Mod Rheumatol (2009) 19:1–11
DOI 10.1007/s10165-008-0123-3

REVIEW ARTICLE

Methotrexate for the treatment of juvenile idiopathic arthritis: process to approval for JIA indication in Japan

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Received: 22 May 2008 / Accepted: 19 August 2008 / Published online: 25 September 2008

Abstract Methotrexate (MTX), the primary treatment for the articular-type juvenile idiopathic arthritis (JIA), is effective and brings about radiological improvement. Patient compliance is good, and it is recognized that its known side effects, namely, disruption of liver function and induction of pulmonary lesions, are unlikely to be severe at the low MTX doses that are administered. In Japan, MTX was granted approval in 1999 by the then Ministry of Health and Welfare specifically for treating rheumatoid arthritis in adult patients, allowing it be generally used in medical institutions for patients having National Health Insurance. However, in the pediatric field, its use outside the indications has so far been unavoidable, and has been left to the discretion of the physician. Finally, at the present conference, expansion of the indications of MTX for JIA was approved in Japan. It is noteworthy that this expansion of indications was achieved without requiring clinical trials on children sponsored by the pharmaceutical company: it was achieved rather by collecting necessary information through ongoing efforts (including collection and analysis of information about approval status in foreign countries, adequate evidence from the literature, implementation of a clinical use survey in Japan, etc.). It also merits attention that the maximum dose (10 mg/m^2) was set on the basis of pharmacokinetic data from children, rather than relying on the dosing method and dose for adults.

Keywords Juvenile idiopathic arthritis · Childhood · Methotrexate · Expansion of indication

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Introduction

It has already been demonstrated in randomized, controlled trials that methotrexate (MTX), the treatment of choice for articular-type juvenile idiopathic arthritis (JIA), which is also called "juvenile rheumatoid arthritis (JRA)", is more effective than a placebo and brings about radiological improvement. Patient compliance is good. Furthermore, side effects, namely, disruption of liver function and induction of pulmonary lesions, are unlikely to be severe at the low MTX doses that are administered.

Outside Japan—for instance, in the United States and in the European Union—it has already been approved for the treatment of chronic arthritis. In Japan also, it was granted approval in 1999 by the then Ministry of Health and Welfare specifically for treating rheumatoid arthritis (RA) in adult patients, and could then generally be used in medical institutions for patients having National Health

Insurance. As a result, it has proved useful for reducing symptoms in many patients with swollen and painful joints and for inhibiting the progression of arthritis. However, in the pediatric field, its use outside the indications has so far been unavoidable, and has been left to the discretion of the physician.

In the present study, in addition to fulfilling the conditions for obtaining approval overseas, we expanded the range of indications by collecting large amounts of evidence from the literature and by surveying the conditions of use in Japan without conducting pediatric clinical trials; moreover, we were able to set the maximum child dose on the basis of the pharmacokinetics in children without being restricted to the method and dosage of administration in adult RA. As for this report, the contents were examined closely in the working group of MTX for JIA, and discussion was accomplished in the study group on pediatric drug therapy in Ministry of Health, Labour and Welfare. Finally, this expansion of the indications was approved after prior evaluation by Pharmaceutical Affair / the first Food Sanitation Investigation Council Medical Supplies Sectional Meeting, and the application was completed by a notice of examination management chief in the Medicine Food Station on 30 March 2008.

Present status of MTX therapy for JIA in Japan

Juvenile idiopathic arthritis is a chronic systemic inflammatory disease developing during childhood [1, 2]. According to a nationwide survey in Japan, this disease develops in about one out of 100,000 children per year, with a prevalence of 9.74 of 100,000 children less than 16 years of age [3, 4]. Major symptoms include articular swelling and pain associated with persistent inflammation. Tissue destruction and fibrosis tend to accumulate over time in patients with this condition. Unless treated appropriately, patients with this disease are likely to suffer deformation and contracture of joints due to articular collapse as well as osseous rigidity of joints affected by advanced JIA, leading to severe dysfunction. When this disease develops at an early age, there is a risk of growth retardation.

At present, non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat inflammation in the early stages JIA [5]. In the USA, three drugs (aspirin, naproxen, tolmetin) have been approved for use in the treatment of JIA. Ibuprofen is also used in the USA ("off-label") for the treatment of JIA, since the dose of this drug for children is given in the package insert. In Japan, however, no NSAIDs have been approved for use in JIA treatment, and ibuprofen is used only for pain control. Thus, the drugs available in Japan for children with this disease are quite limited, and only steroids are indicated for JIA.

