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Improvement of functional ability in children with Juvenile Idiopathic Arthritis by treatment with etanercept

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Objective. To investigate the functional ability i.e. the physical aspect of the health related quality of life and it's determining factors during therapy with etanercept in children with JIA.

Methods. Assessment of the Child Health Assessment Questionnaire (CHAQ), the number of active joints, duration of morning stiffness, ESR, C-reactive protein, parent's global assessment of the overall patient's well-being, physician's global assessment of the overall disease activity, concomitant treatment with methotrexat, number of aids/devices needed and calculation of the PedACR-score.

Results. Data of 437 children were analyzed for disease severity and impact of the disease on functional abilities. Data of 114 children with a complete data set and a continuous treatment for at least 24 months were used for analysis of the impact of treatment on functional abilities.

Before treatment with etanercept patients with systemic arthritis and seropositive or seronegative polyarthritis were disabled more heavily than those with other subtypes of JIA. There was a correlation between high CHAQ scores and the number of active joints, aids/devices needed, parent's global assessment of the overall patient's well-being, morning stiffness, physician's global assessment of the overall disease activity and C-reactive protein ($p < 0.005$). Of the 8 areas, "dressing and grooming", "arising", "eating", "walking", "hygiene", "reach", "grip" and "activities", the latter was most severely affected.

96.5%, 93.8% and 90.3% of the patients reached a Ped-ACR-30, -50 and -70 score upon treatment with Etanercept for 24 months. The areas eating and walking were best before therapy and showed highest improvement with therapy. Under therapy with etanercept patients of all JIA subgroups significantly improved their functional ability ($p < 0.0001$), but patients with polyarthritis less frequently improved their physical functioning.

Conclusion. Disease activity and the physical aspect of health related quality of life including functional ability improved significantly during therapy with etanercept in children with JIA. Duties of everyday life were easier to accomplish.

INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) is the most common chronic autoimmune disease in childhood. It results not only to painful and swollen joints but also to a limitation of functional ability and of everyday life in children (1, 2).

Etanercept, which inhibits TNF-alpha, is licensed for treatment of active, refractory polyarticular chronic arthritis in childhood. The introduction of biologics like etanercept had a major impact on the outcome of patients with polyarticular JIA. The safety and the efficiency of etanercept had been proved in open and controlled studies as well as in long term studies (3-13).

Several measures for functional ability in children with JIA were introduced in the past years. Among those the Child Health Assessment Questionnaire (CHAQ) is the most common tool used to measure functional ability in children with JIA. The CHAQ is well established for the use in children with JIA (14) and is used as one of six core response variables in clinical drug trials (15-20). It has been validated and evaluated in the German language (21). Furthermore, it has been shown to be a useful tool for evaluating outcome in longitudinal studies (22-24).

The outcome of JIA is variable depending on the subgroup of JIA. In some subgroups many children experience spontaneous remission of their joint disease while in other subgroups persistent destructive arthritis frequently occurs. Clinical experience suggests that more children than expected have ongoing disease in adulthood. Though the physical outcome of patients with JIA is relatively good compared to adult patients with rheumatoid arthritis, many patients still have active disease in adulthood and health status and quality of life are reduced in patients with all types of JIA (25). Approximately half of the patients with JIA have changes in their body function and structure after disease duration of more than 15 years. Fortunately less than 10% are severely disabled or handicapped (26).

The purpose of the present study was to evaluate the alteration of functional ability in children with JIA before and during treatment with etanercept. Eight areas of everyday life with impact on the functional ability were measured with the CHAQ: “dressing and grooming”, “arising”, “eating”, “walking”, “hygiene”, “reach”, “grip” and “activities”.

