European Journal of Internal Medicine 67 (2019) 97–101

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Cytopenia induced by low-dose methotrexate: An analysis of 433 cases from the French pharmacovigilance database

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A B S T R A C T

Introduction: Up to 5% of individuals exposed to low-dose methotrexate (MTX) (i.e., ≤30 mg/week) may develop cytopenia. However, MTX-induced cytopenia have been poorly described.

Material and methods: All cases of cytopenia (i.e., anaemia, leukopenia, thrombocytopenia, bi- or pancytopenia) in patients receiving low-dose MTX reported to the French pharmacovigilance database during 2006–2016 were analysed. Three groups were defined: cytopenia due to MTX medication errors (e.g., daily rather than weekly administration), cytopenia in people receiving several medications including MTX, cytopenia in people receiving only MTX.

Results: 433 cases were analysed. Eighty-four cases (19.4%) were due to medication errors, 180 (41.6%) occurred in individuals exposed both to MTX and other drugs, and 169 (39.0%) occurred in individuals only exposed to MTX. By comparison to other patients, those with cytopenia due to medication errors were older (74 ± 13 vs 69 ± 15 years, p = 0.002), received more frequently MTX orally (92.9% vs 65.3%, p < 0.001) and had more frequently pancytopenia (71.4% vs 54.4%, p = 0.005). By comparison to individuals exposed to multiple drugs (n = 180), those exposed only to MTX (n = 169) were older (71 ± 15 vs 67 ± 14, p = 0.02), and had more often pancytopenia (62.7% vs 46.7%, p = 0.001). Among those only exposed to MTX, most cases (n = 140, 82.8%) were considered as toxic rather than idiosyncratic reactions and a trigger (e.g. diarrhoea) was found in 59.3% of those cases. Overall 30 (6.9%) deaths occurred, including 8 in the "medication error" group and 8 in the "MTX only" group.

Conclusion: These data may be useful for defining optimal biological monitoring of patients prescribed low-dose MTX.

1. Introduction

Methotrexate (MTX) is an antimetabolite drug which has been used first in oncology and then in dermatology and rheumatology since the late 1940s [1]. Its efficacy when prescribed at immunomodulatory doses (i.e., ≤30 mg/week) has been demonstrated for many dermatological (e.g., psoriasis), rheumatic (e.g., rheumatoid arthritis) and gastrointestinal diseases (e.g., Crohn's disease). It is estimated that millions of patients receive MTX worldwide. Adverse events of MTX are well known at the oncological doses but the safety of this treatment at immunomodulatory doses has long been a subject of debate [2–4]. Although rare, MTX-induced pancytopenia is one of the most feared adverse event because of its high mortality rate [5–7]. Furthermore, beside pancytopenia, up to 5% of patients receiving low-dose MTX develop mono- (i.e., anaemia, leuco-neutropenia, thrombocytopenia) or bi-cytopenia [3,4,8]. Because they might be immunologically mediated, therefore occurring soon after MTX initiation [6,9,10], several international publications recommend complete blood cell count monitoring very frequently during the first weeks of exposure [11–14]. Yet, a cumulative, toxic mechanism seems much more frequently involved, myelosuppression usually occurring months or years after MTX initiation, often after a "trigger" event [5,6,9,10]. However, to date, few studies have focused on MTX-induced cytopenia and, to our knowledge, the larger available cohort studies have included 40–46 patients, respectively [6,9].

The aims of this study were to review all cases of cytopenia that occurred in patients exposed to low-dose (i.e., ≤30 mg/week) MTX reported to the French pharmacovigilance database during a 10-year period and to identify potential determinants for cytopenia.