Extensive clinical studies on MTX in children with arthritis began to be carried out in the 1980s, primarily in Western countries. Adverse reactions were minimal, and the drug was reported to begin suppressing arthritis several weeks after the start of treatment in children with JIA who had only responded to steroids previously [6–8]. In randomized comparative studies as well, MTX was shown to be more effective than the placebo and to produce radiological improvement when used in cases with multiple-joint involvement. Based on these results, this drug was approved in the USA as a means of treating JIA [9]. In the EU, the approval status of MTX varies among different member countries, but sick children have been enjoying major benefits from this drug [10, 11]. In Japan, on the other hand, even the MTX 2 mg preparation, approved as a drug specifically indicated for rheumatoid arthritis, has a precaution in its package insert stating that the safety of this preparation in children and so on has not been established (experience in children and other special cases is poor). Thus, the use of MTX for the treatment of JIA has not been officially authorized in Japan [12]. Under such circumstances, treatment with conventional steroids and NSAIDs has been continued at many of the facilities where clinicians not specializing in JIA care manage JIA patients. At facilities specializing in JIA, MTX has been used as a drug of first choice, but, since the MTX 2 mg preparation used for treatment of JIA is not covered by national health insurance, a cheaper MTX 2.5 mg preparation (officially approved for use in the treatment of malignant tumors) has also been used in addition to the MTX 2 mg preparation. Furthermore, since the MTX 2 mg preparation is not authorized for use in the treatment of JIA and because the MTX 2.5 mg preparation has been authorized solely for treating malignant tumors in Japan, severe adverse reactions to MTX which appear following the use of this drug for treating JIA (even when used appropriately), patients may not be entitled to compensation system (Relief System for Sufferers from Adverse Drug Reactions).

The Association of Children with JIA and Their Parents has been insisting on correction of inter-regional differences in opportunities to receive JIA treatment, pointing out facilities with JIA specialists are confined to particular regions, and that JIA patients have difficulty receiving MTX therapy at non-specializing facilities, resulting in a marked inter-regional difference in the disease remission rate. If MTX is approved for use in the treatment of JIA and if an appropriate dosage, administration method, etc. are established concerning for this therapy, children with JIA across Japan can enjoy benefits equally, and significant impacts are expected in clinical practice related to JIA management. In fact, the cases necessitating treatment of sequelae secondary to JIA have been decreasing since adoption of MTX therapy at facilities specializing in JIA,

etc. Therefore, early adoption of active treatment using MTX will also be useful in reducing the cost of some care which is unnecessary in those treated with MTX.

Another factor making this an urgent issue is that biological preparations indicated for JIA have already been approved in Western countries and have been clinically reported to alleviate arthritis more markedly than is expected of MTX. In Japan, clinical trials on some of these biological preparations have been completed and approvals for these preparations have been or will be issued. New evidence has shown that combined use of MTX is indispensable for maximizing the effects of these biological preparations, particularly their effects on articular collapse [13–15]. A problem with these drugs is their high cost. This problem was also highlighted in Western countries, but these drugs were eventually approved on the basis of the medico-economic view that the total cost could be reduced by the use of these drugs if the cost-to-benefit relationship in patients' social contributions and the impacts on other healthcare costs, etc. were taken into account. In Western countries, the use of these biological preparations is limited to cases in which adequate efficacy cannot be expected of existing treatments. If these biological preparations are clinically introduced in Japan before approval of MTX as a JIA treatment, physicians in Japan will tend to use these preparations excessively, without adequate care, possibly exerting profound impacts on overall healthcare expenditures.

Status of approval in four Western countries (USA, UK, Germany and France)

MTX in JIA is approved in USA, Germany and France as indicated by Tables 1, 2. Additionally, in UK, although only adult RA has been established, guidance on the use of a biological preparation (etanercept) for JIA treatment, prepared by the National Institute for Clinical Excellence (NICE), shows the indication.

Overseas published information, randomized comparative studies and reports on pharmacokinetics

Overseas literature search results

The related literature was sought via Pub Med (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) (1950–2006), a

Table 1 The status of approval in the Western countries

Country	Indications	Dosage and administration
USA	Rheumatoid arthritis including multiple-joint juvenile rheumatoid arthritis	The recommended initial dose is 10 mg/m^2 (once weekly). The dose is changed gradually until adequate efficacy can be achieved. In adults, the incidence of severe adverse reactions (particularly marrow suppression) rises significantly if the dose exceeds 20 mg/week. For children, the maximum reported dose is 30 mg/m^2 per week. However, adequate safety evaluations have not been conducted at doses over 20 mg/m^2 per week. Usually, efficacy appears within 3–6 weeks, and efficacy augmentation lasts for at least 12 weeks. Although the duration of action has not been definitely documented, reports on the use of this drug in adults demonstrated that even when initial clinical efficacy was not sufficiently high, efficacy persisted during a 2-year treatment period. If the drug is discontinued, exacerbation of arthritis usually appears within 3–6 weeks
UK	Adult RA only (except for use of this drug in treating cancer, neither the efficacy nor the safety of the drug in children) has been established[a]	When used for adults with RA, the initial dose is 7.5 mg (once weekly or three 2.5 mg doses at intervals of 12 h/week). The dose may be increased to 15–20 mg (25 mg at maximum) per week. According to the NICE guidance on the use of biological preparations for JIA treatment, MTX is used as a standard drug, and is administered via non-oral routes at a dose of 20 mg/m^2 per week (maximum non-toxic dose) for 3 months
Germany	Multiple-joint juvenile idiopathic arthritis (JIA at age over 3 years)	Dosage and administration: Recommended dose is 10–15 mg/m^2 per week. If adequate efficacy is not obtained, a higher dose (20–30 mg/m^2 per week) is permitted.
France	Juvenile idiopathic arthritis	Recommended initial dose is 10 mg/m^2. Can be increased to 20 mg/m^2 at maximum

[a] Guidance on the use of a biological preparation (etanercept) for JIA treatment, prepared by the National Institute for Clinical Excellence (NICE), includes the statement: "Although MTX is generally used as a DMARDs for the treatment of JIA, the use of DMARDs including MTX has not been approved in the UK. However, the biological preparation is used in cases where MTX is not effective"

