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Persistent Efficacy of Anakinra in Patients With Tumor Necrosis Factor Receptor–Associated Periodic Syndrome

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Objective. **To evaluate the efficacy and safety of treatment with the interleukin-1 receptor antagonist anakinra in patients with tumor necrosis factor receptor–associated periodic syndrome (TRAPS) requiring high cumulative doses of steroids.**

Methods. **Four children (mean age 9.1 years [range 4–13 years]) and 1 adult (age 33 years) with TRAPS were enrolled in the study. The 3 children with cysteine mutations (C52Y, C55Y, C43R) had prolonged and frequent attacks of fever. One child with the R92Q mutation and the adult patient with the C43R mutation displayed a more chronic disease course, with fluctuating, nearly continuous symptoms and persistent elevation of acute-phase reactant levels (including serum amyloid A [SAA]). All patients were treated with anakinra (1.5 mg/kg/day).**

Results. **All of the patients had a prompt response to anakinra, with disappearance of symptoms and normalization of acute-phase reactant levels, including SAA. In all pediatric patients, anakinra was withdrawn after 15 days of treatment. After a few days (mean 5.6 days [range 3–8]) a disease relapse occurred, which dramatically responded to reintroduction of anakinra. During the following period of observation (mean 11.4 months [range 4–20 months]), the patients did not experience episodes of fever or other disease-related clinical manifestations. Levels of acute-phase reactants remained in the normal range. No major adverse reactions or severe infections were observed.**

Conclusion. **Continuous treatment with anakinra effectively controlled both the clinical and laboratory manifestations in patients with TRAPS and prevented disease relapses.**

Tumor necrosis factor receptor–associated periodic syndrome (TRAPS), formerly known as familial Hibernian fever, is a dominantly inherited disorder caused by mutations in the gene for p55 TNF receptor type I (*TNFR1*), which is encoded by the TNF superfamily receptor 1A gene (*TNFRSF1A*) (1,2). The disease usually starts during childhood or adolescence and is characterized by recurrent attacks of fever associated with rashes, musculoskeletal and abdominal pain, and periorbital edema. The duration of the attacks is variable, ranging from a few days to several weeks. Some patients have a fluctuating and subchronic disease course, which is characterized by flares of abdominal pain, arthralgia/myalgia, and ocular manifestations, with or without fever, as well as by a persistent elevation of the levels of acute-phase reactants, including serum amyloid A (SAA). Renal AA amyloidosis represents the most serious long-term complication of TRAPS, with a prevalence ranging from 14% to 25% (3).

Episodes of fever are responsive to corticosteroids. However, escalating doses of steroids and repeated courses of treatment are sometimes needed, especially in patients with frequent relapses or nearly continuous symptoms. The use of immunosuppressive drugs has been reported to be ineffective at reducing the frequency and intensity of the episodes of inflammation and/or preventing the development of amyloidosis in TRAPS patients (3). The observation that the molecular defect of p55 TNFR is associated with impaired shed-

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Table 1. Clinical and laboratory features of the TRAPS patients at the time of enrollment*

Patient/ age/sex	Mutation	Disease duration, years	Disease course	Steroid requirement, mg of prednisone	Global VAS score, cm	CRP, mg/dl	SAA, mg/liter
1/9/M	C55Y	8	Recurrent	600†	7.5	17.5	927
2/13/F	C52Y	12.8	Recurrent	131†	6.15	12.8	508
3/4/F	C43R	3.6	Recurrent	230†	10	29.5	531
4/10/F	R92Q	2.4	Chronic	10 mg/day	5	7.2	542
5/33/M	C43R	32.6	Chronic	12.5 mg/day	9.3	5.64	716

* TRAPS = tumor necrosis factor receptor–associated periodic syndrome; VAS = visual analog scale (0–10 cm); CRP = C-reactive protein (normal <0.45 mg/dl); SAA = serum amyloid A (normal <6.8 mg/liter).
† Cumulative dose during the previous episode of fever.

ding of the receptor from the cell membrane led to the proposal that anti-TNF treatment should be used in this condition (2). Some initial anecdotal evidence supported the efficacy of etanercept in the prevention of disease flares (3,4) and in the treatment of long-term renal complications (5). However, it has subsequently been shown that anti-TNF therapy is ineffective in some patients, but in others, it is unable to completely control the inflammation (6,7).

An excellent short-term response to treatment with recombinant human interleukin-1 (IL-1) receptor antagonist (anakinra) in a patient with TRAPS has recently been reported (6), suggesting that IL-1 blockade may represent a possible alternative strategy, as has been observed in other monogenic autoinflammatory diseases (8). In the present study, we examined the efficacy and safety of anakinra treatment in 5 TRAPS patients with a severe disease course.

