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Methotrexate treatment in rheumatoid arthritis and elevated liver enzymes: A long-term follow-up of predictors, surveillance, and outcome in clinical practice

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Abstract

Aim: To assess predictors of alanine aminotransferase (ALT) elevation in methotrexate (MTX) treated rheumatoid arthritis (RA) patients, and to describe the monitoring of liver enzymes, including handling and outcome of elevated ALT.

Methods: All RA patients starting MTX in January, 2005 to April, 2013 at a rheumatology clinic, (Uppsala University Hospital, Sweden) were identified from electronic medical records. Clinical and laboratory data were obtained from medical records, supplemented by telephone interviews. Predictors for ALT >1.5× over the upper limit of normal (ULN) were identified by multiple regression analysis.

Results: The study comprised 213 RA patients starting MTX. During a mean follow-up of 4.3 years, 6288 ALT tests were performed; 7% of tests with ALT were >ULN. ALT >1.5× ULN was observed in 44 (21%) patients and the strongest predictor was a pre-treatment elevation of ALT (adjusted odds ratio = 6.8, 95% CI 2.2-20.5). Recurrent elevations occurred in 70% of patients who continued treatment, and the proportion was similar in those with and without interventions, for example MTX dose reduction (67% vs 73%, $P = 0.43$). Seven patients (3%) permanently stopped MTX due to ALT elevation, and two were eventually diagnosed with non-alcoholic fatty liver disease. No patient developed hepatic failure.

Conclusion: Only a small number of ALT tests performed during MTX therapy in RA capture an elevation. A pre-treatment elevation of ALT was the strongest predictor for early and recurrent ALT elevations during therapy. This study supports a more individualized approach to monitoring and handling of ALT elevations during MTX therapy in RA than recommended in current guidelines.

KEYWORDS

liver toxicity, liver transaminases, methotrexate, non-alcoholic fatty liver disease, rheumatoid arthritis

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1 | INTRODUCTION

Since the introduction of methotrexate (MTX) in the treatment of rheumatoid arthritis (RA) in the 1980s, the risk for hepatic complications has been a major concern.[1] Although a number of potential risk factors for liver toxicity have been identified, individual risk stratification is still not part of monitoring guidelines. Guidelines, including the widely used American College of Rheumatology guidelines, recommend testing of liver enzymes at intervals of at least 8-12 weeks in all RA patients treated with MTX,[2] making liver enzyme testing one of the most frequent screening tests in rheumatology care. Few studies have explicitly evaluated the performance of existing monitoring guidelines. Two studies assessed the safety of 12 weeks between tests and arrived at the conclusion that this span seems safe as none of the monitored patients developed persistent liver enzyme elevations or clinically serious liver affections during follow-up.[3,4]

However, it is unclear what proportion of all performed monitoring tests capture liver enzyme elevations, how elevated liver enzymes are handled and what happens after an alanine aminotransferase (ALT) elevation in clinical practice. Such information could be helpful for future revisions of guidelines. Moreover, identified predictors for liver toxicity have not been consistent between studies which may be due to differences in the studied populations regarding, for example sex distribution, age, MTX dosing, and the use of folic acid supplementation.[5-8]

In this study we aimed to assess predictors of ALT elevation in a contemporary and unselected population of MTX-treated RA patients and to describe monitoring of liver enzymes in long-term follow-up in clinical practice, including compliance to guidelines and the handling and outcome of elevated ALT levels.

2 | MATERIALS AND METHODS

2.1 | Study population

We performed a retrospective cohort study of all RA patients at the Rheumatology Department at Uppsala University Hospital, Sweden, who started MTX treatment between 1 January, 2005 and 30 April, 2013. Patients were identified from electronic medical records (n = 232) and asked to participate in the study, which also included a telephone interview. Sixteen patients declined participation and three were excluded since they were not able to take part in the telephone interview (severe dementia or communication problems), resulting in a total of 213 included patients.