Table 2 Double-blind randomized study of MTX for JIA in the Western countries

Author	Journal	Comparison	Summary
Giannini et al. [9]	N Engl J Med. 1992	Placebo	A total of 127 patients with JIA younger than 18 years and satisfying the ACR criteria (mean age: 10.1 years, mean duration of sickness: 5.1 years) were enrolled into the following three groups: Group A (46: once weekly with MTX 10 mg/m^2; dose increased to 15 mg/week at maximum), Group B (40: once weekly with MTX 5 mg/m^2) and Group C (41: placebo). Efficacy was evaluated in 114 cases, with the response rate (percentage of cases showing improvement) being significantly higher in Group A (63%) than in Group B (32%) or Group C (36%). Side effects (SEs) were noted in 6 cases (13%) from Group A, 8 (20%) from group B and 5 (12%) from Group C. Major SEs observed were gastrointestinal disorders, stomatitis, headache, abdominal pain and dizziness, none of which was severe. The investigators stated that MTX therapy (10 mg/m^2/week) provides a valid means of treating therapy-resistant JIA
Woo et al. [10]	Arthritis Rheum. 2000	Placebo	A total of 88 children with JIA younger than 16 years of age were studied, including 43 children satisfying the criteria for erosive osteoarthritis (EOA) and 45 satisfying those for generalized arthritis. MTX or placebo was orally administered once weekly at a dose of 15–20 mg/m^2 for the first 4 months, followed by 4-month administration of placebo or MTX in an alternating fashion after a two-month cessation. When the data from both disease groups were combined, MTX therapy resulted in significant clinical improvement ($P = 0.006$). Major SEs observed were nausea, upper gastrointestinal disorders, stomatitis, dysthymic disorder and elevated AST, but there were no significant differences in SEs between the MTX and placebo groups. Thus, this short-term study revealed that oral MTX treatment (15–20 mg/m^2 once weekly) was effective against EOA and systemic JIA
Giannini et al. [17]	Semin Arthritis Rheum. 1993	Leflunomide	A total of 94 patients with multiple-joint JIA (age: 3–17) were enrolled. The JIA response rate was high for both leflunomide (LEF) and MTX, but MTX seemed to be more effective against JIA than LEF at the doses studied

literature database of the National Library of Medicine, National Institutes of Health (NIH), USA, and the EMBASE (1974–2006) operated by Elsevier Science B.V., the Netherlands. Among the numerous reports contained in these databases, our search and quotation focused on papers related to expansion of the indications for MTX in JIA (primarily those cited by the Cochran Review).

Double-blind randomized comparison of MTX with placebo

A double-blind study was carried out, dividing 127 patients with JIA younger than 18 years and satisfying the ACR criteria (mean age: 10.1 years, mean duration of sickness: 5.1 years) into the following three groups and administering MTX or placebo once weekly for 6 months: Group A (46 patients treated once weekly with MTX 10 mg/m^2; dose increased to 15 mg/week at maximum), Group B (40 patients treated once weekly with MTX 5 mg/m^2) and Group C (41 patients treated with a placebo) [9]. Concomitant use of prednisone (10 mg/day or less) and two non-steroidal anti-inflammatory drugs was permitted. The percentage of concomitant prednisone users was 33% (15 cases) in Group A, 37% (15 cases) in Group B and 34% (14 cases) in group C. Efficacy and safety were evaluated in accordance with the Guidelines prepared by the Pediatric Rheumatology Collaborative Study Group [16]. Efficacy was evaluated in 114 cases, with the response rate (percentage of cases showing improvement) being significantly higher in Group A (63%) than in Group B (32%) or Group C (36%) ($P = 0.013$). Group A showed a significantly greater reduction from the baseline as compared to Group C in terms of the number of painful joints during exercise (−11.0 vs. −7.1), pain severity score (−19.0 vs. −11.5), number of joints with restricted range of motion (−5.4 vs. −0.7) and erythrocyte sedimentation rate (−19.0 vs. −6.0 mm/h). Side effects (SEs) were noted in 6 cases (13%) from Group A, 8 (20%) from group B and 5 (12%) from Group C. Major SEs observed were gastrointestinal disorders, stomatitis, headache, abdominal pain and dizziness, none of which was severe. Treatment was discontinued because of SEs in two cases from Group A (abnormal liver enzyme levels and hematuria) and one case from Group B (eruption). All of these SEs subsided rapidly after discontinuation of the drug. The investigators stated that MTX therapy (10 mg/m^2 per week) provides a valid means of treating therapy-resistant JIA and that it is a safe therapy if administered for a short period of time (6 months or less).

