university of groningen

University Medical Center Groningen

University of Groningen

Neuropsychiatric adverse drug reactions associated with low dose methotrexate in rheumatoid arthritis patients

Van Lint, Jette A; Bakker, Tom; Ten Klooster, Peter M; van Puijenbroek, Eugene P; Vonkeman, Harald E; Jessurun, Naomi T

Published in:
Expert Opinion on Drug Safety

DOI:
10.1080/14740338.2022.2003328

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Van Lint, J. A., Bakker, T., Ten Klooster, P. M., van Puijenbroek, E. P., Vonkeman, H. E., & Jessurun, N. T. (2022). Neuropsychiatric adverse drug reactions associated with low dose methotrexate in rheumatoid arthritis patients. *Expert Opinion on Drug Safety*, *21*(3), 417-423. https://doi.org/10.1080/14740338.2022.2003328

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Taylor & Francis
Taylor & Francis Group

Expert Opinion on Drug Safety

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ieds20

Neuropsychiatric adverse drug reactions associated with low dose methotrexate in rheumatoid arthritis patients

Jette A. Van Lint, Tom Bakker, Peter M. ten Klooster, Eugene P. van Puijenbroek, Harald E. Vonkeman & Naomi T. Jessurun

To cite this article: Jette A. Van Lint, Tom Bakker, Peter M. ten Klooster, Eugene P. van Puijenbroek, Harald E. Vonkeman & Naomi T. Jessurun (2021): Neuropsychiatric adverse drug reactions associated with low dose methotrexate in rheumatoid arthritis patients, Expert Opinion on Drug Safety, DOI: 10.1080/14740338.2022.2003328

To link to this article: https://doi.org/10.1080/14740338.2022.2003328

Published online: 15 Nov 2021.

Submit your article to this journal

Article views: 76

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=ieds20

EXPERT OPINION ON DRUG SAFETY
https://doi.org/10.1080/14740338.2022.2003328

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

Check for updates

Neuropsychiatric adverse drug reactions associated with low dose methotrexate in rheumatoid arthritis patients

Jette A. Van Lint [a,*], Tom Bakker[a,*], Peter M. ten Klooster [b,c], Eugene P. van Puijenbroek [a,d], Harald E. Vonkeman [c,e] and Naomi T. Jessurun [a]

[a]Netherlands Pharmacovigilance Centre Lareb, 'S-Hertogenbosch, The Netherlands; [b]Transparency in Healthcare B.V, Hengelo, The Netherlands; [c]Department of Psychology, Health & Technology, University of Twente, Enschede, The Netherlands; [d]Pharmacotherapy, Epidemiology and Economics, Groningen Research Institute of Pharmacy, University of Groningen, Groningen, The Netherlands; [e]Department of Rheumatology and Clinical Immunology, Medisch Spectrum Twente, Enschede, The Netherlands

ABSTRACT

Background: Neuropsychiatric adverse drug reactions (NPADRs) are not commonly associated with low dose methotrexate (LDMTX) in patients with rheumatoid arthritis (RA).

Research design and methods: In this case series assessment, we described the nature and frequency of NPADRs with LDMTX in the Dutch DREAM-RA registry, including causality of NPADRs, the impact on further LDMTX treatment and the impact on patient reported Health Related Quality of Life (HRQoL).

Results: A total of 71 NPADRs (frequency 6.8%) associated with LDMTX were captured in the DREAM-RA registry. NPADRs were registered for 62 (5.9%) out of 1048 patients with 10.9 NPADRs per 1000 patient years. Headache, dizziness and depression were most frequently reported. The causality was considered probable for 67 NPADRs (94.4%) and definite for 1 NPADR (1.4%). NPADRs led to LDMTX withdrawal in 34 cases (47.9%) and was not restarted in 16 cases (47.1%). Median mental HRQoL was significantly decreased around the occurrence of the NPADR and remained significantly lower after the event. Median physical HRQoL was not significantly affected.

Conclusions: Knowledge on the nature, frequency and impact of the demonstrated NPADRs during LDMTX therapy will enhance attention toward these potential ADRs allowing better risk assessment and communication to patients.

ARTICLE HISTORY
Received 3 June 2021
Accepted 3 November 2021

KEYWORDS
Adverse drug reactions; methotrexate; registries; rheumatoid arthritis

1. Introduction

Methotrexate (MTX) has become the central, key disease-modifying anti-rheumatic drug (DMARD) in rheumatoid arthritis (RA). The low price and favorable cost-effectiveness ratio contribute to making MTX the most widely used conventional synthetic DMARD [1]. MTX is also administered for oncologic purposes in a high dose chemotherapeutic scheme. Although many adverse drug reactions (ADRs) are associated with low dose methotrexate (LDMTX) (5 mg up to 30 mg weekly), neuropsychiatric ADRs (NPADRs) have mainly been described with high dose methotrexate (HDMTX). HDMTX use in oncology is associated with severe NPADRs like cognitive dysfunction and neurotoxicity [2,3]. Insights into the occurrence and characteristics of NPADRs during LDMTX therapy is lacking [4]. Central nervous system (CNS) toxicity associated with weekly LDMTX treatment was described in a retrospective cohort of 25 patients and suggested that CNS toxicity is more common than previously reported, particularly in older patients with mild renal insufficiency [5]. Although several NPADRS, such as headache, dizziness and depression, have been described, other, less common NPADRs, such as disturbance in attention, have only been mentioned in one study [6,7].