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https://doi.org/10.1016/j.ejim.2019.07.016
Received 14 November 2018; Received in revised form 15 July 2019; Accepted 17 July 2019
Available online 23 July 2019

2. Material and methods

2.1. The French pharmacovigilance database

The French pharmacovigilance database gathers spontaneous reports of adverse drug reactions from French health practitioners or patients. Its organization and methods have been detailed elsewhere [15]. Each report is validated by clinical pharmacologists and when needed by specialist physicians in the relevant regional pharmacovigilance center before being recorded in the database. Adverse drug reactions are then encoded using the Medical Dictionary for Regulatory Activities (MedDRA) classification. Under French law, spontaneous reporting of adverse drug reactions is mandatory for every health practitioner in France, without consent of the patient. French law authorizes the regional pharmacovigilance centers "Centres Régionaux de PharmacoVigilance" to collect data from spontaneous reporting and to use these data for their pharmacovigilance mission. They ensure patients' and practitioners' anonymity.

2.2. Search for MTX-induced cytopenia

The database was screened for all cases of cytopenia in patients exposed to low-dose MTX recorded between January 1st 2006 and December 31th 2016. We defined low-dose MTX as a prescribed dose of ≤30 mg/week. We conducted an automated search through the database for the cases reported as involving the substance "methotrexate" and we excluded all patients for whom MTX had been used intravenously in order to exclude high-dose MTX usually prescribed for haematological malignancies. To analyse all types of cytopenia, we gathered all cases which satisfied the previous criteria and were registered in the categories of "anaemia non-haemolytic and marrow depression" (MedDRA code: 10002086), "white blood cell disorder" (MedDRA code: 10047954), "platelet disorder" (MedDRA code: 10035534), and "red blood cells disorder" (MedDRA code: 10038158).

2.3. Statistical analyses

Variables are reported as mean ± standard deviation or median [interquartile range] for continuous variables or counts (percentages) for categorical variables. Comparisons between groups were performed using the chi-2 test for categorical variables and the Student *t*-test (or the non-parametric Wilcoxon's test when appropriate) for continuous variables. Two-sided p-value ≤ 0.05 was considered significant. All analyses were performed using Stata, version 14.0.

3. Results

3.1. Study population

During the study period, 545 cases of cytopenia in patients receiving low-dose MTX were reported to French pharmacovigilance database, among which 112 were excluded (Fig. 1). Therefore, 433 cases were included in the analyses. The mean age of these patients was of 70 ± 14 years and 299 (69.1%) were women. The disease for which MTX had been prescribed was rheumatoid arthritis (n = 273, 63.1%), psoriasis or psoriatic arthritis (n = 46, 10.6%), spondyloarthropathy (n = 20, 4.6%), vasculitis (n = 20, 4.6%), connective tissue disease (n = 17, 3.9%), inflammatory bowel diseases (n = 11, 2.6%), or other/unknown diseases (n = 46, 10.6%). One hundred and ten (25.4%) patients presented with monocytopenia, 73 (16.9%) with bicytopenia and 250 (57.7%) with pancytopenia (haemoglobin level: 8.6 g/dL [7.5–9.9], leucocytes count: 1700/mm^3 [900–2600], neutrophil count: 589/mm^3 [220–980], platelet count: 47000/mm^3 [20000–99,000]). In 84 cases (19.4%), myelosuppression was due to MTX medication errors, in 169 cases (39.0%) MTX was the only reported suspect drug, and in 180 cases (41.6%) there was at least one other drug suspected for the cytopenia (Fig. 1). Overall 30 (6.9%) deaths occurred, including 8 in the medication error group and 8 in the MTX only group.

3.2. MTX medication errors

In the 84 (19.4%) patients for whom cytopenia was due to an error, 64 (76.2%) took the treatment daily instead of weekly. In these 64 patients, only one had been prescribed sub-cutaneous MTX, all other prescriptions were for oral drug. Three (3.6%) other patients took the treatment daily because they had been wrongly given by their pharmacist MTX instead of Meteoxane® (simeticone and phloroglucinol, a drug for intestinal pain). Ten (11.9%) patients receiving MTX weekly should not had been prescribed the treatment because of severe renal insufficiency (i.e., glomerular filtration rate ≤30 ml/min/m^2) or undergoing dialysis. Lastly, 7 (8.3%) patients had cytopenia "induced by MTX overdose" without any supplementary information available. By comparison to the 349 other patients without MTX medication errors, these 84 patients were older (74 ± 13 vs 69 ± 15 years, p = 0.002), received more frequently MTX orally than by subcutaneous route (92.9% vs 65.3%, p < 0.001) and had more frequently pancytopenia (71.4% vs 54.4%, p = 0.005) (Table 1).

