Rheumatologists' recommended patient information when prescribing methotrexate for rheumatoid arthritis

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Abstract

Introduction

Accurate communication of information concerning the risks and benefits of medications is essential for adherence and patient safety. A diverse array of information and sources makes it difficult to know exactly what to tell a patient with rheumatoid arthritis about methotrexate.

Objective

Our objective is to determine what key information patients must know about methotrexate and the key reasons they should call their doctor while they are taking methotrexate.

Methods

Three hundred and forty-four Canadian rheumatologists were sent a survey containing open-ended questions to gain uncued narrative perspectives from each individual's experience. The survey was designed to determine what must all patients taking methotrexate know and when must patients taking methotrexate call a physician? Emergent coding was used to establish a set of categories to form a checklist for coding. A second member checking survey was sent to gain confirmation and validation of themes developed from the initial survey.

Results

One hundred and seventy out of 344 (49.5%) surveys were completed. Regular blood testing, once weekly dosing, risk of infection, pregnancy and lactation information, alcohol limitation, potential lung toxicity, and drug interactions were thought to be important. Patients should call if they became pregnant, developed symptoms suggestive of lung toxicity, developed an infection, severe mouth sores, or were concerned about any side effects warranting the discontinuation of the medication.

Conclusion

This study is the first to describe, from a rheumatologist's perspective, the key important information that all patients should know and when patients should call their doctor when taking methotrexate.

Key words

Rheumatoid arthritis, methotrexate, patient, information, DMARDs

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Introduction

Methotrexate is widely prescribed for the treatment of rheumatoid arthritis. The American College of Rheumatology recommends the initiation of methotrexate or leflunomide monotherapy for patients with all disease durations and for all degrees of disease activity, irrespective of poor prognostic features (1). All Canadian rheumatologists frequently prescribe methotrexate in rheumatoid arthritis (2) and recent estimates show methotrexate initiation in early rheumatoid arthritis occurs in over 90% of patients (3).

Despite its widespread use, methotrexate product materials for patients remain diverse and incomplete (4). Examination of supplementary methotrexate information pamphlets found wide variation in content between information pamphlets with important information often omitted (4). This review of 18 methotrexate pamphlets from Australia identified 9 headings in the generic structure of a methotrexate information pamphlet. The only common sections in all pamphlets were dosage instructions and information pertaining to side-effects. The authors concluded that this variability suggests no standard approach to instructions or patient information, and little agreement among practitioners either about the purpose or extent of information that should be provided.

Given the frequency of use and the diverse array of information about methotrexate, it is important, yet difficult, to know exactly what to tell a patient with rheumatoid arthritis when prescribing methotrexate. Current patient information pamphlets are largely derived from methotrexate product monographs (5). The product monographs present recommendations derived from valid preclinical trial experiences but do not include the entire range of post-marketing experience, off-label indications (5), and often are not concordant with current treatment paradigms (1). Especially critical for deriving patient information, they do not place a relative weighting on the importance of common or potentially serious risks and what the patient should do when the risk develops. Furthermore, many methotrexate product monographs are confusing because they combine indications for neoplastic disease and disease modifying anti-rheumatic drugs (5).

Through anecdotal reports it is clear that rheumatologists recognise these shortcomings and have developed their own litany of essential patient information when initiating methotrexate for rheumatoid arthritis. In support of these endeavours, evidence exists that the use of a methotrexate information booklet can improve the understanding of the medication (5). Physicians and patients would further benefit by having the key information patients must know about methotrexate and why a patient should call their doctor while taking the medication.

The goal of this study was to determine, from practicing rheumatologists, what information about methotrexate they consider essential for patients to know and the key reasons (symptoms and other health conditions) that patients should call their doctor while taking methotrexate. This step is an important initial step to create valid content for use in patient-information material pertaining to methotrexate.

Methods

This study was conducted at St. Joseph's Health Centre, an academic teaching hospital affiliated with the Schulich School of Medicine, University of Western Ontario, London, Ontario, Canada. This research was approved by the institutional review boards of the University of Illinois and the University of Western Ontario.

Rheumatologists were asked:

1. What must all patients know when taking methotrexate?
2. What do you tell patients as the reasons why they should call their doctor while on methotrexate?

All 344 Canadian rheumatologist members of the Canadian Rheumatology Association (CRA) were invited via e-mail to participate in this study. The membership of the CRA is a geographical representation of all Canadian rheumatologists working in a diverse array of clinical practices treating diverse patient populations including a

wide variety of patient care experiences from across the country.

