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Title page

Article type: Consensus statement

Title: An international eDelphi study to reach consensus on the methotrexate dosing regimen in psoriasis

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Key Points:

Question Can we gain consensus on the dosing of methotrexate in psoriasis patients?

Findings After a systematic review of the literature, 21 proposals were formulated involving methotrexate dosing in adults, children and vulnerable patients. On 20 of these proposals, consensus was reached in three eDelphi survey rounds and an online consensus meeting.

Meaning This consensus can be implemented in guideline documents and may be used for further optimization of methotrexate treatment in psoriasis patients.

Abstract

Importance

A clear dosing regimen for methotrexate in psoriasis is lacking and this might lead to a suboptimal treatment. Since methotrexate is affordable and globally available, a uniform dosing regimen could optimize the treatment of psoriasis patients around the world.

Objective

Our objective was to reach international consensus among psoriasis experts on a uniform dosing regimen for methotrexate in adult and pediatric psoriasis patients. We also aimed to identify potential future research topics.

Design

Between September 2020 and March 2021, a survey study with a modified eDelphi procedure ran over three rounds. The proposals on which no consensus was reached, were discussed in a conference meeting (June 2021). Participants voted on 21 proposals with a 9-point scale (1-3 disagree, 4-6 nor agree/nor disagree, 7-9 agree).

Setting

This survey study was developed and distributed by the Amsterdam University Medical Center and completed by 180 participants from all over the world of whom 34.5% resided in non-Western countries.

Participants

Participants were recruited through the Skin Inflammation and Psoriasis International Network and European Academy of Dermatology and Venereology in June 2020. Apart from being a dermatologist/dermatology resident, there were no specific criteria for participation in the survey. The participants worked mainly at a university hospital (58.6%) and were experienced in treating psoriasis patients with methotrexate (88.7% had >10 years of experience).

Main outcome(s) and Measure(s)

In a survey with eDelphi procedure we tried to reach consensus on 21 proposals. Consensus was defined as less than 15% voting disagree (1-3). For the consensus meeting, consensus was defined as less than 30% voting disagree.

Results

From all participants, 71.7% (180/251) completed all three survey rounds and 58 participants joined the conference meeting. We achieved consensus on 11 proposals in round 1, on 3 proposals in round 2 and on 2 proposals in round 3. In the consensus meeting, we achieved consensus on 4 items. Especially for the proposals on folic acid and the dosing methotrexate in subpopulations -like children and vulnerable patients- more research is needed.

Conclusion and relevance

We reached consensus on 20 out of 21 proposals involving methotrexate dosing in psoriasis patients. This consensus may be used to harmonize the treatment with MTX in psoriasis patients.

Introduction

Methotrexate (MTX) -a dihydrofolate reductase inhibitor- is one of the four available classical systemic treatments for psoriasis and has been widely prescribed for psoriasis for over 60 years.[1-3] Effectiveness and safety of MTX are acknowledged in psoriasis guidelines from around the world.[4-6] It is also one of the key disease-modifying antirheumatic drugs (DMARDs) in rheumatology.[7]

MTX was approved by the Food and Drug Administration (FDA) before dose ranging studies were performed and therefore a clear dosing regimen is lacking. In the first years of use, Rees et al. reported a daily dosage of 1.5 – 2 mg which should be administered for 3 – 12 days in a row.[8] In 1969, a weekly oral dosage of 25 mg MTX was described by Roenigk et al.[9] Three years later, Weinstein and Frost reported a three weekly divided dose in which 2.5 - 5 mg of the drug was administered every 36 hours.[10]

In current practice, uniformity in the dosing regimen is lacking as well; a global survey study, conducted by Psoriasis International Network (PIN, which is currently named Skin Inflammation and Psoriasis International Network, SPIN[11]), showed that starting doses differ from 5 – 22.5 mg/week.[12] Comparable questionnaire results were reported from Iran,[13] and this issue also arises in guidelines.[14] The variability in treatment regimens might contribute to suboptimal treatment with MTX or can lead to early discontinuation of treatment due to limited efficacy or - in case of over treatment - side effects. Since MTX is available worldwide and the drug is affordable (around $16.17/week for six 2.5 mg tablets[15]), uniformity in the dosing regimen can contribute to global improvement of the treatment of psoriasis patients.

