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RESEARCH ARTICLE

Severe MTX Toxicity in Rheumatic Diseases - Analysis of 22 Cases

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Abstract

Background: Severe MTX (methotrexate) toxicity due to low dose MTX used in rheumatic diseases is rare but linked with a high mortality ranging from 13 to 44%. We analyzed 22 cases with a minimum toxicity of CTC (common toxicity criteria) grade 2, that were admitted to our hospital.

Methods: We retrospectively analyzed epidemiological data, the weekly MTX dosage, renal function before and at the beginning of the adverse event, co-medication with influence on MTX toxicity or on renal function and potential other co-factors like infections, as well as the outcome, respectively.

Results: 22 patients were involved in the study. Three patients died due to pneumonia, all other patients recovered. The main reason for toxicity was an impaired renal function (82%), either from acute renal failure or from acute on chronic renal failure or chronic renal disease stage 4. In 5 cases a dosing error, mainly with daily instead of weekly MTX intake, was the reason. Only in one case the reason remains unclear.

Discussion: An impaired renal function with an estimated glomerular filtration rate (eGFR) of 11-54 ml/min was the main cause for MTX toxicity with dosage errors being the second numerous reasons. Our data are in accordance with previous case series, but the influence of reduced renal function is still higher than in the most reports. One reason might be that most case series took only into account the serum creatinine but not a calculated GFR. Serum creatinine alone underestimates the stage of renal failure in patients with lower muscle mass.

Keywords

Low dose MTX, Toxicity, Pancytopenia, Renal insufficiency, Risk factor

Introduction

MTX is the first line disease modifying antirheumatic drug (DMARD) recommended in many rheumatic diseases like rheumatoid arthritis (RA) [1,2], limited ANCA associated vasculitis (AAV) [3,4] or as a steroid sparing drug in the case of relapses in giant cell arteritis (GCA) [5]. MTX toxicity occurs often, but in most cases, toxicity is mild to moderate and is transient [6] and patients recover rapidly after stopping the treatment. Schmajuk, et al. found moderate elevations of liver enzymes in about 6% of 659 incident MTX users [7]. Risk factors were obesity, untreated high cholesterol, pre-MTX liver enzyme elevations, use of biological disease modifying antirheumatic drugs (bDMARDs), and lack of folic acid supplementation, respectively. Abasolo, et al. [7-9] reports adverse drug reactions (ADR) in 12.9% in a population of 1202 patients with RA and treatment with different DMARDs. With an incidence rate (IR) of 7.6 per 100 patient years in this study population MTX presented with the lowest ADR incidence of all cDMARDs. Also, in this paper recent onset RA (< 1 year) had a nearly doubled risk for ADR than patients with long lasting disease.

The most often reported adverse events are gastrointestinal intolerance, infections and elevated liver enzymes [8]. Severe side effects like hematotoxicity with leukopenia, thrombocytopenia and anemia can occur. There are only few systematic reviews about this severe and potentially lethal adverse event [10].

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Table 1: CTC classification for haematotoxicity, mucositis, diarrhea and nausea.

	Stage 0	Stage 1 mild	Stage 2 moderate	Stage 3 severe	Stage 4 life threatening	Stage 5 Death
Leucocytes	> 4.000/µl	1.500 - < 2.000/µl	1.000 - < 1.500/µl	500 - < 1.000/µl	< 500/µl	-
Thrombocytes	2100.000/µl	75.000 - 99.999/µl	50.000 - 74.999/µl	25.000 - 49.999/µl	< 25.000/µl	-
Hemoglobin	> 11 g/dl	10 - 11 g/dl	8 - < 10 g/dl	6.5 - < 8 g/dl	< 6.5 g/dl	-
Nausea	No nausea	Marginal, food intake normal	Moderate, food intake reduced	Heavily, no food intake	-	-
Vomiting	No vomiting	1 ×/d	(2 - 5) ×/d	(6 - 10) ×/d	> 10 ×/d	-
Diarrhea	No diarrhea	(2 - 3) ×/d	(3 - 6) ×/d or moderate abdominal cramping	(7 - 9) ×/d or severe abdominal cramping	> 9 ×/d or bloody diarrhea	-
Stomatitis/mucositis	No stomatitis	Erythema, painless erosions	Ulcera, solid food possible	Ulcera, liquid diet	No food intake possible	-

