Hacettepe University Journal of the Faculty of Pharmacy
Volume 33 / Number 1 / January 2013 / pp. 1-24

Consensus Development on Requirements in Methotrexate Prescribing, Monitoring and Patient's Self-Care in the Treatment of Rheumatoid Arthritis

Received : 20.02.2013
Revised : 09.11.2013
Accepted : 12.11.2013

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Introduction

Rheumatoid arthritis (RA) is a type of inflammatory arthritic condition which is an autoimmune, chronic debilitating disease affecting 0.5-1% of the population worldwide[1] and affects approximately 600,000 people in the UK population[2].

Methotrexate (MTX) is an immunosuppressive agent and its use as a disease modifying anti-rheumatic drug (DMARD) in the long term treatment of inflammatory arthritis has increased as evidence has emerged of the benefits of early aggressive treatment[3-5]. A study conducted in the UK indicated that methotrexate is the DMARD most likely to be continued long term where less than 45% of patients had discontinued after 8 years of treatment[6 7]. Although it has potential advantages in the treatment of RA, treatment requires close clinical monitoring and places self-monitoring demands on patients. Methotrexate toxicity, including gastro-intestinal effects, liver enzyme abnormalities, hematological and pulmonary effects, is a major concern that can limit the length of treatment. It has been reported that the proportion of patients discontinuing treatment within 12 months has varied in studies from 14% to 30%[8-10].

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It has been indicated that although consultation rates in primary care for RA in the UK are declining, RA still constitutes just over half of the rheumatology workload in secondary care and is responsible for about 54 general practitioner (GP) consultation per year in the average general practice[2].

The survey indicated that distribution of rheumatology specialists does not adequately match distribution of health care needs of patients in the UK. The figures showed that there are 37 consultants in Scotland who provide care in two ambulatory clinics per week for a 100,000 population which only meets 41% of optimal provision in year 2001 (calculated by the need for one whole-time equivalent -WTE- consultant rheumatologist per 85,000 population). Throughout the UK, the number of hours that rheumatologists are working has increased since 1997, at present consultants spend 46% of their time in clinics and 14% in ward rounds. The number of consultants that have an established multi-disciplinary teams in their current practices increased from 75% to 81%, between 1999-2001[11].

Roberts and his colleagues surveyed GP's perceptions and opinions on management of musculoskeletal disease in primary care settings[12]. It has been shown that GPs are less confident to manage early rheumatoid arthritis with their own skill and knowledge or with advice from a consultant. Thirty-four percent of GPs, whom they felt able to make the diagnosis, would prefer to refer to a specialist for management. The interviews with GPs revealed demands for multidisciplinary-interactive education for GPs and concerns over lack of resources in supporting services which emphasized a need for a multidisciplinary approach.

Guidelines are available for the management of rheumatoid arthritis and monitoring of DMARDs therapies[13-19]. However, those guidelines do not reflect the findings of recent studies that have prompted new strategies for the development of the patient self-care concept, particularly in methotrexate therapy.

Self-care is a concept that has been recognized and exploited in strategies for chronic disease management. The implementation of the principles of self-care within chronic disease management has yielded a new perspective for patient-centered and multidisciplinary health care approaches, which emphasize the patient's participation.

A multinational consensus development research were undertaken among 751 rheumatologist from 17 countries[20] indicated agreements about methotrexate therapy on certain issues, such as the work-up before initiating methotrexate, optimal dosage and route, use of folic acid, monitoring, management of hepatotoxicity, long-term safety, mono versus combination therapy and management in the perioperative period and before/during pregnancy. Similarly, results of a national consensus development study by Pavy et al.[21] was shown a level of agreement regarding issues on initiation and monitoring of MTX therapy. However those studies did not specifically focus on patient factors for MTX related risks, details on MTX monitoring in the process of multidisciplinary shared-care disease management and patient self-care activities. On the other hand, Canadian study on MTX therapy covers issues on drug interactions, predictors of response, strategies to reduce non-serious side effects and incorporating patient preference into decision-making[22] which could help to reveal patient self-care activities in MTX therapy.

This study aims to identify health care professionals' opinions regarding the use of methotrexate and to achieve a consensus amongst rheumatology specialists in Scotland on the concept of prescribing and monitoring of methotrexate therapy and the principles of patient self-care processes in the treatment of rheumatoid arthritis.

Material and Methods

The Delphi technique was chosen for a consensus building process in order to achieve an agreement on the prescribing and monitoring of methotrexate and the patient self-care concept. The study was initiated in July 2001 and initially three rounds were anticipated, but four rounds were undertaken.

