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CASE BASED REVIEW

# Etanercept as a successful therapy in autoinflammatory syndrome related to *TRNT1* mutations: a case-based review

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## Abstract

Mutations in the gene encoding tRNA nucleotidyltransferase 1 (*TRNT1*) are associated with heterogeneous phenotypes and multisystem involvement of variable severity and progression. Immunodeficiency and inflammation are recurrent-associated features. The use of cytokine inhibitors in suppressing the inflammatory phenotype has been recently reported, with a 3-year follow-up for patients treated with Etanercept. We report on two unrelated patients sharing the same clinical condition, who had been referred to our Pediatric Rheumatology Unit because of recurrent fever associated with cutaneous lesions and increased levels of inflammatory markers since their first months of life. Whole exome sequencing allowed to identify compound heterozygosity for functionally relevant variants in *TRNT1* as the only molecular event shared by the two patients. Both patients have been treated with Etanercept during 11 years, documenting normalization of inflammatory indexes and resolution of recurrent fever and associated symptoms. This is the longest follow-up assessment of Etanercept treatment in patients with *TRNT1* mutations. Our findings confirm efficacy and safety of the treatment.

**Key Points**
- *Mutations in TRNT1 have been associated with phenotypic heterogeneity.*
- *We report on two patients with early-onset autoinflammatory syndrome.*
- *Whole exome sequencing led to reveal compound heterozygosity for two variants in TRNT1 in both patients.*
- *The patients were successfully treated with Etanercept for more than 10 years, the longest follow-up described in literature.*

**Keywords** Autoinflammatory syndrome · Etanercept · SIFD · TNF inhibitors · TRNT1

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## Introduction

*TRNT1* is a nuclear gene encoding the ubiquitous CCA-adding tRNA nucleotidyl transferase, an enzyme that is necessary for aminoacylation of both mitochondrial and cytosolic tRNAs, a fundamental prerequisite for mature tRNAs to become aminoacylated and to participate in protein biosynthesis [1, 2]. Mutations in *TRNT1* have been associated with different disorders of variable severity and progression, such as congenital sideroblastic anaemia with immunodeficiency, fevers, and developmental delay (SIFD), retinitis pigmentosa and foetal hydrops [3–6]. Moreover, presence of recurrent fever associated with elevation of inflammatory indexes, without evidence of infections, led to consider *TRNT1* mutation-related disease an autoinflammatory syndrome [7].

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Phenotypic heterogeneity results in treatment heterogeneity. In patients with prevalence of haematological and immunological alterations, treatment is supportive in the first instance, based on blood transfusions and immunoglobulin replacement therapy. Weditilake et al. [8] reported median age of death of 37.5 months (range 10 months–14 years). In this study, we report on two unrelated patients, actually 22 and 13 years old, with superimposed clinical phenotype sharing compound heterozygosity for functionally relevant variants in *TRNT1*, who have been treated with Etanercept for more than one decade, confirming the long-term efficacy and safety of this treatment.

## Case report

**Patient 1** (**P1**) is a 22-year-old female (Figs. 1 and 2). She was born to non-consanguineous parents of Italian descent, following an uneventful pregnancy, with a weight of 3.0 kg at 38 weeks of gestation. At 3 weeks of age, she presented febrile illness associated with painful edema of upper and lower extremities. No infective cause was found, and she recovered from this episode with symptomatic treatment. However, over the following months, she had recurrent fever accompanied by swelling of the hands, diffused painful non-itching wheals followed by desquamation, elevated inflammatory markers and anaemia. The symptoms were moderately controlled by corticosteroid therapy. One of these episodes was characterized by severe anaemia (Hb 6.6 g/dl), requiring blood transfusion. At the age of 8 months, she was found to have mild hypogammaglobulinemia confirmed by further examinations (IgA 13 mg/dl, IgG 192 mg/dl, IgM 40.2 mg/dl), but no other alterations were noted. She showed normalization of the immunoglobulin levels at the age of 22 months. Physical examination documented occurrence of facial dysmorphisms, brittle hair, developmental delay, microcephaly and splenomegaly, confirmed by abdomen ultrasound. During the following years, recurrent fever, every 2 weeks, persisted, associated with vomit, diarrhoea, metabolic acidosis and dyselectrolytemia from the age of 5 years. At the age of 8 years, she was diagnosed with bilateral sensorineural deafness. At the age of 10, she was diagnosticated with posterior subcapsular cataract, probably related to chronic steroid treatment.

