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LETTER TO EDITOR

Variable Responses to Tocilizumab in Four Patients with Schnitzler Syndrome

Jonas Claus [1,2] · Steven Vanderschueren [1,2]

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To the Editor,

Variable responses to tocilizumab in four patients with Schnitzler syndrome.

Schnitzler syndrome (SchS) is a rare chronic autoinflammatory disease that is characterized by an urticarial rash and a monoclonal gammopathy, usually immunoglobulin (Ig) M class [1]. Other symptoms include intermittent fever, lymphadenopathy, and joint, bone, and muscle pains. In 2013, diagnostic criteria, the Strasbourg criteria, were established [1]. In the past, treatment was frustrating, with > 35 therapies reported without reliable responses. In 2005, a marked effect of anti-interleukin-1 (anti-IL-1) treatment was described [2].

Anakinra, a recombinant human IL-1 receptor antagonist, is widely regarded as the treatment of choice, although its universal availability is hampered by cost and reimbursement issues [1, 2]. Anakinra proved to be effective in all initially reported cases. In recent years, however, cases with suboptimal responses were published, so the quest for effective and safe alternatives continues. In 3 out of 3 patients who had insufficient relief with anti-IL-1 therapy, anti-interleukin-6 (IL-6) treatment induced complete remission [3]. This letter is, to the best of our knowledge, the only published report on anti-IL-6 treatment in SchS.

Here, we describe four patients with SchS, treated with anti-IL-6 treatment (intravenous tocilizumab, 8 mg/kg/4 weeks). Two of the four patients showed rapid and complete remission after initiation of anti-IL-6 treatment. The other two patients had no or partial response.

A first patient, a 56-year-old man had a 3-year history of chronic urticarial rash, periodic fever, and severe bone pain. A monoclonal IgM kappa and sclerotic bone lesions on bone scintigraphy supported the diagnosis of SchS (Table 1). Initial treatments including ruxolitinib (because of erroneous initial diagnosis of a myeloproliferative syndrome) were ineffective (Fig. 1). Anakinra induced a complete remission. However, after 4 months, symptoms recurred and, after 17 months, anakinra was discontinued. Tocilizumab was started in monotherapy but symptoms worsened. Because of uncontrolled disease activity, tocilizumab was stopped after 4 months. Anakinra was restarted and 2 years later, a partial remission is maintained.

A second patient, a 59-year-old woman, was diagnosed with SchS following a 1-year history of periodic fever, urticaria, arthralgia, a low-level monoclonal IgM lambda, and elevated acute-phase reactants (Table 1). Only high-dose glucocorticoids (> 1 mg/kg) improved the symptoms (Fig. 1). Anakinra was given for 7 weeks, without benefit. Twenty-one months after diagnosis, tocilizumab was added to glucocorticoids and colchicine, with complete remission. Reduction of glucocorticoids resulted in relapse, so a dose of 4 mg methylprednisolone was continued. Complete remission was seen after 4 months. Two and a half years after the initiation of tocilizumab, the patient is still in complete remission.

A third patient, a 60-year-old lady with a monoclonal IgG kappa was diagnosed with SchS after a 4-year history of arthralgia, urticaria, periodic fever, and fatigue. Only non-steroidal anti-inflammatory drugs (NSAIDs) with high-dose glucocorticoids (> 1 mg/kg) produced pain relief and inflammatory control (Fig. 1). Complete remission was seen 4 months after tocilizumab was added to the treatment with methylprednisolone, colchicine, and azathioprine. Because discontinuation of azathioprine resulted in disease relapse, the agent was reintroduced. Twenty-two months after the start of tocilizumab, the patient is still in complete remission, with tocilizumab, methylprednisolone (4 mg daily), colchicine, and azathioprine.

✉ Steven Vanderschueren
steven.vanderschueren@uzleuven.be

[1] Clinical Department of General Internal Medicine, University Hospitals Leuven, Herestraat 49, B-3000 Leuven, Belgium

[2] Research Department of Microbiology, Immunology and Transplantation, Laboratory for Clinical Infectious and Inflammatory Disorders, KU Leuven, Herestraat 49, 3000 Leuven, Belgium

