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CASE REPORT

Clinical, biological and sonographic response to IL-1 blockade in adult-onset Still's disease

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Introduction

Adult-onset Still's disease (AOSD) is an uncommon systemic inflammatory disorder of unknown etiology, characterized by high-spiking fever, evanescent salmon-pink rash, leukocytosis, hepatic dysfunction, polyserositis, lymphadenopathy, splenomegaly, arthritis or arthralgias (1). Although its pathogenesis remains unclear, abnormalities in cytokine serum levels documented a Th1 predominance with high serum concentration of IL-1, IL-6, TNF-α, IFN-γ and soluble IL-2 receptor, candidating AOSD as a Th1 mediated disease (2). Several conventional treatments have been used in AOSD, such as non-steroidal anti-inflammatory drugs, often in combination with corticosteroids, and immunosuppressive therapy (methotrexate, azathioprine, cyclosporine A, leflunomide, and cyclophosphamide) or intravenous gammaglobulins (3). More recently, anti-cytokine agents (anti-TNF-α anti-IL1, anti-IL6) have been sporadically used in refractory AOSD, opening new avenues to the therapeutic approach of this disease, which, up to now, remains empirical. The IL-1 receptor antagonist (IL-1Ra) anakinra seems to be effective for AOSD (4-12) even if neutralisation of IL-1 might be more effective in patients with highly active systemic disease than in patients with chronic arthritis, with no or less intense systemic symptoms (12) (Table I).

We report three cases of AOSD with severe joint involvement resistant to conventional treatment where anakinra administration resulted in sustained remission. Moreover, the benefit on arthritis was confirmed by musculoskeletal ultrasound (US).

Patients and methods

Between 2000 and 2007, 18 patients with AOSD classified according to Yamaguchi criteria were seen in the Department of Rheumatology, Sapienza Università di Roma.

Among them, 3 were considered refractory to traditional treatment and, after obtaining informed consent, were treated with anakinra (100mg/subcutaneously daily). The patients were evaluated at baseline and after 3 months of anakinra treatment for systemic symptoms (fever, exanthema, lymphadenopathy, hepatosplenomegaly, and serositis), tender joint count (TJC), swollen joint count (SJC), physician global assessment of disease activity, patient assessment of pain; DAS28 was calculated and ACR response considered (13). The following laboratory values were also collected: haematological profile, first-hour erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum ferritin levels. Laboratory data and joint scores before treatment are summarized in Table II.

US was performed in hand and wrist bilaterally in the patients 1, 2 and 3; in patient 1 knee joint was also studied. The joints evaluated were chosen because they were involved in our patients. US was performed by an experienced rheumatologist sonographer, using a Philips/HP Image Point HX machine equipped with 10 and 14 MHz linear probes for knee and wrist/hand respectively. Power Doppler (PD) was also applied with the following settings: frequency 7.5 MHz, PRF 700-1000Hz, gain 18-40dB, low filter. The joints were examined according to EULAR guidelines for ultrasonography in Rheumatology and the presence of alterations within the joint and periarticular soft tissues were considered to be present according to OMERACT definitions for ultrasonographic pathology related to common pathological lesions seen in patients with inflammatory arthritis (14, 15). The presence of inflammation was documented in joints and/or periarticular tissues (joint effusion, synovial proliferation, hyperaemia in the synovial tissue, tenosynovitis) together with the presence of permanent damage (bone erosions and cartilaginous abnormalities). For all the changes a semiquantitative score (0-3) was used for each structure examined, where 0 indicated the absence of any change and 1 to 3 the presence, respectively, of slight, moderate, and severe changes. The subsequent summed total was used as an indicator of global change in each joint (single-joint score). The sum of the single-joint scores was used as an indicator of overall polyarticular involvement in each patient (total score) (16).

Table I. Anakinra therapy in AOSD. Principal studies published so far.

