Original article

Rates and predictors of methotrexate-related adverse events in patients with early rheumatoid arthritis: results from a nationwide UK study

Ahmad A. Sherbini [1], James M. Gwinnutt [1], Kimme L. Hyrich [1,2], RAMS Co-Investigators and Suzanne M. M. Verstappen[1,2]

Abstract

Objectives. To estimate prevalence rates and identify baseline predictors of adverse events (AEs) over the first year of treatment in patients with RA starting MTX.

Methods. Data came from the UK Rheumatoid Arthritis Medication Study (RAMS), a prospective cohort of patients with RA starting MTX. This analysis included patients aged ≥18 years with physician diagnosed RA and symptom duration ≤2 years, who were commencing MTX for the first time. AEs were recorded by interviewing patients at 6- and 12-month follow-up visits. The period prevalence rates of AEs are reported for 0–6 months, 6–12 months and 0–12 months of follow-up. The associations between baseline characteristics and AEs were assessed using multi-variable logistic regression.

Results. A total of 1069 patients were included in the analysis. Overall, 77.5% experienced at least one AE. The most commonly reported AEs were: gastrointestinal (42.0%), neurological (28.6%), mucocutaneous (26.0%), pulmonary (20.9%), elevated alanine transaminase (18.0%) and haematological AEs (5.6%). Factors associated with increased odds of AEs were: women *vs* men (gastrointestinal, mucocutaneous, neurological) and alcohol consumption (nausea, alopecia, mucocutaneous). Older age, higher estimated glomerular filtration rate and alcohol consumption were associated with less reporting of haematological AEs.

Conclusions. AEs were common among patients over the first year of MTX, although most were not serious. Knowledge of the rates and factors associated with AE occurrence are valuable when communicating risks prior to commencing MTX. This can help patients make informed decisions whether to start MTX, potentially increasing adherence to treatment.

Key words: rheumatoid arthritis, DMARDs, methotrexate, adverse events, prognostic factors

CLINICAL SCIENCE

Rheumatology key messages

- Patients often worry about adverse events associated with MTX treatment, such as nausea and alopecia.
- Gastrointestinal adverse events, mainly nausea, were experienced by around two in every five patients in the first year of treatment with MTX.
- Modifiable factors, such as alcohol consumption, were associated with increased odds of developing nausea and alopecia.

Introduction

MTX is currently the DMARD of first choice for newly diagnosed patients with RA due to its low-cost and established efficacy [1]. However, adverse events (AEs) associated with MTX have a considerable impact on treatment retention rates; a 2014 review estimated that

[1]Centre for Epidemiology Versus Arthritis, Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester and [2]NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

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Correspondence to: Suzanne M. M. Verstappen, Centre for Epidemiology Versus Arthritis, Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester Academic Health Science Centre, Stopford Building, 99 Oxford Road, Manchester M13 9PG, UK. E-mail: suzanne.verstappen@manchester.ac.uk

during the first year of treatment 16% of patients discontinue MTX because of AEs [2, 3]. AEs account also for over one-third of the reasons reported for non-adherence to MTX [4], leading to patients not achieving treatment targets, and prompting potentially unnecessary switches to more costly treatments.

Patients commencing MTX often report feelings of concern about AEs, and better knowledge about the risk of AEs could help alleviate this [5]. Numerically communicating the risk of AEs associated with treatments can help to increase the willingness to start the treatment [6, 7]. Furthermore, understanding the risk of AEs before commencing MTX can help patients make informed decisions, and increase engagement with subsequent follow-up visits and monitoring; however, the rates of MTX associated AEs are poorly understood, with considerable variation reported between studies. A recent systematic review on the prevalence of AEs in patients receiving MTX for RA found the prevalence of any AE ranged between 13% and 100% (pooled estimate: 74%, 95% CI: 66%, 81%), and withdrawal due to AEs ranged between 2% and 38% (pooled estimate: 8%, 95% CI: 6%, 11%) [8]. This observed variation was more evident across different study designs; participants of randomized controlled trials (RCTs) reported more AEs than participants of observational studies, perhaps explained in part by the stricter protocols and closer monitoring in RCTs and the differences in patient inclusion criteria.

In addition to understanding rates of AE occurrence, the ability to predict AEs will move us closer to precision medicine. Previous studies have examined predictors of MTX treatment outcomes, such as MTX withdrawal due to AEs, development of any AE and elevated liver enzymes [9–12]. The number of identified predictors was limited by small sample sizes or insufficient control of other factors in these studies. Some AEs, such as mucocutaneous and haematological AEs, have received less attention to date, although they can be a major concern for patients and physicians. A comprehensive study to assess the risk of different MTX associated AEs in a large cohort of patients with RA is needed.