The participants:

The 'expert' population for this Delphi survey included rheumatology specialists, who;

- had considerable amount of experience in rheumatology area
- were currently practicing in the health care system in Scotland at the time of the study

- had considerable amount of knowledge and experience about methotrexate treatment and its complications

The consultant rheumatologists were considered as 'experts', because they were trained and specialised in rheumatological diseases, are in a position to give advice to GPs to initiate the methotrexate therapy for patients diagnosed with RA, and expect co-operation on the patient monitoring during the treatment process.

The consultant rheumatologists were identified from the 'Scottish Society for Rheumatology' mailing list. There were 38 consultant rheumatologists identified in Scotland at the time of the study. The potential participants were contacted by the researcher via letter, which explained the purpose of the study, the Delphi technique and the proposed time required for completion of the survey. The acknowledgement letter and a copy of the 1st round questionnaire were included along with a self-addressed pre-paid envelope. They were asked to return an acknowledgement letter in order to indicate their decisions for participation in the study.

Development of the questionnaires

The questionnaire for the 1st round of the Delphi survey was initially drafted by the researcher in collaboration with hospital pharmacists, rheumatology specialists and independent academic researchers. The researcher identified potential issues regarding methotrexate therapy and patient self-care from the literature reviews, available guidelines and also from the emergent themes in the previously undertaken exploratory study. The conceptual framework for the first round of the Delphi survey was drafted and discussed with various health care professionals (three hospital pharmacists, one specialist nurse and two consultant rheumatologists) in July 2001. Discussions with health care professionals were undertaken in order to clarify the researcher's ideas and enable them to be adapted according to the concept of current health care practices. The researcher also had contacts with an independent academic researcher (in August 2001), who have had previous experience with the Delphi technique and who was considered an eligible person to discuss methodological issues in order to gather opinions regarding the study.

Following several revision processes, the questionnaire for the first round of the Delphi survey was structured and the final version

consisted of 13 multiple choice questions which covered two main areas in methotrexate treatment; 'prescribing and dose increments', and 'patient monitoring'. The questionnaire also encouraged the participants to express their further opinions regarding each question in a space provided. This allowed the researcher to identify previously hidden or uncovered issues as they emerged from the subsequent rounds.

The second round of the Delphi questionnaire was designed by the researcher in the light of the result from the 1st round and was discussed with two consultant rheumatologists and two independent researchers in February 2002. There were 32 questions, which were grouped under three headings; 'prescribing and dose increments', 'patient monitoring' and 'patient self-care'. The second round questionnaire also allowed the participants to expose their opinions about their current practice when necessary. In the third and the fourth rounds, the same questionnaire that was posted in the 2nd and 3rd rounds were sent to the participants respectively, including quantitative feedback regarding the results of the previous round.

The process

The first round of the Delphi questionnaire was sent in November 2001 and expected to be returned by December 2001. The non-responders were followed up by telephone and a reminder of 1st round questionnaire has been re-sent when required. The second round of the Delphi questionnaire was sent in March 2002 and expected to be returned in two weeks time (in beginning of April 2002). The non-responders were followed up by telephone and a copy of the 2nd round questionnaire was re-sent when required. In May 2002, the third round of the Delphi questionnaire was sent to the participants, who had replied to the 2nd round questionnaire, and they were asked to return the 3rd round questionnaire in two weeks time (by June 2002). The non-responders were followed up by telephone and a copy of 3rd round questionnaire was re-sent when necessary. Although it was intended to do only three rounds for the Delphi survey, the fourth and the last round questionnaire was sent in August 2002 and the participants were asked to return by September 2002. The last round questionnaire was sent to the participants who replied to the previous round and follow-ups were undertaken by telephone when necessary.

The number of rounds that have been used in this Delphi study was comparable with other studies reported in the literature[23 24]. Since the first

round intended to explore the ideas in detail and did not ask respondents to rank their opinion on each statement included in the questionnaire, the researcher aimed to allow respondents to re-consider their opinions during at least two more rounds of the Delphi study. Therefore, the Delphi processes was initiated as three rounds, but was completed after the fourth.

The questionnaire statements were considered as 'agreement' if the group's median was ≥ 7 at end of the fourth round of the Delphi. A final degree of consensus was considered as 'good' and 'very good' if the agreed statements were rated by ≥ 70-84% and ≥ 85%, respectively.

Results and Discussion

Analysis of the 1st round

The analysis of the first round of the Delphi survey has been completed in January 2002. There were 28 out of 38 (74%) questionnaires returned at the end of the first round. Five non-participating specialists indicated their reasons for not accepting the invitation; lack of time for full commitment (2), not seeing any patients with RA therefore not using methotrexate (1) and being retired (2). Five other specialists did not return the questionnaire or the acknowledgement letter.

