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CASE BASED REVIEW - CASES WITH A MESSAGE

Canakinumab efficacy and long-term tocilizumab administration in tumor necrosis factor receptor-associated periodic syndrome (TRAPS)

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Abstract Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominantly inherited autoinflammatory disease caused by mutations in the *TNFRSF1A* gene. Treatment is aimed at preventing acute disease attacks, improving quality of life, and preventing long-term complications such as systemic reactive amyloidosis. Biologic agents have significantly improved TRAPS management. In particular, interleukin 1 (IL-1) inhibition either with the recombinant IL-1 receptor antagonist anakinra or with the human IgG1 anti-IL-1β monoclonal antibody canakinumab has recently shown to induce a prompt and stable disease remission. Conversely, the successful experience with IL-6 inhibition is nowadays limited to a single patient. Anyway, introduction of new treatment options for patients requiring a lifelong therapy is desirable. We describe two TRAPS patients (son and father) successfully treated with canakinumab and tocilizumab, respectively. In particular, we highlight the clinical and laboratory efficacy as well as the good safety profile of tocilizumab during a 42-month follow-up period.

Keywords Autoinflammatory disorders · Canakinumab · Follow-up · Therapy · Tocilizumab

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Introduction

Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) (OMIM 142680) is an autosomal dominantly inherited autoinflammatory disease caused by mutations in the *TNFRSF1A* gene, encoding the TNF receptor type, and characterized by recurrent episodes of fever typically lasting more than 1 week, myalgia, arthralgia, migrating erysipelas, and serositis [1–3].

TRAPS treatment is aimed at preventing acute disease attacks, improving quality of life, and preventing the development of systemic reactive amyloidosis, the most troublesome long-term TRAPS complication [4–6]. Notably, despite considerable success achieved in recent times, TRAPS treatment is more challenging than other monogenic autoinflammatory diseases probably due to the genetic heterogeneity and protean clinical phenotype [4]. A few patients gain some symptomatic relief from non-steroidal anti-inflammatory drugs (NSAIDs), while colchicine or immunomodulators produce little advantage. Patients may benefit from high-dose oral corticosteroids; however, some of them require a prolonged therapy because of a fluctuating or chronic disease course leading to steroid-related side effects [4]. Furthermore, steroids do not seem to provide complete protection from the risk of developing reactive amyloidosis [7].

Among biologic agents, the TNF-blocker etanercept initially yielded promising results [8–10]; however, the efficacy may decline over time [11, 12], and resistant patients have also been reported [13]. On the contrary, the chimeric anti-TNF monoclonal antibody infliximab and the fully human anti-TNF monoclonal antibody adalimumab can induce a paradoxical disease flare [12, 14]. More recently interleukin 1 (IL-1) inhibition either with the recombinant IL-1 receptor antagonist anakinra or with the human IgG1

anti-IL-1β monoclonal antibody canakinumab has shown to induce a prompt and stable disease remission [15–20]. Conversely, the experience with IL-6 inhibition is limited to a single patient resistant to etanercept and anakinra and successfully administered with the humanized anti-IL-6 receptor antibody tocilizumab [6].

We report herein on two TRAPS patients (son and father) successfully treated with canakinumab and tocilizumab, respectively, highlighting the first long-term follow-up of a TRAPS patient administered with tocilizumab.