Gutierrez-Ureña reported in his review [11] 70 cases of pancytopenia found in a Medline search over a period of 15 years with a mortality of 17%. In various studies the incidence of pancytopenia after low dose MTX in RA patients ranged between 1.4% and 4% [11-13], but unfortunately pancytopenia was not graduated.

A review on MTX drug interactions [14] found only few potential drug interactions between MTX and other medications. These are the simultaneous use of trimethoprim-sulfamethoxazole and non-steroidal antiinflammatory drugs (NSAID) in view of cytopenia and the use of isoniazid or high-dose sulfasalazine (ASA) regarding elevated liver enzymes.

Method

We retrospectively analyzed patients with MTX induced toxicity CTC grade 2 [15] (Table 1) and higher in one item (leucopenia, anemia, thrombocytopenia or mucositis) who had been admitted to our hospital between 2005 and 2017. Included were age, the weekly MTX dose, renal function before and at the beginning of the adverse event, laboratory values of the last 3 months before (primary care doctor, mentoring rheumatologist), co-medication with influence on MTX toxicity or on renal function and potential other co-factors like infections and the outcome, respectively.

Results

We report on 22 patients (15 female and 7 male) with CTC grade ≥ 2 toxicity (Table 1) under MTX treatment. The age ranged from 43 to 89 years (mean 68.8 ± 11.8 years, median 69.7). Sixteen patients suffered from rheumatoid arthritis, two from primary Sjoegren´s syndrome (pSS), two from psoriasis (PS), one from psoriasis arthritis (PSA) and one from ANCA associated vasculitis (AAV). In eighteen patients a pancytopenia occurred, in three patients we found a bicytopenia (2x leukopenia/thrombocytopenia; 1x leukopenia/anemia), and one patient developed isolated leukocytopenia and neutropenia. Thirteen patients had additional symptoms of toxicity like mucositis (n = 11), pneumonia (n = 7), diarrhea (n = 1) and thrush esophagitis (n = 2). Three patients (13.6%) died (i.e. CTC grade 5). All other patients recovered completely. Eight patients had CTC grade 4 toxicity, seven suffered from grade 3 and four from grade 2 toxicity in one organ system, respectively.

The mean values for leukocytes were 1474 ± 878/µl (range 100 - 3300), for hemoglobin 8 ± 1.7 g/dl (range 5.7-11.7) and for thrombocytes 46,273 ± 38,962/µl (range 7000-165,000) (for individual values see Table 2).

In five patients a dosage error was the underlying cause for the toxicity, in one patient this was combined with an acute renal failure (ARF) and in another one combined with chronic renal failure (CRF) stage 4 (eGFR 18 ml/min). Four patients took their MTX on a daily schedule instead of once weekly as prescribed. One patient continued oral MTX additionally to the newly initiated subcutaneous MTX and additionally suffered from ARF.

In one patient the reason for MTX induced toxicity remained unclear. This patient neither had renal function impairment nor additional conditions with increased risk for MTX toxicity, however, the cytopenia resolved after cessation of MTX. In all remaining patients an impaired renal function was the main reason for the toxicity. In four patients a preexisting chronic renal insufficiency stage 4 (eGFR < 30 ml/min) was not considered when MTX was initiated. Available previous laboratory values over the last 3 months demonstrated a stable renal function in these patients. Additionally, one of these four patients erroneously administered MTX in a daily schedule. Another four patients suffered from ARF without any preexisting renal dysfunction. In two cases ARF was due to severe diarrhea and dehydration, in one case acute interstitial nephritis was identified, one case suffered from ARF due to systemic infection with fever and exsiccosis. In all other cases a combination of acute on chronic renal failure resulted in a renal function with an eGFR between 10 - 54 ml/min (mean 29 ± 10.7 ml/min). Six patients had a previously known reduced renal function (CRF stage 3) with an eGFR between 30 and 60 ml/min without reduction of MTX dosage. In 14 patients the weekly MTX dose was 15 mg, in 3 patients combined with leflunomide and in one patient with tocilizumab. These patients had been on

Table 2: Individual blood values (leukocytes, haemoglobin, thrombocytes), the additional signs of MTX toxicity and the outcome.

