Mikhail M. Kostik, Irina A. Chikova, Eugenia A. Isupova, Maria N. Likhacheva, Tatyana S. Likhacheva, Margarita F. Dubko, Vera V. Masalova, Ludmila S. Snegireva, Ekaterina V. Gaidar, Olga V. Kalashnikova, Vyacheslav G. Chasnyk

St. Petersburg State Pediatric Medical University, St. Petersburg, Russian Federation

Etanercept Treatment Results in Children with Non-Systemic Juvenile Idiopathic Arthritis: Remission, Recrudescence, and Adverse Events. Retrospective Cohort Study

Corresponding author:
Mikhail M. Kostik, MD, PhD, Associate Professor of the Department of Hospital Pediatrics at the SPbSPMU
Address: 2, Litovskaya Str., St. Petersburg 194100, **phone:** +7 (812) 416-52-98, **e-mail:** kost-mikhail@yandex.ru
Article received: Feb 9, 2018; **submitted to publication**: Apr 26, 2018

Background. *Etanercept is a biological drug most commonly used in patients with juvenile idiopathic arthritis (JIA). The results of its use are showed in local studies.* ***Objective.*** *Our aim was to evaluate the efficacy and safety of the use of etanercept in children with non-systemic JIA, to determine the predictors of remission and the risk factors for the development of exacerbations.* ***Methods****. In a retrospective cohort study, the results of etanercept treatment (remission, exacerbations, adverse events) in children with non-systemic JIA have been analyzed. The minimum follow-up period is 6 months.* ***Results****. The period of remission within 6-36 months occurred in 77/131 (58.8%), exacerbations developed in 18/129 (14.0%) patients. Predictors of achieving remission were the age of JIA onset < 8 years [relative risk (RR) 2.05; 95% confidence interval (CI) 1.27–3.23], the age of prescribing etanercept ≤10 years (RR 1.7, 95% CI 1.22–2.38), the time of the disease prior to etanercept prescription <2.5 years (RR 2.4, 95% CI 1.4–4.4), the presence of HLA-B27 antigen (RR 2.15, 95% CI 0.98–4.75; p =0.06). The risk of exacerbations was higher in children with polyarticular JIA (RR 2.7, 95% CI 0.9–8.2; p =0.08), whereas methotrexate therapy reduced the risk of exacerbations (RR 0.32, 95% CI 0.1-1.15; p =0.05). Etanercept was discontinued due to primary (improvement by the* ACR_{pedi} *criteria after 3 months of therapy <30%) or secondary (loss of previously achieved ≥30% improvement) failure in 14/152 (9.2%) patients; de novo uveitis developed in 8/152 (5.3%) patients; reactions at the injection site — in 6/152 (4.0%) patients.* ***Conclusion****. Therapy involving etanercept is more likely to induce remission in younger patients with JIA onset at the age of 8 years and a history of less than 2.5 years. A high risk of exacerbations was noted in patients with polyarticular JIA, and low one — in those receiving methotrexate as a part of combined therapy.*

Key words*: children, juvenile idiopathic arthritis, etanercept, remission, exacerbations, risk factors.*

(***For citation***: Kostik Mikhail M., Chikova Irina A., Isupova Eugenia A., Likhacheva Maria N., Likhacheva Tatyana S., Dubko Margarita F., Masalova Vera V., Snegireva Ludmila S.., Gaidar Ekaterina V., Kalashnikova Olga V., Chasnyk Vyacheslav G. Etanercept Treatment Results in Children with Non-Systemic Juvenile Idiopathic Arthritis: Remission, Recrudescence, and Adverse Events. Retrospective Cohort Study. *Voprosy sovremennoi pediatrii — Current Pediatrics.* 2018; 17 (2): 138–147. doi: 10.15690/vsp.v17i2.1880)

Results

Table 1. Characteristics of patients with non-systemic JIA included in the study

Parameters	Values
Girls, abs. (%)	101 (66.4)
Age of JIA onset, years	4.8 (2.3; 8.5)
Predisposing factor, abs. (%)	
• Joint injury	16 (10.5)
• Infection	34 (22.5)
Age of etanercept therapy initiation, years	9.6 (5.9; 13.7)
• Time after JIA onset, years	2.4 (1.2; 5.7)
JIA subtypes by ICD-10, abs. (%)	
• M08.0 JRA (RF-)	91 (59.9)
• M08.0 JRA (RF+)	6 (3.9)
• M08.1 JAS	15 (9.9)
• M08.3 CJP	15 (9.9)
• M08.4 JuA, pauciarticular	5 (3.3)
• M08.8 Other juvenile arthritis	13 (8.6)
• M08.9 Juvenile arthritis, unspecified	1 (0.7)
• M09.0 Juvenile arthritis in psoriasis	6 (3.9)
Variants of JIA course, abs. (%)	
• Oligoarticular	67 (44.1)
• Polyarticular	85 (55.9)
Antinuclear factor (+), abs. (%)	40/136 (29.4)
HLA-B27 (+), abs. (%)	23/82 (28.0)
Therapy (at the time of etanercept prescription), abs. (%)	
• NSAIDs	27/143 (18.9)
• Glucocorticosteroids	70/144 (48.6)
• Sulfasalazine (monotherapy)	5/144 (3.5)
• Methotrexate	138/144 (95.8)
• Combined therapy*	32/144 (22.2)
Administration of GEBDs (before etanercept prescription), abs. (%)	20/152 (13.2)

