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Beneficial Effect of Interleukin 1 Inhibition with Anakinra in Adult-onset Still's Disease. An Open, Randomized, Multicenter Study

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ABSTRACT. Objective. To study the efficacy of anakinra versus disease-modifying antirheumatic drugs (DMARD) in refractory adult-onset Still's disease (AOSD).

Methods. In a 24-week study, 22 patients with AOSD taking prednisolone ≥ 10 mg/day received anakinra (n = 12) or DMARD (n = 10). The primary endpoint was achievement of remission.

Results. At 8 and 24 weeks, 7/12 and 6/12 receiving anakinra and 5/10 and 2/10 receiving DMARD achieved remission. Anakinra induced greater improvement in physical health measured by Medical Outcomes Study Short-Form 36 (SF-36; $p < 0.011$). During an open-label extension (OLE) of 28 weeks, 7/14 patients taking anakinra and 2/3 taking DMARD were in remission.

Conclusion. Anakinra induced more beneficial responses than DMARD in patients with AOSD and was favored in the OLE phase. (ClinicalTrials.gov Protocol Registration NCT01033656). (First Release Aug 1 2012; J Rheumatol 2012;39:2008–11; doi:10.3899/jrheum.111549)

Key Indexing Terms:

ADULT-ONSET STILL'S DISEASE
RANDOMIZED

ANAKINRA
MULTICENTER

INTERLEUKIN 1
WISSLER'S SYNDROME

The pathogenesis of adult-onset Still's disease (AOSD) implicates dysregulation of cytokine-mediated signaling cascades¹. Many *in vivo* effects of the cytokines interleukin 1 (IL-1), IL-6, and tumor necrosis factor- α (TNF- α) correspond to the distinctive features of AOSD².

There is no consensus on treatment, but corticosteroids^{3,4} are frequently required. Disease-modifying antirheumatic drugs (DMARD) including cyclosporine A (CSA)⁵, methotrexate (MTX)^{6,7}, azathioprine (AZA), sul-

fasalazine (SSZ)⁸, leflunomide (LEF)⁹, and anti-TNF therapy are helpful in refractory AOSD¹⁰. Positive results with anakinra in patients with even severe AOSD or systemic-onset juvenile idiopathic arthritis have been reported^{11,12}. Tocilizumab¹³ is another promising approach.

In this randomized trial we compared the effect of anakinra with that of a DMARD in patients with AOSD refractory to corticosteroids. The study was approved by local independent ethics committees.

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MATERIALS AND METHODS

Patients. Twenty-two patients from 10 centers in Finland, Norway, and Sweden were included for study (Table 1). All fulfilled the following criteria (comprehensive inclusion/ exclusion criteria given in the Appendix): (1) AOSD diagnosed according to the preliminary classification by Yamaguchi, *et al*¹⁴; (2) treatment with corticosteroid and possibly a DMARD for ≥ 2 months prior to randomization; and (3) refractory to corticosteroids and DMARD, defined as active disease in spite of prednisolone ≥ 10 mg/day with or without concomitant DMARD.

All patients gave their written informed consent before entering the study.

Study design. This was an open, randomized (1:1), multicenter trial with 2 parallel patient groups with refractory AOSD. The objective was to follow 3 clinical variables describing remission for 24 weeks in patients receiving anakinra or a DMARD (MTX, AZA, LEF, CSA, or SSZ) plus corticosteroids. A 28-week open-label extension (OLE), with switching or add-on treatment with the comparator drug, was possible if improvement did not occur within 24 weeks.

The primary endpoint was remission according to specific criteria at 8 weeks [afebrile ($\leq 37^{\circ}\text{C}$ body temperature, measured twice from armpit), in

Table 1. Patient characteristics at study entry.