PATIENTS AND METHODS

Study design and Patients. Criteria for inclusion in our analysis were diagnosis of JIA subclassified into the 6 JIA subgroups according to the International League of Associations for Rheumatology (ILAR) criteria and registration in the German etanercept registry from 2001 until 2006 (2). In order to be eligible for treatment with etanercept, failure to respond or intolerance to methotrexate was required (27). Patient data were collected at start of therapy with etanercept and every six months during therapy. Data of 437 children were analyzed for disease severity and impact of the disease on functional abilities. Owing to the study-character not all criteria were available from every point in time from every patient. Data of 114 children with a complete data set and a continuous treatment for at least 24 months were used for analysis of the impact of treatment on functional abilities.

Functional ability. The patient of at least 13 years of age or parents of patients younger than 13 years was asked to complete the CHAQ. The CHAQ includes 30 questions concerning 8 areas of daily living “dressing and grooming”, “arising”, “eating”, “walking”, “hygiene”, “reach”, “grip” and “activities”. The response modalities range on a 4-point ordinary scale with 0 for “no difficulty”, 1 for “some difficulties”, 2 for “much difficulties” and 3 for “unable to do”. An additional response modality, “not applicable for age”, could be used if a child was too young for a certain activity. Besides the 30 items the CHAQ contains 14 questions related to the use of

aids/devices plus 8 questions that are related to the child's need of help from another person. Each of the 8 areas is scored as the highest item in that area. If aids/devices or assistance from another person for one of the 8 CHAQ areas are required for an activity, the score is further corrected to at least 2 points for the corresponding area. The 8 areas of the CHAQ are averaged to calculate the CHAQ disability index (CHAQ DI) which ranges from 0 (no or minimal physical dysfunction) to 3 (very severe physical dysfunction).

Besides the 30 items the CHAQ includes a patient's or parent's global assessment of the overall patient's well-being in the previous week on a 0-10 cm visual analogue scale (VAS) (0=very well; 10=very poor) and a patient's or parent's global assessment of the child's pain in the previous week on a 0-10 cm VAS (0=no pain; 10=very severe pain).

JIA disease activity. Efficacy was assessed with the PedACR30, 50 and 70 criteria including the German CHAQ. These core set parameters consisted of 1) physician global assessment of disease activity, on a 10-cm visual analogue scale (VAS); 2) parent/patient global assessment of overall well-being, on a 10-cm VAS; 3) the CHAQ; 4) the number of joints with active arthritis, defined by the presence of swelling or, if no swelling was present, limitation of motion accompanied by pain, tenderness, or both 5) the number of joints with limited range of motion; and 6) the erythrocyte sedimentation rate. The PedACR30 was reached if there was an improvement of $\geq 30\%$ in at least 3 of 6 core variables, with no more than 1 of the remaining variables worsened by $\geq 30\%$ (28). Patients were also evaluated for improvement of $\geq 50\%$ or $\geq 70\%$ improvement in at least 3 of 6 core variables, with no more than 1 of the remaining variables worsened by $\geq 30\%$ (PedACR50 and PedACR70). Other assessments not included in the PedACR score were the duration of morning stiffness, and serum C-reactive protein levels.

Statistical Analysis. Data were collected using Microsoft Excel and statistical analysis was processed with SPSS for windows 14.0.

Continuous variables were evaluated with descriptive statistic analysis using means and SD. Categorical variables were evaluated using frequencies and percentages.

Statistical tests included 1-way analysis of variance, Chi-Square test, Kruskal-Wallis test, ANOVA and GLM repeated measures. P values less than 0.05 were considered to be significant.

The dimension of functional limitation was categorized by a system proposed by Ruperto et al. (1997). A CHAQ DI 0 implicates no disability, 0.1-0.5 implicates a mild disability, 0.6-1.5 implicates a moderate disability and >1.5 implicates a severe disability (29).

RESULTS

Until June 1st, 2006 data on 437 patients (70% female) feasible for analysis have been collected. Patients were treated in several pediatric rheumatology centers all over Germany and Austria for 1 to 72 months (mean (\pm SD) 16 (\pm 14.6) months, median 12 months). The main demographic, clinical and laboratory features of the total group of JIA patients are shown in table 1. According to the ILAR criteria 76 (17.3%) of the patients had systemic JIA, 138 (31.6%) had seronegative polyarthritis, 53 (12.1%) had seropositive polyarthritis, 15 (3.4%) had persistent oligoarthritis, 73 (16.7%) had extended oligoarthritis, 51 (11.7%) had enthesitis related arthritis and 31 (7%) had psoriasis arthritis. During therapy with etanercept concomitant treatment with methotrexate was used in 362 (82.5%) patients.

