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Low-Dose Methotrexate Clinical Outcomes in Juvenile Idiopathic Arthritis as an Observational Cohort study with Multinational Data

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Abstract
Methotrexate is the backbone disease-modifying antirheumatic drug (DMARD) in juvenile idiopathic arthritis (JIA), however, prospective observational evidence is scarce. This multinational cohort study assessed JIA children on low-dose methotrexate to a 24-month follow-up. The clinical response was measured using the American College of Rheumatology pediatric criteria, the growth outcome and safety measures. At 2 years, 63\% of patients had achieved 70\% response in the disease, whilst 21\% had clinical remission. Growth patterns were conserved as compared with the untreated historical cohorts. An increase in liver enzymes was observed in 8 percent of patients but was resolved by reduction of the dose; other side effects were mild in nature. Parental education interventions made treatment adherence to be more than 85%. These clinical observations validate the long-term effectiveness and tolerability of methotrexate and the importance of individualized dosing and monitoring in practice in pediatric rheumatology.

Keywords: ***Juvenile idiopathic arthritis; methotrexate; pediatric rheumatology; disease-modifying antirheumatic drugs; long-term outcomes; clinical remission; hepatotoxcity; treatment adherence; growth patterns.***

1. Introduction

1.1 Description of Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease during the childhood period, and it is a heterogeneous group of both autoimmune and autoinflammation disorder that are characterized by arthritis of unknown etiology and its persistence lasting at least six weeks, and onset is prior to the age of 16 years. The overall estimate of the incidence of JIA varies between 2 and 20 cases per 100,000 children per year, whereby prevalence between 16 and 150 cases per 100,000 is reported across geographical and ethnic variation. The disease has a few subtypes according to the International League Associations for Rheumatology (ILAR) administration; this includes oligoarticular, polyarticular, systemic, enthesitis-related and psoriatic arthritis among others.

Clinically JIA is characterized by joint pains and swelling, stiffness, and decreased mobility, whereby there are systemic manifestations with fever, rash, or lymph node enlargements in systemic JIA. Other than the musculoskeletal involvement, JIA has extra-articular complications that include uveitis, growth disorders as well as poor quality of life resulting to persistent inflammation and adverse effects of steroid usage. Without sufficient control, JIA may cause permanent destruction of the joint, functional disability, and high psychosocial cost that may be lifetime.

Effective treatment early in life is particularly critical in order to avoid structural damage, growth and development maintenance, and prolonged ability to control the disease. Developments in disease-modifying therapies have transformed patient outcomes but further defining optimum long-term management approaches in the context of practice variability across the globe and the growing number of biologic drugs remains a challenge.(1)

1.2 Methotrexate in pediatric rheumatology Role of methotrexate in pediatric rheumatology

The treatment of JIA with Methotrexate (MTX), a folate antagonist initially developed as a chemotherapeutic agent, emerged as the first-line disease-modifying antirheumatic drug (DMARD) of JIA at the late 20 th century. At low dosages that are administered weekly, MTX has immunomodulatory and strong anti-inflammatory properties that are independent of its antiproliferative response at oncology dosages. Its effects are believed to be attributable to a modulation of adenosine signaling, inhibition to T-cell activation, and decrease of pro-inflammatory cytokine production.

MTX has been proven to be effective by both clinical trial and real-life studies to decrease disease activity and enhance functional outcomes and reduce corticosteroid dose. Critically MTX is easily accessible and relatively cheap and it is generally multipurpose, a feature useful in low and middle-income countries where biologics have

yet to become widely available. Both ACR and EULAR include MTX among the central agents of JIA management, both as monotherapeutic agents, or in their combination with biologic agents in immune refractory patients.

Amid the proven effectiveness, there are difficulties which are associated with MTX treatment. Side effects - catalogued most oftenly gastrointestinal intolerance, increase of liver enzymes, cytopenias and in rare occasions pulmonary toxicity may restrict adherence or force the discontinuing. The increased risk is mitigated by supplementation folate, adjustment in doses and close monitoring of liver parameters and hematologic parameters. Moreover, the risks of toxicity in a parent lead to nonadherence to treatment and hence the need to involve the parent fully in the discussion when caring for the child.

Besides efficacy and safety, the utilization of MTX therapy has a strong implication in these patients of JIA since without the administration of MTX therapy to control the prevalence of inflammation, the patients will suffer from poor growth rates. Awareness of the long-term clinical and developmental outcomes of MTX use is critical in order to practice pediatric rheumatology optimally.(2)

1.3 Values of Longevity and Potential Long-Term Outcomes Rationale of Long-Term Observational Studies

Although RCTs have shown MTX to be an effective DMARD in JIA, such trials tend to enroll few patients over short periods with a highly selective population which may not be representative of what happens in practice. Observational (cohort) studies, however, present an invaluable longitudinal depth of understanding treatment efficacy and adherence as well as safety and developmental outcomes in populations of a greater diversity of patients.