PATIENTS AND METHODS

The main clinical and laboratory features of the TRAPS patients at the time of enrollment are summarized in Table 1. A total of 5 patients (4 children and 1 adult) were studied. Patients 1–3 had a recurrent disease course, which was characterized by frequent and severe attacks that limited their normal daily activities, despite symptomatic treatment with steroids and nonsteroidal antiinflammatory drugs (NSAIDs). During the previous 6 months, these 3 patients experienced ≥3 episodes of fever. The mean duration of each episode was 32 days in patient 1, 12.6 days in patient 2, and 15 days in patient 3. Patients 4 and 5 had a chronic course, with fluctuating, nearly continuous symptoms and persistent elevation of the levels of acute-phase reactants, including SAA, despite continuing treatment with steroids. None of the patients had renal amyloidosis or proteinuria.

Based on our previous experience in treating patients with other autoinflammatory diseases, anakinra was administered subcutaneously at a dosage of 1.5 mg/kg/day (9). Patients were treated for 15 days, and then the treatment was withdrawn. In the event of a new disease flare, treatment was restarted. Disease activity at the time of enrollment and during the followup period was measured by evaluating the patient's/parents' global assessment of disease activity (using a 0–10-cm visual analog scale), the number and duration of episodes of fever, the type of associated symptoms, and the serum levels of C-reactive protein (CRP) and SAA. Laboratory evaluations were performed on days 0, 3, 7, and 15, at the time of disease relapse after treatment withdrawal, and monthly thereafter.

Patient 2 had been treated with etanercept when she was 10 years old. After an initially complete control of episodes of fever for 8 months, she experienced a gradual loss of efficacy of anti-TNF treatment, with a progressively increased frequency of attacks of fever. After 24 months of therapy, etanercept was withdrawn.

Treatment with anakinra was started after informed consent was obtained from the patients' parents and, when applicable, from the patients. The study was approved by the Ethical Board of Giannina Gaslini Institute.

RESULTS

Patients 1–3, who had a recurrent disease course, were treated 3–5 days after the beginning of a new episode of fever. After the first 2 days of treatment, all 5 of the study patients experienced a prompt response to anakinra, with disappearance of the fever and other clinical manifestations of TRAPS (Figure 1). A dramatic decrease in levels of acute-phase reactants was also observed, with normalization after 15 days of treatment (Figure 1). The 3 patients with a recurrent disease course did not receive steroids before or during anakinra treatment, whereas the 2 patients with a chronic disease course were maintained on stable dosages of prednisone (Table 1).

In all pediatric patients (patients 1–4), anakinra was withdrawn after 15 days of treatment. After a few days (mean 5.6 days [range 3–8 days)], they experienced a disease relapse. Reintroduction of anakinra resulted in a prompt and dramatic response (Figure 1). After this failed attempt to withdraw the anakinra, all of the

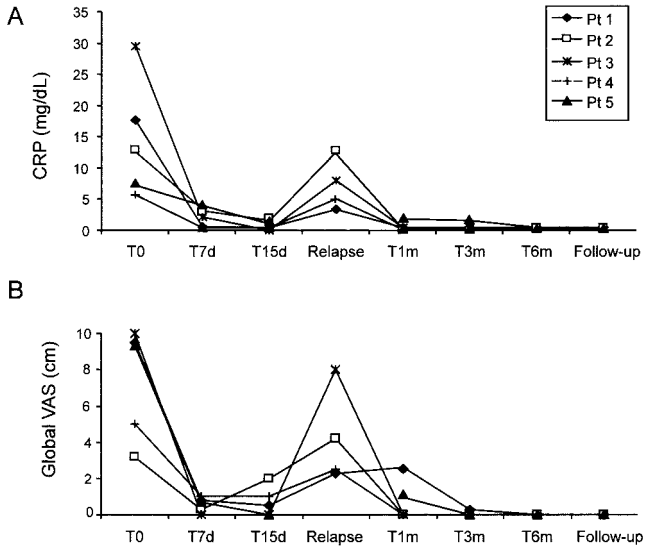

Figure 1. Response to anakinra in 4 pediatric patients and 1 adult patient with tumor necrosis factor receptor–associated periodic syndrome (TRAPS). Changes in **A,** the acute-phase reactant C-reactive protein (CRP) level and **B,** the patient's/parents' global assessment of disease activity, as determined with the use of a 10-cm visual analog scale (VAS), during the first days and months of anakinra treatment and at followup in the 5 TRAPS patients are shown. After 15 days of treatment, anakinra was withdrawn in the pediatric patients (patients 1–4). All 4 of these patients experienced a disease relapse during the following days, but showed a prompt response to reintroduction of anakinra (see Results for details). Followup assessment was performed at 20 months in patient 1, at 12 months in patients 2 and 5, at 9 months in patient 4, and at 4 months in patient 3.

patients were given continuous treatment according to the decision of the physician in charge and the willingness of the patients and their parents to continue therapy.

During the following period of observation (mean 11.4 months [range 4–20 months]), patients who had previously had recurrent disease flares experienced no episodes of fever or other disease-related clinical manifestations, and therefore no longer required steroid therapy. In addition, 1 of the 2 patients with a chronic disease course (patient 4) was able to discontinue steroid treatment. In patient 5, who also had allergic asthma, the prednisone dosage was progressively tapered and maintained at a dosage of 5 mg/day in order to control his respiratory symptoms. Levels of acute-phase reactants remained in the normal range. The mean SAA at followup was 3.4 mg/dl (range 2.1–6.2 [normal <6.8 mg/liter]).