The mean (\pm SD) age for disease onset in children with JIA was 6.6 ± 4.6 years. Earliest disease onset was found in children with systemic JIA (3.9 ± 3.4 years). Children with enthesitis related arthritis and with seropositive polyarthritis were oldest at disease onset (11 ± 3.1 years and 10.3 ± 3.5 years). The mean (\pm SD) disease duration before therapy with etanercept was 5.1 ± 4.0 years.

At start of therapy with etanercept the mean (\pm SD) age of the patients was $12.1 (\pm 4.5)$ years. As expected, patients of the single JIA subgroups differed in part markedly from patients of other subgroups. Patients with seropositive (14.3 ± 3.1 years) and seronegative polyarthritis (12.3 ± 4.2 years), those with enthesitis related arthritis (15 ± 2.9 years) and those with psoriasis arthritis (13.5 ± 3.8 years) were older than patients with systemic arthritis (9.2 ± 5.1 years) or persistent or extended oligoarthritis (10.0 ± 4.7 years).

High disease activity was reflected by high numbers of active joints, elevated ESR and C-reactive protein and a prolonged duration of morning-stiffness (table 1). Patients with polyarthritis had the highest numbers of active joints (13 ± 10), patients with persistent oligoarthritis had the lowest numbers (3 ± 2). Highest inflammatory parameters were observed in patients with systemic JIA (ESR 56 ± 32 mm/h, C-reactive protein 73.2 ± 66.0 mg/l). Morning stiffness was longest in patients with seropositive polyarthritis and in patients with extended oligoarthritis (51 ± 63 min and 49 ± 67 min), while patients with persistent oligoarthritis had the shortest duration of morning stiffness (3 ± 5 min). Among patients with JIA those with systemic arthritis and with seronegative polyarthritis

most frequently needed aids/devices (mean number 3 ± 4). Physician's global assessment of the overall disease activity was worst in patients with systemic arthritis (7.7 ± 2.1 cm on a 10 cm VAS) as well as patients's/parent's global assessment of the overall patient's well-being (6.3 ± 2.7 cm on a 10 cm VAS).

The mean (\pm SD) CHAQ DI of all patients was 0.9 ± 0.7 . This implicates a moderate disability according to the categorization of Ruperto et al. (16). Higher scores in the CHAQ DI were present in patients with systemic arthritis, seropositive or seronegative polyarthritis and extended oligoarthritis ($p<0,0001$ in the Kruskal Wallis test), patients with elevated ESR, C-reactive protein, patients with a large number of active joints, patients experiencing prolonged duration of mornings-stiffness, those with higher scores in physician's global assessment of the overall disease activity and parent's global assessment of the overall patient's well-being and with the need of many aids/devices. Univariant analysis showed a significant correlation of the parameters of JIA-severity (number of active joints, duration of morning stiffness, parent's global assessment of the overall patient's well-being, need of aids/devices, physician's global assessment of the overall disease activity, CRP) with the CHAQ DI ($p<0.005$, table 1).

At start of treatment with Etanercept, the scores of the eight functional CHAQ areas varied (table 2). According to the classification by Ruperto et al. children had a moderate disability in most functional areas before etanercept therapy. The rheumatic disease had the greatest impact on "activities" (1.4 ± 1.0), "reach" (1.1 ± 0.9), "dressing and grooming" (1.0 ± 1.0) and "grip" (1.0 ± 1.0). "Eating" (0.7 ± 0.9) and "walking" (0.7 ± 0.9) were less affected. Patients with systemic arthritis and patients with enthesitis related arthritis had more severe disability while doing "activities" (1.6 ± 1.1 and 1.6 ± 1.0). "Eating" was easiest ("mild disabilities") for children with persistent oligoarthritis, enthesitis related arthritis, psoriasis and arthritis and extended oligoarthritis (0.1 ± 0.4 , 0.3 ± 0.6 , 0.4 ± 0.8 , 0.5 ± 0.8). Children with persistent oligoarthritis had "mild disability" in all functional areas except for "activities" (0.9 ± 0.9). Significant differences ($p<0,005$ in the Kruskal Wallis test) between the JIA-Subtypes were found for the CHAQ-areas "dressing and grooming", "eating", "hygiene", "reach" and "grip".