Authors	Patients	Concomitant therapy	Follow-up	Patients evaluation
Rudinskaya A *et al*. (2003)[4]	1 pt	PDN, MTX	12 months	ESR, CRP, ferritin, WBC
Aelion J et al (2004)[6]	2 pt	Pt 1: PDN, MTX Pt 2. no therapy	Not specified	ESR, ferritin, WBC
Haraoui B *et al*. (2004)[7]	3	Pt 1. PDN, Cy Pt 2: PDN, MTX, HCQ Pt 3: PDN, MTX	Pt 1: 6 months Pt 2: 4 months Pt 3: 5 months	Only clinical response
Fitzgerald AA *et al*. (2005) [9]	4 pt	Pt 1: PDN Pt 2: PDN Pt 3: PDN, MTX Pt 4: PDN	Pt1*: 12 months Pt 2**: 14 months Pt 3: 6 months Pt 4: 12 months	Pt 1: ferritin, CRP, WBC, IL18 Pt 2: ESR, WBC Pt 3: CPR, WBC, ferritin Pt 4: CPR, WBC, ESR, ferritin
Vasques Godinho FM *et al*. (2005) [5]	1 pt	PDN, MTX	18 months	ESR, WBC
Kalliolias GD *et al*. (2007) [10]	4 pt	PDN	5-17 months	Clinical evaluation, WBC ESR, CRP, ferritin
Kötter I *et al*. (2007) [11]	4 pt	Pt 1: PDN, LFN Pt 2: PDN, MTX Pt 3: PDN, MTX Pt 4: PDN; MTX	12 months	Clinical evaluation, ESR, CRP, IL-6, TNF-α
Lequerrè T *et al*. (2007) [12]	15 pt	12 pts: PDN 10 pts: MTX 1 pt: MMF + col 1 pt: col	1-27 months	ACR response, HAQ, clinical evaluation

*On two different occasions the patients witheld anakinra with reactivation of the disease. She finally progressed to macrophage activation syndrome and cyclosporine was added. **On one occasion anakinra was stopped and successfully restarted.
(MTX: methotrexate; PDN: prednisone; Cy: cyclophosphamide; MMF: mycophenolate mofetil; LFN: leflunomide; HCQ: hydroxychloroquine; col: colchicine; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cell).

Table II. Laboratory parameters, joint clinical and sonographic scores before and after three months of treatment with anakinra.

	Patient 1		Patient 2		Patient 3	
	Baseline	After 12 weeks	Baseline	After 12 weeks	Baseline	After 12 weeks
ESR (mm/h)	18	4	8	9	68	8
CRP (mg/dl)	6	1	5	2	32	3
Ferritin (ng/ml)	1130	28.3	118	13.3	820	62.5
Tender joint	12	4	18	1	14	2
Swollen joint	10	1	8	0	6	0
Prednisone (mg/daily)	25	5	25	12.5*	25	7.5
VAS for activity disease of patient	76	20	64	5	72	10
VAS for activity disease of physician	78	46	58	5	70	5
DAS28 index	5.91	2.79	5.66	2.10	6.77	2.3
ACR response	–	ACR50	–	ACR50	–	ACR20
US score	18	4	48	12	22	6

*on alternate days.

PD evaluation was performed for the analysis of vascularization of the synovial membrane with a scoring system ranging from 0 to 3 (indicating respectively absence of increased perfusion or minimal, moderate severe perfusion) (17). The single joint scores were added to obtain a global US score.

Case 1

A 32-year-old north African woman presented with symmetric poliarthritis of wrists, hands and knees, intermittent fever (up to 39°C), faringodynia and rash associated to increase in C-reactive protein (CRP) level (60mg/liter), ESR 38 mm/h and ferritin (1030 ng/ml). After the exclusion of infective, neoplastic and other rheumatic disorders, AOSD was diagnosed. The patients responded only partially to treatment (methotrexate 15 mg/im weekly for five months, hydroxychloroquine (HCQ) 400 mg/daily added to methotrexate (MTX) in the last 2 months, oral prednisone 25 mg/daily and indometacine) and even if biological markers of activity ameliorated, an invalidating hand, wrist and knee arthritis persisted. US, perfomed in the involved joints, showed wrists synovial proliferation with erosions of radio-carpal bone surface, tenosynovitis of left flexor carpi radialis and flexor carpi ulnaris, synovitis of second and third MCP and knee joint effusion. MTX was stopped and

anakinra started with a progressive improvement of joint symptoms. By the end of the 8th week of treatment the patient developed a diffuse itching rash of the face, limbs and abdomen. Anakinra was discontinued and MTX was reintroduced. US performed after anakinra discontinuation showed improvement of the synovitis in the second and third MCP, resolution of synovitis and tenosynovitis in the wrist and of joint effusion in the knee. The patient, treated with MTX 15 mg weekly and low doses of oral corticosteroids, was still in clinical remission 6 months after anakinra discontinuation.

Case 2

A 32-year-old Caucasian women presented fever up to 39°C, evanescent macular rash, lymphadenopathy, arthritis of hands and wrists, fatigue and myalgia. Laboratory evaluation showed a white blood cell (WBC) count of 15,530/µl, ESR 120mm/h, CRP 47mg/dl and ferritin 993ng/ml. Other neoplastic, inflammatory and infective diseases were excluded and AOSD diagnosed. She was initially treated with MTX 15 mg im/weekly, HCQ 400 mg /daily, prednisone 25 mg with disappearance of fever, rash and lymphadenopathy, amelioration of laboratory inflammatory markers but persistence of severe joint involvement. It was not possible to taper prednisone. At baseline US evaluation of hand and wrist showed bilateral effusion in 2nd, 3 nd and 4 nd MCP and wrist joints with synovial proliferation and positive PD. Moreover, tenosynovitis was present in flexor tendons of 2nd, 3nd and 4nd fingers. Anakinra was started and after three months, US performed in the same joints studied at baseline, demonstrated the resolution of tenosynovitis of hand and wrist, with persistence of mild effusion in 2nd and 3 nd MCP and wrist joints bilaterally. Prednisone could be was tapered up to 12.5 mg on alternate days.

