

## Successful Treatment with Infliximab of a Patient with Tumor Necrosis Factor-associated Periodic Syndrome (TRAPS) Who Failed to Respond to Etanercept

To the Editor:

Tumor necrosis factor (TNF)-associated periodic syndrome (TRAPS) is an autosomal dominant autoinflammatory disorder, previously known as Hibernian fever<sup>1</sup>, renamed TRAPS following the elucidation of *TNFRSF1A* as the susceptibility gene<sup>2,3</sup>, with mutations occurring generally on chromosome 12p13. The condition is autoinflammatory as there is no involvement of antigen-specific T cells, pathogens, or antibody production. TRAPS is characterized by recurrent febrile attacks of > 1 week duration, severe abdominal pain, myalgia, rash, conjunctivitis, headache, periorbital edema, and pleuritis<sup>4</sup>.

Treatment options for TRAPS have met with limited success. Nonsteroidal antiinflammatory drugs are beneficial in controlling fever, but not abdominal and musculoskeletal symptoms. Glucocorticoids, although effective for inflammatory symptoms, do not prevent future attacks and the use of escalating doses is limited by toxicity<sup>5</sup>. Anti-TNF agents have demonstrated variable efficacy<sup>5-14</sup>. We describe the case of a 48-year-old woman of Italian Catalanian descent with TRAPS who was treated successfully with infliximab.

At disease onset in 1994, our patient presented with fevers lasting 7–14 days with monthly periodicity, increasing to twice monthly 3 years later. With the attacks, she experienced recurrent migratory rashes that were tender, red, raised, papular, and nodular, and serpinginous and annular plaques over her body including face and trunk (Figures 1A and 1B). She had recurrent oral ulcers, sore throat, arthralgias, arthritis with knee effusions, myalgias, pleuritic-like chest pain, abdominal pain, eye redness and swelling, and debilitating fatigue. In 1998, attacks became almost continuous, with only 7 days of symptom-free relief per month. She could no longer function at her occupation as a photography laboratory receptionist.

Acute-phase reactants were only modestly elevated during attacks

(Figure 2). Antinuclear antibodies, rheumatoid factor, antineutrophil cytoplasmic antibodies, VDRL, angiotensin-converting enzyme, anti-DNA antibodies, and C3 and C4 were not diagnostic.

Between 1994 and 1999, therapeutic trials of colchicine, methotrexate, azathioprine, and cyclosporine A were unsuccessful. Daily oral steroids (20 mg prednisone) attenuated the manifestations, but the “attacks” persisted.

A report in 1999<sup>11</sup> prompted submission of our patient’s serum for analysis to the US National Institutes of Health (NIH), Arthritis and Musculoskeletal and Skin Diseases Branch. A molecular diagnosis of TRAPS was confirmed with an R92Q-type mutation identified on the 12p13 chromosome of the *TNFRSF1A* gene.

The patient was 1 of 15 symptomatic patients enrolled in an NIH-sponsored open-label pilot study to evaluate the safety and efficacy of etanercept in TRAPS (no. 00-AR-0112)<sup>14</sup>. After a 12-week observation period, she received etanercept 25 mg twice weekly for 12 weeks. She experienced reduction of fever, but still required moderate doses of prednisone to control other symptoms. Etanercept was increased to 25 mg 3 times weekly in the next phase, but her periodic attacks continued. Sixteen weeks into active treatment, she experienced chest pains and shortness of breath and withdrew from the study. In October 2000, she received infliximab at an induction regimen of 3 mg/kg at 0, 2, and 6 weeks, without significant response. Prednisone requirements averaged 25 mg/day. When infliximab was increased to 5 mg/kg every 6 weeks, attacks became mild and the prednisone dose could be lowered to 5 mg/day. Subsequent increases of infliximab to 7.5 mg/kg and then to 10 mg/kg every 4 weeks led to cessation of fever and associated symptoms, and permitted discontinuation of steroids (Figure 2).

Infliximab has dose-dependently normalized erythrocyte sedimentation rate and reduced glucocorticoid use by 90% from baseline. She now enjoys long attack-free periods (Figure 2). Infusions have been maintained on a monthly basis. Average doses of prednisone have not exceeded 5 mg/day for short intervals. Attempts at prolonging the infusion interval have been consistently associated with an increase in attack frequency and severity.

