical features include migratory erythematous plaques, myalgia, joint and ocular symptoms (4, 5); serosal membrane inflammation is also common, usually in the form of polyserositis (3-11). The mean age at disease onset is around 3. Nevertheless, TRAPS is reported to be the most variable and heterogeneous entity amongst autoinflammatory diseases, both in terms of age at disease onset and clinical manifestations (3-7, 10, 12-16).

The genetic basis of TRAPS

First identified in a single family of Irish/Scottish ancestry (17), TRAPS was originally assigned the moniker of "familial Hibernian fever". Over the past 15 years, genome-wide searches and linkage analysis in affected families have pinpointed the susceptibility locus at chromosome 12p13 (3), a chromosome region encompassing several candidate genes: *CD4*, *LAG-3*, *CD27*, *C1R*, *C1S* and *TNFRSF1A* (18). Several mutations were identified in the *TNFRSF1A* gene, and low levels of soluble TNFRSF1A were found in some TRAPS patients, thus indicating TNFRSF1A as a likely culprit in the development of TRAPS-related symptoms (19). More than 70 *TNFRSF1A*

mutations are currently associated with TRAPS, mainly localised in the first two N-terminal cysteine-rich domains CRD1 and CRD2 (www.fmf.igh.cnrs.fr/infevers/) (20). CRD1, the pre-ligand binding assembly domain, appears to mediate TNFRSF1A self-assembly (21), and CRD2 interacts with trimeric TNF-α (22). Most mutations associated with TRAPS (about 94%) are single-nucleotide missense variants within exons 2, 3, 4, and 6, encoding for the extracellular region of the receptor (Fig. 1). However, there are reports of other variants in the extracellular domain, specifically three deletions and one deletion/insertion. Around half of the reported structural mutations involves cysteine residues, being associated with a higher disease penetrance (5). As cysteine residues are known to be involved in intramolecular disulphide bonds, which are crucial elements of the receptor's three-dimensional structure, mutations involving cysteine residues undermine the conformation and stability of the TNFRSF1A extracellular portion. There are also some other genetic variants that involve residues critical to the secondary structure of TNFRSF1A, *i.e.* mutations that introduce or eliminate proline residues (P46L, L67P, S86P, R92P), or alter the receptor's hydrogen-bond stabilisation (T50M, I170N) (23). The non-structural mutations, of which several are known, are associated with a milder disease (24). Two of these (R92Q and P46L) are low-penetrance variants occurring in 1–5% of the general population and are associated with distinguishing clinical features (24, 25). No mutations that encode for a widely deleted receptor have been found to date, and this seems to indicate that synthesis of the mutated receptor is crucial to disease pathogenesis.