Characteristic	DMARD, n = 10	Anakinra, n = 12
Women/men	5/5	6/6
Age, mean (SD) yrs	39 (17)	39 (18)
Duration of disease, mo, median (range)	19 (3–204)	14 (2–240)
CRP, mg/l, mean (range)	25 (0.2–116)	25 (0.5–104)
Ferritin, $\mu\text{g/l}$, mean (range)	186 (17–680)	354 (18–1740)*
ESR, mm/h, mean (range)	17 (1–37)	24 (5–84)
White blood cell count, mean (range)	13.2 (7.4–21.4)	10.6 (3.6–22.4)
Platelet count, mean (range)	298 (234–417)	355 (158–573)
Physician global, mm, mean (range)	21 (2–43)	21 (6–45)
Patient global, mm, mean (range)	28 (0–65)	25 (3–60)
Swollen joints, mean (range)	2 (0–10)	2 (0–13)
Tender joints, mean (range)	3 (0–14)	4 (0–20)
Fever, n (%)	1 (10)	1 (8)
Rash, n (%)	8 (80)	9 (75)
Prednisolone dose, mg, mean (range)	18.5 (10–25)	22.5 (10–60)*
Drug therapy (patients on drug)	MTX 6, AZA 3, LEF 1	anakinra 12

* Significant difference ($p < 0.001$). CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MTX: methotrexate; AZA: azathioprine; LEF: leflunomide; DMARD: disease-modifying antirheumatic drug.

the absence of nonsteroidal antiinflammatory drugs (NSAID) 24 hours prior to measurement, decrease of CRP and ferritin to reference limits] and normal swollen (SJC) and tender joint counts (TJC).

Assessments. At Week 4 the effect of therapy was assessed. Enhancement of the DMARD dose was allowed, but escalation of corticosteroids implied treatment failure. Efficacy was assessed at Weeks 8, 12, and 24. Full response was defined as body temperature $\leq 37^\circ\text{C}$, C-reactive protein (CRP) $\leq 10\text{ mg/l}$, and ferritin $\leq 200\text{ }\mu\text{g/l}$ female, $\leq 275\text{ }\mu\text{g/l}$ male, and normal SJC/TJC. Health Assessment Questionnaire (HAQ), SF-36, and global and disease-related assessments of health were applied.

Treatments. All patients initially received prednisolone $\geq 10\text{ mg/day}$ and NSAID if needed. Corticosteroid dosage had to be kept constant for 4 weeks from randomization. Study drugs were as follows: daily anakinra 100 mg with subcutaneous injection in prefilled syringe, or MTX 10–25 mg weekly oral/subcutaneous/intramuscular; AZA 1–3 mg/kg/day oral; LEF 20 mg/day oral; CSA 2.5–5 mg/kg/day divided into 2 oral doses; SSZ 1000–2000 mg/day oral. Two intraarticular corticosteroid injections in 24 weeks were allowed.

Injection site reactions (ISR). To alleviate acute pain the syringe was warmed and a cold pack was applied to the injection site. Delayed reactions were mitigated by topical hydrocortisone or antihistamine cream¹⁵. ISR were graded on a scale of 1–5, where grade 3 indicated a serious reaction requiring hospitalization.

Statistics. Originally, the number of patients needed for statistical power was calculated to be 30 in each group. Randomization was done according to a computer-generated blocked (block size 10) randomization list. Statistical comparisons between groups were made by permutation-type tests.

RESULTS

Twenty-two patients fulfilled the inclusion criteria and were randomized (Table 1), 12 to anakinra and 10 to DMARD (6 MTX, 2 AZA, 2 LEF). Patient groups were comparable except for baseline ferritin and prednisolone dose.

Efficacy in randomized phase. More patients receiving anakinra than those on DMARD achieved remission. In remission at Week 4 were 6/12 versus 3/10 and at Week 8,

7/12 versus 5/10 (Figure 1). At Week 24, 6/12 on anakinra were in remission versus 2/10 on DMARD. These differences did not reach statistical significance. By Week 24 mean prednisolone doses had been reduced in both the anakinra and the DMARD group (Figure 2A). Three patients on anakinra but none on DMARD were able to discontinue oral corticosteroids ($p = 0.22$). Two patients on DMARD needed 1 intraarticular injection each. CRP nor-

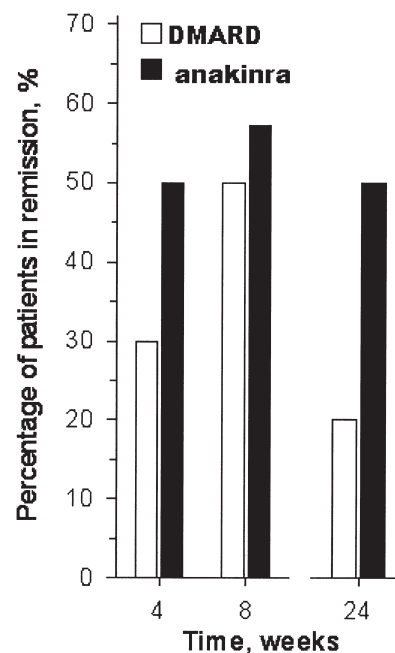


Figure 1. Percentage of patients in remission (primary endpoint: patients must be afebrile, with normal C-reactive protein and ferritin and normal swollen/tender joint counts). DMARD: disease-modifying antirheumatic drugs.