A multicenter placebo-controlled double-blind randomized crossover comparative study was carried out in 88 children with JIA younger than 16 years of age, including 43 children satisfying the criteria for erosive osteoarthritis

(EOA) and 45 satisfying those for generalized arthritis [10]. Forty-three patients with EOA and 45 with generalized arthritis were enrolled in the study. MTX or placebo was orally administered once weekly at a dose of 15 mg/m^2. The dose was gradually increased to 20 mg/m^2 during the 2-month period. Either MTX or placebo was administered for the first 4 months, followed by 4-month administration of placebo or MTX in an alternating fashion after a 2-month cessation. In the EOA group, significant improvement was noted in 3 of 5 major parameters, i.e., erythrocyte sedimentation rate (ESR) and overall disease activities assessed by the physician or by the parents. In addition, significant overall improvement was noted in the EOA group according to the primary improvement criteria. In the generalized arthritis group, significant improvement was noted in only two of the five parameters (overall disease activities assessed by the physician or by the parents, with no significant difference in systemic characteristic scores between the MTX and the placebo treatment periods). However, in terms of therapeutic efficacy, there was no significant difference between the EOA and systemic arthritis groups. When the data from both disease groups were combined, MTX therapy resulted in significant clinical improvement ($P = 0.006$). Major SEs observed were nausea, upper gastrointestinal disorders, stomatitis, dysthymic disorder and elevated AST, but there were no significant differences in SEs between the MTX and placebo groups. Thus, this short-term study revealed that oral MTX treatment (15–20 mg/m^2 once weekly) was effective against EOA and systemic JIA. The investigators emphasized the necessity of examining the long-term efficacy of this drug in future studies.

Double-blind randomized studies comparing MTX with other drugs

A multi-country, double-dummy randomized comparative study was carried out on 94 patients with multiple-joint JIA (age: 3–17). The JIA response rate was high for both leflunomide (LEF) and MTX, but MTX seemed to be more effective against JIA than LEF at the doses studied [17].

Other randomized comparative studies

Evaluation of the effects of MTX dose increase [18]

The 595 JIA patients, who began MTX therapy at a standard dose (8–12.5 mg/m^2 per week, oral, subcutaneous or intramuscular), were followed for 6 months. Of these patients, 80 failed to show 30% improvement in ACR [19, 20], and were assigned at random to either the medium MTX dose group (15–20 mg/m^2 per week, $n = 40$) or the high MTX dose group (30–40 mg/m^2 per week, $n = 40$) and received intramuscular or subcutaneous injections of the drug for another 6 months. The results suggest that the efficacy of MTX against JIA plateaus at a dose of 15 mg/m^2 per week (non-oral) and that treatment needs to be continued for 9–12 months to evaluate the efficacy of MTX.

Evaluation of the influence of concomitant use of folic acid on the clinical efficacy of MTX [21]

A randomized placebo-controlled double-blind 13-week cross-over comparative study was carried out to evaluate the influence of concomitant use of folic acid (1 mg/day) on the efficacy of MTX administered to control disease activity in JIA patients. In these patients, concomitant use of 1 mg of folic acid at the time of weekly oral MTX treatment did not affect the clinical efficacy of MTX.

Literature dealing with in vivo drug kinetics

In vivo kinetics following an oral dose of MTX to children

The report made by Balis et al. suggests that when MTX is orally administered in an amount exceeding a certain level, saturation of its absorption needs to be taken into account [22]. When MTX (6.8–28.1 mg/m^2) was orally administered to children between 4 and 14 years of age (ALL: 14 cases, dermatomyositis: one case), those receiving 12 mg/m^2 or higher doses showed prolongation of the absorption phase from 1.5 ± 0.6 h to 2.5 ± 1.1 h ($P < 0.05$) and a reduction in the absorption rate from 87 to 51% ($P < 0.05$), suggesting a mechanism for saturation of absorption.

Kinetics in patients with JIA

Ravelli et al. [23] analyzed plasma MTX levels following oral administration of MTX (6.4–11.2 mg/m^2 per week) to 33 patients with severe JIA (ages: 1–19 years). The plasma MTX level at 3 h after administration was higher in "the MTX + salicylic acid treatment group" than in "the MTX + other NSAID treatment group" (mean: 0.23 vs. 0.39 μM). There was no difference in the MTX dose or plasma MTX level between responders (15 cases) and nonresponders (seven cases) or between those with (15 cases) and without (seven cases) elevated serum transaminase levels. Albertioni et al. [24] analyzed the kinetics of MTX and its metabolite 7-OHMTX following a single oral dose of MTX (0.14–0.24 mg/kg; median = 0.21 mg/kg) to 13 patients with JIA (ages: 5–16 years). Larger amounts of MTX are reportedly needed to treat pediatric JIA than adult RA since the AUC of MTX is lower in children. The age-related changes in MTX kinetics revealed by these studies may explain this finding.

Drug interactions

Dupuis et al. [25] evaluated the effects of NSAIDs with recognized MTX interactions. They analyzed changes in MTX kinetics following a single MTX dose (5–8.9 mg/m^2 per week, oral) or of MTX in combination with one or more NSAIDs (tolmetin, indomethacin, naproxen and aspirin) in seven children with chronic arthritis (ages: 8–18 years). In six of these seven cases, multiple NSAIDs were administered. Following combined MTX + NSAID treatment, the mean half-life of MTX was significantly prolonged (1.7 ± 0.5 vs. 1.2 ± 0.1/h, $P = 0.03$). However, no significant change was noted in MTX clearance (10.6 ± 5.5 vs. 13.1 ± 3.5 L/h, $P = 0.19$), AUC (2.1 ± 1.0 μmol/L per h vs. 1.5 ± 0.6 μmol/L per h, $P = 0.08$) or distribution volume (Vd; 23 ± 6.2 vs. 21.9 ± 6.4 L, $P = 0.53$). Based on these results, the investigators pointed out the necessity of considering MTX dose reduction when the NSAID dose is increased or additional NSAIDs are used.