The Netherlands Pharmacovigilance Center Lareb has received various spontaneous reports of NPADRs associated with LDMTX [8]. This suggests that LDMTX is more often associated with NPADRs than generally assumed. NPADRs have also been registered by healthcare professionals in the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. The aim of this real world data (RWD) registry is to monitor and evaluate the safety and effectiveness of RA treatment in daily clinical practice [9–11]. Since December 2015, ADRs captured in the DREAM-RA registry are directly forwarded to the Netherlands Pharmacovigilance Center Lareb. This RWD may provide further insights and understanding of the experiences and impact of ADRs such as frequencies and impact on health-related quality of life (HRQoL).

As neuropsychiatric complaints may not be commonly associated with LDMTX treatment in clinical practice, NPADRS may remain unrecognized and proper actions may not always be taken or even considered, while their impact on patients may be high. Therefore we conducted a case-series assessment of all NPADRs captured in a rheumatology department that participated from the onset in the DREAM-RA registry [12]. We aimed to describe the frequency and characteristics of NPADRs associated with LDMTX treatment in RA patients. We assessed their causality

CONTACT Jette A. Van Lint j.vanlint@lareb.nl Netherlands Pharmacovigilance Centre Lareb, 'S-Hertogenbosch, 'S-Hertogenbosch, The Netherlands

*Contributed equally

© 2021 Informa UK Limited, trading as Taylor & Francis Group

with the Naranjo Probability Scale (Naranjo) and explored the impact on further treatment and self-reported HRQoL of the patients.

2. Patients and methods

2.1. Study design

In this case series assessment, all NPADRs associated with LDMTX collected from one of the participating centers of the DREAM-RA registry were evaluated. The frequency and characteristics of the NPADRs were calculated and described and the causality was assessed with Naranjo.

2.2. Data source

DREAM is a network of Dutch hospitals working together by sharing and implementing treatment protocols such as treat-to-target and drug-tapering strategies, benchmarking outcomes of care and collaborating in studies, thus aiming to stimulate the quality of care, efficient use of means and clinical research. The initiative started in 2003 with a registry for monitoring RA patients using biologic DMARDs [13]. From 2006 onwards, the DREAM-RA registry has expanded with cohorts of early RA patients treated according to specific treat-to-target (remission induction) strategies and finally by including all RA patients treated in participating hospitals [14–16]. All patients in these cohorts are initially treated with methotrexate. All data in the registry is collected in the course of routine clinical practice. Since December 2015, all ADRs captured in the DREAM-RA registry are deidentified and forwarded directly to the Dutch Pharmacovigilance Center Lareb. In addition, all ADRs prospectively collected between 2003 and 2015 were retrospectively forwarded to Lareb. These ADR reports include the drug suspected to cause the ADR (including start and stop dates of the drug), the ADR descriptions including start and stop dates, combination therapy, outcome of the ADR and action taken with respect to the drug causing the ADR. Since no additional data are collected in the DREAM registry other than data collection in routine clinical practice and non-burdensome questionnaires, the Ethical Committee waived the need for ethical approval for the study in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO). Written consent was given by all patients before inclusion in the DREAM registry, which included the use of the data by Lareb [17]. In DREAM, ADRs can be continuously reported both by rheumatology healthcare professionals (HCPs) and by patients in the online data collection system 'mijnreumacentrum' (www.mijnreumacentrum.nl). All patient-reported ADRs were verified and scored by the respective rheumatology HCP before registration in the database.

2.3. Data selection

To obtain a consistently captured dataset over a large period of time, in this study we included all patients treated with LDMTX for RA in the Medisch Spectrum Twente (MST) hospital (Enschede, the Netherlands) that were intensively monitored in DREAM-RA. The MST hospital has participated in the DREAM-RA from its inception and has included the largest portion of RA patients in the registry. The ADRs forwarded to Lareb were assessed case-by-case by trained pharmacovigilance assessors and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21 [18]. All ADR reports in the MedDRA system organ class (SOC) 'Psychiatric disorders' and 'Nervous system disorders' associated with LDMTX were collected from the DREAM-RA registry until 29 February 2020. We provided all reported MedDRA Preferred Terms (PT) in both SOCs of the NPADRs associated with LDMTX.

