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Retrospective Cohort Study of Effectiveness and Safety of Adalimumab Use in Children with Juvenile Idiopathic Arthritis in the Republic of Bashkortostan

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Methotrexate is the first-line drug for treating patients with juvenile idiopathic arthritis (JIA). If it is ineffective or intolerable, prescription of genetically engineered biopharmaceuticals is indicated. ***The study was aimed*** *at assessing effectiveness and safety of genetically engineered biopharmaceutical adalimumab for treating children with JIA.* ***Methods:*** *a retrospective cohort study was conducted to analyze results of treating patients with JIA aged 2-17 years. Adalimumab would be prescribed biweekly in the dose of 24 mg/m^2 (body surface) subcutaneously (if body weight is under 30 kg) or in the dose of 40 mg/m^2 (if body weight is > 30 kg). Effectiveness and safety would be assessed after 4-12-24-48-96 weeks.* ***Results:*** *we analyzed treatment results of 17 patients (15 children with active joint syndrome, 2 – with active uveitis). All patients with active joint syndrome had been receiving adalimumab for 12 weeks, 12 patients – for 24 weeks, 8 – for 48 weeks, 5 – for 96 weeks. 30/50/70% improvement in terms of the ACR_{pedi} criteria was observed in 15/11/4 children after 4 weeks, after 12 weeks – in 15/13/11 patients, after 48 weeks – in 7/6/6 patients. The status of inactive disease was established in 5 patients (33%) after 12 weeks, after 24 weeks – in 9 children (75%), after 48 weeks – in 7 children (70%), after 96 weeks – in 4 (80%) children. Active uveitis was terminated in all 5 patients with signs of eye damage in the treatment onset. 1 patient suffered from exacerbation of the disease after 48 weeks of therapy; the drug was withdrawn. Tubercular infection without local manifestations was established in 1 patient after 96 weeks (positive Mantoux test, papule – 10 mm). Adalimumab injection was terminated for the period of chemotherapy.* ***Conclusion:*** *adalimumab has a sufficiently high effectiveness and safety for long-term (up to 2 years) treatment of children with JIA.*
Keywords: *children, juvenile idiopathic arthritis, genetically engineered biopharmaceuticals, adalimumab.*

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RATIONALE

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disorder in children [1]. According to an epidemiological study carried out in the Republic of Bashkortostan in 2004, the prevalence and incidence of JIA totaled at 83.8 and 12.3 per 100,000 of pediatric population aged up to 16, respectively [2].

JIA treatment is targeted at suppressing inflammation whilst achieving a remission, reducing the pain syndrome and preserving the joint function [3]. For background anti-JIA therapy, doctors mostly use methotrexate; in case it is inefficient or intolerable, they prescribe genetically engineered biological drugs [4, 5]. According to the current recommendations, the first-line drugs are inhibitors of tumor necrosis factor (TNF) α [1, 4]. This class includes adalimumab, a recombinant monoclonal antibody to TNF α that neutralizes its biological functioning by blocking its interaction with surface cell TNF α receptors.

A number of randomized clinical trials have proven the efficiency and safety of adalimumab [6-8]. An analysis of long-term safety of adalimumab has revealed that the safety profile of this drug in children aged 2 to 17 is comparable to that in adults with rheumatoid arthritis; there has been found no case of neoplasms, opportunistic infections in, or death of any patient [7].

For instance, one study involved children aged 4–13; in 106 weeks after such treatment started, all the patients had a 30% status improvement per the American College of Rheumatology criteria (ACR_{pedi}), 96% had a 50% improvement, and 71% reached the "inactive disease" status, which is a 90% improvement per ACR_{pedi} criteria [8]. The disease was apparently controllable over six years [8]. Studies have shown that the safety and efficiency profile of adalimumab in children aged 2 to 4 is comparable to that in children older than 4 [9].

Clinical trials carried out in Russia also prove the efficiency and safety of adalimumab when used to treat children [10, 11]. For instance, E.I. Alexeyeva et al. have pronounced a 1-year remission in 85% of children [10]. The drug was efficient and well-tolerated where use other biological drugs resulted a primary failure, had an only partial effect, or their effect was nullified over time. 98% of patients had an "inactive" status and 96% had a remission after a 2-year follow-up [11].