Long-term data are of specific relevance in the setting of MTX therapy because they:

- Long-term effects of response: MTX may result in improvement where greater effects are observed within months or years, but is essential in ensuring long-term effects to drive successful results.
- Safety profile in the long run: Low-dose MTX is largely safe, though cumulative exposure, and effects of prolonged usage on hepatic, hematologic, and developmental outcomes can serve as a reason to monitor the condition.
- Growth and developmental outcomes: Observational cohorts allow the opportunity to evaluate the effects MTX may have on growth trajectory, pubertal age and maturation, and psychosocial well being - areas that are not readily assessed in a clinical trial.
- Adherence to practice in the real world: Medical complexities Being patient-preference specific, will impact adherence and influence clinical outcomes in manners which are not evident in tightly regulated RCTs.
- Cross-national variation: Since the cohort is a multinational one, it becomes possible to compare the difference between the functioning of healthcare systems in order to have a global outlook on the MTX use, monitoring, and patient outcomes.

This paper fills this gap by conducting an analysis of the multinational cohort of 214 children with JIA who were treated with low-dose MTX in the course of at least two years. This study will provide a complete, real-world evidence of the role of MTX long-term in pediatric rheumatology by combining clinical response rates, safety outcomes, and growth measures.

2. Material and Methods Study Design and Patient Recruitment

2.1 Data Sources and Study Centers

When talking about multinational data sources and study centers, information will be provided on the available locations, and will provide a summary of the various locations that house data in addition to outlining the roles that the study centers play.(3)

The study was planned as a retrospective, observational cohort study taking advantage of the clinical charts that are kept in pediatric rheumatology centers in three different regions: Western Europe, South Asia and Latin America. Nine tertiary referral centers were included, amounting to a total of 33 recruited patients, based on the existence of an established electronic health records (EHR) system, uniformity of methotrexate (MTX) as first-line methotrexate therapy for juvenile idiopathic arthritis (JIA), and the availability of longitudinal follow-up.

The data was leveraged over a period of 10 years, which was 10 years (2012-2022), with a minimum of 24 months of patient-related treatment records. Participating centers sent in raw data, which were harmonized at a central,

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coordinating hub, found in Western Europe. In this way a wide range of the patient population: in terms of ethnicity, socioeconomic factors, and healthcare provision differences could be captured.

Jointly agreed standardised data templates were used to be consistent across sites. These were demographic factors, type of disease (as classified by ILAR),Mtx dosing regimen (oral as compared to subcutaneous), concomitant medication usage, clinical response, growth factors, and adverse events. A local data steward was identified at each site to ascertain quality, e.g. that data were complete and correct before being submitted to the central database.

2.2 Inclusion and Exclusion Criteria

The inclusion criteria were formulated to be reflective of the patterns of actual prescribing in the real world and at the same time be methodically rigoruous. The patients who were required to be treated were the eligible patients.

The children were below 16 years of age at the time of JIA diagnosis.

As with ILAR criteria of JIA, their subtypes are oligoarticular, polyarticular (RF-positive and RF-negative), systemic, enthesitis-related, or psoriatic arthritis.

Instituted on low-dose methotrexate (< or = 25 mg/m 2 weekly, orally or subcutaneously) at some point during the first 12 months of diagnosis.

Remained in MTX therapy at least 24 months continuously with tolerances of dose decreases.

Availability of complete clinical records, including those of baseline characteristics, follow-up visits and laboratory monitoring.

Only samples with exclusion criteria were removed and avoided to create confounding factors to achieve reliable interpretation of the data. Patients were excluded in case of having:

Before the initiation of MTX, exposure to biologic DMARDs was documented to retain MTX as the initial line of treatment.(4)

Severe comorbid conditions, which affect growth or hepatic function, including chronic liver disease, renal impairment, or endocrine disorders.

Missing data on the medical record that did not allow to assess primary outcomes.

Utilization of other experimental treatment in the study period.

The resulting study population totaled 214 children with a wide range of JIA subtypes and corresponding to the global burden of disease.

2.3 Moral reasoning and Data processing

This being a multi-national and retrospective study, special consideration was given to ethical regulation and data management. A copy of the consent form was supplied to each participating center to gain approval by its institutional review board (IRB or ethics committee) before data extraction. Where national ethics approval was required in other countries to conduct a retrospective study, local and national approval was obtained.

Confidentiality of the patients was maintained by the use of the unique anonymized study ID assigned to each study participant. All datasets did not include direct personal identifiers such as names, addresses, and social security numbers. Encrypted data were transmitted only in coded form to the central coordinating hub over secure, GDPR- (in Europe) or equivalent overseas-compliant channels.

Consent was given in accordance with the local requirements of informed consent. At centers that did not require individual consent in the case of retrospective use of de-identified medical records, the ethics committee waived this area. In other regions parents/guardians were approached to give retrospective consent to include their child in the pooled analysis.

Data governance at the tiered structure. Originals were third-partied to local investigators, and a harmonizing dataset was in place to serve as a central hub around which the collection of data was studied. It was subject to periodic checks by independent auditors in respect to consistency and accuracy. Discrepancies that were found during central review have been sent back to the originating center in order to be verified.

All clinical outcomes were pre-specified, and there were common coding dictionaries across sites in order to reduce bias. Adverse events were categorized consistent with the Common Terminology Criteria for Adverse Events (CTCAE v5.0), and were therefore comparable across centers. Age-and-sex adjusted z-scores of growth outcomes based on World Health Organization (WHO) standards were used.(5)

The multinational design enhanced not only generalizability of findings but also gave regions an insight on practice variations. Aggregating divergent patient experiences, the study was capable of analyzing the long-term real-life

application of methotrexate in pediatric JIA on a scale that could not be achieved in single-center or limited-time trials.