3.3. Co-prescriptions of other drugs

In 180 (41.6%) cases, cytopenia occurred in low-dose MTX exposed patients who were also receiving at least one other suspect drug. The co-suspect drugs are detailed in Fig. 2. The mean number of co-suspect drug was of 1 [1,2]. One quarter (25%) of these co-suspect drugs were antibiotics (beta-lactamins 47.0%, fluoroquinolones 16.5%, macrolides 12.9%, sulfonamides 11.8%). Respectively 12%, 9% and 8% of co-suspect drugs were monoclonal antibodies (e.g., anti-CD20 or anti-TNF antibodies), non-steroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors.

3.4. MTX as the only suspect drug

For 169 (39.0%) patients, MTX was considered the only suspect drug for cytopenia. As compared with patients with co-suspect drugs, these patients were older (71 ± 15 vs 67 ± 14 years, p = 0.02), more frequently received oral MTX (70.4% vs 60.6%, p = 0.05), and more frequently had pancytopenia (62.7% vs 46.7%, p = 0.003) (Table 2).

Overall, cytopenia occurred after a mean of 31 ± 46 months of MTX exposure (median: 12 [3–36] months). For 135 of the 169 patients (80.0%), cytopenia developed after more than two months of exposure. A toxic mechanism was hypothesized for these patients. Cytopenia occurred within the first two months of exposure in 34 (20.0%) patients. The characteristics of these 2 groups of patients are presented in Table 3. Those with an early reaction more frequently received MTX subcutaneously (p = 0.01).

Regarding the 34 patients with cytopenia occurring early in the MTX course, 5 (14.7%) had been receiving MTX previously for months and cytopenia developed when they switched from oral to subcutaneous administration (n = 3) or after dosage increase (n = 2). A toxic mechanism rather than an idiosyncratic reaction (i.e., individual unpredictable reaction including immune-mediated toxicity) was hypothesized in these 5 patients. For 17 (50%) patients, cytopenia developed early and no predisposing factor was evidenced. An idiosyncratic reaction was therefore considered. Lastly, for 12 (35.3%) patients, insufficient data was available to retain a toxic one mechanism over the other.

Regarding the overall 140 cases considered most probably resulting from a toxic mechanism, a triggering factor was recorded for 83 (59.3%): 28 patients (20.0%) had a severe folate deficiency diagnosed on blood tests and/or bone-marrow aspiration, 26 (18.6%) presented renal insufficiency induced by factors other than MTX (such as diarrhoea, surgery, infection), 12 (8.6%) presented acute infection (no