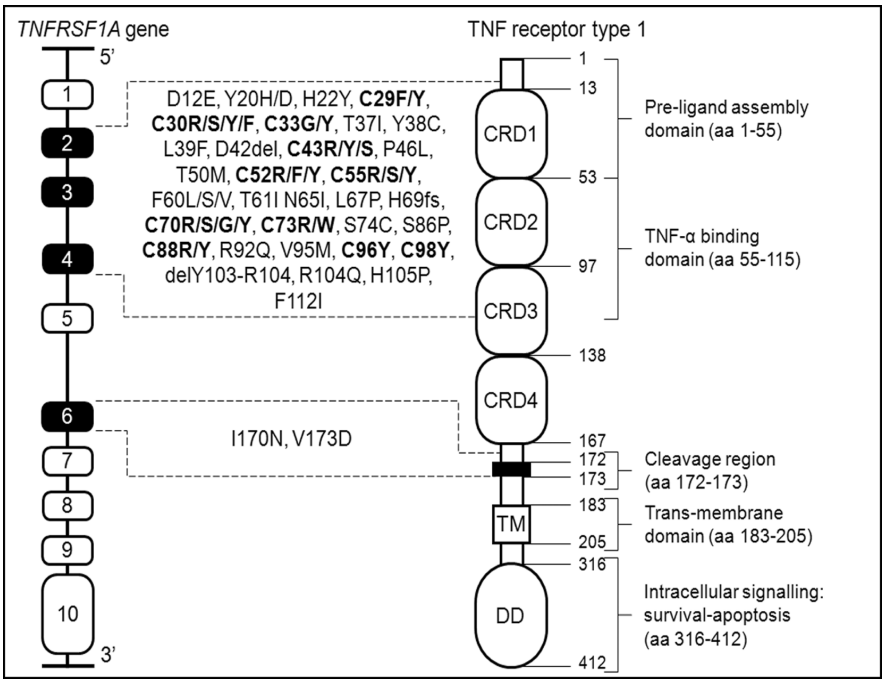

Fig. 1. Schematic representation of the tumour necrosis factor receptor-associated periodic syndrome (TRAPS) mutations in the *TNFRSF1A* gene and their related exons and TNF receptor type 1 domains. TRAPS mutations occur within exons 2, 3, 4 and 6. The majority of them, linked to a higher disease penetrance, involving cysteine residues that are localised within CRDs (cysteine-rich domains), are crucial for the TNF receptor function.

TRAPS pathogenesis

TNF-α is a type-II transmembrane protein produced primarily by monocytes and macrophages, as well as by lymphocytes, natural killer cells, polymorphonuclear leukocytes, keratinocytes and astrocytes. One of the main cytokines involved in systemic inflammation, TNF-α is known to mediate a number of biological processes including cell proliferation, immune modulation, apoptosis, inflammation, arthritis, autoimmune diseases and other pathological conditions: TNF-α transmits its signal by binding to two different cell surface receptors, TNFRSF1A (or TNFR1, p55/p60-TNFR, CD120a) and TNFRSF1B (or TNFR2, p75/80-TNFR, CD120b), components of the superfamily of receptors for TNF (Tumour Necrotic Factor Receptor SuperFamily, TNFRSF). By recruiting various signalling proteins, these receptors promote different pathways leading to activation of transcription factors, such as nuclear factor-κB (NF-κB) and c-Jun/activator protein 1 (AP-1), apoptosis and protein-kinase pathways which can be activated by mitogens. TNFRSF1A pertains to the TNF receptor superfamily and is a transmembrane protein with an extracellular domain made up of the tandem repeat of four cysteine-rich subdomains (CRD1-4), a transmembrane region and an intracellular death domain (DD) (28). The N-terminal region of CRD1, referred as the PLAD (Pre-Ligand Assembly Domain), mediates homotypic receptor interactions and thus permits efficient ligand binding and consequent signal transduction (22). The extracellular domain contains intramolecular disulfide bridges that serve as the binding site for TNF-α and mediate TNFRSF1A self-assembly (Fig. 2). CRD3 and CRD2 domains, interacting with trimeric TNF-α, bring about recruitment of the adaptor protein TRADD through TNFRSF1A's cytoplasmic DD (22). TRADD then recruits other proteins, setting off a signal transduction cascade, leading either to activation of NF-κB and the successive production of proinflammatory cytokines, or to caspase activation and consequent apoptosis (30). Following activation of the TNFRSF1A, its extracellular portion is shed from the cell surface through metalloprotease cleavage and moves into the extracellular compartment, where a pool of soluble TNFRSF1A binds circulating TNF-α, an important control strategy during acute inflammation (31). Our understanding of the pathogenic mechanism by which *TNFRSF1A* mutations beget the autoinflammatory phenotype of TRAPS is still insufficient. In the past few years, researchers have pro-