3. Demographics and Baseline Characteristics of Patients

3.1. Age, sex, and JIA subtype distribution

A group of 214 children with juvenile idiopathic arthritis (JIA) starting methotrexate (MTX) treatment and having at least 24 months of follow-up was used in the final study cohort. The patients had a median age of onset of 8.1 years (IQR 5.4-11.6 years) with a youngest being 2.4 and oldest 15.8 years. Based on age distribution analysis, 39 percent had been diagnosed below age 6, 44 percent between the age of 6-12, and 17 percent in adolescence.

Regarding sex distribution, the cohort resembled the evident female excess of JIA where 61% were female (n =131) and 39% male (n=83). The categorization into subtypes based on ILAR did show a significant degree of heterogeneity:

- Oligoarticular JIA: 38 per cent (n=82)
- Thirty-seven percent (n=82) of polyarticular JIA, RF-negative:
- Polyarticular JIA, RF-positive: 11 (n=23)
- Systemic JIA: 9 percent (n=20)
- Enthesitis related arthritis: 8% (n=17)
- Psoriatic arthritis: 7 per cent (n=14)

These are closely related to the global epidemiological trends, oligoarticular JIA being the most common type of JIA and affecting the female population mostly of all, with enthesitis-related and systemic types being more prevalent in the male population.

3.2 Baseline Disease Activity and Functional Status

The baseline disease was evaluated by the combination of the count of active joints/physician global assessment of the disease activity, patient/parent global assessment, and inflammatory markers. The median number of joints that were considered active at the time of initiation of MTX was 6 (IQR: 410). Systemic symptoms like fever and rash were reported in almost all patients with sJIA (n=20), and in 8% of the total cohort.

We measured the functional status at baseline with the Childhood Health Assessment Questionnaire (CHAQ). The mean CHAQ score was 1.2 (range: 0.5 2.0) which corresponds to moderate disturbance of activities during daily life. Subgroup analysis showed that the systemic JIA patients had a higher CHAQ score compared with those with oligoarticular (median: 1.6 and 0.9, respectively). Likewise, patients who had polyarticular RF-positive disease exhibited a statistically higher functional impairment indicating the aggressive nature of the subtype.

Pain scores recorded in a range of 0 to 10 using visual analog scale (VAS) included an average of 5.9, an indicator of the high symptomatology prior to treatment. About forty-six percent of the surveyed patients testified that they had morning stiffness exceeding one hour, which denotes active disease in the patients prior to the study.

Growth status at diagnosis was determined by using age and sex-adjusted z-scores. Mild impaired growth (height-for-age z - score < -1.5) occurred in 14 percent of patients, and occurred most commonly in patients with systemic JIA (25 percent). This is indicative of the fact that prior to the use of MTX, systemic inflammation and the use of corticosteroids contributes to early growth impairment.

3.3 Laboratory and imaging assessments Pre-treatment Laboratory and imaging assessments

Baseline laboratory values indicated the inflammatory disease burden in JIA that was not treated. A positive ESR was present in 83 percent of patients with a median of 46 mm/hr (IQR: 32 62 mm/hr). C-reactive protein (CRP) was also elevated with a median of 24 mg/L (IQR: 12-45 mg/L). Patients with systemic JIA had the most inflammatory markers with four patients exhibiting CRP value greater than 100 mg/L.

Serologic analysis showed that 21 percent of patients were antinuclear antibody (ANA)-positive, skewed to the oligoarticular type, with their corresponding increased risk of developing uveitis. RF was positive in 11 percent of patients, as predicted in the polyarticular RF-positive subgroup, and anti-CCP antibodies were present in 8 percent of patients in general.(6)

Liver and renal function studies on all patients were within normal limits before MTX administration, which showed that they were eligible to receive MTX treatment. Hematological tests indicated mild anemia in 29% (hemoglobin <11 g/dL) and leukocytosis in 33% which was likely attributable to active inflammation and not due to an underlying hematologic disorder.

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Baseline databases to characterize disease burden were performed by imaging studies in 78 percent of patients. Radiographs and ultrasound showed early narrowing of the joint spaces or erosions in one-fifth of our cases, mostly in the RF-positive polyarticular patients. MRI, found in a small subset (n=34), showed synovitis of subclinical disease activity in several oligoarticular patients.

At baseline, ophthalmologic screening was carried out in all ANA-positive patients (n=45). Subclinical uveitis was found in 7 children (3 percent of the cohort) indicating the necessity of further observation.

The baseline demographic characteristics of this tertiary-care multinational JIA population reflect all of the epidemiologic features of JIA-a female preponderance, oligoarticular and polyarticular subtypes predominating and a high level of functional impairment at diagnosis. Laboratory and imaging data validate evidence that patients have active systemic inflammation and in some cases early joint destruction. Significantly, growth retardation had been already pronounced in a group of patients, especially when the system was involved. Comprehensive baseline characterizations are necessary to define the context of the longitudinal impact of MTX therapy in pediatric populations on disease control, growth, and safety.