According to BIKER, a German register, adalimumab was comparably efficient both as a first-line drug and as a secondary biological agent used to treat JIA-affected children [12]. These observations are of importance, because studies based on JIA case registers allow to collect data on the efficiency and safety of GEBD when used in real clinical practice.

The goal of the study was to assess the efficiency and safety of adalimumab when used to treat JIA-affected children in the Republic of Bashkortostan.

Methods

STUDY DESIGN

We have carried out a retrospective cohort study and analyzed the treatment progress of JIA-affected children registered with the Republican Pediatric Clinical Hospital (RPCH, Ufa, Republic of Bashkortostan).

FITTING CRITERIA

The inclusion criteria were as follows:

- age of 2 to 17;
- clinical data are in compliance with the JIA criteria of the International League of Associations for Rheumatology, ILAR [13];
- the patient had been treated with adalimumab when admitted to the RPCH, if such therapy had been initiated at a federal healthcare institution; alternatively, adalimumab treatment at the RPCH;
- availability of necessary data in the medical documents under analysis: the "articular" status; erythrocyte sedimentation rate (ESR); C-reactive protein concentration, CRP;
- patient’s or parents’ informed consent on the use of examination data in scientific research.

Exclusion criteria: patient's or parents' non-compliance with the recommended schedule of visits to RPCH for examinations.

DATA SOURCE

We analyzed the medical records of inpatients and outpatients, histories of child development as well as data from the regional segment of the Federal Register of Juvenile Arthritis Patients followed-up at the cardiorheumatology unit and the consultative polyclinic of the RPCH from February 2009 till November 2015.

RESEARCH EVENTS

The research events under this analysis were: achieving the inactive disease status (primary event) as well as achieving a 30/50/70 percent improvement per the ACR_{pedi} criteria; a lower score of functional deficiency per the Childhood Health Assessment Questionnaire and the Juvenile Arthritis Disease Activity Score 27. The efficiency and safety of such therapy was estimated in 4, 12, 24, 48, and 96 weeks of treatment.

EVENT REGISTRATION METHODS

Inactive disease status criteria [14]:

- no joints with active arthritis;
- no fever, rashes, serositis, splenomegaly or generalized lymphadenopathy, which are typical for juvenile arthritis;
- no active uveitis;
- ESR and/or CRP within the normal range;
- no disease activity per the 100-m visual analog scale, VAS;
- morning stiffness lasts less than 15 minutes.

To pronounce that the disease was inactive, the patient had to meet all the above criteria. Drug-induced clinical remission was pronounced where the drug-based therapy had kept the disease inactive for 6 months in a row. Non-drug-induced clinical remission was pronounced if the disease had been inactive for 12 months in a row without anti-rheumatic drugs.

Disease activity criteria included the number of joints with active arthritis (27 joints accounted), the doctor's evaluation of disease activity, and mother's evaluation of the child's health per the 100mm VAS, as well as Westergen ESR calculated using the formula:

ESR (mm/h) – 20/10

The total of the above indicators constituted the integral disease activity score, JADAS-27 [15].

The intensity of functional deficiency in patients was evaluated using the Russian version of the CHAQ [16]. CHAQ equal to, or less than 1.5 indicated minimal or moderate intensity; >1.5 stood for pronounced intensity.

Therapy efficiency was evaluated per the ACR_{pedi} criteria using the following variables:

- doctor's general assessment of disease activity per VAS;
- patient's or parents' general assessment of disease severity per VAS;
- functional deficiency score per the CHAQ;
- number of joints with active arthritis;
- number of joints with limited motion;
- ESR or CPR concentration.

ACR_{pedi} criteria for a 30, 50, or 70 percent improvement were a decrease of at least 3 of these 6 variables by 30, 50, or 70 percent. It was admissible that one of the indicators could worsen by

30% or more. Treatment effect was deemed satisfactory in case of a 30% improvement per ACR_{pedi}, good in case of a 50% improvement, excellent in case of a 70% or greater improvement.
Functional deficiency (functional class, FC) was determined using the Steinbrocker classification:

- FC I – functional ability of joints preserved;
- FC II – adequate for normal activities and self-care despite limited self-care capabilities;
- FC III – limited to little or none of the duties of usual occupation or self-care;
- FC IV – incapacitated, largely or wholly bed-ridden or confined to a wheelchair with little or no self-care.