Influence of diet

Because diet was shown to influence MTX therapy in some children, administration of this drug in a fasted state has been recommended. Pinkerton et al. [26] analyzed the influence of diet on absorption of orally administered MTX (15 mg/m^2) in ten children with acute lymphoblastic leukemia (ages: 3–15 years). Each child received three doses of MTX. The drug was first administered in a fasted state (A), then with a milk-dominant meal (B) and finally during an orange-dominant meal (C). Mean Cmax were 0.91, 0.55 and 0.71 μM following doses A, B and C, respectively. Mean Tmax were 1.30, 2.15 and 1.88 h, mean AUC 2.18, 1.56 and 1.91 μM/h per L following doses A, B and C, respectively. Thus, administration of MTX with a milk-dominant meal resulted in a significantly lower blood MTX level ($P < 0.05$), and absorption of MTX was delayed by its intake with either of the two meal types. The AUC during the absorption phase of the drug was significantly lower in the milk-dominant meal group than in the 'empty stomach' group ($P < 0.05$). Dupuis et al. [27] administered MTX to 14 patients (ages: 2.8–15.1 years, including 10 females) for 3 weeks using three dosing methods (administration after a meal, administration after overnight hunger, and intravenous administration). They compared the data from 13 patients for whom evaluation was possible. Blood was sampled 0, 0.5, 1, 1.5, 2, 3, 4 and 6 h after oral treatment, 0, 0.08, 0.25, 0.5, 1, 1.5, 2, 3, 4 and 6 h after intravenous treatment. The mean excretion rate constants were 0.27 ± 0.065, 0.26 ± 0.067 and 0.25 ± 0.11/h for the post-meal, 'empty stomach' and intravenous groups, respectively. The corresponding AUC were 1.87 ± 0.83, 1.50 ± 0.51 and 1.85 ± 0.80 μmol/L h. Thus, there were no inter-group differences in excretion rate constant or AUC. Peak blood drug concentration (Cmax) was significantly lower in the post-meal group (0.39 ± 0.18 μmol/L) than in the 'empty stomach' group (0.65 ± 0.33 μmol/L) ($P = 0.0022$). The time until peak blood drug concentration also differed between the 'empty stomach' group (0.94 ± 0.41 h) and the post-meal group (1.32 ± 0.68 h) ($P = 0.1464$). As a result, bioavailability was higher in the 'empty stomach' group (1.1 ± 0.51) than in the post-meal group (0.88 ± 0.35) ($P = 0.0211$).

Clinical pharmacodynamic studies

Bannwarth et al. [28] reported their clinical pharmacodynamic analysis of MTX following intermittent low-dose administration, using immunoassay. Following a low oral dose of MTX (≤10 mg/m^2), the absorption rate averaged 70% both following a post-meal dose and a dose given on an 'empty stomach'. The mean serum albumin binding rate of MTX was 42–57%. They reported that there was no evident relationship of pharmacodynamic parameters to clinical efficacy or toxicity of MTX in patients with rheumatoid arthritis. They additionally stated that when using MTX for children, it should be taken into account that pharmacokinetics vary depending on age.

Relationship between blood MTX level and toxicity

Wallace et al. [29] reported on the relationship between the blood MTX level and toxicity. They orally administered MTX (0.11–0.6 mg/kg per week) for 1.6 years (median) to 23 patients with JIA (age: 4.3–18.8 years) and attempted to determine safe and effective doses of MTX through analysis of blood drug levels in relation to clinical findings. MTX was used in combination with NSAIDs (ibuprofen, indomethacin, naproxen, piroxicam, salicylic acid, sulindac or tolmetin), sulfasalazine, hydroxychloroquine or PDN. In seven cases, serum transaminase levels rose slightly. In three of these seven cases, medication was temporarily suspended. In the other four cases, the abnormality subsided without requiring dose discontinuation or reduction. For the former three cases, medication was resumed at a lower dose after enzyme level normalization, and no problems were noted thereafter. The blood MTX level was not affected by concomitant use of any other drugs. In 21 cases, symptoms were significantly alleviated. The investigators concluded that safe MTX doses would be 0.6 mg/kg per week or less.

Other comparative studies

The influence of vaccination was evaluated in individuals receiving hepatitis B immunizations [30]. Thirty-nine

children with JIA who were serologically hepatitis B surface antigen (HbsAg) negative and 41 healthy children were compared. The children with JIA showed adequate responses to hepatitis B vaccination, showing no effects of the immunosuppressant administered. The data suggested administering the drug 0, 1 and 6 months after vaccination to be more favorable to than administering it 0, 1 and 3 months after vaccination.

Reviews of peer-reviewed journals, reports on meta-analyses

Cochran Review [31] involved a search and review of randomized comparative studies using the Cochran Controlled Trials Register (CCTR) and MEDLINE. The criterion used for selection was randomized comparative studies or clinical comparative studies, involving comparison of MTX therapy with placebo or standard care in patients with JIA. A systematic review was conducted on the effects of MTX therapy on mechanical capabilities, range of motion, quality of life, overall satisfaction and pain in JIA patients. Two studies on JIA patients [9, 10] were reviewed. The review revealed that MTX therapy resulted in greater improvement as compared to placebo treatment in terms of range of joint motion, number of painful joints, number of swollen joints, assessments by the physician and by the parents, allowing the conclusion that treatment with MTX can alleviate disorders to a degree equivalent to or higher than the minimal clinically significant level (>20%).

