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 interest[1]. 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 sJIA[1].

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 criteria[2]. 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 ≥ 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 (non-responders). 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 Saccamanno, *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, × 10^3/mm^3	12.75 (2.4–52.9)	11.3 (4–21)	0.26
Neutrophil count, × 10^3/mm^3	8.45 (0.6–43.6)	8.5 (1.9–18.6)	0.78
Platelet count, × 10^3/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.

SEZA OZEN, MD, Division of Rheumatology, Department of Pediatrics, Hacettepe University Faculty of Medicine; SELCAN DEMIR, MD, Division of Rheumatology, Department of Pediatrics, Hacettepe University Faculty of Medicine; EZGI DENIZ BATU, MD, Division of Rheumatology, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey. Address correspondence to Dr. S. Ozen, Department of Pediatrics, Division of Rheumatology, Hacettepe University Faculty of Medicine, Ankara 06100, Turkey.
E-mail: sezaozen@gmail.com

REFERENCES

1. Saccomanno B, Tibaldi J, Minoia F, Bagnasco F, Pistorio A, Guariento A, et al. Predictors of effectiveness of anakinra in systemic juvenile idiopathic arthritis. J Rheumatol 2019;46:416-21.
2. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-2.
3. Kearsley-Fleet L, Beresford MW, Davies R, De Cock D, Baildam E, Foster HE, et al. Short-term outcomes in patients with systemic juvenile idiopathic arthritis treated with either tocilizumab or anakinra. Rheumatology 2019;58:94-102.
4. Nigrovic PA, Mannion M, Prince FH, Zeft A, Rabinovich CE, van Rossum MA, et al. Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. Arthritis Rheum 2011;63:545-55.
5. Pardeo M, Pires Marafon D, Insalaco A, Bracaglia C, Nicolai R, Messia V, et al. Anakinra in systemic juvenile idiopathic arthritis: a single-center experience. J Rheumatol 2015;42:1523-7.
6. Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis 2011;70:747-54.
7. Vastert SJ, de Jager W, Noordman BJ, Holzinger D, Kuis W, Prakken BJ, et al. Effectiveness of first-line treatment with recombinant interleukin-1 receptor antagonist in steroid-naive patients with new-onset systemic juvenile idiopathic arthritis: results of a prospective cohort study. Arthritis Rheumatol 2014;66:1034-43.
8. Gattorno M, Piccini A, Lasiglie D, Tassi S, Brisca G, Carta S, et al. The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum 2008;58:1505-15.

First Release June 15 2019; J Rheumatol 2019;46:10;
doi:10.3899/jrheum.190238