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Prognostic Factors for the Response to Tocilizumab Therapy in Patients with Juvenile Idiopathic Arthritis without Systemic Manifestations: a Cohort Study

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Background. *To assign genetically engineered biologic drugs, we need data on the predictors for response to therapy. Prognostic factors for the response to tocilizumab in patients with juvenile idiopathic arthritis (JIA) without systemic symptoms are poorly studied.* ***Objective.*** *Our aim was to reveal early predictors for the response to tocilizumab therapy in patients with JIA without systemic symptoms.* ***Methods****. A retrospective cohort study enrolled patients with JIA without systemic symptoms who received tocilizumab therapy between July 2009 and August 2017. We assessed the association between the initial demographic, clinical, and laboratory parameters in patients and the best response (according to the ACR90 criteria) to treatment after a year.* ***Results****. The study included 95 (girls 85%) patients; the mean age was 10.3 (6.0; 13.6). During the first year of therapy, 71 (75%), 55 (58%), 38 (40%), and 22 (23%) patients achieved the improvement according to ACR30/50/70/90 criteria, respectively; 22 (23%) patients reached disease inactive stage according to the Wallace criteria. When performing multivariate analysis, the following improvement predictors were revealed based on the ACR90 criteria after a year of treatment: decrease in serum C-reactive protein level during the first month of therapy [odds ratio (OR) 1.024; 95% confidence interval (CI) 1.007–1.051], decrease in disease activity score on the visual analogue scale according to the parent/patient assessment (OR 1.048; 95% CI 1.005–1.105), early onset of the disease (OR 0.38; 95% CI 0.16–0.72), persistent oligoarthritis according to the ILAR (OR 9.9; 95% CI 1.5–109.3). During the first year of tocilizumab administration, neutropenia was registered in one patient, leukopenia — in three cases, and urticaria — in one case.* ***Conclusion****. The variant of JIA, the age at the disease onset, and the disease course pattern in the first month of tocilizumab therapy are the predictors of treatment efficacy throughout the year.*

Key words*: children, juvenile idiopathic arthritis, therapy, response predictors, genetically engineered biologic drug, tocilizumab.*

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Table 1. Demographic and anamnestic characteristics of patients at the onset of tocilizumab therapy

Parameters	**Value**
Demographic parameters	
Sex (girls), abs. (%)	81 (85)
Diagnosis upon the ILAR: • Enthesitis-related arthritis, abs. (%) • Extended oligoarthritis, abs. (%) • Persistent oligoarthritis, abs. (%) • RF-positive polyarthritis, abs. (%) • RF-negative polyarthritis, abs. (%)	 4 (4) 3 (3) 21 (22) 4 (4) 63 (66)
Diagnosis upon the ICD-10: • Juvenile rheumatoid arthritis, abs. (%) • Juvenile ankylosing spondylitis, abs. (%) • Juvenile polyarthritis, abs. (%) • Pauciarticular juvenile arthritis, abs. (%)	 4 (4) 4 (4) 62 (66) 24 (25)
Age at the onset of tocilizumab therapy, years	10.3 (6.0; 13.6)
Duration of the disease prior to the study, years	4.9 (1.7; 8.7)
Age of JIA onset, years	3.0 (1.7; 5.4)
Concomitant uveitis, abs. (%)	42 (44)
Age of uveitis onset, years	5.0 (3.8; 8.1)
Prior therapy	
NSAIDs, abs. (%)	95 (100)
GEBDs, abs. (%)	65 (68)
Methotrexate, abs. (%)	93 (98)
Other DMARDs, abs. (%)	40 (42)
Oral glucocorticosteroids, abs. (%)	26 (27)

Note. JIA — juvenile idiopathic arthritis, NSAIDs — non-steroidal anti-inflammatory drugs, GEBDs — genetically engineered biologic drugs, DMARDs — disease-modifying anti-rheumatic drugs.