At initiation of MTX, all patients were prescribed 7.5 mg/wk orally in combination with folic acid (at least 5 mg/wk, not the same day as MTX), according to Swedish guidelines The dose of MTX was gradually increased during a period of 1-3 months to a maximum of 25 mg/wk based on individual decisions by the treating physician. Patients were scheduled to perform ALT tests according to Swedish guidelines, that is every 14 days during the first 3 months of MTX treatment, thereafter every month for 3 months, followed by tests every 3 months as long as MTX treatment was maintained. The guidelines concerning MTX treatment were stable during the study period.

Ethics approval was obtained from the Regional Ethical Review Board, Uppsala, Sweden (Uppsala 2010/231). All participating patients were required to be at least 18 years of age and able to provide written informed consent.

2.2 | Clinical and laboratory data and follow-up

All patients were followed for clinical data and ALT test results from MTX start until MTX was permanently stopped for any reason or until 30 September, 2013 (end of study period).

In patients who had visits at the clinic before MTX start, information about the RA disease and comorbidities covering the period from the first contact with the clinic was included. We also obtained all available ALT values in the laboratory database recorded before initiating MTX (missing values for five patients). For patients who permanently stopped MTX due to ALT elevation, an extended follow-up for clinical and laboratory data was performed until 30 November, 2015. Clinical data were obtained from the medical records and completed with a telephone interview performed within 3 months from inclusion. The collected data included RA disease characteristics, details about the MTX treatment and actions taken at ALT elevations, comorbidities, concomitant medication, body mass index (BMI), smoking habits and alcohol consumption, measured as standard glasses per week. The recorded data regarding weight and alcohol consumption consistently reflect the situation at the telephone interview, as this information was often missing in the medical records.

Alanine aminotransferase was analyzed at the clinical chemistry laboratory at Uppsala University Hospital with results recorded in a computerized laboratory database. The upper limit of normal (ULN) values for ALT were set to >0.75 μcat/L (45 units/L) in women and >1.1 μcat/L (66 units/L) in men for tests analyzed after 3 October, 2005. Prior to this, ULN was set to >0.63 μcat/L (37.8 units/L) in women and >0.83 μcat/L (49.8 units/L) in men. The change of reference values had limited effect on the results of this study as only 3 elevations were registered before 2005.

2.3 | Statistical analysis

Alanine aminotransferase elevation was defined as ALT > ULN when addressing how ALT elevations were handled in clinical practice. For the predictor analyses we used the definitions ALT >1.5× ULN, ALT >2× ULN, and ALT >3× ULN. For comparative analyses between the groups with or without elevated ALT, *t* tests and Mann-Whitney *U* tests were used for continuous data, and Chi-square tests and Fisher´s exact test for categorical data. Univariate and multiple logistic regression were used to estimate predictors of ALT elevation expressed as crude and adjusted odds ratios (OR) with 95% confidence intervals (CI). The multiple regression model included the following

variables: sex, age at MTX start, anti-cyclic citrullinated peptide antibody positivity, rheumatoid factor positivity, MTX maximum dose, BMI, pre-treatment ALT elevation, total units of alcohol per week, smoking, concomitant medications at maximum ALT value (separate for hydroxychloroquine/chloroquine phosphate, prednisolone, non-steroidal anti-inflammatory drugs, statins, proton pump inhibitors, paracetamol, antihypertensive drugs, biological disease-modifying anti-rheumatic drugs and comorbidities during MTX therapy (diabetes, psoriasis). Age, BMI, alcohol consumption and MTX maximum dose were analyzed as continuous variables. Three patients with suspected other explanations for the ALT elevation than MTX were excluded from the predictor analysis. As a definition of non-compliance to monitoring guidelines, we set a time span between ALT tests of more than 21 days during the first 3 months, more than 44 days during the next 3 months, and more than 120 days during the rest of the first 3 years of treatment.