2.4. Data analysis

We assessed the following patient demographics and clinical characteristics: gender, age (years), MTX dosage (mg/week), concomitant medication (folic acid, prednisolone, hydroxychloroquine, NSAID, biologic and sulfasalazine), rheumatoid factor (positive/negative/unknown) and anti-CCP (positive/negative/unknown). We described the nature of these NPADRs by including seriousness according to the Council for International Organizations of Medical Sciences (CIOMS) criteria [19]. This includes ADRs that are life threatening, fatal, cause hospitalization, result in disability or cause congenital anomalies. Furthermore, we described action taken after the NPADR (MTX dose increased, dose not changed, dose reduced, drug withdrawn, unknown), outcome of the ADR (recovered, recovering, not recovered, unknown) and dechallenge and rechallenge information. Dechallenge was defined as withdrawal of LDMTX from the patients' therapeutic regimen. A positive dechallenge was defined as recovery of the NPADR after withdrawal of LDMTX without additional treatment. Rechallenge was defined as restart with LDMTX after a NPADR. A positive rechallenge was defined as recurrence of the same NPADR after restarting LDMTX.

2.5. The frequency of the NPADRs

The frequency of NPADRs was defined as the number of NPADRs divided by the total number of patients using LDMTX in the DREAM-RA registry data (unit: %). The incidence density was expressed as the number of NPADRs per total number of patient years of LDMTX use in the DREAM registry (unit: NPADR/1,000 patient years).

The total number of patient years was calculated with the treatment time intervals between the start and stop date of LDMTX. All patient years of LDMTX therapy were calculated until 29 February 2020, also when the stop date was unknown. Cases with unknown LDMTX start dates were considered invalid and were not included in the calculated patient years. The total number of patient years of all valid LDMTX treatment time intervals was calculated.

2.6. Causality assessment

The probability of a causal association between LDMTX and NPADRs was assessed by an assessor at Pharmacovigilance Center Lareb by applying the Naranjo Probability Scale in a case-by-case manner [20,21]. Naranjo consists of 10 different

questions and the total score represents the probability of an association, which includes definite (total score ≥ 9), probable (total score 5 to 8), possible (total score 1 to 4) or doubtful (total score ≤ 0). The following information was included for assessing the probability using Naranjo: the nature of the NPADR, previously published research on the LDMTX-NPADR association, latency time between start of LDMTX and occurrence of NPADR, information on laboratory testsaction and outcome of the NPADR and rechallenge information.

2.7. Impact of NPADRs

The impact of the NPADRs was described by assessing dechallenges, rechallenges and any subsequent MTX therapy. Patients participating in the DREAM registry regularly complete patient reported outcome measures (PROMs). To further explore the impact of the NPADRs on health-related quality of life (HRQOL), available Dutch 36-Item Short Form version 2 (SF-36v2) questionnaires that had been completed by patients within 3–6 months (± 2 weeks) before, around (± 2 weeks), or 3–6 months (± 2 weeks) after the NPADR occurred were described [22]. Only patients that completed the SF-36v2 twice (around the time of the event and before or after the event) were included for this subgroup analysis. The SF-36v2 scores are aggregated into two distinct (orthogonal) higher-order summary scores: a physical component summary (PCS) and a mental component summary (MCS). The component summary scores have been standardized using normative data from the 1998 US normal population with a mean score of 50 and a standard deviation of 10.

3. Results

3.1. NPADRs and patients

In the DREAM-RA registry, 1048 patients used LDMTX with a total of 6540 patient years of LDMTX use. A total of 71 NPADRs (frequency 6.8%) were captured in 62 unique patients (5.9%), with 10.9 NPADRs per 1000 patient years of LDMTX use. Patient characteristics and NPADR characteristics are summarized in Table 1.

Table 1. Baseline characteristics of DREAM-RA patients using methotrexate with at least one neuropsychiatric adverse drug reaction.

Characteristics N = 62	N (%)
Female sex	40 (64.5%)
Age in years, mean (± SD), range	59.8 (± 13.1), 25–82
Rheumatoid factor	
Positive	43 (69.4%)
Negative	13 (21.0%)
Unknown	6 (9.7%)
Anti-CCP, n (%)	
Positive	34 (54.8%)
Negative	19 (30.7%)
Unknown	9 (14.5%)
Methotrexate dosage in mg/week, mean (± SD)	18.7 (± 5.9)
Specific methotrexate dosage	
< 15 mg/week	5 (7.0%)
15 mg/week	28 (39.4%)
20 mg/week	11 (15.5%)
25 mg/week	14 (19.7%)
30 mg/week	5 (7.0%)
Unknown	8 (11.3%)
Concomitant medication at moment of NPADR (N = 71)	
Folic acid	68 (95.8%)
Prednisolone	20 (28.2%)
Hydroxychloroquine	20 (28.2%)
NSAID	13 (18.3%)
Biologic	12 (16.9%)
Sulfasalazine	2 (2.8%)

Anti-CCP: anti cyclic citrullinated peptides, NPADR: neuropsychiatric adverse drug reaction, SD: Standard Deviation, NSAID: non-steroidal anti-inflammatory drug

Reproduced from [AB0254 NEUROPSYCHIATRIC ADVERSE DRUG REACTIONS ASSOCIATED WITH LOW DOSE METHOTREXATE IN RHEUMATOID ARTHRITIS PATIENTS, J. Van Lint, T. Bakker, P. Ten Klooster, H. Vonkeman, N. Jessurun, Ann Rheum Dis, volume 80, page 1153, 2021] with permission from BMJ Publishing Group Ltd [12].