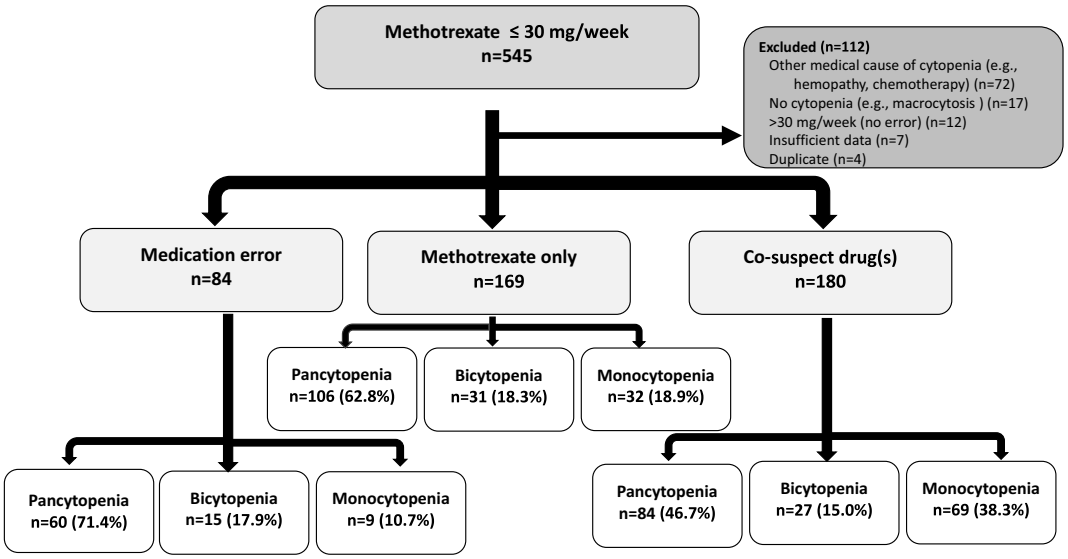

Fig. 1. Study flow chart.

Table 1
Comparison of patients with cytopenia due to MTX medication errors to patients with cytopenia not due to MTX medication errors.

	Errors (n = 84)	Normal dose (n = 349)	p
Age, years	74 ± 13	69 ± 15	**0.002**
Female, n (%)	57 (67.9)	242 (69.3)	0.79
Methotrexate taken orally, n (%)	78 (92.9)	228 (65.3)	**< 0.001**
Dosage, mg/day or mg/week	10 ± 8[a]	13 ± 5[b]	–
Duration of exposure, days or months	11 ± 5[c]	33 ± 52[d]	–
Type of cytopenia, n (%)			**0.002**
Monocytopenia	9 (10.7)	101 (29.0)	
Bicytopenia	15 (17.9)	58 (16.6)	
Pancytopenia	60 (71.4)	190 (54.4)	
Underlying disease, n (%)			0.08
Rheumatoid arthritis	52 (61.9)	221 (63.3)	
Psoriasis/psoriatic arthritis	8 (9.5)	38 (10.9)	
Spondylarthropathy	2 (2.4)	18 (5.2)	
Vasculitis	4 (4.8)	16 (4.6)	
Connective tissue disease	2 (2.4)	15 (4.3)	
Inflammatory bowel disease	0	11 (3.1)	
Other / unknown	16 (19.0)	30 (8.6)	
Folate supplementation, n (%)			0.10
No	14 (16.7)	76 (21.8)	
Yes	20 (23.8)	111 (31.8)	
Unknown	50 (59.5)	162 (46.4)	
Evolution			0.56
Favorable	73 (86.9)	316 (90.5)	
Death	8 (9.5)	22 (6.3)	
Unknown	3 (3.6)	11 (3.2)	

Significant values (i.e., ≤ 0.05) are in bold.
[a] Per day.
[b] Per week.
[c] Days.
[d] Months.

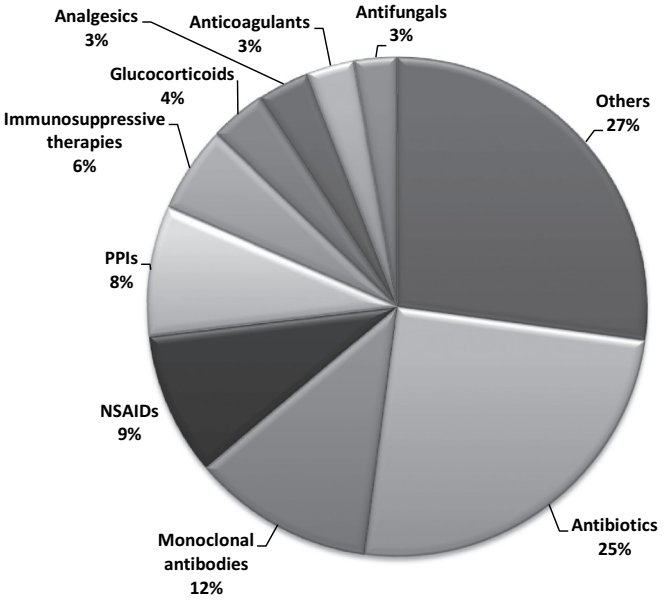

Fig. 2. Distribution of co-suspect drugs.