• Infliximab	4 (2.6)
• Abatacept	8 (5.2)
• Adalimumab	5 (3.3)
• Tocilizumab	3 (1.9)

Note. * — combination of methotrexate with sulfasalazine, cyclosporine, leflunomide or hydroxychloroquine. JIA — juvenile idiopathic arthritis, JRA — juvenile rheumatoid arthritis, JAS — juvenile ankylosing spondylitis, JuA — juvenile arthritis, CJP — chronic juvenile polyarthritis, RF — rheumatoid factor, NSAID — non-steroidal anti-inflammatory drug, GEBD — genetically engineered biological drug.

Table 2. Dynamics of juvenile idiopathic arthritis activity indices during therapy including etanercept

Parameters	**Initially (*n* = 152)**	**M6 (*n* = 58)**	**M12 (*n* = 52)**	**M18 (*n* = 35)**	**M24 (*n* = 32)**	**M30 (*n* = 16)**	**M36 (*n* = 19)**	**M42 (*n* = 7)**	**M48 (*n* = 11)**	**M54 (*n* = 5)**	**M60 (*n* = 3)**	***p****
TJCs, abs.	2.0 (0; 5)	0 (0; 1)	0 (0; 1)	0 (0; 0)	0 (0; 0)	0 (0; 0)	0 (0; 0.5)	0 (0; 1)	0 (0; 1)	0 (0; 0)	0 (0; 0)	0.005
SJCs, abs.	3 (1; 11)	1 (0; 3)	0 (0; 1)	0 (0; 1)	0 (0; 0.5)	0 (0; 2.5)	0 (0; 0)	0 (0; 1)	0 (0; 1)	0 (0; 0)	0 (0; 1)	0.016
RJCs, abs.	3 (1; 9)	0 (0; 1)	0 (0; 2)	0 (0; 1)	0 (0; 0)	0 (0; 0)	0 (0; 1)	0 (0; 3)	0 (0; 2)	0 (0; 0)	0 (0; 1)	0.012
AJCs, abs.	7 (2; 14)	2 (0; 4)	1 (0; 5)	0 (0; 2)	0 (0; 2)	0 (0; 3.5)	0 (0; 1)	0 (0; 4)	0 (0; 2)	0 (0; 2)	0 (0; 2)	0.006
ESR, mm/h	8 (3; 15)	3 (2; 7)	2 (2; 7)	2 (2; 8)	2 (2; 10)	2 (2; 5)	5 (2; 7)	5 (2; 9)	2 (2; 7)	2 (2; 6)	2 (2; 8)	0.001
CRP, mg/L	1.7 (0.8; 4.4)	0.6 (0.2; 1.4)	0.6 (0.2; 1.9)	0.5 (0.2; 2.2)	0.9 (0.2; 2.2)	0.3 (0.2; 1.3)	0.4 (0.2; 1.0)	0.4 (0.2; 1.1)	0.3 (0.2; 0.5)	0.5 (0.2; 0.8)	0.6 (0.2; 1.5)	0.002
Disease activity (doctor's assessment by VAS), mm	40 (30; 58)	20 (0; 28)	10 (0; 24)	0 (0; 20)	0 (0; 10)	0 (0; 18)	0 (0; 10)	0 (0; 10)	0 (0; 30)	0 (0; 0)	0 (0; 40)	0.001
Disease activity (parent's assessment by VAS), mm	47 (35; 65)	24 (0; 34)	22 (0; 32)	0 (0; 25)	0 (0; 12)	10 (0; 29)	0 (0; 20)	0 (0; 10)	0 (0; 10)	0 (0; 10)	0 (0; 10)	0.001
JADAS71, scores	15.8 (9.6; 25.7)	6.4 (1.2; 9.0)	5.5 (0.0; 8.8)	0.0 (0.0; 6.8)	0	0	0	0	0	0	0	0.02
FC, abs. (%) • I • II • III	 24 (17) 104 (76) 9 (7)	 38 (66) 20 (34) 0 (0)	 33 (65) 18 (36) 0 (0)	 29 (83) 6 (17) 0 (0)	 26 (81) 6 (19) 0 (0)	 13 (81) 3 (19) 0 (0)	 14 (74) 5 (26) 0 (0)	 5 (71) 1 (14) 1 (14)	 6 (55) 5 (45) 0 (0)	 4 (80) 1 (20) 0 (0)	 2 (67) 1 (33) 0 (0)	0.001
Remission, abs. (%)	0	9 (16)	18 (35)	19 (54)	19 (59)	8 (50)	13 (68)	4 (57)	6 (55)	4 (80)	1 (33)	0.001