No	Age [y]	Leucocytes [/µl]	Haemoglobin [g/dl]	Thrombocytes [/µl]	Toxicity	Outcome
1	57	400	6.8	10.000	Pancytopenia, mucositis stage IV, pneumonia	Died
2	73	1500	10.9	99.000	Leukopenia, thrombocytopenia	Restitutio
3	43	1900	9.2	110.000	Pancytopenia, mucositis III	Restitutio
4	53	1300	8.8	26.000	Pancytopenia	Restitutio
5	66	1100	7.6	12.000	Leucopenia, mucositis stage III	Restitutio
6	75	2100	8.2	54.000	Pancytopenia, mucositis stage IV, pneumonia	Died
7	79	3200	8.8	52.000	Pancytopenia	Restitutio
8	54	1300	6.4	26.000	Pancytopenia, mucositis stage II	Restitutio
9	55	3200	8.6	165.000	Leucopenia, anemia, pneumonia	Restitutio
10	82	1400	8.8	18.000	Pancytopenia, mucositis stage III, fever, soor esophagitis	Restitutio
11	71	2100	11.5	75.000	Pancytopenia, mucositis stage III, pneumonia	Restitutio
12	78	900	7.3	31.000	Pancytopenia, pneumonia	Restitutio
13	83	3300	8.6	37.000	Pancytopenia	Restitutio
14	64	300	8.5	7.000	Pancytopenia	Restitutio
15	84	700	8.1	53.000	Pancytopenia, mucositis stage III, diarrhea	Restitutio
16	66	1600	9.4	20.000	Pancytopenia	Restitutio
17	68	2000	6.4	76.000	Panzytopenia, mucositis stage III	Restitutio
18	78	1800	7.7	66.000	Pancytopenia	Restitutio
19	61	1200	5.7	21.000	Pancytopenia	Restitutio
20	62	700	7.8	20.000	Pancytopenia, mucositis stage III, pneumonia	Restitutio
21	72	330	13.1	19.000	Leucopenia, thrombocytopenia, mucositis stage III pancytopenia, mucositis stage IV, soor esophagitis	Restitutio
22	89	100	7	21.000	Pneumonia	Died

Table 3: Causes for MTX toxicity in each case.

No	age [y]	disease	MTX-dosage [mg/w]	Reason of toxicity	GFR before [ml/min]	Minimal GFR [ml/min]	Cofactors	Relevant comedication	Toxicity	Outcome
1	57	RA	150	Dose error	90	90			Pancytopenia, mucositis, pneumonia	Died
2	73	RA	15	ARF on CRF II	72	40		LEF, ARB	Leukopenia, thrombocytopenia	Recovery
3	43	RA	105	dose error	90	90	Previous diarrhea		Pancytopenia, mucositis	Recovery
4	53	pSS	15	ARF	68	20	Unkown LCDD		Pancytopenia	Recovery
5	66	PS	12.5	CRF IV	29	27		ARB, LD	Leucopenia, mucositis	Recovery
6	75	RA	15	CRF IV	28	24	Use of painkiller	ACE	Pancytopenia, mucositis, pneumonia	Died
7	79	RA	15	ARF on CRF II	65	37	Diarrhea (Noro-Virus)	NSAID, ACE	Pancytopenia	Recovery
8	54	RA	15	ARF on CRF III	58	36	Acute interstitial nephritis		Pancytopenia, mucositis	Recovery
9	55	RA	15	ARF	92	36		ACE	Leucopenia, anemia, pneumonia	Recovery
10	82	RA	15	ARF on CRF III	55	24			Pancytopenia, mucositis, fever, soor esophagitis	Recovery
11	71	AAV	15	ARF on CRF III	59	43	Infection with fever	ARB, HCT	Pancytopenia, mucositis, pneumonia	Recovery
12	78	RA	15	ARF on CRF 111	53	21			Pancytopenia, pneumonia	Recovery
13	83	RA	15	ARF on CRF III	51	32		ARB	Pancytopenia	Recovery
14	64	RA	70	dose error	90	90	Urinary retention		Pancytopenia	Recovery
15	84	RA	7.5	ARF on CRF II	66	15	Infection with fever	ACE, COX	Pancytopenia, mucositis, diarrhea	Recovery