Therapeutic efficacy of the treatment with etanercept.

For analysis of the influence of treatment with etanercept on functional ability those patients were included who had been treated for at least 24 months and in whom a complete set of data was available. By this way, 114 patients could be identified. There was a significant improvement of the

CHAQ DI before therapy to the CHAQ DI during therapy in the JIA population in the GLM repeated measures ($p < 0.0001$). The mean \pm SD of the CHAQ DI before therapy was 0.92 ± 0.77 (median 0.75). After six months of treatment the CHAQ DI decreased to a mean \pm SD of 0.39 ± 0.53 (median 0.13) and after 18 months to a minimum of 0.32 ± 0.5 (median 0, figure 1). At start of therapy the mean CHAQ DI corresponded to “moderate disability”, after six months and thereafter to “mild disability” (29).

Comparing the subtypes there were markedly higher CHAQ DI in patients with seropositive or seronegative polyarthritis than in other JIA subgroups as outlined in table 3. Seronegative polyarthritis patients were the largest patient group ($n=33$) in this analysis and remained with the highest CHAQ DI during etanercept therapy followed by patients with seropositive polyarticular JIA. Disability disappeared in the majority of patients leading to a decrease of the mean CHAQ DI. At month 0, 6, 12, 18 and 24 the mean CHAQ DI in seronegative polyarticular JIA patients was 0.96, 0.68, 0.62, 0.53 and 0.57, in seropositive polyarticular JIA it was 1.0, 0.37, 0.36, 0.41 and 0.46. The CHAQ DI for patients with persistent oligoarthritis were the lowest at all points of time (0.25, 0.03, 0.05, 0.05 and 0.03 at 0, 6, 12, 18 and 24 months).

High disease activity was accompanied by large numbers of active joints, elevated ESR and C-reactive protein, high scores in physician’s global assessment of the overall disease activity, high scores in parent’s global assessment of the overall patient’s well-being and a prolonged duration of morning-stiffness and was reflected by a high CHAQ DI at start of therapy (table 1). Significant improvement in active joints, parent’s global assessment of the overall patient’s well-being, physician’s global assessment of the overall disease activity, duration of morning stiffness, ESR and C-reactive protein was seen after 6, 12, 18 and 24 months ($p < 0.0001$ for all parameters and all points of time) (table 4). Functional ability improved though parameters of disease activity were high before therapy. While high scores in active joints, CRP, ESR, parent’s global assessment of the overall patient’s well-being, physician’s global assessment of the overall disease activity and morning stiffness were attended by high DI before therapy, patients reached lower levels of CHAQ DI during therapy.

At start of therapy with etanercept, those children treated with a combined therapy of methotrexate and etanercept had a higher CHAQ DI (0.9 ± 0.79). However, they showed a marked improvement of

scores during therapy and reached after 24 months a minimum level of 0.33 ± 0.52 . Patients treated with etanercept monotherapy at start of therapy had a CHAQ DI of 0.72 ± 0.61 which decreased to 0.34 ± 0.53 after 24 months of treatment.

All functional areas of the CHAQ improved significantly during therapy with etanercept ($p < 0.0001$) (figure 2). Before therapy children had most problems with “activities”, “dressing and grooming”, “reach” and “grip” (mean score of those areas 1.44, 1.12, 1.05, 0.94). These scores corresponded to “moderate disability”. At 24 months of therapy the patients still had most problems with “activities”, “reach”, “dressing and grooming” and “grip” (mean score of those areas 0.61, 0.51, 0.44, 0.38). These levels of disabilities finally corresponded to “mild disability” in all functional areas except for “activities” with a “moderate disability”.