other drug prescribed), 6 (4.3%) showed acute significant weight loss, 5 (3.6%) had a MTX dosage increase, 3 (2.1%) had surgery and 3 (2.1%) had severe hypoalbuminemia.

4. Discussion

Among the 433 cases of cytopenia in people receiving low-dose MTX reported in this study, 84 (19.4%) were due to errors in MTX prescription/administration, 180 (41.6%) occurred in individuals exposed both to MTX and other medications (mostly antibiotics) and 169 (39.0%) occurred in patients for whom MTX was the only suspect drug. Among these 169 patients, a toxic mechanism (82.8%) was much more frequently involved than an idiosyncratic reaction (10.1%).

In our study, one fifth of cases were due to MTX medication errors. Even though this proportion does probably not reflect the real life proportion (cases of MTX errors being probably more likely to be reported to the pharmacovigilance network), such errors are still frequently reported, with a high mortality rate [16,17]. Errors can occur throughout the chain going from prescription to ingestion. In a previous study of medication errors reported to American Food and Drug Administration, 37% of MTX dosing errors were attributed to the prescriber, 20% to the patient, 19% to dispensing, and 18% to administration by a health care professional [17]. Several suggestions, including adjusting the packaging, improving dispensing software, and education of both healthcare professionals and patients have been previously proposed to lower MTX medication errors [6,16,17]. Our results evidence that education seems particularly important in older

Table 2
Comparison of patients with MTX as the only suspect drug to patients exposed to several suspect medications (medication errors excluded).

	MTX only (n = 169)	Several medications (n = 180)	p
Age, years	71 ± 15	67 ± 14	**0.02**
Female, n (%)	109 (64.5)	133 (73.9)	0.06
Methotrexate taken orally, n (%)	119 (70.4)	109 (60.6)	**0.05**
Mean dosage, mg/week	13 ± 5	13 ± 5	0.44
Duration of exposure, months	12 [3–36]	12 [4–36]	0.57
Type of cytopenia, n (%)			
Monocytopenia	32 (18.9)	69 (38.3)	< **0.001**
Bicytopenia	31 (18.4)	27 (15.0)	
Pancytopenia	106 (62.7)	84 (46.7)	
Underlying disease, n (%)			0.45
Rheumatoid arthritis	99 (58.6)	122 (67.4)	
Psoriasis/psoriatic arthritis	24 (14.2)	14 (7.7)	
Spondylarthropathy	10 (5.9)	9 (5.0)	
Vasculitis	9 (5.3)	7 (3.9)	
Connective tissue disease	8 (4.7)	7 (3.9)	
Inflammatory bowel disease	4 (2.4)	7 (3.9)	
Other/unknown	15 (8.9)	15 (8.2)	
Folate supplementation, n (%)			**0.01**
No	46 (27.2)	30 (16.7)	
Yes	43 (25.4)	68 (37.8)	
Unknown	80 (47.4)	82 (45.5)	
Evolution			0.49
Favorable	156 (92.3)	160 (88.9)	
Death	8 (4.7)	14 (7.8)	
Unknown	5 (3.0)	6 (3.3)	

Significant values (i.e., ≤ 0.05) are in bold.

Table 3
Comparison of patients with cytopenia occurring early to patients with cytopenia occurring late after MTX initiation.