Descriptive data analyses were conducted using the Statistical Package for Social Sciences for Windows version 24 (IBM, Armonk, NY, USA). R version 3.2 (R Corporation, Vienna, Austria) was used for the regression analyses using the packages rms and Hmisc. A P value <0.05 was considered statistically significant.

3 | RESULTS

The study comprised of 213 RA patients (67% women) starting MTX therapy. The mean follow-up from MTX start until end of MTX therapy or until 30 September, 2013 was 4.3 years (range 8 weeks to 8.8 years). MTX was the first disease-modifying anti-rheumatic drug (DMARD) for most of the patients (87%) and the mean maximum dose of MTX was 17.35 mg/wk (range 7.5-25). All patients were treated with folic acid. Patient characteristics are listed in Table 1.

3.1 | Results of ALT testing and compliance to guidelines

During the study period, 6288 ALT tests were performed, corresponding to a mean of seven tests per treatment-year or 30 (range 3-75) tests per patient. ALT levels >ULN were observed in 84 (39%) patients and on 467 occasions (7% of all ALT tests). ALT >1.5× ULN was observed in 44 (21%), ALT >2× ULN in 32 (15%), and ALT >3× ULN in 13 (6%) patients. MTX treatment was permanently stopped due to elevated ALT in 7 (3%) patients.

The mean time from initiation of MTX to the first elevated ALT > ULN was 78 weeks with a wide range (1-379 weeks). Of all first elevated values, 25 (30%) were observed during the first 3 months after treatment start, 49 (58%) within the first year, and 74 (88%) within the first 3 years after treatment start (Tables 2 and 3).

Compliance to scheduled blood tests was lowest the first year after treatment start. On average 63% of the patients followed the recommendations of the tighter controls during the first year, but compliance improved up to 82% during the next 2 years. An inferior compliance was noted in men compared to women (P = 0.004) and in those with a lower mean age at MTX start (52 vs 58 years, P = 0.001). There were no significant differences between those with compliance to testing guidelines and those with less frequent testing the first year regarding the proportion of patients with

TABLE 1 Characteristics of included patients

Characteristics	All patients N = 213
Females, n (%)	143 (67)
Age at RA diagnosis, mean ± SD (min-max), y	54.8 ± 14.3 (17-81)
Rheumatoid factor positivity, n (%)	149 (70)[a]
Anti-CCP positivity, n (%)	145 (68)[b]
Age at MTX treatment start, mean ± SD (min-max), y	55.8 ± 13.8 (18-81)
Duration of MTX treatment (follow-up) mean ± SD (min-max), wk	225 ± 129 (8-456)
MTX maximum weekly dose, mean ± SD (min-max), mg	17.35 ± 4.3 (7.5-25)
Folic acid supplement, n (%)	213 (100)
Concomitant treatment at maximum ALT level[c]	
Sulfasalazine, n (%)	12 (6)
Hydroxychloroquine/chloroquine phosphate, n (%)	9 (4)
TNF inhibitors, n (%)	33 (16)
Prednisolone, n (%)	113 (53)
NSAID, n (%)	23 (11)
Paracetamol, n (%)	7 (3)
Proton pump inhibitor, n (%)	24 (11)
Statin, n (%)	18 (8)
Comorbidities	
Hypertension, n (%)	62 (29)
Diabetes, n (%)	14 (7)
Psoriasis, n (%)	9 (4)
Hepatic disease,[d] n (%)	4 (2)
Cardiac failure, n (%)	2 (1)
Kidney disease, n (%)	2 (1)
Other characteristics	
Body mass index, mean ± SD (min-max), kg/m^2	26.5 ± 4.7 (17-43.5)
Body mass index > 30, n (%)	44 (21)
Ever smoker, n (%)	97 (45.5)
Alcohol standard glasses/wk, mean ± SD (min-max)	2.67 ± 2.78 (0-14)

