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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Please address correspondence to: Dr. Sandra Guignard, Meaux 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, 000x10^3/mm³), hyperferritinemia (>10, 000 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 lead 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 recurred, associated with 6000 eosinophils/mm³. 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, hypeeosinophilia 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, volvemic expansion and vasopressors. The initial laboratory results showed: white blood cell 19.9x10^3/mm (normal range, 4.0-10.0x10^3/mm³), eosinophils 1.39x10^3/mm³ (0.04-0.40x10^3/mm³), C reactive protein 113 mg/l (< 5 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 triglycerides 2.1 mmol/l (< 1.7 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

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 some cases spectacular (13-15). 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, 000x10^3/mm³), hyperferritinemia (>10, 000 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 lead 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 recurred, associated with 6000 eosinophils/mm³. 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, hyper eosinophilia 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, volemic expansion and vasopressors. The initial laboratory results showed: white cells 19.9x10^3/mm (normal range, 4.0-10.0x10^3/mm³), eosinophils 1.39x10^3/mm³ (0.04-0.40x10^3/mm³), C reactive protein 113 mg/l (< 5 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 triglycerides 2.1 mmol/l (< 1.7 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
broad-spectrum antibiotic treatment was prescribed 15 days with cipro-
foxacin and cetfrixone, 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 meth-
otrexate 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 intro-
duction of anakinra and the occurrence of SIRS, the question of the respon-
sibility 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 inflam-
atory 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. Never-
thless, 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 bio-
logical agent. The other hypothesis is the induction by anakinra of a haemopha-
gocytic syndrome (which may be drug induced) which could be respon-
sible for the SIRS. Although all argu-
ments for a haemophagocytic syndrome are not present in this observation, this does not exclude the diagnosis. Fever, hepato-splenomegaly, high ferritinemia, elevated aminotransferases, normal fi-
brinogen with biological inflammatory syndrome, mild elevation of triglycer-
ids are elements of a haemophagocytic syndrome. However, we cannot con-
firm this diagnosis since osteomodular biopsy was not performed.

Another hypothesis is anakinra hyper-
sensitivity, because of previous possi-
ble allergy to infliximab, the intro-
duction of anakinra 10 days before the shock and the presence of elevated eosinophils at arrival. Local allergic re-
actions with anakinra have been largely reported, and appeared to be more im-
portant in patients with previous al-
lergy 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 effi-
cacious 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 poten-
tial association. Further monitoring of anakinra in adult onset Still’s disease is required.

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