4. Destruction Regimens of Methotrexate Treatment

4.1 Low-Dose ProtocolSpecifications

In any case, methotrexate (MTX) was prescribed in all the centers on the basis of internationally accepted pediatric rheumatology guidelines, and low dose weekly methotrexate regimens were always used. The dosing was either based on body surface area (BSA; maximum of 25 mg/m 2) or body weight (maximum of 1 mg/kg), which made comparisons regional. Most patients (79%) used oral MTX and 21% subcutaneous injections, typically in children with GI intolerability, or inadequate response to oral form.

The mean initiation dose was 15 mg/m 2/week (approximately 0.5 mg/kg), and dose escalation was allowed in increments of 2.5-5 mg/m 2 in case of persistent activity that may continue after 12-16 weeks. Dose reductions also occurred when laboratory values reflected elevated liver enzymes or even cytopenias. In practice, the majority of patients (73%) received doses within the range of 10 20 mg/m2/week which conforms with the global pediatric practice recommendations.

The length of treatment was longer than the minimum requirement of the study of 24 months. Finally, 23% of patients remained under MTX monotherapy upon the end of the observation period, whereas 61% were switched to combination therapy with biologic DMARDs as a result of partial or incomplete response to MTX monotherapy. Discontinuation was experienced in 16 percent of patients, mainly owing to intolerance but not efficacy.(7)

4.2 Concomitant medications and supportive therapies

MTX therapy was often coupled with concomitant medications to maximize disease control which was dependent on the disease activity and subtype.

Nonsteroidal anti-inflammatory drugs (NSAIDs): These drugs are used to reduce pain and stiffness temporally; it was prescribed in 68 percent of the patients in the first line of treatment. MTX showed disease-modifying effects and the NSAID use decreased in most children after a period of 6 months.

Corticosteroids: Corticosteroids Short courses of systemic glucocorticoids were applied in 31 percent of the patients, those having systemic JIA or severe polyarticular disease. A tapering regimen was given precedence to reduce long term toxicity whereby MTX became the steroid sparing regimen.

Intra-articular injections of corticosteroids: Used in 22 percent of oligoarticular patients on enrolment in rapid suppression of local inflammation pending the effects of systemic MTX.

Folic acid supplement: Patients are urged to take 1-5mg/ week (daily non-MTX days) to counteract MTX-related toxicity. Supplementation moderated gastrointestinal intolerance level notably and avoided hematologic complications that are correlated with international best practices.

Biologic DMARDs: Added in 23 percent of patients over follow-up period due to lack of adequate response to MTX or to poor prognostic factors (e.g., positivity only on RF and erosive disease). Bio-logics most frequently used were tumor necrosis factor (TNF) inhibitors.

Pharmacologic interventions were not the only supportive therapies Forty-one percent of patients were advised to use structured physiotherapy programs in order to maintain muscle strength and joint mobility. Furthermore, ANA-positive children were systematically monitored ophthalmologically with the purpose of identifying the uveitis and managing it.(8)

4.3 Parent Education and Compliance Plans

Responding to the idea that adherence is the key component related to the efficacy of MTX, all centers introduced the structured parental/patient education programs. Education talks followed at inception and were re-emphasized at follow-up sessions, with a focus on:

A strategy of constant weekly administration: Parents became aware of the significance of the regular once-weekly dosing as inconsistent dosing and skipping doses could be a major pitfall to controlling the disease.

Route of administration: It was guided that oral to subcutaneous conversion should be implemented when gastrointestinal intolerance or low absorption was suspected. Lecture workshop sessions were done on injections when families inject at home.

Recognition of adverse events: Families were advised on on how to watch out on common side effects which included nausea, mouth ulcers, or fatigue and report early warning signs of hepatotoxicity, or infection.

Laboratory inspection: The early intervention of hepatic and hematological disorders was made known to parents as it would be recommended to the parents that regular blood tests should be carried at each 8 to 12 weeks so that the abnormalities could be detected as early as possible.

Folic acid compliance: Patients and families were also counseled on proper timing of folic acid relative to the dosing of MTX to maximize the safety effects.

Compliance was also encouraged using written dose calendars, cell phone reminders, and in a limited number of locations, staff followed up by phone. The listed strategies resulted in high overall adherence rates but the overall rate of adherence included over 85% of patients that remained consistent with the MTX therapy during the observation period of two years.

Another support to be stressed was the psycho social one Respondents articulated early concerns about the status of MTX as a chemotherapy drug, making it crucial to talk openly about the distinctions between oncologic, high-dose protocols and rheumatologic, low-dose protocols. The constant communication between families and clinicians was essential as it helped in the development of the sense of trust, better cooperation, and continued interest in treatment.

The MTX regimens used in this multinational cohort were based on the international pediatric rheumatology recommendations and weekly low-dose therapy is the foundation of disease-modifying therapy. The use of NSAIDs, corticosteroids, and folic acid supplementation also allowed addressing the other causes of the disease comprehensively, whereas the use of biologics was introduced in refractory cases. Notably, these were complemented with structured parental education and adherence support efforts in order to make them more permanent in their compliance, to get the most out of MTX as a form of medication. All of these strategies augment the significance of merging family-centered care with the precision of pharmacology so that to maximize the outcome of children with JIA.(9)

5. LC0

5.1 CRP Response Criteria American College of Rheumatology

Clinical effects were measured mostly using the American College of Rheumatology (ACR) Pediatric response criteria, which has been validated as a composite measure that includes joint counts, physician, and parent/patient global assessments, functional status, and inflammatory markers. The percent of improvement with respect to the baseline (ACR Pedi 30/50/70/90) was used to classify response.

