

Letter to the Editor

Successful canakinumab treatment identifies IL-1 β as a pivotal mediator in Schnitzler syndrome

To the Editor:

Schnitzler syndrome is a chronic disabling autoinflammatory disorder characterized by the association of chronic urticaria and paraproteinemia with symptoms and signs of systemic inflammation, such as fever, bone pain, arthralgia or arthritis, and increased levels of inflammatory markers.^{1,2} More than 160 cases have been reported to date, but it is likely to be highly underdiagnosed. The effectiveness of the IL-1 receptor antagonist anakinra in more than 40 cases to date implies a crucial pathophysiological role of IL-1 but does not discriminate between IL-1 α and IL-1 β .³⁻⁵ The burden of painful daily injections increased the need for longer-acting agents, and *in vitro* findings hinted at IL-1 β as the principal proinflammatory cytokine involved in the pathophysiology.⁶

Canakinumab is a human anti-human IL-1 β mAb that generally requires administration only once every 4 to 8 weeks. It is effective in cryopyrin-associated periodic syndrome, a rare hereditary autoinflammatory disorder caused by increased IL-1 β activation, which has phenotypic similarities to Schnitzler syndrome.^{7,8} We therefore investigated whether canakinumab is effective in the treatment of Schnitzler syndrome.

On approval of local and national ethics committees and receipt of the patients' informed consent, we started treatment with canakinumab (150 mg administered subcutaneously once every 4

weeks) in 3 patients with Schnitzler syndrome. A 66-year-old man, a 51-year-old man, and a 67-year-old woman had Schnitzler syndrome for 14, 5, and 6 years with classical symptoms (fever, arthralgias, urticaria, and IgM or IgG paraproteinemia) and had been asymptomatic with daily anakinra injections for 4½, 2½, and ½ years, respectively. To enter the study, the patients would stop their treatment with anakinra and report to us at time of recurrence of symptoms.

Within 36 hours after stopping anakinra, the patients fell ill and gradually developed general malaise, pruritic-to-burning urticaria, fever (patients 2 and 3), and arthralgia as before initiation of anakinra. Four to 5 days after discontinuing anakinra, they presented with disseminated urticaria (Fig 1), arthralgia (arthritis in patient 3), strongly increased serum C-reactive protein concentrations (Fig 2), and neutrophilic leukocytosis. Upon a single subcutaneous injection of 150 mg of canakinumab, their symptoms started to abate within 6 to 16 hours, and all were asymptomatic after 2 days. The C-reactive protein concentration decreased dramatically within the first week and remained low or undetectable (Fig 2). Patient 1 reported scarce, short-lived, faint, nonpruritic urticaria-like lesions in the fourth and eighth weeks, without any increase in inflammatory markers. Adverse events in patient 1 were localized nonpruritic erythema at the injection site (once after the first injection), fleeting light-headedness when rising in week 8, and a single spell of palpitations in week 5, all of which were not considered serious adverse events. Patient 2 was receiving acenocoumarol anticoagulation therapy because of aortic valve



FIG 1. Rapid resolution of urticaria and arthritis on the first canakinumab injection. Pictures show urticarial rash in patients 1 and 2, arthritis of the left hand in patient 3 before canakinumab administration, and resolution of symptoms 4 days after injection.

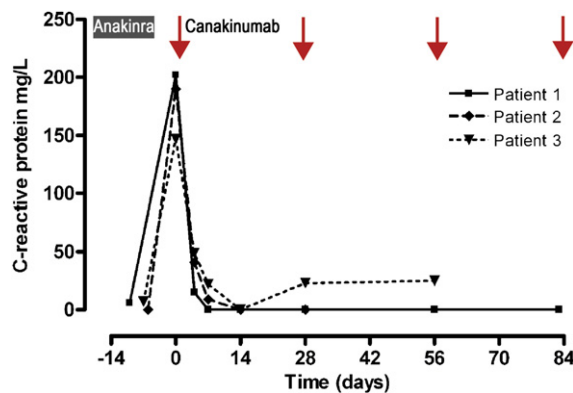


FIG 2. Canakinumab treatment induces long-term suppression of systemic inflammation in patients with Schnitzler syndrome. C-reactive protein concentrations increased dramatically on cessation of anakinra and rapidly normalized after canakinumab administration (normal, <10 mg/L).

replacement caused by a calcified bicuspid valve in 2007. His acenocoumarol dose needed to be adjusted after the start of canakinumab, possibly because of interaction with canakinumab. Patient satisfaction is high, and follow-up of complete or clinical remission is now 12, 7, and 8 weeks, respectively.

These data suggest that monthly injection with canakinumab is an effective long-acting treatment for Schnitzler syndrome. We have initiated a 6-month trial of canakinumab in patients with Schnitzler syndrome (ClinicalTrials.gov NCT01276522), which will determine the long-term safety and efficacy in more patients. Whereas anakinra blocks the action of both IL-1 α and IL-1 β , canakinumab specifically blocks IL-1 β . Consequently, these data single out IL-1 β as the key cytokine responsible for inflammation in patients with Schnitzler syndrome, thereby providing a pivotal pathophysiological clue for this enigmatic disorder and corroborating the evidence for its autoinflammatory nature.

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