

Letter to the Editor

Complete remission in 3 of 3 anti-IL-6-treated patients with Schnitzler syndrome

To the Editor:

Schnitzler syndrome (SchS) is a rare chronic inflammatory disease that usually occurs in patients older than 50 years and is characterized by urticarial rash and monoclonal gammopathy, usually of the IgM class. Further clinical symptoms include episodes of fever, arthralgia or arthritis, lymphadenopathy, and bone and muscle pain.¹ SchS is severely debilitating and notoriously hard to treat.

Patients with SchS lack the NLRP-3 mutation but show many of the signs and symptoms of cryopyrin-associated periodic fever syndromes, which have recently been reported to respond very well to anti-IL-1 treatment.^{2,3} Because of this, SchS is widely held to be a prototype late-onset autoinflammatory disease and anti-IL-1 treatment (although not licensed for this indication) is now the treatment of choice. In fact, anti-IL-1 treatment has been reported to be effective in all cases, without a single treatment failure.⁴⁻⁷

Here, we report 3 cases of SchS that did not respond to anti-IL-1 and multiple other treatments but showed rapid and complete remission after initiation of anti-IL-6 treatment with tocilizumab. The first patient, a 70-year-old male pensioner, presented to us with a 5-year history of chronic urticarial rash, intermittent fever, eye redness, and severe joint and bone pain. The diagnosis of SchS was made by evidence of monoclonal gammopathy (IgM kappa) and exclusion of underlying causes. Treatment with multiple antihistamines in standard and higher than standard doses, thalidomide, cyclosporin A, dapsone, and pefloxacin had not been successful. Psoralene/ultraviolet A therapy improved skin symptoms temporarily, and systemic glucocorticoids showed significant benefit only in doses greater than 1 mg/kg. Surprisingly, anakinra treatment (100 mg/d) also did not result in any improvement in the symptoms or in the reduction of markers of inflammation, and anakinra was discontinued after 8 weeks. Since anti-IL-1 treatment had been reported to be successful in all patients with SchS ever treated, the patient then received rilonacept (loading dose 320 mg, followed by weekly doses of 160 mg), another IL-1–targeted therapy. However, this treatment, which the patient stayed on for 3 months, also did not result in a reduction of either symptoms or markers of inflammation. In June 2010, the patient was started on tocilizumab (8 mg/kg/mo), an anti-IL-6 receptor antagonist licensed for the treatment of rheumatoid arthritis. Three weeks after the first treatment, our patient reported that his joint and bone pain was less severe and that the urticarial rash was less pronounced. C reactive protein (CRP) and serum amyloid A (SAA) levels, at this time, were found to be significantly reduced from baseline levels (CRP 4.3 mg/dL and SAA 89 mg/L before tocilizumab treatment) and within the normal range (CRP 0.03 mg/dL and SAA 3.3 mg/L) (Fig 1, A). Tocilizumab therapy had to be discontinued (because the patient's health insurance provider withdrew funding for further treatment), and all the previous symptoms reoccurred and remained as severe as they had been before tocilizumab treatment until this therapy was reinitiated 2 weeks later. The patient showed quick and complete remission of all symptoms within 6 weeks, and since that time, he has been on tocilizumab treatment. The

patient has had no further symptoms or elevation of markers of inflammation except during the 3 to 5 days before his monthly tocilizumab infusions when he consistently shows mild urticaria.

Our second patient, a 63-year-old female pensioner, was diagnosed with SchS following a 5-year history of cold-exacerbated urticaria, arthralgia, conjunctivitis, and fatigue with monoclonal gammopathy (IgM lambda). Treatment with azathioprine, dapsone, thalidomide, systemic glucocorticoids, cyclosporin, and nonsteroidal anti-inflammatory drugs did not result in improvement of any symptoms. Subsequent anakinra therapy (100 mg/d) even lead to exacerbation of clinical symptoms, particularly skin symptoms, and was discontinued after 6 weeks. Treatment with rilonacept (160 mg/wk, loading dose 320 mg) resulted in only very limited improvement of clinical symptoms without a reduction of inflammation markers. In November of 2010, we initiated tocilizumab treatment (8 mg/kg/mo) and our patient was nearly free of symptoms within 8 weeks. Clinical response was accompanied by normalization of CRP and SAA levels (CRP 1.43 mg/dL and SAA 8.8 mg/dL before start of treatment; CRP 0.04 mg/dL and SAA 5.6 mg/dL after 2 weeks of treatment with tocilizumab) (Fig 1, B). She remains on tocilizumab and has not shown any symptoms or increased markers of inflammation up to now.

