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**Early Prognostic Factors for Remission Achievement at Etanercept Therapy in Patients with Juvenile Idiopatic Arthritis Without Systematic Manifestations: Prospective Cohort Study**

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***Background****. Prognosis of therapy results of patients with the juvenile idiopatic arthritis (JIA) without systematic manifestations is the precondition of their treatment efficiency enhancement.* ***Objective.*** *Our aim was to establish early predictors for remission achievement in patients with JIA without systematic manifestations who received Etanercept therapy.* ***Methods.*** *The therapy results of patients with JIA without systematic manifestations hospitalized from December, 2009 to August, 2014 and administrated with Etanercept are analysed. The association of initial demographic indicators as well as initial and registered after a month of treatment clinical and laboratory indicators with remission achievement after a year of treatment according to the Wallace criteria is estimated.* ***Results.*** *The research included 197 patients with JIA without systematic manifestations who received Etanercept in 0.4 mg/kg dose twice a week subcutaneously (the maximum single dose ― 25 mg). In addition to Etanercept 136 (69%) patients received Methotrexat, 121 (61%) ― non-steroidal anti-inflammatory drugs, 10 (5%) ― glucocorticosteroids, 6 (3%) ― Sulfasalazine. After a year of treatment remission was recorded in 77 out of 197 (39.1%) patients. According to multivariate analysis the remission predictors are the following: tender joint count ≤ 4 (odds ratio (OR) 4.38; 95% confidential interval (CI) 2.33−8.55), duration of illness before Etanercept therapy ≤ 2 years (OR 1.28; 95% CI 1.02–2.15), disease activity decline according to JADAS71 index ≥ 10 points in a month of the therapy including Etanercept (OR 2.59; 95% CI 1.38−5.03). Model sensitivity was 32% (all three criteria in 25/77 patients with remission), specificity ― 94% (lack of even one criteria in 113/120 patients who did not achieve remission).* ***Conclusion.*** *The predictors of remission in patients with JIA without systematic manifestations in 1 year of Etanercept therapy are smaller tender joint count prior to therapy, smaller duration of illness as well as significant disease activity decline in a month of the therapy.*

***Key words:*** *children, juvenile idiopatic arthritis, therapy, predictors, risk factors, genetically engineered biologic drugs, Etanercept, adverse effects.*

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**RESULTS**

**Table 1**. Predictors of outcomes after therapy with Etanercept in earlier studies

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Parameters** | **G. Horneff [13]** | **M. Otten [10]** | **N. Solari [12]** | **T. Geikowski [9]** | **L. Kearsley-Fleet [15]** | **E. Alexeeva [11]** | **M. Kostik [4]** | **Y. Su [14]** | **Present study** |
| Number of patients | 787 | 262 | 173 | 863 | 496 | 197 | 152 | 58 | 197 |
| Duration of the study | 12 mos | 15 mos | 12 mos | 6 mos | 12 mos | 12 mos | 6–36 mos | 12–136 mos | 12 mos |
| Outcome | Inactive disease and remission (Wallace) | Inactive disease (Wallace) | Inactive disease (Wallace) | ACR70 | ACR90 | Minimal disease activity (JADAS71) | АКР90 and inactive disease (Wallace, JADAS71) | Remission (Wallace) | Remission (Wallace) | Remission (Wallace) |
| ***Response predictors*** |
| Low CHAQ | (< 0,77) |  |  |  |  |  |  | - |  |  |
| Early age at the start of the therapy |  |  |  |  |  |  |  | (< 10 yrs) |  |  |
| Early disease onset | (< 0,9 yrs) |  | (< 3,6 yrs) |  |  |  |  | (< 8 yrs) |  |  |
| Little number of DMARD in anamnesis |  |  |  |  |  |  |  |  |  |  |
| Absence of concomitant treatment with GKS |  |  |  |  |  |  |  | * -
 |  |  |
| Lower count of joints with active arthritis | (≤ 1) |  |  |  |  |  |  |  |  |  |
| Lower count of joints with motion decrease |  |  |  |  |  |  |  |  | - |  |
| Lower count of tender joint |  |  |  |  |  |  |  |  | - | (≤ 4) |
| No radiocarpal joints involvement  | - | - |  | - | - | - | - | - | - | - |
| Smaller duration of illness before therapy start | (< 0,9 yrs) |  |  |  |  |  |  | (< 2,4 yrs) |  | (< 2 yrs) |
| High ESR  |  |  |  |  |  |  |  |  |  |  |
| Uveitis | - | - | - | - |  |  |  | - | - |  |
| HLAB27 | - | - | - |  | - | - | - |  | - | - |
| Persistent oligoarthritis |  |  |  |  |  |  |  |  |  | - |
| JADAS71 changes in a month  | - | - | - | - | - | - | - | - | - | (≥ 10 points) |
| Achievement of paediatric ACR70 at 4 months | - | - | - | - | - | - | - | - |  | - |

*Note*. \* ― the threshold level for response predictor was not specified, the data was not presented elsewhere.