ALT, alanine aminotransferase; CCP, cyclic citrullinated peptide; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; SD, standard deviation; TNF, tumor necrosis factor.
[a]Missing data from one patient
[b]Missing data from eight patients
[c]Other treatment: fewer than five patients were treated with abatacept, leflunomide, rituximab or tocilizumab
[d]Two patients with non-alcoholic fatty liver disease and two patients with chronic hepatitis B infection

TABLE 2 Results of alanine aminotransferase testing in 213 patients with rheumatoid arthritis starting methotrexate therapy followed for a mean treatment period of 4.3 y

ALT > ULN, n (%)	84 (39)
ALT > 1.5× ULN, n (%)	44 (21)
ALT > 2× ULN, n (%)	32 (15)
ALT > 3× ULN, n (%)	13 (6)
MTX permanently stopped due to increased ALT, n (%)	7 (3)
Number of ALT tests	6288
MTX weekly dose at first ALT elevation, mean ± SD (min-max), mg	14.93 ± 4.8 (7.5-25)
Mean time from treatment start to first ALT elevation (min-max), wk	78 (1-379)
Number of patients with first ALT elevation	
First 3 mo of MTX treatment, n (%)	25 (30)
First year of MTX treatment, n (%)	50 (59)
First 3 y of MTX treatment, n (%)	74 (88)

ALT, alanine aminotransferase; MTX, methotrexate; SD, standard deviation; ULN, upper limit normal.

TABLE 3 Maximum registered ALT elevation in 84 patients with rheumatoid arthritis before and after starting methotrexate therapy

	Pretreatment elevation	Treatment elevation
ALT > ULN, n	20	84
ALT > ULN but ALT < 1.5× ULN, n	10	40
ALT > 1.5× ULN, n	10	44
ALT > 1.5× ULN but ALT < 2× ULN, n	2	12
ALT > 2× ULN, n	8	32
ALT > 2× ULN but ALT < 3× ULN, n	8	19
ALT > 3× ULN	0	13

ALT, alanine aminotransferase; ULN, upper limit normal

observed ALT > ULN (39% vs 38%) ($P = 0.81$), patients who eventually permanently stopped MTX due to any reason (22% vs 23%) ($P = 0.92$), and the mean time to first registered ALT > ULN (490 vs 726 days) ($P = 0.14$).

3.2 | Predictors for elevated ALT after MTX initiation

The strongest predictor for ALT >1.5× ULN was a former known elevation of ALT > ULN recorded before onset of MTX therapy (adjusted OR = 6.8, 95% CI 2.2-20.5), followed by ongoing statin treatment (adjusted OR = 7.8, 95% CI 1.4-42.6) and female sex (adjusted OR = 5.7, 95% CI 1.7-19.7). A borderline association was seen with increasing BMI (adjusted OR = 1.1, 95% CI 1.0-1.2) (Table 4). No additional risk factors for ALT >2× and >3× ULN were detected, although statistical power was limited due to few patients in these groups (data not shown).

TABLE 4 Predictors of ALT > 1.5× upper limit of normal after commencing MTX[a]

Predictor	Univariate OR (95% CI)	Adjusted[b] OR (95% CI)
Elevated ALT before[c] MTX treatment	6.3 (2.8-14.1)	6.8 (2.2-20.5)
Female sex	4.5 (1.7-12.0)	5.7 (1.7-19.7)
Statin at time of maximum ALT	1.0 (0.3-3.3)	7.8 (1.4-42.6)
Body mass index[d]	1.1 (1.0-1.2)	1.1 (1.0-1.2)
Age at start of MTX[d]	1.0 (1.0-1.0)	1.0 (0.9-1.0)

ALT, alanine aminotransferase; CI, confidence interval; MTX, methotrexate; OR, odds ratio.
[a]Assessed in 210 patients; three patients with possible alternate explanations of ALT elevation excluded
[b]Variables included in the model: sex, age at MTX start, anti-cyclic citrullinated peptide antibody positivity, rheumatoid factor positivity, MTX maximum dose, body mass index, pre-known ALT elevation, total units of alcohol per week, smoking, concomitant medications at maximum ALT value, comorbidities during MTX therapy
[c]Mean pre-treatment observation period 1.5 y (0-379 wk)
[d]By increase of 1