	Early cytopenia (n = 34)	Late cytopenia (n = 135)	p
Age, years	71 ± 16	70 ± 15	0.87
Female, n (%)	19 (55.9)	90 (66.7)	0.24
Methotrexate taken orally, n (%)	18 (52.9)	101 (74.8)	0.01
Mean dosage, mg/week	14 ± 7	13 ± 5	0.46
Duration of exposure, months	1.5 [1–2]	15 [11–60]	0.004
Type of cytopenia, n (%)			0.73
Monocytopenia	6 (17.7)	26 (19.3)	
Bicytopenia	8 (23.5)	23 (17.0)	
Pancytopenia	20 (58.8)	86 (63.7)	
Underlying disease, n (%)			0.22
Rheumatoid arthritis	14 (41.2)	85 (63.0)	
Psoriasis / psoriatic arthritis	6 (17.7)	18 (13.3)	
Spondylarthropathy	3 (8.8)	7 (5.2)	
Vasculitis	3 (8.8)	6 (4.4)	
Connective tissue disease	1 (2.9)	7 (5.2)	
Inflammatory bowel disease	2 (5.9)	2 (1.5)	
Other / unknown	5 (14.7)	10 (7.4)	
Folate supplementation, n (%)			0.17
No	5 (14.7)	41 (30.4)	
Yes	11 (32.4)	32 (23.7)	
Unknown	18 (52.9)	62 (45.9)	
Evolution			0.45
Favorable	30 (88.3)	126 (93.3)	
Death	3 (8.8)	5 (3.7)	
Unknown	1 (2.9)	4 (3.0)	

Significant values (i.e., ≤ 0.05) are in bold.

patients prescribed MTX orally. Noteworthy, as a consequence of saturable absorption when given orally, MTX toxicity correlates much better with duration and extent of exposure than peak serum concentration [18]. As a result, all MTX medication errors reported in the present study were in patients who took MTX every day for several days, not in patients with massive ingestion on one day [18]. Our results also suggest that MTX should preferably be prescribed subcutaneously in people at risk of errors in MTX prescription/administration, in particular older people. On top of being associated with a lower risk of errors, it is important to note that subcutaneous MTX has a better bioavailability, is more efficient, and has a better tolerability profile than oral MTX [19].

Most cases included in our study occurred in patients for whom at least two drugs (including MTX) were considered as suspect drugs for cytopenia. For these patients, it is impossible to know whether MTX or the other(s) drug(s) was the only suspect drug or if an interaction between MTX and another drug was responsible for the cytopenia. In one quarter of cases this other medication was an antibiotic. In oncology, it is known that weak organic acids such as penicillin G, piperacillin, or aspirin may inhibit excretion of high-dose MTX [20,21]. On the other hand, low-dose MTX is usually considered to have limited drug interactions, with the exception of some antibiotics such as trimethoprim-sulfamethoxazole and NSAIDs (including high-dose acetylsalicylic acid) [22,23]. Nevertheless, as bacterial infections result to several factors that may combine and contribute to MTX toxicity (e.g., antibiotic prescription combined with fever, risk of dehydration and renal impairment), it may be prudent to temporarily suspend MTX administration when antibiotics are needed for a patient.

Regarding cases for which MTX was the only suspect drug for cytopenia, most occur months or years after MTX initiation, suggesting a cumulative, toxic effect. In our study 80% of cytopenia occurred more than two months after MTX initiation which is consistent with previous reports [9,24]. Further, as in our study, a trigger event (e.g., dehydration, infection) was found in most patients developing cytopenia after many weeks/months of MTX exposure [5,9,10]. More rarely, cytopenia occur early, within the first weeks of MTX exposure, possibly due to an idiosyncratic reaction. Among these patients, a central mechanism is much more likely than an immune-allergic, peripheral reaction, suggesting a still undetermined, individual (genetic?) factor predisposing to MTX toxicity. In patients exposed to high-dose MTX, an association between cytopenia and MTHFR (methylenetetrahydrofolate reductase) gene polymorphisms has been evidenced [25]. Findings are more discordant in patients exposed to low-dose MTX [26–28].