The results of the first round questionnaire were also categorised according to the degree of agreement that has been achieved amongst participants and indicated in Table I and Table II. The items were included in the subsequent rounds if were rated by ≥70% but less than 85% of respondents. If ≥85% of respondents agreed, achieving greater consensus was not thought necessary and such items were excluded from the next round. The items that have achieved less than 70% of responses were disregarded in the following rounds unless they were considered ambiguous by the rheumatology specialists and warranted a need to be explored in detail.

Analysis of the 2nd round

The second round Delphi questionnaires were sent to 28 consultant rheumatologists who replied to the previous round and 25 (89%) questionnaires were returned at the end of the second round. The reasons

TABLE I
Summary of the first round of the Delphi study: Methotrexate prescribing and dose increments (n=28)

Methotrexate prescribing and dose increments			
AGREEMENT	**Very Good**	**Good**	**Less Good**
	≥ 85%	**70-84%**	**<70%**
Methotrexate start 7.5 mg/week		75%	
Dose increment 2.5 mg/week	100%		
Dose increases at 4 weeks			46%
Maximum dose 25 mg/week			64%
Maximum dose in frail elderly, up to 10 mg/week			42%
Use as single dose/week		72%	
Folic acid dose, 5 mg	96%		
Folic acid, weekly	85%		
Folic acid, 3-4 days after MTX dose			63%
NSAIDs not avoided	96%		
Factors to consider in the process of			
Starting MTX (n=22); Alcohol consumption/drug abuse Reproductive risk Previous MTX experience Patient's judgment		77%	 65% 55% 54%
Assessing risk of MTX unwanted effects (n=22); Previous side effects during MTX therapy Alcohol consumption/drug abuse Compliance with MTX therapy Co-morbidities Dose of MTX	 91% 89% 89%	 78% 74%	 68%

MTX: methotrexate; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

for not participating in the second round were not indicated by three rheumatology specialists. In the second round, the participants were asked to indicate their agreements for each statement (42 statements in total including the subheadings of question 32) in the questionnaire on a 9-point Likert scale which ranged from strongly disagree (1) to strongly agree (9).

TABLE II

Summary of the first round of the Delphi study: Patient monitoring (n=28)

Patient monitoring: Investigation			
AGREEMENT	**Very Good**	**Good**	**Less Good**
	≥ 85%	**70-84%**	**<70%**
Before starting MTX;			
FBC, U&E's, Creatinine, LFTs	100%		
ESR and CRP	96%		
Chest X-ray		73%	
Induction phase (during dose increments); fortnightly tests			
FBC	85%		
LFTs		73%	
Creatinine			40%
ESR and CRP			32%
U&E's			31%
Maintenance phase (during stable dose); tests every 4 weeks			
FBC	88%		
LFTs		72%	
Creatinine			46%
ESR and CRP			38%
U&E's			32%
Perform routine Chest X-ray			8%
Recommend routine chest X-ray			15%
Patient monitoring: MTX unwanted effects			
ALT/AST >3x upper limit of normal			
Withhold treatment		70%	
Discontinue permanently			44%
WCC/Platelets below normal			
Monitor and review			32%
Discontinue permanently		71%	
Anemia (Hb<9 g/dL)			
Monitor and review		71%	
Mouth Ulceration			
Reduce MTX dose			62%
Increase folic acid dose			27%
Cr>2x upper limit of normal			
Reduce MTX dose			54%
Withhold treatment			39%
Hair thinning			
Monitor and review			63%
Reduce MTX dose			38%

ALT: Alanine aminotranferase; AST: Aspartate aminotransferase; Cr: Creatinine; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; FBC: Full Blood Count; Hb: Hemoglobin; LFTs: Liver Function tests; MTX: methotrexate; U&E's: Urea and Electrolytes; WCC: White Cell Count.

Analysis of the 3rd round

The third round of the Delphi questionnaires were only sent to the participants who have already replied to the 2nd round (25 specialists), and 24 (96%) questionnaires were returned. The reasons for not returning the questionnaire for the third round were not indicated by the non-respondents. In the third round, the participants were asked to re-rate their agreements for each statement (42 statements in total) in the questionnaire on a 9-point Likert scale. They were provided feedback about the results of the 2nd round, including the group median (interquartile range-IQR), the percentages of responses for the top three/four Likert scale scores and the participants' previous ratings for each statement.

Analysis of the 4th round

The fourth round Delphi questionnaires were only sent to the participants who have replied to the 3rd round (24 specialists), and 23 (96%) questionnaires were returned at the end of the fourth round. The reasons for not participating in the fourth round were not indicated by non-respondent specialists. In the fourth round, the participants were asked to re-rate their agreements for each statement (42 statements in total) in the questionnaire on a 9-point Likert scale. They were provided feedback about the results of the 3rd round, including the group median (interquartile range-IQR), percentages of responses for the top three/four Likert scale scores and the participants' previous ratings for each statement.