This report aims (i) to determine the prevalence of AEs (gastrointestinal, mucocutaneous, neurological, pulmonary, haematological and elevated liver enzymes) over the first year of treatment in patients with RA starting MTX for the first time, and (ii) to identify baseline factors associated with the development of AEs.

Methods

Study population

The Rheumatoid Arthritis Medication Study (RAMS) is a prospective observational cohort of patients with RA, 18 years or older commencing MTX for the first time, recruited from 38 rheumatology centres across the UK [13]. All treatment decisions were made by the patient's rheumatologist.

Ethical approval was obtained from Central Manchester NHS Research Ethics Committee (REC number 08/H1008/25) and all participants provided written informed consent.

Baseline assessments

Detailed data were collected at baseline from various sources, including case report forms (CRF) completed by a research nurse interviewing the patient and extracting relevant information from clinical notes and questionnaires completed by patients.

Demographic and lifestyle baseline data included age, gender, BMI, smoking status (never/current/former), alcohol consumption (yes/no) and caffeine intake (typical number of caffeinated beverages per day).

Disease related data included symptom duration, 28 tender and swollen joint count, and visual analogue scale (VAS) (0–100 mm) for general well-being [14]. History of co-morbidities was recorded from a list, including hypertension, diabetes, cardiovascular disease, asthma, chronic obstructive pulmonary disease, peptic ulcer disease, liver disease, renal disease, depression and cancer.

Laboratory values for haemoglobin, creatinine, alanine transaminase (ALT) and aspartate transaminase were documented from contributing centres. Estimated glomerular filtration rate (eGFR) was calculated for each patient based on creatinine level, age, sex and race. Serum samples were collected for central measurement of CRP, RF and anti-citrullinated protein antibodies (ACPA). The four-component disease activity score (DAS28-CRP) was calculated [15].

The following patient-reported outcomes (PROs) were collected: the British version of the HAQ Disability Index (0–3 scale) [16, 17]; VAS (0–100 mm) for pain and fatigue; the Hospital Anxiety and Depression Scale (HADS) (0–21) [18]; and the Beliefs about Medicines Questionnaire (BMQ) [19]. The BMQ consists of two 5-point Likert scales assessing patients' beliefs about the necessity of medication to control the disease (BMQ-necessity), and patients' concerns about their prescribed medication and the potential AEs (BMQ-concern).

Medication-related data were captured at baseline, including MTX dose and route of administration, and if patients were receiving other conventional synthetic (cs)DMARDs, steroids and any other medications. Data on MTX planned dose increment at baseline were examined to estimate the intended final dose as a predictor of AEs in a *post hoc* analysis. The classification of baseline concomitant csDMARD was based on patients who started other csDMARD any time until MTX start date, and did not stop the treatment before the start of MTX therapy.

Follow-up assessments

Patients were followed up at 6 and 12 months. Data on MTX intake, change in dose or route of administration, and other DMARDs were recorded at each follow-up.

A questionnaire with a pre-defined list of AEs was completed by a research nurse interviewing the patient

and reviewing case records at 6- and 12-month follow-up visits. The list was planned to capture systematically the occurrence of different AEs, including gastrointestinal, mucocutaneous, neurological, pulmonary, haematological AEs, and laboratory values of ALT enzyme. These groups of AEs, in addition to nausea (a prevalent AE) and alopecia (due to the concern it can cause for patients) are the main outcomes of this study. Upper limit of normal (ULN) for ALT was defined based on each hospital's cut-off.

Statistical analysis

This analysis included patients with reported symptom duration of less than 2 years who completed both the 6- and 12-month follow-up visits (Supplementary Fig. S1, available at *Rheumatology* online), regardless of whether they continued their MTX over the duration of the first year. Baseline characteristics and reasons for MTX discontinuation were compared between included patients and those who were excluded due to missing follow-up (Supplementary Tables S1 and S2, available at *Rheumatology* online).

To determine prevalence, the proportion of patients who reported having an AE was calculated from baseline to 6 months, from 6 to 12 months, and from baseline to 12 months of follow-up. Patients with more than one event recorded in each interval were only counted once for each AE.

Potential predictors of each outcome were selected *a priori* based on previous literature [8], and clinical plausibility. To assess the association between baseline predictors and AEs, separate multivariable logistic regression models were used for each AE.