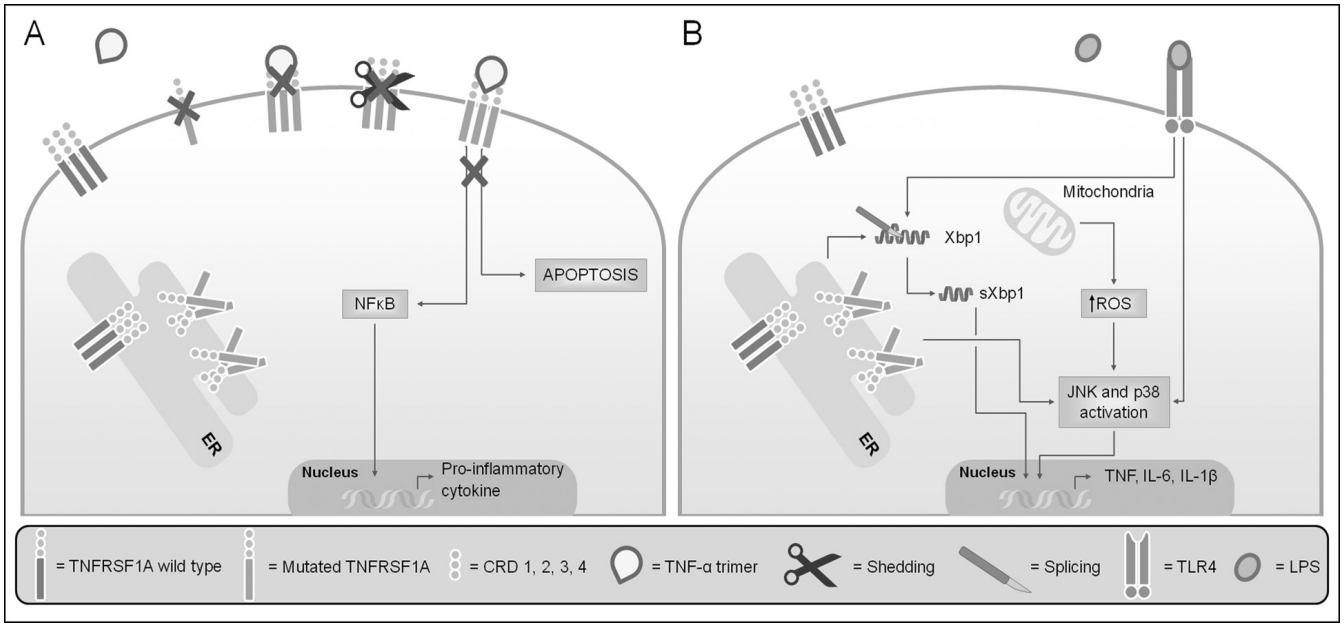

Fig. 2. Pathogenetic mechanisms involved in tumour necrosis factor receptor-associated periodic syndrome (TRAPS). **A)** Several studies have demonstrated that TNFR mutants lead to: **i)** accumulation of mutated TNFRSF1A in the endoplasmic reticulum (ER); **ii)** alteration of mutated TNFRSF1A trafficking to the cell surface; **iii)** lessening of TNF-α binding affinity; **iv)** reduction of TNFRSF1A extracellular domain cleavage (shedding); **v)** alteration of TNF-α induced activation of transcription factors (*e.g.* nuclear factor-κB, NF-κB) and apoptosis. **B)** More recent studies have demonstrated that TNFR mutant intracellular accumulation leads to enhanced inflammatory response by unconventional unfolded protein response (UPR), through enhanced splicing of X-box binding protein 1 (XBP1). Moreover, TRAPS cells have shown increased levels of mitochondrial reactive oxygen species (ROS), that potentiate the inflammatory response (such as by lipopolysaccharide, LPS) due to sustained MAPK activation (JNK and p38).