During a pre-operatory cardiological assessment, the patient showed severe left ventricular hypertrophy on ECG and

**Fig. 1** Patient 1 at the age of 22 years old. Hypostenic build with marked hypotrophic muscle

**Fig. 2** . Facial dysmorphism of patient 1 presenting with microcephaly, brittle hair, sunken eyes and protruding backed nose

echocardiographic features of left ventricular noncompaction (LVNC), characterized by an enlarged, poorly contracting left ventricle (EF= 30%), with deep recesses and multiple chordae involving the midportion of the infero- and antero-lateral wall and the whole apex. Nt-pro-BNP was elevated (1415 pg/dl). She was started on ACE inhibitors, β-blockers, digitalis, diuretics and acetylsalicylic acid (ASA). The clinical features led to the suspect of an autoinflammatory disease. Molecular analysis of *MVK*, *TNFRSF1A*, *MEFV* and *CIAS1* was performed resulting negative, but due to the suggestive history, she was started on Anakinra. After 6 months of combined cardiological and biological therapy, a significant improvement had been evidenced at echocardiography but the elevation of inflammatory index, mild microcytic anaemia and typical symptoms persisted. Therefore, at 11 years of age, the treatment was shifted from Anakinra to Etanercept with good response. LVNC was no more detected. Isolated growth hormone deficiency (GHD) was diagnosticated at the age of 3 years and was treated with recombinant human GH (rhGH) for the next 5 years, without improvement. Considering the prolonged absence of the autoinflammatory episodes during therapy with Etanercept, stimulation tests for GH secretion and brain MRI were performed, confirming diagnosis of GHD and anterior pituitary hypoplasia. Treatment with rhGH was restarted at the age of 14 with partial improvement. At the age of nineteen, menarche was induced.

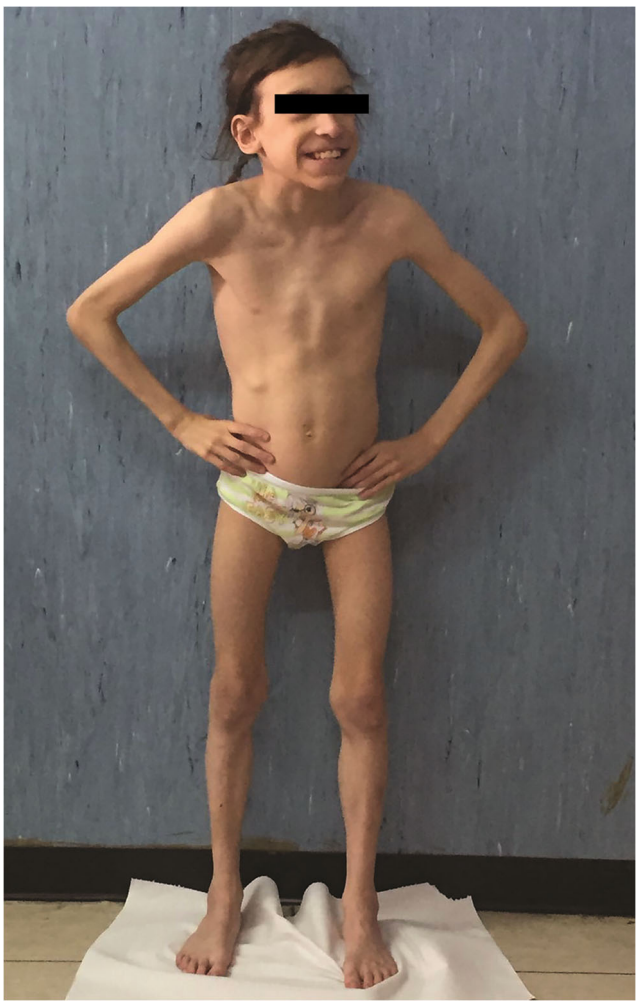

**Fig. 3** Patient 2 at the age of 13 years old. Hypostenic build with marked hypotrophic muscle mass and mild pectus excavatum

