

Severe systemic inflammatory response syndrome in a patient with adult onset Still's disease treated with the anti-IL1 drug anakinra: a case report

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ABSTRACT

Interleukin 1 (IL1) plays an important role in adult onset Still's disease. Anakinra (Kineret®), a recombinant IL1 Receptor Antagonist (IL 1 RA) was therefore recently proposed in adult onset Still's disease with great efficacy. Anakinra appeared to be well tolerated and safe. The case of a patient with refractory adult onset Still's disease who experienced a Systemic Inflammatory Response Syndrome and Adult Respiratory Distress Syndrome requiring intensive care unit hospitalization 10 days after the introduction of anakinra is reported.

Introduction

Adult onset Still's disease is characterized by high spiking fever, evanescent rash, arthritis, neutrophilic leucocytosis, elevated total ferritin levels with low glycosylated ferritin (1, 2). Systemic and visceral manifestations as well as haemophagocytic syndrome have been described (3-5). In adult onset Still's disease, Acute Respiratory Distress Syndrome (ARDS) (6) and Severe Systemic Inflammatory Response Syndrome (SIRS) (7-9) are extremely rare. Interleukin 1 (IL1) is the major cytokine produced in adult-onset Still's disease flares (11, 12). Anakinra (Kineret®), a recombinant IL1 Receptor Antagonist (IL 1 RA), was recently proposed in adult onset Still's disease. Its efficacy appeared satisfactory and in some cases spectacular (13-15). Anakinra was well-tolerated and safe in adult onset Still's disease case reports and in rheumatoid arthritis large prospective studies: mild to moderate injection site reactions occurred in 71% of the patients, more frequently in patients with a history of allergy. Serious adverse events were rare (16, 17). To our knowledge, SIRS has not been reported with anakinra. The case of a patient with adult onset Still's disease developing a life threatening SIRS with ARDS 10 days after the introduction of anakinra is reported.

Case report

In January 2000, a 23-year-old Caucasian man was admitted to Besancon General Hospital with high spiking

fever, throat and abdominal pain, arthritis, cutaneous rash. The C reactive protein was 118 mg/l and the sedimentation rate 83 mm at first hour. Biology showed polynuclear leucocytosis ($21,000 \times 10^3/\text{mm}^3$), hyperferritinemia ($>10,000 \text{ ng/l}$), and low glycosylated ferritinemia (18%). The diagnosis of adult onset Still's disease was confirmed. The patient was treated with prednisone (1 mg/kg) and hydroxychloroquine, then methotrexate (30 mg/week) without efficacy. For his refractory disease, he was referred to Cochin Hospital, Paris, in November 2004. Infliximab (18) was introduced in November 2004 (5 mg/kg every 8 weeks) and led to one year complete remission. Corticosteroids were progressively tapered to 15 mg/day and methotrexate to 15 mg/week. After one year of treatment, the initial symptoms reoccurred, associated with $6000 \text{ eosinophils}/\text{mm}^3$. Extensive explorations to explore the high eosinophil count were negative. The patient was treated with intravenous high dose steroids (15 mg/kg methylprednisolone) with success and infliximab was interrupted for inefficacy and possible allergy. Within 4 months, hypereosinophilia disappeared spontaneously. In July 2005, anakinra (100 mg/day) was introduced because of a new flare. Ten days later, the patient complained of sudden fever, tachypnoea and was hospitalized in intensive care unit because of brutal severe respiratory distress and hemodynamic shock, requiring endotracheal intubation, vollemic expansion and vasopressors. The initial laboratory results showed: white cells $19.9 \times 10^3/\text{mm}^3$ (normal range, $4.0-10.0 \times 10^3/\text{mm}^3$), eosinophils $1.39 \times 10^3/\text{mm}^3$ ($0.04-0.40 \times 10^3/\text{mm}^3$), C reactive protein 113 mg/l ($< 5 \text{ mg/l}$), elevated aminotransferases, fibrinogen 3.51 g/l (2-4 g/l), creatinin 191 g/l (71-115 g/l), ferritinemia 8482 ng/l (25-380 ng/l) and triglycerids 2.1 mmol/l ($< 1.7 \text{ mmol/l}$). The chest radiograph showed dense bilateral alveolar infiltrates consistent with ARDS. The diagnosis of SIRS was made. All bacteriological and serological tests were negative. Pulmonary and abdominal tomodensitometry confirmed bilateral alveolar infiltrates and hepato-splenomegaly. A

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broad-spectrum antibiotic treatment was prescribed 15 days with ciprofloxacin and ceftriaxone, as well as corticosteroids (1mg/kg). Because of the use of vasopressive drugs, distal ischemia of feet and hands developed. The patient was extubated after 6 days and was discharged from intensive care after 10 days. The only sequel was a persistent ischemia of the third toe of the right foot which required surgery. Corticosteroids were maintained at 1 mg/kg one month and progressively tapered to 20 mg per day with methotrexate 15 mg per week. In July 2006 he was in remission.

Discussion

This article reports the first case of SIRS in a young adult onset Still's disease patient, occurring 10 days after the introduction of anakinra. Because of the short delay between the introduction of anakinra and the occurrence of SIRS, the question of the responsibility of this drug in inducing the SIRS arises. In SIRS, TNF alpha and IL1 are secreted in large amounts. IL1 is one of the first and most important cytokines produced during any inflammatory process, shock or SIRS. Anakinra is a receptor blocking IL1, and it is therefore difficult to comprehend that anakinra could induce a shock through its specific action mechanism. Nevertheless, some paradoxical effects of different cytokine blockers have been described, especially with anti-TNF drugs (multiple sclerosis, vasculitis, Crohn's disease flares...). This could also occur with anakinra, another biological agent. The other hypothesis is the induction by anakinra of a haemophagocytic syndrome (which may be drug induced) which could be responsible for the SIRS. Although all arguments for a haemophagocytic syndrome are not present in this observation, this does not exclude the diagnosis. Fever, hepato-splenomegaly, high ferritinemia, elevated aminotransferases, normal fibrinogen with biological inflammatory syndrome, mild elevation of triglycer-

ids are elements of a haemophagocytic syndrome. However, we cannot confirm this diagnosis since osteomedullary biopsy was not performed.

