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References


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Failure of tocilizumab treatment in a CINCA patient: clinical and pathogenic implications

Sir, Chronic infantile neurologic cutaneous articular (CINCA) syndrome is an autosomal-dominant disease due to mutations of NLRP3/cryopyrin, representing the more severe phenotype of cryopyrin-associated periodic syndromes (CAPS). NLRP3 plays a pivotal role in the activation and secretion of IL-1β, and CAPS patients display an oversecretion of IL-1β [1]. Anti-IL-1 blockers are highly effective in all CAPS phenotypes. Unfortunately IL-1 blockers are not yet approved and registered in all countries. Since another potent pro-inflammatory cytokine, IL-6, is classically considered to act downstream of IL-1β [2], the use of IL-6 blockers could theoretically be of benefit for CAPS patients.

The patient is a first male child of non-consanguineous parents. At 1 month of age he presented with urticarial rash, fever and persistent elevation of acute phase reactants. Macrocranium with frontal bossing (supplementary Fig. 1, available at Rheumatology Online) was present and papilloedema was detected on eye examination. Hydrocephaly and brain atrophy were detected on brain MRI. Growth retardation and delay in mental development were also observed. Audiometry was normal. The clinical diagnosis of CINCA syndrome was confirmed by molecular analysis of the NLRP3 gene revealing the F443L mutation (see http://fmf.igh.cnrs.fr/infevers/).

Glucocorticosteroids were ineffective at controlling the clinical manifestations. Since IL-1 blockers were not available in Russia, treatment with antibody against IL-6 receptor (tocilizumab) was proposed after approval from the institutional ethics committee of Saint-Petersburg State Pediatric Medical University. Written consent was obtained according to the Declaration of Helsinki.

Tocilizumab (10 mg/kg i.v. every 3 weeks) was started at the age of 23 months.

After the first infusion (D0), fever and rash quickly disappeared with a simultaneous decrease of acute phase reactants and white blood cells (WBCs). However, after 2 weeks, a relapse of the clinical manifestation (fever and rash) was observed, together with elevation of ESR and CRP.

After a second infusion (D21), the patient displayed a transient amelioration of clinical manifestations, with a clear relapse after 1 week (Fig. 1). After the last (third) infusion, only a partial clinical response was observed (reduction of fever and rash). Acute phase reactants and WBCs persisted at high levels. Infusion reaction (irritability) was also observed. The treatment was therefore withdrawn. Canakinumab is presently registered in Russia for CAPS. The child will receive this treatment.

In the present study we report on the failure of anti-IL-6 treatment in a CINCA patient.

Theoretically there is evidence that could support the use of IL-6 blockers in an IL-1-mediated disease such as CAPS: (i) IL-1β induces IL-6 transcription [2]; (ii) higher levels of circulating IL-6 are detected in CAPS patients compared with healthy individuals [3]; (iii) IL-1 blockers in CAPS reduce IL-6 serum levels [3] and (iv) other diseases that present a favourable response to IL-1 blockade, such as systemic-onset JIA (SoJIA) [4], are also successfully treated with IL-6 inhibitors [5].

There is a single report on the use of tocilizumab in a CINCA patient [6]. The patient presented only a partial response to anakinra, which was rapidly withdrawn after 5 months (maximum dose 1.6 mg/kg). Tocilizumab treatment was used at a dose of 8 mg/kg every week. After an initial amelioration of the clinical manifestations and a reduction in acute phase reactants, after 2 months of treatment the patient suddenly died. A diagnosis of acute congestive heart failure and interstitial pneumonia was made [6]. Our report clearly shows that despite the initial good response after the first injection, tocilizumab had only a partial effect on disease activity and poor tolerability.

Recent evidence from the literature sheds some light on a possible explanation for the failure of anti-IL-6 treatment in CAPS patients. Despite similarities with SoJIA, the levels of IL-6 in these patients are significantly higher compared with untreated CAPS patients [3]. This is also true for other soluble biomarkers, such as S100A12 and MRPA/14 [7, 8], suggesting that, despite similarities in clinical manifestations and response to IL-1 blockade, the serological signature observed in CAPS patients might differ substantially from that observed in SoJIA. The apparent paradox of a limited increased level of circulating IL-6 in a classical IL-1-mediated disease such as CINCA has been recently addressed [9]. Monocytes from
Fig. 1 Clinical and laboratory changes before, during and after tocilizumab treatment.

D: day; WBC: white blood cells \( \times 10^9/l \); Tcz: tocilizumab. CRP in mg/dl; ESR in mm/h (Westergren). Fever measured as °C. Rash intensity rates were measured from mild to severe according to physician’s opinion.

CAPS patients display signs of stress, including elevated levels of reactive oxygen species. This condition is linked to accelerated secretion of activated IL-1β soon after stimulation with Toll-like receptor ligands, eventually leading to protein synthesis inhibition with a strong impairment of production of cytokines downstream of IL-1, such IL-6 and IL-1Ra, which is not observed in other autoimmune conditions [9].

In conclusion, the failure of anti-IL-6 treatment in CAPS patients confirms the peculiarity of this monogenic disease in the spectrum of inflammatory conditions responding to IL-1 blockade. The widespread availability of IL-1 blockers in all countries is needed for these patients. In the case of non-complete response to one IL-1 blocker, the use of increasing doses or equivalent drugs should be strongly preferred with respect to IL-6 inhibitors [10].

**Rheumatology key message**
- CAPS is a classical IL-1-mediated disease with a limited increased level of circulating IL-6.

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**Supplementary data**

Supplementary data are available at Rheumatology Online.

**References**