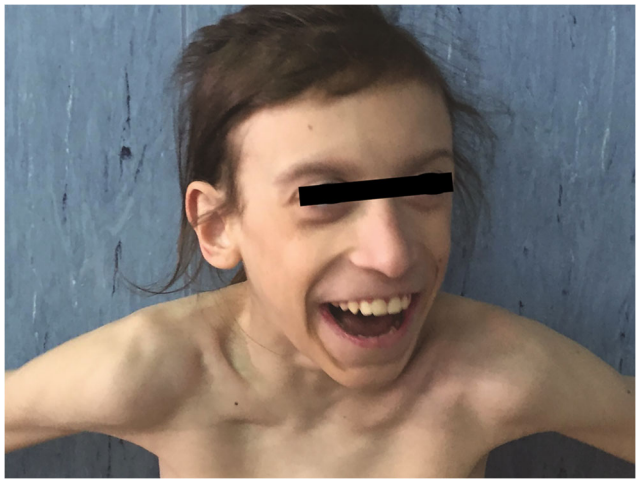

**Fig. 4** Facial dysmorphism of patient 2 presenting with microcephaly, brittle sparse hair, protruding backed nose, relatively slender limbs

**Patient 2** (**P2**) is 13-year-old female (Figs. 3 and 4). She was born to non-consanguineous parents of Italian descent, following a routine pregnancy, with a weight of 2.380 kg at 37 weeks of gestation. Since the fourth month of life, she was affected by recurrent fever lasting 2–3 days, every 3 weeks, treated with antibiotics even if no infection was detected. Inflammatory markers resulted elevated during the episodes. From the age of 11 months of life, occurrence of subcutaneous nodules, painless, not attached to surrounding, located on the extensor surface of joint, particularly the knees. She was referred to our Department at 13 months; the clinical examination evidenced failure to thrive, neurodevelopmental delay, facial dysmorphisms, brittle hair, microcephaly, hepatosplenomegaly and arthritis of the right ankle. Laboratory assessment showed no detectable IgA with other isotypes in the range of age (IgM 31.2 mg/dl, IgG 272 mg/dl). No switched memory lymphocytes were detected, without story of documented recurrent infections. She got three doses of pneumococcal conjugate vaccine at 12 months of age without antibody response. Brain MRI was performed resulting normal by age. At the age of 18 months, she was diagnosticated with bilateral sensorineural hearing loss and, after 10 months, bilateral cataract was documented. At the age of 5 years, she started therapy with rhGH for GHD. Suspecting autoinflammatory syndrome, molecular analysis of *MVK*, *TNFRSF1A*, *MEFV* and *CIAS1* was performed resulting negative. Array - Comparative Genomic Hybridization and karyotype study was uninformative. Due to the persistence of recurrent fever associated with cutaneous lesions, arthritis of

right ankle, assuming undefined inflammatory syndrome, Anakinra was started with partial response. Therefore, due to the similar clinical features to P1, negativity of performed genetic analysis, not significant improvement of the symptoms and persistence of inflammatory indexes, therapy was shifted to Etanercept after 4 months with resolution of symptoms and normalization of acute phase reactants.

## Molecular analyses

Based on the superimposed clinical presentation, the two subjects were considered to have the same unclassified condition. Genomic DNA of the both subjects was extracted from circulating leukocytes and whole exome sequencing (WES) analysis was performed by using Nimblegen SeqCap EZ v3 as enrichment kit. WES raw data were processed and analysed using an in-house implemented pipeline previously described [9–11], which is based on the GATK Best Practices [12]. WES statistics and data output are reported in Suppl. Table 1. Among the high-quality variants predicted to have functional impact on protein transcript or protein function, compound heterozygosity for two variants in *TRNT1* emerged as the only event shared by the two patients (P1: c.608G>A, p.Arg203Lys, and c.1246A>G, p.Lys416Glu; P2: c.938delT, p.Leu313fs, and c.1246A>G, p.Lys416Glu). In both patients, each variant had been inherited from their unaffected heterozygous parents. Of note, c.1246A>G, which had previously reported as a pathogenic variant (Table 1), was shared by the two patients. Similarly, the c.608G>A had been identified as disease-causing (Table 1), further confirming the clinical relevance of the WES findings.