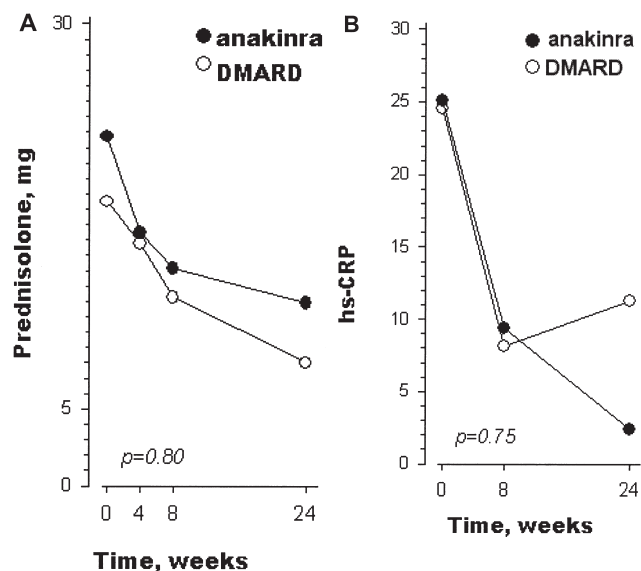


Figure 2. A. In both the anakinra and the disease-modifying antirheumatic drugs (DMARD) group by Week 24, prednisolone equivalent doses could be significantly reduced by mean 10.8 and 10.5 mg, respectively. Three anakinra patients compared with 0 DMARD patients were able to discontinue oral corticosteroids (data not shown). No significant differences between groups were detected. B. C-reactive protein (CRP) normalized by Week 8 in both groups, with no statistical difference between groups.

malized by Week 8, but with no difference between the groups (Figure 2B). More patients on anakinra than on DMARD achieved improvements in the SF-36 physical health summary (Figure 3; $p = 0.011$).

Adverse events. Only 3 patients experienced serious adverse events, that is, worsening of AOSD (lack of efficacy) in 1 on

anakinra (visit 5) and in 2 on DMARD (MTX visit 1; LEF visit 4). The patient on anakinra continued in the OLE with combined anakinra and MTX, the patient receiving MTX withdrew prematurely, and the patient receiving LEF started anakinra in the OLE and finished the study.

Seven patients out of 12 receiving anakinra reported grade 1 ISR and 1 patient reported a grade 2 ISR. Four additional patients in the OLE reported grade 1 ISR. No subject withdrew from the study because of ISR.

Open-phase extension. The OLE was completed by 17 patients, 9 of whom originally received anakinra and 8 DMARD. At Week 52, 8/9 originally receiving anakinra had anakinra as monotherapy and 1 received anakinra and MTX. Only 3 patients originally on DMARD (2 on MTX and 1 on AZA) remained on the same medication at Week 52. Among DMARD patients, 2 had switched to MTX and anakinra, 1 to LEF and anakinra, 1 to anakinra monotherapy, and 1 to infliximab. At Week 52, 7/14 had anakinra (+ combinations) and only 2/3 on DMARD were in remission.

DISCUSSION

In this first randomized study of refractory AOSD, more patients taking anakinra than DMARD achieved remission. One patient on anakinra withdrew because of flare and completed the study on anakinra and MTX. Two patients on DMARD withdrew because of lack of efficacy. One of them entered the OLE and completed the study using anakinra. In the OLE, further withdrawals occurred among patients originally on DMARD. Differences between groups did not reach statistical significance, but patients on anakinra seemed to show more robust responses. Normalization of CRP and ferritin and reductions/discontinuations of corti-