The objective of this electronic Delphi ('eDelphi') study was to reach international consensus on the dosage of MTX in psoriasis patients and to identify existing knowledge gaps. Items included in this eDelphi were test dose, start dose, the increase or decrease of the dose, administration form, maximum dose, administration and the use of folic acid specified for specific populations (adults, children and vulnerable patients). This consensus may help to uniform MTX dosing in clinical practice and it can be used to develop a consensus project in other (off-label) dermatoses, e.g. atopic dermatitis (AD),[16] morphea[17] and alopecia areata.[18]

Materials and methods

The eDelphi consisted of three sequential survey rounds, held in September 2020, November 2020 and February 2021. After the last survey round, an online consensus meeting was organized in June 2021. For the reporting of these results, the SQUIRE 2.0 guidelines[19] were followed.

Working group

To determine for which items consensus was required, an international working group (AH, SM, RG, LI, RW, MH, PS) was formed. Members were selected on their experience with MTX and psoriasis research. This working group identified 7 items related to dosage of MTX (test dose, start dose, the increase or decrease of the dose, administration form, maximum dose, administration and the use of folic acid). They decided to study these items in three different populations; adults, children and 'frail patients' like elderly or patients with impaired kidney function (frail patients was later changed to 'vulnerable patients'). Hereafter, a literature search using the same search terms as the systematic review from 2016 from Menting et al.[14] was performed. With this literature review, clinical expertise and outcomes of the PIN survey[12], the working group formulated 21 proposals regarding the 7 items. These proposals were used for the first eDelphi round.

Recruitment of the participants

All SPIN members (professionals on chronic inflammatory skin diseases, n=4500) from around the world were invited to participate.[11] We sent an additional e-mail to the national representatives (n=108) and scientific committee (n=35) of SPIN, asking them to recruit at least 10 psoriasis experts in their country. The European Academy of Dermatology and Venereology (EADV) promoted the eDelphi through social media (Twitter). We also asked our working group to share the eDelphi in their network. Only dermatologists, dermatology residents and researchers (participating in psoriasis research or guideline development) were allowed to participate. The sample size was not predefined, but we set the minimum on 100 participants as a representative number of psoriasis experts.

eDelphi rounds 1-3

The software chosen for this eDelphi was 'LimeSurvey'. This questionnaire software fulfills all privacy requirements from the Amsterdam University Medical Centers from which this eDelphi was send to the participants.[20] It was pretested by an independent data manager and two authors (AH and PS). The eDelphi ran over three rounds, taking approximately 3 months each. In every round, all participants received an e-mail with a link to the survey and their personal token. In the survey, they voted on a proposal using a 9-point scale where 1-3 is disagree, 4-6 nor agree/nor disagree and 7-9 agree. Below every proposal, relevant references could be found.

In the first round of the eDelphi, alternative proposals for consensus could be added by the participants, preferably supported by evidence. The proposals where no consensus was met, were slightly adjusted by the working group according to the most frequently send alternative proposals.

In the second round, participants were able to vote on the remaining proposals. They could also view the distribution of the scores per proposal together with the alternative proposals.

In the third round, participants that disagreed with the proposal could vote on the different alternatives collected in the first round.

All eDelphi questions were mandatory and participants were encouraged to choose 4-6 (nor agree/nor disagree) as little as possible. Weekly reminder e-mails were sent to increase the response rate.

Consensus meeting

To resolve potentially remaining disagreements and adjust the final proposals for which no consensus was reached, we organized an online consensus meeting. The consensus meeting was held on June 17th, 2021 through the videoconference setting of ZOOM.[21] Participants were asked to register themselves before this meeting. Due to their different time zones, it was not possible to make this meeting mandatory for everyone. Participants that could not attend the meeting, had the possibility to share their opinion through e-mail in advance.