Case 3

A Caucasian women with Turner's disease (mosaicism 90%XX; 10%XO) periodically treated with intravenous immunoglobulins because of selective IgG1 deficiency was diagnosed with AOSD (wrist and hand arthritis, remittent fever up to 39°C, maculopapular rash, increase of ESR, CRP, ferritin and transaminases) at the age of 16 and she was successfully treated with oral prednisone. At 22 years old, there were new episodes of fever and skin rash, hepatic involvement and severe hand and wrist arthritis; this last feature was resistant to HCQ 400 mg/daily and oral prednisone 25 mg/daily while other symptoms had subsided. US showed intrarticular effusion with synovial proliferation at the radio-carpal joints, mild intra-articular effusion at the MCPs; tenosynovitis of the 2nd and 4nd finger flexor tendons. Anakinra 100 mg fl sc/daily was started with dramatic improvement; prednisone could be tapered to 7.5 mg daily. US performed after three months in the same joints showed the presence of bilateral mild effusion in the radio-carpic joint and 2nd and 3nd MCP joint.

Results

Table II shows laboratory parameters, joint clinical and sonographic scores before and after three months of treatment with anakinra. A relevant improvement of joint involvement was recorded in all the patients, in particular the mean DAS28 reduced from 6.1 to 2.2; when considering the ACR response criteria, 2 patients achieved ACR50 response and one patient ACR20 response. US evaluation demonstrated a good response to treatment: mean US score decrease from 29.3 to 6.6. (Fig. 1). The mean dose of steroids could be reduced in all the patients.

Further follow-up

Two patients (cases 2 and 3) are currently treated with anakinra, with mean follow-up duration of 92 weeks. Patient 2 is still in remission after 29 months without side effects; patient 3 was in

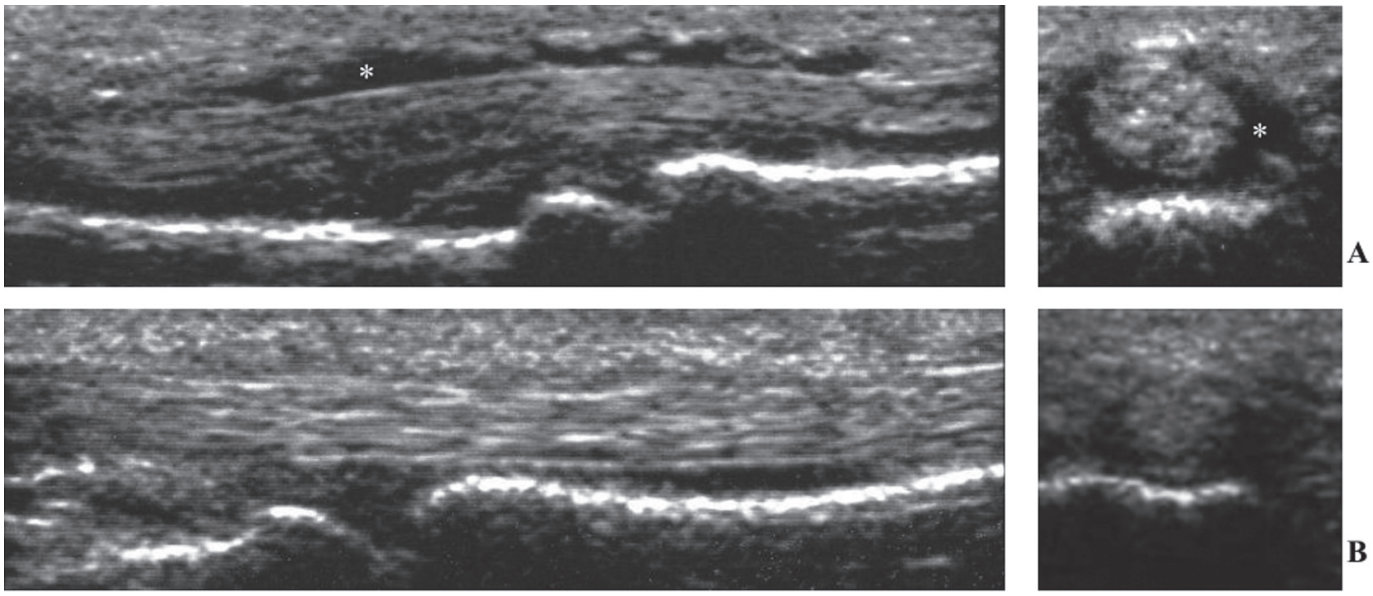

Fig. 1. Longitudinal and transverse scan of superficialis and profundus flexor tendon of the second finger before (**A**) and after therapy with anakinra in patient 2. (**A**): hypoechoic region (*) around flexor tendon as from tenosynovitis; (**B**): disappearance of hypoecoic region, as from resolution of tenosynovitis.

remission up to 12 months of anakinra treatment, when presented a flare-up of hand and wrist arthrits with improvement after increase of steroid dosage.