3.3 | Patients with known ALT elevation prior to MTX treatment

Among the 34 patients with an ALT elevation (ALT > ULN) prior to MTX treatment (mean pre-treatment observation period 1.5 years, range 0-379 weeks), 20 (59%) patients developed ALT > ULN during MTX treatment. The reason(s) for elevated pre-treatment values were not clarified in the medical records. We found no significant differences between patients with and without pre-treatment ALT elevation in any of the examined characteristics, including sex, age, comorbidities, concomitant medications, BMI or alcohol use. In comparison to the other 64 cases with ALT elevation the patients with pre-treatment ALT elevation had a significant shorter mean time (27 vs 97 weeks) to first ALT elevation after initiation of MTX treatment ($P < 0.0001$). Of the first elevations, 55% were observed within the first 3 months of treatment and 90% within the first year. All patients with a pre-treatment ALT elevation had recurrent ALT elevations during MTX treatment. Three stopped MTX permanently due to recurrently elevated ALT. When comparing the maximum ALT value before MTX treatment to maximum ALT during treatment, 14/20 (70%) had a higher value during treatment, at average an increase of 137% (range 7%-500%).

3.4 | Interventions following elevated ALT

We compared the patients where the treating physician decided not to perform any intervention or only a new ALT test ahead of schedule at the first ALT elevation (n = 61) with those where an intervention (ie further laboratory or radiographic investigation, dose reduction or temporary interruption of MTX or of other concomitant potentially liver-toxic drugs) was performed (n = 21) (information missing

TABLE 5 Interventions and outcome of first ALT elevation[a]

	No intervention N = 61	Intervention[b] N = 21	*P*
First ALT > ULN, mean relative increase ± SD (min-max relative increase)	116% ± 19 (101%-250%)	269% ± 219 (110%-800%)	<0.001
Normalized ALT value, n (%)	60 (98%)	21 (100%)	1.0
Mean time to recorded normalized ALT value (min-max), d	93 (4-1139)	46 (11-154)	0.26
New ALT > ULN, n (%)	44/60 (73%)	14/21 (67%)	0.43
Mean time to new recorded ALT > ULN (min-max), d	386 (7-2136)	121 (14-364)	0.12

ALT, alanine aminotransferase; SD, standard deviation; ULN, upper limit normal
[a]Missing information in two patients
[b]Interventions include further laboratory or radiographic investigation, dose reduction or temporary interruption of MTX or of other concomitant potentially liver-toxic drugs

TABLE 6 Patients who permanently stopped MTX due to ALT elevation

	Permanent cessation of MTX due to elevated ALT N = 7
Mean time to first ALT elevation from MTX start (min-max), wk	57 (2-107)
Mean time from MTX start to stopping MTX (min-max), wk	99 (15-258)
Relative ALT increase followed by permanent MTX cessation (min-max)	260% (150%-460%)
Normalized ALT after stopping MTX, n (%)	6 (86)[a]
Time to recorded normalized ALT after stopping MTX (min-max), d	76 (8-340)
New ALT > ULN after stopping MTX, n (%)	4/6 (67)
Time to new recorded ALT > ULN (min-max), d	137 (7-298)

ALT, alanine aminotransferase; MTX, methotrexate; ULN, upper limit normal
[a]One patient had persistent ALT elevation after stopping MTX and was later diagnosed with non-alcoholic fatty liver disease

for two patients) (Table 5). The mean relative ALT elevation > ULN was higher in those where active interventions were performed, but with a wide range and overlapping of ALT values at the different interventions. In all but one of the 84 patients with ALT elevation, the first elevation was followed by normalization irrespective of intervention. No patient stopped MTX permanently at the first ALT elevation. After the first normalization, new elevations occurred in 70% of the patients. Two of the patients in the study were eventually investigated and diagnosed with non-alcoholic fatty liver disease (NAFLD), of which one stopped MTX permanently due to elevated ALT.