Missing baseline data were imputed using multiple imputation by chained equations (10 datasets). Results from imputed datasets were pooled using Rubin's rules [20]. All data management and analyses were performed using Stata (14.0, StataCorp LLC, College Station, TX, USA).

Results

Overall, 2364 participants have been recruited to RAMS between July 2008 and May 2019. A total of 1069 patients with early RA were included in this analysis (Supplementary Fig. S1, available at *Rheumatology* online). The mean (s.d.) age at start of MTX was 59.2 (13.5) years and 698 patients (65.3%) were women. The mean (s.d.) duration of symptoms was 7.7 (5.6) months, and mean (s.d.) DAS28-CRP was 4.2 (1.4) (Table 1).

The majority (98.7%) of the patients started MTX orally, and the starting dose was ≥15 mg per week in half of the population (50.5%); 99.7% of the patients were prescribed folic acid supplements. At baseline, 266 patients (24.9%) were taking at least one other csDMARD with MTX: 86.5% hydroxychloroquine, 7.9% sulfasalazine and 5.6% both.

At the 6- and 12-month visits, 957 patients (89.5%) and 902 patients (84.4%) were still taking MTX, respectively, but 106 (9.9%) and 169 (15.8%) had switched to subcutaneous MTX by 6 and 12 months, respectively. Furthermore, 149 (13.9%) patients and 244 (22.8%) patients were taking other DMARDs (including biologics) at 6- and 12-month visits, respectively. Also, 294 (27.5%) and 197 (18.4%), respectively, were taking oral steroids at these two visits.

Rates of adverse events occurrence

Over the 12-month follow-up period, a total of 828 patients (77.5%) reported having at least one AE. Of those, 250 reported only one AE, 169 reported two AEs and the other patients reported three or more AEs (Supplementary Fig. S2, available at *Rheumatology* online). Gastrointestinal AEs were the most common over the study period (42.0%), with nausea as the most reported single event (31.2%). General AEs such as fever, weight loss and fatigue were also common (39.6%), followed by neurological (28.6%), mucocutaneous (26.0%) and pulmonary AEs (20.9%). The rates of haematological AEs and elevated ALT above the ULN were 5.6% and 18.0%, respectively (Table 2). Fatigue and headache were prevalent and reported in 29.4% and 19.0% of the patients, respectively. The prevalence rate of alopecia was 9.2% over the study period.

At the 6-month follow-up visit, 684 patients (64.0%) reported having AEs. Again, gastrointestinal AEs were the most prevalent group (33.7%). The number of patients reporting AEs during months 6–12 was lower across most of the AEs (general, gastrointestinal, mucocutaneous, neurological and pulmonary), compared with rates observed during the first 6 months (Table 2). For objective AEs, haematological AEs were 3.1% and 3.4%, and ALT >1× ULN were 11.2% and 11.1% at 6- and 12-month visits, respectively. A total of 192 patients (18.0%) had an elevated ALT >1× ULN over 12 months of follow-up, and 33 patients (3.1%) had ALT >2× ULN. Around 5% of the total population had an elevated ALT >1× ULN at the start of MTX therapy.

Although many patients reported pulmonary AEs (20.9%), these were mainly for subjective symptoms and only one case of suspected pneumonitis (0.1%) was reported during follow-up. Anaemia accounted for most of the haematological AEs; leukopenia and thrombocytopenia were only reported in 1.4% and 0.7%, respectively.

Additional analysis comparing the baseline characteristics and the rates of AEs over 1 year of follow-up in patients who started MTX as monotherapy and those who started MTX in combination with other csDMARDs is reported in Supplementary Tables S3 and S4 (available at *Rheumatology* online). Patients who were on concomitant DMARD with MTX had slightly higher mean DAS28-CRP and HAQ scores at baseline, and a higher percentage with RF positive and co-morbidities compared with those who started MTX monotherapy.

Baseline predictors of adverse events

Different predictors were identified for each group of AEs in the multivariable models, as shown in Table 3.

