Benefits and risks of targeted treatment in rheumatoid arthritis

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CHAPTER 9.

Risk of alanine transferase (ALT) elevation in patients with rheumatoid arthritis treated according to a dynamic strategy - A subanalysis from the BeSt study

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ABSTRACT

Objective

To determine incidence of increased levels of ALT >2x upper limit of normal (ULN) in patients receiving methotrexate (MTX), treated according to a dynamic strategy, and to identify predictors of ALT >2x ULN.

Methods

Data of 508 recent-onset RA patients from the BeSt study, randomized to initial monotherapy or combination therapy, were used. Treatment was dynamic, aiming at a disease activity score =<2.4. ALT was measured every three months. With logistic regression analyses, baseline variables predictive of first ALT >2x ULN were identified and the association between use of concomitant anti-rheumatic drugs, the actual and cumulative dose of MTX and ALT >2x ULN was determined.

Results

In total, 498 patients ever initiated MTX, with a total duration on MTX of 1416 patient-years. In 89 patients a first incidence of ALT >2x ULN occurred. Incidence rate was 6.3/100 patient-years and cumulative incidence 18%. ACPA positivity and baseline ALT >1x ULN were independent predictors of later ALT >2x ULN (OR 1.8, 95%CI: 1.1-3.1 and OR 3.1, 95%CI: 1.6-6.2, respectively). Smoking showed a trend (OR 1.6, 95%CI: 0.98-2.7). Mean MTX dosage over time was higher in patients with an ALT >2x ULN. Patients who did *not* have an ALT >2x ULN used more concomitant DMARDs and longer.

Conclusion

In RA patients treated with methotrexate according to a dynamic strategy resembling daily clinical practice, incidence of increased ALT >2x ULN was lower than previously reported, and also without treatment adjustments, persistence was rare. The recommendations for ALT monitoring may be reevaluated.

INTRODUCTION

Methotrexate (MTX) is the disease modifying anti-rheumatic drug (DMARD) of first choice in the treatment of rheumatoid arthritis (RA) and the anchor drug in combination therapy.(1) The individual dosage and duration on MTX depends on both disease activity and potential adverse reactions. Among other side effects, increases of liver enzymes are thought to occur most often. Persistent and severe liver disease in patients using MTX appear to be rare(2), but mild elevations of liver enzymes have been frequently reported, with a frequency of 17/100 person years.(3) It is possible that the frequency of increased liver enzyme has changed since previous reports, now that methotrexate is frequently used in combination with other antirheumatic drugs, while the dose may be increased and tapered depending on disease activity.

Currently, intensive monitoring of liver enzymes is recommended: when a patient initiates MTX, alanine transferase (ALT) measurement with or without aspartate transferase (AST), creatinine and complete blood count should be performed every 1-1.5 month until a stable dose is reached and 1-3 months thereafter. It is advised to adjust the dose if ALT or (AST) levels are persistently elevated, and to stop methotrexate if the increase exceeds 3 times the upper limit of normal (ULN), in which case also additional diagnostic procedures are recommended.(1) Prolonged ALT monitoring every 1-3 months may present a logistic and financial challenge. Identification of patients particularly at risk, or not at risk, would be helpful to determine in whom monitoring should be more or might be less intensive. Therefore, the aim of this study was to determine the incidence of elevated levels of ALT in patients receiving MTX, treated according to a dynamic DAS steered strategy which advised a temporary reduction of the MTX dose if ALT was >2x ULN. We also looked for predictors of increased ALT >2x ULN.

METHODS

Patients

All data were collected in the setting of the BeSt study, a randomized clinical trial comparing four different treatment strategies in DMARD-naïve patients who fulfilled the revised inclusion criteria for RA as defined by the American College of Rheumatology (ACR) in 1987. The Medical Ethics Committee at each participating center approved the study protocol

and all patients provided written informed consent prior to enrolment and before continuing in the extension study. Patients were randomized to one of four treatment strategies: sequential monotherapy, step-up therapy (both starting with methotrexate monotherapy), initial combination therapy of methotrexate with sulfasalazine and a tapered high-dose of prednisone, or initial combination therapy of methotrexate and infliximab. All patients treated with MTX received folic acid 5 mg/week. Treatment adjustments were made every three months aiming at a disease activity score (DAS) ≤ 2.4, indicating the dynamic nature of the trial. Patients with ALT >3x ULN were excluded from participation. More details on the BeSt study design were previously published.(4;5)

Drug exposure definition and outcomes

The protocol required that ALT was measured locally at the participating hospitals every three months and dose reduction was advised if ALT was >2x ULN. The upper limit of normal (ULN) reference values for ALT ranged from 31-45 IU/l for women and from 40-45 IU/l for men. For the current analysis ALT >2x local ULN was considered a significant abnormality. Persistence was defined as ALT >2x ULN more than six months after the first incidence.

