Evidence-based recommendations for treatment with methotrexate in rheumatic disorders

Specialist agreement in Denmark with Danish and multinational results from the 3E initiative in rheumatology

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ABSTRACT

INTRODUCTION: The aim of this study was to develop 3E (Evidence, Expertise, Exchange) recommendations (RCs) on the use of methotrexate in rheumatic disorders and to assess the agreement among Danish rheumatologists.

MATERIAL AND METHODS: Based on a systematic literature review and Delphi votes, national and multinational (MN) RCs were developed by 751 rheumatologists from 17 countries including Denmark, and the degree of agreement among the participants was assessed. Subsequently, a survey regarding the agreement on the MN RCs was sent to all Danish rheumatologists.

RESULTS: A total of 24 Danish RCs were elaborated by 43 rheumatologists at a national meeting. 71-100% (median 94%) of the participants agreed with each of the RCs. A total of 73 rheumatologists answered the survey on the ten MN RCs. On numerical rating scales with values ranging from zero to ten, the median agreement score for each of these RCs ranged from eight to ten. The RCs were already applied in daily practice by 70-100% (median 91%) of the specialists. Any direct conflict between the national and MN RCs was not evident.

CONCLUSION: Based on evidence and expert opinion in a MN approach, national and MN RCs on methotrexate therapy were developed and a high level of agreement among Danish rheumatologists was evidenced.

Appropriately designed and conducted research is necessary to improve patient care and optimize health outcomes, but access to best evidence is not enough to ensure optimal treatment as busy clinicians often do not have the time or resources to review all relevant publications [1]. The 3E (Evidence, Experts, Exchange) Initiative in Rheumatology is a multinational (MN) effort of rheumatologists aiming to improve the routine clinical practice for patients with rheumatic diseases by formulating evidence-based recommendations (RCs) for practical problems [2-8]. In contrast to guidelines developed by a limited panel of experts, the 3E initiative involves a large number of experts including practising rheumatologists and it addresses specific questions relevant to clinical practice.

The aim of the 2007-2008 3E Initiative was to develop practical RCs for the use of methotrexate (MTX) in rheumatic disorders, by integrating systematically generated evidence and expert opinion from a broad panel of international specialists in rheumatology [9]. MTX is the anchor disease-modifying antirheumatic drug (DMARD) in the treatment of rheumatoid arthritis (RA) and it is also used in other systemic rheumatic disorders [10]. Despite widespread use for more than two decades, considerable controversy exists regarding dosage, safety monitoring, treatment termination, folic acid supplementation and use in the perioperative period and during pregnancy [11, 12].

The present study was performed as part of the 3E process and aimed to develop Danish 3E RCs for the use of MTX in rheumatic diseases and to examine the degree to which Danish rheumatologists agreed with the national and MN 3E RCs.

MATERIAL AND METHODS

A total of 751 rheumatologists from 17 countries including Denmark participated in the process (**Figure 1**). Each country was represented by a scientific committee consisting of 5 to 16 members. Six international research fellows were selected to perform the literature review. They were guided by three mentors. During the first international meeting (n = 87 participants), ten clinically relevant questions on the use of MTX in rheumatic disorders were formulated and selected by a Delphi vote (**Table 1**). Each country was allowed to formulate a supplementary national question. In cooperation with experienced librarians, the research team then performed a systematic literature review. For each question, relevant data were extracted and appropriate statistics were calculated [13, 14].

In the second round, the evidence from the literature search was presented and discussed during national meetings (total n = 751 participants) and a set of RCs

ORIGINAL ARTICLE

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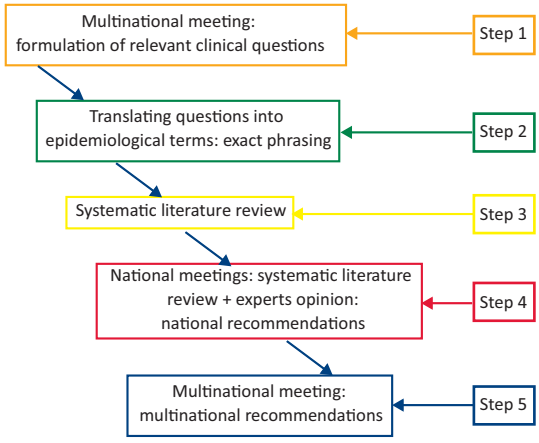
Dan Med Bul 2010;57(10):A4190

FIGURE 1

The 3E process.



addressing the predefined clinical questions was defined. In Denmark, the meeting took place in Copenhagen on January 11th and 12th, 2008. All Danish rheumatologists (n = 204) were invited to participate. After discussions in break-out groups and in plenum, a Delphi vote session took place and the final RCs were defined. The degree of agreement with the RCs was assessed in a last vote (fully disagree, disagree, neither agree nor disagree, agree, fully agree). The compiled agreement and disagreement was taken and stored as the sum in percentage of ''agree'' and ''fully agree'' and the sum of ''fully disagree'' and ''disagree'', respectively. Furthermore, the participants were asked a number of questions regarding their experience with the meeting using the above-mentioned statements. After the meeting, the strength of each RC was graded by the scientific committee according to the Oxford Levels of Evidence [15].

