On-demand treatment with anakinra: a treatment option for selected TRAPS patients

Sir,

The TNF receptor-associated periodic fever syndrome (TRAPS) is a hereditary autoinflammatory syndrome which commonly manifests as recurrent episodes of high fever accompanied by abdominal pain, pleurisy, migratory rash and myalgia [1]. Current treatment approaches include NSAIDs and/or steroids to alleviate or abort inflammatory attacks. Maintenance therapy with biologic agents is used for the most severe cases [2, 3]. Even though therapeutic options for these severely affected patients are not yet standardized, continuous treatment with IL-1 or TNF blockade is admitted to be necessary, because the few patients treated with an intermittent regimen of IL-1 blockade relapsed immediately after withdrawal of injections [4]. We present here two of our paediatric TRAPS patients with a favourable response to a 2-year on-demand treatment with anakinra.

Patient 1 is a 15-year-old teenager symptomatic since the age of 18 months. Mutation analysis revealed a C70Y (p.Cys99Tyr) in the TNFRSF1A gene. Before treatment, his attacks occurred every 2 months and lasted from 3 to 6 weeks. The main clinical signs comprised high fever, asthenia, vomiting, arthralgia, myalgia and periorbital oedema. During inflammatory attacks, CRP was peaking over 300 mg/l. Even if the clinical signs disappeared between the inflammatory attacks, the serum amyloid A level did not normalize (lowest serum amyloid A level in between attacks 170 mg/l), but he did not have signs of secondary amyloidosis. To treat inflammatory attacks, patient 1 initially received high doses of corticosteroids (CS) that provoked severe side effects (gastrointestinal bleeding and growth retardation), contraindicating all further use of this therapeutic class.

We offered both patients an on-demand treatment with anakinra (2 mg/kg/day). They were advised to start anakinra within 24 h of the first signs of an attack and to continue it for 5–7 days depending on the length of their usual attacks. Informed consent was obtained according to the Declaration of Helsinki because the use of anakinra was off-label.

After 24–48 h, both patients experienced a complete clinical response to anakinra as shown by the significant decrease of the activity score Auto-Inflammatory Diseases Activity Index [5] (Fig. 1). A normalization of the

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levels of acute-phase reactants—including serum amyloid A—was also observed within a few days of treatment. Furthermore, in patient 2, the number of attacks decreased in a yearly period to fewer than three. Unfortunately, after 2 years of on-demand treatment, the frequency of attacks increased in patient 1, so that he currently needs to use anakinra >14 days/month. Neither of the patients experienced major side effects except local injection site reactions. Unlike the observations of other published paediatric cases [4], we did not observe a relapse of the disease after withdrawal of the drug; the frequency of the attacks decreased even in patient 2. Unlike the study of Bodar et al. in Hyper IgD syndrome (HIDS) patients, we did not observe a less good response to IL-1 inhibition with frequent use [6]. Patient 1 continued to respond well to the treatment even if the number of attacks increased with time. We believe that this increase in the number of attacks reflects the natural history of TRAPS rather than a decreased efficacy after 2 years of on-demand use of anakinra. Indeed, patients with a cysteine mutation are known to have a more chronic and severe disease than patients with non-cysteine mutations [1], and maintenance therapy is often necessary [2].

Even though this positive experience concerned only two patients, in our opinion an on-demand treatment with anakinra in patients with well-identified attacks and periods of complete absence of symptoms is a good therapeutic option, especially if CSs are contraindicated or provoke severe side effects. An on-demand treatment gives the patients the possibility to intervene when symptoms start, instead of suffering helplessly through a fever attack. Such a treatment modality gives the patients the added benefits to be off treatment during remission, probably with a lower risk of infectious complications, and to keep the maintenance therapy for later life periods when the disease becomes more chronic. Further controlled studies of such an on-demand treatment are, of course, necessary, especially regarding the quality of life and the long-term complications of these TRAPS patients.

Rheumatology key message

- On-demand treatment with anakinra is a safe and efficacious treatment option in paediatric TRAPS patients.

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Tyrosine kinases encoded by fusion genes (e.g. FIP1L1-PDGFRα) are important in the pathogenesis of hypereosinophilic syndrome (HES), whose clinical features are often similar to those of EGPA. The FIP1L1-PDGFRα fusion gene, when found, is considered to rule out EGPA while supporting a diagnosis of primary HES [5]. Here, we describe the first case of a patient with EGPA carrying the FIP1L1-PDGFRα rearrangement and discuss whether this finding is relevant in the differential diagnosis between HES and EGPA.

A 41-year-old woman was admitted to our unit for fever and severe asthma. One month earlier she had been diagnosed with EGPA in a neurology unit because she had mononeuritis multiplex with wrist and foot drop, asthma, nasal polyposis and rhinosinusitis, bloody diarrhoea, peripheral eosinophilia and P-ANCA positivity, which tested anti-MPO by ELISA (>100 EU/ml, normal <10). Endoscopy had revealed gastric erosions, with histological evidence of eosinophil-rich inflammation of the lamina propria (Fig. 1A). The patient received a pulse of 6-methylprednisolone (125 mg/day for 3 days), followed by oral prednisone and i.v. immunoglobulins (400 mg/kg/day for 5 days), with good clinical response. The off-label treatment with rituximab was approved by the AOU Careggi Hospital ethics committee, and informed consent was obtained.

On admission to our unit, she was taking 10 mg/day prednisone; laboratory tests showed persistent eosinophilia (5590/mm³) and mild anaemia (haemoglobin 10.2 g/dl). MPO–ANCA positivity was confirmed. Given the persistence of eosinophilia despite ongoing steroid therapy, bone marrow biopsy was also performed, and showed mild eosinophilic hyperplasia, without atypias (Fig. 1B). Moreover, we searched for FIP1L1-PDGFRα using a nested RT-PCR and for FIP1L1-PDGFRβ and FGFR1 fusion genes using FISH. This analysis revealed the presence of the FIP1L1-PDGFRα rearrangement (Fig. 1C; patient characteristics and details of the genetic analysis are reported in supplementary Table S1, available at Rheumatology Online).

The patient resumed 1 mg/kg/day prednisone, which induced symptom remission; however, epigastric pain, myalgia, neuropathy and blood hypereosinophilia flared when prednisone was tapered below 20 mg/day. Therefore, we added rituximab (1000 mg on days 0 and 6-methylprednisolone (125 mg/day for 3 days), followed by oral prednisone and i.v. immunoglobulins (400 mg/kg/day for 5 days), with good clinical response. The off-label treatment with rituximab was approved by the AOU Careggi Hospital ethics committee, and informed consent was obtained.

To the best of our knowledge, the FIP1L1-PDGFRα fusion gene has never been described in EGPA. To assess the frequency of this finding in EGPA, we conducted an exploratory analysis of the FIP1L1-PDGFRα fusion gene in 11 additional consecutive patients with systemic EGPA (detailed data are reported in supplementary Table S1, available at Rheumatology Online), all of whom tested negative. Nevertheless, we believe that our finding has potential pathogenic and clinical implications. Together with previous reports showing the efficacy

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