TABLE 1 Baseline characteristics of included patients

Characteristic	All patients (n = 1069)	Data availability (%)
Demographic and lifestyle factors		
Sex, female, n (%)	698 (65.3)	1069 (100)
Age, mean (s.d.), years	59.2 (13.5)	1069 (100)
Alcohol intake, yes, n (%)	732 (70.2)	1043 (97.6)
Smoking status, never, n (%)	425 (40.1)	1059 (99.1)
Former, n (%)	447 (42.2)	
Current, n (%)	187 (17.7)	
BMI, mean (S.D.), kg/m^2	28.0 (5.7)	982 (91.9)
Caffeine intake, median (IQR), cups/day	4 (2, 6)	831 (77.7)
Clinical and disease related factors		
Symptom duration, mean (s.d.), months	7.7 (5.6)	1069 (100)
RF positive, n (%)	578 (65.6)	881 (82.4)
ACPA positive, n (%)	552 (62.5)	883 (82.6)
DAS28-CRP, mean (s.d.)	4.2 (1.4)	1030 (96.4)
eGFR, mean (s.d.), ml/min/1.73m^2	87.5 (15.6)	992 (92.8)
Elevated ALT >1× ULN, n (%)	50 (5.0)	999 (93.5)
Patient-reported outcomes		
HAQ score (0–3), mean (s.d.)	1.05 (0.75)	1006 (94.1)
HADS Depression (0–21), mean (s.d.)	5.5 (4.0)	1001 (93.6)
HADS Anxiety (0–21), mean (s.d.)	6.2 (4.3)	999 (93.5)
VAS Patient (0–100mm), mean (s.d.)	41.0 (24.6)	1064 (99.5)
VAS Pain (0–100mm), mean (s.d.)	46.9 (27.3)	991 (92.7)
VAS Fatigue (0–100mm), mean (s.d.)	47.5 (29.2)	989 (92.5)
BMQ-Necessity scale (5–25), mean (s.d.)	19.5 (3.7)	967 (90.5)
BMQ-Concerns scale (5–25), mean (s.d.)	15.0 (3.9)	962 (90.0)
Co-morbidities, n (%)		
Hypertension	291 (27.2)	1030 (96.4)
Diabetes	92 (8.6)	1064 (99.5)
Peptic ulcer	10 (0.9)	1043 (97.6)
Liver disease	3 (0.3)	1060 (99.2)
Renal disease	11 (1.0)	1061 (99.3)
Asthma	113 (10.6)	1040 (97.3)
Chronic obstructive pulmonary disease	29 (2.7)	1054 (98.6)
Cerebrovascular disease	8 (0.8)	1036 (96.9)
Oncological disease	28 (2.6)	1010 (94.5)
Depression	124 (11.6)	969 (90.7)
History of any previous co-morbidity	514 (48.2)	1066 (99.7)
Medication related factors		
MTX starting dose, median (IQR), mg/week	15 (10, 15)	1058 (99.0)
Currently on oral steroids, yes, n (%)	261 (24.4)	1065 (99.6)
Dose, mean (s.d.), mg/day	12.9 (9.9)	253 (96.9)
Intra-muscular steroids, yes, n (%)	244 (22.8)	1045 (97.8)
NSAIDs, yes, daily or as required, n (%)	502 (53.5)	939 (87.8)
Concomitant csDMARDs, yes, n (%)	266 (24.9)	1069 (100)

ACPA: anti-citrullinated protein antibodies; ALT: Alanine transaminase; BMQ: Beliefs about Medicines Questionnaire; csDMARD: conventional synthetic DMARD; DAS28-CRP: Disease Activity Score 28 joint counts; eGFR: estimated glomerular filtration rate; HADS: Hospital Anxiety and Depression Scale; IQR: interquartile range; ULN: upper limit of normal; VAS: visual analogue scale.

Gastrointestinal AEs

Older age was associated with less reporting of gastrointestinal AEs (odds ratio [OR] 0.98 per year increase in age [95% CI: 0.97, 1.00]). Women were more likely to report gastrointestinal AEs compared with men (OR 2.03 [95% CI: 1.49, 2.75]). Alcohol consumption was associated with increased odds of reporting gastrointestinal AEs (OR 1.20 [95% CI: 0.89, 1.61]), but the effect estimate was not statistically significant. Higher levels of concern using the BMQ scale was also associated with increased odds of reporting gastrointestinal events (OR 1.05 [95% CI: 1.01, 1.09]), meaning that patients who were more concerned about MTX treatment were more likely to report gastrointestinal AEs. Further analysis found similar predictors of nausea. In addition, alcohol consumption (OR 1.39 [95% CI: 1.01, 1.91]) and higher

TABLE 2 Rates of adverse events reported at 6-month, 12-month, and during the whole follow-up period