Measuring therapeutic efficiency by the maximal improvement of the PedACR-Score reached during 24 month of therapy, 96.5%, 93.8% and 90.3% of the patients reached a PedACR-30, -50 and -70 score. Subtype analysis showed that 90.9%, 81.8% and 72.7% of the patients with systemic arthritis reached a Ped-ACR-30, -50 and -70 score which was somewhat lower than in children with non-systemic JIA, who reached a PedACR-30, -50 and -70 score with 97.1%, 95.1% and 92.2% of their patient-group (Figure 3).

In our patient population 8.8% of the patients discontinued the therapy due to inefficiency, 5.1% discontinued due to intolerance. About 7% discontinued treatment due to remission.

DISCUSSION

This study provides data about children who started treatment with etanercept in Germany between 2001 and 2006. Data of 437 children were analyzed for disease severity and impact of the disease on functional abilities. Data of 114 children with a complete data set and a continuous treatment for at least 24 months were used for analysis of the impact of treatment on functional abilities. Patients have still not been treated so far and could therefore not be included. Only a minority of 8.8% of patients of the registry cohort discontinued due to inefficacy, only 5.1% discontinued due to intolerance. About 7.0% discontinued treatment due to remission. The results confirm previous

studies on the German etanercept registry (6; 9). The major gains of etanercept therapy were as follows:

- Children with long standing JIA had poor functional ability and high disease activity before start of treatment with etanercept.
- Among those, patients with either seronegative or seropositive polyarthritis, extended oligoarthritis and with systemic JIA suffered from higher disease activity concerning the number of active joints, inflammatory parameters (ESR, C-reactive protein), duration of morning-stiffness, parent's global assessment of the overall patient's well-being, physician's global assessment of the overall disease activity and number of aids/devices needed.
- JIA patients with higher disease activity parameters also had higher CHAQ DI.
- There was a high response rate to etanercept in children who previously were unresponsive or intolerant to several antirheumatic drugs.
- There was a rapid improvement during the first six months of therapy concerning CHAQ DI and disease activities which remained at lower levels during 24 months of treatment.
- Combination therapy of etanercept and MTX led to higher improvement-rates and led to better abilities in fulfilling every day's duties.

Our results indicate that functional ability improves strongly during 24 months of therapy with etanercept. Clinical improvement was indicated by a decrease of the CHAQ DI and by an improvement according to the PedACR-30, -50 and -70 score. An improvement of the CHAQ DI was already evident after 6 months of treatment and persisted until 24 months with a further decrease of the mean CHAQ DI. A marked decrease of all clinical parameters was noted after six months. The results of this long term study confirm previous findings by Lovell et al. (3-5) on a limited number of patients as well as several other case series that were published thereafter (6-13). Lovell et al. first started a randomized placebo-controlled study. Later on patients of this study went in a long-term open-label extension study. 69 patients started the initial study with a mean CHAQ DI 1.5 (± 0.1), one year later the mean CHAQ DI was 0.8 (± 0.1) and four years later the CHAQ DI was 0.6 (± 0.1). After eight years of therapy a PedACR 70 was achieved all patients who continued on treatment.

Functional ability was lowest in patients with either seronegative or seropositive polyarthritis. Patients with polyarthritis remained to have higher CHAQ DI scores during therapy than patients

with other JIA-subtypes. This effect suspected that a lower physical ability remains during therapy in patients with higher numbers of affected joints.

Patients with systemic JIA who responded to etanercept and continued treatment for 24 months had an equal improvement of their disease activity as patients with other JIA-Subtypes. This finding is similar to a finding of Prince et al. This Dutch long term follow up study included 146 JIA-patients who were treated with etanercept for a median of 2.5 years (13).