For all the patients, doctors carried out biochemical and clinical blood tests once a month; tubercle test (Mantoux test), CT scans or thoracic cage X-ray study per performed every 6 months; ophthalmologic examination on a slit lamp was carried out every three months.

ETHICAL EXPERTISE

No ethical expertise was carried out, as the study was retrospective, and treatment under consideration was within the framework of existing standards and clinical recommendations. When admitted to the RPCH, the patient (if aged 15 or older) or one of their parents signed an informed consent for medical care and use of examination data for scientific research.
Adalimumab was prescribed on the basis of non-registered indications (with the patient's age below manual-specified values) at federal healthcare institutions (Nasonova Research Institute of Rheumatology, the Scientific Center of Children's Health, and Sechenov First Moscow State Medical University Clinic). In this case, such prescription was approved by the local ethical committees of these institutions.

STATISTICAL ANALYSIS

Sample size was not calculated preliminarily. The results were analyzed statistically using STATISTICA v. 6.0 by StatSoft Inc., USA> When describing quantitative data, we indicated the median as a central tendency measure, and the 25th and 75th percentiles as a measure of dispersion. Indicator dynamics as affected by treatment was assessed using the Wilcoxon test.

Results

CHARACTERISTICS OF JIA-AFFECTED PATIENTS.

Over the entire retrospection period, the cardiorheumatology units and the consultative polyclinic of the RPCH followed-up 17 children, a boy and 16 girls, aged 2.9 to 17.9 (Table 1). Most patients (n = 14) were schoolchildren (7 years or older). The onset of this disease was identified in these children when aged 4 months to 15 years; for most patients (n = 14), the age of onset was 3 years or less.
More than a half of the patients had a polyarticular version of JIA, 1 patient had RF-positive JIA (RF stands for rheumatoid factor); every third patient had oligoarticular JIA. Active articular syndrome was noted in 15, or 88%, of children. 2 patients without such syndrome were prescribed adalimumab because of their active uveitis. Uveitis was diagnosed in every third child (Table 1).
The articular junction was disordered in 16 of 17 patients with active articular syndrome (94%). The median of the number of joints with limited motion was 7 (3; 12). In six patients, functional deficiency of joints limited their self-care capacities (FC III and IV), of whom 2 needed outside assistance (FC IV).
The median of the functional deficiency evaluation per the CHAQ was 1.5 points (0.5; 2.0).

4 children had severe functional deficiency, with the CHAQ index exceeding 1.75; 6 patients had moderate deficiencies (0.64 to 1.75). Functional deficiency was minimal in 3 patients (0.14 to 0.63) and not identified in 2 patients. The CHAQ was not applied to 2 of the kids aged 3 and 4. High JADAS-27 score, with a median of 21 (10.5; 29) indicated moderate or high activity of the disease.

Table 1. Characteristics of juvenile idiopathic arthritis patients treated with adalimumab

Indicator	Values (*n* = 17)
Girls, abs. (%)	16 (94)
Age when treatment started, years	13.6 (9.7; 16.8)
Age of onset, years	3.8 (1.5; 10.1)
How long the disease had lasted, years	4.6 (1.2; 7.7)
Oligoarthritis, abs. (%) • persistent, abs. • disseminated, abs.	6 (35) 4 2
Polyarthritis, abs. (%) • RF-negative, abs. • RF-positive, abs.	10 (59) 9 1
Enthesitis-associated arthritis, abs. (%)	1 (6)
Uveitis, abs. (%)	6 (35)

PRIOR THERAPY

Before adalimumab was prescribed, all the patients had undergone combined antirheumatic therapy at the RPCH (Table 2). Almost all the children had been administered intramuscular injections of methotrexate on a weekly basis; in three cases, the drug was combined with cyclosporine A. Besides, the children had been administered prednisolone as well as other genetically engineered biological drugs. Local anti-uveitis therapy included application of drops containing nonsteroidal anti-inflammatory drugs and mydriatics. Despite such treatment, active articular syndrome and/or active uveitis persisted in these patients, and so did their moderately or severely increased inflammatory activity.