Our study has several strengths, including the fact that each analyzed report had been validated before being recorded in the database, the large number of cases, from a population-based sample of individuals, with a wide range of diseases affecting both sexes and all age-groups. This enabled us to separately compare different groups of patients and to determine predictors for cytopenia depending on the suspected underlying mechanism.

There are, however, some limitations. First it is a retrospective study of cases declared by practitioners, with possible selection bias, the most severe cases (e.g., pancytopenia, cases leading to patient's death) or adverse reactions occurring after MTX administration errors being more likely to be reported. Therefore, our study population is not exhaustive of the overall population with MTX-induced cytopenia and does not allow any calculation of incidence, mortality or determination of proportion of cases due to medication errors. Further, some factors that could be involved in occurrence of cytopenia were not systematically recorded in the analysed forms. For instance, data regarding folate supplementation was missing for half of cases and level of albuminemia was missing for most patients. The proportion of cytopenia with a trigger event (i.e., 59.3%) may therefore represent an underestimation of the true proportion.

In the era of biotherapies which are expensive and not available to every patient, MTX is an efficient and cheap drug available worldwide. Moreover, MTX is usually safe, with the exception of some rare but serious adverse event, including cytopenia. Current international recommendations advise to monitor complete blood cell count very frequently during the first weeks of exposure and then regularly every

2–3 months [11–14]. However, because a toxic mechanism following a trigger event is much more frequently involved than an “idiopathic” idiosyncratic reaction, a monitoring adapted to at-risk situations (e.g., infection, dehydration, new medication) would be probably more useful than a systematic monitoring. Further, it seems useful to remind that folate supplementation is strongly recommended in all individuals exposed to low-dose MTX, even during long-term exposure.

Financial support

None.

Decleration of Competing Interests

The authors declare no conflict of interest for this work.