In December 2007, the survey was e-mailed to all 344 Canadian rheumatologists with a cover letter stating the study purpose and obtained consent. Participation in the questionnaire was voluntary, anonymous, and IRB approved with all questionnaire data stored in a password protected file known only to the principal investigator. The survey was developed and delivered using Survey Monkey (www.surveymonkey.com), a well known commercial internet based survey tool. Non-responders after one week were sent an e-mail reminder and then a third reminder the following week.

The survey questions were divided into four sections: (a) frequency of methotrexate use; (b) important information all patients should know about methotrexate; (c) important reasons to call a doctor when taking methotrexate; and (d) demographic data about the rheumatologist and their practice. The survey consisted of only open-ended questions so as to provide un-cued narrative perspectives from each individual's experience. Content-analysis methodology, a well-established qualitative research method in medical education was used to analyse the survey results. Content analysis can be defined as a systematic, objective, quantitative analysis of message characteristics (6). Content analysis was an appropriate methodology for this study because the primary research questions concerned analysis of information rheumatologists' provide patients when prescribing methotrexate for rheumatoid arthritis. Using *emergent coding*, preliminary examination of the data was performed by the principal investigator, a practicing rheumatologist, to establish a set of categories to form a checklist for coding (6). This checklist was compared to current patient information about methotrexate and agreed upon by 4 practicing academic rheumatologists. This checklist was used by the principal investigator to code survey results into the appropriate category.

On completion of the initial content analysis a second survey was sent to the respondents of the first survey as a form of validation. The second survey presented the results of the content analysis and asked the respondents to rate the results as important or not. Further details about some of the results were further explored such as, "How much alcohol do you tell your patients is safe to consume while taking methotrexate?" or "How frequent do you order bloodwork monitoring?" Contacting the same potential respondents from the CRA was an essential validation process in this study. In the second survey, respondents were given a synthesis of the findings from the first survey and asked to confirm the veracity of these findings as well as clarify details about some findings. The iterative process, which is central to content analysis, validated the initial findings, produced further refinements, and added richness to the findings. Some researchers consider this form of validation as the strongest available check on the credibility of qualitative data collection (7). Again, participation in the second questionnaire was voluntary, anonymous, and IRB approved with all questionnaire data stored in a password protected file known only to the principal investigator.

The survey was developed and delivered using Survey Monkey. Non-responders after one week were sent an e-mail reminder and then a third reminder the following week.

Table I. Demographics of rheumatologists responding to survey.

ITEM	Total number of respondents	Range	Responses (%)
Age	135	21–30	3 (2.2)
		31–40	24 (17.8)
		41–50	45 (33.3)
		51–60	41 (30.4)
		61–70	21 (15.6)
		71+	1 (0.7)
Gender	135	Male	75 (55.6)
		Female	60 (44.4)
Practice type	134	Academic practice	65 (48.5)
		Community practice with Academic affiliation	46 (34.3)
		Community practice	23 (17.2)
Province of practice	134	British Columbia	20 (14.9)
		Alberta	13 (9.7)
		Saskatchewan	3 (2.2)
		Manitoba	4 (3.0)
		Ontario	58 (43.3)
		Quebec	24 (17.9)
		New Brunswick	5 (3.7)
		Nova Scotia	4 (3.0)
		New Foundland	1 (0.7)
		Other	2 (1.5)
Clinic days per week	170	0–1	12 (7.1)
		1.5–2	18 (10.6)
		2.5–3	22 (12.9)
		3.5–4	39 (22.9)
		4.5–5	67 (39.4)
		5+	12 (12.0)
Patients seen per day	168	0–10	21 (12.5)
		11–20	88 (52.4)
		21–30	57 (33.9)
		31–40	2 (1.2)
		40+	0 (0)
Patients taking methotrexate in a typical day	170	1–5	50 (29.4)
		6–10	88 (51.8)
		11–15	26 (15.3)
		16–20	4 (2.4)
		21–25	2 (1.2)
		26+	0 (0.0)

Results

Demographics and methotrexate use

Surveys were completed by 170 of 344 (49.5%) members of the CRA. Table I shows the demographics of the respondents to the survey. Not all of the survey respondents gave answers to each question accounting for the discrepancy in numbers. The majority of responses were by men (55.6%) versus women (44.4%) and 67 percent of the rheumatologists were between the ages of 41 and 60. Most respondents had high clinical volumes working 3.5 or more clinic days per week (74.3%); most see between 11 to 30 patients per day. Nearly all (97%) reported prescribing methotrexate. On a typical day these rheumatologists had visits from six to 20 patients on methotrexate (69.5%). Most respondents were from Ontario (43.3%) followed by Quebec (17.9%), British Columbia (14.9%) and Alberta (9.7%) with 48.5% holding positions within an academic institution. The geographic distribution, gender, and type of practice for the sample was representative of the distribution for the entire CRA membership (Table II).

