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Factors Associated With Treatment Response to Etanercept in Juvenile Idiopathic Arthritis

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Context Since the introduction of biologic therapies, the pharmacological treatment approach for juvenile idiopathic arthritis (JIA) has changed substantially, with achievement of inactive disease as a realistic goal.

Objective To determine the response to therapy after initiation of etanercept therapy among patients with JIA and to examine the association between baseline factors and response to etanercept treatment.

Design, Setting, and Patients The Arthritis and Biologicals in Children Register, an ongoing prospective observational study since 1999, includes all Dutch JIA patients who used biologic agents. All biologically naive patients who started etanercept before October 2009 were included, with follow-up data to January 2011. Among the 262 patients, 185 (71%) were female, 46 (18%) had systemic-onset, and the median age at initiation of etanercept treatment was 12.4 years.

Main Outcome Measures Excellent response (inactive disease or discontinuation earlier due to disease remission), intermediate response (more than 50% improvement from baseline, but no inactive disease), and poor response (less than 50% improvement from baseline or discontinuation earlier due to ineffectiveness or intolerance) evaluated 15 months after initiation of etanercept.

Results At 15 months after treatment initiation, 85 patients (32%) were considered excellent responders; 92 (36%), intermediate responders; and 85 (32%), poor responders. Compared with an intermediate or poor response, an excellent response was associated with lower baseline disability score (range, 0-3 points, with 0 being the best score; adjusted odds ratio [OR] per point increase, 0.49; 95% CI, 0.33-0.74); fewer disease-modifying antirheumatic drugs (DMARD) (including methotrexate) used before initiating etanercept (adjusted OR per DMARD used, 0.64; 95% CI, 0.43-0.95), and younger age at onset (adjusted OR per year increase, 0.92; 95% CI, 0.84-0.99). Compared with an intermediate or excellent response, a poor response was associated with systemic JIA (adjusted OR systemic vs nonsystemic categories, 2.92; 95% CI, 1.26-6.80), and female sex (adjusted OR female vs male, 2.16; 95% CI, 1.12-4.18). Within the first 15 months of etanercept treatment, 119 patients experienced 1 or more infectious, noninfectious, or serious adverse events, including 37 among those with an excellent response, 36 with an intermediate response, and 46 with a poor response. Within the first 15 months of treatment, 61 patients discontinued etanercept treatment, including 4 with an excellent response, 0 with an intermediate response, and 57 with a poor response. In a secondary analysis of 262 patients with a median follow-up of 35.6 months after initiation of etanercept, a range of 37% to 49% of patients reached inactive disease. The mean adherence to etanercept was 49.2 months (95% CI, 46.4-52.0) for patients with an excellent response after 15 months, 47.5 months (95% CI, 44.9-50.1) for patients with an intermediate response, and 17.4 months (95% CI, 13.6-21.2) for patients with a poor response.

Conclusions Among patients with JIA who initiated treatment with etanercept, one-third achieved an excellent response, one-third an intermediate response, and one-third a poor response to therapy. Achievement of an excellent response was associated with low baseline disability scores, DMARDs used before initiating etanercept, and younger age at onset of JIA. Achievement of a poor treatment response was associated with systemic JIA and female sex.

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ETANERCEPT, A TUMOR NECROSIS factor α antagonist, was approved a decade ago by the US Food and Drug Administration and the European Medicines Agency for the treatment of juvenile idiopathic arthritis (JIA). The efficacy of etanercept for patients with JIA and a polyarticular course has been established in a randomized placebo-controlled withdrawal trial that showed 30% improvement from baseline according to the American College of Rheumatology (ACRpedi 30) in more than 70% of the patients.[1] Several observational studies, including the Dutch Arthritis and Biologicals in Children (ABC) Register, confirmed the effectiveness of etanercept in daily practice.[2-4] Since the development of biological agents, the pharmacological treatment approach of JIA is changing rapidly, and synthetic disease-modifying antirheumatic drugs (DMARDs) are used earlier in the disease course, which seem to provide better long-term outcomes.[5,6] As a result

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of these successes, a treatment goal of reaching inactive disease now seems realistic. However, inactive disease is still not achieved in a substantial proportion of cases, and current approaches need to be optimized even more.[2-4] Although factors associated with methotrexate response have been analyzed, factors associated with the effect of etanercept treatment in JIA are still unknown.[7] The ability to identify patients who are more likely to respond to etanercept treatment would be an important step toward tailored patient-specific treatment and subsequently could improve current treatment approaches.