Patients and methods

Case report

In July 2013, a four-year-old boy was referred to our department because of intermittent fever up to 40 °C; laterocervical lymphadenitis and arthromyalgia arose 10 days before. A full laboratory workup revealed increased C-reactive protein (CRP: 13 mg/dl), erythrocyte sedimentation rate (ESR: 120 mm/h), serum amyloid A (SAA: 130 mg/L), neutrophilic leukocytosis, anemia (hemoglobin: 9.1 g/dl), and high platelet count (650 × 10^3/mm^3). Clinical history was unremarkable, with the exception of a previous similar episode 1 year before. On that occasion, fever lasted 3 weeks and blood tests normalized in 2 months. Serological tests for infections were negative, and neoplasms and autoimmune disorders were ruled out. More precisely, a full immunologic screening with rheumatoid factor, anti-nuclear antibody, extractable nuclear antigen antibodies, and anti-neutrophil cytoplasmic antibodies was unremarkable. Electrocardiogram, chest X-ray, echocardiogram, abdominal ultrasound, arterial blood gas, and thyroid function tests were normal. The hematological workup microscopic examination of peripheral blood film showed no evidence of lymphoproliferative disorders, and immunophenotypic analysis was normal. Similarly, articular ultrasound excluded idiopathic arthritis and clinical criteria for Kawasaki disease [21] were not fulfilled. As the patient's father also reported similar clinical features since childhood, a genetic disorder was suspected. For this reason, the patient's DNA was analyzed for mutations on *MEFV*, *TNFRSF1A, NLRP3*, *NLRP12*, and *MVK* genes responsible for the most common hereditary periodic fevers, and a heterozygous C96R variant was found in *TNFRSF1A* gene. As a consequence, diagnosis of TRAPS was established, and high-dose prednisone administration was started inducing clinical remission. However, since a further disease flare occurred after steroid tapering, canakinumab 4 mg/kg every 4 weeks was started bringing about a sudden and complete clinical and laboratory response so as to allow prednisone discontinuation. Considering the dramatic good clinical results, at 3-month follow-up visit, canakinumab administration intervals were extended to 6 weeks; at last follow-up visit (after a 9-month lasting therapy), TRAPS disease manifestations were still controlled, SAA was normal (3.0 mg/L), and no side effects were recorded.

Noteworthy, the patient's father had complained from similar recurrent fever episodes since he was 4 years. In addition to fever, he also suffered from arthritis, skin rash, vomiting, diarrhea, and/or unilateral periorbital edema. For this reason, his DNA was analyzed for mutations in *TNFRSF1A*, and a heterozygous C96R mutation was found also in this case.

During the past years of active disease, the patient had been treated with anti-inflammatory drugs (indomethacin and ibuprofen) and disease-modifying antirheumatic drugs (gold salts, hydroxychlorochine, cyclosporine A and methotrexate) leading to a poor clinical response. On the contrary, he had obtained some benefit from long-course steroids administration (prednisone up to 50 mg/day).

In his long clinical history, the patient had been also diagnosed with systemic juvenile idiopathic arthritis (sJIA), leading to infliximab administration. Although a good clinical response had been reported, this therapy was stopped 18 months later because of a paradoxical inflammatory reaction soon after an infliximab administration, reminding similar experiences in TRAPS patients [14].

Based on the previous diagnosis of sJIA, in 2011 the patient had started tocilizumab infusions (8 mg/kg/month) thus showing a complete, rapid, and sustained remission of all symptoms as well as a normalization of all laboratory tests within the normal range in a short time. More precisely, ESR and CRP dropped from 102 to 3 mm/h and from 84.2 to 0.2 mg/L, respectively. As a consequence, steroid treatment had been quickly stopped.

Accordingly, the father presented with no clinical manifestations, and laboratory investigation showed normal ESR (2 mm/h), CRP (0.4 mg/L), and SAA (1.0 mg/L) during our evaluation. For these reasons, tocilizumab therapy was continued even after TRAPS diagnosis in 2013. Presently the disease is still controlled, and no side effects have occurred after 42 months of tocilizumab infusions.

Discussion

TRAPS phenotype is characterized by a significant clinical heterogeneity probably due to the broad spectrum of *TNFRSF1A* mutations [22]. In particular, high-penetrance mutations affecting the *TNFRSF1A* extracellular cysteine-rich N-terminal domains generally induce an early disease onset and more severe clinical manifestations [23]. On the contrary, low-penetrance mutations such as R92Q and

P46L are more frequently associated with an adult disease onset and a less pronounced and typical clinical phenotype [24–33].

