T.V. Sleptsova[1], E.I. Alexeeva[1,2], T.M. Bzarova[1], K.B. Isaeva[1], E.V. Mitenko[1]

1 Scientific Center of Children's Health, Moscow, Russian Federation

2 The First Sechenov Moscow State Medical University, Russian Federation

Experience of using methotrexate in a patient with early oligoarticular juvenile idiopathic arthritis

Author affiliation:

***Alexeeva Ekaterina Iosifovna*, PhD, professor, head of the rheumatology department at SCCH, RAMS.**

Address: 2/1, Lomonosovskii ave., Moscow, 119991, tel.: +7 (499) 134-02-97

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The article describes a case with a severe course of oligoarticular juvenile idiopathic arthritis with the development of contracture and destructive articular alterations. The successful use of methotrexate (15mg/m^2 of body surface per week, subcutaneously) in a child with early arthritis (disease duration – less than 2 years) is described: 6 months after the therapy had started, acute inflammatory articular alterations, arthralgiae, morning stiffness terminated; in 12 months the range of motions in the affected joints recovered completely. The inactive disease phase and remission were registered in 6 and 12 months, accordingly. The remission has continued for 12 months.

Keywords: *children, juvenile idiopathic arthritis, methotrexate, subcutaneous introduction.*

Juvenile idiopathic arthritis (JIA) is one of the most frequent incapacitating rheumatic diseases in children. Its main clinical manifestation is arthritis. Pathological articular alterations are characterized by pain, swelling and deformities [1].

The most frequently affected joints in children are large and medium joints, knee, ankle, wrist, elbow, hip joints in particular, rarer – small carpal and foot joints. Proliferative-exudative articular alterations quickly lead to the development of lasting deformities and contractures, amiotrophy and hypotrophy [2]. As a rule, JIA takes a progressive course, leads to early incapacitation and reduction in the patients' life quality. Moreover, many authors report that JIA shortens the patients' life span by 10 years at the average, although it may be comparable with population mean values in case of a prolonged controlled treatment [3].

Early diagnostics and timely start of adequate immunosuppressive therapy – before the destructive alterations in joints – may change the prognosis, result in a less severe incapacitation degree and bring children back to full life.

It should be noticed that immunosuppressive therapy is the basis of pathogenetic approach to treating JIA [4-8].

Methotrexate is one of the best immunosuppressive drugs.

Methotrexate has been recommended as a first-line drug to use for articular JIA variants; the efficiency of all the new drugs is not to be less than this immunosuppressor's efficiency [5, 9, 10].

We give a case report of a girl with an onset of oligoarticular juvenile idiopathic arthritis at an early age to demonstrate high efficiency of methotrexate for parenteral administration.

Patient K., 5 years of age, has been observed at the rheumatology department of the Scientific Center of Children's Health for 1.5 years. She is the first-pregnancy child (term spontaneous delivery). Birth weight – 3,100g, birth length – 52 cm. The child has been artificially fed since birth. Early physical and psychomotor development was age-appropriate. Preventive vaccination was conducted at maternity hospital; the mother rejected from further vaccination. Earlier diseases: rare acute respiratory infections. Hereditary history on rheumatic diseases is not compromised.

The girl contracted the disease at the age of 4 years when she experienced post-traumatic swelling, pain, motion restriction in the left knee joint and limping. The patient was domiciliary observed by a surgeon on the grounds of arthritis; non-steroid antiinflammatory drug (diclofenac sodium) was prescribed. No positive dynamics was achieved; arthralgiae, knee joint swelling and gait disorder remained. No pathologic alterations were found by clinical blood analysis.

2 months after the disease's onset the girl was consulted by a local rheumatologist; juvenile idiopathic arthritis was diagnosed. The mother rejected from the recommended methotrexate treatment.

9 months after the onset the patient received intraarticular puncture with the administration of betamethasone given the parents' flat refusal of immunosuppressive drugs; physiotherapy was prescribed. In the setting of treatment the effect was momentary, in 2 weeks the child's condition aggravated considerably: she experienced intense pain in the left knee joint, morning stiffness of up to 2.5 hours; flexion contracture developed in the joint.