Therefore, the objectives of this study were to evaluate disease activity after etanercept initiation in daily practice, and to identify baseline characteristics associated with etanercept treatment response in JIA patients.

METHODS

Study Design and Participants

This study is part of a multicenter prospective observational register, the ABC Register, which was founded with the introduction of biologics in 1999 and includes all JIA patients in the Netherlands who use or previously used biological agents.

The study protocol was approved by the medical ethics committee at Erasmus Medical Center Rotterdam and by all participating hospitals. Written informed consent was obtained from parents and from participants older than 12 years. In the register, which became Web based in 2008, patient and disease characteristics are collected at baseline, followed by data collection after 3 months of treatment and yearly thereafter.[8] This includes the variables of the JIA disease activity score (ie, the JIA core set): physician's global assessment of disease activity on a visual analog scale (range, 0-100 mm, 0 best score), the Childhood Health Assessment Questionnaire (CHAQ; range, 0-3, 0 is the best score) by patients or parents, including global assessment of well-being by a visual analog scale, number of active and limited joints, and erythrocyte sedimentation rate (ESR).

In addition to entering follow-up data at 3 months and then yearly, extra data entry times were at the time of any important events including when biologic agents were discontinued, type of biologic agent switched, or when there were safety concerns. On average, 6 data entry points per patient were available.

For this study, we selected all JIA patients in whom etanercept was initiated as the first biologic treatment and who could have had at least 15 months of follow-up. Follow-up data until January 2011 were used.

Response to therapy was assessed using the ACRpedi 30, 50, and 70 criteria. For each variable of the JIA core set improvement from baseline has been expressed as a percentage. The definition of an ACRpedi 30, 50, and 70 response states that there should be at least, depending on the score, 30% or 50% or 70% improvement from baseline in 3 or more variables of the JIA core set, with no more than 1 variable worsening by more than 30%.[9] A modified definition for inactive disease was used and defined as no active arthritis, no systemic features, no uveitis, normal ESR (≤20 mm/h), and physician's global assessment of disease activity indicating no disease activity (defined as a score ≤10 mm).[10]

Factors Associated With Treatment Response

Based on literature, we analyzed the following potential baseline factors for treatment response: sex, age at JIA onset, disease duration until start of etanercept, antinuclear antibody positivity, JIA category (systemic-onset vs all other categories), number of DMARDs (including methotrexate) used before start of etanercept, and, at initiation of etanercept, physician's global assessment of disease activity, CHAQ score, and ESR. Based on the number of patients in the study, we restricted the number of factors and assumed that the number of active joints with arthritis in the physician's global assessment and the number of joints with limited motion in the CHAQ score reflected each other.

An excellent treatment response was defined as achievement of inactive disease after 15 months (range, 12-18 months) of treatment or within this time frame ever discontinuation of etanercept because of disease remission. An intermediate response was defined as achievement of an ACRpedi 50 response after 15 months of treatment, but no inactive disease. A poor response to treatment was defined as no achievement of an ACRpedi 50 response after 15 months of treatment, or within these 15 months ever discontinuing etanercept due to ineffectiveness or adverse events.

Safety Analysis

All infectious and noninfectious adverse events and all serious adverse events were reported by the physician on a continuous basis. Serious adverse events were defined as life-threatening or fatal events, events resulting in persistent or significant disability, events requiring intervention to prevent permanent impairment or damage, congenital anomalies, or hospitalization or prolongation of existing hospitalization. Flaring of JIA was not considered an adverse event but as a measure of treatment response.

We calculated the rate of serious, infectious, and noninfectious adverse events on the basis of the duration of etanercept exposure. We considered recurrent infections as separate events. If noninfectious adverse events were reported repeatedly within the same patient, we counted them only once. Factors to identify patients who experienced adverse events within the first 15 months were analyzed. We also analyzed the number of adverse events between 3 and 15 months of follow-up in those patients using a combination of etanercept and methotrexate and in those using monotherapy etanercept.

Statistical Analysis

The multiple imputation method of the AregImpute function of the *R* Statisti-

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cal Package (http://www.r-project.org) was applied to impute missing values of the JIA core sets at observed follow-up times: 13.6% of the JIA core set variables were missing; 4.0% of active and 7.1% of limited joint counts, 7.6% of ESR values, 19.4% of physician's global assessment of disease activity scores, 23.1% of CHAQ scores, 20.6% of global assessment of well-being scores were missing; and per core set median of 0 (interquartile range [IQR], 0-1) variables were missing.