In a third joint meeting 7-8 March 2008, the scientific committees from all involved countries (n = 94 participants) merged all propositions to a final set of ten MN RCs by discussion and Delphi vote [9]. In February 2009, the MN RCs and a survey concerning agreement with these RCs were sent to all rheumatologists in Denmark (202 rheumatologists identified this time). For each of the ten RCs, the following questions were asked:

1. Do you conceptually agree with this RC? Opinion indicated on a numerical rating scale ranging from zero (I fully disagree) to ten (I fully agree).
2. Where you already applying this RC in your daily practice? Yes or no.
   If yes, how often: Always, sometimes or rarely?
   If no, will your change your practice, based on this RC? Yes or no.
   If no, please indicate the barrier for implementing this RC (multiple answers possible): Not enough evidence, too expensive or too time-consuming.

TABLE 1

International questions and a supplementary Danish question.

International questions	
1.	What is the best dosing strategy for MTX in patients with RA to optimize rapid early clinical and radiographic response and minimize toxicity including: route of administration, rate of dose escalation, starting and maximal doses, dose tapering?
2.	What are the indications for pausing/stopping and reinstitution of MTX therapy in case of elevated liver tests, and when is liver biopsy indicated?
3.	What is the long-term safety of MTX: cardiovascular disease, malignancies, liver disease, infections?
4.	What is the optimal management of usual dose MTX in RA patients in the perioperative period to minimize perioperative morbidity and while maintaining RA control?
5.	How should MTX use be managed when planning pregnancy (male and female patients), during pregnancy and after pregnancy?
6.	Is folic/folinic acid supplementation to MTX useful in reducing toxicity for adult patients with RA? What is the most effective regimen?
7.	Is MTX effective as a glucocorticoid-sparing (adjuvant) treatment in chronic inflammatory rheumatic disorders, such as PMR, SLE, vasculitis, dermatomyositis?
8.	What is the difference between MTX combination therapy vs. monotherapy in terms of efficacy and toxicity in rheumatoid arthritis?
9.	What is the optimal (clinical, laboratory, imaging) safety monitoring of patients with MTX? Which interval of time?
10.	What preadministration work-up is necessary (comorbidities/social behaviour, physical, laboratory and radiographic data) to identify MTX exclusions and/or get a baseline "value"?
National question	
Is it possible to predict MTX efficacy/side effects from pharmacogenetic analyses?	

MTX = methotrexate; PMR = polymyalgia rheumatica; RA = rheumatoid arthritis; SLE = systemic lupus erythemathosis.

STATISTICS

The tests were computed with the software package SPSS/PC+ Statistics V4.01. Data are given as medians, ranges and 50% central ranges. The Mann-Whitney U test was used to compare results from participants with and without experience with 3E meetings. A two-tailed value of $p < 0.05$ was considered statistically significant.

RESULTS

Forty-three rheumatologists (21%) volunteered to participate in the Danish national meeting. The male/female ratio was 22/21. 47% were 40-50 years of age, 53% more than 50 years of age. The main clinical activities took place at: hospital (n = 32), private office (n = 9) or both (n = 2). 95% percent of the rheumatologists were seeing more than ten MTX-treated patients per month.

A total of 24 Danish RCs were formulated. They were distributed on 11 categories addressing the predefined clinical questions including the national question. The national RCs are listed in **Table 2** with the corresponding level of evidence and agreement. The number of voters for each RC ranged from 36-43 (median 40). The first national RC proposes that MTX should initially be given orally. It is seen from Table 2 that the category

TABLE 2

National recommendations for the use of methotrexate in rheumatic diseases.

