EDITORIAL

ROLE OF ETANERCEPT IN THE TREATMENT OF TUMOR NECROSIS FACTOR RECEPTOR-ASSOCIATED PERIODIC SYNDROME: PERSONAL EXPERIENCE AND REVIEW OF THE LITERATURE

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Tumor necrosis factor-α receptor (TNFR1)–associated periodic syndrome (TRAPS) is the most common autosomal-dominant autoinflammatory condition and is caused by mutations in the *TNFRSF1A* gene. TRAPS is characterized by recurrent attacks of fever typically lasting from 1 to 3 weeks; in addition to fever, common clinical features include mainly periorbital oedema, conjunctivitis, a migratory erythematous plaque simulating erysipela with underlying myalgia, and arthritis or arthralgia; serosal membrane inflammation is also possible. The identification of *TNFRSF1A* mutations as the genetic cause of TRAPS coincided with the wider use of biological agents in medicine and raised the possibility that blocking TNF could potentially represent the primary therapeutic goal in TRAPS, thus disclosing new treatment choices for this complex disease. In the past few years, isolated reports and case-series have been published suggesting that inhibition of TNF-α might represent a promising therapeutic approach in TRAPS. We present here our experience with etanercept in the treatment of patients affected with TRAPS, and we also add a review of the literature.

Autoinflammatory disorders are defined by spontaneously relapsing and remitting bouts of systemic inflammation in the absence of pathogens, autoantibodies, or antigen-specific T cells. These disorders can be monogenic or multifactorial and are associated with mutations of genes involved in inflammation and apoptosis (1).

Among monogenic autoinflammatory diseases, the tumor necrosis factor-receptor 1-associated periodic syndrome (TRAPS; OMIM 142680) is the most common autosomal dominant autoinflammatory disorder and is characterized by recurrent attacks of fever typically lasting from 1 to 3 weeks; in addition to fever, common clinical features include mainly periorbital oedema, conjunctivitis, a migratory erythematous plaque simulating erysipela with underlying myalgia, and arthritis or arthralgia; serosal membrane inflammation is also possible (2-3). TRAPS is caused by mutations in the gene *TNFRSF1A*, located on chromosome 12p13,

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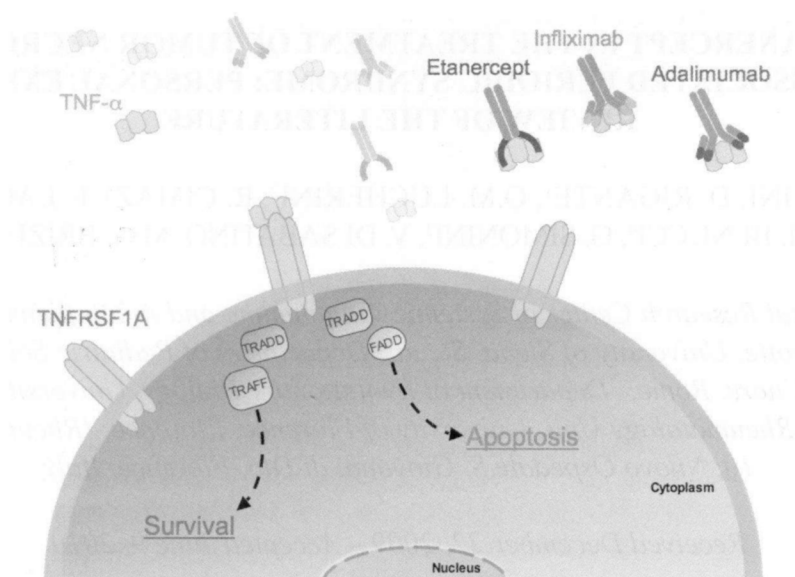e-mail: cantariniluca@hotmail.com

