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://fmr.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, and circulating IL-6 in a classical IL-1-mediated disease such as CAPS. 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 1 Johnston SL, Lock RJ, Gompels MM. Takayasu arteritis: a review. J Clin Pathol 2002;55:481–6.
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**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 and autoinflammatory conditions [9].

In conclusion, the failure of anti-IL-6 treatment in CAPS patients confirms the peculiarity of this monocogenic 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 dosages 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.

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**References**