The child had not received antirheumatic drugs within the following 6 months; the treatment was conducted using only homeopathic drugs.

No positive dynamics of the child's condition was achieved, arthralgiae, swelling, left knee joint's flexion contracture and gait disorder remained. Articular syndrome was progressing; firstly the left hip joint and then the left ankle joint had been involved in the inflammatory process.

Given the articular syndrome's progression and pronounced incapacitation at the age of 5 years, the child was referred to the RAMS SCCH rheumatologic department for examination and treatment 1 year and 4 months after the disease's onset.

The child's condition at admittance was considered moderate. The condition's severity was caused by the girl's pronounced incapacitation. The examination revealed flexion contracture, pain

and motion restriction in the left knee joint, extremity stretching by 2cm; exudative-proliferative alterations in the left ankle joint, pain and movement and rotation restriction in both hip joints. Duration of morning stiffness was 2.5-3 hours (pic. 1-3). No specific laboratory parameters' alterations were found at examination. Moderate hypochromic anemia and insignificant increase in the level of serum immunoglobulin G (tb.). Radiography revealed cystic osteoporosis of articular surfaces, constriction of joint spaces and irregularity of articular surfaces with erosions.

The girl was examined by an ophthalmologist, who ruled out uveitis.

According to the anamnesis and examination, the child's diagnosis "Oligoarticular juvenile idiopathic arthritis" was confirmed; it is characterized by an affection of not more than 4 joints, often normal laboratory parameters and development of destructive articular alterations after 1 year of the disease in case the process recurs intermittently and no adequate antirheumatic therapy is provided.

Thus, the department admitted a 5-year-old girl with JIA of 1 year 4 months and pronounced incapacitation, who had not received immunosuppressive drugs before.

It should be noted that immunosuppressive therapy takes a leading role in treating JIA. Not only disease prognosis, but also patients' lives depend on the choice of drugs, prescription periods, intensity of side effects and ability to delay the progression of anatomic destruction [2].

At present, the "gold standard" of treating JIA is methotrexate – an antimetabolite drug structurally close to folic (pteroylglutamic) acid; unlike the latter, methotrexate has carboxyl amino group in the 4^{th} pteridine molecule's position and methyl group addition to the 10^{th} 4-aminobenzoic acid's position [2].

Used in low and moderate doses (rheumatologic practice), methotrexate has mainly antiinflammatory effect due to excessive accumulation of adenosine – purine nucleoside capable of considerable antiinflammatory action due to the interaction with specific adenosine receptors A2 on the surface of activated neutrophils [11]. Several pharmacological effects of methotrexate may be linked with the influence on the synthesis of polyamines necessary for the proliferation of cells and protein synthesis and take part in cell-mediated immune reactions [2, 12].

Shift from Th_1 to Th_2 immune response is observed in case of therapy using low methotrexate doses; this explains the drug's antiinflammatory and immunomodulatory effects, which are in turn followed by the reduction in synthesis of proinflammatory cytokines and the increase in synthesis of antiinflammatory cytokines (IL4, IL10) [2].

Another point of application of methotrexate's effects is inhibition of production of proteolytic enzymes (collagenase and stromelysin), which play an important role in the destruction of joints in case of atrophic arthritis in adults and JIA. The recently obtained data show that *in vitro* methotrexate stimulates differentiation of monocytes and expression of Fas-antigen; this is

associated with the increased release of antiinflammatory cytokines (soluble antagonist IL1 and pTNF-75p) and, accordingly, with the inhibition of IL1b and TNF α synthesis activity. In general, these data allow suggesting that one of the possible mechanisms of methotrexate's antiinflammatory action is associated with the suppression of recruitment of immature and inflammatory monocytes from marrow to inflammation zone and reduction in the life span of these cells in the inflamed tissues [2, 12].