Fig. 1. *Tumor Necrosis Factor-alpha (TNF-α) inhibitors and pathogenesis of tumor necrosis factor receptor-associated periodic syndrome. Tumor Necrosis Factor Receptor Superfamily 1A (TNFRSF1A) undergoes trimerization, and the binding to trimeric TNF-α induces either survival or apoptotic pathways. Upon receptor activation, TNF Receptor Associated Factor (TRAF) is recruited via the adapter protein, TNF Receptor-Associated Death Domain (TRADD), to the plasma membrane. This activation is important for cell survival and inflammatory signals. TRADD is also associated with fas-associated death domain (FADD), which leads to the induction of apoptosis via the recruitment and cleavage of pro-caspase 8. The monoclonal antibodies (i.e. infliximab, adalimumab) and the receptor analog (etanercept) bind to TNF-α and block it's interaction with TNFRSF1A. In particular, infliximab and adalimumab are chimeric antibodies including mouse and human components, while etanercept is a soluble with p75 Tumor Necrosis Factor Receptor Superfamily 1B (TNFRSF1B)-linked Fc human IgG1 recombinant fusion protein. These agents are designed to bind circulating TNF-α, thus preventing TNF-signaling and TNF-mediated inflammatory response.*

encoding the 55-kD receptor for tumor necrosis factor-α (TNF-α) (TNFRSF1A) (4).

TNFRSF1A is a transmembrane glycoprotein (Fig. 1) which consists of an extracellular region characterized by a distinct pattern of 4 cysteine-rich domains (CRDs 1-4), a transmembrane region, and an intracellular death domain (DD), which promotes TNFRSF1A signaling (5). The binding site for TNFα is formed by CRD2 and CRD3 (6), while CRD1 is the pre-ligand assembly binding domain and is thought to mediate TNFRSF1A self-assembly (7). More than 40 individual mutations have been identified, the majority of which are localised in the CRD1 and CRD2 domains (http://fmf.igh.cnrs.fr/infevers/) (8). Most mutations described involve cysteine residues and are associated with a higher disease penetrance, however several variants involving other residues have been reported (9). *In vitro* studies suggest that these TRAPS-associated *TNFRSF1A* mutations are

responsible for altered TNFRSF1A expression, impaired TNF-α binding and shedding (4), defective trafficking (10-11) and abnormal apoptosis (3, 12).

Typical of TRAPS is a wide variability amongst patients both in terms of age of disease onset and frequency, and length and severity of inflammatory attacks. This heterogeneity is related to the complex phenotypical expression of TRAPS and to the wide spectrum of *TNFRSF1A* mutations (13).

Patients usually tend to develop a chronic disease course with recurrent flares of multi-organ manifestations, with or without fever, as well as persistently elevated acute-phase reactants, including serum amyloid-A (SAA) circulating levels, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and interleukin-6 (IL-6), and IL-8 (14).

Renal AA amyloidosis is the most serious long-term complication of TRAPS, with a prevalence ranging from 14% to 25%, mainly affecting, but not

Table I. *The table summarizes data from the entire cohort of patients enrolled.*

Pt	Age at testing (yrs)	Age at onset (yrs)	Gender	Mutations in *TNFRSF1A*	Clinical Manifestations
1	28	13	M	Δ Y103-R104 heterozygous	Recurrent pericarditis
2	50	34	M	R92Q heterozygous	Recurrent pericarditis
3	32	28	F	R92Q heterozygous	Recurrent pericarditis
4	41	38	F	R92Q heterozygous	Recurrent pericarditis
5	11	7	F	D12E heterozygous	Recurrent fever attacks, mild hepatomegaly and splenomegaly, lower limbs myalgia, conjunctivitis, erythematous rash (face) and a maculopapular rash (trunk, ankles, lower limbs).
6	29	9	F	— *	Recurrent fever attacks, lower limbs myalgia, thoracic and abdominal pain, periorbital oedema, erythematous rash involving trunk and lower limbs and proteinuria (0,650 mg/L).
7	27	26	F	R92Q heterozygous	Recurrent pericarditis, sacroileitis

*Gender, age at disease onset, and the age at the time of genetic testing are shown. The results of genetic testing for mutations of the gene responsible for the tumor necrosis factor-α receptor-associated periodic syndrome (TNFRSF1A gene) and the clinical manifestations are also listed. List of abbreviations: Pt = patient; yrs = years; F = female; M = male; * patient n.6 did not carry mutations, but showed a defective TNFRSF1A shedding (ref.4)*

limited to, patients who carry mutations involving cysteine residues; patients carrying low penetrance mutations may also develop reactive amyloidosis, although they are usually characterized by a milder disease, if they present a persistent acute phase response (15-16).

Treatment strategies

Treatment of TRAPS proves more challenging than other autoinflammatory syndromes due to the wide genetic heterogeneity and to the protean clinical phenotype: some patients experience significant disability over time or develop signs of renal amyloidosis, requiring novel treatment strategies with the aim of better long-term disease control. There are patients who gain some symptomatic relief from high-dose non-steroidal anti-inflammatory drugs, whilst colchicine or immunomodulators such as methotrexate, cyclosporin and thalidomide produce little benefit. Inflammatory attacks usually respond to corticosteroid administration (17), but often require increasing doses, especially in patients with frequent relapses or continuous symptoms, who

become prone to metasteroidal co-morbidities (18).