Note. * **—** the value of *p* is calculated by the Friedman method for data relating to the first 24 months after the initiation of etanercept therapy (*n* = 32). M6–M60 **—** control periods of treatment outcomes (months). TJC **—** tender joint count, SJC **—** swollen joint count, RJC **—** restricted joint count, AJC **—** active joint count, ESR **—** erythrocyte sedimentation rate, CRP **—** C-reactive protein, VAS **—** visual analogue scale, JADAS **—** juvenile arthritis disease activity score, FC **—** functional class.

Table 3. Comparative characteristics of patients* depending on the achievement of remission with therapy involving etanercept

Parameters	Remission		*p*
	Yes (*n* = 77)	No (*n* = 54)	
Girls, abs. (%)	52 (67)	33 (61)	0.450
Age of JIA onset, years	3.9 (2.3; 7.1)	6.5 (2.6; 11.8)	**0.015**
Age of etanercept prescription, years	8.0 (4.4; 11.5)	11.9 (8.2; 15.3)	**0.001**
Time prior to etanercept prescription, years	1.9 (1.1; 5.3)	3.4 (1.3; 5.3)	0.124
White blood cells , $\times 10^9$/L	7.0 (5.6; 8.7)	6.6 (5.7; 8.4)	0.742
Platelets, $\times 10^9$/L	327 (279; 375)	312 (250; 352)	0.167
Hemoglobin, g/L	124 (117; 132)	125 (116; 134)	0.742
ESR, mm/h	8 (3; 14)	10 (6; 17)	0.241
CRP, mg/L	2.1 (0.8; 6.3)	1.7 (0.9; 3.3)	0.423
TJCs, abs.	2 (0; 5)	2.0 (0; 8)	0.438
SJCs, abs.	4 (1; 13)	4 (2; 11)	0.840
RJCs, abs.	3 (1; 9)	3 (1; 12)	0.739
AJCs, abs.	5 (2; 14)	7 (3; 16)	0.455
VAS (doctor's assessment), mm	46 (32; 58)	38 (30; 58)	0.312
VAS (parent's assessment), mm	48 (35; 65)	47 (35; 65)	0.659
JADAS71, scores	15.7 (9.6; 26.4)	17.8 (10.0; 27.8)	0.514
FC, abs. (%) • I • II • III	 14 (20) 51 (72) 6 (9)	 6 (13) 40 (83) 2 (4)	 0.339 (df = 2)
Polyarthritis, abs. (%)	39/70 (56)	31/61 (62)	0.575
RF (+), abs. (%)	2/71 (3)	4/52 (8)	0.215
ANF (+), abs. (%)	23/70 (33)	12/49 (25)	0.324
HLA-B27 (+), abs. (%)	12/40 (30)	8/32 (25)	0.638
Glucocorticosteroids, abs. (%)	41/76 (54)	24/53 (45)	0.333
Methotrexate, abs. (%)	54/67 (81)	38/47 (81)	0.973

Note. * — immediately at the time of therapy initiation. JIA — juvenile idiopathic arthritis, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein, TJC — tender joint count, SJC — swollen joint count, RJC — restricted joint count, AJC — active joint count, VAS — visual analogue scale, JADAS — juvenile arthritis disease activity score, FC — functional class, RF — rheumatoid factor, ANF — antinuclear factor.

Table 4. Predictors for achieving remission (multivariate analysis data)

Parameters	RR	95% CI	*p*
Age of the onset < 8 years	2.02	(0.88; 4.62)	0.095
Age of etanercept prescription ≤ 10 years	0.83	(0.42; 1.64)	0.591
Time prior to etanercept prescription ≤ 2.4 years	2.43	(1.37; 4.31)	0.002

Note. The model is designed for 131 patients; patients withdrawn from the analysis by the main characteristics of juvenile idiopathic arthritis indicated in Table 1 ($p < 0.05$) did not differ from those included in the analysis.