Descriptive statistics were reported as absolute frequencies or as median values with IQR. Depending on the variable tested, the Mann-Whitney U test and the Pearson χ^2 test were used to perform comparisons. Univariable and multivariable logistic regression analyses were performed to identify potential baseline factors associated with achieved treatment response (comparing excellent response vs poor and intermediate response combined and comparing poor response vs intermediate and excellent responses combined). To identify patients who experienced adverse events within the first 15 months, a multivariable logistic regression analysis for binary outcome was performed. Results are presented as adjusted odds ratios (OR; the OR for each covariate was adjusted for the effects of the other covariates) with 95% confidence intervals; *P* values were calculated with the Wald test.

We also conducted secondary analyses of longer-term outcomes. Adherence to etanercept was estimated with Kaplan-Meier plots (truncated until at least 10% of the original population was in follow-up) and differences between the systemic-onset JIA and all other JIA categories (ie, nonsystemic categories) were defined by the log-rank test. To account for correlations between repeated measurements and missing follow-up times generalized linear mixed models for binary response data (according to the GLIMMIX procedure) were used to perform the long-term effectiveness analyses.

All reported *P* values were based on 2-sided tests for significance, and *P* values $<.05$ were considered statistically significant. SPSS version 17.0.1, R statistical package 2.12.1, and SAS version 9.2 were used for the analyses.

Table 1. Patient and Disease Characteristics at Baseline

Baseline Characteristics	No. (%) of Patients			
	All JIA Patients (N = 262)	Excellent Responders (n = 85)[a]	Intermediate Responders (n = 92)[a]	Poor Responders (n = 85)[a]
Patient characteristics				
Female	185 (71)	57 (67)	60 (65)	68 (80)
Age at JIA onset, median (IQR), y	6.9 (3.6-11.1)	6.5 (3.3-9.8)	7.0 (3.4-11.3)	9.0 (3.7-12.2)
Age at start of etanercept, median (IQR), y	12.4 (9.3-14.9)	12.0 (9.1-15.1)	12.6 (9.0-14.7)	12.5 (9.4-15.5)
Disease duration before start etanercept, median (IQR), y	3.0 (1.5-6.8)	3.6 (1.8-7.8)	3.1 (1.5-6.6)	2.3 (1.2-4.5)
JIA characteristics				
Systemic onset	46 (18)	11 (13)	15 (16)	20 (24)
Polyarticular rheumatoid factors				
Negative	102 (39)	32 (38)	38 (41)	32 (38)
Positive	23 (9)	5 (6)	8 (9)	10 (12)
Oligoarticular type				
Persistent	5 (2)	4 (5)	1 (1)	0 (0)
Extended	57 (22)	22 (26)	18 (20)	17 (20)
Arthritis psoriatica	17 (6)	6 (7)	7 (8)	4 (5)
Enthesitis-related arthritis	12 (5)	5 (6)	5 (5)	2 (2)
ANA positivity	60 (23)	20 (24)	19 (21)	21 (25)
Use of medications before start of etanercept				
NSAIDs	257 (98)	83 (98)	92 (100)	82 (96)
Corticosteroids				
Systemic	133 (51)	37 (44)	49 (53)	47 (55)
Intra-articular	66 (25)	26 (31)	25 (27)	15 (18)
Methotrexate	227 (87)	72 (85)	78 (85)	77 (91)
Other DMARDs	115 (44)	36 (42)	47 (51)	32 (38)
DMARDs used, median (IQR)[b]	1 (1-1)	1 (1-2)	1.5 (1-2)	1 (1-2)
Concomitant medication at start of etanercept				
NSAIDs	217 (83)	67 (79)	86 (93)	66 (78)
Corticosteroids				
Systemic	96 (37)	25 (29)	37 (40)	34 (40)
Intra-articular	8 (3)	4 (5)	4 (4)	0 (0)
Methotrexate	234 (89)	75 (88)	86 (93)	73 (86)
Other DMARDs	19 (7)	3 (4)	11 (12)	5 (6)
Disease characteristics at start of etanercept, median (IQR)				
VAS disease activity by physician, mm	63 (45-75)	57 (40-73)	67 (56-78)	61 (43-72)
No. of active joints	10 (6-18)	8 (5-15)	10 (6-22)	12 (8-18)
No of limited joints	7 (4-13)	6 (2-12)	10 (4-15)	6 (4-13)
CHAQ score (0-3)	1.5 (1.0-2.1)	1.1 (1.1-2.0)	1.8 (1.2-2.3)	1.8 (1.1-2.0)
VAS by patient/parent, mm				
Pain	57 (29-76)	52 (17-77)	54 (31-72)	56 (30-75)
VAS well-being	53 (29-75)	50 (21-77)	54 (30-75)	60 (35-75)
Erythrocyte sedimentation rate, mm/h	21 (9-37)	19 (10-33)	29 (12-44)	15 (8-35)