During the consensus meeting, the results from the 3 eDelphi rounds were presented by AH. Then, the 5 remaining proposals for which no consensus was achieved in the 3 eDelphi rounds, were discussed. For every proposal AH gave an overview of the literature and proposed alternatives, after which PS and SM lead the discussion with the participants. If needed, the proposals were further adjusted. Hereafter, participants could vote on these proposals in three categories; disagree, nor agree/nor disagree and agree.

Definition of consensus

Consensus was defined as less than 15% scores 1 to 3 (disagree) in the eDelphi rounds. For the consensus meeting, consensus was defined as less than 30% scores 1 to 3 (disagree). IBM Statistical Package for the Social Sciences for Windows version 26.0. Armonk, NY: IBM Corp. was used to analyze the results.

Ethical considerations

For this project the Medical Ethics Review committee of the Academic Medical Centre in Amsterdam (reference number W20_300 # 20.335) stated the Medical Research Involving Human Subjects Act (WMO) did not apply.

Privacy and data management

Participants gave their consent for use of their personal data when registered through e-mail.
A privacy officer was consulted before the start of the project. A data privacy impact assessment was written to identify potential privacy risks and take adequate measurement according to the Dutch Privacy Law (Algemene Verordening Gegevensbescherming, AVG).
Data were pseudonymized collected through tokens. The eDelphi results were password protected. Only AH and PS could access the online results.

Results

Participants characteristics and response rates

In total, 251 participants registered themselves for the first round (contact rate 5.6% (251/4500)), of which 180 participants (71.7%) completed all eDelphi rounds. Participants were working mainly at university hospitals, were member of an international dermatology society or psoriasis interest group and had 10 – 20 years of experience in treating psoriasis patients with MTX. Two patients started the eDelphi by accident, but did not finish the first round and were excluded from further participation. See also Table 1 for the baseline characteristics.

eDelphi rounds 1-3

In total, 21 proposals were included in round 1 (Table 2). Consensus was reached on 11 proposals. On the 10 proposals that were left, participants added 41 (deduplicated) alternative proposals. These alternative proposals were summarized below the involving proposals in the next rounds. 201 of the 251 participants (response rate 80.1%) completed round 1.

In the second round, participants voted on the 10 remaining original proposals and consensus was reached on 3 of them. Of the remaining 201 participants, 190 people (response rate 94.5%) completed this eDelphi round.

In the third round, 7 original proposals were included, of which consensus was reached on 2 proposals. To collect information for the discussion during the consensus meeting, participants also voted on alternative proposals. 180 of the 190 participants (response rate 94.7%) completed this last round. The numbers of consensus per eDelphi round can be found in Figure 1.

Consensus meeting

The 5 remaining proposals were discussed in a consensus meeting (Table 2). Not all participants could join the consensus meeting throughout the whole meeting. The maximum number of attendees was 58. Five proposals were discussed and on consensus was reached 4 proposals.

Most participants agreed a test dosage in vulnerable patients and children was not needed when using a low dose MTX. Idiosyncratic hepatotoxicity can be prevented by lowering the starting dose. Besides, physicians are very careful when treating this population with MTX.

Important remarks made on the proposals about 'frail patients' involved the lack of a clear definition. It was therefore decided to change it to 'vulnerable patients'. It was concluded that no specific maximum dosage in vulnerable patients was needed and this dose could be equal to the maximum dosage in adults.

The last proposals discussed during the consensus meeting, involved the use of folic acid and whether the dose should be increased when increasing the dose of MTX. Participants stated the evidence is controversial and therefore consensus on this proposal was not possible. On the proposal involving the weekly administration of folic acid, consensus was reached.

For two proposals the definition of frail patients had to be adjusted and the sentence had to be rewritten in active voice. This was done by the working group after voting. In total, we achieved consensus on 7 items involving 20 proposals, see Table 2 and Figure 2a and 2b.

