Real-life practice of methotrexate toxicity monitoring in juvenile idiopathic arthritis in Germany, Switzerland and Austria: results of a cross-sectional assessment conducted in 2012

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Abstract

Objective

Methotrexate (MTX) is used at low doses to treat rheumatologic disorders in the paediatric age group. Toxicity is observed despite the low doses used. Even though recommendations for monitoring of early signs of toxicity exist in many countries, real-life practice may vary. We therefore assessed current practice in Germany, Switzerland and Austria.

Methods

A 22-item questionnaire regarding practices of monitoring MTX therapy was sent by email to all members of the Society for Paediatric and Adolescent Rheumatology (GKJR, n=224). Responses were compared to evidence-based recommendations.

Results

72 of 209 physicians with valid e-mail addresses returned a completed questionnaire (response rate, 34%). Of these, 8 (11%), 18 (25%), 25 (34%) and 21 (29%) reported that they had been treating paediatric patients with rheumatologic disorders for <5 years, 5-10 years, 10-20 years, and >20 years, respectively. Of the tests recommended for routine monitoring, haemogram and liver transaminases were used by all respondents, followed by serum creatinine (97%) and urinalysis (88%). Of the tests not recommended for this purpose, abdominal ultrasound (including liver and kidney), echocardiography, and pulmonary function tests were reported by 51%, 36%, and 51%, respectively, and all three modalities by 28%. The latter was positively associated with a longer duration of practicing paediatric rheumatology but not with the number of patients seen annually.

Conclusion

Real-life practice of MTX toxicity monitoring in the studied population deviated from evidence-based recommendations in the direction of overusing equipment-based testing, which apparently was more pronounced among more senior practitioners.

Key words

methotrexate, juvenile idiopathic arthritis, cross-sectional study, questionnaire, toxicity, Germany

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Introduction

Methotrexate (MTX) is used at low doses to treat juvenile idiopathic arthritis and other rheumatologic disorders. Despite the relatively low doses used, toxicity, mostly affecting the liver, may be observed (1-4). For instance, a systematic review involving 47 studies identified that the pooled cumulative incidence of elevated liver enzymes was about 31% in the first 3 years of MTX treatment in adult patients with rheumatoid and psoriatic arthritis (5). Valentino *et al*. conducted a meta-analysis of hepatotoxicity caused by MTX and found that around 10% of paediatric patients with inflammatory bowel disease (a pooled estimate across 12 studies) treated with MTX developed varying degrees of abnormal liver biochemistry (6). MTX toxicity, mostly manifesting as abnormal liver values, has also been observed in paediatric patients with rheumatologic disorders under MTX therapy (7, 8). Even pulmonary hypersensitivity to MTX, a typical adverse effect in adults, has been reported in paediatric patients, albeit very rarely (9, 10). MTX therapy may also be associated with an increased risk of bloodstream infections in paediatric patients (11).

MTX toxicity can presumably be minimised by dose reduction or cessation of therapy according to results from monitoring end-organ function. Checking liver and kidney function through blood chemistry and urinalysis is usually recommended, and specific evidence-based schedules are recommended by paediatric rheumatology professional associations in many countries (12-15). For instance, the American College of Rheumatology recommends repeated measurements of serum creatinine, complete blood cell count and liver enzymes prior to initiation of MTX therapy, 1 month later, then every 3-4 months, and then 1 to 2 months after any increase of MTX dose (12). In German-speaking countries, the Working Group "Paediatric Rheumatology Germany and Paediatric Rheumatology Austria" issued evidence-based guidelines for the treatment of JIA, but these did not address MTX toxicity monitoring (16). Indeed, national guidelines for MTX toxicity monitoring do not exist in the German speaking countries of Europe to this day, and it appears that practitioners who wish to follow guidelines obtain them from other countries or from the evidence-based literature. Two systematic reviews on MTX therapy and toxicity monitoring were published in 2005 and 2006 in English language journals by German paediatric rheumatologists (15, 17). It was recommended to use differential blood counts, liver function tests, renal function tests, and urinalysis for routine monitoring of MTX therapy, but equipment-based tests such as pulmonary function tests, liver or kidney sonography, or echocardiography only in exceptional circumstances, such as to evaluate abnormal laboratory results suggestive of MTX toxicity (15, 17). However, these two publications did not constitute official guidelines issued by a professional medical association. In the absence of such guidelines, it thus appeared likely that real-life practice by treating physicians in the German-speaking countries of Europe may differ from international guidelines or the evidence-based literature. Indeed, a survey in the UK among centres treating paediatric and adolescent patients with rheumatologic disorders revealed significant variation in use of laboratory tests for MTX toxicity monitoring, even though most respondents reported that they followed national or local guidelines (18). We thus performed a cross-sectional, questionnaire-based study among the members of the Society for Paediatric and Adolescent Rheumatology (*Gesellschaft für Kinder- und Jugendrheumatologie, GKJR*), which is headquartered in Berlin, Germany, but draws members (physicians who treat paediatric and adolescent patients with rheumatologic disorders) from Germany, Austria, and Switzerland. We found that self-reported practice varied greatly and deviated from the evidence-based literature in the direction of over-using equipment-based testing.