Abbreviations: ANA, antinuclear antibody; CHAQ, Childhood Health Assessment Questionnaire; DMARDs, disease-modifying antirheumatic drugs; IQR, interquartile range; JIA, juvenile idiopathic arthritis; NSAIDs, nonsteroidal anti-inflammatory drugs; RF, rheumatoid factor; VAS, visual analog scale.
[a] Measured after 15 months (range, 12-18 months) of treatment.
[b] Includes methotrexate.

RESULTS

Patient Characteristics and Medications

A total of 262 previously biologically naive JIA patients who started etanercept were included in the analysis.

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TABLE 1 presents the patient and disease characteristics of these patients. The total follow-up duration was 881.4 patient-years (of which 683.7 patient-years were exposure to etanercept), with a median follow-up time of 35.6 months per patient (IQR, 17.4-53.6 months).

At etanercept initiation, 37% of patients used concomitant systemic corticosteroids, 89% methotrexate, and 7% other DMARDs. After 15 months of etanercept treatment, systemic corticosteroids were discontinued in 69% of the patients using them at start, methotrexate in 42%, and other DMARDs in 88%. During the first 15 months of treatment, only small numbers of patients started concomitant medication (9 systemic corticosteroids, 2 methotrexate, and 5 other DMARDs).

Response to Therapy at 15 Months

Of the 262 patients, 85 (32%) were considered excellent responders after 15 months of treatment (81 patients achieved inactive disease after 15 months and 4 patients discontinued etanercept up to that time point because of remission). A total of 85 patients (32%) were considered poor responders (44 patients had discontinued etanercept because of ineffectiveness, 13 because of adverse events, and 28 patients had not reached an ACRpedi 50 response after 15 months of treatment). The remaining 92 patients were considered intermediate responders. Table 1 presents the patient and disease characteristics for the excellent, intermediate, and poor responders.

The adjusted ORs are shown for association between prespecified baseline variables and response to therapy in logistic regression analysis, comparing excellent responses vs poor and intermediate and comparing poor responses vs intermediate and excellent (TABLE 2). Compared with achieving an intermediate or poor response, achievement of an excellent response was associated with lower baseline CHAQ scores (adjusted OR per point increase, 0.49; 95% CI, 0.33-0.74); low number of DMARDs (including methotrexate) used before introduction of

Table 2. Factors Associated With Response to Etanercept

Variable	Absolute Risk, %[a]		Excellent vs Intermediate and Poor Responders			
			Univariable		Multivariable	
	Excellent Responders (n = 85)	Intermediate or Poor Responders (n = 177)	OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Female vs male	67	72	0.78 (0.45-1.36)	.38	0.85 (0.45-1.59)	.61
Systemic-onset JIA vs nonsystemic subtypes	13	20	0.60 (0.29-1.26)	.18	0.49 (0.20-1.18)	.11
ANA positivity vs negativity	24	23	1.05 (0.57-1.95)	.87	0.73 (0.37-1.46)	.38
Age of onset JIA, per year increase in age at onset	6	7	0.94 (0.89-1.00)	.06	0.92 (0.84-0.99)	.03
Disease duration before start of etanercept, per year	10	11	1.08 (1.01-1.15)	.04	1.05 (0.96-1.15)	.26
No. of DMARDs used before start of etanercept, per DMARD used[b]	17	18	0.90 (0.64-1.25)	.52	0.64 (0.43-0.95)	.03
VAS disease activity by physician at start of etanercept, per 10-point increase	10	11	0.86 (0.67-0.97)	.02	0.89 (0.77-1.02)	.10
CHAQ score at start of etanercept, per 1-point increase	33	42	0.49 (0.34-0.71)	<.001	0.49 (0.33-0.74)	.001
ESR at start of etanercept, per 1-unit mm/h increase	3	3	0.84 (0.50-1.41)	.51	1.03 (0.57-1.85)	.92
	Poor Responders (n = 85)	Intermediate or Excellent Responders (n= 177)	Poor vs Intermediate and Excellent Responders			
			OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Female vs male	80	66	2.05 (1.11-3.80)	.02	2.16 (1.12-4.18)	.02
Systemic-onset JIA vs nonsystemic subtypes	24	15	1.79 (0.93-3.43)	.08	2.92 (1.26-6.80)	.01
ANA positivity vs negativity	25	22	1.16 (0.63-2.13)	.63	1.29 (0.66-2.52)	.47
Age of onset of JIA, per year	7	7	1.07 (1.01-1.14)	.02	1.08 (0.99-1.16)	.07
Disease duration before start of etanercept, per year[c]	11	10	0.92 (0.85-1.00)	.04	0.95 (0.87-1.05)	.31
No. of DMARDs used before start of etanercept, per DMARD used[b]	19	17	0.98 (0.70-1.36)	.89	1.21 (0.83-1.76)	.33
VAS disease activity by physician at start of etanercept, per 10-point increase	11	11	0.96 (0.85-1.09)	.14	0.95 (0.83-1.09)	.53
CHAQ score at start of etanercept, per 1-point increase	42	37	1.31 (0.93-1.85)	.13	1.47 (0.98-2.20)	.07
ESR at start of etanercept, per 1-unit mm/h increase	3	3	1.00 (1.00-1.00)	.77	0.99 (0.98-1.00)	.21

