

Efficacy of Interleukin 1 Receptor Antagonist (Anakinra) on a Refractory Case of Schnitzler's Syndrome

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Sir,

Schnitzler's syndrome (SS) is a rare condition defined by the association of a chronic urticarial rash and a monoclonal immunoglobulin M (IgM) component and at least 2 of the following criteria: fever, arthralgia or arthritis, bone pain, lymphadenopathy, hepatosplenomegaly, elevated erythrocyte sedimentation rate (ESR), leukocytosis and abnormal findings on bone morphologic investigations (1). Management of SS is often disappointing (1, 2). However, interleukin 1 receptor antagonist (IL-1Ra) (anakinra) seems to give promising results; to date approximately 10 cases of SS have been treated successfully with no reported failure (3–8). Here, we add a new report illustrating that treatment with anakinra should be initiated in disabling forms of SS when corticosteroids have failed.

CASE REPORT

A 50-year-old man presented in 1996 with widespread urticarial and pruritic rash, low-grade intermittent fever, asthenia, arthralgias, myalgias hepatomegaly without spleen enlargement or lymphadenopathy, hyperleukocytosis, elevated ESR, monoclonal IgM kappa gammopathy, and abnormal enhanced isotope uptake in various bones on the scintigraphy. Skin biopsies disclosed only a perivascular lymphocytic infiltration without neutrophils in the dermis. According to aforementioned criteria (1), a diagnosis of SS was made. For the past 10 years, numerous therapies have been tried, but proved to be either ineffective or lead to adverse effects: antihistamines, psoralen plus ultraviolet A, plasmapheresis, dapson, chlorambucil, colchicine, thalidomide, azathioprine, methotrexate, cyclosporine, cyclophosphamide alone or in association with rituximab and, lastly, fludarabine. Meanwhile, high doses of prednisone above 25 mg/day were given, providing some relief without clearing the urticaria or arthralgias. Attempts to taper the doses resulted in recurrences of urticaria. Long-term prednisone therapy was responsible for iatrogenic hypercortisolism. In addition, explorations (computer tomography scan, bone marrow examination) disclosed no signs of myeloma or Waldenström's macroglobulinaemia. The patient also presented chronic bilateral oedemas of the legs, repeated explorations having ruled out heart, liver, and kidney failure, and venous insufficiency.

In May 2006, IgM levels reached a peak, at 11.3 g/l (normal 0.4–3.1 g/l). Encouraging reports of the efficiency of IL-1Ra (9, 10) prompted us to use anakinra (Kineret®, Amgen France, Neuilly-sur-Seine, France) at a dose of 100 mg/day, starting in August 2006. Prior to initiation of the therapy, the patient presented widespread urticaria and arthralgias with no other symptoms. Laboratory tests revealed normal haemoglobin level and white blood count, elevated ESR (71 mm/h), C-reactive protein ((CRP) 24 mg/l) and IgM (9.45 g/l). Within the first 24 h after injection, a dramatic improvement was observed

as urticaria vanished completely and arthralgias improved markedly. The treatment was well tolerated and allowed the prednisone dose to be tapered quickly and treatment switched to hydrocortisone (30 mg/day). After 5 weeks of treatment, the patient stopped anakinra treatment because of bilateral leg oedemas. Urticaria relapsed within the following days. He was hospitalized 2 weeks later and prednisone was given again (40 mg/day). It is noteworthy that the IgM level had meanwhile decreased to 7.84 g/l. The patient's long-term history of bilateral oedema and the absence of such reported side-effects with anakinra made us reintroduce the treatment. Again, after 24 h, the urticarial eruption vanished. The patient was discharged home with anakinra and prednisone 15 mg/day. A more progressive scheme of prednisone tapering was scheduled. After 7 months of daily treatment with anakinra, prednisone has been reduced slowly to 2 mg/day. No local reaction at the site of injection was observed, but the patient complained of asthenia related to morning injection of anakinra. Hypercortisolism symptoms improved as well as leg oedemas. More importantly, no flare-up of the disease has occurred so far, and inflammatory parameters (ESR, CRP) have returned to the normal range.