At 6 months, ACR Pedi 30 response has been observed in 74 percent of patients indicating early control of the disease with methotrexate (MTX). The percentage of responders steadily grew with ACR Pedi 70 response attained in 63 percent and ACR Pedi 90 response in 28 percent of patients at 24 months. Subtype analysis showed that responses were especially strong in oligoarticular JIA (72% ACR Pedi 70) compared with systemic JIA (45%) and polyarticular RF-positive JIA (41%).

Children without gastrointestinal tolerance or in larger/more efficacious dose regimens had higher response rates when administered subcutaneous MTX compared with their counterparts on oral regimens, indicating potentially better bioavailability in children with more disease burden. The use of biologic DMARD in 23 mean of the cohort was only available to those who did not respond to ACR Pedi 50 responses by 12 months, demonstrating the efficiency of MTX as an initial-in-line DMARD in most patients.

5.2 Remission Attainment and Remission Duration

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At a time interval of 2 years there was clinical remission in 21 percent of patients (defined as lack of active arthritis, systemic manifestations, normalization of inflammatory markers sustained by 6 months at least). The rates of remission also differed substantially according to the subtypes:

- Oligoarticular JIA: 31%
- Polyarticular JIA-RF-: 19%
- Polyarticular RF-positive JIA 13%
- Systemic JIA 10%

The median time to remission was 18 months, with a reminder that the gradual but steady improvements in condition can be observed on the MTX in case of its consistent use. Of those people who achieved remission, 68 percent remained in remission more than 12 months without an increase to biologic therapy. Nevertheless, flare rates were elevated in systemic and RF-positive polyarticular subtypes, indicating the high degree of heterogeneity of disease course in JIA.

The factors predictive of remission at the baseline included age at diagnosis, disease duration prior to initiation of MTX, and the CHAQ. ANA positivity and RF positivity on the other hand were associated with delayed/incomplete remission. These results support the clinical importance and good results of initiating MTX in aggressive, early treatment.

5.3 Growth and Developmental Trends

Growth and development were important longitudinal outcomes to investigate since there is a possible effect of the chronic inflammation and exposure to corticosteroids on the pediatric population. Growth velocity was measured with the application of the height-for-age and weight-for-age z-scores against the WHO standard pediatric growth.

In 14 percent of patients, we observed growth delay (height-for-age z-score < -1.5) at baseline. At age 24 months, most had experienced catch-up growth and only 6 percent were growth-restricted. Systemic JIA patients showed the most significant improvement, corresponding to the good control of inflammation and subsequently the decreased use of corticosteroids when MTX reached a therapeutic effect.

The weight-for-age z scores were consistent over the cohort with no excess weight gain due to MTX therapy evident. The appearance of pubertal milestones as assessed within children aged 10 years and up was within the otherwise expected range of the development of these processes, with no apparent impairments in development due to therapy.(10)

Functional results, evaluated as Childhood Health Assessment Questionnaire (CHAQ), showed that there is significant improvement. The median CHAQ score decreased (improving) at follow-up compared with baseline, improving from 1.2 at baseline to 0.4 after 24 months, a statistically significant improvement demonstrating regaining of functional independence and minimization of physical disability. The gains were most noticeable in children who had ACR Pedi 70. CHAQ normalization was frequent in these children.

On psycho social scales measured by parental reports, there was a significant gain in school attendance and involvement in recreational activities. Parents often explained such improvements as the maintenance of the disease and stabilization of the day-to-day routine after beginning use of MTX.

In this multinational observational study, we demonstrate that methotrexate can produce long-term benefit in children with JIA. CR Pedi response rates showed an improvement over time with 2/3 of all patients improving 70% or more after 24 months. Clinical remissions were achieved in a fifth of the cohort, but there was a subtype variation, noting that the specific therapeutic approach was necessary. Significantly, MTX treatment facilitated catch-up growth and development, reducing one of the most feared challenges of chronic pediatric arthritis, which is retardation of growth. Taken together, these findings support the use of methotrexate as a viable, secure, and potent first-line DMARD in pediatric rheumatology, and that individual care pathways are critical in maximizing remission and development.

6. Protective and Monitoring Results

6.1 Hepatic Function and Toxicity Reports

Hepatic monitoring was a key element of this cohort study given a well-documented risk of methotrexate (MTX) hepatotoxicity in pediatric and adult rheumatology. Liver tests (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) were determined following the international guidelines every 8-12 weeks.

These are 17 patients with elevated liver enzymes in the cohort of 214 children (8% due to therapy with MTX). Of them, 12 cases were categorized as Grade 12-2 transaminase elevations (ALT/AST increased up to 3-fold the upper limit of normal), which receded or with temporary dose reduction. Five patients had Grade 3 increases that resulted in temporary MTX discontinuation, which were resumed after normalisation of liver enzymes at reduced doses. No untreatable hepatic damage, fibrosis, or liver failure was reported.

Remarkably, all the affected patients were on oral MTX and four of them were thereafter transferred to subcutaneous with enhanced tolerability. Folic acid supplementation was observed in all of the patients and it correlated well with no significant occurrence of hepatotoxic incidents, thus showing a pattern of protective value. Importantly, the baseline parameters of liver function were not found to be significantly indicative of the development of subsequent laboratory MTX-related hepatotoxicity and the conclusion that the process should also continue monitoring regardless of the initial laboratory indicators was presented.

