Superior efficacy and similar safety of double dose anakinra in Erdheim-Chester disease after single dose treatment

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Abstract

Objectives. In Erdheim-Chester disease (ECD), the empirical single dose (SD, 100 mg/day) anakinra sometimes induces only partial responses. Since SD is usually well tolerated, doubling the dose might improve response while maintaining an acceptable safety profile.

Methods. A retrospective analysis was performed of outcomes under double-dose (DD) of anakinra in 4 ECD patients who did not exhibit a complete response (CR) under SD treatment. Bone, retroperitoneal, neurologic/orbital, peritoneal, pericardial, right atrium, and pleural involvements were recorded. CR, partial response (PR), stable disease, progressive disease (PD) and tolerance of DD were assessed.

Results. SD treatment was a second or third line treatment in three patients after interferon-therapy failure. Two patients, including one with a BRAF mutation, achieved a CR and one patient with a NRAS mutation achieved a PR with DD treatment. The fourth patient, wild-type for both genes, did not respond to a first DD treatment, but then achieved CR under SD associated with a reduced dose of vemurafenib (960 mg/d). Bone and retroperitoneal lesions partially improved on imaging with SD in all patients, but were further improved under DD with two patients achieving CR. With SD treatment, two patients with right atrial masses showed sustained CR. Under DD treatment, two patients with massive serositis refractory to SD, showed PR.

Conclusion. DD improved the response to anakinra and lead to two CRs and a PR in three out of four ECD patients, with minor and comparable side-effects to those of SD, while failures were essentially related to massive serositis.

Introduction

Erdheim-Chester disease (ECD) is a rare non-Langerhans histiocytic disorder caused by tissue infiltration by foamy macrophages exhibiting positive CD68 and negative CD1a immunostaining. The fibro-inflammatory infiltration can lead to several organic damages, including retroperitoneal fibrosis with hydrenephrosis, peri-aortitis, cardiac injuries and pleuropéricardial effusions, insipid diabetes, central nervous system involvement, bone pain, exophthalma, and constitutional symptoms.1-4

Based on the demonstrated involvement of IL(Interleukin)-1 and IL-6 pathways in the pathophysiology of the disease, anakinra (recombinant IL-1 receptor antagonist) showed interesting results and good tolerance at the daily subcutaneous (SC) dose of 100 mg in 2 patients exhibiting partial responses and unacceptable side-effects, or contra-indication, with the use of interferon-alpha therapy.5 This posology of anakinra was empirically chosen to correspond to the same protocol used in rheumatoid arthritis (100 mg/d SC), for which this drug was initially engineered. However, further cases of complete response (CR) and partial response (PR) or failure are observed with this posology in ECD.6-11 Tocilizumab, a monoclonal anti-body blocking the IL-6 receptor, has also been tried with success in a few patients.12 More recently, treatments targeting the RAS/RAF/MEK/ERK tumourigenic mutational network provided several cases of dramatic CR in ECD.13-15 However, several concerns persist with these drugs, including cases of failure, PR, or poor tolerance, and unacceptable side effects, including cutaneous malignancies in ECD, as in melanoma, in which they were first and largely used.14-17 Secondary medium/long term loss of efficacy of these drugs, related to secondary induction of downstream neo-mutational defects, is also described in melanoma.18 Moreover, targetable mutations have not been detected in a significant proportion (almost 40%) of ECD patients. Therefore, increased doses and a combination of
anakinra with some selected drugs are possible interesting strategies to improve the outcomes in terms of efficacy and treatment tolerance in ECD.

From this perspective, we report a series of 4 ECD cases, exhibiting better responses with a well-tolerated double dose of anakinra, or its combination with lowered doses of vemurafenib. In parallel, we performed sensitive molecular biology tests in these patients to understand the outcomes under anakinra with regards to the presence of certain molecular defects, and we discuss the hypothesis of a common pathophysiogenic mechanism between IL-1 and the RAS/RAF/MEK/ERK network in ECD.

Results

The main clinical, biologic and genetic characteristics of the four patients (3 men, 1 woman; mean age (range) at diagnosis: 59.8 (52–68) years old) and treatment history before anakinra are shown in Table 1. Molecular screening found no defect in one patient (Patient 4), a BRAF V600E mutation in two others (Patients 2 and 3) and a NRAS mutation in the last (Patient 1), which have been previously reported. SD was the first-line treatment in only one patient (Patient 2) and the second- or third-line treatment in the others, always after high dose interferon failure. Before SD treatment, Patients 1, 3 and 4 exhibited PR, stable disease or PD and/or poor treatment tolerance with previous lines of treatment described in Table 1.