Of the 62 patients with NPADRs during LDMTX use, 40 patients (64.5%) were female with a mean (± SD) age of 59.8 ± 13.1 years (range: 25 to 82 years) at the time of ADR. The mean MTX dosage for each individual NPADR was 18.7 ± 5.9 mg/week. Concomitant folic acid use by patients was reported in 68 (95.8%) NPADRs and prednisolone in 20 (28.2%) NPADRs. In total, 51 (71.8%) NPADRs were related to the SOC 'Nervous system disorders' and 20 (28.2%) to the SOC 'Psychiatric disorders.' In total 25 different NPADRs (PT) were registered (Table 2). Headache (n = 18, 25.4%), dizziness (n = 17, 24.0%) and depression (n = 4, 5.6%) were reported most frequently. Only one NPADR (1.4%) qualified

Table 2. Number of neuropsychiatric adverse drug reactions captured in the DREAM registry by MedDRA preferred terms.

Preferred terms SOC 'Nervous system disorders'	Number of NPADRs	Number of unique patients	Preferred terms SOC 'Psychiatric disorders'	Number of NPADRs	Number of unique patients
Headache	18	18	Depression	4	2
Dizziness	17	16	Listless	2	2
Tremor	3	3	Depressed mood	2	2
Disturbance in attention	3	3	Mood swings	2	2
Dysgeusia	2	2	Emotional disorder	2	2
Paresthesia	2	2	Abnormal behavior	1	1
Poor quality sleep	1	1	Agitation	1	1
Somnolence	1	1	Anxiety disorder	1	1
Polyneuropathy	1	1	Thinking abnormal	1	1
Sensory disturbance	1	1	Affective disorder	1	1
Memory impairment	1	1	Loss of libido	1	1
Head discomfort	1	1	Insomnia	1	1
			Restlessness	1	1

NPADR: neuropsychiatric adverse drug reaction SOC: system organ class

as serious according to the CIOMS criteria, based on hospitalization due to a treatment-based depression.

3.2. Causality of NPADRs

The causality of each individual NPADR (in PT) is summarized in Table 3. The outcome of the Naranjo assessment was definite in 1 (1.4%) NPADR, probable in 67 NPADRs (94.4%) and possible in 3 (4.2%) NPADRs. The outcome of neurologic ADRs (51 ADRs) was probable in 49 (96.1%) ADRs and possible in 2 ADRs (3.9%, 1 paresthesia, and 1 dizziness). The outcome of the psychiatric ADRs individually (20 ADRs) was definite in 1 ADR (5.0%, depression), probable in 18 ADRs (90.0%) and possible in 1 ADR (5.0%, mood swings). No NPADRs scored doubtful.

3.3. Impact of NPADRs

3.3.1. Outcome of NPADRs and the impact on the subsequent treatment

LDMTX therapy was discontinued following 34 NPADRs (47.9%), the dose was reduced following 14 NPADRs (19.8%) and the dose was increased following 1 NPADR (1.4%). LDMTX therapy was not changed following 11 NPADRS (15.5%). The action taken was unknown for 11 NPADRs (15.5%). Two positive rechallenges were reported for one patient with depression and one positive rechallenge was reported for dizziness. Out of 34 NPADRs leading to LDMTX withdrawal, the patient recovered (dechallenge) from the NPADR in 24 cases (70.6%). Patients recovered from most NPADRs (n = 47, 66.2%) and were still recovering from six NPADRs (8.5%) at the moment of registration. The patient had not recovered from the NPADR at the moment of registration in two cases (1 polyneuropathy, 1 paresthesia; 2.8%). The outcome of 16 NPADRs (22.5%) was unknown.

LDMTX was restarted after withdrawal in 15 cases (44.1% of NPADRs with LDMTX discontinuation). LDMTX was restarted with a dose reduction in six cases (3 headache, 1 depression, 1 somnolence, 1 abnormal behavior; 40% of cases with LDMTX restart). LDMTX was restarted with an increased dose in two cases (1 headache, 1 dysgeusia; 13.3% of cases with LDMTX restart). LDMTX was restarted with unknown dose adjustments in four cases (2 dizziness, 1 headache, 1 mood swings; 26.7% of cases with LDMTX restart). LDMTX was restarted without dose adjustments in three cases (1 emotional disorder, 1 depression, 1 head discomfort; 20% of cases with LDMTX restart). The mean time until LDMTX was restarted in all cases was 21.4 ± 37.6 months (median: 16.2 months). LDMTX was withdrawn and not restarted during the study period in 16 cases (47.1%).

Table 3. Distribution of the Naranjo Probability Scale score for each neuropsychiatric adverse drug reaction.