Another hypothesis is anakinra hypersensitivity, because of previous possible allergy to infliximab, the introduction of anakinra 10 days before the shock and the presence of elevated eosinophils at arrival. Local allergic reactions with anakinra have been largely reported, and appeared to be more important in patients with previous allergy phenomena (6). Severe allergy phenomena with shock have also been described with other cytokine blockers, such as anti-tumor necrosis factor alpha drugs, but to our knowledge, no SIRS with severe shock has been reported to date with anakinra.

Conclusion

To date, anakinra appears to be efficacious and safe in adult onset Still's disease. In this case report, a severe adverse event appeared 10 days after introduction of anakinra. Though the causality remains unproven, because of the severity of the symptoms and their life-threatening character, physicians should take into account this potential association. Further monitoring of anakinra in adult onset Still's disease is required.

References

1. COFFERNILS M, SOUPART A, PRADIER O, FEREMANS W, NEVE P, DECAUX G: Hyperferritinemia in adult onset Still's disease and the hemophagocytic syndrome. *J Rheumatol* 1992; 19: 1425-7.
2. KUMAKURA S, ISHIKURA H, MUNEMASA S, ADACHI T, MURAKAWA Y, KOBAYASHI S: Adult onset Still's disease associated hemophagocytosis. *J Rheumatol* 1997; 24: 1645-8.
3. FERREIROS J, REGINATO AJ, SCHUMACHER HR JR, BAKER DG, O'CONNOR CR, FERREIROS J: Adult onset Still's disease: experience in 23 patients and literature review with emphasis on organ failure. *Semin Arthritis Rheum* 1987; 17: 39-57.
4. A WOUTERS JM, VAN DE PUTTE LB: Adult-onset Still's disease; clinical and laboratory features, treatment and progress of 45 cases. *Q J Med* 1986; 61: 1055-65.
5. POUCHOT J, SAMPALIS JS, BEAUDET F *et al.*:

Adult Still's disease: manifestations, disease course, and outcome in 62 patients. *Medicine* 1991; 70: 118-136.

6. HIROHATA S, KAMOSHITA H, TAKETANI T, MAEDA S: Adult Still's disease complicated with adult respiratory distress. *Arch Intern Med* 1986; 146: 2409-10.
7. IGLESIAS J, SATHIRAJU S, MARIK PE: Severe systemic inflammatory response syndrome with shock and ARDS resulting from Still's disease: Clinical response with high-dose pulse methylprednisolone therapy. *Chest* 1999; 115: 1738-40.
8. RANGEL-FRAUSTO MS, PITTET D, COSTIGAN M, HWANG T, DAVIS CS, WENZEL RP: The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. *JAMA* 1995; 273: 117-23.
9. MUCKART DJ, BHAGWANJEE S: American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions of the systemic inflammatory response syndrome and allied disorders in relation to critically injured patients. *Crit Care Med* 1997; 25: 1789-95.
10. RAVELLI A, CARIA MC, BURATTI S, MALATTIA C, TEMPORINI F, MARTINI A: Methotrexate as a possible trigger of macrophage activation syndrome in systemic juvenile idiopathic arthritis. *J Rheumatol* 2001; 28: 865-7.
11. DINARELLO CA: Blocking IL-1 in systemic inflammation. *J Exp Med* 2005; 201: 1355-9.
12. VENCOVSKY J, JAROSOVA K, RUZICKOVA S *et al.*: Higher frequency of allele 2 of the interleukin-1 receptor antagonist gene in patients with juvenile idiopathic arthritis. *Arthritis Rheum* 2001; 44: 2387-91.
13. VERBSKY JW, WHITE AJ: Effective use of the recombinant interleukin 1 receptor antagonist anakinra in therapy resistant systemic onset juvenile rheumatoid arthritis. *J Rheumatol* 2004; 31: 2071-5.
14. VASQUES GODINHO FM, PARREIRA SANTOS MJ, CANAS DA SILVA J: Refractory adult onset Still's disease successfully treated with anakinra. *Ann Rheum Dis* 2005; 64: 647-8.
15. FITZGERALD AA, LECLERCQ SA, YAN A, HOMIK JE, DINARELLO CA: Rapid responses to anakinra in patients with refractory adult-onset Still's disease. *Arthritis Rheum* 2005; 52: 1794-803.
16. LANGER HE, MISSLER-KARGER B, KINERET: Efficacy and safety in daily clinical practice: an interim analysis of the Kineret response assessment initiative (kreative) protocol. *Int J Clin Pharmacol Res* 2003; 23: 119-28.
17. FLEISCHMANN RM: Addressing the safety of anakinra in patients with rheumatoid arthritis. *Rheumatology* 2003; 42 (Suppl. 2): ii29-35.
18. BENUCCI M, LI GF, DEL ROSSO A, MANFREDI M: Adalimumab (anti-TNF-alpha) therapy to improve the clinical course of adult onset Still's disease: the first case report. *Clin Exp Rheum* 2005; 23: 733.