Criteria for good practice in methotrexate therapy have been identified on particular issues at the end of the fourth round. According to the definitions by the RAND Corporation, the statements are considered as 'valid' when the group's median reached between the score 7 and 9 on a nine-point Likert scale without any disagreement[25]. The statements generated in this Delphi study, which achieved an agreement amongst the rheumatology specialists are indicated in bold characters for their median values in Table III.

Therefore, it has been indicated that methotrexate therapy should be initiated at the dose of 7.5 mg/week for the patients with rheumatoid arthritis and the weekly MTX dose should not be given by splitting the dose throughout the day. Although an agreement on the initial dose of MTX is found to be lower than the results from Visser et al.[20]; this difference could be partly explained by the expanding evidence regarding MTX

TABLE III

The results of the Delphi questionnaire throughout the four consecutive rounds

Questionnaire items	**2nd round**		**3rd round**		**4th round**	
	Group median (IQR)	**% scored ≥ 7**	**Group median (IQR)**	**% scored ≥ 7**	**Group median (IQR)**	**% scored ≥ 7**
Prescribing and dose increments						
Initial dose of MTX is 7.5 mg/week	7.0 (5.5-8.0)	68%	7.0 (5.25-8.0)	71%	7.0 (5.0-8.0)	70%
Max. dose of MTX is no more than 25 mg/week	4.0 (3.0-6.0)	20%	6.0 (4.0-7.0)	42%	6.0 (4.0-7.0)	48%
Weekly MTX is given as single daily dose	6.5 (4.0-8.0)	50%	7.0 (4.0-8.0)	54%	7.0 (4.0-8.0)	65%
The GP decides on the tablet strength	3.0 (1.0-5.0)	12%	3.0 (1.0-5.0)	5%	2.0 (1.0-5.0)	-
The GP prescribes only 2.5 mg tablet strength	6.0 (3.0-9.0)	48%	6.5 (4.0-9.0)	50%	6.0 (4.0-8.0)	48%
The dose is changed by rheumatologist	7.0 (4.5-7.5)	52%	7.0 (6.0-8.0)	64%	7.0 (6.0-7.0)	65%
The dose may be changed by the GP	6.0 (4.0-7.0)	40%	6.0 (4.0-7.0)	44%	6.0 (4.0-7.0)	39%
The dose changes are delegated to another HCP	6.0 (3.0-7.0)	36%	6.0 (3.0-7.0)	39%	6.0 (4.0-7.0)	35%
The dose changes is delegated to a GP practice nurse	2.0 (1.0-3.5)	4%	2.0 (1.0-3.0)	-	2.0 (1.0-3.0)	-
The dose changes is delegated to a specialist nurse	7.0 (5.5-8.0)	56%	7.0 (6.0-7.0)	61%	7.0 (6.0-7.0)	61%
The dose changes is delegated to a community pharmacist	1.0 (1.0-3.0)	4%	1.0 (1.0-2.0)	-	1.0 (1.0-2.0)	-
The dose changes is delegated to a primary care pharmacist	2.0 (1.0-4.0)	4%	2.0 (1.0-3.0)	-	1.0 (1.0-3.0)	-
The dose changes is delegated to a hospital pharmacist	2.0 (1.0-5.0)	8%	2.0 (1.0-3.75)	-	2.0 (1.0-4.0)	-
The dose changes delegated to patient	3.0 (1.0-5.5)	12%	2.5 (1.0-3.0)	8%	2.0 (1.0-3.0)	-

