Two cases of anakinra-induced neutropenia during auto-inflammatory diseases: Drug reintroduction can be successful
Neutropénie sous anakinra au cours de deux maladies auto-inflammatoires: perseverare non diabolicum !

Anakinra is a recombinant interleukin-1 receptor antagonist (IL-1Ra) approved a decade ago for the treatment of rheumatoid arthritis. Since then it has demonstrated a promising efficacy in several rare inflammatory diseases such as cryopyrin-associated periodic syndromes [1], systemic juvenile idiopathic arthritis [2], adult-onset Still’s disease (AOSD) [2,3], and Schnitzler syndrome (SS) [4]. Neutropenia is a rare adverse effect of IL-1Ra [5], for which scientific data and management guidelines are scarce. Its occurrence can cause a difficult therapeutic dilemma when alternative therapies are lacking.

We report two cases of early IL-1Ra–related grade III-IV neutropenia occurring in patients with acquired auto-inflammatory diseases (one with SS, the other AOSD). Given the disabling and refractory course of the underlying disease, a careful reintroduction has been attempted, and proved successful.

Case 1
A 68-year-old man with SS suffered recurrent episodes of fever and arthritic period associated with profound weight loss and anaemia. Corticosteroids were partially effective and poorly tolerated. Colchicine had been stopped several months previously due to lack of efficacy and poor tolerance. Pefloxacin had no steroid-sparing effect and was also stopped. The patient suffered continuous high-grade fever and maculopapular rash, therefore IL-1Ra therapy was started (100 mg/day). Before IL-1Ra, C-reactive protein (CRP) level was 103 mg/L and blood counts showed 8660 leukocytes/mm$^3$, 6190 neutrophils (PMN)/mm$^3$, inflammatory anemia (10.4 g/dL), and a normal platelet count. Twenty-four hours after IL-1Ra introduction, skin rash and fever disappeared and CRP fell to 40 mg/L. IL-1Ra was stopped by day 4 because of isolated persistent neutropenia (750 PMN/mm$^3$). The neutrophil count normalized within 2 days after its withdrawal (figure 1). SS symptoms recurred within 48 hours. The first reintroduction of IL-1Ra-induced a marked decrease in PMN count (1120/mm$^3$) (figure 1). Several months later a second attempt led to a complete remission of the disease, with only a mild decrease in the PMN count which remained in normal range: it felt from 3800 to 1500/mm$^3$ but returned to 3000/mm$^3$ within 5 days. At last follow-up, the patient was still in complete remission under IL1-Ra and his neutrophil count was stable around 2000–3000/mm$^3$. The drug causality assessment according to the French imputability method was C3S2B3.

Case 2
A 48-year-old man developed a severe form of AOSD, complicated by respiratory distress and tissue-proven macrophage activation syndrome. Despite pulse corticosteroids and 24 hours of intravenous ciclosporine the patient remained febrile (39–40 °C) and dependent upon non-invasive mechanical ventilation. Blood test exhibited severe hepatitis (ASAT and ALAT level were 70 and 24 upper normal limit [UNL], respectively) and coagulopathy (prothrombin ratio [TP] was 51%). Blood counts showed 8040 leukocytes/mm$^3$, inflammatory anemia (9.6 g/dL) and 122,000 platelets/mm$^3$. CRP and ferritin level were 83 mg/L and 278,500 μg/L, respectively. The addition of IL-1Ra (100 mg/day) had a dramatic efficacy: on day 3, fever and hypoxemia had markedly decreased, CRP, ASAT and ALAT had fell to 15 mg/L, 8 and 14 UNL, respectively, and TP had risen to 72%. However, a sharp decrease in leukocyte count was noticed (figure 1). During subsequent days all clinical and biological parameters showed continuous improvement: 10 days after IL1-Ra introduction the patient was afebrile and only required 1L/min nasal oxygen, ASAT and ALAT were 1-2 UNL, CRP and ferritin level were 8 mg/L and 10,100 μg/L. TP and platelet count had normalized (91% and 234,000/mm$^3$, respectively). However, a profound neutropenia persisted (320 PMN/mm$^3$). No other drug was introduced and ciclosporine dose was unchanged. Bone marrow aspirate smear was poor, and hemophagocytosis was no longer observed. Two days after the IL-1Ra interruption, the PMN count rose to 2130/mm$^3$. However, even though high dose steroids and ciclosporine were still administered, the fever recurred and CRP rose to 217 mg/L. Reintroduction of IL1Ra induced a rapid clinical response, with a paradoxal hyperleucocytosis with myeloma (up to 35%) and monocytesis (up to 3200/mm$^3$) (figure 1). Drug causality assessment was scored C1S1B3.
**Discussion**

AOSD and SS are inflammatory diseases of unknown etiology, which share several clinical characteristics (high-grade fever, neutrophilic urticarial dermatosis and osteo-articular involvement) [6]. Further, both entities appear to be driven by innate inflammatory cytokines IL-1, IL-6 and IL-18 and can exhibit a dramatic improvement upon IL-1 or IL-6 blockade [2–4,7–10]. These clinico-biological features are reminiscent of cryopyrinopathies and led several authors to consider AOSD and SS as late onset acquired auto-inflammatory diseases [11]. However, the very *primum movens* of the dysregulations of innate immunity observed in these diseases remains to be identified.