High spread of JIA allowed conducting numerous scientific studies worldwide, which made up a strong case-based proof of methotrexate's efficiency [13-19]. Clinical studies of methotrexate's efficiency at JIA indicated that the drug's effect appeared only after several weeks of intake and good tolerance of patients who had earlier responded only to the glucocorticoid therapy [14, 15]. Randomized comparative studies showed that methotrexate's dose of 10-15 mg/m^2 is more effective than placebo and other basic antiinflammatory drugs [16-19].

One of the largest recent studies dedicated to the efficiency and safety of methotrexate was a retrospective analysis of the German register's data in 2005-2009 [15]. Therapy efficiency was being evaluated in 411 children who had been treated with regular methotrexate's doses for at least 6 months. The drug's administration form remained the same. Improvement 30/50/70 according to the pediatric criteria of the American College of Rheumatology (ACR) after 6 months of treatment was registered in 72, 66 and 51% of patients, accordingly. Oligoarticular JIA was diagnosed in 136 patients involved in the study. Improvement 30/50/70 after 6 months of therapy was registered in 84, 82 and 62% of patients, accordingly.

Wide range of methotrexate's doses, effective for children, depends on many factors, especially on the fast clearance of this drug, especially in small children [20].

The multicenter randomized study of efficacy and safety of methotrexate therapy using moderate (15-20 mg/m^2 per week, not more than 20 mg/week) and high (30 mg/m^2 per week, not more than 40 mg/week) doses in patients with polyarticular articular syndrome in the setting of JIA was the largest in the last 10 years [21]. The study results showed that 15-20 mg/m^2 of body surface per week intramuscularly or subcutaneously is the optimal dose in treating children with JIA; methotrexate therapy effect can only be measured after 9-12 months of treatment. According to the authors, methotrexate therapy efficacy is the same in moderate and high doses and a simple increase of the dose by more than 20 mg/m^2 per week does not improve therapy efficacy.

It may be assumed that simple escalation of the dose higher than the certain threshold does not result in a better effect; probably, change of the administration mode may be a factor of overcoming refractoriness.

Czech scientists studying methotrexate's bioavailability proved that there is a significant difference between oral intake and subcutaneous administration in children; appreciable difference

in the drug's absorption between its tableted and parenteral administration starts manifesting itself with the dose of more than 10 mg/m^2 [22], which is why parenteral (subcutaneous, intramuscular) administration is more effective.

Comparative studies of methotrexate's efficacy depending on the mode of administration are of high interest.

Efficacy appraisal of methotrexate's subcutaneous administration in children with insufficient response to peroral intake was conducted in Canada. The study involved 61 children with JIA (43 girls, 18 boys; 8 had systemic arthritis, 25 – polyarthritis, 14 – oligoarthritis, 5 – enthesitis-associated arthritis, 9 – undifferentiated arthritis). Subcutaneous administration of methotrexate was prescribed to 31 children due to no effect of peroral intake (in 13), insufficient efficacy (in 7) and development of nausea (in 18 patients) [23]. Improvement was registered in 77% of children after 3 months of treatment; methotrexate's hepatotoxicity was lower in the group of children with parenteral (subcutaneous) administration, than in children with peroral intake.

Long-term use of methotrexate in rheumatologic practice allowed studying well the range of its side effects [24, 25]. It has been established that the ratio "efficacy/toxicity" in methotrexate is considerably higher than in other basic antirheumatic drugs.

Thus, methotrexate has been recognized as the first-line drug for treating JIA; multiple studies showed that the use of methotrexate in the dose of 15 mg/m^2 of body surface per week allows reducing the rheumatoid process's inflammatory activity significantly. In order to achieve the maximal effect it is reasonable to apply subcutaneous or intramuscular mode of administration.

Analysis of the girl's case history, namely early arthritis, patient's age, oligoarticular variant of disease, and world experience of methotrexate's use given differences in absorption between its tableted and parenteral forms substantiated methotrexate's subcutaneous prescription in the dose of 15 mg/m^2 of body surface per week (Metoject, MEDAC, Germany, subcutaneous administration of 15 mg/week at 15 mg/m^2 of body surface per week).