Questionnaire items	2nd round		3rd round		4th round	
	Group median (IQR)	% scored ≥ 7	Group median (IQR)	% scored ≥ 7	Group median (IQR)	% scored ≥ 7
Patient monitoring						
Withheld treatment when AST/ALT level >3x upper limit of normal	8.0 (7.5-9.0)	88%	9.0 (8.0-9.0)	100%	9.0 (9.0-9.0)	100%
Monitor patient when Alk. Phos. level 1-2x upper limit of normal	5.0 (3.0-7.5)	40%	5.5 (3.0-7.0)	42%	6.0 (3.0-7.0)	%30
Withhold treatment when WCC <4x109/L	7.0 (6.0-9.0)	72%	7.0 (7.0-9.0)	96%	7.0 (7.0-9.0)	100%
Withhold treatment when neutrophils <2x109/L	9.0 (6.5-9.0)	76%	9.0 (8.0-9.0)	96%	9.0 (8.0-9.0)	100%
Withhold treatment when platelets <150x109/L	7.0 (6.0-8.0)	56%	7.0 (6.0-8.0)	71%	7.0 (6.0-8.0)	65%
Monitor patient when Hb<9g/dL	6.0 (3.5-7.0)	44%	6.0 (4.25-7.0)	38%	6.0 (5.0-7.0)	27%
Hb <9g/dL is attributable to MTX	4.0 (2.5-6.0)	20%	3.0 (2.0-5.0)	4%	3.0 (2.0-5.0)	-
Perform LFTs fortnightly at induction phase	7.0 (4.0-9.0)	60%	7.5 (5.0-8.75)	58%	8.0 (5.0-9.0)	57%
Perform LFTs every 4 weeks at maintenance phase	7.0 (4.5-8.5)	56%	8.0 (5.0-9.0)	58%	8.0 (6.0-9.0)	74%
Perform chest X-ray only at baseline	7.0 (7.0-8.75)	83%	7.0 (7.0-8.75)	83%	7.5(7.0-8.25)	91%
Community pharmacist clarifies patients' expectation of their MTX therapy	4.0 (2.0-5.0)	20%	3.0 (2.0-4.0)	-	3.0 (2.0-4.0)	-
Important to show monitoring card to the community pharmacist	3.0 (2.0-6.0)	24%	3.0 (2.0-5.0)	17%	3.0 (2.0-5.0)	9%
Verification of the monitoring card for dispensing MTX prescription	3.0 (1.0-5.5)	20%	3.0 (1.0-5.0)	8%	3.0 (2.0-5.0)	4%
More attention for appropriate monitoring	6.0 (4.0-7.0)	40%	7.0 (5.25-7.0)	54%	7.0 (5.0-7.0)	61%
Routine enquiries by HCPs between clinic visits	5.0 (3.0-7.0)	32%	5.0 (3.0-7.0)	33%	5.0 (3.0-7.0)	43%

Questionnaire items	2nd round		3rd round		4th round	
	Group median (IQR)	% scored ≥ 7	Group median (IQR)	% scored ≥ 7	Group median (IQR)	% scored ≥ 7
Patient self-care						
Dosage alteration in response to mild unwanted GI effects	6.0 (4.0-7.0)	32%	6.0 (4.25-7.0)	29%	6.0 (4.0-6.0)	21%
Withholding treatment in response to unwanted GI effects	6.0 (5.0-7.0)	28%	6.0 (5.0-7.0)	29%	6.0 (5.0-6.0)	22%
Arranging blood sampling in response to GI side effects	3.0 (3.0-5.0)	16%	3.0 (3.0-4.0)	8%	3.0 (3.0-4.0)	4%
Withholding treatment in response to bruising	7.0 (5.5-9.0)	56%	7.0 (6.0-9.0)	67%	7.0 (6.0-9.0)	70%
Arranging blood sampling in response to bruising	8.0 (7.0-9.0)	79%	8.0 (7.0-9.0)	95%	8.0 (8.0-9.0)	96%
Withholding treatment in response to fever	7.0(5.25-8.75)	63%	7.0(6.25-8.75)	75%	7.0 (7.0-9.0)	78%
Arranging blood sampling in response to infection	6.5 (5.0-8.0)	50%	7.0 (5.25-8.0)	58%	7.0 (6.0-8.0)	74%
Seeking professional advice in response to infection	8.0 (7.25-9.0)	92%	8.0 (8.0-9.0)	96%	8.0 (8.0-9.0)	100%
Stopping MTX in response to breathlessness	8.0 (4.5-9.0)	71%	8.0 (6.25-9.0)	75%	8.0 (7.0-9.0)	78%
Checking blood results	5.0 (4.0-6.75)	25%	5.0 (4.0-6.0)	22%	5.0 (4.0-5.0)	17%
Self-administration of parenteral MTX	7.5 (5.0-9.0)	67%	8.0 (5.5-9.0)	75%	9.0 (5.0-9.0)	74%

Alk.Phos: Alkalen Phosphatase; ALT: Alanine aminotranferase; AST: Aspartate aminotransferase; GP: General Practitioner; Hb: Hemoglobin; HCP: Health Care Professional; MTX: methotrexate; WCC: White Cell Count.

therapy since this study was undertaken. The participating rheumatology specialists agreed that the dose changes in methotrexate therapy should only be decided by the rheumatologist; however, there was a belief in favor of delegation of this responsibility to a nurse specialist within a protocol.

The study showed that the rheumatology specialists were reluctant about delegation of particular care responsibilities to the primary care health providers (except the GPs) in the management of rheumatoid arthritis with methotrexate treatment. It is believed that the GP should be advised to prescribe methotrexate therapy only with 2.5 mg tablet strength regardless of the weekly dose of MTX that the patient needs to take. However, despite the fact that there are reported incidents of confusion with methotrexate tablets in the community, this recommendation did not reach a strong agreement amongst the rheumatology specialists.