Table II. Comparison to CRA membership.

Variable		Survey respondents (%)	CRA membership (n=344)
Gender	Female	60 (44.4)	135 (39.2)
	Male	75 (55.6)	209 (60.8)
Affiliation	University	65 (48.5)	161 (46.8)
	Community	69 (51.5)	183 (53.2)
Province of practice	British Columbia	20 (14.9)	49 (14.2)
	Alberta	13 (9.7)	33 (9.9)
	Saskatchewan	3 (2.2)	9 (2.6)
	Manitoba	4 (3.0)	10 (2.9)
	Ontario	58 (43.3)	138 (40.1)
	Quebec	24 (17.9)	68 (19.8)
	New Brunswick	5 (3.7)	8 (2.3)
	Nova Scotia	4 (3.0)	13 (3.8)
	New Foundland	1 (0.7)	5 (1.5)
	Other	2 (1.5)	10 (2.9)

Table III. What patients must know about methotrexate.

Item	Responses (out of 141)
Regular blood tests	111 (78.7%)
Avoiding or limiting alcohol	71 (50.4%)
Potential lung toxicity	62 (44.0%)
Take methotrexate only once a week	56 (39.7%)
Stop or call if you think you have an infection	55 (39.0%)
Do not get pregnant and use reliable birth control	53 (37.6%)
Potential drug interactions	47 (33.3%)

Table IV. When patients taking methotrexate must call a physician (initial survey).

Item	Responses (out of 135)
Lung toxicity	76 (56.3%)
Concern about potential side effects including persistent nausea or vomiting	70 (51.9%)
Infection or fever	67 (49.6%)
Pregnancy	20 (14.8%)
Mouth sores (stomatitis)	19 (14.1%)
Surgery	15 (11.1%)

What patients must know about methotrexate

One hundred and forty-one respondents provided un-cued narrative responses about what patients taking methotrexate must know. Table III summarises the essential information patients must know about methotrexate according to Canadian rheumatologists. Most frequently identified was the importance of regular blood testing while taking methotrexate (111/141, 78.7% of responses). Rarely mentioned were specifics about the frequency of blood testing; a typical comment on the first survey was captured by the phrase patients must know to "do blood tests regularly" (76 respondents answered similarly). In the follow-up survey, recommended frequency of blood testing was usually between 1 and 2 months. This broad range of responses is congruent with the confusion about current monitoring guidelines which are based on very little empirical evidence and are largely based on expert consensus (1). The single response that captured some of the thinking behind this recommendation is expressed by this nuanced response, "Remember to have your blood work at the frequency prescribed by your physician (I would not specify what the frequency should be as it will vary depending on how long the patient has been on the drug and whether or not they are still consuming "some" alcohol)".

Another important patient instruction was to "limit alcohol consumption" while taking methotrexate (71/141, 50.4%). All respondents recommended "avoiding alcohol" or "limiting alcohol intake" with little guidance as to the actual amount of recommended alcohol per week. In the follow-up survey, the most common response was to "avoid alcohol completely" followed by "limiting alcohol to 1 to 2 drinks per week".

Next in priority, sixty-two rheumatologists (44%) felt it was important that patients must know about the potentially serious lung toxicity associated with methotrexate. Rheumatologists identified these lung toxicity symptoms as a new cough, shortness of breath, or fever, that patients should recognise and immediately call their doctor.

Dosage recommendations emphasising once weekly dosing was next in importance identified by 56 respondents (37.2%). One comment captured the rationale for prescribing: "Methotrexate is only taken once a week, but it is several tablets on that one day out of the week – Why? Seniors tend to need this point clarified several times."

Infection and fever were identified by 55 respondents (36.4%) as important for patients to call or seek medical attention. Fifty-three respondents felt it was important to advise women to avoid pregnancy while taking methotrexate (35.1%). Finally, medication interactions were identified as important information for patients by 47 respondents (33.3%). The most specific medication interaction mentioned was between methotrexate and trimethoprim.

When patients must call while taking methotrexate

Rheumatologists provided un-cued narrative responses about when patients should stop taking methotrexate and call their physician. Table IV summarises these recommendations. Most commonly identified by 76 of 135 respondents were symptoms of potential lung toxicity from methotrexate (76/135, 56.3%). Symptoms identified were a persistent unexplained cough or new shortness of breath. Often mentioned associated with these symptoms was a general feeling of malaise and sometimes a fever.