Preferred terms	Number of NPADRs	Doubtful	Possible	Probable	Definite
Headache [n]	18			18	
Dizziness [n]	17		1	16	
Tremor [n]	3			3	
Disturbance in attention [n]	3			3	
Dysgeusia [n]	2			2	
Paresthesia [n]	2		1	1	
Poor quality sleep [n]	1			1	
Somnolence [n]	1			1	
Polyneuropathy [n]	1			1	
Sensory disturbance [n]	1			1	
Memory impairment [n]	1			1	
Head discomfort [n]	1			1	
Depression [p]	4			3	1
Listless [p]	2			2	
Depressed mood [p]	2			2	
Mood swings [p]	2		1	1	
Emotional disorder [p]	2			2	
Abnormal behavior [p]	1			1	
Agitation [p]	1			1	
Anxiety disorder [p]	1			1	
Thinking abnormal [p]	1			1	
Affective disorder [p]	1			1	
Loss of libido [p]	1			1	
Insomnia [p]	1			1	
Restlessness [p]	1			1	

n: nervous system disorders p: psychiatric disorders, NPADR: neuropsychiatric adverse drug reaction

3.3.2. Health-related quality of life

Ten patients completed the SF-36v2 questionnaire in the selected period of two weeks around the NPADR and 3–6 months before (n = 9) or after (n = 9) the event. The ADRs concerned headache (n = 5), paresthesia (n = 2), emotional disorder (n = 1), dysgeusia (n = 1) and loss of libido (n = 1). The results are shown in Figure 1. The median mental component summary of the HRQoL significantly decreased around the occurrence of the NPADR (median = 32.1, IQR = 28.8–41.2) compared to the period before the ADR (median = 42.6, IQR = 33.0–50.5; Wilcoxon signed-rank test, p = 0.028) and remained significantly lower at 3–6 months after the event (median = 31.6, IQR = 27.1–42.6; p = 0.050). The median physical component summary did not significantly change during (p = 0.214) or after the event (p = 0.779).

4. Discussion

This case series assessment is the first study to systematically assess NPADRs associated with LDMTX using longitudinal RWD from a patient registry. By linking this data to a pharmacovigilance center we gained more insights in NPADRs associated with LDMTX, regarding their frequency, causality and impact.

Awareness that NPADRs can occur during LDMTX treatment is important because we observed a significant frequency of NPADRs and impact on the patients' treatment and HRQoL in our study population. In the current study, 5.9% of the patients in the DREAM-RA registry experienced a NPADR. A similar prevalence (5.5%) was described in a review of long-term safety of MTX monotherapy in RA for neurological events, amongst others: headache, depression, transient ischemic attack, stroke, vertigo, lethargy [7]. Wernick *et al*. retrospectively reviewed charts of 25 patients, of which 5 patients (20%) reported one or two of the following adverse drug reactions: unpleasant cranial sensations or memory impairment/cognitive dysfunction [5]. Attar *et al*. described central nervous system disorders in RA patients using LDMTX with a frequency of 18.3% of 116 patients, including headache,

