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Positive clinical and biochemical responses to anakinra in a 3-yr-old patient with cryopyrin-associated periodic syndrome (CAPS)

Sir, Cryopyrin-associated periodic syndromes (CAPS) consist of a subgroup among hereditary periodic fever syndromes that includes familial cold-induced autoinflammatory syndrome (FCAS; MIM no. 120100), Muckle–Wells syndrome (MWS; MIM no. 191900) and chronic infantile neurological, cutaneous, articular (CINCA) syndrome (MIM no. 670115), also known as neonatal-onset multisystem inflammatory disease (NOMID), representing different degrees of disease severity. All of them have been recently associated with heterozygous mutations in the 
CIAS1/PYPAF1/NALP3 gene, which encodes the cryopyrin protein [1, 2]. This protein was found to be a constituent of inflammasome, an intracellular multiprotein complex involved in the cleavage and activation of proinflammatory cytokines IL-1β and IL-18 [3].

Here we present the case of a 3-yr-old male patient, without a familial history of periodic fever, diagnosed with possible MWS. His symptoms began when he was 9 months old, and consisted of long inflammatory episodes, recurring every 4–6 weeks, characterized by high fever, urticarial rash, abdominal pain, headache and irritability secondary to mild chronic aseptic meningitis, conjunctivitis, arthralgia, arthritis and occasionally diarrhoea. Neither reactive AA-type amyloidosis nor sensorineural deafness were present. A strong acute-phase response, with important elevation of C-reactive protein (CRP) and serum amyloid (SAA-1) protein, was detected in all these episodes (Fig. 1).

The diagnosis of CAPS was confirmed by the detection of the de novo heterozygous T348M mutation in the 
CIAS1/PYPAF1/NALP3 gene, as has been previously reported [4].

Non-steroidal anti-inflammatory drugs and corticosteroid treatment administered before CAPS diagnosis gave a negative response. Therefore, taking in account previous experience of treatment in adult patients with MWS and CINCA/NOMID syndrome [5–7], we started a therapeutic approach with anakinra, the human recombinant interleukin (IL)-1-receptor antagonist (Kineret; Amgen), that inhibits the pro-inflammatory IL-1 signalling pathway. This treatment was initiated during an inflammatory episode by means of subcutaneous injections, in doses of 1 mg/kg/day. The patient was hospitalized for the first week to detect any of the possible side-effects, and afterwards we maintained an ambulatory routine for 4 weeks, monitoring the clinical and biochemical responses weekly. Eventually, we established periodical controls every 2 weeks. A positive clinical response was detected, with a complete disappearance of skin rash, irritability, periodic fever, conjunctivitis and abdominal pain at 24 h after the first injection, and joint involvement at 48 h.

The strong acute-phase response resolved during the first week of treatment, decreasing noticeably the plasma levels of acute-phase reactants during the first week of treatment, decreasing noticeably the plasma levels of acute-phase reactants. These positive clinical and biochemical responses have persisted during 9 months of follow-up (Fig. 1). No side-effects have been identified. An attempt to reduce the anakinra dose to 0.75 mg/kg/day was unsuccessful, due to the appearance of low fever (37.5°C), headache and discomfort. When the initial dosage was reinstated these symptoms disappeared.

The most severe complications that have been described in patients with MWS are reactive AA-type amyloidosis and progressive bilateral sensorineural hearing loss. The strong decrease and normalization of plasma levels of acute-phase reactants detected in this paediatric patient during continuous treatment with anakinra suggests to us a hopeful decrease in his risk of developing reactive AA-type amyloidosis, due to its relationship with the plasma levels of SAA-1 protein [8]. Longer clinical and biochemical follow-up would be necessary to establish this risk accurately. However, we are not able to state that these positive clinical and biochemical responses to anakinra might prevent the development of sensorineural deafness in the future.

Dierselhuis et al. [9] have recently suggested that intermittent administration of anakinra during acute episodes instead of continuous treatment could be a therapeutic approach in some recurrent autoinflammatory disorders. However, the appearance of some clinical symptoms during an attempt to reduce the anakinra dose in this patient, and the advisability of maintaining his plasma levels of acute-phase reactants at normal values, led us to think that continuous treatment is most convenient in this patient.

We think that it is worthwhile publishing this positive experience with anakinra, because other children with CAPS could benefit from this treatment. As Hawkins et al. [7] suggested, early and prolonged therapeutic trials with anakinra are warranted in patients with CAPS to establish its efficacy and possible side-effects during long-term treatments, and to known if the most severe complications of CAPS—CNS involvement, papilloedema, sensorineural deafness and deforming arthropathy—could be prevented.

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<td><strong>There was a positive response to continuous anakinra therapy in a paediatric CAPS patient.</strong></td>
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**Fig. 1.** Serial measurements of plasma levels of CRP and SAA-1. The vertical arrow indicates when treatment with anakinra began. The horizontal discontinuous line marks the upper value of the normal (N) range of CRP (N<5 mg/l) and SAA-1 (N<10 mg/l).
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