Materials and methods

Study design and questionnaire

This was a cross-sectional, questionnaire-based study involving all members of the GKJR (n=224). The ques-

tionnaires were sent out in May 2012 to all members of whom email addresses were available, requesting to return the completed questionnaire by email or (in printed form) by land mail or fax within 14 days. A first reminder was sent after 2 weeks and a second reminder after 3 months (August 2012). The self-administered 22-item questionnaire was designed in electronic form using Adobe LiveCycle Designer, v. 7.0. It was designed to capture the following information: years of experience in treating paediatric patients with rheumatologic disorders, number of patients with paediatric rheumatologic disorders treated in the past 12 months, guidelines for treatment with MTX used, use of folic acid, current use of any of the following tests (pulmonary function tests, abdominal sonography, hepatic sonography, renal sonography, echocardiography, complete blood count, serum liver transaminases, serum creatinine, urinalysis), and previous use of these tests (but subsequently discontinued). Free text could be entered for guidelines followed for treatment with MTX. Finally, we asked whether the study participants were willing to be contacted in case of any questions or whether they wished to have their contact information deleted. An English translation of the questionnaire is available online.

Statistical analysis

First, the data were analysed descriptively; frequencies were calculated for categorical variables. Percentages were rounded up or down to two significant figures. The Venn diagrams were made with the R Foundation for Statistical Computing (v. 3.0.2), package "VennDiagram". We used logistic regression analysis to test whether there was an association between equipment-based testing and duration of treatment of paediatric patients with rheumatologic disorders or the number of such patients treated in the last 12 months. "Multi-testing" was defined as using all equipment-based tests for routine monitoring that were not recommended for this purpose, *i.e.* pulmonary function tests, abdominal sonography and echocardiography. We estimated crude and adjusted odds ratios (OR) and the corresponding 95% confidence intervals (CI). Data were analysed with IBM SPSS Statistics for Windows, v. 19.

Ethics approval

The study was approved by the Ethics Committee of the Medical Faculty "Carl Gustav Carus" of the Technical University Dresden, in Dresden, Germany.

Table I. Selected characteristics of the participants.

Questionnaire item	Number	Percent
How long have you been treating paediatric patients with rheumatologic disorders?		
Less than 5 years	8	11
5-10 years	18	25
10-20 years	25	35
More than 20 years	21	29
How many patients did you treat in the last 12 months?		
Less than 10 patients	10	14
10-24 patients	11	15
25-49 patients	17	24
50-100 patients	16	22
More than 100 patients	16	22
Missing values	2	2.8
Following GKJR S2 guidelines for MTX therapy of JIA		
No	13	18
Yes	57	79
Missing values	2	2.8
Use of folic acid under MTX therapy		
Yes, always	32	44
No, only by gastrointestinal complaints, abnormal haematological values, or abnormal liver function tests	40	56

Results

The questionnaires were sent out in May 2012 and the last completed questionnaire was received in early September 2012. Out of the 224 emails sent, 12 messages could not be delivered because of incorrect email addresses or other technical problems. Three physicians reported that they had left the field of paediatric rheumatology. Of the remaining 209 individuals contacted, 72 returned a completed questionnaire, corresponding to a response rate of 34%. Of these, 58 (80%) returned the questionnaire by email, 9 (13%) by fax, and 5 (7%) by regular mail. All items were completed in 67 questionnaires, one item was not completed in 4 questionnaires, and 2 items were not completed in one questionnaire.