posed several pathogenic mechanisms, but have failed to explain why not all TNFRSF1A mutants show similar defects. Early hypotheses suggested that TRAPS mutations either constitutively brought about TNFRSF1A activation or increased binding affinity to TNF-α. However, these hypotheses were discarded on the basis of studies analysing control and TRAPS patients' peripheral blood mononuclear cells (3). Researchers then suggested that TRAPS mutations might result from impaired metalloprotease-dependent cleavage of TNFRSF1A, producing soluble "shed" receptors (3), since patients with structural mutations including C33Y, T50M, C52F and C88R had been shown to have significantly lower levels of soluble receptor in the serum than healthy donors (3-5). But some TRAPS patients have been reported as having normal receptor shedding (5), and administration of the fusion protein etanercept to block TNF-α has not always proven effective in reducing TRAPS symptoms (32, 33). *In vitro* studies show possible causative links between TRAPS-associated *TNFRSF1A* mutations and impaired TNF-α binding, abnormal apoptosis and altered NF-κB pathway (19, 35, 36), as well as defective receptor trafficking to the cell surface (37). One or more of these impairments may be linked to the anti-inflammatory effect (*e.g.* reduced binding of TNF-α to the mutated receptor, reduced cell-surface expression, and diminished TNF-induced NF-κB activation). Then, several studies have shown elements of a mutated TNFRSF1A pro-inflammatory effect, such as defective TNF-α-induced apoptosis in TRAPS patients carrying mutations involving cysteine residues (38).

Some TRAPS-associated mutations, particularly those with intramolecular disulphide bond alterations, have been linked to defective TNFRSF1A trafficking. Abnormal oligomerisation of mutant receptors results in their intracellular retention in the endoplasmic reticulum, as shown by *in vitro* experiments confirmed by molecular modeling of TNFRSF1A mutants (37).

The intracellular retention of TNFRSF1A mutants has also recently been found in peripheral blood mononuclear cells of TRAPS patients, as well as in multiple cell types from two independent lines of knock-in mice carrying TRAPS-associated *TNFRSF1A* mutations (39). This research demonstrated that TRAPS-associated *TNFRSF1A* mutations engendered intracellular TNFRSF1A accumulation, which sensitised cells to the effects of other innate stimuli, such as lipopolysaccharide (LPS) (caused by spontaneously-increased MAPK activation), inducing an excessive autocrine TNF-α secretion-dependent pro-inflammatory response (39).

Additionally, Bulua *et al*. showed mitochondrial reactive oxygen species (ROS) to be an important component of the inflammatory response in hyper-responsive TRAPS cells, as well as in normal cells, in mononuclear blood cells from TRAPS patients and mouse embryonic fibroblasts (MEFs) from knock-in mice carrying TRAPS-associated *TNFRSF1A* mutations (40). Most interesting, they observed altered mitochondrial function with enhanced oxidative capacity and mitochondrial ROS generation in TRAPS cells, resulting in intensified production of pro-inflammatory cytokines in response to LPS by means of sustained MAPK activation (40).

These data are in agreement with a more recent finding of increased ROS levels in TRAPS monocytes, compared to healthy controls, both in basal condition and upon IL-6 stimulation (41). Moreover, it is well known that intracellular protein accumulation can cause an associated unfolded protein response (UPR), whereby cells respond to stress by inducing expression of genes to restore the proper function of endoplasmic reticulum (42). Several authors have demonstrated the misfolding and abnormal oligomerisation of TNFRSF1A mutants, notwithstanding the activation or abnormality of the classic UPR, where not observed in these cells (38). Conversely, an *in vitro* study showed co-localisation of TNFRSF1A mutant receptors with BiP, a UPR-associated protein (43).