A combination therapy with etanercept and MTX was well accepted by the patients. Physical ability improved in both groups. However the extend of improvement of the CHAQ DI was higher in patients with combination therapy of methotrexate and etanercept than in those with etanercept monotherapy. In another analysis of data of the German registry on a patient cohort of 604 patients similar results have been described for the PedACR-Score (9). Here, the likelihood of achieving a PedACR 70 increased with combination therapy. Earlier studies including fewer patients confirm our results (6; 11; 30).

The 8 functional areas of the CHAQ differed before and during therapy. Functional ability improved in all areas and the discrepancy between the areas decreases during therapy. Before and during therapy “activities”, “dressing” and “reach” were hardest for children with JIA, “eating” and “walking” were less affected. Duties of everyday life concerning actions that are indispensable in everyday life like “cutting meat”, “lift up a cup or glass to mouth”, “open a new cereal box”, “walk outdoors on flat ground” and “climb up five steps” were easier to practice and to accomplish than duties that can be avoided or need fine motor skills. Examples are “cut fingernails” or “ride bike or tricycle”. Avoided skills or skills which claim fine motor skills cause higher counts in the respective areas since the question with the highest count is used for calculation the CHAQ. Another aspect was stated by Pouchot et al. They found that for the “run and play” item, it is possible that parents of older children may consider the “run” activity, whereas parents of younger children may concentrate on the “play” activity (31). If this is correct one can argue that “running” may be a more difficult activity than “playing”.

Oliveira et al. found in their study about health related quality of life (HRQOL) that children with JIA have a greater impairment in physical well-being than in psychosocial health and that physical disability and pain are important determinants of HRQOL (23). These findings indicate that improvement of physical ability and reduction of pain are the major goals of JIA therapy.

In summary, we found dramatical improvement of functional ability in children with severe and so far treatment resistant JIA. The major findings of our study were a rapid improvement of functional

ability and disease activity parameters already evident after six months of therapy which was prolonged and further improved during at least 24 months. Duties of everyday life were easier to accomplish and HRQOL improved.

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Figure 1 : Improvement of CHAQ DI in the first 24 months of therapy with etanercept (n=114). ▲: median, ▼: mean, grey: 25th-75th percentile.

Figure 2. Functional ability in 8 functional areas of the CHAQ during therapy.

Figure 3: Therapeutic efficiency measured by the Ped-ACR-Score after 24 month of therapy comparing systemic and non-systemic JIA

Table 1. Demographic, Clinical and laboratory characteristics of the study participants before therapy with etanercept*

Characteristic	Systemic arthritis n=76	Seronegative Polyarthritis n=138	Seropositive Polyarthritis n=53	Persistent Oligo-arthritis n=15	Extended Oligo-arthritis n=73	Enthesitis related Arthritis n=51	Psoriasis-arthritis n=31	All JIA patients* n=437	P °
Age at therapy start, years	9.2 ± 5.1	12.3 ± 4.2	14.3 ± 3.1	9.7 ± 3.9	11.0 ± 4.2	15.0 ± 2.9	13.5 ± 3.8	12.1 ± 4.5	0.06
Age at JIA onset, years	3.9 ± 3.4	6.1 ± 4.1	10.3 ± 3.5	5.9 ± 5.0	3.7 ± 3.9	11.0 ± 3.1	8.0 ± 4.5	6.6 ± 4.6	0.3
Disease duration, years ~	4.8 ± 4.3	5.7 ± 4.0	3.4 ± 3.0	3.3 ± 3.5	7.0 ± 4.0	3.2 ± 2.4	5.0 ± 4.5	5.1 ± 4.0	0.04
Female gender, no. (%)	45 (59.2)	106 (76.8)	45 (84.9)	9 (60)	56 (76.7)	25 (49.0)	20 (64.5)	306 (70)	0.6
Concomitant therapy with MTX, no. (%)	62 (84.9)	109 (79.0)	52 (92.9)	14 (93.3)	58 (78.4)	44 (83.0)	23 (76.7)	362 (82.5)	0.3
No. of active joints	10 ± 11	13 ± 10	13 ± 9	3 ± 2	8 ± 6	5 ± 5	6 ± 4	10 ± 9	< 0.0001
Physician's global assessment of the overall disease activity \$	7.7 ± 2.1	6.5 ± 2.3	6.3 ± 2.7	4.7 ± 3.0	6.6 ± 2.2	6.1 ± 2.3	4.9 ± 2.6	6.5 ± 2.4	0.002
Erythrocyte sedimentation rate, mm/h	56 ± 32	29 ± 24	36 ± 26	19 ± 20	37 ± 26	34 ± 28	28 ± 24	36 ± 28	0.02
C-reactive protein mg/l	73.2 ± 66.0	23.7 ± 30.4	30.4 ± 28.0	12.3 ± 18.8	32.5 ± 41.8	21.5 ± 21.8	31.6 ± 74.3	34.7 ± 46.8	0.003
Morning stiffness (minutes)	37 ± 56	41 ± 56	51 ± 63	3 ± 5	49 ± 67	42 ± 70	47 ± 68	42 ± 61	< 0.0001