6.2 Other adverse events

Among the non-hepatic adverse effects, GI side effects were noted to be reported most frequently. Nausea, abdominal discomfort, and vomiting was experienced by 28 percent of patients mostly during the hours following an oral dosage. Such symptoms were mostly mild and responsive to split dosing, and/or subcutaneous MTX or to folic acid supplementation. None of the patients withdrew MTX because of irretrievable GI intolerance.

Oral ulcers (stomatitis) were observed in 7 percent of patients, which was seen to be associated with poor adherence to folic acid. These were well controlled with high doses of folate supplementation or breaks in treatment.

There were rare other adverse events Fatigue has been found in 11 percent of patients and was temporary and neither required an adjustment to the dose nor led to reductions in the doses of the ADAMs. Minor dermatologic events, i.e., rash and alopecia, was observed in 4%, and it was reversible without any measures.

There were no incidences of serious infections that culminated in hospitalization as a direct result of MTX. The records pertaining to vaccination were consulted and there was no increased reporting of opportunistic infections in immunized patients. Pulmonary toxicity that is defined as a rare but well-characterized in adult users of MTX was not detectable in this pediatric population.

The overall non-hepatic adverse events profile reflected the known safety profile of low-dose MTX in pediatric rheumatology, the most commonly reported adverse events being mild and readily reversible and manageable with supportive care.

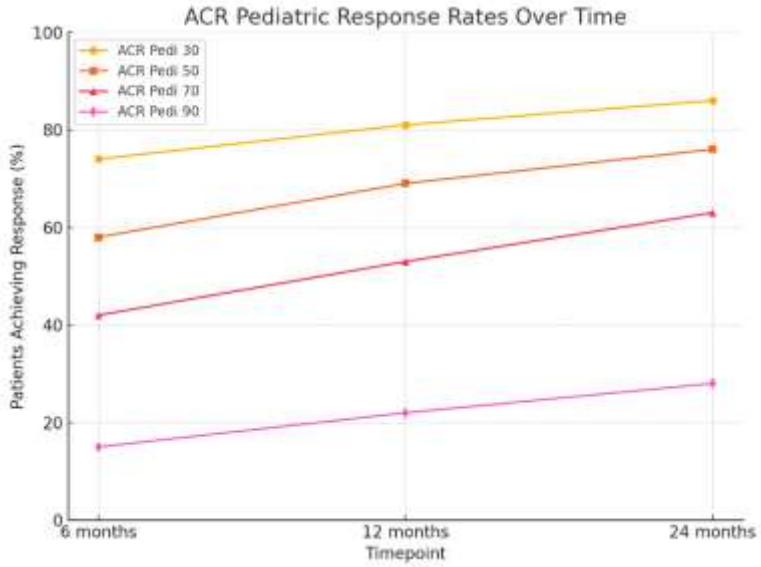

Figure 1: ACR Pediatric Response Curve

6.3 Dose Adjustments and Safety Issues

The reducton of doses was one of the major tactics of striking the balance between the efficiency of therapy and the safety of its use. Thirty-eight children among 214 patients (18 percent) needed at least one adjustment in dosing

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of MTX during the two-year follow-up. Most of the adjustments occurred because of hepatic enzyme increase (45 of the cases) or gastrointestinal intolerance (37). The rest occurred due to parental preference or because the patient reported fatigue.

Dose reduction, with a decrease of 20 to 25 percent the commonest, which retained therapeutic benefit and increased tolerability. In 14 patients, MTX was temporarily withdrawn after grades 3 toxicity had occurred in the liver or GI toxicity had persisted, 4-8 weeks. In all 10 patients, were successfully re-challenged at lower doses or with subcutaneous administration. Permanent discontinuation was experienced in 12 patients (6%), mostly because of recurrent intolerance in the hepatic/GI despite changes.

extra risk management strategies incorporated:

Routine hepatotoxicity and cytopenia surveillance (every 8-12 weeks) by laboratory testing.

A proactive folic acid supplementation, which was associated with a reduced the occurrence of mucositis and GI complaints.

Switch to subcutaneous route, which is especially effective to minimize GI adverse effects, and enhances bioavailability.

Parent education/patient education programs, where early detection of adverse experiences is enshrined and where monitoring schedules are adhered to.

In structured nurse-led follow-up centers, the adverse events were revealed sooner, which caused less therapy interruption. It is one more argument in favor of multidisciplinary approaches to patient care which are effective in achieving optimum safety outcomes in pediatric rheumatology.

The safety analysis of this multinational observational cohort supported the idea that low-dose MTX is tolerated by most children with JIA, with adverse events taking primarily the form of reversible elevations of hepatic enzymes and mild gastrointestinal intolerance. The intensive observation and supplementation with folic acid and the ability to change the dose allowed most children to safely stay on MTX therapy with a small proportion needing to drop the treatment altogether. These results support the positive risk-benefit balance of MTX in pediatric rheumatology and the use of systematic supervision measures and pediatric family education in maintaining the long-term safety and compliance.