Giannini et al. [32] conducted a meta-analysis of the efficacy and safety of MTX administered at two low doses [5MTX (5 mg/m^2 per week), 10MTX (10 mg/mg^2 per week)] in comparison to D-penicillamine (10 mg/kg per day), hydroxychloroquine (6 mg/kg per day) and auranofin (0.15–0.20 mg/kg per day) in 520 JIA patients enrolled in three randomized placebo-controlled studies. Their analysis revealed that only 10MTX resulted in marked improvement as compared to the placebo treatment in terms of overall assessment by physicians, overall index and erythrocyte sedimentation rate. Responses to treatment were highest in the 10MTX group in evaluation of all joints. Short-term safety did not differ between any two groups. The results suggested that low-dose MTX would be useful as the first-line drug therapy for JIA. It was concluded that the minimum effective dose of MTX is 10 mg/m^2 per week.

The review by Ravelli et al. [33] on MTX therapy for JIA discussed the dose, route of administration, toxicity, timing of treatment start, timing of discontinuation of the drug, differences in the efficacy of MTX for JIA depending on the time of disease onset, capability of the drug to modify the course of JIA, and the significance of using MTX in combination with second-line drugs. To briefly summarize the discussions in this review, MTX is an effective, well-tolerated and low-cost drug for JIA treatment. Although the investigators did not refer to the possibility that MTX could alter the long-term prognosis of JIA patients, they stated that the drug markedly altered the short-term and mid-term outcomes in many sick children. Recent studies of adult RA yielded results supporting the use of MTX in combination with etanercept and infliximab (new anti-tumor necrosis factor preparations).

MTX in the guidelines for JIA management prepared by academic societies or organizations

A guide to treatment of JIA (JRA) using MTX was published in August 2007 by the Pediatric Rheumatology Association of Japan, under the title "Guide to Initial Management of Juvenile Idiopathic Arthritis (2007)" [34]. Currently, in parallel with the discussions at this conference, a revised version is now being prepared to provide more detailed statements to ensure proper use of MTX.

Among overseas guidelines, use of etanercept for JIA treatment was recently published by the NICE [11] and refers to the role of MTX in JIA treatment as follows:

Treatment of JIA uses NSAIDs and DMARDs. MTX is a major DMARD for treating this disease. Since MTX is expected to be effective in about 85% of multiple-joint type JIA cases, it is used as the first-line drug. For patients not responding to at least 3 months of MTX therapy at a dose of 20 mg/m^2 per week (the maximum dose inducing no marked adverse reaction), etanercept (a biological preparation) should be selected.

Use of MTX for JIA patients in Japan

According to the questionnaire survey conducted in 2000 at eight facilities in Japan, specializing in pediatric rheumatology (70 subjects, 19 males and 51 females), the mean age at disease onset was 6.9 years, mean duration of sickness 8.2 years and mean age at start of MTX therapy 13.2 years. The survey revealed approximately 73% of cases showed disease remission in response to combined MTX therapy. The duration of MTX therapy was 1–3 years in 25% and over 3 years in 61% of all cases, indicating that about 80% of all cases were able to take this drug for prolonged periods of time [35].

In the clinical use survey conducted to prepare this particular report, involving 68 cases of JIA (nine males and 59 females), the weekly dose of MTX per unit body surface area was 3.12 mg/m^2 at a minimum, 17.26 mg/m^2 at a maximum,

with a median of 7.19 mg/m^2 and an average of 8.73 ± 3.72 mg/m^2. The absolute MTX dose was 2 mg/week at minimum, 20 mg/week at a maximum, with a median of 7.5 mg/week as, and average of 8.37 ± 3.70 mg/week. Thus, the amount of MTX used was greater than 8 mg/week (the maximum dose authorized for adults in Japan) in 26 (38.2%) of the 68 cases. The MTX dosing period was 3 months at a minimum, 20 years and 7 months at a maximum, with a median of 8 years, and an average of 5.11 ± 4.12 years. Adverse events were noted in 10 cases (14.7%), including four with nausea/vomiting and one each with diarrhea, headache, malaise, varicella complication, aggravation of arthritis and duodenal ulcers (a causal relationship of the last event to the drug was noted by the attending physician to be unlikely since the symptoms worsened after increasing the NSAID dose). Of these events, all but duodenal ulcers were non-severe, and all subsided rapidly. The frequency of dosing per week was once in 18 cases and twice in 50 cases, with a mean of 1.74 ± 0.44. No case received the drug in three or more divided doses.

Acquisition for approval to expand indications

At the Pediatric Drug Therapy Conference organized under the Ministry of Health, Labour and Welfare, there have been discussions regarding expansion of the indications for MTX to include JIA accompanied by articular symptoms, on the basis of the information presented above, including the status of approval in four Western countries with similar drug approval systems (USA, UK, Germany and France), the overseas literature (randomized comparisons, pharmacokinetic studies), published reports (reviews, meta-analyses, etc. published in peer-reviewed journals), references in textbooks or the like to MTX as a standard therapy, and domestic MTX use survey data.