* ― there is link between parameter and outcome;
* ― there is no link between parameter and outcome;

(-)  ― the link between parameter and outcome was not.

ACR ― American College of Rheumatology, DMARD ― disease-modifying anti-rheumatic drugs, GKS ― glucocorticosteroids, ESR ― erythrocyte sedimentation rate.

**Table 2**. Characteristic of patients with JIA without systematic manifestations (*n* =197)

|  |  |
| --- | --- |
| **Indicators** | **Value** |
| Gender (female), abs (%) | 137 (69,5) |
| Age\*, years | 7 (4; 12) |
| JIA onset age, years  | 3 (2; 7) |
| JIA duration\*, years | 2 (1; 5) |
| Diagnosis according to the ILAR, abs (%):* RF positive polyarthritis
* RF negative polyarthritis
* persisting oligoarthritis
* extended oligoarthritis
* enthesitis-related arthritis
* psoriatic arthritis
 | 1 (0,5)64 (32,5)84 (42,6)23 (11,7)24 (12,2)1 (0,5) |
| Comorbid uveitis\*, abs (%) | 7 (3,6) |
| Prior therapy \*\*NSAID, abs (%)Disease-modifying drugs, abs (%)* Methotrexat
* Other drugs\*\*\*
* Leflunomide
* Cyclophosphamide
* Hydroxychloroquine
* Sulfasalazine
* Cyclosporine
* ≥ 2 drugs simultaneously in addition to Methotrexat

Glucocorticosteroids (*per os*)GEBD-naive patients, abs (%)One GEBD in past medical history, abs (%)Two and more GEBD in past medical history, abs (%) | 194 (98,4)162 (82,2)84 (42,6)5 (2,5)1 (0,5)11 (5,6)49 (24,9)38 (19,3)17 (8,6)39 (19,8)153 (77,7)37 (18,8)7 (3,5) |
| Concomitant therapy \*\*\*\** Methotrexat, abs (%)
* Sulfasalazine, abs (%)
* NSAID, abs (%)
* Glucocorticosteroids (*per os*), abs (%)
 | 136 (69,0)6 (3,0)121 (61,4)10 (5,1) |

*Note.* \* ― before treatment with Etanercept; \*\* ― any drugs taken before treatment with Etanercept; \*\*\* ― Leflunomide, Cyclophosphamide, Hydroxychloroquine, Sulfasalazine and/or Cyclosporine; \*\*\*\* ― drugs taken on the start of treatment with Etanercept. JIA ― juvenile idiopatic arthritis, GEBD ― genetically engineered biologic drugs, NSAID ― non-steroidal anti-inflammatory drug.

**Table 3**. Dynamics of clinical and laboratory indicators of JIA activity initially and after a month of treatment with Etanercept

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Indicators** | **Initially\*** | **After 1 month** | **Delta\*\*** | ***p*** |
| ESR, mm/h | 21 (12; 35) | 10 (5; 16) | 9 (3; 21) | 0,001 |
| C-reactive protein, mg/l | 6,6 (1,9; 19,7) | 1 (0; 4,6) | 5,3 (1; 12) | 0,001 |
| Duration of morning stiffness, min | 30 (0; 60) | 0 (0; 0) | 30 (0; 60) | 0,001 |
| Tender joint count, abs | 4 (2; 8) | 0 (0; 2) | 3 (1; 7) | 0,001 |
| Swollen joint count, abs | 4 (2; 8) | 2 (0; 5) | 2 (0; 3) | 0,001 |
| Joint with motion decrease count, abs | 4 (2; 11) | 2 (1; 6) | 0 (0; 3) | 0,001 |
| Active joint count, abs | 4 (2; 10) | 2 (0; 6) | 2 (0; 4) | 0,001 |
| Illness activity estimation according to VAS (doctor), points | 60 (45; 80) | 28 (18; 40) | 30 (16; 47) | 0,001 |
| Health assessment according to VAS (parent/patient), points | 68 (50; 82,5) | 32 (18; 46) | 31 (17; 46) | 0,001 |
| CHAQ, points | 1,3 (0,5; 1,9) | 0,3 (0,1; 1) | 0,5 (0,3; 1) | 0,001 |
| JADAS71, points | 19,2 (13,8; 28,5) | 8,1 (5; 14,9) | 9,8 (5,3; 14,8) | 0,001 |

*Note.* \* ― at start of treatment with Etanercept; \*\* ― delta between initial level and level after 1 month of the treatment.