Table 2. Dynamics of laboratory and clinical parameters of the disease activity in patients with JIA before and after 1 month of treatment with tocilizumab

Parameter	Initially*	After 1 month	*p*
Erythrocyte sedimentation rate, mm/hr	14 (6; 30)	3 (2; 5)	0.001
C-reactive protein, mg/L	6.8 (1; 17)	0 (0; 2)	0.001
Duration of morning stiffness, min	15 (0; 60)	0 (0; 15)	0.001
Painful joint count, abs.	4 (1; 17)	1 (0; 4)	0.001
Swollen joint count, abs.	2 (1; 9)	0 (0; 2)	0.001
Count of joints with restricted range of motion, abs.	6 (2; 17)	4 (2; 10)	0.001
Active joint count, abs.	3 (1; 14)	0 (0; 2)	0.001
Assessment of disease activity on a VAS (doctor), scores	62 (50; 72)	37 (23; 50)	0.001
Assessment of disease activity on a VAS (parent/patient), scores	67 (53; 77)	42 (27; 53)	0.001
CHAQ, scores	2 (1.5; 2)	1.25 (1; 1.5)	0.001
JADAS71, scores	18.5 (13; 29)	9 (5; 14)	0.001
Inactive disease upon the Wallace criteria, abs. (%)	0	5 (5)	0.001

Note. * — at the onset of tocilizumab therapy. VAS — 100-mm visual analogue scale.

Table 3. Predictors of achieving $ACR_{pedi}90$ after 1 year of tocilizumab therapy: the results of a single factor logistic regression analysis

Factor	OR (95% CI)	*p*
Age of the onset of tocilizumab therapy	1.222 (1.086–1.395)	0.002
Change in erythrocyte sedimentation rate*	0.966 (0.941–0.99)	0.008
Age of JIA onset	1.428 (1.128–1.975)	0.012
Change in C-reactive protein*	0.985 (0.97–0.996)	0.023
Achieving ACR50 after 1 month	2.949 (1.119–8.091)	0.031
Intake of etanercept (in past medical history)	0.254 (0.056–0.831)	0.040
Change in the assessment of disease activity on a VAS (doctor)*	0.973 (0.944–1.000)	0.057
Active uveitis after 1 month of therapy	2.461 (0.939–6.704)	0.070
Diagnosis of persistent oligoarthritis (upon the ILAR)	2.637 (0.897–7.574)	0.072
Age of uveitis onset	1.243 (0.983–1.676)	0.102
Number of GEBD withdrawals due to remission (in past medical history)	0.26 (0.034–1.332)	0.121
CHAQ after 1 month of therapy	2.094 (0.823–5.615)	0.128
Change in the assessment of disease activity on a VAS (parent/patient)*	0.982 (0.958–1.006)	0.145

Switching from etanercept to tocilizumab	0.225 (0.012–1.307)	0.170
Change in the duration of morning stiffness*	0.996 (0.991–1.002)	0.175
History of uveitis	1.929 (0.738–5.147)	0.181
Change in the CHAQ*	0.491 (0.168–1.389)	0.181
Diagnosis of RF-negative polyarthritis upon the ILAR	0.518 (0.194–1.392)	0.186

Note. * — the calculation of OR values (95% CI) was performed for the difference in the initial values of the parameter and its values after 1 month of therapy with tocilizumab. For quantitative parameters, the OR value was calculated to change the parameter values by the corresponding unit. We provide factors of all studied parameters with a significance level $p < 0.2$. OR — odds ratio, CI — confidence interval, JIA — juvenile idiopathic arthritis, VAS — 100-mm visual analogue scale, GEBD — genetically engineered biologic drug.

Table 4. Predictors of the improvement upon the $ACR_{pedi}90$ criterion after 1 year of therapy with tocilizumab: the results of a multifactorial logistic regression analysis

Parameter	**OR (95% CI)**	***p***
Change in C-reactive protein*	1.024 (1.007–1.051)	0.024
Age of the disease onset	0.375 (0.155–0.72)	0.011
Diagnosis of persistent oligoarthritis (upon the ILAR)	9.9 (1.5–109.3)	0.030
Withdrawal of other GEBD due to remission (in past medical history)	6.342 (0.658–59.787)	0.088
Change in the assessment of disease activity on a VAS (parent/patient)*	1.048 (1.005–1.105)	0.046

Note. * — the calculation of OR values (95% CI) was performed for the difference in the initial values of the parameter and its values after 1 month of therapy with tocilizumab. For quantitative parameters, the OR value was calculated to change the parameter values by the corresponding unit. OR — odds ratio, CI — confidence interval, GEBD — genetically engineered biologic drug, VAS — 100-mm visual analogue scale.

