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Experience of intramuscular methotrexate use in a patient with early polyarticular juvenile idiopathic arthritis

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This article presents a case of severe course of polyarticular juvenile idiopathic arthritis. Active articular syndrome, high laboratory parameters of disease activity, severe incompetence were observed in a child by the therapy initiation. Successful use of intramuscular methotrexate in the dose of 15 mg/m^2 of body surface per week is described. Exudative articular alterations, arthralgiae, morning stiffness duration reduced as early as one month after the therapy initiation in a child. Acute inflammatory articular alterations cut off, range of motions recovered completely in 4 out of the 6 affected joints, laboratory parameters of disease activity reduced and normalized (ESR and CRP), inactive disease stage was registered after 6 months of treatment. We did not observe any undesirable phenomena in the setting of methotrexate therapy.
Keywords: *children, polyarticular juvenile idiopathic arthritis, methotrexate, intramuscular administration.*

Juvenile idiopathic arthritis (JIA) is one of the most frequent incapacitating rheumatic diseases in children. Its primary clinical manifestation is arthritis. Pathological articular alterations are characterized by pain, swelling and deformations. Large and medium joints, particularly, knee, ankle, wrist, elbow and hip joints (less often – small joints of hands and feet), are the most JIA-susceptible in children. Proliferative-exudative articular alterations quickly lead to the development of fixed deformities and contractures, amyotrophy and hypotrophy. Juvenile arthritis is usually progressive and results in early incapacitation and reduction in the quality of life of the patients [1, 2].

Methotrexate (MT) is a major drug for juvenile idiopathic arthritis (JIA); according to the present protocols, it has been recognized as the "gold standard" of articular JIA therapy [1-5]. Timely methotrexate prescription – before occurrence of destructive articular alterations and the patient's incapacitation – helps to change prognosis of the disease, prevent progression of incapacitation and bring the child back to the fully adequate life [6-8].

At the same time, deviation from treatment protocols, late diagnosis and inadequate therapy quickly lead to the development of fixed articular deformities and contractures, amyotrophy, hypotrophy, osteocartilaginous destruction progression, severe incapacitation, as well as social, psychological and professional deadaptation of children [2, 9-11]. Arthritis is a burden not only for the patients, but also for their families and the society [12]. Moreover, it has been reported that JIA reduces life expectancy of the JIA patients by 10 years on the average, although it may be comparable with the average population life expectancy in the event of the long-term controlled treatment [13].

We present a case study of a girl with polyarticular JIA demonstrating high efficacy of early prescription of methotrexate for parenteral administration.

Patient P., 15 years of age, had been observed at the rheumatology department of the Scientific Center of Children's Health for 6 months. Born of the first pregnancy (normal pregnancy, term birth). The girl's birth weight was 2,950 g, body length – 49 cm. Physical and psychomotor development was age-adequate in the early period. Preventive vaccination was conducted in accordance with the National vaccination calendar. Hereditary rheumatic history was non-compromised.

The girl developed the disease at the age of 15 years, when swelling if the right wrist joint occurred for no apparent cause. The girl was prescribed a nonsteroidal anti-inflammatory drug (sodium diclofenac) for arthritis. No positive dynamics in the child's condition was achieved; articular swelling persisted. The girl was admitted to the local hospital with diagnosis "Osteomyelitis"; the child underwent osteoperforation of the right radial bone and wrist joint puncture. The treatment yielded only a short-term effect; the child's condition considerably aggravated in 2 weeks: the girl suffered from swelling of knee, ankle and both wrist joints, marked articular pains and could barely stand up.

Due to the insufficient effect of the treatment, the child was forwarded to the inpatient rheumatology department of the Scientific Center of Children's Health.

The patient was admitted to the SCCH rheumatology department for the first time 6 weeks after the disease onset for examination and therapy correction.

The child's condition was considered severe due to pain and restriction of motion in both knee, ankle and wrist joints and morning stiffness of up to 3 hours. Examination revealed exudative-proliferative alterations in both wrist, knee and ankle joints, painful flexion contractures in both knee joints, pain and exudative alterations in tarsal joints on both sides and restriction of motion in all the affected joints (pics. 1-4). Clinical blood analysis detected hypochromic anemia: hemoglobin – 86 g/l, leukocytosis – 12.5 x 10^9/l, thrombocytosis – 631 x 10^9/l, erythrocyte sedimentation rate (ESR) increase up to 89 mm/h; immunoassay: serum C-reactive protein (CRP) level increase up to 74 mg/l (normal range – up to 5 mg/l; tb.).