Efficacy of the conducted therapy was appraised by the ACR improvement criteria for pediatric patients (-pedi). These criteria involve the following parameters: patient's general well-being assessment by parents, disease activity assessment by a doctor using visual analog scale (VAS), functional ability (CHAQ – Childhood Health Assessment Questionnaire), number of joints with active arthritis, number of malfunctioning joints (motion restriction) and erythrocyte sedimentation rate (ESR). The disease was deemed non-active in case of normal ESR and serum C-reactive protein concentration rates, no active synovitis, uveitis and no disease activity according to the doctor's general assessment (using VAS) [26]. Remission was registered in case the disease had been non-active in the setting of the conducted therapy for 6 subsequent months.

After 3 months of methotrexate's therapy, duration and intensity of morning stiffness, exudative alterations in the left knee and ankle joints and flexion contracture intensity reduced and arthralgiae terminated in the girl (see tb.). 30% improvement was registered according to the ACR-pedi criteria. After 6 months of treatment, acute inflammatory articular alterations terminated and the volume of motions in the knee and hip joints increased considerably. 90% improvement was registered according to the ACR-pedi criteria, non-active disease stage. After 12 months of treatment the volume of motions in all the affected joints recovered completely, no joints with active inflammation signs were found; disease remission was registered (pic. 4-6). According to radiography, the unevenness of articular surfaces and number of erosions of the left shinbone reduced.

Within the subsequent 6 months the child was regularly receiving methotrexate with dose syringes for subcutaneous administration in the dose of 15 mg/m^2 per week. The girl is in the state of clinical laboratory remission. No side effects of the therapy have been noted.

Conclusion

The given clinical case demonstrates aggressive course of oligoarticular JIA in a child who had not received immunosuppressive therapy. Mother's rejection from the prescription of methotrexate led to the pathological process's spread to other joints, continuously recurring disease course, development of destructive alterations in the knee joint and child's incapacitation.

Despite the relatively late prescription of methotrexate to the patient with intense functional insufficiency and the 2nd anatomic stage (constriction of joint space and erosions of articular surface (according to the X-ray imaging)), in 3 months the articular syndrome's activity reduced considerably; in 6 months acute inflammatory articular alterations terminated completely, incapacitation reduced and the child's quality of life improved.

Disease remission was registered after 1 year of therapy, the function recovered in 3 out of the 4 affected joints. It should be noted that methotrexate's prescription allowed avoiding peroral prescription of glucocorticoids and intraarticular administration of betamethasone and, thus, avoiding such severe consequences as hormone dependence, osteoporosis, delay of sexual and physical development. The results of treating patient K. correlate with literary data confirming the drug's high efficacy and safety.

In patients with oligoarticular JIA, methotrexate must be prescribed not later than 6 months after the disease's onset in case non-steroid antiinflammatory drugs and intraarticular injections of glucocorticoids are ineffective; otherwise the process will progress and incapacitation will increase, as we have observed in the given clinical case.

Prescription of methotrexate on the early disease stages, correct choice of dose and mode of administration provide for the disease remission and avert incapacitation in more than 50% of children with oligoarticular JIA.