Type of adverse event	Number of patients (%)		
	0–6 months	6–12 months	0–12 months
General	300 (28.1)	263 (24.6)	423 (39.6)
Fever	23 (2.2)	15 (1.4)	35 (3.3)
Weight loss	34 (3.2)	26 (2.4)	56 (5.2)
Fatigue/general malaise	230 (21.5)	182 (17.0)	314 (29.4)
Sore throat	42 (3.9)	43 (4.0)	78 (7.3)
Other general[a]	43 (4.0)	49 (4.6)	88 (8.2)
Gastrointestinal	360 (33.7)	258 (24.1)	449 (42.0)
Anorexia	29 (2.7)	17 (1.6)	42 (3.9)
Nausea	256 (24.0)	184 (17.2)	333 (31.2)
Vomiting	42 (3.9)	39 (3.7)	69 (6.5)
Stomach pain	62 (5.8)	42 (3.9)	92 (8.6)
Diarrhoea	123 (11.5)	81 (7.6)	164 (15.3)
Other gastrointestinal	10 (0.9)	20 (1.9)	28 (2.6)
Mucocutaneous	198 (18.5)	150 (14.2)	278 (26.0)
Alopecia	64 (6.0)	51 (4.8)	98 (9.2)
Oral ulcers	87 (8.1)	71 (6.6)	128 (12.0)
Itching	61 (5.7)	33 (3.1)	84 (7.9)
Other mucocutaneous	20 (1.9)	23 (2.2)	41 (3.8)
Neurological	225 (21.1)	162 (15.2)	306 (28.6)
Headache	152 (14.2)	100 (9.4)	203 (19.0)
Dizziness	94 (8.8)	61 (5.7)	134 (12.5)
Blurred vision	32 (3.0)	26 (2.4)	54 (5.1)
Other neurological	10 (0.9)	19 (1.8)	26 (2.4)
Pulmonary	132 (12.4)	130 (12.2)	223 (20.9)
Cough	97 (9.1)	85 (8.0)	157 (14.7)
Dyspnoea	29 (2.7)	35 (3.3)	55 (5.1)
Pneumonitis	0 (0.0)	1 (0.1)	1 (0.1)
Chest infection	15 (1.4)	20 (1.9)	34 (3.2)
Other Pulmonary	25 (2.3)	23 (2.2)	44 (4.1)
Haematological	33 (3.1)	36 (3.4)	60 (5.6)
Anaemia	24 (2.3)	23 (2.2)	42 (3.9)
Leucopoenia/neutropenia	8 (0.8)	9 (0.8)	15 (1.4)
Thrombocytopenia	3 (0.3)	4 (0.4)	7 (0.7)
Pancytopenia	0 (0.0)	3 (0.3)	3 (0.3)
Elevated ALT enzyme			
ALT >1× ULN	120 (11.2)	119 (11.1)	192 (18.0)
ALT >2× ULN	19 (1.8)	17 (1.6)	33 (3.1)
Any adverse event	684 (64.0)	604 (56.5)	828 (77.5)

[a]Included upper respiratory tract and other minor infections, psychological adverse event (e.g. insomnia, low mood and poor concentration), weight gain, reduced libido and menstrual abnormalities. ALT: alanine transaminase; ULN: upper limit of normal.

DAS28-CRP score (OR 1.16 [95% CI: 1.02, 1.31]) were associated with increased odds of nausea over the first year of follow-up.

Mucocutaneous AEs
Female gender (OR 1.98 *vs* male [95% CI: 1.41, 2.78]) and alcohol consumption (OR 1.35 *vs* none [95% CI: 0.97, 1.87]) were both associated with mucocutaneous AEs, as was higher BMI (OR 1.03 per kg/m^2 increase in BMI [95% CI: 1.00, 1.05]). Higher DAS28-CRP score (OR 0.83 per unit increase in DAS-CRP [95% CI: 0.72, 0.95]) and starting MTX ≥15 mg per week (OR 0.68 *vs* <15 mg per week [95% CI: 0.50, 0.91]) were associated with fewer mucocutaneous AEs. Female gender, alcohol

consumption and higher HAQ score were associated with alopecia, with a greater effect size compared with mucocutaneous AEs (Table 3).

Neurological and pulmonary AEs
Females were more likely to report neurological AEs compared with males (OR 1.50 [95% CI: 1.10, 2.05]). Past smokers were more likely to report pulmonary AEs compared with never smokers (OR 1.49 [95% CI: 1.05, 2.11]). Higher HAQ score at baseline was associated with increase in the odds (OR 1.41 per unit increase in HAQ [95% CI: 1.06, 1.88]), but the use of concomitant csDMARDs was associated with less reporting of pulmonary AEs (OR 0.68 [95% CI: 0.47, 0.99]).