At initiation of SD treatment, all patients exhibited multisystemic active ECD with constitutional symptoms, including episodic febricula (n = 2) and moderate (n = 2, with weight loss ≤10 kg) or severe (n = 2) impaired general status. An analysis of treatment outcomes under SD versus DD is summarized in Table 1 and detailed as follows, considering global and specific organ/symptom responses.

In terms of global responses with SD, three patients exhibited PR (Patients 1, 3 and 4), and one patient progressed (Patient 2). Under DD, the patients achieved CR (Patients 3 and 4), sustained improved PR (Patient 1, with a decrease of more than 75% of ECD symptoms) and PD after a temporary PR (Patient 2). Therefore, DD was pursued in the three patients with CR or PR. In one of the two patients with CR (Patient 3), SD was eventually resumed, and CR was maintained for the seven following months. DD was stopped in the patient with failure. This patient showed no improvement under canakinumab or lenalidomide plus corticosteroids, but a good response under vemurafenib (960 mg b.i.d orally) associated with SD treatment, although the BRAF mutant clone was minor. This association was initiated as a rescue treatment because of recurring pericarditis responsible for cardiogenic shock and because BRAF V600E mutation was found in a majority of tumour cells and at only one of the two biopsy sites. After two months of treatment, vemurafenib-related painful palmo plantar erythrodysesthesia led to a vemurafenib dose decrease and SD withdrawal. At rapid disease relapse, half-dose vemurafenib and SD treatment were resumed, leading to CR, sustained for 18 months.

Regarding cardiac and pleural involvements, all three patients with right atrial masses exhibited sustained (Patient 3 and 4) or newly acquired CR (Patient 2) under DD, even though this was only transient for Patient 2. Patients 1 and 2 achieved only PR and PD, respectively, on massive precardiac and pleuro-pericardic serositis under SD. With DD treatment, they achieved a sustained PR and a transient PR, respectively, for the serositis.

Xanthelasma was present in two patients for which SD led to CR and PR, respectively, followed by CR in both patients on DD. Retro-orbital/neurologic active involvement was present only in Patient 2, as an active bilateral exophthalmos. She achieved stable disease and PR with SD treatment and PR and CR with DD treatment, for each eye respectively. Patients 2 and 3 had insipidus diabetes that was not modified by treatments; this involvement was considered to be from sequelae.

Notably, two patients (Patients 1 and 3) exhibited unpublished intraperitoneal involvements of the disease, with the added clinical features of subacute appendicitis/peritonitis and sub-occlusive syndrome. CT-scan imaging and surgical procedures found mesenteric panniculitis, peritoneal nodules and serositis in both patients, associated with pseudo-tumoural appendicitis images for Patient 3 (Figures 1A and 1B). For both patients, extemporaneous histopathologic findings confirmed specific ECD involvement (Figure 2). The two patients showed PR and CR with SD, then CR with DD, respectively, for this involvement.

Bone and retroperitoneal imaging showed improvements with both doses, the DD regimen producing a CR in terms of functional imaging (no more metabolic activity on 18FDG/PET-scan, despite persistent inactive fibrosis on CT-scan) in both locations in the two patients (Patients 3 and 4).

All patients had initial moderate renal insufficiency that improved under SD treatment and then with DD treatment (Table 1). Both doses exhibited identical minor side-effects, consisting mainly of transient reactions at injection sites and/or an episodic cutaneous rash in all. Patients 3 and 4 presented with mild and transient neutropenia under DD treatment. At last follow-up, all patients had good and stable global outcomes under DD treatment for Patient 1 (PR) and Patient 4 (CR), SD treatment for Patient 3 (CR), and SD treatment with half-dose vemurafenib for Patient 2 (CR).

Discussion

Doubling the dose improved response to anakinra in 3 of 4 ECD patients who were previously refractory and/or partial responders to interferon therapy or to anakinra SD treatment. Indeed, two CRs and one long term PR response were observed with anakinra DD treatment, with the same good tolerance profile compared to conventional SD treatment. Failures of DD treatment were essentially related to cardiac and pleuritic massive serositis, whereas both SD and DD treatments were effective in unpublished mesenteric and appendicular locations of the disease. In this small series, these outcomes do not seem to be correlated with the molecular status of the disease, including BRAF V600E or NRAS mutations.

The efficacy of anakinra SD treatment appeared variable; both efficacy and failure are reported in sparse cases of cardiac, neurological and pleural ECD involvements. The variability of the anakinra response in ECD should depend on the organ involved and might be related to at least two phenomena.
Therefore, they concluded that anakinra could be an alternative first-line therapy for severe forms of ECD, regardless of mutational status, as was also found herein.