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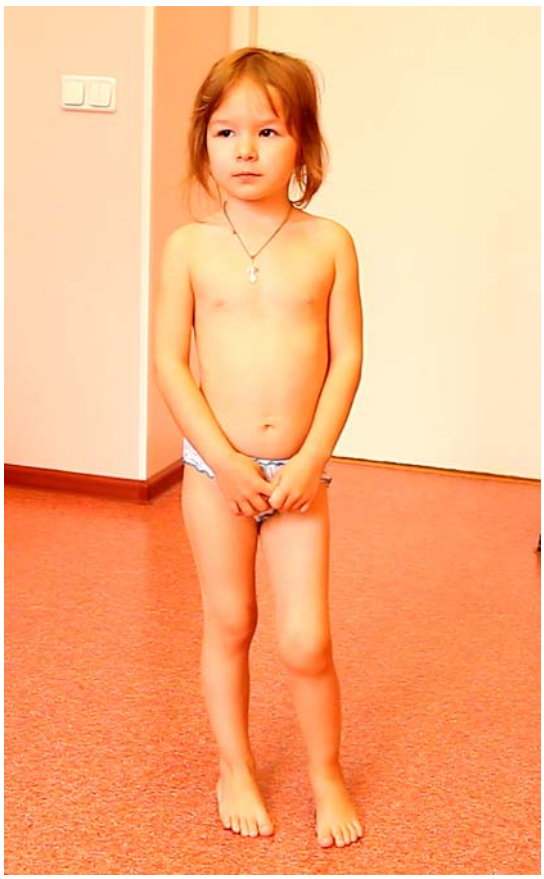
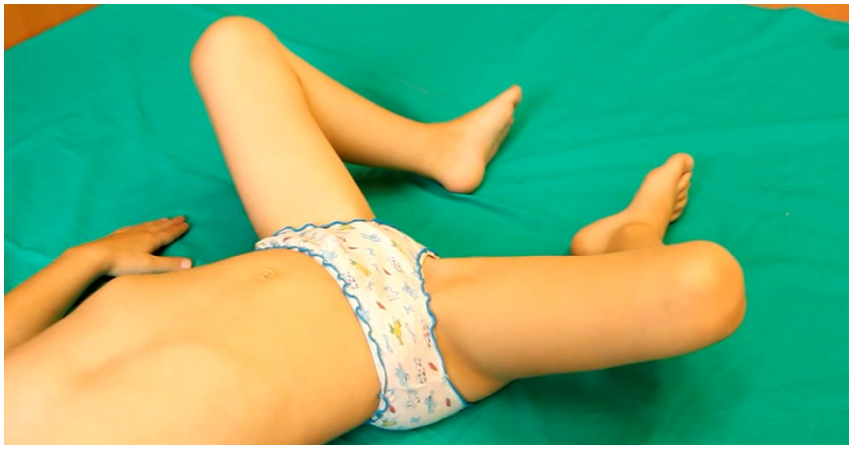
Pic. 1. General appearance of the patient before methotrexate therapy. Exudative-proliferative alterations in the left knee joint before methotrexate therapy

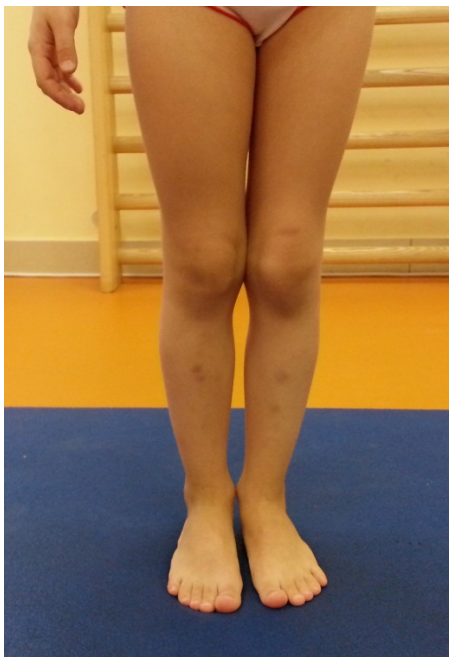


Pic. 2. Functional capability of the left knee joint before methotrexate therapy

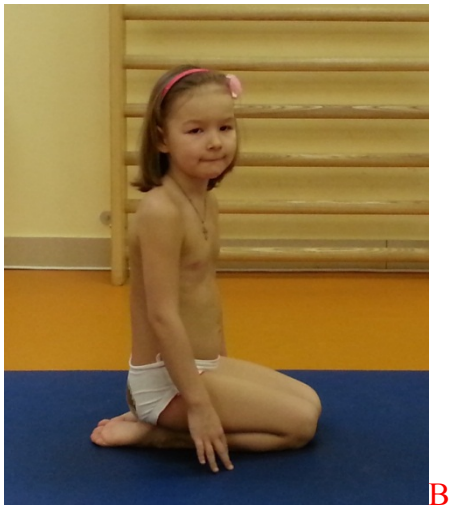
Pic. 3. Functional capability of hip joints before methotrexate therapy