Future research

The identification of potential future research was one of the aims of this project. Based on the findings in our systematic literature review, the eDelphi and discussion during the consensus meeting, we identified a few potential future research topics. We suggest to focus potential future research on MTX dosing in specific populations e.g. children (different ages) and elderly or patients with an impaired kidney function. For folic acid different doses (increased with higher dosages of MTX) and schedules should be studied.

Discussion

During this project, consensus was reached on 20 out of 21 proposals involving the MTX dosage in psoriasis patients; in the first round on 10 proposals, in the second round on 3 proposals, in the third round on 3 proposals and in the consensus meeting on 4 proposals. This consensus may help clinicians to optimize the treatment of psoriasis patients with MTX around the globe, since MTX is an important drug, being affordable and globally accessible. This consensus can be implemented in current practice and guidelines. The identified knowledge gaps can be the basis for future research.

Consensus

No consensus was achieved on the proposal 'The dosage of folic acid should be increased when increasing the dosage of MTX.' During the consensus meeting it was discussed that there is a lack of evidence and the available evidence is inconclusive. We therefore could not adjust the proposal in a manner that consensus was a possibility.

We eventually reached consensus on all items involving children and MTX dosing. However, most proposals were based on studies from rheumatology due to a lack of evidence in dermatology.

The proposals on 'frail patients' sparked the most discussion. The working group decided to keep the definition broad and added a definition of frail patients to the eDelphi including elderly, renal dysfunction, liver disorders (e.g. non-alcoholic steatohepatitis), ulcerative colitis, history of hepatitis, lack of compliance, gastritis, diabetes mellitus, previous malignancies and congestive heart failure. Many participants however, stated this definition was too broad. During the consensus meeting we deviated from the protocol and the term frail patients was changed to 'vulnerable patients', which only included elderly patients and patients with impaired kidney function. The participants believed vulnerable patients was the subpopulation for which special cautions for MTX dosing were needed.

Strengths and limitations

Firstly, a strength of our consensus is that it is supported by actual RCTs and guidelines, since we updated the systematic literature review from Menting et al.[14]

Secondly, we recruited different participants from all 7 continents in the world. The participants were mainly academic dermatologists with an experience in treating patients with MTX. Thirdly, due to frequent reminders, we reached a high total response rate of 71.7% (180/251 participants).

Another strength is the design of this study; the anonymous eDelphi avoided the possibility of dominance by one of the participants, but during the consensus meeting the proposals could also be discussed live.

Some limitations remain; for the consensus, we decided to define the percentage of participants that scored 1-3 (disagree). Other studies have also defined the percentage of scores 6 to 9 (agree) during an eDelphi exercise,[22] but we expected a consensus would not be reached with a predefined percentage for 'agree'. In retrospect, (see Table 2) setting a minimum of 70% agree did not change the consensus.

Another limitation is the method of recruitment. We choose to recruit patients among SPIN and EADV members and decided not to limit our selection to psoriasis experts only. Eventually, it turned out that most physicians were experienced in treating this population with MTX (90% treated psoriasis patients with the drug for more than 10 years).

The scope of this survey project is a limitation as well, since we did not include proposals on the screening and safety monitoring of patients treated with the drug. For example, the use of transient elastography and measurement of procollagen III N-terminal peptide (PIIINP) for the assessment of liver fibrosis.[23] We decided to focus on the dosing of MTX to prevent the survey being too extensive, since this could discourage participants to complete the survey rounds.

Lastly, we aimed for a global consensus, but most participants were from Europe. The overrepresentation of western nationalities may limit the generalizability of this consensus, since MTX is a very important drug in non-western countries due to less availability of biologics.[24]

Future research

Though, we achieved consensus, more high-quality studies could support our proposals. RCTs or prospective observational studies focusing on the use of folic acid and dosing in different subpopulations (children and vulnerable patients) are needed. It should also be defined for which subpopulation (elderly, impaired kidney function or liver disorders) a specific dosing schedule is required. We do not think this consensus is translatable to other inflammatory disease. For atopic dermatitis (AD) we found studies, arguing that the dose MTX for AD should be higher compared to psoriasis, since the systemic T-cell subsets show a higher activation status in AD than in psoriasis[25] and the immunosuppressive effect of MTX is mediated by its ability to induce apoptosis and clonal deletion of activated T cells[26]. Therefore, separate consensus should be achieved for other (off-label) disease, as AD, morphea and alopecia areata.