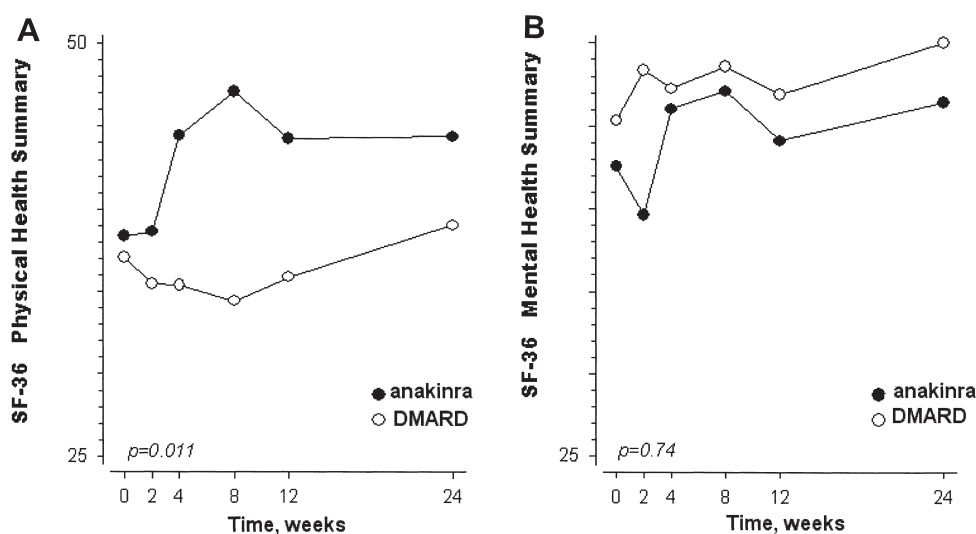


Figure 3. A significantly greater number of patients using anakinra achieved improvements according to the Medical Outcomes Study Short-Form 36 (SF-36) physical health summary compared to patients using disease-modifying antirheumatic drugs (DMARD; A; $p = 0.011$). SF-36 mental health summary showed no differences between groups (B).

costeroids were documented, still with no differences between the groups. The fact that all patients had been pre-treated with corticosteroids for at least 2 months allows less possibility for dramatic responses. Anakinra induced rapid responses, indicated by significant improvements in physical health.

There were only 3 serious adverse events, namely disease flares, 2 in the DMARD and 1 in the anakinra cohort. Other adverse events included flu-like symptoms, diarrhea, and myalgias. ISR caused by anakinra were reported by several patients, but these did not result in withdrawals and were treated as described¹⁵.

A majority of patients receiving anakinra but only 3 patients on DMARD completed 52 weeks using the medication they received at randomization. During the OLE half of the patients randomized to DMARD had a disease flare. In the OLE they converted to anakinra as monotherapy or combined with DMARD. This part of the protocol, reflecting real clinical experience, resulted in anakinra monotherapy or an anakinra/DMARD combination in 14 patients, half of whom were in remission at Week 52. Only a few patients using DMARD reached 52 weeks on the same drug.

Anakinra is a valuable drug for inducing remission in refractory AOSD, especially when DMARD therapy has failed.

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APPENDIX. Details of inclusion and exclusion criteria.

Patients fulfilled the following inclusion criteria:

1. Diagnosed with AOSD according to Yamaguchi, *et al*¹⁴.
2. Exposed to a corticosteroid and possibly a DMARD for ≥ 2 months prior to randomization because of diagnosed AOSD.
3. Considered refractory to corticosteroids and DMARD. Refractory state was defined as need for prednisolone ≥ 10 mg/day (or equivalent) with or without concomitant use of DMARD, and unacceptable disease activity as determined by the investigator.
4. ≥ 18 years of age at the time of consent.
5. For women, not pregnant (negative pregnancy test was done before the first study drug and conducted via a reliable screening, if not surgically sterile or at least 5 years post-menopausal). Both female and male patients must have used medically acceptable contraceptive/preventive precautions throughout the study, as determined by the investigator.
6. Doses of NSAID and oral corticosteroid had been stable for ≥ 2 weeks before randomization.
7. If using DMARD, doses had been stable for ≥ 4 weeks before randomization.
8. If randomized to anakinra, the patient was able to self-inject the drug, or must have a caregiver do it.
9. If previously treated with anti-TNF agents, patients had discontinued etanercept ≥ 4 weeks and infliximab or adalimumab ≥ 8 weeks prior to starting the study medication.