Observation time for each patient lasted from initation of MTX (at study entry) until discontinuation of MTX, whether because of failure to achieve the low DAS target or because of toxicity. Data collection was censored after 5 years follow-up. Since patients could restart MTX several times during the follow-up period, each patient could contribute multiple times to the total amount of person-years on MTX. When a patient had an ALT level >2x ULN, further measurements were censored for the analysis that focused on initial ALT >2x ULN but registered until normalization. Incidence per person-years of elevated levels of ALT >2x ULN in patients on MTX was determined.

Statistical analysis

Demographic and clinical baseline characteristics for patients with and without an ALT >2x ULN were analyzed using descriptive statistics. With univariate logistic regression analyses, baseline variables showing an association (p<0.10) with having a first ALT >2x ULN were identified. These variables were entered as possible predictors in a multivariate logistic regression analysis together with possible confounders such as age, gender, body mass index (BMI) and center. With a backward selection procedure, using a p-value of 0.10 as the removal criterion, significant independent predictors were identified. Next, with univariate logistic regression analysis, the association between the use of concomitant anti-rheumatic

drugs, the actual and cumulative dose of methotrexate and ALT elevation >2x ULN was determined.

RESULTS

In total, 498 patients used MTX and were included in this analysis. Demographic and disease-related patient characteristics are shown in table 1. At baseline, patients were on average 54 years old, with a mean BMI of 26, 68% of the patients were female and 65% of the patients were rheumatoid factor (RF) positive and 62% were anti-citrullinated protein antibodies (ACPA) positive. Patients had active RA with a mean disease activity score (DAS) of 4.4. Thirty-five percent of the patients smoked at baseline, 48% used alcohol and for 9 patients (2%) a previous medical history of 'liver disease' was reported.

The mean duration of MTX use per person was 2.8 years, with a total of 1416 patient-years. In total 5592 threemonthly ALT measurements were done for patients on MTX, and on 140 occasions (2.5%) an ALT >2x ULN was measure, in 89 patients. The incidence rate of ALT >2x ULN was therefore 6.3/100 patient-years and the cumulative incidence was 18% (figure 1A). Fifty-one percent of the patients had a first ALT >2x ULN in the first year of MTX treatment, 73% within the first two years and the others later (figure 1B).

In 39 of the 89 (44%) cases where patients had a first ALT >2x ULN, no action was taken by the physician concerning the MTX dose. For 23 of the 89 patients (26%), the MTX dose was reduced. In 11/23 of these patients this reduction was permanent and in 2/23 MTX was ultimately stopped. In the remaining 10/23 patients, MTX was temporarily reduced, but later increased to the same or a higher dosage. In 15 of the 89 patients (17%) MTX was temporarily discontinued. In 8 of these 15 patients, ALT was >3x ULN. After this temporary discontinuation, MTX was restarted in a lower dose in 9/15 of the patients and in the other 6/15 patients in the same or a higher dose. In 3 of the 89 (3%) patients MTX was discontinued for a long period, but eventually restarted in a low dose (7.5 mg/wk). MTX was permanently discontinued in 9 of the 89 (10%) patients.

In 80 of the 89 patients, ALT normalized within 3 months. In six patients ALT normalized in the following 3 months, and three patients (3%) had persistence of abnormal values more than six months after the first incidence. Permanent liver damage such as fibrosis/cirrhosis was not reported for any of the patients. No biopsies were performed.

Univariate significant predictors for an ALT >2x ULN were ALT level at baseline, HAQ at baseline, smoking, and RF and ACPA positivity. A history of liver disease and intake of

alcohol were not significantly associated with ALT >2x ULN (table 2). In the multivariate logistic regression analysis, ACPA positivity and baseline ALT level >1x ULN were the only significant independent predictors of ALT >2x ULN (OR, 1.8, 95% CI: 1.1-3.1 and OR, 3.1, 95% CI: 1.6-6.2, respectively). Smoking showed a trend (OR, 1.6, 95% CI: 0.98-2.7).

The number of other DMARDs as concomitant therapy, the duration on sulfasalazine, prednisone or infliximab and the mean dosage of MTX were significantly and inversely associated with ALT >2x ULN (table 3). Thus, patients who did *not* have an ALT >2x ULN, used more DMARDs combined with MTX than patients who *did* have ALT >2x ULN, and used sulfasalazine, prednisone or infliximab as concomitant treatment for a longer period. The mean dosage of MTX was significantly higher in patients who did have a first ALT >2x ULN than the mean dosage over time in patients who did not (19 mg/week versus 17 mg/week, $p<0.01$).

DISCUSSION

In patients dynamically treated with methotrexate mono- or combination therapy for recent onset active rheumatoid arthritis, the frequency of increased levels of ALT >2x ULN was 6.3/100 patients years, which is lower than previously reported.(3) Persistence of ALT >2x ULN was rare, although in 44% of cases treatment adjustment took place.

In accordance with international recommendations, the BeSt study protocol advised to measure ALT every 3 months, and every 3 weeks in the first 3 months after the start of MTX. Participating rheumatologists were advised to temporary reduce the dose if ALT >2x ULN. In practice, dose reduction occurred in 26% of the patients who experienced a first ALT >2x ULN, and MTX was (temporarily or permanently) withdrawn in 27% of patients, in particular if ALT was >3x ULN as the international recommendations advise.