Discussion

Evidence-based medicine guidelines for the management of AOSD are lacking and this disease still represents a therapeutic challenge. Recent advances in AOSD pathogenesis advocate a key role for inflammatory cytokines such as IL-1 and IL-18 in the disease pathogenesis, favouring the usage of blocking agents against these molecules in refractory AOSD treatment (18-20).

IL-1 is a potent pyrogen and hematopoietic growth factor and it is known to up-regulate, through IL-6 synthesis, the expression of acute-phase reactants. Moreover IL-1 appears to mediate the disease also at articular level by interacting with other cytockines such as IL-18 and TNF-α (21). All these data correlate with the biological effects observed in AOSD patient after anakinra administration, showing marked decrease in IL-1, IL-18, IL-6 levels, significant clinical improvement with fever and leucocytosis disappearance (22-25).

Reports of anakinra use in AOSD are limited. Rudinskaya *et al*. report the case of an adult patient with AOSD, previously refractory to conventional therapies, who dramatically responded to the addition of anakinra to MTX (4). Similar results were subsequently obtained in other cases (5-9) even in the absence of the concomitant administration of MTX. IL-1 blockade seems to lead to a sustained remission and allows the tapering if not complete steroid withdrawal.

Recently, Kalliolias described 4 patients who experienced a fast and safe response to anakinra, with a steroid sparing effect (10). Kötter confirmed this result in 4 other patients, underlying that IL-18 serum levels, CRP, ESR, liver enzymes, ferritin, and WBC, may be helpful in assessing disease activity and response to treatment (11). Lequerrè reported the results obtained in 20 patients with systemic-onset juvenile idiopathic arthritis (SoJIA) and 15 AOSD patients with active arthritis, treated by anakinra, defining the response as a resolution of systemic symptoms and an improvement of the ACR score. The response to anakinra after 3 and 6 months was rapid and sustained in most patients with AOSD and in a significant proportion of SoJIA patients: 11 of the 15 AOSD patients achieved at least a 50% improvement for all disease markers (12) The authors suggest that anakinra might be more effective in patients with highly active systemic disease than in those with chronic arthritis. Although AOSD arthritis is known to be not progressive or deforming (25), in our patients joint involvement and the consequent physical inability were the most prominent clinical features, while systemic symptoms and laboratory abnormalities had partially responded to conventional treatment. High degree of inflammation was shown by US in the affected joints, as demonstrated by the presence of signs of synovitis, joint effusion, hyperperfusion, tenosynovitis. Over the last few years, US has become an established imaging technique in rheumatology because of its ability to visualize soft tissue changes and it is nowadays considered a first line tool for monitoring disease activity and response to treatment also with biological agents (16).

As far as we know, US has never been used to evaluate response to anakinra in AOSD: with this tool we could document a frank improvement of arthritis after the blockade of IL-1 receptor. Adopting a sonographic scoring system to evaluate the severity of joint involvement it was possible to quantify the improvement obtained with anakinra. For the same reason, as previously done (12), we chose to calculate DAS 28 and ACR response. Even if larger studies should be performed, possibly with a longer follow-up, our report, strenghtened by the use of US, suggests that anakinra might be useful in AOSD also in the presence of severe arthritis. This observation is partially in contrast to what previously reported by Lequerré (12). We could also confirm a steroid sparing activity of anakinra as lower levels of corticosteroid were required for all our patients after three months of treatment. Of note, in one of our patient, resistant to MTX clinical response persisted after anakinra withdrawal for adverse effect and clinical remission was maintained with methotrexate (previously ineffective) only, supporting the role of this drug even in remission induction. Even if an association between Turner's syndrome and inflammatory arthritis have been already described (26), the third case can be considered a peculiar one in that she had also a IgG1 deficiency which was periodically treated with i.v. immunoglobulins. Such treatment had no impact on AOSD systemic symptoms nor on the arthritis which finally resolved with anakinra. Of note, no side effects were recorded in this case.

In conclusion, this observation suggests that anakinra might be useful for AOSD with severe joint involvement resistant to conventional treatment.

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