Abbreviations: ANA, antinuclear antibody; adjusted OR, adjusted odds ratio; CHAQ, child health assessment questionnaire; CI, confidence interval; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; VAS, visual analog scale.

[a] For dichotomous variables, of the poor responders, 80% were female, whereas of the intermediate and excellent responders combined 66% were female. For continuous variables, a 33% increase in excellent responders was seen for each point increase of CHAQ score, whereas a 42% increase in intermediate and poor responders combined was seen for each point increase of CHAQ score. The OR for each variable was adjusted for the effects of the other variables.

[b] Includes methotrexate.

[c] The confidence intervals in the univariable analysis were rounded from 0.923 (95% CI, 0.854-0.997).

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etanercept (adjusted OR per DMARD used, 0.64; 95% CI, 0.43-0.95), and younger age at onset (adjusted OR per year increase, 0.92; 95% CI, 0.84-0.99). Compared with achieving an intermediate or excellent response, achievement of a poor response was associated with systemic JIA (adjusted OR systemic JIA vs nonsystemic categories, 2.92; 95% CI, 1.26-6.80), and female sex (adjusted OR female vs male, 2.16; 95% CI, 1.12-4.18). Treatment response did not appear to be associated with antinuclear antibody positivity, disease duration, physician's global assessment of disease activity, or ESR at baseline.

Adverse Events During First 15 Months

Within the first 15 months of treatment, 119 patients experienced 1 or more adverse event (infectious, noninfectious, or serious; including 37 patients with an excellent response, 36 with an intermediate response, and 46 with a poor response) and 53 patients reported at least 1 infectious adverse event or an infectious serious adverse event. These patients could not be identified beforehand with regard to antinuclear antibody status, JIA category, disease duration, and concomitant drugs used (TABLE 3). Of the 245 patients with 15 months of follow-up, 104 patients used concomitant methotrexate between 3 and 15 months of follow up, and 84 patients used monotherapy etanercept. Between 3 and 15 months of treatment these patients experienced 0.48 adverse events and 0.24 infectious adverse events per patient-year of etanercept-methotrexate combined therapy, and 0.39 adverse events and 0.13 infectious adverse events per patient-year of etanercept monotherapy (infectious adverse events: $P = .058$, Pearson χ^2).

Drug Discontinuation During First 15 Months

During the first 15 months of treatment, 61 patients (23% of all 262 patients) discontinued etanercept. Forty-four patients discontinued because of ineffectiveness of treatment, 13 patients because of adverse events. Four patients discontinued etanercept because of disease remission after a median of 14.1 months (IQR, 12.8-14.5 months), of whom 3 patients relapsed and restarted treatment after a median of 3.8 months.

Longer-term Follow-up

In the long-term, for patients with an excellent response after 15 months, mean drug survival (ie, mean duration from start until first discontinuation due to ineffectiveness or adverse events) was 49.2 months (95% CI, 46.4-52.0) vs 17.4 months (95% CI, 13.6-21.2) for patients with a poor response. TABLE 4 shows the response to treatment following introduction of etanercept over a 7-year follow-up period on the basis of intention-to-treat (ie, regardless of discontinuations of etanercept or switching to other treatments). By 51 months of treatment, 94% (95% CI, 89%-98%) of the patients reached an ACRpedi 50 response, 76% (95% CI, 65%-87%) an ACRpedi 70 response, and 40% (95% CI, 26%-54%) inactive disease.