The identification of *TNFRSF1A* mutations as the genetic cause of TRAPS coincided with the wider use of biological agents in medicine, thus disclosing new treatment choices for this complex disease. The fact of the defect in TNFRSF1A shedding and subsequent inappropriate TNF inhibition suggested that blocking TNF - even though TNF is not increased in most patients (14) - could potentially represent the primary therapeutic goal in TRAPS (19). Anti-TNF therapy in TRAPS has been based on etanercept, a recombinant human TNFR (p75)-Fc fusion protein comprising two receptors linked by an IgG_1 Fc fragment. The exact therapeutic profile and dosing regime of etanercept in the long-term management of TRAPS, however, has yet to be established.

The efficacy of etanercept has been shown in single patients and/or in case-series of patients of different ages with fully penetrant TRAPS phenotypes, as evidenced by decreased frequency of attacks and/or decreased severity of disease (20-21). Even unusual manifestations such as non-suppurative

panniculitis and small-vessel vasculitis were controlled by etanercept in 2 adult patients (22). In a recently reported case series of 7 patients affected with TRAPS who were treated with etanercept for 24 weeks, although the drug did not completely eliminate inflammatory attacks, it was able to reduce disease activity, also in terms of acute-phase response, and allowed for reduction of corticosteroid dose administration in all cases (23). Amyloidosis in TRAPS usually presents with nephrotic syndrome, and early treatment of renal involvement with corticosteroids, colchicine or chlorambucil usually fails to prevent end-stage renal failure. Anecdotal reports of successful treatment with etanercept of patients with TRAPS characterized by nephrotic syndrome have recently been described (24). In addition, etanercept slowed the progression of renal failure due to renal amyloidosis in an 18-year-old patient who underwent renal transplantation at the age of 14 (25).

In contrast, the administration of other anti-TNF agents, such as infliximab, a mouse-human chimeric monoclonal IgG_1 antibody to TNF, or adalimumab, a fully humanised anti-TNF monoclonal antibody, may lead to enhanced anti-apoptotic activity, over-secretion of pro-inflammatory cytokines (IL-1, IL-1R, IL-6, IL-8, and IL-12) (11) and paradoxical exacerbation of the TRAPS clinical picture (12, 23, 26). Differences in response to treatment with different TNF-inhibitors seem to be related to the more stable binding complexes with soluble TNF and to their much higher binding avidity to transmembrane TNF of monoclonal antibodies than etanercept (27). Moreover, it has been hypothesized that mutations altering the extracellular conformation of TNFR fail to shed infliximab-bound TNF/TNFR from the cell surface, thus leading to the induction of inflammatory responses (12).

A decrease in responsiveness to etanercept over time has been described in few patients; the authors hypothesized that etanercept efficacy in TRAPS might be non-specific and may reflect 'generic' anti-inflammatory properties of the molecule (28-29).

There are promising results deriving from the use of anakinra, a recombinant interleukin-1 receptor antagonist, in etanercept-resistant patients; in these patients, anakinra prevented disease relapses in the short-term, raising the hypothesis that the

dysregulation of IL-1 secretion might represent the final common pathway of different autoinflammatory diseases (30-31). To date, the initial results obtained in patients with TRAPS through IL-1 inhibition, though promising, are restricted to very few cases and must be subjected to further evaluation in larger cohorts of patients.

Personal experience

To date, of the patients affected with TRAPS whom we are treating with etanercept, 7 have reached a 12-month follow-up. Six patients out of 7 are adults (32-33), and 1 is of pediatric age (34). Of the 6 adults, 4 were characterized by adult disease-onset, whereas 2 reported the onset of symptoms during childhood. Table I summarizes the main characteristics of our cohort of patients. Four patients out of 7 presented recurrent pericarditis as the sole clinical manifestation (32), and of these, 3 carried the low-penetrance R92Q mutation in *TNFRSF1A*. In addition, one of these patients presenting with recurrent pericarditis as the sole clinical manifestation carried a novel heterozygous ΔY103-R104 deletion in the exon 4, characterized by a six-nucleotide heterozygous deletion (TACCGG nucleotide sequence) and causing the loss of the aminoacid tyrosine and arginine at position 103 and 104, respectively (32). The functional implication of this deletion is currently under investigation in our laboratories. One patient out of the 5 carrying the R92Q mutation was characterized by an unusual association of sacroileitis and pericarditis, in the absence of the most typical clinical signs of TRAPS (33). The R92Q mutation is common in patients of Mediterranean origin, and in a recent study its frequency in healthy Italian individuals was 2.25%. Moreover, in most of the *R92Q* patients, the *mutation* was inherited from one healthy parent (3). Nevertheless, its increased frequency among patients with periodic fever suggests that it is a low-penetrance mutation rather than a benign polymorphism (9).