Slightly more than half of respondents (51.9%) said any serious concerns while taking the medication should warrant a call to the rheumatologist. Specifically, they recommended a patient should call if they felt very unwell (often this is nausea and/or vomiting), were concerned about any other side effects, or just could not tolerate the medication and felt they need to stop. Two quotes from respondents summarised this recommendation, "If they develop side effects sufficient to consider stopping the drug or if they have any question that makes them question the wisdom of continuing with therapy" and "if for any reason they think they should stop methotrexate".

Symptoms of a potential infection including fever, need for antibiotics, or "think they have an infection" warrant grounds to call the rheumatologist as recommended by 67 respondents (47.5%). Finally, 20 respondents felt that pregnancy or planning pregnancy was a good reason to call a rheumatologist, 19 mentioned severe mouth sores as a reason to call, and 15 mentioned upcoming surgery as a reason to notify the rheumatologist.

Table V. What patients must know about methotrexate.

Item	Percentage of respondents who thought it was important (n=184)
Regular blood tests	100%
Do not get pregnant and use reliable birth control	99.4%
Avoiding or limiting alcohol	95.6%
Take methotrexate only once a week	92.2%
Potential lung toxicity	86.7%
Stop or call if you think you have an infection	73.8%
Potential drug interactions	67.5%

Table VI. When patients taking methotrexate must call a physician.

Item	Percentage of respondents who thought it was important (n=135)
Pregnancy	99.4%
Lung toxicity	97.2%
Concern about potential side effects including persistent nausea or vomiting	90.1%
Mouth sores (stomatitis)	89.0%
Infection or fever	76.0%
Surgery	58.7%

Respondent validation

Validation of the initial responses was obtained by sending the same population of rheumatologists (members of the CRA) a second survey containing results of the initial survey asking for confirmation of recommendations and more details on some questions.

One hundred and eighty-four out of 344 (53.5%) individuals responded to the second questionnaire. Table V summarises respondents' responses to the second survey. All respondents recommended including instructions to patients about the importance of regular blood testing and information regarding pregnancy contraindication with methotrexate. When probed further, 55% of respondents recommended monthly blood testing, when methotrexate is initially prescribed; whereas, over 80% felt that blood testing should be performed between two and six weeks when starting methotrexate.

Most rheumatologists (95.6%) identified important clear patient instructions about avoiding or limiting alcohol consumption. More specifically, 72% of rheumatologists advised patients that "safe" alcohol use was complete alcohol abstinence to 2-3 drinks per week. Potential drug interactions were identified as important by 67.5% of respondents. The most important drug interactions identified were between methotrexate and sulfa antibiotics or methotrexate and other hepatotoxic medications such as leflunomide.

Table VI summarises findings from the second survey confirming initial survey recommendations about instructing when patients should call a doctor. Nearly every respondent recommended patients contact their rheumatologist if the patient was pregnant or planning a pregnancy. Not quite unexpected nearly all respondents (97.2%) recommended patients contact their doctor if there were symptoms of potential lung toxicity. Known side effects of methotrexate treatment were identified as important reasons for patients to call their doctor such as persistent nausea or vomiting (90.1%); mouth sores (89%); and infection or fever of unknown origin (76%). Although rheumatologists' thought planned surgery was an important reason to contact their doctor most felt (58.7%) that it was the peri-operative team who should be giving advice rather than the rheumatologist.

Discussion

The study takes the rheumatologist's perspective in asking the question what key information should all patients know about methotrexate when

Table VII. Canadian rheumatologists' recommended patient information when prescribing methotrexate for rheumatoid arthritis.