DISCUSSION

Treatment of SS is often difficult and disappointing (1, 2). The case described here illustrates a patient with a "refractory" disease who tried a large number of drugs with limited success. Treatment usually includes non-steroidal anti-inflammatory drugs, systemic steroids and immunosuppressive drugs (1, 2). A large number of therapies have been proposed in selected cases, with inconsistent results (1, 2). IL-1 is a powerful pro-inflammatory cytokine responsible for systemic manifestations such as fever, chills, skin rash, urticaria, neutrophilia, anaemia and elevated ESR (9). Dysregulation of IL-1 secretion has been observed in inflammatory diseases for which anakinra has proven efficiency, i.e. systemic-onset juvenile idiopathic arthritis, adult Still's disease and systemic auto-inflammatory disorders (7). IL-1 would play a role in the physiopathology of SS (1–8). Anakinra is undoubtedly an effective therapeutic alternative for SS. Our patient displayed the "typical" response to anakinra as formerly reported (3–8), as the latter induced a quick and complete remission of the symptoms within the first 24 h. Moreover, as observed by de Koning et al. (2, 8), when withdrawn, a flare-up appeared within a day and reintroduction induced a new remission. The short half-life *in vivo* of anakinra means that daily injections are required. Thus, patients who skip an injection may experience a rapid flare-up of the

disease (2). We did not observe any local reaction at the site of injection in this case, but the patient complained of asthenia after morning injections, which prompted us to propose evening injections instead.

Finally, we wish to speculate on alternative treatments blocking the IL-1 pathway (9), such as IL-1 soluble receptor (IL-1 trap) or caspase-1 inhibitor (pralnacasan), or the IL-6 pathway, such as tocilizumab, a monoclonal antibody against human IL-6 receptor (10), as elevated IL-6 levels were observed in some patients (11, 12). These treatments are still under development, but they may prove helpful in the future in the management of refractory SS.

The authors declare no conflicts of interest.

REFERENCES

1. Lipsker D, Veran Y, Grunenberger F, Cribier B, Heid E, Grosshans E. The Schnitzler syndrome. Four new cases and review of the literature. *Medicine (Baltimore)* 2001; 80: 37–44.
2. de Koning HD, Bodar EJ, van der Meer JW, Simon A, Schnitzler Syndrome Study Group. Schnitzler syndrome: beyond the case reports: review and follow-up of 94 patients with an emphasis on prognosis and treatment. *Semin Arthritis Rheum* 2007; 37: 137–148.
3. Treudler R, Kauer F, Simon JC. Striking effect of the IL-1 receptor antagonist anakinra in chronic urticarial rash with polyclonal increase in IgA and IgG. *Acta Derm Venereol* 2007; 87: 280–281.
4. Crouch R, Akhras V, Sarkany R. Schnitzler's syndrome: successful treatment with anakinra. *Australas J Dermatol* 2007; 48: 178–181.
5. Eiling E, Moller M, Kreiselmaier I, Brasch J, Schwarz T. Schnitzler syndrome: treatment failure to rituximab but response to anakinra. *J Am Acad Dermatol* 2007; 57: 361–364.
6. Schneider SW, Gaubitz M, Luger TA, Bonsmann G. Prompt response of refractory Schnitzler syndrome to treatment with anakinra. *J Am Acad Dermatol* 2007; 56: 120–122.
7. Martinez-Taboada VM, Fontalba A, Blanco R, Fernandez-Luna JL. Successful treatment of refractory Schnitzler syndrome with anakinra: comment on the article by Hawkins et al. *Arthritis Rheum* 2005; 52: 2226–2227.
8. de Koning HD, Bodar EJ, Simon A, van der Hilst JC, Netea MG, van der Meer JW. Beneficial response to anakinra and thalidomide in Schnitzler's syndrome. *Ann Rheum Dis* 2006; 65: 542–544.
9. Burger D, Dayer JM, Palmer G, Gabay C. Is IL-1 a good therapeutic target in the treatment of arthritis? *Best Pract Res Clin Rheumatol* 2006; 20: 879–896.
10. Nishimoto N, Kishimoto T. Interleukin 6: from bench to bedside. *Nat Clin Pract Rheumatol* 2006; 2: 619–626.
11. Worm M, Kolde G. Schnitzler's syndrome: successful treatment of two patients using thalidomide. *Br J Dermatol* 2003; 148: 601–602.
12. de Kleijn EM, Telgt D, Laan R. Schnitzler's syndrome presenting as fever of unknown origin (FUO). The role of cytokines in its systemic features. *Neth J Med* 1997; 51: 140–142.