Other consensus projects can focus on the screening and monitoring of this drug,[27] how often and which tests should be performed, and whether special precautions are needed in children, elderly and other subpopulations.[28]

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Data integrity: Astrid van Huizen and Phyllis Spuls had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data analysis: Astrid van Huizen

Conflicts of interest:

AH was involved as sub-investigator in clinical trials and observational studies for Abbvie, Janssen, LeoPharma, Lilly, Sanofi and UCB.

SM has no conflicts of interest.

RG has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by: Abbvie/Abbott, Amgen, Bristol-Myers Squibb, Eli Lilly, EGIS, Janssen Cilag, Leo Pharma, , Novartis, Pfizer, GlaxoSmithKlineUCB, TEVA and Sanofi-Genzyme.

LI has no conflicts of interest.

GK has no conflicts of interest.

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PS has done consultancies in the past for Sanofi 111017 and AbbVie 041217 (unpaid), received a departmental independent research grants for TREAT NL registry Pharma since December 2019 for the TREAT NL registry, is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of e.g. psoriasis and atopic dermatitis, for which financial compensation is paid to the department/hospital and, is Chief Investigator (CI) of the

systemic and phototherapy atopic eczema registry (TREAT NL) for adults and children and one of the main investigator of the SECURE-AD registry.

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Tables and figures

Figure legends

Figure 1. Consensus per eDelphi round

Number of proposals on which participants could vote and on which consensus is reached.

Figure 2A. Proposals and voting percentages in the survey

Percentage disagree, nor agree/nor disagree and agree during the eDelphi rounds.

Black vertical line: cut-off for consensus, defined as <15% disagree.

Figure 2B. Proposals and voting percentages in the consensus meeting

Percentage disagree, nor agree/nor disagree and agree during the consensus meeting.

Black vertical line: cut-off for consensus, defined as <30% disagree.

Tables

Table 1. Baseline characteristics

	Participants completed first round n=201 (%)	**Participants completed three rounds n=180 (%)**	**Participants in consensus meeting n=58 (%)**
Age *(years)*			
20-29	1 (0.5)	1 (0.5)	0 (0)
30-39	31 (15.4)	25 (13.9)	10 (17.2)
40-49	57 (28.4)	52 (28.9)	18 (31.05)
50-59	65 (32.3)	57 (31.7)	18 (31.05)
60-69	42 (20.9)	40 (22.2)	11 (19.0)
> 70	5 (2.5)	5 (2.8)	1 (1.7)
Country of residence *(per continent)*			
Africa	5 (2.5)	4 (2.2)	2 (3.4)
Asia	27 (13.4)	24 (13.3)	10 (17.3)
Europe	114 (56.7)	102 (56.7)	34 (58.6)
North America	18 (9.0)	15 (8.4)	4 (6.9)
Oceania[a]	9 (4.5)	8 (4.4)	0 (0)
South America	28 (13.9)	27 (15)	8 (13.8)
Current position			
University hospital	104 (51.7)	97 (53.9)	34 (58.6)
Non-university hospital	12 (6.0)	7 (3.9)	3 (5.2)
Private practice	26 (12.9)	23 (12.8)	5 (8.6)