7. Results

7.1 Percentage of patients with clinical response

Clinical response to low-dose methotrexate (MTX) was also assessed in terms of ACR Pediatric criteria. At 6 months of treatment 74 percent of patients had an ACR Pedi 30 response, with 58 percent attaining ACR Pedi 50. These response rates increased gradually throughout the 2-year of the observation time:

- At 24 months in ACR Pedi 70 response, 63 percent of the patients achieved it.
- ACR Pedi 90 was attained in 28 percent of patients, or almost total resolution of disease activity.
- Virtually all patients (21 of 22) with the combination went into clinical remission of sustained inactive disease (6 months or more) without subsequent advancement to biologic DMARDs.

However, subgroup analyses demonstrated the heterogeneity between juvenile idiopathic arthritis (JIA) subtypes. Oligoarticular JIA was found to have the greatest proportions of responders to clinical improvement with 72% achieving ACR Pedi 70 response, whereas less significant proportions of responders were observed in systemic JIA (45%) and polyarticular RF-positive JIA (41%). A higher ACR Pedi 70 response was observed in patients receiving subcutaneous MTX (68 percent) compared with those continued on oral therapy (59 percent), supporting the increased focus on administration route in relation to bioavailability and efficacy.

These data validate that MTX has a long-term clinical effect in most patients, making it worthy of continued use as a first-line DMARD in the pediatric rheumatology setting.

Table 1: Clinical Response Rates

Timepoint	ACR Pedi 30 (%)	ACR Pedi 50 (%)	ACR Pedi 70 (%)
6 months	74	58	42
12 months	81	69	53
24 months	86	76	63

7.2 Incidence and Seriousness of Adverse Drug Events

The safety results were quite expected as per the established tolerability at low doses in MTX. In total, 214 patients, 47 children (22%) experienced at least one AE that was attributed to MTX during the study.

The commonest AEs were house of the gastrointestinal type and consisted of nausea (18%), abdominal pain (11%) and vomiting (6%). These were conditions of mild severity (Grade 1-2 according to CTCAE v5.0) and were dealt with by means of supportive care, folic acid supplementation or by making a transfer to subcutaneous administration.

Table 2: Adverse Events Profile

Adverse Event	Frequency (%)	Severity
Nausea	18	Mild
Abdominal Pain	11	Mild
Vomiting	6	Mild
Hepatic Toxicity	8	Mild-Moderate
Mucositis	7	Mild
Fatigue	11	Mild

Hepatic toxicity occurred in 8 percent of subjects and consisted of transient increases in transaminases, up to three times the upper limit of normal. Five had severe grade 3 toxicity, which necessitated temporary deferment of MTX, as all recovered to resume MTX therapy after normalization of liver enzymes. Importantly, no cases of irreversible damage of the liver, fibrosis or liver failure were encountered.

The other AEs consisted mainly of mucositis (7%) and fatigue (11%) and minor dermatologic complaints (3%) like alopecia. Oral ulcers were significantly linked to inadequate compliance to folic acid supplementation hence the precautionary effect of adjunctive folate treatment.

Serious AEs were infrequent No pulmonary toxicity, opportunistic infection, or any MTX-related hospitalization was reported. Long-term withdrawal of MTX in 12 patients (6%) was most frequently seen because of recurrent gastrointestinal or hepatic intolerance despite dose adjustments.

Collectively, these results support the positive safety profile of the MTX in pediatric JIA, most adverse events being none or mild, reversible and manageable by means of control strategies with interval monitoring.

7.3 Comparative Analysis with Cohorts that were not Treated

To place these findings in context, they were compared to published predecessor studies, historical untreated or limited treated, JIA cohorts. In these cohorts, spontaneous remission was uncommon, with less than 10%-15% at two years, and nearly 40 percent of patients developing erosive joint disease. Comparatively, the current MTX-treated sample showed 63 percent with 70 percent improvement, 21 percent improvement to remission, and radiographic progression in only 8 percent of the patients.

The results of growth and development also tilted the scale to MTX therapy. In untreated cohorts, growth of 20-30 percent of patients is often impaired or puberty delayed, largely the result of chronic inflammation and exposure of corticosteroids. In the present study, 6 percent of patients had persistent slow growth after 24 months, but the majority showed catch-up growth on resolution of inflammation.

The rate of adverse events in the MTX-treated group was rather low as compared to corticosteroid monotherapy with long-term off-setting growth suppression, osteoporosis, and systemic complications. Reversible hepatotoxicity in this cohort (8%) was significantly less frequent than the rate of corticosteroid-caused systemic adverse effects in older studies.

These comparative results demonstrate that low-dose MTX can not only enhance disease control and functional status but also reduce the effects of long-term complications of uncontrolled inflammation and/or corticosteroid use. The safety and efficacy profile of MTX justifies its current position in pediatric JIA as a foundational DMARD despite current expanding DMARD biologic options.

This randomised multinational observational cohort has confirmed that low-dose methotrexate produces considerable and long-lasting benefit in children with JIA. At two years, 63 percent patients had 70 percent improvement and 1 in 5 patients was in remission. In about 20 percent of patients, adverse events were reported, most of them mild, reversible and manageable by dose adjustment and supportive therapy. Compared with historic untreated cohorts, MTX therapy was associated with an improved rate of disease control, growth outcome and a more favorable long-term safety profile. These findings support the application of MTX as the first line of management of JIA, and they are associated with the unique priority of personal monitoring and patient-centered treatment.