We also noted a sex-related difference. Occurrence of any ALT elevation and a lower mean relative ALT increase more often led to interventions in men than in women. Thus, in men 54% of elevated ALT tests led to interventions compared to 37% in women ($P = 0.002$). The average increase of ALT leading to interventions in men was 1.6× ULN (1.76 μcat/L) and in women 2.0× ULN (1.50 μcat/L) ($P = 0.003$). We found no differences in characteristics between men and women that could explain this difference (data not shown).

We identified a group of patients whose ALT remained normal throughout the study after a spontaneous normalization of a first ALT elevation (n = 16). These patients had a lower mean ALT increase (1.2× ULN vs 1.6× ULN) ($P = 0.003$) and a longer mean time to the first elevation than the 68 with recurrent ALT elevations (148 vs 62 weeks) ($P < 0.001$). Other characteristics and follow-up times were similar in both groups.

3.5 | Patients with permanent cessation of MTX therapy

Among the seven patients who eventually permanently stopped MTX due to elevated ALT, 5 (71%) had continued ALT elevations after stopping MTX (Table 6). The mean follow-up time after stopping MTX in the seven patients was 6.7 years (3.8-8.6 years). None of the patients in this study developed signs of hepatic failure.

4 | DISCUSSION

In this study we have examined the incidence of ALT elevations and the clinical consequences of the elevations in a cohort of MTX-treated contemporary RA patients followed for a long time and beyond the first ALT elevation. The mean weekly dosage of MTX (17.35 mg) was relatively high, folate substitution was prescribed to all patients and older patients were not excluded from the therapy. The mean follow-up period, during which the patients were treated with MTX, was 4.3 years. During this period, 39% of the patients developed

ALT > ULN, 22% ALT >1.5× ULN and 15% >2× ULN, figures coherent with prior studies.[6,7,9-11] Also similar to more recent studies of MTX toxicity, only a small proportion of the patients (3%) discontinued their MTX medication due to pathological ALT tests and no patients developed signs of severe liver toxicity.[4-6] However, it should be noted that the exact definitions and cut-off values for ALT elevation may differ between studies which may hamper detailed comparisons.

The results of this study add new insights into the background of ALT elevations during MTX therapy, supporting a multifactorial background to liver toxicity. We identified ALT elevation recorded before MTX commencement as the strongest predictor for ALT elevation during MTX therapy. Some previous studies have reported ALT elevation at MTX commencement as a predictor for ALT elevations following the start of MTX therapy.[9,13,14] By incorporating ALT for a longer pre-treatment period, also including values antedating the onset of RA, we identified pre-MTX ALT elevations in 20 of the 84 patients (24%) with ALT elevation, and all of them experienced recurrent ALT elevations during MTX therapy. This suggests that all available pre-treatment ALT values, and not only baseline values, should be considered before MTX start and elevations seem to identify a group of patients in which a tight control of liver tests is justified. We also found that the ALT values after starting MTX on average reached higher values than during the pre-treatment period, which implies a combined effect on the liver by MTX and the pre-treatment cause of ALT elevations.

Two of the patients were later investigated and diagnosed with NAFLD. It could be speculated that NAFLD could be a cause of recurrent ALT elevations in more of the patients, if they had been properly investigated. It is obvious that NAFDL and MTX-related liver toxicity share risk factors, which could support a common background for both conditions. NAFLD is linked to overweight and obesity, diabetes type 2, insulin resistance and hyperlipidemia.[15,16] The disease is becoming increasingly common, especially in Western countries. A potentially serious form of NAFDL, non-alcoholic steatohepatitis (NASH), may progress to cirrhosis and liver failure.[15,16] Primary treatment of NAFDL includes weight reduction and physical activity.[17]