Although soluble TNFRSF1A serum levels do not seem to increase with attacks, monocytes from patients bearing the R92Q substitution show TNFRSF1A membrane staining and receptor shedding comparable to controls, suggesting that additional pathogenetic mechanisms may be

operative in TRAPS (9). Recently, Lobito et al reported that the R92Q variant TNFRSF1A behaves like wild-type TNFRSF1A, with apparently normal folding, identical surface expression and TNF binding (10). The authors suggested that the pathogenesis of TRAPS in patients harboring only the R92Q variant is probably different from that of patients carrying other mutations. The R92Q allele may therefore cause milder disease, and may often be associated with an oligosymptomatic course (16, 35).

The low-penetrance TNFRSF1A variant seems to contribute to atypical inflammatory responses in TRAPS, including cardiac diseases (myocarditis and pericarditis) (17, 32-33, 36). In addition, we recently further confirmed the potential role of mutations in the *TNFRSF1A* gene in patients with recurrent idiopathic pericarditis (37).

The pediatric patient, on the other hand, presented with a severe clinical picture, although she carried a low-penetrance D12E mutation characterized by a T to G transition in exon 2 which substitutes an aspartic acid for a glutamic acid at position 12 (D12E; c.123T>G). The D12E mutation was initially supposed to determine a milder disease and also a shorter duration of fever attacks (3). The same mutation was subsequently described by Gattorno et al. in a patient who was also carrying a homozygous M680I mutation on the *MEFV* gene, responsible for familial Mediterranean fever (FMF); that patient was classified as having FMF (31).

Although missense substitutions of cysteine or threonine residues are associated with a more aggressive disease course (10), patients with severe TRAPS caused by a non-cysteine mutation (T50M) in the *TNFRSF1A* gene have been reported (2, 9, 25). The functional implication of the D12E mutation is also currently under investigation in our laboratories.

All 7 of our patients had previously been treated with prednisone, and they required chronic administration of high doses in order to prevent flares and achieve good disease control. In addition, SAA circulating levels increased even during symptom-free intervals. For these reasons, treatment with etanercept was started.

Etanercept determined the resolution of fever and of other disease-related clinical manifestations and allowed the reduction of corticosteroid

administration, up to suspension in all cases. At 1-year follow-up, none of the patients showed any sign of disease relapse and, in addition, SAA levels checked at least three times were persistently within normal range. Apart from skin reactions at the site of the injections, which were observed in 2 out of 7 patients, no serious adverse events were observed.

CONCLUSIONS

To date, etanercept has been shown to be efficacious in treating TRAPS in most cases; its administration may prevent disease flares and/or permit reduction of corticosteroid administration. Anecdotal reports also describe its efficacy in the treatment of TRAPS-related reactive amyloidosis. Nevertheless, a decline in responsiveness may occur in some cases. Among the TNF-α neutralizing agents, infliximab and adalimumab may cause paradoxical inflammatory attacks, and caution is strongly advised when prescribing them to patients with TRAPS. In etanercept-resistant patients, IL-1 inhibition proved successful. Though promising, the results obtained with IL-1 antagonists are, to date, limited to very few cases and must undergo further evaluation in larger cohorts of patients. Our data, although obtained with patients carrying low-penetrance mutations (5/7) and presenting incomplete disease (4/7), confirm etanercept as a possible first-line treatment option in the treatment of TRAPS. Nonetheless, the definite role of etanercept in the management of TRAPS and its long-term benefit and potential adverse effects will be further assessed in large-scale trials.

REFERENCES

1. Masters SL, Lobito AA, Chae J, Kastner DL. Recent advances in the molecular pathogenesis of hereditary recurrent fevers. Curr Opin Allergy Clin Immunol 2006; 6:428-33.