Recommendation	Category of evidence	Strength of recommendation	Agreement with recommendation agree/neutral[a]/disagree, %
Treatment with MTX should initially be given orally	III	C	95/3/2
If the treatment response is insufficient or if gastrointestinal side-effects occur, switching to subcutaneous or intramuscular treatment may be beneficial	III	C	100/0/0
In case of remission, the dose of MTX can be reduced following a careful evaluation of the individual patient	III	C	98/2/0
The treatment should be temporarily withdrawn or the dose should be reduced if AST/ALT is elevated more than 3 times the ULN and/or is permanently elevated more than twice the ULN	III	C	100/0/0
Dosage should be re-evaluated when AST/ALT has decreased to less than twice the ULN	III	C	88/9/3
If AST/ALT is not normalized after 3 months, the use of liver biopsy should be discussed with a gastroenterologist	III	C	88/7/5
As a rule, the initial dose of MTX should be 10-15 mg/week	III	C	98/0/2
As a rule, the MTX dose should be increased by 2.5-5 mg every week to the maximal tolerated dose, as a rule no more than 30 mg/week	III	C	86/7/7
MTX treatment in itself does not require that patients are monitored for developing infections, cardiovascular disease, malignant lymphoma or cancer	III	C	100/0/0
In case of a severe infection, treatment should be temporarily withdrawn. Development of cancer or a history of previous cancer does not in itself contraindicate treatment with MTX	III	C	100/0/0
Treatment with MTX should be preferred before other DMARDs due to a favourable effect vs. side-effect profile	III	C	98/2/0
MTX treatment should be kept unchanged in the perioperative period	Ib	B	90/5/5
Male and female patients on MTX treatment should be recommended to stop the treatment 3-4 months before planned conception (pregnancy). Female patients should be recommended not to restart the treatment until the lactation is terminated	III	C/D	88/2/10
When a pregnancy occurs during MTX treatment the treatment should as a rule be terminated. The patient should be informed about the risk of congenital malformations and be referred to an obstetrician	IV	D	92/5/3
Folic acid in doses of minimum 5 mg per week should be used in addition to MTX treatment to reduce gastrointestinal toxicity in adults with rheumatoid arthritis. Folic acid dose can be increased in case of side-effects without reducing the MTX efficacy. It is not needed to skip folic acid on the day of MTX treatment	Ib	B	71/7/22
In GCA, MTX treatment should be started simultaneously with prednisolone in order to reduce prednisolone dose and the risk of relapse	Ia	A	98/2/0
In PMR, MTX can be initiated simultaneously with prednisolone in order to reduce prednisolone dose and the risk of relapse	Ib	A	90/0/10
In case of symptoms from joints or skin in patients with SLE, MTX can be used to reduce symptoms and prednisolone dose	Ib	A	93/2/5
No recommendations for other diseases than GCA, PMR and SLE	IV	D	90/8/3
MTX as monotherapy is recommended in DMARD naive patients but in selected cases MTX can be started in combination with other DMARDs. With persistent activity with MTX as monotherapy after 3-4 months MTX can be given in combination therapy	Ib	A	95/5/5
Starting MTX therapy or increasing MTX dose one should measure haematology (haemoglobin, white blood cells with differential cell count and platelets), ALT and creatinine after 2-4 weeks and hereafter every 6-12 weeks	IV	D	93/0/7
Contraindications for MTX are pregnancy, lactation, severe liver disease and severe impaired hematopoiesis. Relative contraindications are hepatitis B and C, pulmonary- and renal disease and alcohol and drug abuse	IV	D	97/3/0
Preadministration work-up include haematology (haemoglobin, white blood cells with differential cell count and platelets), AST/ALT, alkaline phosphatase, creatinine, albumin and alcohol intake and for high-risk patients hepatitis serology. Chest X-ray less than 1 year old when starting therapy	IV	D	92/5/3
At present, pharmacogenetic analyses have no relevance in daily clinical practice	III	C	100/0/0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; DMARD = disease-modifying antirheumatic drug; GCA = giant-cell arthritis; MTX = methotrexate; PMR = polymyalgia rheumatica; SLE = systemic lupus erythemathosus; ULN = upper limit of normal.

of evidence was III and the strength corresponded to C. 95% agreed with the RC, 3% felt neutral and 2% disagreed. Corresponding data are shown for each individual RC. 71-100% (median 94%) of the rheumatologists agreed with each of the RCs, whereas 0-22% (median 3%) disagreed. At the end of the meeting, 73% agreed or fully agreed that their opinion had been taken into consideration during the break-out sessions, 21% felt neutral, 6% disagreed and none fully disagreed. The corresponding percentages regarding the plenary session were 89, 8, 0 and 3. 97% agreed or fully agreed that the meeting had been educational, 3% were neutral and none disagreed. 94% would like to participate in a similar meeting another time.