Adherence to etanercept for different JIA categories is shown in the FIGURE. The median adherence to etanercept was lower for systemic-onset JIA (29.0 months; 95% CI, 11.0-47.0) than for the nonsystemic categories (76.8 months; 95% CI, 45.7-108.0; log-rank test $P = .03$).

During follow-up, 142 patients (54% of all 262 patients) discontinued etanercept. The reason for discontinuation in 78 patients was ineffectiveness of treatment; these patients discontinued etanercept after a median treatment duration of 14.2 (IQR, 5.7-27.2) months; however, 12 patients restarted etanercept after 4.4 years (IQR, 2.3-6.5 years). In 25 patients etanercept was discontinued because of adverse events after a median duration of 8.3 months (IQR,

Table 3. Factors Associated With the Occurrence of Adverse Events Within the First 15 Months After Etanercept Initiation

		Adverse Events					
		No. per Patient, Rate (SD)		Multivariable Logistic Regression Model			
				All		Infectious	
Characteristic	Coding	All	Infectious	Adjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
ANA status	Positive	0.85 (1.04)	0.23 (0.56)	1.39 (0.77-2.53)	.28	0.83 (0.39-1.78)	.64
	Negative	0.67 (0.95)	0.24 (0.51)	1 [Reference]		1 [Reference]	
JIA category	Systemic-onset JIA	0.70 (1.07)	0.30 (0.66)	0.77 (0.37-1.58)	.47	1.42 (0.59-3.44)	.44
	Nonsystemic categories	0.72 (0.95)	0.23 (0.49)	1 [Reference]		1 [Reference]	
Concomitant corticosteroid use at start of etanercept	Yes	0.79 (1.12)	0.22 (0.57)	1.03 (0.59-1.81)	.92	0.59 (0.28-1.24)	.17
	No	0.67 (0.87)	0.25 (0.50)	1 [Reference]		1 [Reference]	
Concomitant methotrexate use at start of etanercept	Yes	0.69 (0.95)	0.24 (0.52)	0.69 (0.31-1.52)	.35	0.71 (0.28-1.79)	.46
	No	0.93 (1.09)	0.29 (0.53)	1 [Reference]		1 [Reference]	
Disease duration before start of etanercept	Per year increase			0.96 (0.89-1.03)	.21	0.97 (0.89-1.06)	.47

Abbreviations: ANA, antinuclear antibody; JIA, juvenile idiopathic arthritis; OR, odds ratio.

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2.5-17.6 months); of these 25 patients, 6 temporarily discontinued etanercept.

Withdrawal of etanercept because of disease remission (according to the judgment of the treating physician) occurred in 39 patients after a median of 36.9 months (IQR, 24.0-48.1 months). Of the patients who discontinued etanercept because of remission (median follow-up duration after etanercept discontinuation for these patients was 13.4 months [IQR 5.3-24.7 months]), 15 had flaring and restarted etanercept treatment. These 15 patients had an initial shorter course with etanercept (28.6 months; IQR, 18.6-41.3 months) than patients who did not have flaring (45.0 months; IQR, 28.0-55.6 months; $P=.03$). At the time of treatment discontinuation due to remission, 10 of 39 patients (26%) still used concomitantly methotrexate and 6 of 39 patients (15%) nonsteroidal antiinflammatory drugs, no patients used concomitantly systemic corticosteroids.

Safety Analysis

During etanercept treatment, patients experienced a total of 31 serious, 99 infectious, and 179 noninfectious adverse events. This resulted in 0.05 serious adverse events, 0.14 infectious, and 0.26 noninfectious adverse events per patient-year of etanercept exposure. (All reported adverse events are summarized in eTable 1 and eTable 2, available at http://www.jama.com).

COMMENT

Comparing excellent with intermediate and poor response combined and poor response with intermediate and excellent response combined allowed us to analyze factors associated with etanercept treatment response after 15 months of treatment. An excellent response, reached in one-third of the patients after 15 months, was associated with lower disability scores and fewer DMARDs used before the introduction of etanercept.