2. Dodé C, André M, Bienvenu T, et al. French Hereditary Recurrent Inflammatory Disorder Study Group. The enlarging clinical, genetic, and population spectrum of tumor necrosis factor receptor-associated periodic syndrome. Arthritis Rheum 2002; 46:2181-8.

3. D'Osualdo A, Ferlito F, Prigione I, et al. Neutrophils

from patients with TNFRSF1A mutations display resistance to tumor necrosis factor-induced apoptosis: pathogenetic and clinical implications. Arthritis Rheum 2006; 54:998-1008.

4. McDermott MF, Aksentijevich I, Galon J, et al. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. Cell 1999; 97:133-44.

5. Hehlgans T, Pfeffer K. The intriguing biology of the tumour necrosis factor/tumour necrosis factor receptor superfamily: players, rules and the games. Immunology 2005; 115:1-20.

6. Banner DW, D'Arcy A, Janes W, et al. Crystal structure of the soluble human 55 kd TNF receptor-human TNF beta complex: implications for TNF receptor activation, Cell 1993; 73:431-45.

7. Chan FK, Chun HJ, Zheng L, Siegel RM, Bui KL, Lenardo MJ. A domain in TNF receptors that mediates ligand-independent receptor assembly and signaling. Science 2000; 288:2351-4.

8. Touitou I, Lesage S, McDermott M, et al. Infevers: An evolving mutation database for auto-inflammatory syndromes. Human Mutation 2004; 24:194-8.

9. Aksentijevich I, Galon J, Soares M, et al. The tumor-necrosis-factor receptor-associated periodic syndrome: new mutations in TNFRSF1A, ancestral origins, genotype-phenotype studies, and evidence for further genetic heterogeneity of periodic fevers. Am J Hum Genet 2001; 69:301-14.

10. Lobito AA, Kimberley FC, Muppidi JR, et al. Abnormal disulfide-linked oligomerization results in ER retention and altered signaling by TNFR1 mutants in TNFR1-associated periodic fever syndrome (TRAPS). Blood 2006; 108:1320-7.

11. Nedjai B, Hitman GA, Yousaf N, et al. Abnormal tumor necrosis factor receptor I cell surface expression and NF-kappaB activation in tumor necrosis factor receptor-associated periodic syndrome. Arthritis Rheum 2008; 58:273-83.

12. Nedjai B, Hitman GA, Quillinan N, et al. Proinflammatory action of the antiinflammatory drug infliximab in tumor necrosis factor receptor-associated periodic syndrome. Arthritis Rheum 2009; 60:619-25.

13. Kimberley FC, Lobito AA, Siegel RM, Screaton

GR. Falling into TRAPS-receptor misfolding in the TNF receptor 1-associated periodic fever syndrome. Arthritis Res Ther 2007; 9:217.

14. Nowlan ML, Drewe E, Bulsara H, et al. Systemic cytokine levels and the effects of etanercept in TNF receptor-associated periodic syndrome (TRAPS) involving a C33Y mutation in TNFRSF1A. Rheumatology (Oxford) 2006; 45:31-7.

15. Galon J, Aksentijevich I, McDermott MF, O'Shea JJ, Kastner DL. TNFRSF1A mutations and autoinflammatory syndromes. Curr Opin Immunol 2000; 12:479-86.

16. Hull KM, Drewe E, Aksentijevich I, et al. The TNF receptor-associated periodic syndrome (TRAPS). Emerging concepts of an autoinflammatory disorder. Medicine 2002; 81:349-68.

17. McDermott EM, Smillie DM, Powell RJ. Clinical spectrum of familial Hibernian fever: a 14-year follow-up study of the index case and extended family. Mayo Clin Proc 1997; 72:806-17.

18. Rigante D. Autoinflammatory syndromes behind the scenes of recurrent fevers in children. Med Sci Monit 2009; 15:RA179-87.

19. Nigrovic PA, Sundel RP. Treatment of TRAPS with etanercept: use in pediatrics. Clin Exp Rheumatol 2001; 19:484-5.

20. Arostegui JI, Solis P, Aldea A, et al. Etanercept plus colchicine treatment in a child with tumour necrosis factor receptor-associated periodic syndrome abolishes auto-inflammatory episodes without normalising the subclinical acute phase response. Eur J Pediatr 2005; 164:13-16.

21. Stojanov S, Dejaco C, Lohse P, et al. Clinical and functional characterisation of a novel TNFRSF1A c.605T>A/V173D cleavage site mutation associated with tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS), cardiovascular complications and excellent response to etanercept treatment. Ann Rheum Dis 2008; 67:1292-8.