Fig. 1. Cumulative probability of achieving remission, depending on the time of etanercept prescription (Kaplan–Meier curves)

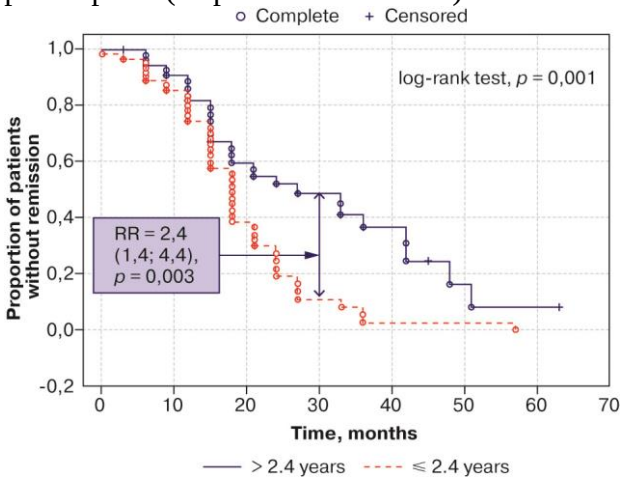
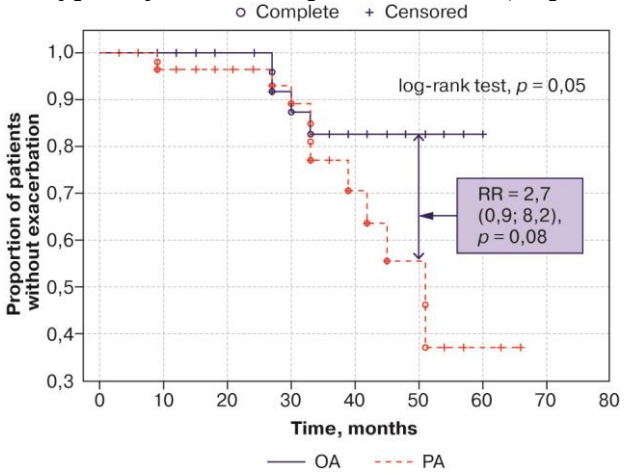
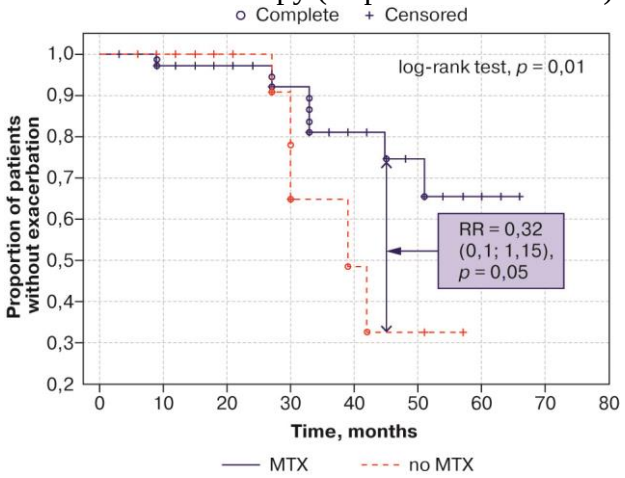


Fig. 2. Cumulative probability of developing exacerbations in children, depending on the subtype of juvenile idiopathic arthritis (Kaplan–Meier curves)



Note. OA — oligoarticular arthritis, PA — polyarticular arthritis.

Fig. 3. Cumulative probability of developing exacerbations in children, depending on the use of methotrexate in therapy (Kaplan–Meier curves)



Note. MTX — methotrexate.

Limitations of the Study

The authors understand that patient selection for etanercept prescription was partly subjective (the opinion of the attending physician), which, together with the peculiarities of concomitant therapy, could affect the final results of the study. Given the similarity of the results obtained both in previous studies performed in Russia and international studies, the study results can be applied to other Russian patients with JIA. Among the shortcomings of the study, it is necessary to indicate the use of data obtained from secondary information sources (medical records, case histories of children) for description of the sample of outcome measures and their predictors that do not always contain complete information received in the required time and in all patients. The lack of necessary data occurred due to a change in the place of residence/follow-up, the transition to an adult rheumatologic-patient follow-up network, refused therapy. It is impossible to unambiguously determine how the 'missed' data or the spread in time frames of the available information assessment could affect the evaluation of the study outcomes. However, it should be noted that the 'discharged' patients did not differ by the main characteristics (JIA subtype, current activity and duration of the disease, sex) from the group of patients whose examination results were included in the multivariate model of predictors. The follow-up period was acceptable for assessing the efficacy (achieving remission), but we understand that even a five-year follow-up period is not sufficient to assess not only the long-term efficacy, but, more importantly, also remote safety (cancer risks, impact on the reproductive potential and the next generation). In addition, the study did not have a control group, which does not allow to unequivocally attribute the effect of therapy to the action of etanercept.

FINANCING SOURCE

The article has been published with the support of Pfizer.

CONFLICT OF INTERESTS

Mikhail M. Kostik receives fees for lecturing from Pfizer, AbbVie, Roche, Novartis.
The other contributors confirmed the absence of a reportable conflict of interests.