Exclusion criteria:

1. Use of corticosteroids below prednisolone equivalent of 10 mg/day.
2. Any grade 3 or 4 adverse event, or laboratory toxicity, at the time of the screening visit or at any time during the study, that in the opinion of the investigator would preclude participation in the study.
3. Pregnant or breast-feeding women.
4. Female or male patients not willing to use med-

ically acceptable contraceptive/preventive precautions as determined by the investigator.

5. Total white blood cell count $< 2.0 \times 10^9/l$, neutrophil count $< 1.0 \times 10^9/l$, or platelet count $< 100 \times 10^9/l$.
6. Elevated serum creatinine (≥ 1.5 H upper limit of normal).
7. Elevated serum ALT or AST (≥ 3 H upper limit of normal).
8. Abnormal hemoglobin or erythrocyte count (outside 30% of the upper/lower limits of normal).
9. Severe comorbidities (e.g., diabetes mellitus, cardiovascular or pulmonary diseases, history of cancer) that may prevent inclusion, according to the investigator's opinion.
10. History of recurrent or chronic infection, including tuberculosis; any malignancy; any other major chronic inflammatory disease; drug or alcohol abuse; known positive for hepatitis B or C, or HIV.
11. Use of anti-TNF agents ≤ 4 weeks (etanercept) or ≤ 8 weeks (infliximab or adalimumab) prior to randomization, or need for using them during the entire study.
12. Known hypersensitivity to active or inactive substances in study drugs (e.g., allergy to sulfonamide in patients receiving sulfasalazine).
13. Use of a live vaccine 90 days prior to or during the study.
14. Treatment in the past with anakinra.

REFERENCES

1. Choi JH, Su CH, Lee YM, Suh YJ, Lee SK. Serum cytokine profiles in patients with adult-onset Still's disease. *J Rheumatol* 2003;30:2422-7.
2. Dinarello CA. Blocking IL-1 in systemic inflammation. *J Exp Med* 2005;201:1355-9.
3. Khraishi M, Fam AG. Treatment of fulminant adult Still's disease with intravenous pulse methylprednisolone therapy. *J Rheumatol* 1991;18:1088-90.
4. Koizumi R, Tsukada Y, Ideura H, Ueki K, Maezawa A, Nojima Y. Treatment of adult Still's disease with dexamethasone, an alternative to prednisolone. *Scand J Rheumatol* 2000;29:396-8.
5. Shojania K, Chalmers A, Rangno K. Cyclosporin A in the treatment of adult Still's disease. *J Rheumatol* 1995;22:1391-2.
6. Aydintung AO, D'Cruz D, Cervera R, Khamashta MA, Hughes GR. Low dose methotrexate treatment in adult onset Still's disease. *J Rheumatol* 1992;19:431-5.
7. Fautrel B, Borget C, Rozenberg S, Meyer O, Le Loet X, Masson C, et al. Corticosteroid sparing effect of low dose methotrexate treatment in adult Still's disease. *J Rheumatol* 1999;26:373-8.
8. Bliddal H, Helin P. Leucopenia in adult Still's disease during treatment with azathioprine and sulphasalazine. *Clin Rheumatol* 1987;6:244-50.
9. Cefle A. Leflunomide and azathioprine combination in refractory adult-onset Still's disease. *Ann Pharmacother* 2005;39:764-7.
10. Fautrel B, Sibilia J, Mariette X, Combe B. Tumour necrosis factor alpha blocking agents in refractory adult Still's disease: An observational study of 20 cases. *Ann Rheum Dis* 2005;64:262-6.
11. Pascual V, Allantaz F, Arce E, Punaro M, Banchereau J. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J Exp Med* 2005;201:1479-86.
12. Fitzgerald AA, LeClerc 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.
13. Puechal X, De Bandt M, Berthelot J-M, Breban M, Dubost J-C, Kahn J-E, et al. Tocilizumab in refractory adult Still's disease. *Arthritis Care Res* 2011;63:155-9.
14. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H. Preliminary criteria for classification of adult Still's disease. *J Rheumatol* 1992;19:424-30.
15. Kaiser C, Knight A, Nordström D, Pettersson T, Fransson J, Florin-Robertsson E, et al. Injection-site reactions upon Kineret (anakinra) administration — Experiences and explanations. *Rheumatol Int* 2011;32:295-9.