

Testing the Model for Predicting Effectiveness of Anakinra in Systemic Juvenile Idiopathic Arthritis

To the Editor:

We read the article by Saccomanno, *et al*, "Predictors of effectiveness of anakinra in systemic juvenile idiopathic arthritis," with great interest¹. They reported that shorter disease duration, fewer active joints, higher ferritin levels, and greater activity of systemic manifestations were independently correlated with achievement of complete clinical response at 1 year (CCR1) in systemic juvenile idiopathic arthritis (sJIA). They proposed a model with 4 variables (disease duration ≤ 3.9 yrs, active joint count ≤ 10 , ferritin > 444 ng/ml, systemic manifestation score > 3) to predict response to anakinra in sJIA¹.

We have analyzed these variables and tested this model in our cohort of patients with sJIA. The patients (0–18 yrs old) treated with anakinra at Hacettepe University Pediatric Rheumatology Department between January 2006 and January 2018 were included. The patients were classified with sJIA according to the International League of Associations for Rheumatology criteria². Demographic data, clinical manifestations, laboratory findings, and CCR1 were documented. The study was approved by the ethics committee of Hacettepe University (GO 16/154) and written consent from the patients/parents was obtained according to the Declaration of Helsinki.

These factors were the same as those stated in the article by Saccomanno, *et al*¹: the definition for CCR (absence of fever, negative C-reactive protein, physician's global assessment ≤ 1 , active joint count ≤ 1 , and $\geq 75\%$ reduction of corticosteroid dose from baseline), systemic manifestation score, and the inclusion/exclusion criteria for patients to keep the results comparable. The normality of distribution of numerical variables

was investigated using visual (histogram, probability plots) and analytic methods (Shapiro-Wilk's test), and descriptive analyses were presented using medians, minimum, and maximum values. Chi-square or Fisher's exact test was used to compare categorical variables, and Mann-Whitney U test was used to compare the non-normally distributed variables between 2 groups. A p value of < 0.05 was considered a statistically significant result.

A total of 45 patients with sJIA were included; 28 (62.2%) were complete responders while 17 (37.8%) did not achieve CCR1 (nonresponders). The characteristics of the patients are presented in Table 1.

The median active joint count was lower (0 vs 3; $p = 0.005$) while the ferritin level was higher (620.5 vs 162 ng/ml) and the disease duration was shorter (6 vs 24 mos) at initiation of anakinra treatment in complete responders compared to nonresponders. However, 2 latter differences were statistically insignificant. Significantly more patients were still receiving anakinra (85.7% vs 41.2%; $p = 0.002$) while fewer patients were taking corticosteroids at 1 year (3.6% vs 82.4%; $p < 0.001$) in the complete responder group compared to the nonresponders. Flares under anakinra treatment were more frequently observed among nonresponders than complete responders. The model proposed by Saccomanno, *et al*¹ was tested in all patients (Table 2). Significantly higher numbers of complete responders than nonresponders met all 4 variables (67.9% vs 8.3%, respectively; $p = 0.001$). Of note, only 1 patient among the 12 nonresponders who had complete information for the 4 variables of the model met all variables in this model.

The rate of CCR1 in our sJIA cohort (62.2%) is in the high range among the rates (31–85%) reported in previous studies^{1,3,4,5,6,7}. In our patients, the number of active joints at initiation of anakinra was significantly higher in complete responders compared to nonresponders, and the model proposed by Saccomanno, *et al*¹ seems to be associated with higher rate of CCR1.

Table 1. The characteristics of children with systemic juvenile idiopathic arthritis treated with anakinra (n = 45).