Overall evaluation of efficacy

The Cochran Assessment states that: "Little evidence has been collected for efficacy of MTX in treatment of JIA. The evidence currently available is mostly based on non-controlled clinical studies. Although the data from controlled studies reportedly endorsed significant alleviation of clinical symptoms, there are open questions on its efficacy." However, as stated above, MTX is referred to in many of the representative domestic and overseas textbooks, review papers published in leading journals, guidelines and so on. The response rate to MTX was 70%–90% in many reports. In randomized controlled studies, MTX was shown to be more effective than a placebo and to induce radiological improvements. In the USA and Germany, the indications for MTX are "polyarticular JIA". Some textbooks also refer to the efficacy of MTX in the treatment of polyarticular JIA. Some reports, however, show that this drug is also effective against the systemic type or the less-joint affecting type of this disease. In France, the indications for this drug are not confined to multiple-joint type disease. In the UK, approval of MTX preparation has not been issued directly, but the guidelines for etanercept using biological preparations (the most powerful means of treatment currently available) state that these preparations are used in cases failing to respond to MTX, without limiting the subjects of MTX treatment to those with multiple-type joint disease. In the Japanese guidelines as well, there is a statement that the drug is used even in systemic type cases if arthritis symptoms constitute the only major abnormalities. We therefore judged it to be appropriate to set the indications for MTX in Japan as "JIA accompanied by articular symptoms."

We may say that there is adequate evidence supporting approval of this drug as a means of treating this disease in Japan.

Global assessment of safety

According to the PK data available on children of the corresponding ages, the Cmax of MTX following oral administration was 0.4–1.0 μM/L, higher than the known toxic range of MTX (over 0.1 μM/L). However, Tmax was achieved in 1–2 h, and T1/2 was 1–2 h. Thus, the blood MTX level rapidly dropped below the toxic range. There are also reports on the results of controlled studies (double-blind, etc.) and other major studies as well as reports on adverse reactions and case reports. Definite evidence for the safety for this drug is thus available. When using MTX, care is needed of delayed absorption and increased Cmax, AUC, etc. following the use of MTX in combination with NSAIDs, since reports on such changes are available. This point is already noted in the package insert for MTX in Japan.

Adverse reactions to MTX used for JIA treatment are summarized in the aforementioned Nelson Textbook of Pediatrics (17th edition, 2004) [36]. MTX is well tolerated by children and the dose needed is low. Therefore, adverse reactions to MTX used for JIA treatment are minimal as compared to those known for its use in cancer treatment. The adverse reactions also differ qualitatively when this drug is used for JIA. Regarding the known hepatotoxicity of MTX in adults with RA, minute attention should be paid when MTX is used for children. However, liver biopsy in JIA children receiving long-term MTX therapy revealed no abnormalities in most cases. When used for adults, lymphoproliferative disorders developing after initial EB virus infection have been reported. A direct association of MTX with this event can not be ruled out.

In Japan, the results of re-examining the Rheumatrex® Capsule (2 mg) used for treatment of adult RA (published on December 26, 2006) [37] include the following data. Among 3,839 cases included in the safety evaluation, the incidence of adverse reactions was 18.62%. When the incidence of adverse reactions was analyzed by system organ class, it was highest for hepatobiliary (5.37%, 206 cases), followed by gastrointestinal (4.74%, 182 cases) and general (2.27%, 87 cases) disorders. The incidence of adverse reactions likely to follow severe courses was 1.48% (57 cases) for respiratory disorders and 1.38% (53 cases) for white blood cell and reticuloendothelial system disorders. As compared to the incidences of adverse reactions described in the Nelson Textbook of Pediatrics, those in this survey were lower for gastrointestinal and hepatic disorders. This difference seems to be attributable to the mean MTX dose for patients in whom data on doses were available being below 6 mg/week (in divided doses) in 97.77% of all cases (1,712/1,751), resulting in a much lower dose per unit body surface area as compared to that for children. Regarding adverse reactions likely to follow severe courses (i.e., leucopenia and interstitial pneumonia), incidences were lower in children described in the Nelson Textbook of Pediatrics than in this domestic survey of adult RA cases.

In this clinical use survey, adverse events were noted in ten cases (1.47%), including four with nausea/vomiting and one case each of diarrhea, headache, malaise, varicella complication, aggravation of arthritis and duodenal ulcers (a causal relationship of the last event to the drug was noted by the attending physician to be unlikely since the symptoms worsened after the NSAID dose was increased). Of these events, all but duodenal ulcers were non-severe, and all subsided rapidly, allowing a judgment that none had given rise to significant safety problems.

If these survey data and the adverse reaction findings described in package inserts, literature, textbooks, etc. are combined for general evaluation, there is no noteworthy difference in the safety profiles of this drug between Japan and foreign countries, and we can thus judge that there are no safety problems which could serve as obstacles to the approval of this drug for pediatric use in Japan.