TABLE 3 Baseline characteristics associated with later development of adverse events

Baseline factors	Odds ratio (95% CI)							
	Gastrointestinal (449 events)	**Nausea (333 events)**	**Mucocutaneous (278 events)**	**Alopecia (98 events)**	**Neurological (306 events)**	**Pulmonary (223 events)**	**Haematological (60 events)**	**ALT >1× ULN (192 events)**
Demographic and lifestyle								
Age (years)	**0.98 (0.97, 1.00)**	**0.97 (0.96, 0.99)**	1.00 (0.98, 1.01)	1.00 (0.98, 1.02)	0.99 (0.98, 1.00)	1.01 (0.99, 1.02)	**0.97 (0.95, 0.99)**	0.99 (0.97, 1.00)
Female *vs* male sex	**2.03 (1.49, 2.75)**	**2.09 (1.50, 2.91)**	**1.98 (1.41, 2.78)**	**4.87 (2.52, 9.44)**	**1.50 (1.10, 2.05)**	1.08 (0.77, 1.53)	1.32 (0.69, 2.53)	0.79 (0.55, 1.15)
Current *vs* never smokers	0.93 (0.63, 1.38)	1.02 (0.68, 1.53)	1.20 (0.80, 1.82)	0.95 (0.50, 1.81)	1.38 (0.93, 2.04)	0.89 (0.55, 1.43)	0.71 (0.32, 1.59)	1.14 (0.70, 1.85)
Former *vs* never smokers	1.13 (0.84, 1.52)	0.92 (0.67, 1.27)	1.10 (0.80, 1.53)	1.21 (0.76, 1.96)	1.31 (0.95, 1.80)	**1.49 (1.05, 2.11)**	1.01 (0.55, 1.85)	0.93 (0.63, 1.36)
Alcohol consumption (yes *vs* no)	1.20 (0.89, 1.61)	**1.39 (1.01, 1.91)**	1.35 (0.97, 1.87)	**1.69 (1.02, 2.80)**	1.08 (0.80, 1.47)	0.92 (0.66, 1.29)	**0.54 (0.30, 0.95)**	1.15 (0.79, 1.69)
BMI (kg/m²)	**1.03 (1.00, 1.05)**	1.02 (1.00, 1.05)	**1.03 (1.00, 1.05)**	—	—	—	—	1.02 (0.99, 1.05)
Caffeine intake (cups per day)	1.04 (0.98, 1.10)	1.05 (0.99, 1.12)	—	—	—	—	—	1.03 (0.96, 1.10)
Disease activity and patient-reported outcomes								
DAS28-CRP (0.96–9.4)	1.10 (0.97, 1.24)	**1.16 (1.02, 1.31)**	**0.83 (0.72, 0.95)**	0.89 (0.73, 1.09)	1.07 (0.94, 1.22)	1.01 (0.88, 1.16)	0.89 (0.69, 1.15)	1.04 (0.89, 1.22)
HAQ score (0–3)	1.11 (0.85, 1.46)	1.03 (0.78, 1.35)	1.25 (0.96, 1.63)	**1.62 (1.09, 2.41)**	1.14 (0.87, 1.50)	**1.41 (1.06, 1.88)**	1.03 (0.62, 1.70)	0.92 (0.66, 1.26)
VAS pain (0–100)	1.00 (0.99, 1.01)	1.00 (0.99, 1.00)	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.02)	1.00 (0.99, 1.01)
HADS depression (0–21)	1.02 (0.98, 1.06)	—	—	—	—	—	—	—
BMQ concern scale (5–25)	**1.05 (1.01, 1.09)**	**1.06 (1.02, 1.10)**	—	—	—	—	—	—
Laboratory tests								
ACPA positive	0.99 (0.67, 1.46)	1.01 (0.64, 1.59)	0.83 (0.53, 1.30)	—	0.97 (0.63, 1.48)	0.88 (0.55, 1.42)	0.88 (0.37, 2.07)	0.85 (0.49, 1.47)
RF positive	0.92 (0.62, 1.36)	0.85 (0.53, 1.38)	0.89 (0.54, 1.47)	1.01 (0.62, 1.65)	0.85 (0.54, 1.32)	1.17 (0.72, 1.90)	1.47 (0.57, 3.81)	0.88 (0.50, 1.52)
eGFR (ml/min/1.73m²)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	—	—	—	**0.98 (0.96, 1.00)**	0.99 (0.98, 1.01)
ALT (IU/l)	—	—	—	—	—	—	—	**1.04 (1.03, 1.05)**
Medication related								
MTX starting dose ≥15mg per week	0.96 (0.73, 1.25)	0.92 (0.69, 1.23)	**0.68 (0.50, 0.91)**	0.80 (0.51, 1.25)	0.90 (0.67, 1.19)	**0.66 (0.48, 0.91)**	0.68 (0.38, 1.20)	1.13 (0.80, 1.59)
Concomitant csDMARDs	0.82 (0.60, 1.12)	0.81 (0.58, 1.12)	0.86 (0.62, 1.21)	0.75 (0.44, 1.26)	0.87 (0.63, 1.21)	**0.68 (0.47, 0.99)**	1.47 (0.82, 2.62)	**0.61 (0.39, 0.94)**
Oral steroids	1.17 (0.86, 1.59)	—	0.90 (0.64, 1.27)	—	—	—	—	1.00 (0.68, 1.47)
NSAIDs	1.28 (0.94, 1.73)	1.12 (0.82, 1.52)	1.05 (0.74, 1.49)	—	—	—	—	0.94 (0.66, 1.33)
Co-morbidities								
Hypertension	1.19 (0.86, 1.65)	—	—	—	—	—	—	—
Diabetes	0.91 (0.56, 1.48)	0.88 (0.51, 1.49)	—	—	—	—	—	1.19 (0.67, 2.14)
Peptic ulcer disease	0.86 (0.22, 3.31)	0.56 (0.11, 2.86)	—	—	—	—	—	—
Asthma	—	—	—	—	—	1.08 (0.66, 1.77)	—	—
COPD	—	—	—	—	—	1.66 (0.73, 3.76)	—	—