In adult patients with rheumatoid arthritis, many studies showed an association between lower disability scores and fewer DMARDs used before etanercept and good responses to etanercept.[11-16] The Pediatric Rheumatology International Trials Organisation (PRINTO)[7] group analyzed factors associated with poor response to methotrexate treatment in JIA patients and found, among others, an association with longer disease duration and higher CHAQ scores. These results seem to indicate that longer disease duration with more disability is associated with a worse response, indicating a window of opportunity. The observation that the achievement of better outcomes was related with earlier treatment introduction has been reported previously for methotrexate and sulfasalazine.[5,6]

In this study, the strongest association with a poor response to etanercept was the systemic-onset JIA. Systemic-onset JIA patients had 3-times higher odds to achieve a poor treatment outcome compared with the nonsystemic JIA categories and more systemic-onset JIA patients discontinued etanercept over time. This negative relation with the systemic-onset JIA was expected because it is the most therapy-resistant JIA category. However, 11 of 46 patients (24%) with systemic-onset JIA included were excellent responders after 15 months of treatment. Surprisingly, the PRINTO group found no association between poor methotrexate response and systemic-onset JIA, although 14% of their JIA patients had the systemic-onset JIA.[7] Our results for less favorable treatment response are consistent with 2 recent studies, both reporting on the association between discontinuation of etanercept due to ineffectiveness and systemic-onset JIA.[17,18]

Results of observational studies with anakinra, an IL-1-receptor antagonist, are promising.[19-21] The ACR recommends anakinra for systemic-onset JIA with active systemic features, and equally etanercept or anakinra for systemic-onset JIA with active arthritis.[22] Also, our results indicate that some systemic JIA patients do

Table 4. Improvement From Baseline After Etanercept Initiation; Long-term Follow-up[a]

Duration After Etanercept Initiation, mo	No. of Patients	Response Groups as Defined at 15 Months of Follow-up, % of Patients			Mixed Model, % (95% CI)			
					ACRpedi Response			
		Poor	Intermediate	Excellent	30	50	70	Inactive Disease
3	262	32	35	32	89 (84-94)	72 (64-80)	48 (39-56)	11 (6-16)
15	245	28	38	35	93 (90-97)	87 (82-93)	70 (62-77)	32 (24-40)
27	177	28	38	34	93 (88-97)	88 (82 (93)	70 (61-79)	37 (27-47)
39	130	22	46	32	88 (81-95)	85 (77-92)	74 (64-83)	37 (26-48)
51	83	17	53	30	95 (91-99)	94 (89-98)	76 (65-87)	40 (26-54)
63	60	22	52	27	92 (85-100)	89 (80-97)	80 (68-92)	41 (24-58)
75	30	23	53	23	90 (79-101)	87 (74-100)	66 (44-88)	49 (24-73)
87	17	41	53	6	82 (64-101)	70 (43-97)	63 (34-93)	45 (13-77)

[a] Data for this table are developed from an intention-to-treat analysis (ie, response since introduction of etanercept; discontinuations of etanercept, or switching to other treatments were not taken into account) with the use of generalized linear mixed models for binary response data to account for correlations between repeated measurements and to account for missing follow-up times. The percentages of patients who reached American College of Rheumatology (ACRpedi) 30, 50, or 70 responses and inactive disease at the different follow-up moments since the start of etanercept are given. The percentages of patients that reached the criteria for ACRpedi 30, 50, or 70 responses and inactive disease are not mutually exclusive. Patients who achieve inactive disease are also included in the ACRpedi responses. Patients who achieved an ACRpedi 70 response are also included in the ACRpedi 30 and 50 responses, etc.

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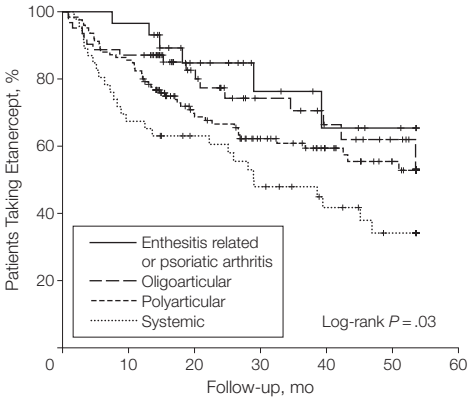
Figure. Adherence to Treatment After Introduction of Etanercept



No. at risk						
Enthesitis related or psoriatic arthritis	29	28	17	9	6	4
Oligoarticular JIA	62	54	32	20	15	10
Polyarticular JIA	125	107	66	48	33	21
Systemic onset JIA	46	31	25	19	13	8

