#### **LETTERS**

# Corneal response to Canakinumab in Cryopyrin associated periodic fever syndrome

We describe the cases of a 15-year-old girl and her father. She first presented at the age of 9 to Southampton University Hospital Ophthalmology department with recurrent attacks of iritis and corneal infiltrate denser in the left eye compared to the right (figure 1). Her past medical history suggested that her condition started in the neonatal period when her immunisations were missed as she developed a rash at 8 weeks. She regularly experienced rashes and high fevers with some episodes requiring hospital admission.

At the ocular inflammatory stage of her condition, rheumatological assessment revealed tenderness in her feet, ankles and knees, and combined with the ophthalmic presentation, a diagnosis of juvenile idiopathic arthritis was made. MRI and ultrasound scans showed no evidence of synovitis. The severity of her arthritis was related to the exacerbations of her ocular features. The patient's inflammatory markers were all negative. She was managed with NSAIDS (naproxen) with mild relief.

Since the age of 9 years, she also experienced episodic mouth ulcers occurring every 2 to 3 months lasting for 3 weeks. The patient was initially started on colchicine, which was discontinued after a vasovagal episode.

The patient's father gave a similar medical history. He developed eye problems in childhood, associated with arthritis at 5 years of age with erythematous skin rashes. He regularly developed mouth ulcers when tired. His mother also suffered from eye problems throughout her life.

At the age of 9 years old, she first visited the eye clinic with red eyes and photophobia. Corneal assessment revealed bilateral central corneal stromal opacification (denser in the left eye) and anterior



**Figure 2** Six months after the beginning of canakinumab treatment. Only a faint scar is visible. Access the article online to view this figure in colour.

uveitis (figure 1), and treated with a tapering dose of topical steroids. After five further visits to the eve department and paediatric rheumatology with similar symptomatology that suggested an autoinflammatory syndrome with autosomal dominant pattern inconsistent with her previous diagnosis, blood samples of both the patient and her father were sent to the National Amyloidosis Centre for investigation of underlying periodic fever syndrome. This confirmed cryopyrinassociated periodic syndrome (CAPS) mutation in exon 3 of NLRP3 gene and treatment with canakinumab (IL-1 receptor antagonist) was started after a negative QuantiFERON investigation. At this point, the patient's vision had dropped to 0.62 LogMar in both eyes from 0.12 LogMar at the patient's first visit.

A mutation of the *NLRP3* gene that encodes for cryopyrin causes the cryopyrin inflammasome to constantly overproduce IL-1 $\beta$  instead of only in response to infections. This overproduction of IL-1 $\beta$  causes many CAPS symptoms to be present at birth or in early infancy, and persist or increase throughout life.<sup>1</sup>

After initiation of canakinumab, the corneal infiltrate reduced in density and by 6 months only a faint scar was present in both eyes (figure 2) with corresponding improvement in visual acuity from 0.62 LogMar (uncorrected and pinhole) pretreatment to 0.28 uncorrected and 0.14 pinhole.

Cryopyrin Associated Periodic Syndromes are a rare, hereditary group of inflammatory disorders that comprise three conditions: familial cold autoinflammatory syndrome (FCAS) with the mildest phenotype, Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (MONID) with the most severe form of the disease.<sup>2</sup> It is estimated that

there are 1-2 cases out of 1 million inhabitants in the USA and 1/360 000 in France.<sup>3</sup> CAPS are caused by autosomal dominant gain-of-function mutations in the NLRP3 gene, located on chromosome 1q44. Characteristic features of CAPS include nonpruritic, migratory, atypical urticarial rash on the trunk and limbs.2 Neurological features include headaches, progressive hearing loss, raised intracranial pressure and meningitis.4 Common ophthalmic manifestations include conjunctivitis, uveitis, and more rarely, optic disc swelling. Rheumatological features include pain and inflammation of usually larger joints associated with endochondrial ossification.3 Systemic amyloidosis occurs in about 25% of CAPS patients, affecting primarily the kidneys.<sup>1</sup>

Canakinumab is an IL-1 $\beta$  fully human, monoclonal antibody that is specific for IL-1 $\beta$  and not other members of the IL-1 family.<sup>3</sup> Canakinumab has been FDA approved for CAPS in adults and children older than 4 years old. It has a half-life of 28 to 30 days, and therefore, has a convenient dosing schedule by subcutaneous injection every 8 weeks.

Corneal infiltrates associated with CAPS have been recently described and treated with anakira (interleukin-1 antagonist) and penetrating keratoplasty.<sup>4</sup> <sup>5</sup> To the best of our knowledge, this is the first CAPS case with corneal involvement that resolved with canakinumab treatment, leading to restoration of the patient's reduced visual acuity.

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Competing interests None.

Patient consent Obtained.



**Figure 1** Before the initiation of canakinumab treatment. Access the article online to view this figure in colour.

## **PostScript**

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