ACPA: anti-citrullinated protein antibodies; ALT: alanine transaminase; BMQ: Beliefs about Medicines Questionnaire; COPD: chronic obstructive pulmonary diseases; csDMARD: conventional synthetic DMARD; DAS28-CRP: disease activity score 28 joint counts; eGFR: estimated glomerular filtration rate; HADS: Hospital Anxiety and Depression Scale; ULN: upper limit of normal; VAS: visual analogue scale. Odds ratio in bold indicates a statistically significant association at the 95% confidence level.

Haematologic AEs

Older age, alcohol consumption and higher eGFR were associated with fewer reported haematological AEs (OR 0.97 [95% CI: 0.95, 0.99], 0.54 [95% CI: 0.30, 0.95] and 0.98 [95% CI: 0.96, 1.00], respectively). In contrast, the use of other csDMARDs with MTX at baseline was associated with increased odds of haematological AEs (OR 1.47 [95% CI: 0.82, 2.62]).

Elevated ALT enzyme

Higher values of baseline ALT (OR 1.04 per IU/l increase [95% CI: 1.03, 1.05]) was associated with increase in ALT $>1\times$ ULN. Patients receiving other csDMARDs were less likely to have elevated ALT $>1\times$ ULN (OR 0.61 [95% CI: 0.39, 0.94]).

Supplementary analysis was carried out combining data on planned final dose of MTX in those with a dose escalation strategy (34.2%) with starting dose for those without a dose escalation strategy. Overall, similar findings were observed when MTX planned dose ≥15 mg per week was used in the model compared with using only MTX starting dose, but with slight changes in the effect size of different predictors (Supplementary Table S5, available at *Rheumatology* online). Mainly, the effect estimate in the associations between concomitant DMARDs (*vs* monotherapy) and pulmonary AEs was not statistically significant (OR 0.72 [95% CI: 0.50, 1.04]) compared with the previous model (OR 0.68 [95% CI: 0.47, 0.99]). Furthermore, MTX planned final dose ≥15 mg per week was associated with less reporting of neurological AEs (OR 0.70 [95% CI: 0.52, 0.95]).

Discussion

The study provides detailed prevalence rates of AEs associated with MTX in patients with early RA commencing MTX for the first time. AEs of the gastrointestinal system were the most prevalent during the first year of follow-up, followed by neurological, mucocutaneous, pulmonary, elevated ALT enzyme and haematological AEs. Nausea (31.2%) was the most reported AE, followed by fatigue (29.4%) and headache (19.0%). Despite patients' concern about alopecia, <1 in 10 patients reported this in the study period.

We observed that older age was associated with less reporting of gastrointestinal and haematological AEs, whereas women were more likely to report many AEs compared with men, including gastrointestinal, mucocutaneous, neurological and alopecia. Although there is no known causal link, drinking alcohol and increased BMI (both modifiable factors) were associated with increased odds of mucocutaneous AEs. Higher doses of MTX at treatment start were associated with fewer mucocutaneous AEs; however, the dose of MTX was not constant over the study period and many patients who started with lower doses had an increase within a few weeks. The results also showed that higher baseline HAQ score was associated with more reporting of pulmonary AEs. Higher HAQ scores may indicate poorer physical health

and higher degree of disability, which could be related to frailty or comorbid conditions. Therefore, HAQ may be acting as a marker of frailty, and thus frailty is associated with increased odds of pulmonary AE occurrence. Furthermore, the observed association could be explained by reverse causation. For instance, low-level lung involvement at baseline may be influencing baseline HAQ scores by restricting movement, creating a pseudo-association with later lung involvement when this manifests after baseline (so-called protopathic bias).