## Discussion

*TRNT1* is a nuclear gene encoding a protein belonging to the tRNA nucleotidyltransferase/poly(A) polymerase family. The enzyme plays a role in the essential post-transcriptional modification of tRNAs, specifically adding the cytosine/cytosine/adenine (CCA) trinucleotide to the 3′end of newly synthesized tRNAs, a necessary modification for amino acid attachment, proper tRNA positioning at the ribosome and translation. In addition, TRNT1 is involved in surveillance of tRNA quality by selectively marking structurally unstable tRNAs for degradation [1, 23]. It has been recently hypothesised that hypomorphic TRNT1 mutations will negatively affect the expression of both mature cytosolic and mitochondrial tRNAs, leading to accumulation of reactive oxygen species in damaged mitochondria—known trigger of inflammatory response—and dysregulation in protein homeostasis. Under stress conditions, TRNT1-deficient cells fail to upregulate protein clearance pathways and perturbations in proteostasis activation of the innate immune system resulting in overproduction of interleukin-1 (IL-1) and tumour necrosis factor (TNF) [3]. Due to the key role in cellular processes and its ubiquitous expression, complete loss of TRNT1 function is embryonically lethal. Barton et al. described the only case of foetal hydrops, the index case of two siblings [4]. Homozygotic, heterozygotic and compound heterozygotic mutations, available up to now, are listed in Table 1. In 2014, biallelic loss-of-function variants in the *TRNT1* gene were reported in association with a syndromic condition characterized by sideroblastic anaemia with immunodeficiency, periodic fevers and developmental delay (SIFD), an autosomal recessive disorder with severe multi-organ disease often resulting in death within the first decade of life [5]. Although developmental delay, recurrent fever and immunodeficiency are reported in most patients in literature, sideroblastic anaemia is described in less than half of patients (47%), confirming heterogeneous presentations of the disease. Moreover, urinary tract infections, sinusitis, rhinitis, otitis and bronchitis are widely described in patients with immunodeficiency, but recurrent fever in absence of any documented infections has also been reported in more than half of patients, suggesting superimposed immunodeficiency and autoinflammatory phenotype, as in our patients. Mucocutaneous and musculoskeletal manifestations occurred frequently, typically in association with fever, including oral ulcers, cellulitis, panniculitis, subcutaneous nodules, recurrent swelling of hands and feet, dactylitis, arthralgia and arthritis. Both described patients presented musculoskeletal and skin involvement with different manifestations. Table 2 reports clinical manifestations in *TRNT1* mutations by frequency. Laboratory alterations mainly involve haematological, immunological and inflammatory parameters. Even though sideroblastic anaemia was firstly described [5], microcytic anaemia without evidence of sideroblasts has been reported in 30% of patients. Elevation of inflammatory indexes is reported in 49% of patients. Hypogammaglobulinemia is mostly reported (67%) with lymphocyte subsets ranging from absent B-cells to normal B-cells. B lymphocyte immunodeficiency has been reported in 57% of patients: some patients showed initially low B-cells which normalized, in other patients B-cell numbers fluctuated, dropping to nadir levels during inflammatory crises but partially recovering between attacks [8, 24]. The reason for the selective decrease in B cells in SIFD is not entirely clear, but recent studies suggest that TRNT1 deficiency may promote increased endoplasmic reticulum stress in lymphocytes and induce selective apoptosis [14]. Other reported laboratory findings are as follows: elevated hepatic transaminases, elevated muscle enzyme, metabolic acidosis, electrolyte imbalance as episodic hyponatraemia, hypokalaemia, hypocalcaemia, hypomagnesaemia and hypophosphatemia. [7]

Reported treatment relies on supportive and symptomatic therapy in the first instance, as hemodynamic support, blood transfusions and antibiotics. Steroids have been used as acute