Recently we have investigated ROS pathway and endoplasmic reticulum stress in TRAPS patients. Like Simon *et al*., we have observed that important transcripts of the UPR pathway were not altered in healthy controls and patients. We also reported that another UPR-associated protein, the transcription factor spliced X-box binding protein 1 (sXBP1), is involved in TRAPS pathogenesis (41), thus suggesting that an unconventional UPR activation could be implicated. TRAPS patients had increased s*XBP1* transcripts compared to healthy controls and we also observed an increase in another UPR-associated protein, p-PERK protein. Significantly increased *uXBP1* and *sXBP1* transcripts were observed with LPS stimulation in TRAPS patients' peripheral blood mononuclear cells. Co-treatment with LPS and antioxidants reduced *sXBP1* levels in TRAPS patients by 40%, thus suggesting an association between endoplasmic reticulum stress due to mutant TNFR1 accumulation and enhanced ROS levels mediating LPS hyper-responsiveness through the XBP1 pathway (41). This unconventional UPR activation was described by Lisbona *et al*. (44) in mouse macrophages, where TLR activation was associated with XBP1 activation without activation of classic endoplasmic reticulum stress-induced genes. To the best of our knowledge, ours is the first research to demonstrate this pathway activation in humans and, crucially, with higher induction seen in TRAPS patients' peripheral blood mononuclear cells. It is possible to speculate that mild endoplasmic reticulum stress, through accumulation of mutant TNFR1, results in *XBP1* splicing but not a full classical UPR. The clearance of intracellular protein accumulation, due, for example, to misfolding and abnormal oligomerisation of mutated receptors, may be carried out by proteasome, UPR and/or autophagy pathways. Recent observations have shown a link between inflammation and autophagy, the main mechanism responsible for elimination of both damaged cellular compartments in physiological conditions and insoluble aggregates of mutant proteins, that accumulate under pathological circumstances. In particular, downregulation of autophagy is known to trigger innate immune responses in cells, causing inflammation, as observed in mice lacking autophagy-related proteins (46).

Bacchetti *et al*. first reported that autophagy is responsible for clearance of wild-type TNFR1, but in the presence of TRAPS structurally associated mutations affecting cysteine residues, such as C55Y, the autophagy process is defective, probably accounting for mutant TNFR1 accumulation as well as TRAPS-associated induction of NF-κB activity and excessive IL-1β secretion, leading to chronic inflammation (47). Autophagy inhibition due to TNFR1 mutant proteins can be reversed, as demonstrated by the effects of the antibiotic geldanamycin, which was found to rescue the membrane localisation of mutant TNFR1 proteins, reduce their accumulation and counteract the increased inflammation by decreasing IL-1β secretion. Finally, we can speculate that intracellular accumulation of misfolded receptors plays a crucial role in TRAPS pathogenesis, and that different pathways, such as UPR and ROS, are activated in the attempt to eliminate receptor aggregation. Moreover, TNFRSF1A accumulation sensitises cells to the effects of innate stimuli, resulting in an exaggerated inflammatory response.

TRAPS clinical features

TRAPS is the most variable entity among autoinflammatory diseases in terms of age at disease onset, frequency, length and severity of inflammatory attacks and clinical manifestations. Its heterogeneity is probably linked to the wide spectrum of known *TNFRSF1A* mutations (28, 48).

Its main clinical features include prolonged and recurrent fever attacks, a migratory erythematous skin rash with underlying myalgia, eye inflammation, arthralgia and/or arthritis and thoracic pain (3). Serosal inflammation is commonly observed (49) and the sole involvement of pericardium has also been recently reported (8, 9, 10, 50-52). The average age at disease onset is around 3 years, but the onset of symptoms during adulthood up to the age of 63 has been described as well (7, 8, 13-15, 25, 52). Fever attacks recur either spontaneously or after minor triggers (local injury, minor infection, stress, exercise, and hormonal changes) at varying intervals, and usually initiate with muscle cramps or myalgia that migrate in a centrifugal pattern, followed by other TRAPS typical symptoms. Skin lesions usually initiate as painful and warm macules and papules, which progressively expand at the periphery, subsequently coalescing into large patches or plaques. Skin biopsies usually show a dermal perivascular lymphocytic and monocytic infiltrate (53). Other less common skin lesions may include erysipela-like erythema and urticarial rash. Myalgia likewise displays centrifugal migration and is due to a monocytic fasciitis without muscle involvement and muscle enzyme increase (54). Eye involvement can manifest in the form of a peculiar periorbital edema, but also in the form of conjunctivitis and/or uveitis (5). Arthralgia occurs during fever attacks in about two-thirds of patients, in a monoarticular or oligoarticular form, mainly involving the knees, shoulders, elbows, hips, temporomandibular joints, hands and wrists. Arthritis is less common, but joint effusion may also occur. Atypical sacroiliac involvement has also been reported (9, 55).