Neutropenia is an exceptional side effect of IL-1Ra. In rheumatoid arthritis, IL-1Ra related neutropenia incidence is 1.9%, with a mean time of onset of 71 days [5]. The underlying mechanisms remain unclear. Indeed most cases of drug-induced agranulocytosis are believed to involve toxic or immuno-allergic mechanisms. In these cases the median time to recovery usually ranges from 5 to 10 days [12]. Herein, the lack of recurrence after drug reintroduction argues against these hypotheses. Further, neutropenia occurred within a few days of IL-1 blockade and, even more intriguingly, it quickly recovered after IL-1Ra withdrawal (figure 1). In mice, IL-1 stimulates granulopoiesis and neutrophil migration in inflamed tissues [13], whereas IL-1Ra inhibits IL-1 induced neutrophilia and egress of neutrophil from bone marrow [14]. Hence, the herein reported observations may result from a transient IL-1 blockade-induced imbalance between neutrophil bone marrow efflux and tissue recruitment in the context of a prominent IL-1 driven systemic inflammation.

Eventually, our case reports emphasize that IL-1Ra may be successfully reintroduced after an even profound early IL-1Ra-induced neutropenia. This observation is reminiscent of recent reports of IL-1Ra-induced hepatitis occurring in the context of AOSD [15] or systemic-onset juvenile idiopathic arthritis (sJIA) [16]: 2 patients with sJIA were restarted anakinra with no recurrence of hepatitis [16]. These observations raise questions as to the role of the underlying disease or confounding factors (associated medications, occult infectious agent) in the occurrence of these rare side effects of IL-1Ra. The key point for clinicians to be aware of is that drug reintroduction can be attempted. This is particularly meaningful for patients with refractory auto-inflammatory disorders, for which alternative therapies are often scarce, whereas IL-1 blockade can be lifesaving.

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**References**


Vascularite à IgA révélant une rechute de leucémie à tricholeucocytes traitée par cladribine

IgA vasculitis revealing hairy cell leukemia relapse treated by cladribine

La leucémie à tricholeucocytes (LTL) est un syndrome lymphoprolifératif rare dont l’association aux vascularites est bien connue. L’association à des néphropathies est beaucoup moins classique. Nous rapportons ici le cas d’un patient atteint d’une vascularite cutanée nécrosante et d’une néphropathie à IgA, toutes deux contemporaines d’une rechute de leucémie à tricholeucocytes. Nous effectuons une brève revue de la littérature sur les vascularites et néphropathies associées aux LTL.

Observation

Un patient de 79 ans était hospitalisé pour l’exploration d’une anasarque. Ses antécédents comprenaient une hypertension artérielle, une fibrillation auriculaire et une leucémie à tricholeucocytes en rémission complète après un traitement par interféron-alpha (3 millions d’unités, 3 fois par semaine en sous-cutané, pendant 18 mois). Ce traitement était interrompu depuis un an et le patient régulièrement suivi. Il était traité par fluindione, losartan, hydrochlorothiazide et sotalol. L’histoire récente de la maladie était marquée par l’apparition synchrone et brutale, un mois avant son hospitalisation, d’un ulcère de jambe droite et d’œdèmes des membres inférieurs. À l’examen clinique, l’ulcère était non douloureux, creusant, d’environ 6 cm (figure 1) et les œdèmes des membres inférieurs prenaient le geot.

Le bilan biologique initial montrait une pancytopenie : hémoglobine 7,8 g/dl, réticulocytes 25 000/mm³, polynucléaires neutrophiles 24000/mm³ et plaquettes 60 000/mm³. Le frottis sanguin et la cytrométrie de flux ne décelaient pas de tricholeucocytes. Une insuffisance rénale aiguë était observée : urée 18 mmol/L, créatininémie 165 µmol/L (clairance MDRD à 35 mL/min) avec une protéinurie de 24 heures à 2,52 g et une hypoalbuminémie à 20 g/L. L’immuno-électrophorèse des protéines plasmatiques et le dosage pondéral des IgA étaient normaux. Les anticorps anti-cytoplasme des polynucléaires neutrophiles, les facteurs anti-nucléaires étaient négatifs, le C3 et C4 étaient normaux. Trois recherches successives de cryoglobulines étaient négatives. Une biopsie de peau montrait des lésions de vasculaire nécrosante et thrombosante avec des débris fibrinoides obstruant la lumière des capillaires avec dépôts de C3. Une ponction biopsie rénale montrait des glomérules hypercellulaires avec dépôts mélangées d’IgA et de C3 (figure 1B). Aucun tricholeucocyte n’était visualisé sur ces deux biopsies. Une biopsie ostéomédullaire avec étude par cytométrie de flux montrait un envahissement important de la moelle par 30 % de tricholeucocytes, confirmant ainsi la rechute de LTL.

Un traitement par cladribine avait débuté. Après un mois d’évolution, l’ulcère avait nettement diminué de taille (4 cm contre 6 avant traitement) et était beaucoup moins creusant. Après 3 mois de traitement, la créatininémie avait diminuée à 118 µmol/L (contre 165 µmol/L avant traitement), la protéinurie des 24 h était à 1 g et l’albuminurie à 27 g/L. L’hémoglobine s’était partiellement normalisée à 10,3 g/dl, les plaquettes à 93 000/mm³ et les polynucléaires neutrophiles à 1900/mm³.

Discussion

La leucémie à tricholeucocytes est un syndrome lymphoprolifératif rare, caractérisé par une prolifération lente dans la rate...