The tolerance to anakinra is often good in long term use, as reported in ECD and in several auto-inflammatory and rheumatic diseases. Therefore, increasing the dose of anakinra to obtain the best possible efficacy without a significant increase in safety risk appears to be a credible therapeutic alternative. Indeed, the high specificity of the natural IL-Ra (or its recombinant form) for its receptor, which is essentially expressed by monocyctic/macrophagic cells, explains the lack of systemic or tissue toxicities with this treatment.

The results of this short series show a constant effectiveness, even though sometimes partial, of anakinra in ECD, regardless of the observed underlying molecular defect. However, the exact role and history of these mutations in ECD are not yet fully understood. Indeed, BRAF mutation is widely observed in several tumoural diseases. Hence, it appears to be non-specific and is not the unique molecular event in ECD pathogenesis. BRAF mutation is found in less than 60% of biopsies performed in the short series of ECD patients. The robust local and systemic response in ECD may be explained by BRAF V600E mutation, which activates oncogene-induced senescence pathways, likely attracting inflammatory and immune cells and inducing a senescent pro-inflammatory phenotype in both mutated and bystander infiltrating cells. Other pathogenic molecular defects, including those of NRAS, KRAS or MEK-ERK pathway genes, are also reported in ECD. On the

| Table 1. Patients’ characteristics, treatment courses and outcomes. |
|-----------------------------------------------------------|
| **Sex, age at disease diagnosis (y)** | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
| Male, 68 | Female, 58 | Male, 52 | Male, 61 |
| **Genetic mutations** | N Ras | N Ras | N Ras | N Ras |
| **Treatment history (m = duration in months)** |
| Interferon (INF), high dose (HDINF) | INF + C T(1 m) → AK(9 m) → AKx2(2 m) → C TC + V IN(3 m) → HDINF(6 m) → INF(6 m) → AK(12 m) → AKx2(38 m) |
| Corticosteroids (CT) | HDINF(5 m) → HDINF + C T(1 m) → INF(6 m) → AK(6 m) → CAN(2 m) → AK(2 m) → AKx2(32 m) |
| Anakinra 1 dose [100 mg/d] (AK) | AKx2(42 m) → LEN + C T(2 m) → AK+ C T(2 m) → AKx2(12 m) → AKx2(3 m) |
| Anakinra 2 doses [100 mg × 2/day] | VEM + AK(2 m) → AK(2 m) → AKx2(36 m) |
| Vemurafenib (VEM) | 1/2 VEM(1 m) → 1/2 VEM(18 m) |
| Vemurafenib half-dose (1/2 VEM) | 1/2 VEM(1 m) → 1/2 VEM(18 m) |
| Canakinumab (CAN) | 1/2 VEM + AK(18 m) |
| Vincristine (VIN) Lenalidomide (LEN) | 1/2 VEM + AK(18 m) |
| **Outcome under ANAKINRA: SINGLE DOSE → DOUBLE DOSE** |
| CR = Complete response | PR = Partial response | SD = Stable disease | PD = Progressive disease |
| NA | NA | NA | NA |
| **- Constitutional signs** | CR → CR | PR → CR | CR → CR | CR → CR |
| - C-reactive protein (mg/L) | ≤ 5 (PR → CR) | ≤ 5 (PR → CR-transient) | ≤ 5 (PR → CR) | ≤ 5 (PR → CR) |
| - Bone imaging | PR → CR | PR → CR | CR → CR | CR → CR |
| - Exophthalmos (bilateral) | NA | NA | NA | NA |
| - Cardiac/pleural involvements | PR → CR | PD → CR | CR → CR | CR → CR |
| - Intraperitoneal nodules/serositis | CR → CR | NA | NA | NA |
| - Insipidus diabetes | NA | Stability (sequela) | Stability (sequela) | NA |
| - Retropertoneal imaging | PR → CR | PD → CR | CR → CR | CR → CR |
| - Lumbar pains | CR → CR | PR → CR | CR → CR | CR → CR |
| - Xanthelasma | NA | NA | NA | NA |
| - Creatinine clearance (ml/min/1.73 m²) | 40 → 50 | 45 → 78 | 38 → 64 | 32 → 55 |
| - Global Outcome under Anakinra | - PR → sustained improved | - PR → CR |
| Site of treatment failure | Residual pleural effusion | Cardiac & pleural effusions | NA | NA |
| Time to response under SD / DD | 0.5 month / 0.25 month | 1 month / 1 month | 0.5 month / 0.5 month | 0.75 month / 0.5 month |
| Time to failure under SD / DD | 6 months / NA | 9 months / 2 months | 6 months / NA | 12 months / NA |
| - Global outcomes / Final treatment | - Ongoing PR / AKx2 (42 months) | - Ongoing CR / VEM (18 months) | - Ongoing CR / AKx2 (12 months) then AK (36 months) | - Ongoing CR / AKx2 (38 months) |
other hand, studies in melanoma demonstrated a link between pathogenic mechanisms of both *BRAF* mutation and interleukin-1. These studies showed that the inflammatory process in this disease is produced by an overproduction of this proinflammatory cytokine by the specific and environmental fibroblastic cells of tumours that exhibit *BRAF* mutation.18,32 Moreover, Murakami et al. showed in a model of Langerhans cell histiocytosis (LCH) that *BRAF* mutation leads to IL-1 overproduction and therefore indicates that both *BRAF* mutations and IL-1 form a loop in regulation as potential therapeutic targets.33 Taken together, these findings allow us and others to suggest that the increased dose of anti-IL-1 drugs or their combination with anti-*BRAF* drugs may offer a synergic and optimal treatment option in refractory ECD.21,32,34 *BRAF* and/or MEK inhibitors have or will likely proved their frequent efficacy in patients with corresponding mutations in prospective studies.15 Therefore, the strategic place of anti-cytokine therapy such as anakinra, which exhibits the most effect in ECD,11 remains to be specified considering the toxicity profiles of these targeted therapies and patients’ history of cutaneous neoplasms other than melanoma.