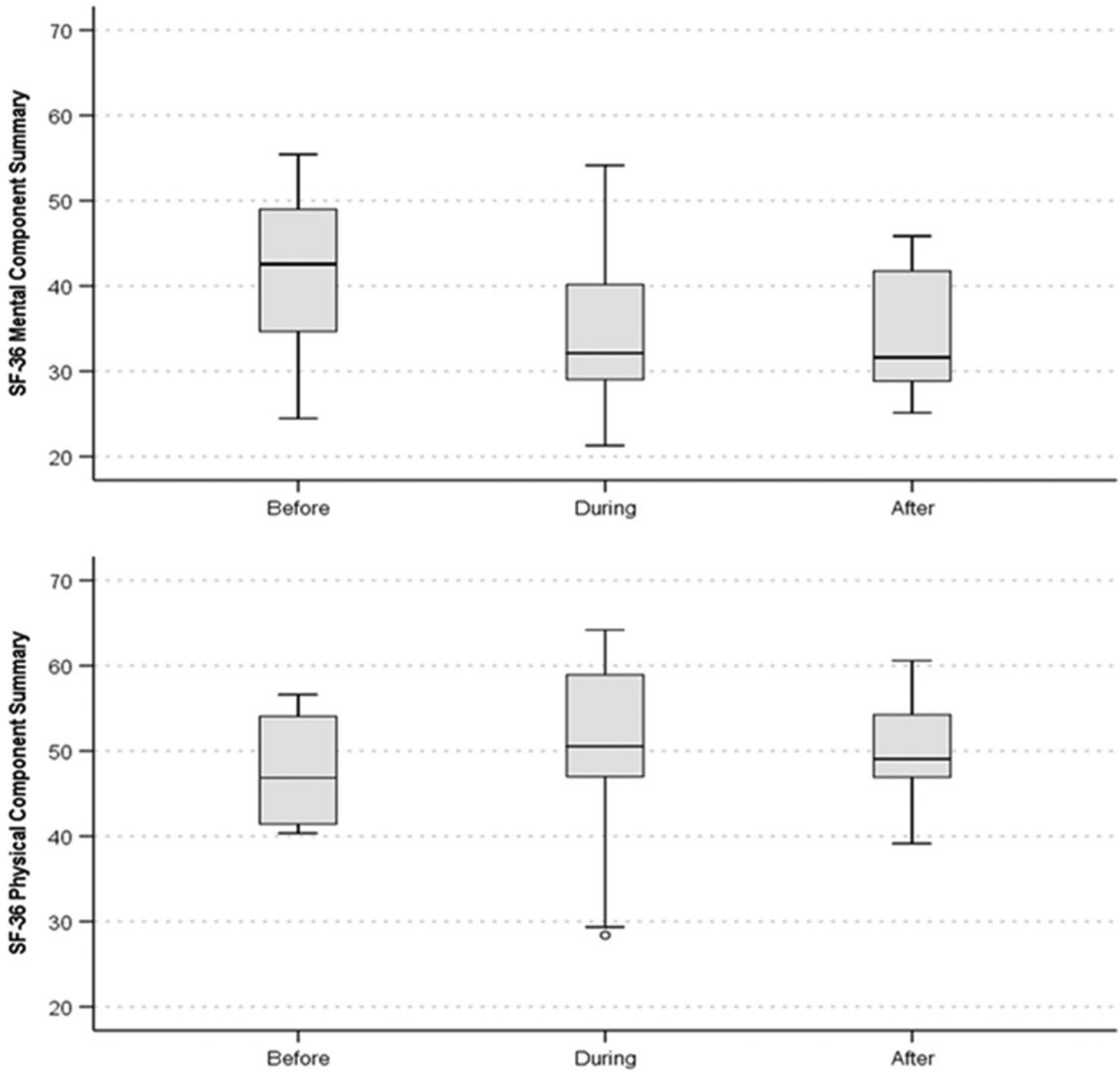

Figure 1. Impact of neuropsychiatric adverse drug reaction on the mental and physical health-related quality of life.

fatigue and an impaired ability to concentrate [6]. In a meta-analysis for safety outcomes of studies for LDMTX in various indications, including RA, the incidence of headache was 7.3% in 2501 safety years, the incidence of dizziness was 4.7% in 854 safety years and the incidence of insomnia was 4.6% in 221 safety years [23]. No treatment limiting NPADRs were reported in this study. HCPs might not relate neuropsychiatric symptoms to LDMTX treatment, resulting in underreporting of NPADRs. Likewise, it is impossible to capture all events that patients endure during their treatments. From this perspective, the frequency of NPADRs associated with LDMTX in our study can be considered as the lower limit of the true occurrence of these events in RA patients in daily clinical practice.

In total, the Netherlands' Pharmacovigilance Center Lareb has received 297 spontaneous reports of ADRs associated with LDMTX for variable indications in the SOCs 'Psychiatric disorders' and 'Nervous system disorders' [8]. When the reports in the DREAM-RA registry are combined with the reports spontaneously sent to Lareb, the most frequently reported NPADRs associated with LDMTX correspond with the NPADRs in our study: headache, dizziness and depression. Even though we have not assessed the spontaneous reports received by Lareb in this study, this could imply that headache, dizziness and depression are the most reported NPADRs with LDMTX use.

The mechanism of methotrexate neuropsychiatric toxicity is not yet fully understood, however multiple theories have been presented. Schmiegelow *et al*. discussed that HDMTX related neurotoxicity is likely the result of increased homocysteine plasma and CSF levels, generating reactive oxygen species, lipid peroxidation, adenosine release and neuronal and endothelial cell injury [24]. Chabner *et al*. related MTX neurotoxicity to excessive liberation of adenosine through inhibition of AICAR-formyltransferase [25] and Boison *et al*. concluded that this process might have a dilating mechanism of cerebral blood vessels, which in term alters neurological functioning [26]. Another theory that may explain the neurotoxic effect of MTX is the association between folate deficiency and cognitive decline [27,28]. The neurotoxic effect was also reported in intensive oral MTX administrations when insufficient doses of folinic acid were administered [29,30]. Even though a clear

mechanism for MTX related NPADRs cannot yet be explained, these theories demonstrate that a potential mechanism is likely to exist.

We recognized a possible association between NPADRs with LDMTX treatment in spontaneous ADR reports and were able to further assess this possible association using data from the DREAM-RA registry. In this registry, patients are systematically monitored for a relatively long period which provides a reliable sample of the real world Dutch RA patient population using MTX which is a strength of our study [31]. However, our study has several possible limitations. Firstly, we did not study the entire registry data but included data from a single center for a consistently captured dataset. Secondly, although the relationship was deemed probable using the Naranjo Probability Scale in more than 90% of all NPADRs, a definite causal relationship cannot be confirmed. Additionally, some patient characteristics which are important for a causality assessment, such as comorbidities and concomitant drugs, were not considered in the Naranjo assessment. Since rheumatology HCPs registered and confirmed the NPADR with LDMTX in routine clinical practice, we can assume that the HCPs did consider comorbidities and concomitant drugs and they were convinced that LDMTX highly contributed to the NPADR. Additionally, HCPs are unlikely to register ADRs for which they do not suspect a causal relationship, considering the administrative burden of ADR registration. As RA is a chronic disease and patients are treated by the same HCPs for years, we regarded this registration of NPADRs as more reliable than Naranjo, which is not extensively validated. Finally, we could not assess a dose-response relationship between MTX and occurrence or severity of NPADRs because MTX serum levels were not measured. On the other hand, NPADRs recurred in some patients that restarted with LDMTX and the NPADR disappeared after LDMTX withdrawal in 70.6% of the patients, suggesting a causal relationship.