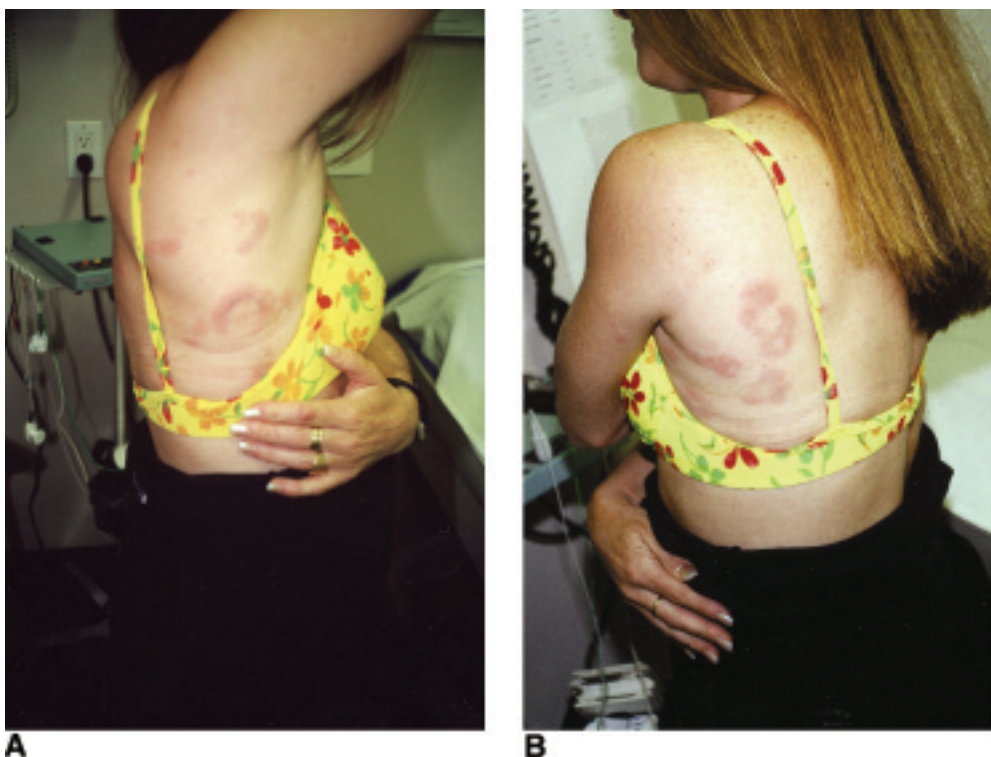


Figure 1. TRAPS-associated cutaneous lesions prior to treatment with infliximab (A, lateral view; B, posterior view).

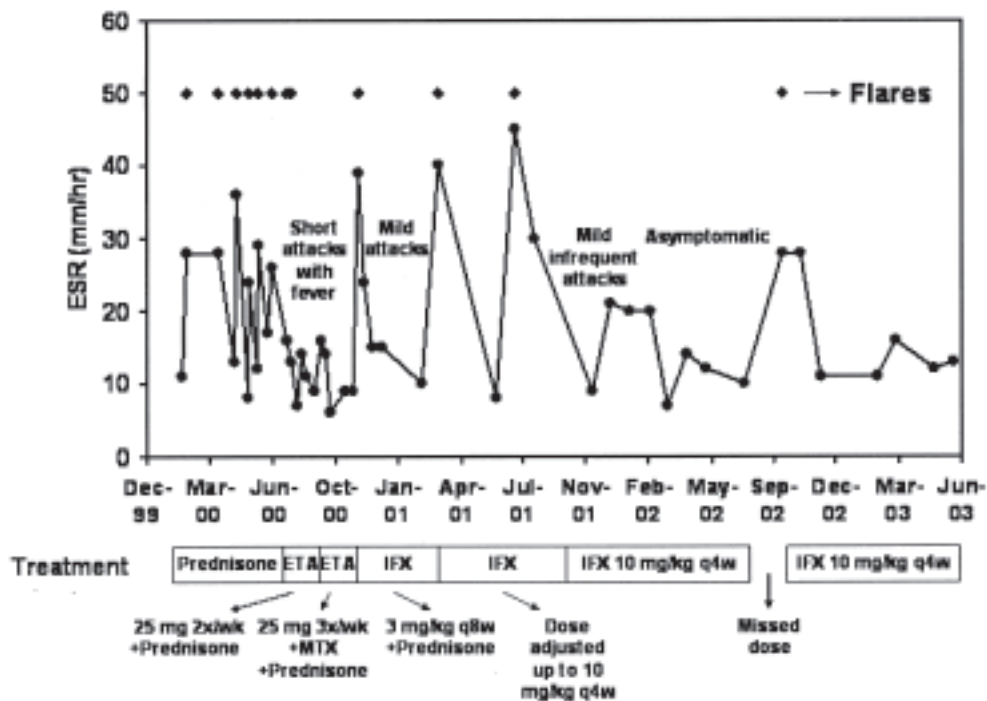


Figure 2. The patient's course: treatment response with clinical status and flares, and associated erythrocyte sedimentation rate (ESR) values. ETA: etanercept; IFX: infliximab; MTX: methotrexate.

She has experienced no adverse reactions related to infliximab, and no evidence of systemic amyloidosis. Acute-phase reactants have been maintained within normal limits. We are monitoring this patient closely to assess the long-term safety and efficacy of therapy. This is the first reported case of successful treatment of TRAPS with infliximab.