The child underwent computed tomography of intrathoracic organs and the affected joints and identification of blood serum antibodies to arthritogenic infections. No data regarding oncohematological and infectious processes, including the specific process, were obtained; no destructive bone alterations were revealed. Computed tomography detected synovitis of knee and wrist joints, cystic osteoporosis of joint surfaces and joint space narrowing. Ultrasound examination of knee joints visualized free fluid in the superior recesses of both knee joints, irregularity of the cortical layer of the joint bones; and hyperechoic formations in the structure of cartilaginous tissue.

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

Diagnosis "Early (6-week-long) seronegative polyarticular juvenile idiopathic arthritis with high degree of activity and marked functional incompetence" was confirmed on the basis of the anamnesis, clinical pattern and results of the laboratory and instrumental tests.

Given the definite diagnosis of polyarticular JIA, it was determined that the child ought to be prescribed immunosuppressive therapy. The drug of our choice was methotrexate, which was prescribed for subcutaneous administration with a syringe in the dose of 15 mg/m^2 per week.

Length and intensity of morning stiffness and exudative alterations in knee joints reduced after 1 month of methotrexate therapy. Exudative alterations in ankle and wrist joints and laboratory parameters (ESR, serum CRP level; see tb.) of disease activity reduced and arthralgiae terminated after 3 months of methotrexate therapy. 50% improvement was registered (according to the pediatric criteria of the American College of Rheumatology [ACR_{pedi}]). According to the ACR_{pedi}, 30, 50 and 70% response in comparison with the initial values of at least 3 out of parameters is observed in the event of 30, 50 and 70% improvement, respectively; aggravation may not exceed 30% or be present in more than 1 parameter.

The ACR_{pedi} criteria include the following parameters:

- patient's (parents') evaluation of the general state of health;
- doctor's evaluation of the disease activity using a visual analog scale (VAS);

- functional capacity assessment using questionnaire CHAQ (Childhood Health Assessment Questionnaire; CHAQ index > 1.5 at marked functional disorders and < 1.5 at minimal and moderate functional disorders);
- number of joints with active arthritis;
- number of joints with functional disorders (restriction of motion);
- ESR.

The child had continuously been receiving methotrexate for subcutaneous administration with a syringe in the dose of 15 mg/m^2 per week for 6 months. No side effects were observed. Acute inflammatory articular alterations terminated after 6 months of treatment, the range of motion recovered in knee joints and considerably improved in wrist joints. 90% improvement (according to the ACR_{pedi} criteria) and inactive disease phase (according to C. Wallace) were registered (pic. 5-8). Instrumental examination data revealed positive dynamics. Ultrasound examination of knee joints did not reveal free fluid in the superior recess; irregularity of the cortical layer of the joint bones and hyperechoic formations in the structure of cartilaginous tissue were less pronounced.

Analysis of this case demonstrates successful use of methotrexate for parenteral administration in the dose of 15 mg/m^2 of body surface per week for treating polyarticular JIA and high safety of the drug. The therapy involving methotrexate for parenteral administration in the dose of 15 mg/m2 per week allowed not only terminating inflammatory articular alterations an recovering the patient's functional capacity, but also preventing osteocartilaginous destruction progression and development of severe incapacitation.

Methotrexate is an antimetabolite. It is structurally similar to folic (pteroylglutamic) acid; the differences consist in the replacement of an amino group by a carboxyl group in the 4th position of the pteridine molecule and addition of a methyl group to the 10th position of the 4-aminobenzoic acid [14].

In low and medium doses (as are used in rheumatologic practice), MT produces a primarily anti-inflammatory effect based on the excessive accumulation of adenosine – a purine nucleoside, which is capable of producing considerable anti-inflammatory effect due to interaction with specific adenosine receptors A2 on the surface of activated neutrophils [15]. Some pharmacological effects of methotrexate may be associated with its influence on the synthesis of polyamines, which are required for cell proliferation and protein synthesis and take part in cell-mediated immune reactions [9, 16].

Data on the drug's influence on cytokine synthesis allow assuming that the therapy involving low MT doses results in cytokine synthesis switch from type Th1 (IL2, γ-interferon) to Th2 (IL10); this explains anti-inflammatory and immunomodulating effects of the drug [9].