Table 1. Demographic, Clinical and laboratory characteristics of the study participants before therapy with etanercept*

Aids/devices needed, no.	3 ± 4	3 ± 4	2 ± 3	1 ± 2	2 ± 3	1 ± 3	1 ± 2	2 ± 3	< 0.0001
Patient's assessment of overall well being \$	6.3 ± 2.7	5.5 ± 2.7	5.5 ± 2.6	4.5 ± 3.3	5.4 ± 2.8	5.8 ± 2.6	5.5 ± 2.1	5.6 ± 2.7	< 0.0001
CHAQ DI §	1.1 ± 0.8	1.0 ± 0.8	1.0 ± 0.7	0.3 ± 0.4	0.8 ± 0.6	0.7 ± 0.6	0.6 ± 0.5	0.9 ± 0.7	

*JIA= juvenile idiopathic arthritis, values are mean ± SD, unless otherwise indicated

\$ on a 10cm visual analogue scale (0= very well, 10=very poor)

§ CHAQ= Childhood Health Assessment Questionnaire, range: 0-3 (0=best, 3=worst)

° Correlation of all JIA-patients with the CHAQ, univariant analysis of variance

~ before therapy with etanercept

Table 2. The 8 functional areas of the CHAQ at start of therapy with etanercept

CHAQ areas §	JIA-Subtypes							<i>p</i> *	All JIA children <i>n</i> =384
	<i>Systemic arthritis n</i> =63	<i>Seronegative polyarthritis n</i> =119	<i>Seropositive polyarthritis n</i> =51	<i>Persistent oligo- arthritis n</i> =14	<i>Extended oligo- arthritis n</i> =62	<i>Enthesitis related arthritis n</i> =50	<i>Psoriasis and arthritis n</i> =25		
Dressing and grooming	1.4 ± 1.1	1.1 ± 1.0	1.1 ± 0.9	0.4 ± 0.7	0.9 ± 0.8	0.7 ± 0.9	0.7 ± 1.0	<0.0001	1.0 ± 1.0
Arising	1.1 ± 1.0	1.0 ± 0.9	0.8 ± 0.8	0.4 ± 0.7	0.8 ± 0.9	0.9 ± 0.8	0.4 ± 0.7	<0.01	0.9 ± 0.9
Eating	0.8 ± 1.1	0.8 ± 0.9	0.8 ± 0.9	0.1 ± 0.4	0.5 ± 0.8	0.3 ± 0.6	0.4 ± 0.8	<0.0001	0.7 ± 0.9
Walking	0.9 ± 0.9	0.8 ± 0.9	0.6 ± 0.8	0.4 ± 0.8	0.8 ± 0.9	0.8 ± 0.8	0.5 ± 0.8	0.2	0.7 ± 0.9
Hygiene	1.3 ± 1.1	1.0 ± 1.0	0.9 ± 0.8	0.1 ± 0.4	0.7 ± 0.9	0.7 ± 0.9	0.4 ± 0.7	<0.0001	0.9 ± 1.0
Reach	1.4 ± 1.1	1.1 ± 1.0	1.2 ± 0.9	0.3 ± 0.6	1.0 ± 0.8	0.9 ± 0.9	0.8 ± 0.7	<0.001	1.1 ± 0.9
Grip	1.2 ± 1.1	1.3 ± 1.1	1.2 ± 0.9	0.1 ± 0.5	0.8 ± 0.9	0.5 ± 0.8	1.0 ± 1.0	<0.0001	1.0 ± 1.0
Activities	1.6 ± 1.1	1.3 ± 1.0	1.4 ± 1.0	0.9 ± 0.9	1.2 ± 0.9	1.6 ± 1.0	0.9 ± 0.9	<0.009	1.4 ± 1.0
CHAQ DI ⌘	1.1 ± 0.8	1.0 ± 0.8	1.0 ± 0.7	0.3 ± 0.4	0.8 ± 0.6	0.8 ± 0.6	0.6 ± 0.5	<0.0001	0.9 ± 0.7