**Table 4**. Predictors for remission achievement in patients with JIA without systematic manifestations (*n* =197) after 12 months of treatment included Etanercept: results of univariate logistic regression analysis

|  |  |  |
| --- | --- | --- |
| **Indicators** | **OR (95% CI)** | ***р*** |
| Female gender | 2,21 (1,15–4,38) | 0,019 |
| RF negative polyarthritis (initially) | 0,39 (0,20–0,75) | 0,006 |
| Persisting oligoarthritis (initially) | 2,67 (1,49–4,85) | 0,001 |
| Enthesitis-related arthritis (initially) | 0,48 (0,17–1,21) | 0,138 |
| JIA onset | 0,94 (0,87–1,02) | 0,156 |
| ***Prior therapy*** |
| Number DMARD (except Methotrexat) | 0,37  (0,21–0,60) | 0,001 |
| DMARD (except Methotrexat) | 0,34 (0,18–0,62) | 0,001 |
| Oral glucocorticosteroids | 0,48 (0,21–0,95) | 0,063 |
| GEBD | 0,51 (0,24–1,04) | 0,071 |
| Sulfasalazine | 0,61 (0,30–1,20) | 0,163 |
| ***Indicators at the start of treatment*** |
| Patient age | 0,90 (0,84–0,96) | 0,002 |
| JIA duration | 0,86 (0,77–0,95) | 0,005 |
| Active joint count | 0,94 (0,90–0,98) | 0,004 |
| Duration of morning stiffness | 0,991 (0,985–0,996) | 0,002 |
| Joint with motion decrease count | 0,94 (0,90–0,97) | 0,002 |
| Tender joint count | 0,92 (0,87–0,96) | 0,001 |
| Swollen joint count | 0,95 (0,90–0,98) | 0,011 |
| ESR | 0,991 (0,976–1,004) | 0,188 |
| CRP | 0,989 (0,976–0,999) | 0,056 |
| Initial illness activity estimation according to VAS (doctor) | 0,987 (0,973–1,001) | 0,08 |
| CHAQ index | 0,69 (0,47–1,01) | 0,057 |
| JADAS71 index | 0,96 (0,93–0,98) | 0,003 |
| Concomitant treatment with Methotrexat | 0,95 (0,92–0,99) | 0,011 |
| ***Indicators after 1 month of treatment***\* |
| Change in medical condition estimation according to VAS (parent/patient) | 1,018 (1,005–1,033) | 0,009 |
| Change in medical condition estimation according to VAS (doctor) | 1,018 (1,004–1,033) | 0,014 |
| Change in morning stiffness duration | 0,993 (0,987–0,998) | 0,013 |
| Change in tender joint count | 0,944 (0,893–0,989) | 0,028 |
| Change in CHAQ index | 1,556 (0,949–2,583) | 0,082 |
| Change in JADAS71 index | 1,022 (0,989–1,058) | 0,197 |

*Note.* \* ― calculation of odds ratio (OR; 95% CI) was performed for the reduction range of initial indicators after 1 month of treatment with Etanercept. For quantitative indicators OR (95% CI) was calculated for indicator changes on corresponding unit. The factors (out of all indicators) for which P-value is <0.2 are presented. DMARD ― disease-modifying anti-rheumatic drugs, GEBD ― genetically engineered biologic drugs, RF ― rheumatoid factor, JIA ― juvenile idiopatic arthritis, ESR ― erythrocyte sedimentation rate, CRP ― C-reactive protein.

**Table 5**. Predictors for remission achievement in patients with JIA without systematic manifestations (*n* =197) after 12 months of treatment included Etanercept: results of multivariate logistic regression analysis

|  |  |  |
| --- | --- | --- |
| **Indicator** | **OR (95% CI)\*** | ***p*** |
| JIA duration before treatment with Etanercept \*\* | 0,89 (0,79–0,99) | 0,036 |
| Tender joint count (initially) | 0,89 (0,84–0,94) | 0,001 |
| Reduction of Illness activity according to JADAS71 index after 1 month of treatment | 1,08 (1,03–1,14) | 0,001 |

*Note.* \* ― value of odds ratio (OR; 95% CI) was calculated for change in quantitative indicator on corresponding unit. Model characteristics: AIC =237.5; R2 =14%.

**Fig**. Results of 12 months treatment with Etanercept

*Note.* Percentage of patients who has reached corresponding outcome was calculated for all 197 patients included in this study.

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**CONFLICT OF INTERESTS**

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