Our third patient, a 59-year-old woman with monoclonal IgG kappa, who was first diagnosed with SchS in 2008, suffered from a 2-year history of chronic urticarial plaques, recurrent fever episodes, and bone and joint pain. She had also received multiple treatments, none of which improved her symptoms. Anakinra treatment (100 mg/d) was tried for 8 weeks without benefit in 2008, before tocilizumab (8 mg/kg/mo) was started in September of 2009. This patient also experienced a rapid onset of improvement with normalization of inflammation markers (CRP 1.01 mg/dL before start of treatment and <0.3 mg/dL after 2 weeks of tocilizumab). Complete clinical remission was achieved after 12 weeks of treatment. Six months after its initiation, tocilizumab was temporarily discontinued followed by immediate recurrence of clinical symptoms and elevation of CRP levels (Fig 1, C). Anti-IL-6 treatment was reinitiated, and the patient has not stopped tocilizumab and has been free of symptoms since the beginning of 2010.

Paraprotein IgM or IgG levels in all 3 patients did not change substantially during the observation period (Table I). Cytokines (IL-1 β levels from LPS-stimulated monocytes and IL-6 serum levels) were measured in patients 1 and 2. IL-1 β levels were within the normal range and did not change following tocilizumab treatment. IL-6 levels too started in the normal range but increased 10 to 20 times above the upper limit of normal following anti-IL-6 treatment in both patients.

As of now, all the patients with SchS we treated with tocilizumab showed rapid and complete remission, indicating that IL-6 can importantly contribute to the pathogenesis of SchS. This is supported by previous reports demonstrating increased IL-6 serum levels in SchS.⁸⁻¹⁰ An increase in IL-6 levels after anti-IL-6 treatment has been described before. It was suggested that tocilizumab competes with IL-6 for binding to IL-6 receptors, thus leading to elevated IL-6 levels in the serum.¹¹ Also, it has been shown that IL-6 is critical for the development of lymphoproliferative disorders such as multiple myeloma,¹² and anti-IL-6 treatment has been successfully used in Castleman's disease, another rare lymphoproliferative disorder.¹³ In SchS,