Table 2. Prior treatment of juvenile idiopathic arthritis patients treated with adalimumab

Drug	Values (*n* = 17)
NSIAD, abs. (%)	15 (88)
Methotrexate (*n* = 16), mg/m^2 per week	12.2 (10.2; 14.0)
Cyclosporine A (*n* = 3), mg/kg	4.0
Prednisolone (*n* = 4), mg/kg	0.5 (0.4; 0.7)
GEBD, abs. (%) • infliximab, (*n* = 3), mg/kg • etanercept (*n* = 4), mg/kg per week • abatacept (*n* = 2) mg/kg • tocilizumab (*n* = 1), mg/kg	10 (59) 5.8–6.0 0.82–0.87 10.0–10.2 8.2
Glucocorticoids i/a, abs. (%)	10 (59)
Local treatment of uveitis, abs. (%)	5 (29)

Note. NSAID stands for non-steroid anti-inflammatory drugs; GEBD stands for genetically engineered biological drugs.

RESULTS OF ADALIMUMAB APPLICATION

In six cases, adalimumab-based therapy was initiated at a federal healthcare institution; in other

cases, it started at the RPCH (Ufa). Adalimumab was administered every two weeks subcutaneously in a dose of 24 mg/m^2 of body surface, if the total body weight was 30 kg or less; the dose of 40 mg/m^2 for children with body weight in excess of 30 kg.
Such treatment reduced the number of active joints and functionally deficient joints as early as the in the first weeks of treatment (Table 3). In 24 weeks, active articular syndrome was completely reversed in 10 of 12 patients. ESR and CRP concentration halved by the 4th week of treatment and continued to decline over the subsequent months; most patients (n = 11) had normal ESR (up to 10 mm/h) and CRP (up to 5 mg/l) values by the 12th week of treatment. As the active inflammatory process was reversed, JIA-affected children had their status improved in terms of functional deficiency per the CHAQ.

Table 3. How treatment with adalimumab affected the activity dynamics of juvenile idiopathic arthritis in children with active articular syndrome.

Indicators	Initially (n = 15)	In four weeks (n = 15)	In 12 weeks (n = 15)	In 24 weeks (n = 12)
Active joints, abs.	6 (3; 10)	4 (2; 7)*	3 (0; 4)**	0 (0; 2)*
Joints with functional deficiency, abs.	9 (5; 13)	6 (3; 10)**	4 (2; 7)0.003	4 (2; 6)*
EESR in mm/h	32 (12; 49)	17 (6; 24)**	12 (4; 19)**	9 (4;13)*
CRP, mg/l	15 (2,9; 47.1)	6.8 (1.1; 15)**	3.5 (0.9; 11.2)**	3.2 (1.1; 5.7)*
CHAQ index	1.5 (0.5; 2.0)	1.0 (0.25; 1.25)**	0.75 (0.12; 1.0)**	0.25 (0; 0.5)**

Note. CRP stands for C-reactive protein; CHAQ stands for the Childhood Health Assessment Questionnaire. * p<0.01, p<0.001, when compared to initial data.

Based on the ACR_{pedi} criteria, all the patients had a 30% improvement in 4 weeks; 11 of 15 (73%) patients had a 50% improvement, and 4 of 15 patents (27%) had a 70% improvement in the same period of time. In 12 weeks after the treatment started, 15 (100%) patients had a 30% improvement; 13 (27%) had a 50% improvement; 11 (73%) had a 70% improvement; the disease was identified as inactive in 5 (33%) patients. In 24 weeks, a 30/50/70 % improvement per the ACR_{pedi} criteria was registered in 11 (92%), 10 (83%) and 10 (83%) of patients, respectively; 9 of 12 patients, or 76%, had reached the inactive disease status. In 48 weeks, 7 of 8 patients, or 88%, met the 30% improvement criteria, while 6, or 75%, met the 50/70% improvement criteria. In one girl, the disease exacerbated, which was believed to indicate the inefficiency of the drug; treatment was canceled. In 96 weeks, the 5 patients still followed-up had shown significant improvements; 4 of them, or 80%, had reached the inactive disease status. Active uveitis was reversed in all the 5 patients who had ocular injury signs at the start of treatment.
For 3 patients, treatment was terminated. In one patient, the drug lost its effect after an initial improvement, due to which they then used another genetically engineered biological drug. In another patient, the disease exacerbated in 6 years after the therapy started, which was regarded as secondary inefficiency. 1 patient had a 50% improvement in 24 weeks, which was deemed an insufficient effect. It is noteworthy that these two patients had a long history of the disease (4 and 8 years); the medical record indicated the secondary inefficiency of prior therapy with TNF α inhibitors (infliximab and etanercept). The remaining 8 patients, who had been receiving other genetically engineered biological drugs prior to adalimumab prescription, the use of adalimumab helped achieve a positive effect, including the 6 patients who reached the inactive disease status.

