

Cutaneous manifestations in mevalonate kinase deficient patients treated with canakinumab

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Key words: mevalonate kinase
deficiency, canakinumab

Accepted in revised form
on November 21, 2019

Competing interests: none declared.

ABSTRACT

Canakinumab is a human monoclonal antibody anti-interleukin-1 β , it is the only biologic drug approved to treat mevalonate kinase deficiency (MKD). Canakinumab injection can trigger several local cutaneous reactions, but also chronic-relapsing skin infections and other manifestations. We report three cases of unusual cutaneous manifestations in patients treated with canakinumab.

Introduction

Mevalonate kinase deficiency (MKD) is a rare recessively inherited autoinflammatory disease, caused by a defect in mevalonate kinase (MK), which is the fourth enzyme on the pathway from Acetyl-CoA to cholesterol. MK deficiency results in shortage of mevalonate-derived isoprenoids (MDI) and of cell cholesterol. MDIs have an important role in post-translational modifications of proteins, modulating several cell functions such as cell growth, differentiation and gene expression. The relation between MKD and inflammation is not completely clear. According to the most accredited hypothesis, the shortage of MDIs such as geranylgeraniol lead to an imbalance of membrane bound signal proteins resulting in excessive IL1- β production (1). However, the shortage of 25OH-cholesterol, a terminal product of the pathway leading from mevalonate to cholesterol, may as well have a role, both in inflammation and in the release of IgA and IgD from immune cells (2). MKD is characterised by recurrent fever attacks associated with abdominal pain, diarrhoea, lymphadenopathy, arthralgias, and inflammatory symptoms involving serosae, skin and mucosae. The latter include maculopapular or morbilliform rash, erythema nodosum and oral ulcers (3); less frequently, purpura or petechiae have been reported, with a picture that may be reminiscent of Henoch-Schönlein purpura (4). Moreover, there are anecdotal reports of perianal abscesses or fistulae similar to those observed in intestinal bowel disease (5). MKD fever attacks have been treated with corticosteroids with partial benefit as reported in the European fever reg-

istry (6). Evidence of excessive IL1- β production support treatment with IL1 inhibitors: anakinra and canakinumab. Canakinumab, a human monoclonal antibody targeted at IL1- β , has been recently demonstrated effective in resolving completely or reducing frequency and severity of MKD fever attacks and is currently the only biologic drug approved to treat MKD (7).

Here we report 3 cases of patients affected by MKD who presented unusual cutaneous manifestations occurred during treatment with canakinumab.

Case 1

Patient 1 is an 18-year-old boy. Since the age of 6 months, he presented recurrent inflammatory attacks accompanied with high degree fever, neck lymphadenopathy, pharyngotonsillitis, abdominal pain and diarrhoea, which recurred every 15–20 days. Due to the severity of attacks and to the development of glucocorticoid dependence, since the age of 5 years he underwent a therapeutic trial with etanercept without any benefit (8, 9), and subsequently treatment with anakinra, with partial control of symptoms. Nevertheless, increased doses of anakinra (up to 8 mg/kg/day) were sometimes necessary to control severe crisis mimicking acute abdomen. At the age of 13 years, the patient started a compassionate treatment with canakinumab with a good control of fever and associated symptoms and after a couple of years he could maintain a substantial clinical remission by taking the medication at the dosage of 150 mg every 6 weeks. At age of 15 years, the patient developed a severe cystic acne of the face (Fig. 1), and underwent several therapeutic attempts with minocycline, adapalene and benzoyl peroxide, clindamycin, dapsone gel 5% without significant improvement. Despite therapies acne did not resolve and had a remitting manifestation, seemingly worsening in the weeks after canakinumab injection and improving two weeks before the following administration, thus suggesting a drug induced skin manifestation. Only after surgical excision of the main lesion and subsequent treatment with oral isotretinoin he could obtain prolonged remission. Moreover,



Fig. 1.

two years later, while in good control of the inflammatory disease, he presented a perianal abscess with fever, which was treated with oral ciprofloxacin and surgical excision.

Case 2

Patient 2 is a 29-year-old woman. Since 6 months of age, she had recurrent fever attacks episodes accompanied with neck lymphadenopathy, erythematous rash of the face, arthralgias, oral aphthae, vomiting, abdominal pain and elevated acute phase reactants. At the age of 9 years, she was diagnosed with MKD. When she was 16, she had an episode of vasculitis with purpura at lower limbs, diagnosed as Henoch-Schönlein purpura. At the age of 18, because of the frequency of fever attacks every week end elevated serum amyloid protein between episodes, anakinra was started. Nevertheless, clinical manifestations showed only partial improvement, and she was enrolled in a trial with canakinumab (CAC7885N2301). In the last phase of the study, clinical remission could be maintained by administration of 150 mg of the drug every 5 weeks. Since then, she had several cutaneous manifestations different from those she presented previously. After 8 months of therapy with canakinumab, she had an itching erythematous rash of the back, groins and right arm, which resolved spontaneously. The rash was characterised by maculo-papular elements (2–3

Fig. 2.