This assumption helps to explain the marked anti-inflammatory and immunomodulating effects of low doses of the drug, which are especially evident in the event of the so called Th1-dependent diseases (such as rheumatoid arthritis). The other methotrexate effect consists in inhibiting production of proteolytic enzymes (collagenase and stromelysin), which play an important role in articular destruction at rheumatoid arthritis. It has also been recently determined that *in vitro* methotrexate stimulates monocyte differentiation and Fas-antigen expression associated with enhanced release of anti-inflammatory cytokines (soluble IL 1 antagonist and tumor necrosis factor receptor TNF-75p) and IL1b synthesis inhibition. Enhanced monocyte differentiation is associated with increase in monocyte sensitivity to the TNF-induced apoptosis. In whole, on the basis of these data we may assume that one of the probable mechanisms of methotrexate's anti-inflammatory effect is associated with suppressed recruitment of immature and "inflammatory" monocytes from bone marrow to the inflammation zone and reduced lifespan of these cells in inflamed tissues [7-9, 16-18].

Clinical studies of MT use in children with JIA have been being conducted since 1980s, primarily in the western countries [7, 8, 17-22]. Clinical studies of methotrexate efficacy for juvenile arthritis indicated occurrence of the drug's effect after several weeks of intake and good tolerability in the patients, who have previously responded only to glucocorticoid therapy [6-8,

15, 18-20]. Randomized comparative studies demonstrated that methotrexate in the dose of 10-15 mg/m^2 is more efficient than placebo and other basic anti-inflammatory drugs [20-22]. The range of efficient doses of this drug for children is wide due to fast MT clearance observed in children, especially in small children [23].

The multicenter randomized study of efficacy and safety of the therapy involving medium (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) MT doses in the patients with polyarticular juvenile idiopathic arthritis completed in 2004 was the largest in the last 10 years [24]. Not even a 30% improvement (according to the ACR_{pedi} pediatric criteria) was registered in 80 out of the 595 patients treated with methotrexate in the dose of 8-12.5 mg/m^2 of body surface per week. That group was divided into two subgroups: the methotrexate dose was increased up to 15 mg/m^2 of body surface per week for the first subgroup patients (n = 40) and to 30 mg/m^2 for the second subgroup patients (n=40). The drug was administered subcutaneously or intramuscularly. 30% improvement (according to the ACR_{pedi} criteria) was registered in 55-62% of the patients after 6 months of treatment; however, no statistically significant differences between subgroups regarding methotrexate efficacy and safety were revealed. Thus, the study demonstrated that the optimal methotrexate dose for children with juvenile arthritis is 15 mg/m^2 of body surface per week administered intramuscularly or subcutaneously. According to the authors, efficacy of the therapy involving medium and high MT doses is the same, so the dose increase by 20 mg/m^2 per week does not make any difference.

We may assume that simple dose increase does not yield the desired effect after a certain threshold, whereas the change of the mode of administration may probably serve as a factor of overcoming refractoriness. The study of methotrexate bioavailability conducted by Czech scientists proved the significant difference in MT bioavailability between oral and subcutaneous administration; the difference in MT absorption between pelleted and parenteral MT administration becomes tangible at the dose as low as 10 mg/m^2 [23]. That is why parenteral (subcutaneous, intramuscular) administration is more efficient.

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

Analysis of subcutaneous methotrexate administration to children with insufficient response to oral intake was conducted in Canada. The study involved 61 children with juvenile arthritis. Methotrexate for subcutaneous administration was prescribed to 31 children due to inefficiency of oral intake, insufficient efficacy and nausea development in 13, 7 and 11 patients, respectively [25]. Improvement was registered in 77% children after 3 months of treatment; it ought to be noted that methotrexate hepatotoxicity was lower in the group of children receiving the drug parenterally (subcutaneously) than in the group of children receiving the drug orally.

Long-term use of methotrexate in rheumatologic practice helped to study its side effects well [26-29].

It has been established that the efficacy/safety ratio of methotrexate is significantly higher, than of any other basic anti-rheumatic drugs.

Thus, methotrexate is the recognized “gold standard” for juvenile arthritis; numerous studies demonstrated have demonstrated that use of methotrexate in the dose of 15 mg/m^2 of body surface per week helps to significantly attenuate inflammatory activity of the rheumatoid process. It is reasonable to use subcutaneous or intramuscular administration of the drug in order to achieve the best result.