**Table 1** Reported pathogenetic variants in *TRNT1*

| References | Patient | Allele 1 | | Allele 2 | |
|---|---|---|---|---|---|
| [5] | 1 | c.569G>T | p.R190I | c.569G>T | p.R190I |
| | 2 | c.569G>T | p.R190I | c.569G>T | p.R190I |
| | 3 | c.668T>C | p.I223T | c.1057-7C>G | p.? |
| | 4 | c.668T>C | p.I223T | c.1057-7C>G | p.? |
| | 5 | c.668T>C | p.I223T | No mutation/deletion detected. | |
| | 6 | c.218_219ins22 | NA | c.668T>C | p.I223T |
| | 7 | c.668T>C | p.I223T | c.668T>C | p.I223T |
| | 8 | c.497T>C | p.L166S | c.461C>T | p.T154I |
| | 9 | c.569G>T | p.R190I | c.569G>T | p.R190I |
| | 10 | c.668T>C | p.I223T | c.1057-7C>G | p.? |
| | 11 | c.977T>C | p.I326T | c.472A>G | p.M158V |
| | 12 | c.608+1 G>T | p.? | c.461C>T | p.T154I |
| | 13 | c.1246A>G | p.K416E | c. del1054_1056+10 | p.? |
| | 14 | c.1246A>G | p.K416E | c. del1054_1056+10 | p.? |
| | 15 | c.668T>C | p.I223T | c.1142insATGT | p.W381fs |
| | 16 | c.668T>C | p.I223T | c.1252_1253insA | p.S418fs |
| [13] | 17 | c.295C>T | p.R99W | c.295C>T | p.R99W |
| [14] | 18 | c.295C>T | p.R99W | c.1234C>T | p.R412* |
| [3] | 19 | c.644A>G | p.H215R | c.644A>G | p.H215R |
| | 20 | c.644A>G | p.H215R | c.644A>G | p.H215R |
| | 21 | c.488A>T | p.D163V | c.668T>C | p.I223T |
| | 22 | c.295C>T | p.R99W | c.488A>T | p.D163V |
| | 23 | c.295C>T | p.R99W | c.488A>T | p.D163V |
| | 24 | c.295C>T | p.T110I | c.383A>G | p.D128G |
| | 25 | c.295C>T | p.T110I | c.383A>G | p.D128G |
| | 26 | c.1246A>G | p.K416E | c.1245_1246insA | p.S418Kfs |
| | 27 | c.668T>C | p.I223T | c.1245_1246insA | p.S418Kfs |
| [4] | 28 | c.608+1 G>T | p.? | c.668T>C | p.I223T |
| | 29 | c.608+1 G>T | p.? | c.668T>C | p.I223T |
| [8] | 30 | c.668T>C | p.I223T | c.342+5G>T | p.? |
| | 31 | c.668T>C | p.I223T | c.342+5G>T | p.? |
| [15] | 32 | c.218_219ins22 | p.I223T | c.218_219ins22 | p.I223T |
| | 33 | c.977T>C | p.1326T | c.977T>C | p.1326T |
| [16] | 34 | NA | | | |
| [17] | 35 | c.565T>C | p.I155T | c.608G>A | p.R203K |
| [18] | 36 | c.1213G > A | p.G405R | c.1057–7C>G | p.? |
| [19] | 37 | c.295C>T | p.R99W | c.295C>T | p.R99W |
| | 38 | c.295C>T | p.R99W | c.295C>T | p.R99W |
| | 39 | c.295C>T | p.R99W | c.295C>T | p.R99W |
| [1] | 40 | c.443C>T | p.A148V | c.443C>T | p.A148V |
| | 41 | c.383A>G | p.D128G | c.518A>T | p.Y173F |
| [6] | 42 | c.1246° | p.S418fs | c.126_128delAGA | p.E43del |
| | 43 | c.1246° | p.S418fs | c.609-26T > C | p.? |
| | 44 | c.1246° | p.S418fs | c.609-26T > C | p.? |
| [20] | 45 | c.977T>C | p.I326T | c.977T>C | p.I326T |
| [21] | 46 | c.525delT | p.L176* | c.938T>C | p.L313S |
| [22] | 47 | c.498_501delATTT | p.F167fs | c.947C>T | p.A316V |
| This study | P1 | c.938delT | p.L313fs | c.1246A>G | p.K416E |
| | P2 | c.608G>A | p.R203K | c.1246A>G | p.K416E |