Fig. 3.



mm of diameter) evolving in pustules and scab with minimal bloody oozing (Fig. 2). It was interpreted as pseudo-folliculitis. Moreover, she had recurrent, HSV eruption of the lips sometimes accompanied by diffuse, treated only with topical acyclovir. She never discontinued canakinumab in the last 3 years and she had no more cutaneous complaints.

Case 3

Patient 3 is a 15-year-old boy. Fever attacks appeared since he was 2 months old with abdominal pain, diarrhoea, anaemia, mild maculo-papular rash and pharyngotonsillitis. IgA, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated. During his first year of life he also de-

veloped a membranoproliferative glomerulonephritis. Anakinra was started when he was 2 years old; since then fever attacks became less frequent and renal involvement was well controlled associating therapy with ACE-inhibitor (9). At the age of 3 years old, he had a vasculitis with purpuric lesions of lower limbs, rectal haemorrhage and macroscopic haematuria as a severe attack of Henoch-Schönlein Purpura. Anakinra was not discontinued and a corticosteroid was associated in order to manage the acute episode. Since then, recurrent oral aphthae were always present, in 2015 he was enrolled in the clinical trial CAC7885N2301. He obtained a fair control of the diseases with canakinumab (150 mg every 4 weeks), rarely requiring add-on treat-

ment with glucocorticoids. However, after 2 years of therapy, an erythematous rash in the armpit area appeared: it was characterised by follicular papules and superficial pustules of 2-4 mm of diameter evolving in scabs. The rash at the beginning was mild and had spontaneous resolution, then involved also the trunk and inguinal region (Fig. 3) as a recurrent manifestation appearing soon after canakinumab injection and resolving 2-3 weeks afterwards. Cutaneous swab isolated a *Staphylococcus aureus* and topical therapy with fusidic acid and steroids was successfully administered. One year later, the patient presented severe cystic acne at the face, closely resembling the lesion described in case 1. After failure of topical treatments, a treatment with isotretinoin was proposed considering the previous experience in case 1.

Discussion

Canakinumab adverse events have been well described. Cutaneous reactions are quite frequent, usually involve the injection site and are characterised by redness, swollen, itching (7). Infections, usually of mild severity, are a typical event, more frequently involving upper and lower respiratory tract, but also cellulitis and abscesses have been reported (10). It is known that acne can be induced by several drugs. Drug-induced acne (DIA) typically involves face and neck in non-sebaceous areas, eruptions are monomorphic inflammatory pustules and comedowns are absent. DIA does not respond to first line acne therapy, it rather resolves stopping the offending drug. Indeed, a fluctuating trend and a clear relation with canakinumab injection could suggest a drug-induced acne (11). However, both in patient 1 and 3, the disease occurred in teenage years, when adolescent acne is quite common. Furthermore, in both cases, treatment with isotretinoin was able to control the symptoms, without stopping canakinumab. Patient 1 also experienced perianal abscess accompanied with fever, which could be a side effect of immunosuppression caused by canakinumab. Even if perianal abscesses are not rare in male adolescents, it had a more severe manifestation in our patient. Moreover,

perianal abscesses and fistulae in MKD can be associated with inflammatory colitis (12), but this was not the case in our patient: he recovered after therapy and did not have any intestinal inflammatory manifestation so far. Patients 2 and 3 experienced a folliculitis appeared during therapy with canakinumab. Folliculitis can be a cutaneous manifestation of Behçet's syndrome, and it has been already speculated that patients with Behçet's could share same features with MKD (13). However, neither patient 2 nor 3 had folliculitis before starting therapy with canakinumab.

The dysregulation of the IL-1 signalling network affects keratinocyte differentiation and antimicrobial barrier (14). Epithelia that cover body surface is a barrier against infections. In healthy skin, keratinocytes produce beta defensin members, a family of host defence peptides. Human β -defensin 2 (hBD2) has a microbicidal role in healthy skin as demonstrated by its protecting role against *S. Aureus* V8 protease-mediated damage. IL1- β stimulation significantly induces hBD2 production by keratinocytes, rising the hypothesis that IL1- β blockade could result in an impaired skin defence (14). On the other hand, in infected tissues IL-1 β plays a central role in initiating the neutrophilic response against *S. Aureus* infections, promoting neutrophil recruitment and bacterial clearance (15).

Moreover, our results rise the possibility that the risk of developing skin infections during canakinumab treatment could be higher in MKD than in other conditions. In fact, subjects with MKD run an increased risk of viral infections, probably due to reduced availability of the antiviral compound 25-hydroxycholesterol (16). However, it is not clear if this defect could play a role also in other kind of skin infections, maybe together with the drug-mediated inhibition of IL-1 β . In conclusion we report three cases with multiple and unusual cutaneous manifestations occurring during therapy with canakinumab in patients with mevalonate kinase deficiency. Our results can raise the attention to chronic-relapsing skin infections in subjects with MKD and other autoinflammatory disorders treated with canakinumab.

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