22. Lamprecht P, Moosig F, Adam-Klages S, et al. Small vessel vasculitis and relapsing panniculitis in tumour necrosis factor receptor associated periodic syndrome (TRAPS). Ann Rheum Dis 2004; 63: 1518-20.

23. Drewe E, McDermott EM, Powell PT, Isaacs JD, Powell RJ. Prospective study of anti-tumour necrosis

factor receptor superfamily 1B fusion protein, and case study of anti-tumour necrosis factor receptor superfamily 1A fusion protein, in tumour necrosis factor receptor associated periodic syndrome (TRAPS): clinical and laboratory findings in a series of seven patients Rheumatology (Oxford) 2003; 42: 235-9.

24. Drewe E, Huggins ML, Morgan AG, Cassidy MJ, Powell RJ. Treatment of renal amyloidosis with etanercept in tumour necrosis factor receptor-associated periodic syndrome. Rheumatology (Oxford) 2004; 43:1405-8.

25. Kallinich T, Briese S, Roesler J, et al. Two familial cases with tumor necrosis factor receptor associated periodic syndrome caused, by a non-cysteine mutation (T50M) in the TNFRSF1A gene associated with severe multiorganic amyloidosis. J Rheumatol 2004; 31:2519-22.

26. Drewe E, Powell RJ, McDermott EM. Comment on: Failure of anti-TNF therapy in TNF Receptor 1-Associated Periodic Syndrome (TRAPS). Rheumatology (Oxford) 2007; 46:1865-6.

27. Scallon B, Cai A, Solowski N, et al. Binding and functional comparison of two types of tumor necrosis factor antagonists. J Pharmacol Exp Ther 2002; 301: 418-26.

28. Aganna E, Hammond L, Hawkins PN, et al. Heterogeneity among patients with tumor necrosis factor receptor-associated periodic syndrome phenotypes. Arthritis Rheum 2003; 48:2632-44.

29. Jesus AA, Oliveira JB, Aksentijevich I, et al. TNF receptor-associated periodic syndrome (TRAPS): description of a novel TNFRSF1A mutation and response to etanercept. Eur J Pediatr 2008; 167:1421-5.

30. Simon A, Bodar EJ, van der Hilst JCH, et al. Beneficial response to interleukin 1 receptor antagonist in TRAPS. Am J Med 2004; 117:208-10.

31. Gattorno M, Pelagatti MA, Meini A, et al. Persistent efficacy of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome. Arthritis Rheum 2008; 58: 1516-20.

32. Cantarini L, Lucherini OM, Cimaz R, et al. Idiopathic recurrent pericarditis refractory to colchicine treatment can reveal tumor necrosis factor receptor-associated periodic syndrome. Int J Immunol Pharmacol 2009; 22:1051-8.

33. Cantarini L, Lucherini OM, Cimaz R, Baldari CT, Laghi Pasini F, Galeazzi M. Sacroileitis and pericarditis: atypical presentation of tumor necrosis factor receptor-associated periodic syndrome and response to etanercept therapy. Clin Exp Rheumatol 2010; 28:290-91

34. Cantarini L, Lucherini OM, Galeazzi M, et al. Tumour necrosis factor receptor-associated periodic syndrome caused by a rare mutation in the TNFRSF1A gene, and with excellent response to etanercept treatment. Clin Exp Rheumatol 2009; 27: 890-1.

35. Gattorno M, Sormani MP, D'Osualdo A, et al. A diagnostic score for molecular analysis of hereditary autoinflammatory syndromes with periodic fever in children. Arthritis Rheum 2008; 58:1823-32.

36. Ravet N, Rouaghe S, Dodé C, et al. Clinical significance of P46L and R92Q substitutions in the tumour necrosis factor superfamily 1A gene. Ann Rheum Dis 2006; 65:1158-62.

37. Trost S, Rosé CD. Myocarditis and sacroiliitis: 2 previously unrecognized manifestations of tumor necrosis factor receptor associated periodic syndrome. J Rheumatol 2005; 32:175-7.

38. Cantarini L, Lucherini OM, Baldari CT, Laghi Pasini F, Galeazzi M. Familial clustering of recurrent pericarditis may disclose tumor necrosis factor receptor-associated periodic syndrome. Clin Exp Rheumatol 2010; 28:405-7.