Several studies have suggested that R92Q is a low-penetrance mutation rather than a benign polymorphism<sup>15,16</sup> based on its increased frequency among patients with periodic fever versus controls (3.3% vs 1.04%, respectively;  $p = 0.02$ ) and results of functional receptor studies<sup>15</sup>. Serum samples from R92Q patients taken during and between febrile attacks revealed that levels of the soluble p55 TNFRSF1A did not increase during the attack, suggesting the presence of an *in vivo* functional abnormality<sup>15</sup>. Our patient may be one of the few symptomatic individuals bearing this low-penetrance mutation<sup>2,15,16</sup>. Recent evidence of increased frequency of R92Q in other inflammatory disorders such as early rheumatoid arthritis<sup>17</sup> and Behçet's disease<sup>18</sup> suggest R92Q may also be a nonspecific factor in other inflammatory diseases.

Mixed results were achieved in a series of uncontrolled clinical trials with etanercept involving 30 patients with TRAPS<sup>5-11</sup>. In several cases, the good initial response waned over time<sup>10</sup>. Both regression and emergence of new cases of amyloidosis are reported<sup>7,12</sup>. Four patients<sup>9,10,13</sup> treated with infliximab experienced a paradoxical acute flare within 12 hours of administration; 2 had previously received etanercept that had been discontinued due to a waning response. One of these had been involved in a 24-week clinical trial of TRAPS, in which 7 patients received etanercept 25 mg subcutaneously twice weekly<sup>5,10</sup>. After completing the study, the patient received a second 24-week treatment cycle, which was discontinued due to declining response. He experienced a flare similar to that with infliximab when subsequently treated with adalimumab<sup>13</sup>. The other 3 patients with flares associated with infliximab had been described in individual case reports<sup>9,13</sup>. Two patients responded favorably to anakinra after failing anti-TNF agents<sup>19,20</sup>, suggesting that interleukin 1 may play a role in the pathogenesis.

Binding of TNF to cell-surface receptors yields a conformational change that induces a cellular signal leading to shedding of the extracellu-

lar portion of the receptor from the cell surface. It then binds circulating TNF, attenuating the inflammatory response. McDermott and coworkers demonstrated that TRAPS patients have reduced levels of soluble TNFRSF1A relative to controls, and suggested that the mutation mediated its effect by impairing the shedding of TNFRSF1 and reducing the quantity of soluble receptor available to bind TNF- $\alpha$ <sup>21</sup>. Other underlying mechanisms may be active<sup>2</sup> including altered intracellular trafficking, impaired TNF binding<sup>22</sup>, and a defect in TNF-induced leukocyte apoptosis<sup>23</sup>. The efficacy of infliximab in controlling TRAPS could be explained in part by its capacity to form very stable complexes with both soluble TNF and membrane-bound TNF (tmTNF)<sup>24</sup>.

Infliximab can lyse TNF-producing cells by activation of complement<sup>23</sup>. The high avidity binding and capacity to crosslink tmTNF seen with infliximab could be a necessary condition to initiate the apoptotic cascade, which appears to be deficient in TRAPS and may be important for the induction of remission. In addition, the dimerization of tmTNF by infliximab could stimulate outside-in signal transduction, leading to apoptosis<sup>25</sup>.

Some investigators have suggested that whereas etanercept may have a beneficial but not sustainable effect in TRAPS, infliximab and possibly adalimumab may cause paradoxical inflammatory attacks<sup>9,10</sup>. Nedjai and coworkers<sup>26</sup> reported that peripheral blood mononuclear cells from a family of TRAPS patients carrying the T50M mutation failed to respond to infliximab through apoptotic induction of caspase 3 activity, as compared to controls. These findings may, however, be limited to the T50M variant and not apply to the R92Q type identified in our patient, and not reflect her positive clinical outcome.

Our patient's excellent response to infliximab could be attributed to the higher 10 mg/kg dose that may have been required to prevent the flares experienced by patients treated with 5 mg/kg. Higher-dose infliximab generated a favorable response in refractory childhood uveitis (10–20 mg/kg)<sup>27</sup> and in dermatomyositis and polymyositis (7–10 mg/kg)<sup>28</sup>.

Given the documented heterogeneity of TRAPS and specifically of the R92Q variant<sup>2</sup>, our patient's condition may be a distinct variant from that of patients who did not respond or who experienced flare while receiving infliximab.

Targeted therapies that block key cytokines have been remarkably effective in some patients with TRAPS. Work is required to identify patients that will benefit from available therapies and optimal dosing regimens. Elucidation of the underlying genetic and pathophysiologic mechanisms will guide development of treatment options for the multiple variants of this challenging condition.

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*This report is dedicated to the late Dr. Adele Fam. He inspired and encouraged a commitment to excellence from everyone who crossed his path.*

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