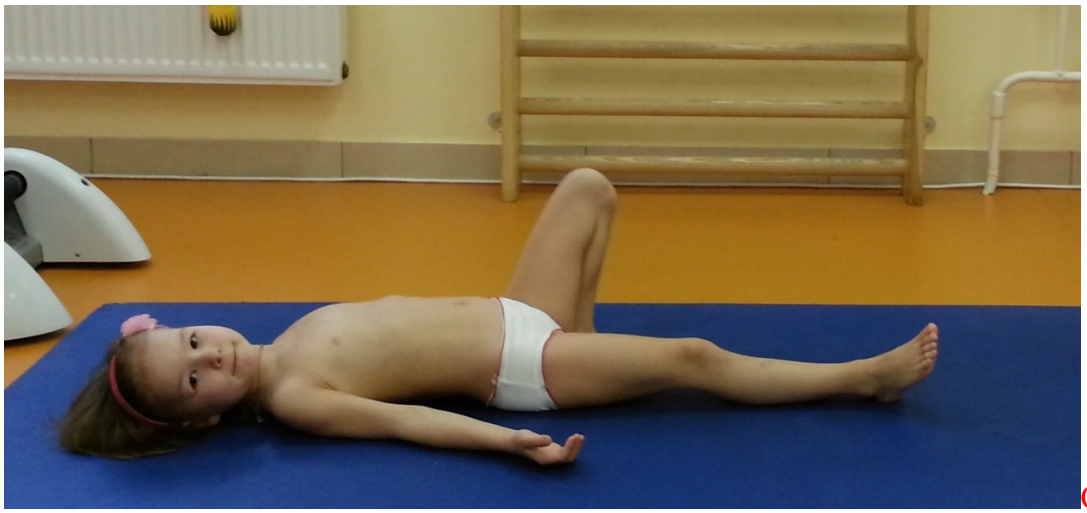
Pic. 4. No swelling and contracture in the left knee joint in the setting of subcutaneous administration of methotrexate in the dose of 15 mg/m^2 of body surface per week



Pic. 5. A, B, C. Functional capability of knee joints in the setting of subcutaneous administration of methotrexate in the dose of 15 mg/m^2 of body surface per week



B

 C

Pic. 6. Functional capability of hip joints in the setting of subcutaneous administration of methotrexate in the dose of 15 mg/m^2 of body surface per week

Table. Dynamics of clinical and laboratory parameters of JIA activity in the setting of methotrexate therapy in patient K., 5 years of age

Parameters	Before methotrexate therapy of 15 mg/m^2 per week subcutaneously	After 3 months of methotrexate therapy of 15 mg/m^2 per week subcutaneously	After 6 months of methotrexate therapy of 15 mg/m^2 per week subcutaneously	After 12 months of methotrexate therapy of 15 mg/m^2 per week subcutaneously
Duration of morning stiffness (minutes)	180	20	no	no
Number of joints with active arthritis	4	3	0	0
Number of joints with restricted function	3	3	1	1
Subjective assessment of disease activity by a doctor using VAS (points)	60	35	0	0
Subjective assessment	75	45	5	0

of well-being by the patients using VAS (points)				
CHAQ, points	0.5	0.3	0.3	0
ESR (mm/h)	11	10	10	6
Hb (g/l)	115	117	126	130
Erythrocytes ($x10^{12}$/l)	4	4.2	4.4	4.43
Leukocytes ($x10^{9}$/l)	7.7	8.1	7.9	7
CRP (mg/l; N up to 5)	3	0.8	0.1	0.1
IgG (g/l; N up to 14.6)	15.3	14.2	13.4	12.6
Non-active disease stage	-	-	+	
Disease remission	-	-	-	+
Improvement % according to the ACR-pedi criteria		30	90	100

Note. VAS – visual analog scale (min – 0, max – 100)