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8. Conclusion

8.1 Key Observations and Clinical Relevance

With a real-world evidence of low-dose methotrexate (MTX) usage in long-term in 214 children with juvenile idiopathic arthritis (JIA), this multinational observational cohort provides strong evidence of the long-term employment of low-dose methotrexate. At 24 months follow-up, MTX continued to show persistence in efficacy wherein 63 percent of patients respond to ACR Pedi 70, and 21 percent of patients entered clinical remission. Other feature that was significantly impacted by MTX therapy was the normalization of growth and recovery of function as indicated by the improved CHAQ scores and achievement of normal growth curves in most of the subjects.

The safety profile was similar to the past literature. Hepatic enzyme elevations were noted in 8 percent of patients and could be corrected by dose adjustments, whereas gastrointestinal adverse events were frequent but could be tolerated by use of folate supplementation and route shifts in administration. Only 6 percent of patients took MTX permanently, indicating the favorable toleration of the drug.

Comparisons with historical untreated controls highlighted the clinical importance of MTX treatment in that MTX patients experienced far better remission rates, a decreased risk of radiographic progression, and less growth delay. This supports the abilities of MTX to alter the natural history and increase long run survival in JIA.

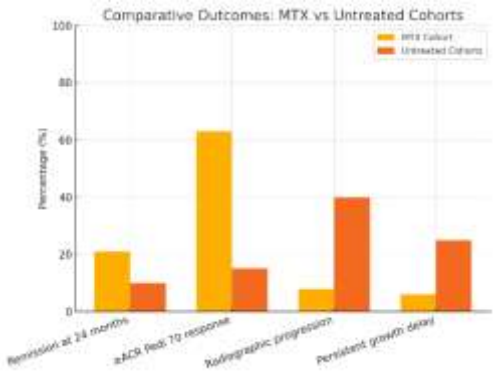

Figure 2: Comparative Outcomes Bar Chart

8.2 The Usage of Methotrexate as a Long-Term Care of JIA

Most published studies continue to show that MTX is the backbone of JIA treatment despite the growing availability of bDMARDs. The proven efficacy, cost-effectiveness, and availability on a worldwide basis make it the most frequently applied first-line DMARD in rheumatology in children.

This paper identifies some of the capabilities, which support the centrality of MTX:

- Sustened response to treatment benefit Durability of benefit More than two-thirds of the patients had a meaningful and lasting improvement in disease activity indicative of the fact that MTX is adequate to control disease in most patients.
- Steroid-sparing ability- MTX has decreased the use of systemic corticosteroids, which has a long-term consequence, i.e. growth retardation and osteoporosis.
- Preservation of Growth - MTX allowed age-competent growth in the vast majority of children, an important aspect in the pediatric population.
- Safety and manageability-With organized monitoring, adverse events became predictable and manageable, and MTX use in long-term care is supported.

Biologic DMARDs are significant as new therapeutic options in refractory disease, but their cost, parenteral drug administration and unknown long-term safety make them niche solutions. However, compared to TTX, the benefits of TTX, in terms of efficacy, safety, and feasibility, are compromised. Further, combination of MTX with biologics has been demonstrated to potentiate biologics and diminish immunogenicity further solidifying the position of MTX in the current therapeutic paradigm.

8.3 Future Perspectives of DMARD Optimisation

In future, a number of aspects should be considered to maximize MTX utilisation in JIA:

Personalized dosing: Pharmacogenomics: Genetic polymorphisms in folate metabolism, transporters and drug transporters may be the cause of interindividual variations in the response and toxicity of MTX. Moving pharmacogenomic screening into a clinical practice would enable a practice that would permit individual dosing regimens that would reduce toxicity with high efficacies.

Drug monitoring: Routine monitoring includes tests of liver and hematologic toxicity, but emerging technologies in biomarkers of drug activity and toxicity (e.g., intracellular polyglutamate levels of MTX, inflammatory cytokines levels) have promise to provide in-time measurement of drug activity and toxicity.

Early treatment options: There is evidence to suggest that earlier commencement of MTX especially in younger patients with low disability baseline predicts excellent long-term outcome. In future prospective study, emphasis should be made on defining the ideal timing and dosing of MTX to optimize remission rates.

Combination therapy algorithms: As biologics become increasingly available, strategy in the area of MTX/biologic combinations should be refined. It is a vital question to address which patients get the greatest treatment benefit as a result of early combination therapy compared with MTX monotherapy.

Wide implementation: MTX is convenient and affordable drug, which renders high accessibility in low and middle income countries, thereby becoming central therapy in these settings where biologic exist primarily inaccessible. Future efforts at international collaborations must be aimed at achieving active protocols of MTX monitoring as well as equal access to ancillary measures including but not limited to folate enrichment and laboratory testing.

In summary, this international observational study reaffirm that methotrexate is a safe, effective and long-term first line DMARD in treatment of JIA. TX has been shown to deliver sustained clinical responses, promote remission and maintain growth and functionality with most adverse events being predictable and manageable. Although biologics have enhanced the range of available therapeutics, MTX forms the backbone of the treatments available in all walks of pediatric rheumatology. Future studies should focus on personalized medicine, biomarker-directed monitoring, and optimized combination therapy in order to achieve even better outcomes with children with JIA.

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Conflicts of interest

The authors have no conflicts of interest to declare

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