16	66	RA	15	ARF	90	31		ACE, TOC	Pancytopenia	Recovery
17	68	PSA	15	unclear	90	90	Acute interstitial nephritis	LEF	Panzytopenia, mucositis	Recovery
18	78	pSS	15	ARF on CRF III	55	38	Previous diarrhea		Pancytopenia	Recovery
19	61	RA	15	ARF	90	10		ARB, NSAID, HCT	Pancytopenia	Recovery
20	62	RA	30	ARF on CRF II and dose error	83	54	Previous diarrhea	LEF, NSAID	Pancytopenia, mucositis, pneumonia	Recovery
21	72	PS	22.5	CRF IV	28	27		LD	Leucopenia, thrombocytopenia, mucositis	Recovery
22	89	RA	90	CRF IV and dose error	20	18			Pancytopenia, mucositis,pneumonia	Died

ARF: acute renal failure, CRF (2-4): chronic renal failure (stage 2-4), LCDD: light chain deposition disease, Medication: LEF: leflunomide, TOC: tocilizumab, ARB: angiotensin receptor blocker; ACE: ACE-inhibitor, LD: loop diuretics, HCT: hydrochlorothiazide, NSAID: nonsteroidal antiinflammatory drugs, COX: cyclooxygenase II-inhibitor.

the combined immunosuppressive treatment for over 6 months. All MTX dosages are demonstrated in Table 3.

All other patients had no additional DMARDs. All patients were treated with folic acid 5 mg once weekly. Ten patients used ACE inhibitors (ACEi) or angiotensin receptor blockers (ARB) with a potential influence on renal blood flow and glomerular filtration rate, two in combination with diuretics and three together with painkillers (NSAID or selective cyclooxygenase II inhibitors (COX)), which also have a potential effect on renal perfusion and glomerular filtration rate. In most cases the acute renal failure had multifactorial causes with a combination from multiple risk factors, e.g. reduced renal blood flow (exsiccosis, painkillers) and ACEi/ARB. Table 3 shows the factors leading to MTX toxicity in each case.

Discussion

The analysis of our 22 cases of MTX toxicity CTC grade 2 and higher demonstrates the most common reason of toxicity in low dose MTX therapy in rheumatic disease to be acute renal failure, chronic renal insufficiency or acute on chronic renal failure. The second most frequent reason was a mistaken dosage. Mortality is high with 13.6%, which is in accordance with previous case series with a reported mortality by MTX induced pancytopenia of 13 - 44% [10,16-20].

The given two main reasons for MTX toxicity can therefore be divided into a patient related and a physician related problem.

Faulty MTX dosage needs to be prevented by explicit and detailed patient information and training combined with a written dosing regimen.

Issues of renal function should lead to greater awareness on the part of the physicians. The presented cases demonstrate that even a mild to moderate preexisting renal insufficiency (CRF stage 2, eGFR 60 - 70 ml/min) is a potential risk factor for developing severe MTX toxicity if additional risk factors like certain co-medication (e.g. NSAID, ACEi), dehydration and higher age result in acute renal failure. In our case series about 32% of patients had a previous eGFR of more than 60 ml/min., but developed acute renal failure due to additional events like acute diarrhea or use of painkillers in combination with ACEi or ARB in the case of acute joint pain. In about half of our cases an advanced chronic renal insufficiency was not adequately considered in the therapeutic decision.