Fig. 1. Dynamics of the achievement of ACR_{pedi}30/50/70/90 and inactive disease (Wallace) during 12 months of tocilizumab therapy

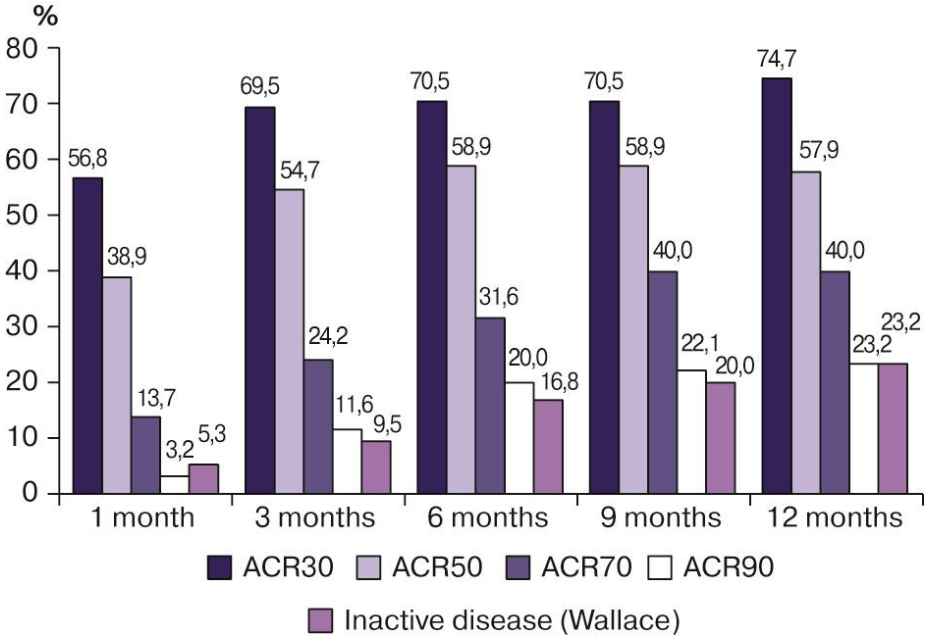
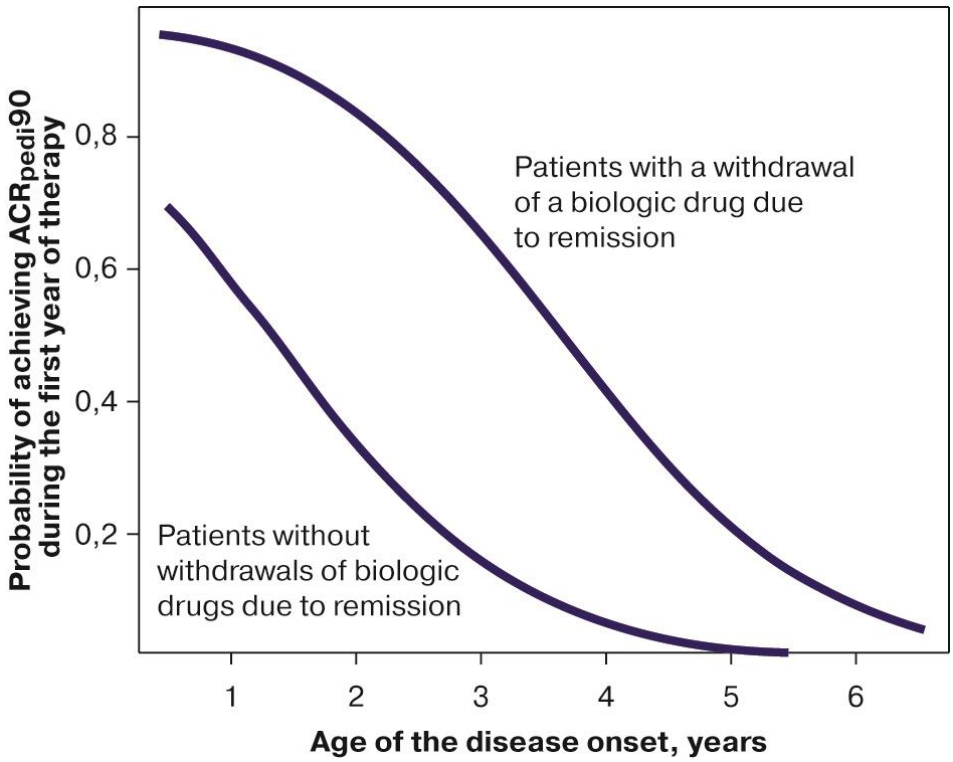


Fig. 2. The probability of the improvement upon the ACR_{pedi}90 criterion during the first year of tocilizumab therapy in patients with persistent oligoarthritis



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CONFLICT OF INTERESTS

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