The most frequent range of duration of experience with treating paediatric rheumatologic disorders was 10-20 years (Table I). Nearly one-quarter of physicians reported to have treated 25–49 paediatric patients with rheumatologic disorders in the last 12 months (Table I). Eighteen percent of the respondents (13/72) stated that they did not follow any guidelines, whereas 79% (57/72) stated that they followed GKJR guidelines for MTX therapy of JIA (17). However, these guidelines do not address toxicity monitoring. Three percent (2/72) did not answer this item. Forty-four percent (32/72) stated that they used folate supplements in all patients on MTX therapy, whereas 56% (40/72) used it only in the presence of potentially MTX-associated complaints or laboratory abnormalities, and this with the following frequencies: gastrointestinal complaints, 93% (37/40); abnormal liver function tests, 75% (30/40); abnormal haematological values, 59% (24/40) (multiple choices were possible). Fig. 1 shows the reported use of various tests to monitor organ-directed toxicity. Of the tests recommended in the evidence-based literature, all respondents reported using complete blood counts and liver function tests, 97% serum creatinine, and 88% urinalysis. Of note, even the tests not recommended by the evidence-based literature for routine monitoring were reported relatively frequently: pulmonary function tests and abdominal sonography by about half of the respondents, and liver or kidney sonography

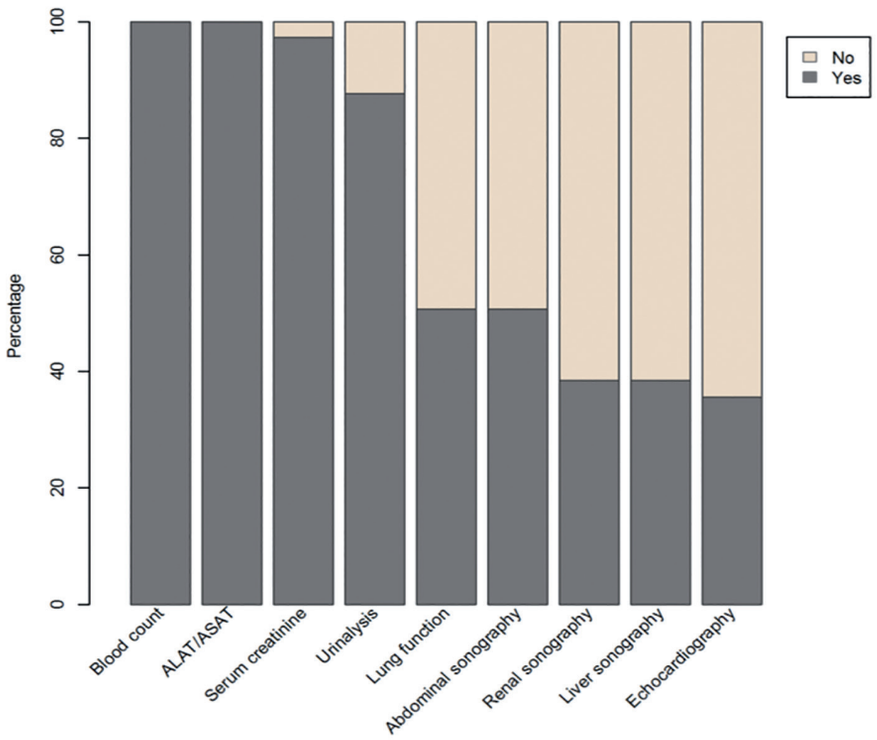

Fig. 1. Reported use of various tests to monitor MTX toxicity.