NA, not available

**Table 2** Clinical manifestations in patients with biallelic inactivating *TRNT1* mutations

| Manifestations (percentage of 49 patients) | |
|---|---|
| Neurological | • Developmental delay (65%) |
| | • Sensorineural deafness (31%) |
| | • Hypotonia (31%) |
| | • Seizures (24%) |
| | • Neuroimaging abnormalities (22%) |
| Systemic | • Recurrent fever (61%) |
| | • Failure to thrive (22%) |
| | • Short stature (12%) |
| | • Hypogonadism (8%) |
| Gastrointestinal | • Vomiting and diarrhoea (59%) |
| | • Splenomegaly (31%) |
| | • Hepatomegaly (18%) |
| | • Pancreatic insufficiency (8%) |
| Ocular | • Retinitis pigmentosa (26%) |
| | • Cataract (18%) |
| Integumentary | • Skin involvement (24%) |
| | • Brittle hair (16%) |
| | • Albinism (2%) |
| Musculoskeletal | • Recurrent swelling (12%) |
| | • Arthritis (8%) |
| | • Myositis (4%) |
| Miscellaneous | • Facial dysmorphism (16%) |
| | • Cardiomyopathy (12%) |
| | • Nephrocalcinosis (6%) |
| | • Renal tubulopathy (4%) |
| | • Minor malformations (4%) |

treatment of recurrent fever with response. However, steroids could not be considered for prolonged treatment due to their adverse effect in pediatric age. Immunoglobulin replacement therapy has been used largely in patients with immunodeficiency, showing good response to reduce bacterial sinopulmonary and urinary infections but minimal influence on the recurrent fever. Allogeneic bone marrow transplantation is generally considered curative intervention, aiming to restore normal immune function and erythropoiesis [1]. So far, 3 patients received bone marrow transplantation (BMT). One patient underwent matched sibling BMT at 5 months and died after 38 weeks with significant neurological complications [4]. One patient underwent myeloablative allogeneic BMT at 9 months of age with resolution of fever, normal growth and development, remaining well more than 3 years posttransplant except for a pigmentary retinitis 32 months posttransplant [24]. The last one remains systemically well 3 years post-BMT, resolved fevers, improved his growth and made some developmental progress, but continues to have moderate hearing loss and retinopathy [8]. More long-term data are needed to understand the complete efficacy of BMT whether completed early in the disease course. Colchicine has been used in four patients with prevalent autoinflammatory phenotype with partial response [3, 14, 16]. Reviewing literature, four patients have been treated with Anakinra [3, 16, 23]. One showed decrease of the recurrent fever episodes, but the treatment has been suspended as side effects presented, while the other three discontinued due to lack of effect on fever episodes. The two patients described in this study received Anakinra with partial response. Giannelou and colleagues [3] firstly reported the response to TNF inhibitors: in that study, four patients have been treating for 3 years with Etanercept, one of them switched to Infliximab and azathioprine due to development of inflammatory colitis. After 12 years on Infliximab, immunohistochemical staining of colon tissue biopsies of the patient showed resolution of inflammatory infiltrates, primarily of neutrophils and macrophages, and reduction in staining for TNF and IL-1. In the other patients, Etanercept showed efficacy in suppressing fevers, normalizing inflammatory biomarkers, decreasing frequency of blood transfusion [3].

Analysis of gene expression profile in whole blood samples of one patient treated with Etanercept identified genes that were differentially expressed before and after treatment. They include pathways that are known to be regulated by TNF, such as leucocyte adhesion and trafficking, and endothelium activation.

Our patients started biological therapy before molecular diagnosis due to the suggestive clinical features of autoinflammatory disease and they shifted to Etanercept, after failed treatment with Anakinra, at the age of 11 and 2 years. During the follow-up, the patients underwent 6-month multidisciplinary assessment. The negativity of inflammatory indexes, improvement of anaemia, absence of recurrent fever and disappearance of musculoskeletal symptoms confirm the efficacy of the treatment. They have been treated with Etanercept for more than 10 years. They are now 22 and 12 years old respectively and still present developmental delay, bilateral sensorineural hearing loss and growth delay.

## Conclusions

The spectrum of conditions related to *TRNT1* mutations has significantly expanded in recent years. Early diagnosis of this condition would enable patients to promptly access to therapies. Symptomatic treatments, including red blood cells transfusions, immunoglobulin replacement therapy and steroids, are the most used; however, mortality is high. Etanercept has been recently described as effective treatment. We report the longest therapy with Etanercept in syndrome related to *TRNT1* mutations, with resolution of inflammatory episodes without adverse reactions. TNF inhibitors can lead to a significative response for those patients who can benefit early in life.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s10067-021-05653-3.

## Declarations

**Consent statement** Authorization for publication was given by parents or guardians.

**Disclosures** None.

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