* Kruskal Wallis test, comparing the JIA-subtypes

§ The range for CHAQ DI is 0-3 (0= best, 3=worst), mean ± SD is expressed

⌘ CHAQ DI is the mean score of the 8 functional areas

Table 3: Mean CHAQ DI (\pm SD) for JIA subtypes during therapy with etanercept (n=114)					
Month after treatment was started	0	6	12	18	24
Systemic arthritis (n=12)	1.0 \pm 0.84	0.21 \pm 0.33	0.23 \pm 0.43	0.27 \pm 0.51	0.19 \pm 0.39
Seronegative polyarthritis (n=33)	0.96 \pm 0.83	0.68 \pm 0.72	0.62 \pm 0.65	0.53 \pm 0.67	0.57 \pm 0.67
Seropositive polyarthritis (n=19)	1.0 \pm 0.84	0.37 \pm 0.46	0.36 \pm 0.47	0.41 \pm 0.52	0.46 \pm 0.6
Persistent oligoarthritis (n=5)	0.25 \pm 0.25	0.03 \pm 0.06	0.05 \pm 0.11	0.05 \pm 0.11	0.03 \pm 0.06
Extended oligoarthritis (n=23)	0.86 \pm 0.72	0.26 \pm 0.39	0.21 \pm 0.33	0.18 \pm 0.32	0.21 \pm 0.35
Enthesitis related arthritis (n=17)	0.82 \pm 0.71	0.22 \pm 0.34	0.09 \pm 0.13	0.1 \pm 0.21	0.13 \pm 0.27
Psoriasis and arthritis (n=5)	0.58 \pm 0.68	0.25 \pm 0.35	0.15 \pm 0.34	0.03 \pm 0.06	0.08 \pm 0.12

Table 4: Characteristics of disease activity during therapy with Etanercept*						
Characteristic \ Time in month	0	6	12	18	24	P°
No. of active joints	10±9	3±7	2±5	3±7	3±6	<0.0001
Physician's global assessment of the overall disease activity §	6.2±2.6	1.6±2	1.5±1.9	1.4±1.9	1.5±2	<0.0001
Erythrocyte sedimentation rate, mm/h	33±26	14±15	14±14	13±14	14±12	<0.0001
C-reactive protein mg/l	40.9±55.2	6.6±19.5	7.9±14.8	10.2±19.9	8.8±15.7	<0.0001
Morning stiffness (minutes)	42±66	3±11	4±10	3±13	5±19	<0.0001
Patient's assessment of overall well being §	5.2±2.8	1.4±1.8	1.4±1.5	1.3±1.6	1.4±1.7	<0.0001
CHAQ DI §	0.92±0.77	0.39±0.53	0.37±0.51	0.32±0.5	0.34±0.52	<0.0001
values are mean ± SD' § on a 10cm visual analogue scale (0= very well, 10=very poor) § CHAQ= Childhood Health Assessment Questionnaire, range: 0-3 (0=best, 3=worst) ° Change of characteristics of disease activity during therapy, GLM repeated measures						