Seventy-six rheumatologists participated in the survey on the MN RCs. Three of the returned questionnaires were not usable, leaving 73 for analysis (36% of possible respondents). Thirty-two of the responding rheumatologists (44%) had participated in the national or MN 3E meeting on the MTX RCs. The male/female ratio was 48/25. The main clinical activities of the participants took place at: university hospital (n = 28), general

hospital (n = 24), private office (n = 21). The number of years in practice was reported to be 22 (2-40), the number of rheumatic patients seen per month 130 (0-400), and the number of RA patients seen per month 40 (0-50). The percentage of RA patients treated with MTX was estimated by the rheumatologists to be 80 (0-95).

Table 3 shows the ten MN RCs together with the results of the Danish survey. The list of the national and MN RCs does not strictly follow the same order or the order of the original questions as the priority of listing was not the same at the national and the final MN meeting. The first of the RCs regards work-up for patients starting MTX treatment. The median agreement score was nine (range 2-10, 50% central range 7-10). 70% of the respondents were already applying the RC in daily practice, 82% of these often, 14% sometimes and 4% rarely. Of those who were not already applying the RC, 32% were planning to do so. Corresponding data are shown for each of the MN RCs. The median agreement score for the RCs ranged from 8-10.

Rheumatologists who had participated in the national or in an MN 3E meeting did not differ statistically significantly (or with a trend) from those who had not participated in a meeting. This applied to all RCs. The RCs were already being used in daily clinical practice by 70-100% (median 91%) of the rheumatologists, with the majority of these following the RCs always or sometimes. Of those who had not previously managed their patients according to the RCs, 32-100% (median 55%) planned to change their practice depending on the specific RC. For three rheumatologists, the reason for not changing practice in respect to the first RC was costs. In all other cases, the reason for no change in daily practice was reported to be lack of evidence.

DISCUSSION

RCs for the management of MTX treatment based on a systematic literature research and the opinion of a large group of clinicians have not previously been defined. Little or no evidence was found for some of the topics, including toxicity monitoring, non-orthopaedic surgery

TABLE 3

Results of the survey on Danish rheumatologists' agreement with the multinational recommendations for the use of methotrexate in rheumatic disorders.

Recommendation (and number of responding rheumatologists)	Agreement as assessed on a numerical rating scale,[a] median/(range)/ 50% central range	Already applying recommendation in daily practice?, % yes (n)	If yes, how often? Always/sometimes/ rarely, % (n)	If no, will you change your practice?, % yes (n)
The work-up for patients starting MTX should include clinical assessment for risk factors of MTX toxicity (including alcohol intake), patient education, AST, ALT, albumin, CBC, creatinine, chest X-ray; consider serology for HIV, hepatitis B/C, blood fasting glucose, lipid profile and pregnancy test (73)	9/2-10/7-10	70 (51)	82 (42)/14 (7)/4 (2)	32 (7)
Oral MTX should be started at 10-15 mg/week, with escalation of 5 mg every 2-4 weeks up to 20-30 mg/week, depending on clinical response and tolerability, parenteral administration should be considered in case of inadequate clinical response or intolerance (73)	9/0-10/8-10	86 (63)	65 (41)/35 (22)/0 (0)	33 (3)
Prescription of at least 5 mg folic acid per week with MTX therapy is strongly recommended (71)	10/0-10/10-10	100 (71)	14 (10)/86 (61)/0 (0)	–
When starting MTX or increasing the dose, ALT with or without AST, creatinine, CBC, should be performed every 1-1.5 months until stable dose is reached, and every 1-3 months thereafter; clinical assessment for side effects and risk factors should be performed at each visit (71)	10/1-10/9-10	96 (68)	94 (64)/6 (4) /0 (0)	67 (2)
MTX should be stopped if there is a confirmed increase in ALT/AST > 3 times the ULN, but may be reinstituted at a lower dose following normalization. If the ALT/AST are persistently elevated up to 3 times the ULN, the dose of MTX should be adjusted; diagnostic procedures should be considered in case of persistent elevated ALT/AST > 3 times the ULN after discontinuation (73)	10/0-10/9-10	92 (67)	90 (60)/9 (6)/1 (1)	100 (6)
Based on its acceptable safety profile, MTX is appropriate for long-term use (73)	10/0-10/10-10	100 (73)	88 (64)/3 (2) /9 (7)	–
In DMARD naive patients the balance of the efficacy/toxicity favours MTX monotherapy over combination with other conventional DMARDs, MTX should be considered as the anchor for combination therapy when MTX monotherapy does not achieve disease control (73)	10/1-10/9-10	96 (70)	81 (57)/16 (11)/3 (2)	67 (2)
MTX, as a steroid-sparing agent, is recommended in giant-cell arteritis and PMR and can be considered in patients with SLE or (juvenile) dermatomyositis (73)	8/1-10/7-10	78 (57)	32 (18)/58 (33) /10 (6)	50 (8)
MTX can be safely continued in the peri-operative period in RA patients undergoing elective orthopaedic surgery (72)	10/0-10/8-10	90 (65)	65 (42)/35 (23)/0 (0)	43 (3)
MTX should not be used for at least 3 months prior to planned pregnancy for males and females, and should not be used during pregnancy or breast feeding (73)	10/0-10/10-10	97 (71)	92 (65) /8 (6)/0 (0)	50 (1)

a) Scale of 0-10.

and the effect of MTX on fertility and lactation. The majority of the RCs, however, are supported by evidence from randomised controlled trials and high-quality cohort studies [16-20].

