

Canakinumab in recessive dystrophic epidermolysis bullosa: a novel unexpected weapon for non-healing wounds?

Sirs,

Recessive dystrophic epidermolysis bullosa (RDEB) is characterised by painful mucocutaneous blisters, resulting in oesophageal strictures, mutilating scars, local and systemic infections and syndactyly. RDEB is caused by *COL7A1* gene mutations, encoding type VII collagen (1). Anti-type VII collagen as well as other anti-skin autoantibodies (anti-BP180, anti-BP230) can be detected, but their pathogenic role is unclear (2). The potential occurrence of AA-amyloidosis suggest that moderate to severe forms of RDEB are systemic inflammatory disorders rather than local skin diseases, thus being eligible for systemic immunomodulating therapy (3).

We report herein the first RDEB patient treated with canakinumab, the fully human anti-interleukin (IL)-1 β monoclonal antibody.

In October 2014, a 22-year-old Caucasian male with RDEB was admitted for spontaneous and due to friction blisters, painful chewing and swallowing; wound-healing associated with atrophic scarring. At the age 6, surgical correction for bilateral syndactyly was needed. His medical history was relevant for severe anaemia and Henoch-Schönlein purpura-like syndrome at the age 18. Betamethasone (1-5 mg/daily), silicone foam, soft clothing and soft diet were ineffective either in preventing lesions or in inducing their healing. He was underweight, with a BMI of 16.14.

Erythrocyte sedimentation rate (ESR) (120 mm/hour; n.v <25) and C-reactive protein (CRP) (7.12 mg/dl; n.v <0.5) were increased. Circulating IL-1 β (28.8 pg/ml; n.v 0-8.7) and IL-6 (61.7 pg/ml; n.v 0-12.7) were also elevated. Anti-type VII collagen, anti-BP180, anti-BP230 antibodies were detected.

After ethics committee approval and written informed consent, canakinumab at a dose of 150 mg subcutaneously was started. The treatment determined the gradual healing of wounds (Fig. 1) and improvement in chewing and swallowing. Following canakinumab, the onset of spontaneous blisters significantly reduced and their size markedly decreased. After 4 weeks a reoccurrence of blisters and a slightly delayed wound healing were noted, therefore two weeks later therapy was re-administered and given every 4 weeks. At 3-month follow-up, the patient was symptom-free, acute phase reactants were normal and IL-1 β (13 pg/ml) and IL-6 (25 pg/ml) serum levels were markedly decreased. BMI increased to 17.93. Nevertheless, four months after starting canakinumab, despite monthly administrations, a disease relapse occurred



Fig. 1. A. Severe blisters on the back with hypertrophy of the granulation tissue before administration of canakinumab; B. Improvement of skin disruption accompanied by lack of spontaneous blisters and reduction of pre-existing lesions at 3-month follow-up after administration of canakinumab.

and the treatment was interrupted. The patient is now under evaluation for beginning a new immunosuppressive agent.

Current approved RDEB therapy consists of palliative wound care. A process involving mechanical and/or oxidative stress in keratinocytes induces IL-1 β over-secretion, which is likely to be co-responsible for the most life-threatening RDEB complications: amyloidosis, skin cancer and cardiac disease (4). Safety and tolerability of canakinumab in different doses have been confirmed by numerous studies in different disease (5, 6). In our patient IL-1 β inhibition with Canakinumab proved successful in achieving wounds resolution, reducing spontaneous blisters and decreasing difficulty in chewing and swallowing, with rapid improvement of thinness and acute phase reactants. No adverse events were observed. However, at 4-month follow-up a disease relapse occurred. Canakinumab loss of efficacy might be linked to several mechanisms, such as an enhanced drug clearance or different drug pharmacokinetics; though a progressive hyper-expression of other pro-inflammatory cytokines, due to the complex network of chemokine homeostasis, would seem to be the most likely cause (7, 8). In particular, the reduction of IL-1 levels observed in our patient may have been counterbalanced by the increased levels of other pro-inflammatory cytokines, which may in turn circumvent the canakinumab action leading to the reactivation of IL-1 hypersecretion (7). After shortening of the interval between canakinumab administrations, we did not consider the possibility to also increase its dosage since we considered it risky in a patient innately at higher risk of developing infections. Treatment with the IL-1 receptor antagonist anakinra was not taken into consideration since performing daily injections might be unsuitable in RDEB patients. Indeed, it is well recognised that these subjects are prone to develop large, severely painful blisters and open wounds also from minor skin trauma. In REDB also IL-6 levels may be higher compared to healthy controls, as in our patient, and IL-6 serum levels correlate

with disease severity (9). Nevertheless, we discarded the option of using an anti-IL-6 since this cytokine may play a crucial role in wound healing, probably by regulating leukocyte infiltration, angiogenesis and collagen accumulation (10). Indeed, in other inflammatory skin diseases the inhibition of IL-6 has been shown to even induce the worsening of skin and mucosal lesions (11). To the best of our knowledge, we have reported the first RDEB patient treated with canakinumab. The treatment induced a rapid and impressive response with a prompt normalisation of acute phase reactants and the healing of wounds, but a waned efficacy over time was noted. Our report might indirectly suggest a potential role for IL-1 in RDEB pathogenesis.

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Letters to the Editors

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