The HRQoL scores indicate that the impact on the HRQoL differs between the mental and physical components. Our results suggest that NPADRS may decrease mental HRQoL. Unfortunately, the number of patients with available HRQoL scores at multiple time points around the occurrence of the NPADR was rather low. However, studies of the patient's perspective on the impact of ADRs are rarely conducted while they can provide valuable information [32]. Our study can be seen as a first step in quantifying the impact of NPADRs on patients' HRQoL. In addition, the possible contribution of longitudinal RWD from patient registries for pharmacovigilance purposes has previously not been extensively assessed. The advantage of gaining and sharing knowledge on MTX treatment for RA patients is of additional value since ADR information available in the enclosed patient information leaflet is usually not specified for LDMTX and HDMTX separately.

5. Conclusions

Our study demonstrates that NPADRs such as headache, dizziness and depression are captured and associated with LDMTX by rheumatology HCPs in the DREAMRA registry. NPADRs may lead to MTX withdrawal or dose reductions and decreased mental HRQoL. These new insights provide knowledge about ADRs in real world practice and it also shows that capturing ADR information in a disease specific patient registry is useful to generate this knowledge. Most NPADRs were considered as probable after assessing the associations with Naranjo and the recovery of patients after withdrawal of LDMTX, including positive rechallenges, also suggests a causal relationship. This knowledge gained from real world data on the nature, frequency and impact of NPADRs will enhance attention toward potential NPADRs during LDMTX therapy and allow better risk assessment and communication to patients.

Funding

No specific funding was received to carry out the work described in this article.

Declaration of interests

HE Vonkeman has received grants or personal fees from AbbVie, Amgen, AstraZeneca, BMS, Celgene, Celltrion, Gilead, GSK, Janssen-Cilag, Novartis, Pfizer, Roche and Sanofi-Genzyme, all outside the submitted work. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Author contributions

TB and JL contributed equally to this manuscript. All authors were involved in the conception and design of the study. TB, JL, NJ, PK were involved in the analysis and interpretation of the data. TB, JL, NJ were involved in the drafting of the paper. All authors were involved in revising of the paper and the final approval of the manuscript and all authors agree to be accountable for all aspects of the work.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Jette A. Van Lint http://orcid.org/0000-0003-2303-6199
Peter M. ten Klooster http://orcid.org/0000-0002-2565-5439
Eugene P. van Puijenbroek http://orcid.org/0000-0002-2236-1398
Harald E. Vonkeman http://orcid.org/0000-0003-3792-7718
Naomi T. Jessurun http://orcid.org/0000-0002-8267-1259

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Benjamin O, Bansal P, Goyal A, et al. Disease modifying anti-rheumatic drugs (dmard). Statpearls. Treasure Island (FL): StatPearls Publishing; 2020.
2. Gibson EM, Nagaraja S, Ocampo A, et al. Methotrexate chemotherapy induces persistent tri-glial dysregulation that underlies chemotherapy-related cognitive impairment. Cell. 2019;176:43–55. e13.
3. Wefel JS, Schagen SB. Chemotherapy-related cognitive dysfunction. Curr Neurol Neurosci Rep. 2012;12:267–275.

4. McKendry RJ, and Dale P. Adverse effects of low dose methotrexate therapy in rheumatoid arthritis. J Rheumatol. 1993;20:1850–1856.
5. Wernick R, and Smith DL. Central nervous system toxicity associated with weekly low-dose methotrexate treatment. Arthritis Rheum. 1989;32:770–775.

** **This reference is of considerable interest because this is one of the first reports addressing NPADRs with LDMTX and also describes positive rechallenges.**

6. Attar SM. Adverse effects of low dose methotrexate in rheumatoid arthritis patients. A hospital-based study. Saudi Med J. 2010;31:909–915.