References

[1] Malaviya AN. Landmark papers on the discovery of methotrexate for the treatment of rheumatoid arthritis and other systemic inflammatory rheumatic diseases: a fascinating story. Int J Rheum Dis 2016;19:844–51.
[2] Kinder AJ, Hassell AB, Brand J, Brownfield A, Grove M, Shadforth MF. The treatment of inflammatory arthritis with methotrexate in clinical practice: treatment duration and incidence of adverse drug reactions. Rheumatology (Oxford) 2005;44:61–6.
[3] Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis 2009;68:1100–4.
[4] Mazaud C, Fardet L. Relative risk of and determinants for adverse events of methotrexate prescribed at a low dose: a systematic review and meta-analysis of randomized placebo-controlled trials. Br J Dermatol 2017;177:978–86.
[5] Nygaard H. Pancytopenia secondary to methotrexate therapy in rheumatoid arthritis: comment on the article by Gutierrez-Ureña et al. Arthritis Rheum 1997;40:194–5. [author reply 195-196].
[6] Ajmani S, Preet Singh Y, Prasad S, Chowdhury A, Aggarwal A, Lawrence A, et al. Methotrexate-induced pancytopenia: a case series of 46 patients. Int J Rheum Dis 2017;20:846–51.
[7] Mameli A, Barcellona D, Marongiu F. Fatal cytopenia induced by low-dose methotrexate in elderly with rheumatoid arthritis. identification of risk factors. Am J Ther 2017;24:e106–7.
[8] West J, Ogston S, Foerster J. Safety and efficacy of methotrexate in psoriasis: a meta-analysis of published trials. PLoS One 2016;11:e0153740.
[9] Mori S, Hidaka M, Kawakita T, Hidaka T, Tsuda H, Yoshitama T, et al. Factors associated with myelosuppression related to low-dose methotrexate therapy for inflammatory rheumatic diseases. PLoS One 2016;11:e0154744.
[10] Gutierrez-Ureña S, Molina JF, García CO, Cuéllar ML, Espinoza LR. Pancytopenia secondary to methotrexate therapy in rheumatoid arthritis. Arthritis Rheum 1996;39:272–6.
[11] Maharaj AB, Chandran V. Treatment of psoriatic arthritis with traditional DMARD's and novel therapies: approaches and recommendations. Expert Rev Clin Immunol 2017;13:319–31.
[12] Warren RB, Weatherhead SC, Smith CH, Exton LS, Mohd Mustapa MF, Kirby B, et al. British association of dermatologists' guidelines for the safe and effective prescribing of methotrexate for skin disease 2016. Br J Dermatol 2016;175:23–44.
[13] Raaby L, Zachariae C, Østensen M, Heickendorff L, Thielsen P, Grønbæk H, et al. Methotrexate use and monitoring in patients with psoriasis: a consensus report based on a danish expert meeting. Acta Derm Venereol 2017;97:426–32.
[14] Nast A, Gisondi P, Ormerod AD, Saiag P, Smith C, Spuls PI, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris—update 2015—short version—EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol JEADV 2015;29:2277–94.
[15] Montastruc J-L, Sommet A, Lacroix I, Olivier P, Durrieu G, Damase-Michel C, et al. Pharmacovigilance for evaluating adverse drug reactions: value, organization, and methods. Jt Bone Spine Rev Rhum 2006;73:629–32.
[16] Cairns R, Brown JA, Lynch A-M, Robinson J, Wylie C, Buckley NA. A decade of Australian methotrexate dosing errors. Med J Aust 2016;204:384.
[17] Moore TJ, Walsh CS, Cohen MR. Reported medication errors associated with methotrexate. Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm 2004;61:1380–4.
[18] Chan BS, Dawson AH, Buckley NA. What can clinicians learn from therapeutic studies about the treatment of acute oral methotrexate poisoning? Clin Toxicol (Phila) 2017;55:88–96.
[19] Bianchi G, Caporali R, Todoerti M, Mattana P. Methotrexate and rheumatoid arthritis: current evidence regarding subcutaneous versus oral routes of administration. Adv Ther 2016 Mar;33(3):369–78.
[20] Levêque D, Santucci R, Gourieux B, Herbrecht R. Pharmacokinetic drug-drug interactions with methotrexate in oncology. Expert Rev Clin Pharmacol 2011;4:743–50.
[21] Agence Nationale de Sécurité du Médicament. Thésaurus des interactions médicamenteuses. ANSM; 2018.
[22] Bourré-Tessier J, Haraoui B. Methotrexate drug interactions in the treatment of rheumatoid arthritis: a systematic review. J Rheumatol 2010;37:1416–21.
[23] Hall JJ, Bolina M, Chatterley T, Jamali F. Interaction between low-dose methotrexate and nonsteroidal anti-inflammatory drugs, penicillins, and proton pump inhibitors. Ann Pharmacother 2017;51:163–78.
[24] Grove ML, Hassell AB, Hay EM, Shadforth MF. Adverse reactions to disease-modifying anti-rheumatic drugs in clinical practice. QJM Mon J Assoc Phys 2001;94:309–19.
[25] Zhu C, Liu YW, Wang SZ, Li XL, Nie XL, Yu XT, et al. Associations between the C677T and A1298C polymorphisms of MTHFR and the toxicity of methotrexate in childhood malignancies: a meta-analysis. Pharmacogenomics J 2018;18:450–9.
[26] Fan H, Li Y, Zhang L, Li Y, Li W. Lack of association between MTHFR A1298C polymorphism and outcome of methotrexate treatment in rheumatoid arthritis patients: evidence from a systematic review and meta-analysis. Int J Rheum Dis 2017;20:526–40.
[27] Chen Y, Zou K, Sun J, Yang Y, Liu G. Are gene polymorphisms related to treatment outcomes of methotrexate in patients with rheumatoid arthritis? a systematic review and meta-analysis. Pharmacogenomics 2017;18:175–95.
[28] Lee YH, Song GG. Associations between the C677T and A1298C polymorphisms of MTHFR and the efficacy and toxicity of methotrexate in rheumatoid arthritis: a meta-analysis. Clin Drug Investig 2010;30:101–8.