Reactive amyloidosis is the most serious long-term complication of TRAPS,

and often leads to a rapid deterioration of kidney function which manifests with proteinuria and kidney failure, potentially leading to death (56, 57). Patients carrying mutations involving cysteine residues, which are known to be associated with a high disease severity, are at great risk of developing amyloidosis (56). These patients are also characterised by an earlier disease onset and a more severe phenotype, showing a high number of fever episodes and a particular severity of febrile attacks. In contrast, patients carrying low-penetrance mutations tend to show a milder phenotype, a later disease onset, olygosymptomatic disease and a lower risk of developing reactive amyloidosis (2% of patients *vs*. 25% patients carrying high-penetrance TNFRSF1A variants) (5, 24).

Adult-onset patients may be characterised by a phenotype that mimics other autoinflammatory disorders, such as familial Mediterranean fever, even in terms of the duration of inflammatory attacks, which can be short, frequently leading to misdiagnosis and improper management (7, 13-15). In addition, adult-onset TRAPS may present an incomplete disease or atypical inflammatory pictures, such as recurrent pericarditis and myocarditis as the sole clinical manifestations, thus mimicking autoimmune disorders (7-9, 11, 13-15, 50, 52, 55, 58, 59). We recently identified low-penetrance *TNFRSF1A* mutations in about 6% of unselected patients affected with idiopathic recurrent pericarditis (IRAP) and therefore we suggested possible clues to detect TRAPS mutations among IRAP patients: a positive family history for pericarditis or periodic fever syndromes, a poor response to colchicine, the number of recurrences after the first year from the index attack or while on colchicine treatment, as well as the need for immunosuppressive agents were clues to the possible presence of *TNFRSF1A* mutations (10).

In addition, TRAPS mutations seem to be responsible for the development of early-onset atherosclerosis, thrombosis and acute myocardial infarction (33, 60-62), though the number of studies investigating the cardiovascular risk in TRAPS patients is limited, and these data still need to be confirmed.

Laboratory investigations in TRAPS

In TRAPS patients, laboratory tests commonly reveal increases in indicators of inflammation during each acute inflammatory episode; in particular, relevant increases are observed for erythro-sedimentation rate and C-reactive protein, as well as fibrinogen and haptoglobin, which characteristically return to normal levels during non-acute intervals. These increases can also be associated with abnormalities in blood cell counts, such as neutrophil leukocytosis, thrombocytosis and hypo- or normochromic anemia, which is typical of chronic inflammatory diseases. Also fairly frequent are findings of polyclonal hyper-gammaglobulinemia, due to stimulation of immunoglobulin synthesis by numerous proinflammatory cytokines, such as IL-6. Acute-phase reactants are often elevated in patients with TRAPS even between fever attacks, although at a lower level than during attacks, but the most determinant laboratory element of the quiescent phase is the finding of low serum levels of the soluble TNF-α receptor (<1 ng/ml), as the illness is linked to a defective release of the receptor from cell membranes (4). Serum amyloid-A (SAA) is an acute-phase protein, synthesised and secreted by the liver upon stimulation by proinflammatory cytokines as IL-1, IL-6 and TNF-α: its amino-terminal fragment may be deposited in various organs in the form of amyloid fibrils, leading to the development of AA-amyloidosis. The measurement of serum SAA is a valuable diagnostic tool, as elevated concentrations are associated with a risk of progressive amyloid-fibril deposits in various parenchymas. In addition, SAA has been shown to be a useful parameter in the evaluation of clinical activity in response to treatment (56). Moreover, attention should be paid every 4–6 months to urinalysis and to laboratory evaluation of renal function: the occurrence of proteinuria >0.5 g/day and/or an impairment of renal function might disclose subclinical amyloid deposits, which are known to anticipate clinically overt AA amyloidosis (63).