The event is defined as the first time a patient discontinued use of etanercept due to inefficacy, adverse events, or nonadherence. Censoring is defined as the time a patient discontinued because of remission or end of follow-up (to adult care), which is represented by the small vertical lines on the curves. Restart of etanercept is not taken into account. The number at risk are patients with systemic onset of juvenile idiopathic arthritis (JIA), polyarticular JIA (rheumatoid factor positive and negative), oligoarticular JIA (persistent and extended), who were still receiving etanercept at the different time points is shown. For systemic-onset JIA the median adherence to etanercept was 29.0 months (95% CI, 11.0-47.0). For nonsystemic JIA categories, the median adherence was 76.8 months (95% CI, 45.7-108.0). Log-rank test compares the drug survival difference between systemic-onset and nonsystemic categories.

benefit from etanercept treatment. More observational data and comparisons of treatment strategies targeting different cytokines for systemic-onset JIA are needed.

A poor etanercept treatment response was also associated with female sex and an excellent response with younger age at onset. It is known that the female sex is associated with worse response for both JIA patients and rheumatoid arthritis patients. This prognostic factor is probably related to the different JIA categories that also reflect different prognosis.

We also found a possible association between concomitant methotrexate use within the first 15 months of treatment and more infectious adverse events; however, this was of borderline significance. At baseline, we were unable to identify patients who were prone to develop adverse events within the first 15 months of treatment. Therefore, the treating physician should always be alert for the development of possible adverse events.

In a secondary analysis of longer-term follow-up, this national observational cohort study shows that, 4 to 7 years after initiation of etanercept, in daily practice, a range of 37% to 49% of the patients had achieved inactive disease. Although of these patients with years of follow-up after etanercept initiation, less than one-third was considered an excellent responder after 15 months. Besides optimization of the different treatment approaches, the duration of etanercept treatment needs to be optimized. Although a range of 37% to 49% of the patients reached inactive disease, only 39 of the 262 patients (15%) tried to discontinue etanercept. Of these 39 patients, 15 relapsed and needed to restart etanercept. This relapse rate after discontinuation (38%) is relatively low compared with studies that reported relapse rates of 47% to 80%.[18,23,24] The optimal duration of inactive disease after which withdrawal of etanercept can be considered is not yet determined.

In the present patient cohort, etanercept was well tolerated. The safety profiles (0.05 serious adverse events per patient-year) are comparable with the open-label extension trial data (0.12 serious adverse events per patient-year), and with the German JIA register (0.02 serious adverse events per patient-year).[2,3] Safety of etanercept and other biologic agents remains an important topic. Until now, no malignancies have been reported in our register, which currently covers a total of 881.4 patient-years of follow-up since introduction of etanercept.

The main strength of the ABC register is that, since the introduction of etanercept in 1999, all JIA patients who initiated etanercept in the Netherlands are included and no selection bias occurred. However, because of the observational study design, reflecting a real-life setting, the choice of treatment is subject to the knowledge of the treating physicians, and differences in approach are known to exist. Furthermore, treatment strategies have changed over recent years. Since our registry covers more than a decade of treatment with etanercept, our study population is also likely to have changed over these years. This study design that requires physicians to record all patients for many years during daily practice increased the risk for missing values. In total 13.6% of the variables of the JIA core set were missing with a median of 0 per core set. Furthermore, detailed information on the used concomitant medications in the period between the yearly follow-up moments is lacking.

A major limitation of this study is the lack of a control group. In fact, none of the above-mentioned studies analyzing baseline factors associated with treatment response (including this study) included a control group. It remains unknown whether patients with a poor response to etanercept would have responded better to other treatment options. Therefore, our findings (and those of previous studies) mainly reflect overall prognostic factors than predictive factors for etanercept treatment in particular. Head-to-head trials comparing different biologic agents are still lacking for JIA; these are urgently needed, as are randomized controlled trials for dif-

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ferent treatment strategies. Furthermore, more research on immunological and genetic parameters is needed to improve treatment prediction and tailored patient care.

In conclusion, 15 months after initiation of etanercept, one-third of the JIA patients achieved an excellent response, one-third an intermediate response, and one-third a poor response. An excellent treatment response was associated with low baseline disability scores, low number of DMARDs used before etanercept introduction, and younger age at onset of JIA, whereas a poor response was associated with systemic JIA and female sex.

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Online-Only Material: eTable 1 and eTable 2 are available at http://www.jama.com.

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