Some of the patients had only moderately elevated serum creatinine levels because of low body weight and sarcopenia, counterfeiting a better renal function than present. Toxic effects such as stomatitis, alopecia, and cytopenias are linked to the antiproliferative effects of MTX and may be dose dependent. With decreasing renal function MTX levels will increase significantly. In patients with moderate renal insufficiency (eGFR < 45 ml/min, CRF stage 3b) MTX levels rise by a factor of 1.3 - 1.6 and elimination half time (t1/2) increases from 13.5 to 22.7 hours compared to patients with an eGFR > 60 ml/min (CRF stage 2) [21], illustrating the influence of a moderate renal insufficiency to MTX levels. Linear regression models revealed good correlations between MTX clearance and creatinine clearance. There are many case reports of fatal pancytopenia in patients with end stage renal disease on hemodialysis treated with low dose MTX [22-28], even when the dose was reduced to 5-7.5 mg/week. Since MTX serum levels become undetectable within 24 hours after administration and MTX toxicity will be mediated by the intracellular polyglutamate derivatives with long halftime which are not measurable, the quantitative estimation of serum MTX levels is not helpful for monitoring.

Compared with other case series of low dose MTX toxicity in patients with rheumatic disease Serraj, et al. [18] likewise found a high impact of renal function on the reported toxicity. Kuitunen, et al. [19] found mildly or moderately elevated serum creatinine levels

only in 44%, unfortunately the authors did not calculate the creatinine clearance. Nevertheless Kuitunen, et al. [19], too, proposed renal insufficiency, advanced age and co-medication with more than five drugs to be risk factors for MTX toxicity. In the paper of Gutierrez [10] 10 out of 12 deceased patients had impaired renal function, however, again, in these patients no eGFR was documented. If the patient's eGFR were calculated with the CKD-EPI formula [29] all patients of the Gutierrez cohort had an eGFR between 17 and 45 ml/min (CRF stage 3b or 4). Even though a reduced MTX dose of 5 - 10 mg/week was used it was fatal in these patients.

Kivity, et al. [20] also declared renal insufficiency a potential risk factor. He reported 13 out of 28 patients (46%) having renal insufficiency, six with ARF and seven with deterioration of previously known CRF. In his paper serum creatinine levels from 23 patients are available. If the renal function were assessed only by serum creatinine, 14 patients had a serum creatinine of greater than 1.3 mg/dl. When applying the CKD-EPI formula to calculate the GFR eighteen patients had renal insufficiency, defined as eGFR < 60 ml/min (CRF stage 3). Two patients had renal insufficiency stage 5 (eGFR < 15 ml/min), six patients stage 4 (eGFR 15-29 ml/min) and six patients' stage 3b (eGFR 30 - 45 ml/min). Thus, by ignoring calculated GFR a marked reduction of renal function was not detected in about 18% of patients.

Whereas liver toxicity usually occurs gradually over time and is mostly recognized before irreversible damage has eventuated, hematological side effects can occur very rapidly, sometimes within a few weeks after initiation of MTX treatment [10,19], especially if MTX levels increase rapidly due to erroneous daily dosage or due to reduced renal excretion.

We therefore recommend calculation of renal function using one of the available formulas (e.g. CKD-EPI, MDRD) to avoid an overestimation of renal function. In patients with marked sarcopenia or increased muscle mass caution is warranted since all these equations are creatinine-based and are therefore directly influenced by the patient's muscle mass [29]. In these patients any calculated GFR < 60 ml/min should be double checked attentively for a potential overestimation of the true renal function. Alternative measurements of GFR could be considered, like cystatin C or GFR calculation by 24-hour collection urine, knowingly that both methods have their limitations. If patients have conditions with a high risk for acute renal failure (e.g. higher age, GFR < 70 ml/min, co-medication of NSAID´s and ACEi or ARB), MTX treatment should be reconsidered and alternative drugs should be debated. Finally, patients should be trained regarding the once weekly MTX intake.

Conflict of Interest Disclosure Statement

The authors have no conflict of interest.

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