Another calcium-binding protein named S100A12 (or calgranulin C), secreted by neutrophil granulocytes, which activates the inflammatory response in the endothelial cells and leukocytes through the NF-κB pathway, closely correlated with disease activity and therapeutic efficacy in different inflammatory diseases, might provide a reliable new marker for future utilisation (64). In recent years, scientific interest in adipose tissue-derived peptides has exploded and several mediators known as adipocytokines such as leptin, resistin, visfatin and adiponectin have been shown to play a relevant role in systemic inflammation: in particular, serum adiponectin levels evaluated in symptom-free phases of TRAPS patients have been shown to be significantly related with the presence of amyloidosis and serum leptin levels significantly correlated with the number of fever attacks/year (65).

TRAPS treatment

Treatment of TRAPS proves more challenging than other autoinflammatory syndromes due to the considerable genetic heterogeneity and to the protean clinical phenotype. The main goals of therapy are:

i) to control symptoms,

ii) to improve patients' quality of life,

iii) to prevent long-term complications.

A few patients gain some symptomatic relief from high-dose non-steroidal anti-inflammatory drugs (NSAIDs), while colchicine or immunomodulators such as methotrexate, cyclosporine and thalidomide produce very little benefit (6).

Inflammatory attacks are often responsive to corticosteroid administration, but patients may often need increasing doses, in cases with frequent relapses, or require chronic administration in order to prevent flares (3, 59). These subjects may become prone to metasteroidal co-morbidities. Furthermore, steroids do not seem to protect completely from the risk of developing reactive amyloidosis, as they do not normalise SAA levels in most patients (56).

Recently, a web-based registry in which clinical information on anonymised patients affected with auto-

inflammatory diseases was collected retrospectively as part of the Eurofever initiative (EAHC Project No. 2007332) indicated that NSAIDs and corticosteroids were prescribed in 48 and 88 patients, respectively, mainly as on-demand therapy, and proved to be beneficial in the majority of cases. Surprisingly, colchicine was beneficial in 21 of 39 patients, three of whom had a complete response. Patients with the low-penetrance R92Q mutation seemed to respond better to NSAIDs and colchicine *versus* patients carrying other *TNFRSF1A* mutations (12).

Recently, the identification of *TNFRSF1A* mutations as the genetic cause of TRAPS raised the possibility that blocking TNF-α – even though elevated TNF-α is not observed in most TRAPS patients (66) – could potentially represent the primary therapeutic strategy in TRAPS. Among biologic agents, the mainstay of TRAPS treatment to date has been etanercept, a recombinant human TNFR (p75)-Fc fusion protein comprising two receptors linked by an IgG_1 Fc fragment. Etanercept administration has been shown to prevent inflammatory attacks and/or to allow the reduction of corticosteroid administration (67). Anecdotal reports describe its efficacy in the treatment of TRAPS-related reactive amyloidosis as well (33, 68-71). Bulua *et al*. have recently shown that although etanercept reduces symptoms and serum inflammatory markers in a dose-dependent manner, it does not completely normalise symptoms or acute-phase reactants in TRAPS patients (72). Long-term adherence to etanercept might be poor and a significant number of patients might need to switch therapy to anti-IL-1β drugs, frequently due to lack of efficacy or development of injection site reactions. A decline in responsiveness may occur in some cases (73, 74) and resistant patients have also been recently reported (76). These data suggest a non-specific anti-inflammatory action of etanercept in TRAPS (76). Accordingly, data from the Eurofever registry showed that etanercept was beneficial in 32 out of 37 patients, even though only 11 (30%) experienced a complete response (12).

On the contrary, in terms of the TNF-α neutralising agents, both infliximab, a mouse-human chimeric monoclonal IgG_1 antibody to TNF-α, and adalimumab, a fully humanised anti-TNF monoclonal antibody, may cause paradoxical inflammatory attacks in TRAPS patients (19, 74). This effect could be induced by:

i) an increase in anti-apoptotic activity and over-secretion of pro-inflammatory cytokines (IL-1, IL-1R, IL-6, IL-8, and IL-12);

ii) more stable binding complexes with soluble TNF-α and their much higher binding avidity to transmembrane TNF of monoclonal antibodies than etanercept (77);

iii) reduced shedding of infliximab-bound TNFα/TNFRSF1A from the cell surface, leading to a marked increase in cytokine secretion and increased proinflammatory response (78).