There was a strong emphasis on patient monitoring during methotrexate therapy. The participants agreed with most of the criteria that have been suggested in the Delphi questionnaire and further acknowledged a general need for more attention to appropriate monitoring of methotrexate treatment. Interestingly, a hemoglobin level less than 9g/dL appeared to be problematic for the rheumatology specialists; they do not consider this condition necessarily attributable to methotrexate toxicity.

There was a substantial disagreement amongst the participants in regards to the community pharmacists' involvement in the monitoring processes. The participants agreed that more attention should be placed on appropriate monitoring; however an involvement of the pharmacist in monitoring process did not get any attention from the rheumatologists. The community pharmacist's role in the monitoring processes was not emphasized by the participants and received lower scores throughout the rounds despite the fact that pharmacists are involved in the dispensing processes for methotrexate prescriptions. This lack of consensus might arise due to absence of evidence supporting the pharmacist's contribution; therefore it has major implications for planning and the use of health service resources in future.

Remarkably, the participants are in a broad agreement about the patient self-care strategies, which achieved high scores on the Likert-scale by the participants and highlighted the importance of these strategies in methotrexate treatment, especially monitoring of symptoms regarding MTX side effects. Therefore, the rheumatology specialists believed that

the patients are in a position to take control over their disease management in their methotrexate therapy, which supports the emerging concept of patient empowerment in chronic disease management. Thompson and Bashook [26] surveyed the rheumatologists preferences about what key information should all patients know about methotrexate and grouped them into two headings as 'must know' and 'must call'. In a view of published studies, self-care activities of patients should be outlined and details of actions on any potential problems regarding MTX should be taught to the patients. Therefore, health care professionals other than rheumatologists are able to take a position in order to maintain patient education and knowledge about disease and its treatment.

The recommendations for good practice in methotrexate therapy that have been suggested in this Delphi study can be categorized as summarized in Table IV. 'Good consensus' was achieved on six out of 14 (43%) of the 'prescribing and dose increments' items; 7 out of 15 (47%) of the 'monitoring' items and 7 out of 11 (64%) of the 'self-care' items. The 'very good consensus' was achieved on only one item (7%) in the 'prescribing and dose increments' recommendations; 3 (20%) in the 'monitoring' and 3 (27%) in the 'self-care' recommendations.

The Delphi technique was chosen for this study in order to achieve a consensus on methotrexate prescribing and monitoring and on the patient self-care processes in treatment of rheumatoid arthritis. Although there is no standard framework or algorithm established for how to process the Delphi technique, the researcher intended to apply the suggestions and recommendations made in the textbooks and literature, but some limitations were inevitable in the study.

It has been suggested that questionnaires can be piloted in order to ensure the content, construct and face validity before the Delphi processes start[23]. Because there were only 38 rheumatology specialists identified in Scotland as the 'expert' population, another group of rheumatology specialists could not easily be achieved in order to pilot the questionnaire for this study. However, the questionnaires were designed by the researcher in collaboration with different health care professionals and academic researchers in order to resolve ambiguities and misunderstandings on the statements included. The RAND Corporation's definition was used in order to assess the validity of the statements included in the questionnaire. According to this definition, a 9-point Likert scale

TABLE IV

Degree of consensus achieved for each recommendation

	Degree of consensus		
	Some	**Good**	**Very good**
Prescribing and dose increments			
Initial dose of MTX is 7.5 mg/week		√	
Maximum dose of MTX is no more than 25 mg/week		√	
Weekly MTX is given as single daily dose		√	
The GP decides on the tablet strength			
The GP prescribes only 2.5 mg tablet strength	√		
The dose is changed by rheumatologist		√	
The dose may be changed by the GP		√	
The dose changes is delegated to another HCPs		√	
The dose changes is delegated to a GP practice nurse			
The dose changes is delegated to a specialist nurse			√
The dose changes is delegated to a community pharmacist			
The dose changes is delegated to a primary care pharmacist			
The dose changes is delegated to a hospital pharmacist			
The dose changes delegated to patient			
Patient monitoring			
Withheld treatment when AST/ALT level >3x upper normal limit			√
Monitor patient when Alk. Phos. level 1-2x upper normal limit		√	
Withhold treatment when WCC $<4x10^9/L$		√	
Withhold treatment when neutrophils $<2x10^9/L$			√
Withhold treatment when platelets $<150x10^9/L$		√	
Monitor patient when Hb <9g/dL		√	
Hb <9g/dL is attributable to MTX			
Perform LFTs fortnightly at induction phase		√	
Perform LFTs every 4 weeks at maintenance phase		√	
Perform chest X-ray only at baseline			√
Community pharmacist clarifies patients' expectation of their MTX therapy			