The survey was not designed to clarify the preference of the Danish rheumatologists for the Danish or the MN RCs. Any direct conflict between the two sets of RCs is not evident, but there are some differences. Both sets suggest an initial dose of 10-15 mg MTX/week and a maximum dose of 30 mg. The MN RCs are more conservative in respect to dose escalation. On the other hand, the Danish RCs are more conservative regarding the frequency of blood samples during the initial phase of MTX treatment. The Danish RCs specifically state that there is no need to avoid folic acid on the day MTX is taken. The MN RCs state that MTX treatment can be continued in the perioperative period in patients undergoing orthopaedic surgery, but the Danish RCs have no restrictions regarding surgery. The Danish RCs strictly states that MTX treatment should be started simultaneously with prednisolone in the case of giant-cell arteritis, but MTX is merely recommended in the MN RCs. According to the Danish RCs, MTX treatment in itself does not require monitoring for developing infections, cardiovascular disease, malignant lymphoma or cancer. This issue is not considered at all in the MN RCs. The differences between the two sets of RCs may reflect that they were not only developed on the basis of the literature, but also on »expert opinion«.

The evidence-based approach and broad participation by rheumatologists was aimed to enhance dissemination and implementation into rheumatologic practice. Accordingly, a high degree of agreement with the Danish RCs was obtained at the national meeting. Our survey regarding agreement with the MN RCs is the first of its kind within the framework of the 3E initiative. The survey revealed a high degree of agreement also with these RCs. The fact that the MN RCs were already applied by 70-100% (median 91%) of the respondents depending on the RC reflects that clinicians were involved in formulating the RCs and indicates that the RCs are usable in daily practice in Denmark. It is also noteworthy that 32-100% (55%) of the rheumatologists who had not previously managed their patients according to the RCs planned to change daily practice, depending on the specific RC. Furthermore, the reported main barrier for implementation was not practical issues, but lack of evidence.

A higher number of participants in the national meeting and in the survey would have been preferred, but there is no obvious reason to believe that rheumatologists who did not participate were more likely to agree or disagree with the RCs than those who did participate. At least the votes at the national meeting and the survey showed a positive attitude to the RCs, whereas no other guidelines have previously been systematically evaluated by a larger number of Danish rheumatologists. Half of the rheumatologists who answered the survey had participated in the national or in a MN 3E meeting, but respondents with and without experience with the 3E process did not differ in their ratings.

In conclusion, national and MN RCs for the use of MTX in rheumatic disorders were developed on the basis of a systematic literature review and expert opinion. Involvement of a large and representative group of rheumatologists resulted in a high level of agreement which may facilitate the use of the RCs in daily clinical practice.

! ABBREVIATIONS

ALT = alanine aminotransferase
AST = aspartate aminotransferase
CBC = complete blood count
DMARD = disease-modifying antirheumatic drug
GCA = giant-cell arthritis
HIV = human immunodeficiency virus
MN = multinational
MTX = methotrexate
PMR = polymyalgia rheumatica
RA = rheumatoid arthritis
RC = recommendation
SLE = systemic lupus erythemathosus
ULN = upper limit of normal

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ACCEPTED: 29 July 2010

CONFLICTS OF INTEREST: All authors received a consulting fee from Abbott for participating in the 3E process. Travel/accommodations expenses were also covered. None of the authors received payment or any kind of support for study design, manuscript preparation or statistical analysis. Several of the authors participate in investigator-initiated studies sponsored by Abbott. IJ Sørensen, A Hansen and MS Hansen wish to add that they previously and unrelated to the 3E initiative have received fees and/or coverage of travel/accommodations expenses from one or more of the following companies: Abbott, BMS, Wyeth, Schering-Plough, Roche and UCB.

FUNDING: The 3E process was supported by an unrestricted grant from Abbott International.

ACKNOWLEDGEMENT: We thank all the members of the 3E Initiative as well as all Danish rheumatologists who participated in the national meeting and in the survey.

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