Currently all patients are required to undergo regular blood monitoring for cytopenia and elevated liver enzymes [21, 22]. Serious haematological AEs were rare ($<2\%$ experienced leukopenia or thrombocytopenia), consistent with previous reports [23, 24]. Anaemia was more common but could also represent anaemia associated with chronic inflammation in this population as it was not recorded if patients were also anaemic at baseline. Haematological AEs were more common among patients receiving combination csDMARD therapy, but this relation could be confounded if combination csDMARD use was more common among those with higher disease activity. Haematological AEs were less common among patients who consumed alcohol, a finding that requires further validation as there was no association between development of haematological AEs and amount of alcohol consumed (data not shown). Unlike haematological AEs, combination csDMARD therapy was associated with a lower odds of elevated ALT $>1\times$ ULN, consistent with a previous finding of an association between lower numbers of DMARDs during MTX treatment and elevated ALT $>2\times$ ULN [10]. Our analysis was limited by the fact that we only required a single reading of ALT $>1\times$ ULN for a hepatic AE to be recorded, which differed from the definition used in some RCTs, which may explain the higher rates of abnormal ALT in our study (18%) compared with previous reports (8.9%) [8]. Overall, the prevalence of most AEs was consistent with previous reports [8].

The findings presented in this report provide further insight into the management of patients with RA starting MTX, allowing better risk–benefit assessment at the start of therapy. Qualitative research has shown that patients are often very concerned before commencing a new treatment, and that lack of knowledge about the disease and treatment is a major source of concern [5]. Worrying about AEs could stop patients from initiating MTX, or reduce adherence to treatment thereafter [25]. The concern associated with AEs could be lessened by stressing the benefits of the treatment alongside a more specific discussion about the rates of AEs. More refined prescribing will also have an economic benefit for the health care system [26]. Resources can be better allocated by identifying patients with higher risk of AEs who require frequent monitoring and additional GP visits rather than a 'one-size-fits-all' approach. This study can also facilitate future research into biological pathways leading to specific AEs. For example, the relationship between certain modifiable factors such as alcohol

consumption, BMI or the use of concomitant medications with AEs can be further studied to explore these associations.

The study has several limitations. First, the observational study design restricts the causal interpretation of the significant predictors identified in our study. Additionally, the findings on the rates and predictors of AEs are limited by the absence of a comparator arm, which makes it harder to attribute the rate of these AEs to MTX alone since many of these AEs may have occurred regardless of MTX use. Similarly, there was no causal assessment at point of ascertainment for the recorded AEs, and therefore the rates of adverse drug reactions causally related to MTX might be lower than reported in our analysis. Furthermore, ascertaining the outcomes by interviewing patients, although a validated method for AEs measurement, can introduce risk of biased estimates of AEs, especially as the patient would be aware they are in a study about their RA treatment. We also excluded patients who did not have completed follow-up at 6 and 12 months of the study, although our analysis did not find substantial numeric differences in the rates of MTX discontinuation between these groups (Supplementary Table S2, available at *Rheumatology* online).

MTX starting dose was initially used as a predictor of AEs; however, many patients on lower doses had a rapid titration of their dose to higher levels. Additional analysis combining data on planned final dose of MTX in those with a dose escalation strategy with starting dose for those without a dose escalation strategy was warranted to reflect the escalation in MTX dose. Consideration in the future of other ways to analyse MTX should be considered, such as time-varying analysis or mean cumulative dose. As the date of occurrence of each AE was not recorded in the RAMS dataset, this was not possible in this analysis. We also included patients on combination therapy, reflective of clinical practice. Therefore, some observed AEs may be associated with DMARDs other than MTX or with unmeasured characteristics of the patients that led to the decision of combination therapy.

In summary, the findings of this study provide a better and more detailed understanding of the AEs associated with MTX in the first year of treatment. Knowledge about the factors associated with AEs could help patients in making informed decisions, potentially aid in identifying patients at high risk of certain AEs, in addition to facilitating mechanistic studies of AEs associated with MTX. Ultimately, this may lead to fewer AEs and thus improved outcomes for patients with RA.

Acknowledgements

Data availability statement

The data underlying this article cannot be shared publicly to protect the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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