Table 1 Disease characteristics of 4 patients with SchS treated with tocilizumab

Disease characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Typical patient with SchS (2)
Age at disease onset (years)	51	58	57	40	51 (#)
Clinical symptoms					
Urticarial rash	+	+	+	+	+
Duration of single lesions (h)	24–48	24–48	12–24	12–24	24–48
Periodic fever	+	+	+	+	+
Arthralgia	+	+	+	+	+
Bone pain	+	+	+	+	+
Fatigue	+	+	+	+	+
Lymphadenopathy	–	–	–	–	±
Hepatosplenomegaly	–	–	–	–	±
Anti-IL treatment before tocilizumab	Anakinra	Anakinra	None	None	
Paraproteins	IgM kappa	IgM lambda	IgG kappa	IgM kappa	IgM kappa (85%) IgG kappa (5%) IgM lambda (8%) IgG lambda (1%)
Baseline (g/L)	10.8	Weakly present	15.9	4.62	
#months after tocilizumab initiation	10.5 (2 months)	Absent	15.3 (8 months)	4.5 (4 months)	
CRP (mg/l) before tocilizumab	51.4	50	24	43.3	
CRP (mg/l) after tocilizumab	8	< 0.3	1.9	1	

SchS Schnitzler syndrome; *IL* interleukin; *Ig* immunoglobulin; *M* monoclonal; *CRP* C-reactive protein

A fourth patient, a 40-year-old man, had a non-itchy urticarial rash and intermittent fever for 2 years. The diagnosis of SchS was supported by a monoclonal IgM kappa in combination with recent joint pain and increased erythrocyte sedimentation rate. Anakinra could not be started initially because reimbursement was not granted. Tocilizumab was added to methylprednisolone 8 mg a day (Fig. 1). A partial response was seen, but after 4 months urticaria, bone pain, and elevation of ESR recurred. Ten months after the initiation, tocilizumab was stopped and anakinra was started with complete remission after a few days.

Thus, two patients treated with tocilizumab showed rapid and complete remission, indicating that IL-6 may contribute to the pathogenesis of SchS, as suggested in previous reports [4].

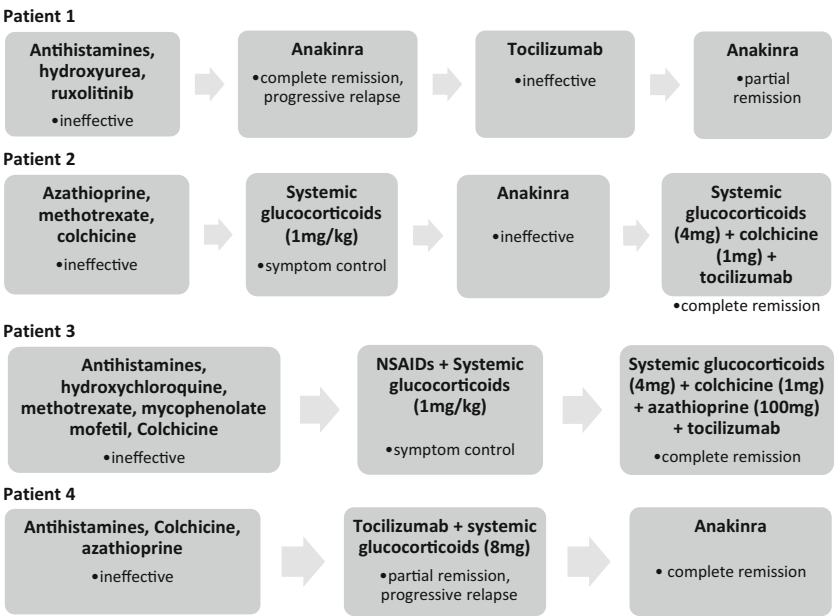

Fig. 1 Timeline of the given therapies in all patients, ending with the current therapy (dose tocilizumab is 8 mg/kg/4 weeks; NSAIDs = nonsteroidal anti-inflammatory drugs)

Chronic dysregulation with high IL-6 expression can induce immune-mediated diseases and lymphoproliferative disorders, for example, rheumatoid arthritis and SchS [5].

However, monotherapy of tocilizumab was not effective, necessitating addition of other drugs, notably of glucocorticoids in low doses, to sustain remission.

Two patients, on the other hand, had an insufficient response, and tocilizumab infusions were discontinued. This present experience somewhat tempers the enthusiasm, raised by an earlier report, with exclusively favorable outcomes with anti-IL-6 treatment in SchS, and suggests complex pathogenesis of SchS. Two of our patients were treated with tocilizumab before anakinra was tried. In one of them, tocilizumab did not generate a durable response and anakinra-induced remission. Overall, anti-IL-1 treatment still seems to remain the treatment of choice for SchS, but directly comparative trials are lacking. Further mechanistic studies are also needed to clarify the roles of both pathways in the pathogenesis of SchS.

In summary, tocilizumab may be considered an alternative therapy in patients with SchS when anti-IL-1 therapy is unavailable, achieves suboptimal response, or is not tolerated (e.g., because of injection site reactions). However, our experience in 4 patients suggests that tocilizumab does not guarantee a universal remission either.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest. Tocilizumab was a kind gift from Roche, Belgium. Otherwise, the firm was not involved in the manuscript.

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