Category	Item	Description
Must know	Blood testing	Have your blood tested EVERY MONTH. This is important to make sure methotrexate isn't harming your LIVER or BLOOD COUNTS.
	Pregnancy	Methotrexate can harm an unborn child. If you are having sex or thinking of having sex and could get pregnant, consult your doctor about continuing to take methotrexate.
	Alcohol	Drinking alcohol while taking methotrexate could damage your liver. It is best to AVOID ALCOHOL
	Dosing	Take your methotrexate only ONCE A WEEK. Choose the same day of the week to be your "Methotrexate Day".
	Lung toxicity	Methotrexate rarely causes a serious lung problem. Call your doctor and STOP taking the methotrexate if you have NEW SHORTNESS OF BREATH (at rest) but don't have a heavy cold (runny nose and fever) or a NEW DRY COUGH for several weeks
	Infection	Methotrexate can make it harder for you to fight infections. It is best to stop taking methotrexate if you have a fever or think you have an infection. Phone your doctor for advice.
	Drug interactions	You must not take SULFA ANTIBIOTICS, such as co-trimoxazole (Septra) or trimethoprim, while taking methotrexate. Always check with your doctor or pharmacist before starting any new medication.
Must call	Pregnancy	Stop methotrexate and immediately call your doctor if you become pregnant while taking methotrexate.
	Lung toxicity	[REPEAT from above]
	Concern	Contact your doctor if you feel you need to stop taking this medication because: • you feel sick (nausea and vomiting) and want to stop • you are concerned about any side effects • you want to or have already stopped for the medication
	Mouth sores	If you develop severe mouth sores, contact your doctor.
	Infection	[REPEAT from above]
	Surgery	If you are planning an upcoming surgery, contact your doctor.

prescribed for rheumatoid arthritis, and under what circumstances should patients call their doctor while taking methotrexate. Table VII summarises the study findings in a manner that might be useful to practicing rheumatologists or even given to patients when prescribing this medication.

This study is part of a larger effort to improve patient information about methotrexate. An example patient information pamphlet with the methotrexate information derived from this study can be found at www.RheumInfo.com under the heading "*methotrexate picto-pamphlet*".

The rheumatologists who responded were all active in clinical practice, often seeing a significant number of patients daily who were prescribed methotrexate. The authors had anticipated a wide range of perspectives, yet there was remarkable agreement in the recommendations about what information to provide patients when prescribing methotrexate.

Even though rheumatologists and their nurses typically instruct patients about this medication, a limitation of the study is not obtaining confirmatory reports from other health professionals and patients. As a follow-up study it would be useful to know what pharmacists tell patients who obtain prescriptions for methotrexate, and what patients consider important to them.

The study findings recommend the minimal necessary information that must be conveyed to patients while taking methotrexate. Equally important, the information is organised into "actionable" statements, meaning that each recommendation is associated with a specific action (*i.e.* avoiding alcohol, taking weekly, contact a doctor if you have mouth sores). Framing information in this manner may give the patient more clear and concise guidance.

The results of this research support and strengthen the 3E initiative practical recommendations for the use of methotrexate in rheumatic disorders (8). However, differences exist as the 3E initiative is rooted in the promotion of evidence-based guidelines to address clinical problems whereas this study is focused on the conveyance of patient-centred information. Specifically, the findings of this study are congruent with the 3E initiative recommendations for regular blood monitoring, consideration of alcohol intake, potential for lung toxicity (baseline chest x-ray), and perioperative use. The grade C recommendation for pregnancy avoidance in the 3E initiative based largely on "expert consensus" is supported by our findings and those found in a recent systematic review (9). The 3E initiative provides grade A evidence for the use of at least 5 mg of folic acid per week with methotrexate use. This finding is absent from our study as only a few respondents identified regular folic acid supplementation as important information for patients. However, given the strength of evidence from the 3E initiative, this should be considered for our patient information pamphlet. This study identified other important issues not identified through the 3E initiative including the risk of infection, the importance of emphasising methotrexate use is only once weekly, medication interactions, and the risk of rare mouth sores. Many practicing rheumatologists with considerable experience with methotrexate use felt that this information was important for patients to know despite the lack of identifiable evidence in the literature.

Our study had several limitations. The response rate was only 49.5% of Canadian rheumatologists, although the response sample is consistent with the demographics of the Canadian Rheumatology Association's entire membership database. A second limitation is that the qualitative data was coded by a single individual. We did not perform an analysis of inter-rater reliability since almost all responses were short

statements and in point form making coding fairly simple with little left to interpretation.

The clear goal is to insure as much as feasible patient comprehension about how to take methotrexate, when to consider stop taking the drug, and when to contact the doctor if there are potential complications from this medication. Future research might focus upon two issues that could further elucidate the high priority instructions to patients taking methotrexate. What do pharmacists and patients consider key guidance for patients, and what are the best communication strategies to convey these instructions to patients?

Conclusion

The study used content analysis to identify key recommendations rheumatologists give patients who are taking methotrexate for rheumatoid arthritis. The findings from this study are potentially helpful not only to rheumatologists when they prescribe methotrexate, but could be distributed as patient instructions if organised into a straightforward list of patient "actions" such as in Table VI or on the website www.RheumInfo.com under the heading "*methotrexate picto-pamphlet*".

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