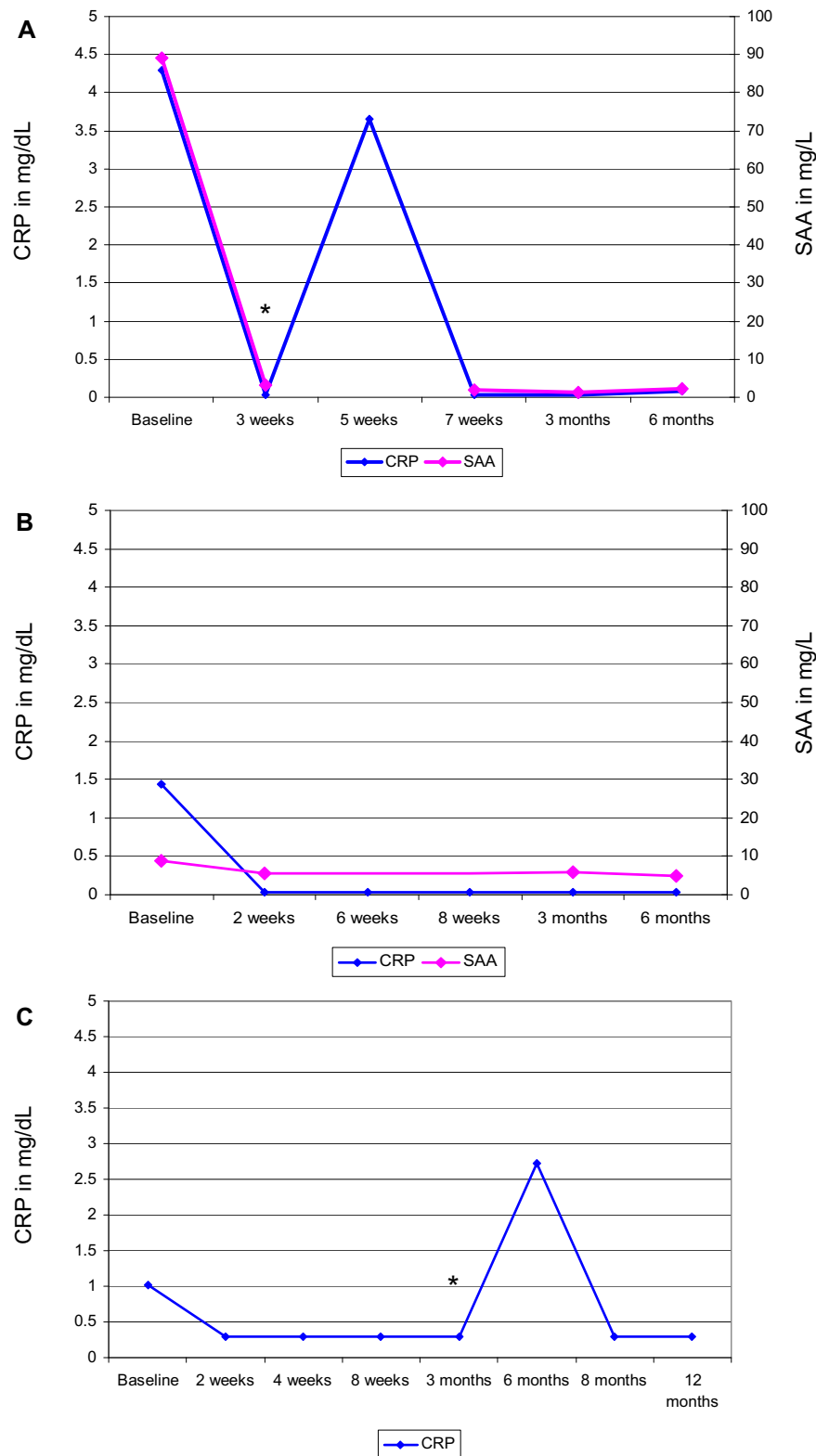


FIG 1. Change in inflammation markers CRP and SAA over the course of treatment with tocilizumab. **A**, Patient 1. **B**, Patient 2. **C**, Patient 3. Reference ranges: CRP <0.5 mg/dL; SAA <6 mg/L. *Tocilizumab temporarily discontinued.

TABLE I. Disease characteristics of patients with SchS

Disease characteristics	Patient 1	Patient 2	Patient 3	Typical patient with SchS ⁷
Age at disease onset (y)	65	58	54	51 (± 12)
Clinical symptoms				
Urticarial exanthema	+	+	+	+
Duration of single lesions (h)	12-24	12-24	24-48	12-36
Periodic fever	+	+	+	+
Arthralgia	+	+	+	+
Bone pain	+	+	+	+
Fatigue	+	+	+	+
Lymphadenopathy	+			+
Hepatosplenomegaly				+
Eye redness/pain	+	+		
Disease exacerbation by cold		+		
Paraproteins (IgM 40-230 mg/dL; IgG 700-1600 mg/dL)	IgM kappa	IgM lambda	IgG kappa	IgM kappa (86%) IgG kappa (7%) IgM lambda (5%) IgG lambda (1%)
Baseline	160 mg/dL	438 mg/dL	1160 mg/dL	
6-10 mo after tocilizumab initiation	132 mg/dL	465 mg/dL	1090 mg/dL	

15% to 20% of patients have been reported to develop a lymphoproliferative disorder, predominantly Waldenström's macroglobulinaemia, but also myeloma and other rare lymphomas.⁷ The fact that IgM and IgG paraprotein levels are stable on anti-IL-6 treatment is in line with earlier observations in patients on anti-IL-1 treatment. Whether or not anti-IL-6 treatment can prevent the development of lymphoproliferative disorders remains to be shown in the long term.

The pathogenesis of SchS is mainly driven by IL-1, which is supported by the excellent responses of patients with SchS to IL-1-targeting therapies in all published cases so far.⁴⁻⁷ However, our data suggest that at least 2 independent pathways may play a relevant role in SchS, that is, via IL-1 (the common pathway) or via IL-6 (the alternative pathway), which both result in the same clinical picture and course of disease. Alternatively, IL-1 may cause SchS via the induction and/or upregulation of IL-6. As of now, we have used anti-IL-6 treatment only in those patients with SchS who had failed anti-IL-1 therapy. It should be noted that the patients' disease characteristics summarized in Table I do not show any differences that could clearly separate these patients from anti-IL-1-responding patients with SchS. Further studies, for example, using anti-IL-6 in anti-IL-1 responders, are needed to clarify the roles and possible interaction of IL-1 and IL-6 in the pathogenesis of SchS. Our findings also suggest that anti-IL-6-responsive disorders such as rheumatoid arthritis may be (co-)mediated by autoinflammatory mechanisms and that treatment studies in SchS, a model for acquired autoinflammatory diseases, could help to dissect these mechanisms on molecular and cellular levels.

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