* **This reference is of interest because it describes adverse effects of LDMTX and central nervous system symptoms are the second most frequent side effect in 116 RA patients**

7. Salliot C, and van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis. 2009;68:1100–1104.

** **This reference is of considerable interest because it is a systematic literature study investigating long term safety of LDMTX used for more than 2 years in rheumatoid arthritis. NPADRs are not extensively described but neurological events as headache, light headedness, fatigue, vertigo are mentioned in 21–38% of patients in one study and remained constant over time.**

8. Netherlands pharmacovigilance centre lareb. [Accessed: 08-05-2020]; Internet]. Available from: www.lareb.nl
9. van Dartel SA, Fransen J, Kievit W, et al. Predictors for the 5-year risk of serious infections in patients with rheumatoid arthritis treated with anti-tumour necrosis factor therapy: a cohort study in the Dutch rheumatoid arthritis monitoring (dream) registry. Rheumatology (Oxford). 2013;52:1052–1057.
10. van Dartel SA, Fransen J, Kievit W, et al. Difference in the risk of serious infections in patients with rheumatoid arthritis treated with Adalimumab, infliximab and etanercept: results from the Dutch rheumatoid arthritis monitoring (dream) registry. Ann Rheum Dis. 2013;72:895–900.
11. Kievit W, Fransen J, Adang EM, et al. Long-term effectiveness and safety of tnf-blocking agents in daily clinical practice: results from the Dutch rheumatoid arthritis monitoring register. Rheumatology (Oxford). 2011;50:196–203.
12. Van Lint J, Bakker T, Ten Klooster P, et al. Ab0254 Neuropsychiatric adverse drug reactions associated with low dose methotrexate in rheumatoid arthritis patients. Ann Rheum Dis. 2021;80:1153.
13. Kievit W, Fransen J, Oerlemans AJ, et al. The efficacy of anti-tnf in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. Ann Rheum Dis. 2007;66:1473–1478.
14. Vermeer M, Kuper HH, Bernelot Moens HJ, et al. Adherence to a treat-to-target strategy in early rheumatoid arthritis: results of the dream remission induction cohort. Arthritis Res Ther. 2012;14:R254.
15. Steunebrink LM, Vonkeman HE, ten Klooster PM, et al. Recently diagnosed rheumatoid arthritis patients benefit from a treat-to-target strategy: results from the dream registry. Clin Rheumatol. 2016;35:609–615.
16. Vermeer M, Kuper HH, Hoekstra M, et al. Implementation of a treat-to-target strategy in very early rheumatoid arthritis: results of the Dutch rheumatoid arthritis monitoring remission induction cohort study. Arthritis Rheum. 2011;63:2865–2872.
17. van de Laar CJ, Oude Voshaar MAH, Vonkeman HE. Cost-effectiveness of different treat-to-target strategies in rheumatoid arthritis: results from the dream registry. BMC Rheumatol. 2019;3:16.
18. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (meddra). Drug Saf. 1999;20:109–117.
19. Bankowski Z, Bruppacher R, Crusius I, et al. Reporting adverse drug reactions, definition of terms and criteria for their use Geneva: Council International Organizations of Medical Sciences (CIOMS); 1999 [cited 2020.
20. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239–245.
21. Adverse drug reaction probability scale (naranjo) in drug induced liver injury. Livertox: clinical and research information on drug-induced liver injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
22. ten Klooster PM, Vonkeman HE, Taal E, et al. Performance of the Dutch sf-36 version 2 as a measure of health-related quality of life in patients with rheumatoid arthritis. Health Qual Life Outcomes. 2013;11:77.
23. West J, Ogston S, and Foerster J Safety and efficacy of methotrexate in psoriasis: a meta-analysis of published trials. Plos One 2016;11:e0153740.

** **This study is of considerable interest because it is a large and relatively recent meta-analysis of published trials that included LDMTX safety. It is also of interest because data concerning patients using LDMTX prescribed for different immune mediated inflammatory diseases is included.**

24. Schmiegelow K. Advances in individual prediction of methotrexate toxicity: a review. Br J Haematol. 2009;146:489–503.
25. Chabner BA, Allegra CJ, Curt GA, et al. Polyglutamation of methotrexate. Is methotrexate a prodrug? J Clin Invest. 1985;76:907–912.
26. Boison D. Adenosine as a modulator of brain activity. Drug News Perspect. 2007;20:607–611.
27. Meng H, Li Y, Zhang W, et al. The relationship between cognitive impairment and homocysteine in a b12 and folate deficient population in China: a cross-sectional study. Medicine (Baltimore). 2019;98:e17970.
28. Hinterberger M, Fischer P. Folate and Alzheimer: when time matters. J Neural Transm (Vienna). 2013;120:211–224.
29. Winick NJ, Bowman WP, Kamen BA, et al. Unexpected acute neurologic toxicity in the treatment of children with acute lymphoblastic leukemia. J Natl Cancer Inst. 1992;84:252–256.
30. Mahoney DH Jr, Shuster JJ, Nitschke R, et al. Acute neurotoxicity in children with b-precursor acute lymphoid leukemia: an association with intermediate-dose intravenous methotrexate and intrathecal triple therapy–a pediatric oncology group study. J Clin Oncol. 1998;16:1712–1722.
31. Basch E. Systematic collection of patient-reported adverse drug reactions: a path to patient-centred pharmacovigilance. Drug Saf. 2013;36:277–278.
32. Rolfes L, van Hunsel F, Taxis K, et al. The impact of experiencing adverse drug reactions on the patient's quality of life: a retrospective cross-sectional study in the Netherlands. Drug Saf. 2016;39:769–776.