Combination of two or three above	59 (29.4)	53 (29.4)	16 (27.6)
Member of international dermatology society/psoriasis interest group *(yes/no)*			
Yes	180 (89.6)	162 (90.0)	54 (93.1)
No	21 (10.4)	18 (10.0)	4 (6.9)
Experience with MTX in psoriasis *(years)*			
<10	20 (10)	17 (9.4)	6 (10.3)
10-20	66 (32.8)	59 (32.8)	21 (36.2)
20-30	61 (30.3)	54 (30)	22 (37.9)
30-40	46 (22.9)	43 (23.9)	8 (13.8)
40-49	8 (4.0)	7 (3.9)	1 (1.7)
>100 patients treated with MTX *(no/yes)*			
No	28 (13.9)	24 (13.3)	9 (15.5)
Yes	173 (86.1)	156 (86.7)	49 (84.5)
Participation in psoriasis research or guideline development *(yes/no)*			
Yes	163 (81.1)	145 (80.6)	51 (87.9)
No	38 (18.9)	35 (19.4)	7 (12.1)

578 a Oceania involves Australia and New Zealand

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581 **Table 2. Proposals and voting percentages in eDelphi round 1, round 2, round 3 and consensus**
582 **meeting**

eDelphi round 1[a]				
Proposal	**References**	**Disagree (%)**	**Nor agree/nor disagree (%)**	**Agree (%)**
1. The MTX dose can be decreased to the lowest effective dose according to treatment goals.	[29-31]	3.5	2.5	94
2. Folic acid should be supplemented in all patients.	[4,6,14,32-50]	3.5	2.5	94
3. MTX should be tried, if needed with increased dosage, at least 3-4 months before the effect can be assessed, according to treatment goals.	[6,29,31,37,51,52]	5	5	90
4. In case of gastrointestinal adverse events it is preferred to switch the MTX route of administration from oral to subcutaneous.	[4,36,37,53]	5	3.5	91.5
5. Folic acid should be dosed in 4-6 mg (depending on availability) when prescribing <15mg MTX.	[4,6,34,38,44,46,50,54-57]	8.4	5.5	86.1
6. The maximum weekly dose of MTX in adults is 25 mg/week.	[14,34-37,51,58,59]	9	4.4	86.6
7. For MTX there is no maximum treatment duration unless there are safety concerns.	[37]	9.5	3.4	87.1
8. Usually, MTX is administered in a single weekly dose.	[4,6,32,34-38,41,43,56,60-63]	10.4	2.5	87.1
9. When starting MTX in children, a dosage of around 10 mg/m2/week is prescribed.	[4,37,64,65]	10.9	9.5	79.6
10. The maximum weekly dose of MTX in children is 15mg/m2/week.	[4,37,64,65]	13.9	12	74.1
11. When starting MTX in vulnerable patients, start with a dosage of 7.5-10mg/week.	[4]	14.9	5	80.1
eDelphi round 2[a]				
1. When starting MTX in adults, no test dosage is needed.	[4,14,38]	11.1	2.6	86.3
2. Usually, MTX is administered orally.	[32-35,43,62,66,67]	14.7	6.8	78.5
3. Folic acid should be administered 24 hours after MTX intake.	[4,6,14,44,46,48,54,57,68]	12.6	4.2	83.2
eDelphi round 3[a]				
1. When starting MTX in adults, start with a dosage of 15 mg/week.	[4,6,14,32,33,38,54,69,70]	14.4	2.2	83.3

2. In case of inefficacy or insufficient effect according to the treatment goals, it is preferred to switch the MTX route of administration from oral to subcutaneous.	[6,34,35,37,71]	10	3.3	86.7
Consensus meeting[b]				
1. A test dosage is not needed in vulnerable patients.	[4]	16	2	82
2. The maximum dosage for vulnerable patients is the same as in adults (25 mg/week).[c]	(expert opinion)	26	7	67
3. When starting MTX in children, a test dosage is not needed.	[72-74]	5	2	93
4. The dosage of folic acid should be increased when increasing the dosage of MTX.[d]	[4,75]	93	2	5
5. Folic acid should be administered once a week.	[4,6,14,44,46,48,54,57,68]	14	7	79

a For the eDelphi round consensus was defined as <15% disagree.

b For the consensus meeting consensus was defined as <30% disagree.

c Adjusted to passive voice after the consensus meeting, some subpopulations is changed to vulnerable patients.