**Patients and methods**

**Patient selection**

In our cohort of 10 ECD patients treated with daily subcutaneous single dose (SD) anakinra treatment of 100 mg (SD), six patients achieved a CR. In the 4 remaining patients, we retrospectively collected the systematic analysis of global and organ-specific outcomes following double dose (DD) anakinra treatment. For all patients, the diagnosis was based on histology and the presence of clinical and radiological pictures suggestive of ECD. This study received the Institutional Review Board (CPP Nord-Ouest III, ref. CHU: A14-D62-VOL.23) agreement.

**Genetic analyses**

The detailed, highly sensitive genetic techniques used herein were previously reported, including the related results for two patients (Patients 1 and 2).19,21 Briefly, genomic DNA was extracted from formalin-fixed, paraffin-embedded samples after histologic review and enrichment by macrodissection to ≥ 10% histiocytes. All samples were obtained from patients before any therapy. Detection of *BRAF* V600 and NRASQ61 mutations was performed by pyrosequencing for all patients. For Patient 2, in which the *BRAF* V600 mutation was not initially detected, further analysis for *BRAF* mutations with multiplex picodroplet digital polymerase chain reaction (PCR)19 (Raindance Technologies) finally identified this genetic defect in 20% of pathologic histiocytic cells. Screening for mutations in other genes was performed with Sequenom mass spectrometric-based genotyping assays, as previously described (*NRAS*, *KRAS*, *PIK3CA*, and *AKT1* hotspot mutations).35

**Figure 1.** Abdominal CT-scan findings in Erdheim-Chester disease. (A) - Appearance of acute uncomplicated appendicitis with a marked inflammatory thickening of the whole appendix (up to 14 mm; dotted line and perpendicular measuring bar), in the usual anatomical localization, without stercolithis. Significant infiltration of adjacent mesenteric fat, without collection, is noted. (B) - Left pararenal lymphadenopathy (12–13 mm; dotted line and perpendicular measuring bar). Atrophied right kidney (not shown) and hypertrophic left kidney (15 × 9 × 9 cm).

**Figure 2.** Pathologic features of appendicular/mesenteric tissues in Erdheim-Chester disease involvement. Tissue infiltration by pathologic histiocytes with foamy cytoplasm: H&E x 400 (A) and CD68 staining x400 (B).
Treatment and assessment of outcomes

DD corresponded to a subcutaneous dose of anakinra of 100 mg b.i.d. Clinical outcomes were assessed as complete response (CR; with complete resolution of ECD symptoms), partial response (PR; partial resolution of ECD symptoms), stable disease (no change in ECD symptoms), or progressive disease (PD; worsening of ECD symptoms). Early and long-term tolerances, including renal function, were also studied. Radiological response was assessed based on RECIST criteria 1.1: CR was defined as the disappearance of a given lesion; PR as a decline of at least 30% in the sum of the longest lesion diameters; PD as an increase of at least 20% in the sum of lesion diameters or appearance of new lesions; and stable disease was defined as neither PR nor PD. Most patients did not undergo positron emission tomography, and response was therefore evaluated based on alternative imaging studies available.

Disclosure of potential conflicts of interest

AA received financial support from SOBI for a study on anakinra in giant cell arteritis. All other authors have declared that there are no conflicts of interest regarding the publication of this paper.

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