For these reasons, caution is strongly advised when prescribing infliximab and adalimumab in patients with TRAPS.

In etanercept-resistant patients, IL-1 inhibitors have recently been shown to induce a better and longer-lasting effect in controlling TRAPS clinical manifestations, and also to induce a prompt and stable normalisation of acute-phase reactants in most patients. Though promising, the results obtained with IL-1 antagonists are, to date, limited to few cases and must undergo further evaluation in larger cohorts of patients (58, 73, 79). The IL-1 receptor antagonist anakinra has been shown to prevent disease relapses in the short-term, and to induce a prompt and stable disease remission (57, 71); in addition, its long-term efficacy and safety in patients with and without AA amyloidosis have also been recently described (79). However, refractoriness to anakinra has also recently been reported in a patient carrying a T50M mutation (80). We recently reported the first TRAPS patient successfully treated with canakinumab, a human IgG_1 anti-IL-1β monoclonal antibody: the patient carried a low penetrance V95M mutation and canakinumab treatment proved to be effective both in bringing about a rapid and complete resolution of clinical manifestations and in normalising all markers of inflammation within a few weeks from the start of therapy. The treatment was well-tolerated, and at 6-month follow-up no adverse events were noted (81). On the other hand, long-lasting drugs targeting IL-1 such as canakinumab and rilonacept, a dimeric glycoprotein consisting of human IL-1 receptor extracellular domains and the Fc portion of human IgG_1, could preclude the need for daily injections and the relative patient discomforts, mainly connected to injection site reactions. A very recent phase-II trial conducted on twenty TRAPS patient showed that canakinumab produced a rapid and effective clinical and serological benefit which was maintained with continued dosing. Relapse, occurring at a median of 3 months after the last dose, was usually mild or moderate, and resolved upon re-dosing (82).

Finally, since IL-6 levels may be elevated in TRAPS (66), it has been hypothesised that tocilizumab, a humanised monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors and inhibits IL-6 receptor–mediated signalling, might be an alternative treatment option. A 52-year-old TRAPS patient resistant to etanercept and anakinra recently underwent tocilizumab administration for 6 months. The treatment aborted an evolving acute attack and prevented further inflammatory attacks. Acute-phase reactants promptly decreased to normal values (83). These preliminary findings need to be confirmed.

In conclusion, in order to prevent reactive amyloidosis, treatment in TRAPS must aim at inducing a persistent normalisation of SAA levels: for this reason a close monitoring of SAA levels is recommended to detect any pathological elevation, which may occur also in symptom-free patients as a reflection of subclinical inflammation (57).

Conclusions

In spite of the large number of studies on TRAPS, its pathophysiology still remains to be completely elucidated, though several hypotheses have been proposed with multiple mechanisms of action of *TNFRSF1A* mutants. The

concerted action of wild-type and mutant TNF receptors with trafficking dysfunction should play a pivotal role in provoking enhanced inflammation and oversecretion of proinflammatory cytokines in TRAPS patients. The clinical mark of these patients is the recurrence of fever, myalgia, arthralgia, rash, chest pain and eye symptoms, that often last longer than two weeks and are evocative of the syndrome. Diagnosis is based on history, examination, nonspecific findings as elevated acute-phase reactants and neutrophilia during attacks and mostly genetic analysis with the recognition of specific *TNFRSF1A* mutations. Patients with TRAPS should be regularly screened for proteinuria, as renal amyloidosis remains the most dreadful complication in patients who are undiagnosed, poorly responsive to medical treatment or noncompliant. New treatment strategies aimed at blocking cytokines, other than IL-1 and TNF-α, or intracellular mediators of inflammation, such as ROS, may help in the future to obtain a better control of the complex TRAPS phenotype.

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