Apart from pre-treatment ALT elevation, we identified female sex, statin treatment and increasing BMI as predictors of ALT elevation during MTX therapy. Similarly, in other studies, commonly reported predictors for liver enzyme elevation during MTX treatment include high BMI,[13] female sex,[11] hypercholesterolemia,[13] hypertriglyceridemia,[5] and a high cumulative MTX dose.[6,10,11] Possibly, and to be further studied, a more active approach toward risk factors such as overweight, hyperlipidemia and inactivity could, as shown in NAFDL, decrease the frequency of ALT elevations and increase the number of patients who could maintain MTX therapy during prolonged periods.

We can further conclude that compliance to monitoring guidelines was good, except during the first year with more frequently scheduled monitoring. It is also clear that the monitoring program leads to a high number of ALT tests and that only a minority, in this study 7%, captures an elevated value. This encourages the development of an alternative to today's monitoring regimen with a more individualized approach to testing that could identify patients at risk of MTX-related liver toxicity more efficiently. In the patients who did not follow the scheduled tighter control during the first year of treatment in this study, we found no signs of missed serious liver toxicity. This could support that selected patients without risk factors for liver toxicity could be tested less frequently during the first year of treatment. Another group of patients with a limited need of further investigations and close monitoring are those with sporadic ALT elevations that normalize without interventions. In this study, 19% of the patients with ALT elevations belonged to this group. These ALT elevations typically occurred late (years after treatment start) and the relative increase was modest (<1.5× ULN). Some other studies have also shown that occasional ALT elevations are common,[13,18] often clinically insignificant[19] and seldom lead to a permanent discontinuation of MTX.[5,20] Accordingly, in patients with small and late-occurring ALT elevations, an approach without interventions and frequent retesting seems reasonable.

Another finding was that a majority of patients with ALT elevations, approximately 70%, had recurrent elevations. Importantly, this proportion was similar in patients in whom active interventions were performed and in those were only a new ALT test was ordered. These observations support the notion of a multifactorial background to the ALT elevations and the need to consider other factors than MTX as the cause of ALT elevations. It also supports that monitoring and interventions of liver toxicity may benefit from a more individualized approach than in the current guidelines.

Some strengths and limitations of the study should be discussed. Strengths include the detailed, congruent clinical information from electronic medical records, additional information on BMI, alcohol intake and smoking habits on all patients through a telephone interview, access to all ALT values in a computerized database both before and after MTX start, and the long follow-up after first ALT elevation.

Limitations include that most of the clinical information was retrospectively collected and some relevant information may have been missing, for example the reasons for the pre-treatment ALT elevations could not be evaluated. There is also a potential risk for recall bias for data from the telephone interview. The observational design confers a risk for channeling bias. Patients with high risk for liver complications may have been prescribed other DMARDs than MTX, but still 87% of the patients received MTX as the first DMARD.

The observational design and the lack of a common routine also entail a variability in the time span to normalization of an ALT elevation which is dependent on the decisions of the individual doctor on how to handle an elevation and when to perform the next ALT test. The group of patients under study is relatively small, especially for the predictor analysis.

In conclusion, this study emphasizes a multifactorial background to ALT elevations during MTX therapy, and pre-treatment ALT elevations as a strong predictor for early and recurrent ALT elevations following start of MTX. NAFDL is one possible underlying reason to

consider pre-treatment and recurrent ALT elevations. During long-term follow-up, only a minority of all performed ALT tests captures elevations. The results suggest that it may be more efficient to find an individualized approach to monitoring of liver toxicity during MTX therapy in RA patients.

CONFLICTS OF INTEREST

None.

AUTHOR CONTRIBUTIONS

JKS, PH, MW and EB planned and designed the study. JKS acquired the data. Interpretation of data was made by JKS and EB. NE and JKS conducted the statistical analyses. EB and JKS drafted the manuscript and all other authors reviewed the final manuscript.

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