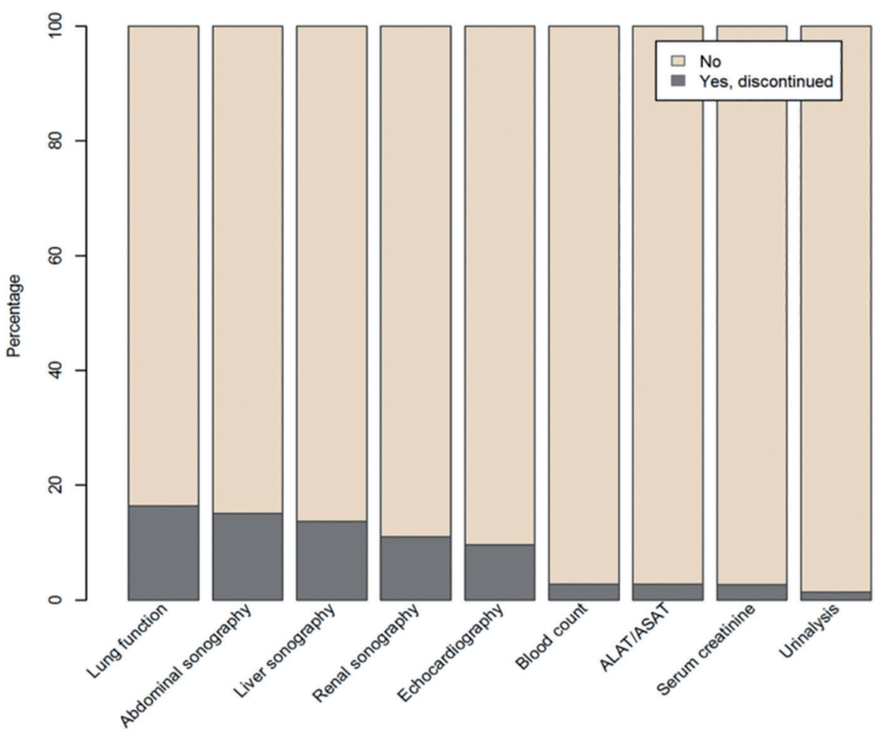

Fig. 2. Reported discontinuation of various tests to monitor MTX toxicity.

by roughly one third. Fig. 2 shows the reportedly discontinued tests to monitor organ-directed toxicity. About 10–20% of the respondents reported to have discontinued any of the sonographic tests or pulmonary function tests. There was an apparent contradiction between the reported discontinuation of complete blood count and serum transaminases, as all respondents reported using them. However, this was a problem in only two returned questionnaires (3%).

We then aimed to find out whether the use of not recommended, equipment-based testing was a feature of a discernable subgroup of respondents. The Venn diagram in Fig. 3A illustrates that use of pulmonary function tests and the sonographic tests clustered (centre of the Venn diagram); around 28% (20/72) reported using all three forms of examination and another 22% (16/72) reported using two of the three tests to monitor MTX toxicity. In contrast, the discontinuation of these tests was relatively evenly spread across the respondents (Fig. 3B).

We then proceeded to look for factors positively associated with this "multi-testing", *i.e.* using all three major forms of equipment-based testing (pulmonary function tests, abdominal sonography, and echocardiography). The number of years treating paediatric patients with rheumatologic disorders was significantly associated with multi-testing: its likelihood was higher among physicians who reported longer durations (>20 years) of practicing paediatric rheumatology (Table II). In contrast, there was no significant association with the number of paediatric patients with rheumatologic disorders treated in the preceding 12 months, *i.e.* practice volume.

Discussion

We performed a survey on recent practice of MTX toxicity monitoring among physicians practicing paediatric and adolescent rheumatology in Germany, Austria and Switzerland and find that common practice deviated from international recommendations and the evidence-based literature in the direction of using equipment-based tests, none of which are recommended for routine MTX toxicity monitoring by guidelines from other countries or the evidence-based literature. A discussion of the use of pulmonary function testing in the retrospective study by Leiskau *et al.* (19) constitutes a possible exception in that a slight decline in some lung parameters was detected after about 3 years of MTX treatment. However, the significance of these findings is uncertain, as they did not correlate with cumulative MTX dose and were not clinically significant. Con-

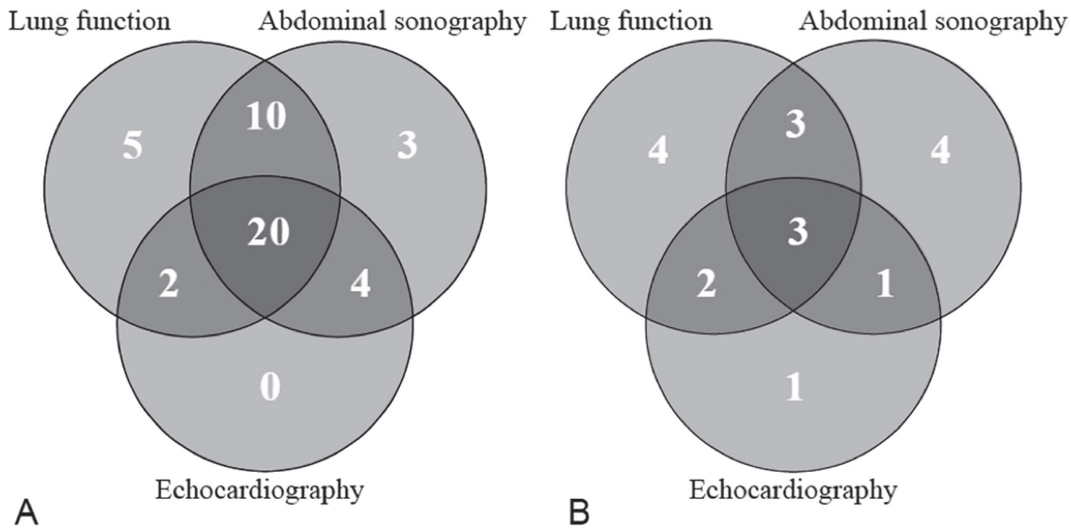

Fig. 3. Venn diagrams of using (**A**) and discontinuing (**B**) pulmonary function tests, abdominal sonography and echocardiography. "Multi-testing" is defined as the use of all three modalities (centres of the diagrams). The values in the circles indicate the number of physicians who use (**A**) or discontinue (**B**) pulmonary function tests, abdominal sonography and echocardiography.