Validity of dosage and administration

Regarding the use of this drug for children in Western countries, the initial dose is usually 10 mg/m^2 per week and the maximum 20 or 30 mg/m^2 per week, as stated above. The dosing method and dosage in Japan have already described in "Overseas published information, randomized comparative studies and reports on pharmacokinetics". That is, in Japan, the drug is often used at an initial dose between 4 and 10 mg/m^2 per week, identical to the routine initial dose in Western countries. MTX is known to exert its efficacy dose-dependently. Adverse reactions appearing in a dose-dependent manner (hepatic dysfunction, mucosal disorders, bone marrow suppression, etc.) are known, and the MTX excretion rate differs depending on the growth stages of individual children. With these and other issues taken into account, it seems advisable to present a range of initial doses (between 4 and 10 mg/m^2 per week) so that physicians can adjust the initial dose based on the features of individual children receiving this drug in Japan. Although no factor allowing clear-cut determination of the maximum dose of this drug is known, it seems essential to bear in mind that the maximum dose in said clinical use survey was 17 mg/m^2 per week, and that the safety of this drug at doses over 20 mg/m^2 per week has not been adequately assessed in the USA.

Regarding the dosing method, once weekly administration is usually adopted for MTX therapy in foreign countries. However, it seems appropriate to set the dosing method at once weekly or 2–3 divided doses per week in view of the following factors: (1) in the domestic clinical use survey, divided doses (two doses/week) were sometimes adopted; (2) self-control is difficult for children, unlike adult patients, thus making it necessary to consider adoption of a once weekly regimen to improve compliance with dosing instructions; and (3) the drug is administered in three divided doses/week when used for the treatment of adult RA in Japan.

According to the current dosing method and dose of MTX for adult RA in Japan, the drug is administered by dividing the weekly dose (6 mg) into three, at intervals of 12 h, with an upper weekly dose limit of 8 mg. In Western countries, the drug is usually used at an initial dose of 7.5 mg/week and at a maximum dose of 20 mg/week. According to the results of re-examination of the Rheumatrex® Capsule (2 mg) used for the treatment of adult RA, the dose was below 6 mg/week in 98% of all cases. However, according to the interim analysis of the data from the thorough survey on etanercept (June 2007), the MTX dose for combined therapy was over 8 mg/week in 38.8% and over 10 mg/week in 5.7% of all cases [38]. According to the survey conducted by the Japan Rheumatism Foundation (2000) as well, 39.8% of physicians pointed out the necessity of an MTX dose exceeding 8 mg/week [39]. Under such circumstances, the enterprise manufacturing and distributing this drug is reviewing the dosing method and dose of this drug for adults. Therefore, although the dosing method and dose now proposed for pediatric use are not completely consistent with the current dosing method and dose for adults, we judge this proposal to be optimal at present, provided that the proposed dosing method and dose are reviewed appropriately in the future on the basis

of the latest data from adults and children. Furthermore, considering a report that tolerability for this drug was lower in adults than children, particular care is needed in determining the dose for preadolescent and older children with juvenile idiopathic arthritis.

Based on these discussions, expansion of the indications for MTX to include JIA was judged to be acceptable, and it was approved at the Pediatric Drug Therapy Conference of the Ministry of Health, Labour and Welfare and at the Pharmaceutical and Food Council.

Revised package insert

- Drug concerned: Rheumatrex® Capsule (2 mg) and all drugs of equivalent efficacy.
- Planned indications: juvenile idiopathic arthritis accompanied by articular symptoms.
- Planned administration and dosage: usually, the drug is orally administered at a dose of 4–10 mg/m^2 per week (on a methotrexate basis). The dose is adjusted accordingly depending on age, symptoms, tolerability, responses, etc.

The drug is orally administered once weekly or by dividing the weekly dose into two or three. If the drug is administered in two or three divided doses, it should be administered at intervals of 12 h on two consecutive days. Cessation is incorporated for the remaining 6 days of the week in case of once weekly treatment or two divided treatments, and for the remaining 5 days in case of three divided treatments. This treatment sequence is repeated for multiple weeks.

Precautions related to administration and dosage: When using this drug, adequate care is needed as to the appearance of adverse reactions, and the dose should be set at an appropriate level for each patient depending on individual circumstances, including assessment of tolerability and responses. Considering a report that the tolerability of this drug was lower in adults than children, particular care is needed in determining the dose for preadolescent and older children with juvenile idiopathic arthritis.

Conclusions

At the present conference, expansion of the indications for MTX in JIA was approved. It is noteworthy that this expansion of indications was achieved without requiring clinical trials on children sponsored by the pharmaceutical company, by collecting necessary information through ongoing efforts (including collection and analysis of information about approval status in foreign countries, adequate evidence from the literature, implementation of a clinical use survey in Japan, and so on). It also merits attention that the maximum dose (10 mg/m^2) was set on the basis of pharmacokinetic data from children, rather than relying on the dosing method and dose for adults.

As to other drugs which can be used in the management of pediatric rheumatism, it is desirable that efforts should be made henceforth on to expand or acquire indications for these drugs, through adequate analysis of the characteristics of pediatric patients, collection of adequate evidence from the literature and implementation of clinical use surveys.

Acknowledgments The authors thank Pediatric Rheumatology Association of Japan and Japan Society of Developmental Pharmacology and Therapeutics to expand the indications for MTX in JIA in Japan. In addition, we deeply thank all the attendants who gave precious comments in MTX working group or the study group on pediatric drug therapy in Ministry of Health, Labour and Welfare. The Japanese version of this work was published as the report from the subcommittee for juvenile idiopathic arthritis in the Japan Pediatric Society. We are grateful to Mr. C. W. P. Reynolds for his careful linguistic assistance with this manuscript.

Conflict of interest statement We declare that no financial conflict of interest exists with any commercial entity whose products are described, reviewed, evaluated or compared in the manuscript.

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