Important to show monitoring card to the community pharmacist			
Verification of the monitoring card for dispensing MTX prescriptions			
More attention for appropriate monitoring		√	
Routine enquiries by HCPs between clinic visits	√		
Patient self-care			
Dosage alteration in response to mild unwanted GI effects		√	
Withholding treatment in response to unwanted GI effects		√	
Arranging blood sampling in response to GI side effects			
Withholding treatment in response to bruising		√	
Arranging blood sampling in response to bruising			√
Withholding treatment in response to fever		√	
Arranging blood sampling in response to infection			√
Seeking professional advice in response to infection			√
Stopping MTX in response to breathlessness		√	
Checking blood results		√	
Self-administration of parenteral MTX		√	

Alk.Phos:Alkalen Phosphatase; ALT: Alanine aminotranferase; AST: Aspartate aminotransferase; GI: Gastrointestinal; GP: General Practitioner; Hb: Hemoglobin; HCPs: Health Care Professionals; LFTs: Liver Function Tests; MTX: methotrexate; WCC: White Cell Count.

is broken down into three tertiles; the statements are scored between 1-3 considered 'invalid', scored between 4-6 is 'equivocal' and scored between 7-9 is 'valid' [25]. Therefore, 19 out of 42 statements (45%) were considered valid in this study, which could help to initiate the design of guidelines on methotrexate treatment.

An analysis of agreement for the consensus development processes has been defined in the literature according to the extent which respondents agree with the issue under consideration (rated on a scale) and the extent which respondents agree with each other (statistical measures of mean and dispersion)[27]. It has been suggested that the mean value (central tendency) is an indicator of a group agreement and a low standard deviation value represents strong agreement amongst participants[28].

However, it is indicated that the use of median and interquartile range (IQR) values are more robust where more than eight participants are available and the distribution is not markedly bimodal[29]. Furthermore, giving more attention on what is happening between the rounds allows understanding on whether an agreement has been maintained throughout the rounds and is reached in the final round, which reflects the reliability of the final decision[28].

The study also had a limitation; it was undertaken about ten years ago, however it still reflects the common pattern of rheumatological practice in different countries. The practice recommendations emerged from this study was comparable with the agreements indicated by Visser et. al[20]. Although initial starting dose of methotrexate 7.5 mg/week was increased to 10-15 mg/week (the maximum dose is to 30 mg/week), the dose increment was still 5 mg every 2-4 weeks depending on prescriber's preference. In this study, expert panel agreed the use of methotrexate as a single weekly dose, however it is now preferable to split the weekly dose or change the route of administration to parenteral in terms of reducing gastrointestinal side effects [22]. The monitoring parameters and frequency of methotrexate treatment is remained as before, except the monitoring intervals of LFTs at induction phase which was extended to every 1-1.5 months. None of the consensus development studies have focused on the patient self-care activities and delegation of activities to the other healthcare providers in monitoring process.

Conclusions

The formal consensus method can be used as an acceptable alternative to the evidence-based approach when developing guidelines in situations in which evidence is scarce, and which the guideline is intended as an aid in linking different stages of care.

This Delphi study was a systematic attempt to develop an instrument of general applicability for the management of rheumatoid arthritis with regards to methotrexate therapy. The study indicated that there are variations in opinions of rheumatology specialists in Scotland on the use of methotrexate therapy in patients with rheumatoid arthritis even though established guidelines are available for current health practice.

Although primary aim of this study was to make a consensus on methotrexate therapy, the study also indicated the importance of multidisciplinary monitoring in disease management and envisaged opportunities for primary care health professionals to get involved in disease management.

It can be concluded from this Delphi study that the study is highly relevant to informing the content, structure and operationalization of protocols and/or guidelines associated with the management of rheumatoid arthritis, in particular with methotrexate prescribing and patient self-care processes in the treatment of rheumatoid arthritis. The recommendations emerged from this consensus building processes are summarized in Panel below.

