Modified Regimen of Etanercept for Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) Like Illness

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Received: August 12, 2013;
Initial review: Septmber 11, 2013;
Accepted: October 28, 2013.

Background: TRAPS, an autosomal dominant autoinflammatory disorder occurs due to mutations of the TNFRSF1A gene. Mutation negative TRAPS (TRAPS like illness) is also known. Anti TNF molecules (etanercept) is the mainstay of therapy. **Case characteristics:** A 11-year-old boy with a 5 year clinical profile indicative of a TRAPS like illness and with negative mutation studies is described. He has been followed up for nearly 2 years after starting etanercept. **Outcome:** He had sustained response to etanercept which has subsequently been titrated (0.4 mg/kg subcutaneously every 23-24 days) to keep him symptom free. **Message:** Mutation negative cases of TRAPS can be diagnosed with a high index of suspicion. Treatment with etanercept is expensive but possibly intervals between doses could be titrated to reduce cost.

Keywords: *Autosomal dominant, Familial, Periodic fever.*

Tumor-necrosis-factor Receptor Associated Periodic fever Syndrome (TRAPS) is characterized by periodic fever, cutaneous rash, conjunctivitis, lymphadenopathy, abdominal pain, myalgia and arthralgia [1]. Several cases of TRAPS are caused by about 80 identified mutations in the gene encoding the tumour necrosis factor receptor super family1A (*TNFRSF1A*) on chromosome 12p13. A subset of patients with a clinical profile suggestive of TRAPS with no mutations in the TNFRSF1A gene has been described, thus suggesting that not all mutations are yet known or that alternative mechanisms might be involved in the pathogenesis [2].

CASE REPORT

A 11-year-old boy presented in June 2006 with a 2 year history of recurrent fevers with irregular periodicity, intermittent periumbilical abdominal pain and urticarial rash. ***Table* I** describes the chronology of events.

In February 2011, the clinical history was reviewed when the child presented again with fever. Considering the prolonged and suggestive clinical profile, a diagnosis of TRAPS was entertained, and mutation testing for TRAPS for the child and parents was requested. Mutations in exons 2,3,4, and 5 of TNFRSF1A gene tested negative. A clinical diagnosis of mutation negative TRAPS (TRAPS like illness) was made, and the child was started on etanercept at a dose of 0.4 mg/kg biweekly in November 2011. His response was dramatic with no fever episodes or illness for next since 1.5 years. He had a weight gain of 6 kg and a height gain of 10 cms. Owing to cost considerations, the etanercept dose has been titrated to reduce its frequency. He currently needs etanercept once every 23-24 days to remain symptom free. Two efforts of increasing the interval further led to breakthrough fever, fatigue and rash.

DISCUSSION

More than 200 cases of TRAPS have been described in international medical literature, with majority of the reports from South and Central Europe. TRAPS is the most common autosomal dominant auto-inflammatory disorder, homogenously distributed among different ethnic groups [3]. An extensive review of literature did not reveal any case reports on TRAPS from India. Age of onset has been reported to range from the first year of life to 53 years. The characteristic features include recurrent fevers of varying duration, abdominal pain, and recurrent cutaneous and synovial inflammation. Migratory myalgia, with overlying migratory erythematous rash, due to monocytic fasciitis, is a specific feature that distinguishes it from the other periodic fever syndromes. Abdominal pain due to serositis is seen in 92% patients, which may sometimes lead to unnecessary abdominal surgery [4]. Ocular symptoms include periorbital edema, conjunctivitis, uveitis and iritis. TRAPS in pediatric age group is most easily confused with systemic onset juvenile idiopathic arthritis, due to fever and migratory rash or inflammatory bowel disease due to the triad of fever, anemia and raised ESR.

Laboratory investigations during episodes typically show an acute phase response, neutrophilia, and thrombocytosis. In addition anemia of chronic disease may be seen. Some, patients have low levels of the soluble tumour necrosis factor (TNF) receptor levels, both during and in between episodes [4]. We were unable to perform this test.

TABLE I TIMELINE OF EVENTS IN OUR PATIENT

Date	*Clinical Features*	*Investigations*	*Actions /Course*
July 2005	Intermittent abdominal pain with short duration fevers every 2-3 months. Episodes of urticarial rash	None	Spontaneously subsiding
May – July 2006	Pain in soles and calf . Fever intensity and duration increased.	MRI – bilateral calf muscle edema, suggestive of myositis.	Naproxen for 3 weeks with positive response.
September – November 2006	Persistent fever, pain in calf muscles, arthralgia, abdominal symptoms generalized adenopathy, hepatomegaly	Elevated ESR and CRP, mild anemia Abdominal ultrasound: marginal splenomegaly, mesenteric lymphadenopathy. Colonoscopy: Normal. Autoantibodies negative. Liver biopsy: Normal. CT scan neck and chest: diffuse lymphadenopathy. Bone marrow and cervical lymph node biopsy: normal	Systemic onset juvenile idiopathic arthritis and inflammatory bowel disease considered and investigated for. Paracetamol and non-steroidal anti-inflammatory drugs. Prednisolone @ 1.25 mg/kg day with dramatic defervescence.
February 2007	Fever recurred while tapering steroids: associated with acute onset back pain.	X ray spine: compression of L1 vertebra	11 doses of weekly subcutaneous methotrexate added to oral prednisolone regimen. No response. Alendronate added for osteoporotic fracture.
November 2010	Acute onset of right sided flank pain with low grade fever for 3 days. An episode of episcleritis.	Leucocytosis. Sonography normal	Appendicectomy. Appendix histopathologically normal

The TNFRFS1A gene, located on short arm of chromosome 12, encodes a 55 kDa receptor for TNF, called TNFR1 [2]. Literature suggests that overall a genetic diagnosis can be made only in less than 35% patients fitting the clinical phenotype of an auto inflammatory syndrome [4]. Aganna, *et al*. reported no mutation in 8 out of 18 families, and in 172 out of 176 sporadic cases consistent with clinical diagnosis of TRAPS [5].

Treatment options in TRAPS include non-steroidal anti-inflammatory drugs, and intermittent corticosteroids, as the first line [6]. The identification of the mutation in TNFRSF1A gene led to the use of anti–TNF drugs, in particular etanercept for the treatment. Etanercept also acts as a steroid sparer and reduces the number of disease flares, symptoms and severity of an attack. A 6 month clinical trial with etanercept at a dose of 0.5 mg per kg twice weekly reported global clinical and biological improvement [7, 8]. Pediatric cases have also been treated efficiently with etanercept [7]. In our patient, we used a modified and individualized regimen of etarnercept after clinical titration, thus achieving disease free periods of about 23 days and reducing the cost of therapy significantly.

Acknowledgments: Dr Ivona Aksentijevich, Clinical Genetics Services, Inflammatory Disease Section, National Human Genome Research Institute, National Institute of Health for performing the genetic testing for TRAPS for our patient.
Contributors: AD: wrote the manuscript and reviewed the literature; RPK: worked up and followed the case.
Funding: None; *Competing interests*: None stated.

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