TRAPS treatment is based on disease activity, and the main targets of therapy are to control symptoms, guarantee a good quality of life, and prevent long-term complications such as reactive amyloidosis [34]. Corticosteroids and NSAIDs "on demand" may be considered in patients with a mild disease course. Accordingly, data from the Eurofever project indicated that patients carrying the low-penetrance R92Q mutation seemed to respond better to NSAIDs and colchicine versus patients with other *TNFRSF1A* mutations [5]. On the contrary, more severe TRAPS phenotype requires a more resolute therapeutic approach with biologic agents [4, 5].

Although the C96R mutation has not yet been described, it is likely to be regarded as an high-penetrance mutation both because it affects an extracellular cysteine-rich N-terminal *TNFRSF1A* domain [23] and because this mutation has proven to be related to a severe clinical pattern in our two patients. For these reasons, basing on preliminary data from a phase-II trial conducted on 20 TRAPS patients [19], our child patient was administered with canakinumab 75 mg subcutaneously every 4 weeks thus confirming the excellent clinical response previously reported in TRAPS patients with anti-IL-1 agents [15–20].

On the contrary, our adult patient continued the successful tocilizumab infusions previously started as a sJIA treatment.

To the best of our knowledge, IL-6 inhibition in TRAPS had been described only once by Vaitla et al. [6], who reported an etanercept- and anakinra-resistant patient successfully treated with tocilizumab for 6 months. After tocilizumab administration, an evolving attack was aborted, and further disease flares were prevented. On these grounds, the authors suggested that tocilizumab could represent a satisfactory treatment for terminating both acute attacks and prophylaxis of TRAPS. In addition, since acute-phase response was normalized and corticosteroid administration discontinued, it was also speculated that tocilizumab could have a role for prevention of amyloidosis and metasteroidal comorbidities in TRAPS patients. However, a thrombocytopenia occurred after the first tocilizumab infusion, and tocilizumab dosage was reduced from 8 to 4 mg/kg monthly. Although this dosage allowed good control of symptoms, prodromal TRAPS manifestations along with a mild increase in the acute-phase response appeared toward the end of each treatment cycle. This problem was solved increasing tocilizumab dosage to 6 mg/kg.

Our experience corroborates these findings and highlights the clinical and laboratory tocilizumab efficacy in a 42-month long-term follow-up. In addition, although our patient continued to take a high tocilizumab dosage, no side effects were recorded.

In agreement with Vaitla et al. [6], we also infer a possible role for IL-6 in the pathogenesis of TRAPS. In support of this, IL-6 levels were found to be elevated in TRAPS patients [35]. Furthermore, macrophages from TNF receptor 1 (TNFR1)-mutant mice have shown to produce more IL-6 than wild-type macrophages in response to lipopolysaccharide [29]. Conversely, Vaitla et al. [6] also found that circulating cytokines (TNF, IL-1, IL-8, and IL-6) were not reduced after tocilizumab administration, thus suggesting that IL-6 inhibition did not affect the underlying TRAPS pathogenesis. However, more recently IL-6 has been proved to induce the production of radical oxygen species (ROS) in monocytes of TRAPS [36]. In turn, ROS are important component of the inflammatory response and are implicated in the activation of several signaling pathways such as mitogen-activated protein kinases and NF-κB [37, 38]. Also, ROS can activate the NACHT, LRR, and PYD domain-containing protein 3 (NALP3) inflammasome leading to mature IL-1β secretion [39]. Noteworthy, Bulua et al. [40] found also a reduction in IL-6 production after ROS inhibition. These findings suggest a pathogenic loop between IL-6 and ROS that can be interrupted with tocilizumab.

Conclusion

We describe two TRAPS patients (son and father) successfully treated with canakinumab and tocilizumab, respectively. In particular, we first describe a long-term tocilizumab treatment in a TRAPS patient highlighting the sustained and complete clinical and laboratory efficacy as well as the good safety profile. The double complete efficacy of canakinumab and tocilizumab in two patients carrying the same *TNFRSF1A* mutation and belonging to the same family strengthens the possibility of administering tocilizumab as a further therapeutic opportunity for TRAPS patients. Nevertheless, although the introduction of new treatment options for patients requiring a lifelong therapy is desirable, further studies should be warranted in order to determine the optimal tocilizumab dosage in such patients.

Conflict of interest None.

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