Apart from variable skin reactions (pain, rash, itching) at the site of the injections, which were observed in all patients during the first weeks of treatment, no serious adverse events were observed.

DISCUSSION

Episodes of fever associated with TRAPS are usually characterized by a number of clinical manifestations (musculoskeletal and abdominal pain, rash, painful periorbital edema) that greatly affect the patients' daily activities. In most patients, the symptomatic use of NSAIDs and oral steroids is able to control the clinical manifestations (3). However, some patients have a high frequency of episodes of fever or develop a chronic, fluctuating disease course that causes severe limitations in normal social activities and requires prolonged therapy with steroids. These patients are at major risk of developing amyloidosis, the most severe long-term complication of TRAPS (10).

Among the 32 individuals with *TNFRSF1A* mutations diagnosed at our institution (11), only a few displayed a particularly aggressive disease course that required almost continuous treatment with steroids. These included the 5 patients in the present study who were treated with anakinra. All 5 of these patients showed a dramatic response to the drug. Moreover, continuous treatment with anakinra completely prevented disease relapses during the followup period (11.4 months [range 4–20 months]).

TRAPS is caused by mutations in the *TNFR1* gene. In their seminal article published in 1999, McDermott and coworkers (2) showed that circulating mononuclear cells from TRAPS patients displayed a defect in the shedding of p55 TNFR. In fact, after cell activation, the extracellular portion of both the p55 and the p75 isoforms of TNFRs may undergo metalloprotease-dependent cleavage from the cell membrane. This process produces a pool of soluble receptors that may scavenge circulating TNF by competing with membrane-bound receptors. This phenomenon represents an important strategy for regulating the effect of circulating free TNF during acute inflammation. It was therefore suggested that the defect in p55 TNFR shedding observed in TRAPS patients could lead to inappropriate TNF inhibition, and therefore uncontrolled inflammation (2). This raised the possibility that blocking the excessive circulating TNF could potentially be the primary therapeutic strategy for TRAPS.

The first reports on the efficacy of etanercept in TRAPS patients described an initially good response in terms of a reduction in the frequency and intensity of episodes (4). However, subsequent studies showed that

treatment with anti-TNF agents was often unable to totally eliminate the clinical and laboratory evidence of inflammation (10). Moreover, as observed in our patient with a C52Y mutation (patient 2), response to treatment may wane with time (6), and resistant cases have been reported (7). This raises the hypothesis that mechanisms other than a lack of TNF buffering due to defective *TNFR1* shedding could play a relevant role in the pathogenesis of the disease.

Indeed, mutations in the *TNFRSF1A* gene have been associated with a number of other cell dysfunctions. Circulating neutrophils and skin fibroblasts from TRAPS patients display a defect in TNF-induced apoptosis (11). Studies of cells transfected with the mutant form of the TNFRI protein have shown a number of relevant functional abnormalities, consisting of alterations in trafficking and signaling of the mutated TNFRI (12), with an accumulation of the protein in the endoplasmic reticulum (13). The intracellular consequences of these functional abnormalities are still matter for study. It is conceivable that they could lead from an imbalance in the cellular response to a more pronounced proinflammatory pathway (14).

The response to anakinra treatment in our TRAPS patients is similar to the response observed in patients with autoinflammatory conditions, such as chronic infantile neurologic, cutaneous, articular (CINCA) syndrome/neonatal-onset multisystem inflammatory disease (NOMID) or Muckle-Wells syndrome (9), due to cryopyrin mutations. Cryopyrin is a key protein of a multiprotein cytoplasmic complex called the inflammasome. In the presence of a number of stimuli, cryopyrin oligomerizes and binds to other intracellular proteins. This association directly activates IL-1–converting enzyme/caspase 1, which in turn, converts proIL-1β into the mature, active 17-kd form.

Recently, it was shown that treatment with anakinra can be effective in other autoinflammatory conditions, such as pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome and familial Mediterranean fever, in which the mutated proteins have been shown to be functionally related to the inflammasome (8), as well as in patients with systemic-onset juvenile idiopathic arthritis (15).

These observations, together with the marked response observed in our TRAPS patients, raise the possibility that a dysregulation of IL-1β production and secretion represents a possible final common pathway of different monogenic or multifactorial inflammatory disorders (8).

In conclusion, even if etanercept is still considered to be the first-line therapy for TRAPS, our study provides evidence of the short-term and long-term efficacy of IL-1 blockade. This suggests that anakinra could be a valid alternative therapy for patients who require prolonged treatment with steroids or who experience frequent and long-lasting episodes of fever that lead to severe limitations in their daily activities.

AUTHOR CONTRIBUTIONS

Dr. Gattorno had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Gattorno, Martini.

Acquisition of data. Gattorno, Pelagatti, Meini, Obici, Barcellona, Federici, Buoncompagni, Martini.

Analysis and interpretation of data. Gattorno, Plebani, Merlini, Martini.

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