ADVERSE EFFECTS

Most patients tolerated such treatment well. They mostly (n = 8) noted pain at the injection site; there also was one hyperemia case. After 96 weeks, 1 patient had a positive Mantoux test (a

10 mm papule) and a dubious result of Diaskintest (hyperemia without an infiltrate). CT of the thoracic cage organs did not reveal any focal-infiltrative alterations. The phthisiatrician found a tubercular infection without local manifestations, which is why they decided to refrain from adalimumab administrations for the period of chemoprophylaxis.

Discussion

In accordance with the current treat-to-target concept of JIA treatment, the main goal of such treatment is about achieving a remission and the inactive disease status [17]. For these goals, rheumatologists have a number of synthetic and genetically engineered biological drugs. The first type of drugs includes methotrexate, which is considered most efficient and safest for treatment of JIA-affected children [1, 3, 4]. The frequency of using methotrexate for treating various JIA versions varies from 40-42 to 100% in different countries [18-20]. Its efficiency reaches up to 70%; however, the duration of treatment is limited by various adverse effects, which, according to JUMBO (a German register), are the leading cause (39%) of treatment termination [21].

Inefficiency of, or intolerance to methotrexate is an indication for prescription of genetically engineered biological drugs, of which TNF α inhibitors (etanercept, adalimumab) are preferable for treating non-systemic JIA. A number of randomized clinical trials have proven the efficiency and safety of adalimumab [6–9]. However, the results of using this drug in ordinary clinical practice are very important. Available data suggest that genetically engineered biological drugs are more efficient if prescribed early; this fact is of special interest [22, 23].

According to the results of our study, treatment with adalimumab allows for a significant reduction in disease activity, a significant improvement in the patient's functional status; it also allows to reach the inactive disease status, which is consistent with the results of other studies [6, 8, 11]. Besides, our pharmacoeconomic analysis (unpublished data) has identified that where the activity of the inflammatory process was reversed, and the inactive disease status was reached, the child needed less and shorter hospitalizations to the cardiorhematology unit of the RPHC; when a complete adalimumab treatment course was provided within the framework of regional aid programs, children needed less and shorter hospitalizations to federal healthcare institutions for high-tech medical care. This resulted in a significant reduction of specialized care costs.

We analyzed our own experience of using adalimumab and identified a number of issues related to the predictability of individual efficiency, the determination of optimal treatment duration when remissions are achieved, and mechanisms of primary and secondary inefficiency development [24-26]. Many topical questions related to the use of adalimumab or other genetically engineered biological drugs can only be answered if we continue to accumulate, generalize, and analyze the experience of long-term treatment. In normal clinical practice, this can only be done by collecting data of multiple centers in a National Patient Register.

LIMITATIONS OF THE STUDY

The cohort of patients studied was small in number and very heterogeneous in terms of JIA versions, onset age, prior antirheumatic therapy. This does not allow analyzing efficiency of the drug in its dependence on the clinical features of the disease or the period of prescription.

Conclusion

The above-mentioned clinical trials and descriptive observations do indicate that adalimumab is an effective and safe drug for treating juvenile arthritis in pediatric patients. The drug helps reach the inactive disease status and a remission in most patients, which is the main goal of treatment in accordance with the current "treat-to-target" concept. Our study also shows that adalimumab is very efficient and safe for treating JIA-affected children, including those, for whom treatment with other genetically engineered biological drugs (including TNF α) is inefficient.

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Conflict of interest

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