Characteristics	Complete Responders, n = 28	Nonresponders, n = 17	p
Female	16 (57.1)	9 (52.9)	0.78
Age at symptom onset, yrs	4 (0.75–15.7)	5 (1–4.6)	0.46
Age at diagnosis, yrs	4.3 (0.9–15.9)	5.3 (2–13)	0.46
Age at initiation of anakinra, yrs	6.5 (1.6–16.1)	8 (2.8–13.2)	0.49
Disease duration at initiation of anakinra, mos	6 (1–142)	24 (2–84)	0.17
Dose of anakinra, mg/kg daily	2 (2–4)	2 (2–5)	0.46
PGA, 0–10 scale, 10 worst	5 (2–7)	5 (4–8)	0.84
Fever	28 (100)	17 (100)	—
Rash	22 (78.6)	11 (64.7)	0.32
Hepatomegaly	9 (32.1)	6 (35.3)	0.82
Splenomegaly	11 (39.3)	5 (29.4)	0.54
Generalized lymphadenopathy	11 (39.3)	4 (23.5)	0.27
Serositis	7 (25)	4 (23.5)	1
Hemoglobin, g/dl	10 (7.6–15.1)	10.3 (6.5–12.6)	0.72
WBC count, $\times 10^3/\text{mm}^3$	12.75 (2.4–52.9)	11.3 (4–21)	0.26
Neutrophil count, $\times 10^3/\text{mm}^3$	8.45 (0.6–43.6)	8.5 (1.9–18.6)	0.78
Platelet count, $\times 10^3/\text{mm}^3$	480 (219–883)	504 (202–820)	0.59
ESR, mm/h, normal range 0–20	46 (10–120)	49 (28–120)	0.81
CRP, mg/dl, normal range 0–0.8	9.41 (1–34)	7.18 (1.6–26)	0.26
Fibrinogen, mg/dl, normal range 144–430	409.5 (206–983)	406.5 (238–1200)	0.74
Ferritin, ng/ml, normal range 11–307	620.5 (312–8849)	162 (50–692)	0.056
Systemic manifestation score	5 (2–8)	3 (2–8)	0.13
Duration of anakinra treatment, mos	17 (3–60)	10 (2–50)	0.26
Still using anakinra at 1 yr	24 (85.7)	7 (41.2)	0.002
Still using corticosteroids at 1 yr	1 (3.6)	14 (82.4)	< 0.001
Presence of flare under anakinra treatment	4 (14.3)	15 (88.2)	< 0.001



Numeric variables are presented as median (min–max) values. Nominal variables are presented as n (%). CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PGA: physician's global assessment; WBC: white blood cell.

Table 2. The variables of the model proposed by Saccomanno, *et al*¹ in the cohort of patients with systemic juvenile idiopathic arthritis treated with anakinra. Data are n (%).

Variables	Complete Responders, n = 28	Nonresponders, n = 17	p
Disease duration ≤ 3.9 yrs	22 (78.6)	11 (68.8)	0.72
Active joint count ≤ 10	27 (96.4)	14 (82.4)	0.14
Ferritin > 444 ng/ml	25 (89.3)	3/12 (25)	< 0.001
Systemic manifestation score > 3	24 (85.7)	8 (47.1)	0.008
Meeting all 4 variables of the proposed model	19 (67.9)	1/12 (8.3)	0.001

Previously reported potential predictors of antiinterleukin (IL)-1 response were older age at disease onset, shorter disease duration, less severe joint disease, elevated white blood cell and neutrophil counts, and anti-IL-1 agents being used as first-line treatment in patients with sJIA naive to disease-modifying antirheumatic drugs (DMARD) or corticosteroids^{4,5,7,8}. In our cohort, there was no significant difference between complete responders and nonresponders regarding white blood cell and neutrophil counts and none of our patients were corticosteroid- or DMARD-naive at initiation of anakinra. There was a trend toward older age at disease onset, longer disease duration, and lower ferritin levels in nonresponders compared to complete responders (Table 1). However, these differences were not statistically significant, probably because of the small sample size.

Verifying and validating the factors predicting anakinra response in sJIA are critical for personalized medicine and choosing the right patient to benefit from anakinra.

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