PANEL. Recommendations on prescribing and monitoring of methotrexate (MTX) and patient self-care strategies in the treatment of rheumatoid arthritis

Prescribing;

- The MTX therapy should be initiated in a dose of 7.5 mg/week
- The weekly MTX dose should be given as a single daily dose
- The MTX dose changes should be decided only by a rheumatologist
- The dose changes can safely be delegated to a rheumatology specialist nurse within a protocol

Monitoring;

- MTX treatment should be withheld until problem resolves, when
  - AST/ALT level >3x upper limit of normal
  - WCC < $4x10^9$/L
  - Neutrophils < $2x10^9$/L
  - Platelets <$150x10^9$/L
- LFTs should be monitored fortnightly at the induction phase (during the dose increments) and every 4 weeks at the maintenance phase (during stable dose) of MTX therapy
- Chest X-ray should only be performed before the MTX therapy, but not thereafter in the absence of chest symptoms

Patient self-care strategies;

- Patients should **withhold the treatment** in response to increased bruising and fever
- Patients should **arrange to go to get their blood sampled for laboratory tests** in response to increased bruising, any infection
- Patients should **seek professional advice** in response to any infection
- Patients should **immediately stop** MTX in response to breathlessness
- Patients should be thought to self-administer their parenteral MTX dose

Summary

The aim of the study was to identify potential problems and concerns of rheumatology specialists regarding methotrexate therapy and to obtain recommendations about good practice standards for methotrexate use in the treatment of rheumatoid arthritis. Four rounds of the Delphi technique were used for a consensus development among 38 rheumatology specialists in Scotland. The participants were asked to indicate their opinion for 42 questions in a total questionnaire using a 9-point Likert scale (1: strongly disagree to 9: strongly agree). The results of each round were analyzed and presented in numbers and percentages of participants answering for each questions and group median (interquartile range) scores. The survey revealed that there were variations in the practice of rheumatology specialists in the use of methotrexate therapy. The participants were practicing in a similar way in terms of methotrexate initial dose and dose increments, monitoring parameters; however they were not willing to delegate monitoring issues to other health care professionals, except nurse specialist. On the other hand, the rheumatologists supported the idea of delegation some of the monitoring issues regarding methotrexate side effects to the patients. Differences in preferences among rheumatology specialists on the criteria for monitoring patients receiving methotrexate treatment and the variability in local guidelines

has led to different practices in the provision of care. Recognition of roles and delegation of certain responsibilities to the other health providers (such as general practitioners and pharmacists) in a multidisciplinary shared care would yield to safe and effective drug use, close monitoring, and continuity of care.

Key words: methotrexate, rheumatoid arthritis, Delphi technique, self-care

Özet

Romatoid artrit tedavisinde metotreksat'ın reçetelenmesi ve izlemine yönelik gereksinimler ve hastanın kendi kendine bakım süreci ile ilgili konsensüs geliştirilmesi

Bu çalışma, romatoid artrit tedavisinde metotreksat kullanımı ile ilgili olarak romatoloji uzmanlarının olası sorunlarını ve endişelerini ortaya çıkarmak ve bunun sonucunda iyi uygulama standartlarını belirleyen önerileri elde etmeyi amaçlamaktadır. Fikir birliğine ulaşabilmek için kullanılan yöntemlerden 4 tekrarlı Delphi tekniği, İskoçya'daki 38 romatoloji uzmanı ile gerçekleştirilmiştir. Katılımcıların fikirlerini, toplamda 42 sorudan oluşan ankette ve 9-kademeli Likert skalası kullanarak (1: Hiçbir şekilde katılmıyorum - 9: Tamamıyla katılıyorum) ifade etmeleri istenmiştir. Her anket tekrarının sonucu analiz edilerek, her soruya verilen cevap katılımcıların sayısı ve yüzdesi ve de grup medyan skoru olarak belirtilmiştir. Çalışma, romatoloji uzmanları arasında metotreksat kullanım uygulamaları açısından farklılıklar olduğunu ortaya koymuştur. Katılımcıların metotreksat başlangıç dozu, doz arttırımları, izlem parametreleri açısından benzer şekilde hareket ettikleri gözlense de; izleme dair hususları, uzman hemşire dışında, diğer bir sağlık personeline devretme konusunda istekli olmadıkları belirtilmiştir. Diğer taraftan, romatoloji uzmanları bazı metotreksat yan etkilerinin izlemini hastalara bırakma fikrini desteklemektedir. Romatoloji uzmanlarının metotreksat kullanan hastaların izlemi konusundaki kriterlerindeki farklı tercihleri ve yerel rehberlerin değişkenlikleri, bakımın sağlanması konusunda farklı uygulamalara yol açmaktadır. Diğer sağlık çalışanlarının (örneğin, aile hekimleri ve eczacılar) multidisipliner olarak ortaklaşa bakım sürecinde rollerinin ve sorumluluklarının

farkına varılması, güvenli ve etkin ilaç kullanımına, yakın hasta izlemine ve bakımın sürekliliğinin sağlanmasına yol açacaktır.

Anahtar kelimeler: metotreksat, romatoid artrit, Delphi tekniği, kendi-kendine bakım

Acknowledgements

I would like to thank Prof. S. Hudson, Dr. S. Fraser, Dr. J. Hunter and Mrs. A.Power for their kind support throughout the study.

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