Genetically engineered biopharmaceuticals are successfully used for treating articular JIA: TNF α inhibitors, IL6 antibodies, T lymphocyte costimulation antagonists etc. [30-33]. The newly obtained data demonstrate that combination thereof with methotrexate improves efficacy of the genetically engineered biopharmaceuticals, particularly, the influence thereof on articular destruction [34, 35].

However, the primary impedance to prescription of these drugs is high cost thereof. This problem is true for the western countries as well, where the use of biopharmaceuticals is

restricted to the cases of unlikely remission in the event of methotrexate use. At the same time, excessive prescription of genetically engineered biological agents as the first choice drugs for articular JIA may result in the increase in total healthcare expenses.
Analysis of the child's anamnesis morbi (the patient's age, severe and aggressive course of arthritis, rapid development of incapacitation) and the international experience of methotrexate use given the difference in absorption between pelleted and parenteral MT forms and the dose response afforded ground for prescribing the drug in the dose of 15 mg/m^2 of body surface per week for parenteral administration (Metoject, MEDAC, Germany; for subcutaneous administration in the dose of 20 mg/week) to the child. The girl had no allergic reaction to methotrexate administration and tolerated the drug well.

CONCLUSION

The described clinical case of severe juvenile idiopathic arthritis demonstrates high efficacy of the therapy involving methotrexate in the dose of 15 mg/m^2 of body surface per week for terminating acute inflammatory articular alterations in the patient with polyarticular JIA.
The selected treatment tactics was justified. Therapeutic efficacy analysis demonstrated that methotrexate prescription to a girl with a 6-week-long disease helped to considerably reduce activity of the articular syndrome after 1 month of therapy; and terminate acute inflammatory articular alterations, reduce incapacitation and improve the quality of life – after 6 months. Use of methotrexate secured functional recovery of most affected joints, normalization of laboratory parameters of activity and the child's return to the fully adequate life. Results of the treatment of patient P. suggest the conclusion that prescription of methotrexate in an adequate dose and correct selection of the mode of administration help to achieve remission and prevent incapacitation in the patients with severe polyarticular JIA.

Pic. 1. General appearance of the patient before methotrexate therapy
A|B

Pic. 2. A-B: exudative-proliferative alterations observed in knee and ankle joints before methotrexate therapy
A|B
C

Pic. 3. A-B: functional capacity of knee joints before methotrexate therapy
A|B

Pic. 4. A-B: functional capacity of wrist joints before methotrexate therapy

Pic. 5. General appearance of the patient in the setting of parenteral intake of methotrexate in the dose of 15 mg/m^2 of body surface per week
B

Pic. 6. Absence of swelling of knee joints in the setting of parenteral intake of methotrexate in the dose of 15 mg/m^2 of body surface per week
A|B
C
D

Pic. 7. A-D: functional capacity of knee joints in the setting of parenteral intake of methotrexate in the dose of 15 mg/m^2 of body surface per week
A|B

Pic. 8. A-B: functional capacity of wrist joints in the setting of parenteral intake of methotrexate in the dose of 15 mg/m^2 of body surface per week

Table. Dynamics of clinical and laboratory parameters of the disease activity in the setting of methotrexate therapy in patient P.

Parameters	**Before methotrexate therapy**	**After 1 month of the therapy involving methotrexate in the dose of 15 mg/m^2 per week intramuscularly**	**After 3 months of the therapy involving methotrexate in the dose of 15 mg/m^2 per week intramuscularly**	**After 6 months of the therapy involving methotrexate in the dose of 15 mg/m^2 per week intramuscularly**
Length of morning stiffness (minutes)	180	30	none	none
Number of joints with active arthritis	10	6	4	0
Number of joints with restricted function	10	6	4	2
Subjective doctor's evaluation of the disease activity using VAS (score)	75	40	22	0
Subjective patient's pain evaluation using VAS (score)	90	45	25	0
ESR (mm/h)	89	32	14	8
Hb (g/l)	86	102	110	118
Erythrocytes (x 10^{12}/l)	2.9	3.2	3.5	3.7
Platelets (x 10^9/l)	631	575	557	442
Leukocytes (x 10^9/l)	12.5	10.2	8.7	7.8
CRP (mg/l) (N – up to 5)	74	24	5	3
Inactive disease phase	-	-	-	+
Improvement % (according to the ACR_{pedi} criteria)	-	-	50%	90%

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

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