sequently, these authors did not conclude that pulmonary function should be monitored routinely in paediatric patients under MTX treatment in the rheumatologic dose range. One reason for the observed great variability of MTX monitoring practices among the respondents in our study may be that, even though there are national guidelines for treatment of JIA in general and with MTX specifically, there have been no national guidelines regarding MTX toxicity monitoring in these countries. More senior practitioners had a greater predilection for using equipment-based tests. Possible explanations for this frequent use of equipment-based testing may be that physicians with long-term experience in a clinical field are more likely to follow their personal judgment than the evidence-based literature and that they may be less likely to follow recent literature. What may be the implications of the reported frequent equipment-based testing? Firstly, the cost due to tests that are not recommended may be substantial. Obviously, this would differ depending on reimbursement schemes in the respective health care delivery systems. Secondly, the burden on patients (and their families/guardians) should not be underestimated. Even though these equipment-based tests are non-invasive, substantial time needs to be spent away from school (patients) or work/household (guardians) to complete the testing. Moreover, even though we could not investigate this aspect in the present study, it appears plausible that unnecessary tests may lead to further tests due to false positive or clinically irrelevant abnormal findings. Taken together, our findings suggest that in the three countries studied, education regarding MTX toxicity monitoring should be directed at established practitioners as well as trainees, and should aim at implementing a stream-lined, evidence based approach that would reduce cost to the health care delivery system and the burden of undergoing testing to the patients. Considering that medical decision-making according to the evidence-based literature is gaining increasing acceptance in many countries, it now is important to study whether real-life practice of MTX toxicity monitoring in the three countries studied has been changing over time. Indeed, we are currently preparing for a 5-year follow-up assessment in the same study population to be conducted in 2017.

Table II. Association between duration of treating paediatric patients with rheumatologic disorders, number of paediatric patients treated in the last 12 months and "multi-testing"*.

Questionnaire item	Crude odds ratio (95% confidence intervals)	Adjusted odds ratio** (95% confidence intervals)
How long have you been treating paediatric patients with rheumatologic disorders?		
Less than 5 years	0.26 (0.04-1.56)	0.26 (0.04-1.72)
5-10 years	0.11 (0.02-0.62)	0.05 (0.01-0.43)
10-20 years	0.23 (0.06-0.83)	0.18 (0.04-0.82)
More than 20 years	reference	reference
How many patients did you treat in the last 12 months?		
Less than 10 patients	2.48 (0.43-14.34)	2.49 (0.36-17.42)
10-24 patients	2.48 (0.43-14.34)	8.29 (0.95-72.04)
25-49 patients	0.58 (0.08-4.01)	0.83 (0.11-6.53)
50-100 patients	3.37 (0.68-16.65)	4.18 (0.73-24.08)
More than 100 patients	reference	reference

*"Multi-testing" was defined as using pulmonary function testing, abdominal sonography and cardiac echo for routine MTX toxicity monitoring (see Venn diagram in Fig. 3).
**Adjusted for all variables in the table.

Limitations of the study.

This study is limited by the response rate of 34%, which, even though it is comparable to similar surveys among health care practitioners (20-22), does not allow us to infer much about MTX toxicity monitoring practices of the other 66% of the study population (non-re-

sponders). A non-responder survey was deemed not feasible as it would have to be conducted by the same (email) or similar (land mail or fax) means of communication as the primary survey. However, there is no apparent reason to suspect that the non-responders would differ substantially from the responders in terms of MTX toxicity monitoring.

Conclusions

Real-life practice of MTX toxicity monitoring in the studied population deviated from commonly accepted recommendations in the direction of equipment-based testing. Education of trainees and established practitioners, for instance through establishing national guidelines and offering continuing medical education (CME) or conference sessions, should be directed at implementing a stream-lined, evidence based approach that would reduce cost to the health care delivery system and the burden to patients due to unnecessary testing.

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