In 5 years time, 5592 threemonthly ALT measurements at an average cost of 15 Euro per measurement were done while patients were on MTX, and 140 (2.5%) of these measurements revealed a value >2x ULN, in 89 patients. We tried to determine risk factors for ALT >2x ULN, so that we might recognize who could benefit most from routine ALT screening. In previous studies patients with pre-existing liver disease, concomitant use of liver sensitive drugs or other DMARDs or anti-TNF, diabetes and (prior) use of alcohol were more prone to liver enzyme elevations while on MTX.(2;3;6-12) Cumulative dose or duration of use of MTX are also reported to increase the risk of liver enzyme elevations.(2;9;10) We found no statistically significant differences between patients with and without increased ALT

regarding the use of alcohol. None of the patients had diabetes at baseline, since this was an exclusion criterion for participation. Also BMI was not associated with ALT increases. Patients who used MTX in combination with other DMARDs, prednisone or infliximab had less often ALT increases >2x ULN than patients who used MTX as monotherapy, and also a higher dose of MTX was inversely associated with ALT >2x ULN. This is probably because patients who did *not* have an ALT >2x ULN used MTX for a significantly longer period than patients who did (5.0 versus 3.1 years, respectively). In that time, these patients were more likely to have a dose increase or addition of other DMARDs as required by protocol if the DAS remained too high. This would also explain why patients without an ALT >2x ULN used other DMARDs longer than patients who had an ALT >2x ULN.

We found as only independent risk factors for ALT >2x ULN baseline ALT >1x ULN and ACPA positivity, and smoking showing a trend. Preexisting mildly increased ALT levels may represent liver abnormalities, which react abnormally to exposure to MTX, or may simply result in exceeding the defined threshold of >2x ULN earlier by starting higher. ACPA positivity is associated with a better response to treatment with MTX in patients with undifferentiated arthritis (13) and possibly early RA. An increased risk for elevations of ALT suggests that ACPA positive (rheumatoid) arthritis is a different disease than ACPA negative RA at a more systemic level than previously suspected. Smoking has probably many negative systemic effects and been suggested to be a risk factor for various hepatic illnesses.(14;15)

This suggests that patients negative for ACPA, with normal ALT levels at baseline and those who are not smoking, as well as those without the known risk factors like alcohol and diabetes, will have a low risk of ALT >2x ULN on MTX and therefore monitoring could be less intensive than is currently recommended. Furthermore, during 5 years of follow up, 50% of first time ALT >2x ULN occurred in the first year of MTX use and an additional 25% occurred in the second year, which suggests that monitoring of ALT could also be less intensive if ALT increase has not occurred within 2 years.

Being based on daily practice, our study has several limitations. First, the very fact that participating rheumatologists followed the recommendations on MTX discontinuation and dose reduction when ALT increases occurred precludes observations of the natural course following such increases. However, recommendations were not always followed, which has also been described before.(16;17) This in itself suggests that some colleagues believe these recommendations are too strict, and it appears that the consequences of not following the recommendations are mild, with normalization of ALT at the next three-monthly test. However, we have no laboratory results or liver biopsies to rule out late effects.

Second, our database only provides the results of three-monthly laboratory screening, and we cannot rule out that participating rheumatologists may have arranged for additional tests and temporary MTX dose adjustments in between three-monthly visits. Given the low frequency of ALT>2x ULN and the relatively high frequency of not following recommendations on dose reduction, extra laboratory screening and treatment adjustments based on that have probably been rare.

Third, we focused on ALT, and have no routine laboratory results of AST and other liver enzymes. Some participating rheumatologists may have included these enzymes in the laboratory screening and may have based dose adjustments on these results. We did monitor reasons for dose adjustments of MTX and found that in 14 patients without ALT >2x ULN, the rheumatologist had adjusted the MTX dose because of 'elevated liver enzymes'. In six of these patients ALT was >1x ULN but <2x ULN and in the other cases ALT was normal, thus other liver enzymes were probably increased. The majority of events occurred in the first year after initiation of MTX. These additional 14 patients would result in a incidence rate of liver enzyme elevations during MTX of 7.4/100 patient- years and a cumulative incidence of 21%.

Finally, we have not looked at blood cell counts, which might be influenced by use of MTX and may require dose adjustments and therefore routine laboratory monitoring. However, severe leucopenia due to use of MTX in RA is rare.(18;19)

How to proceed with ALT screening in RA patients on MTX depends on ones general opinion on the avoidability of risk and the benefits of screening. It is not possible to prescribe MTX, or any effective drug, without risking side effects. The (logistic, financial and possibly emotional) costs of routine ALT screening are considerable, its benefits and consequences unclear. It is unclear whether a single ALT>2x ULN increase predicts irreversible liver damage, unclear whether irreversible liver damage presents with ALT increases(3), and unclear whether dose adjustments of MTX change the risk of liver damage even if they may change the level of ALT.

In conclusion, in patients with recent onset active rheumatoid arthritis dynamically treated with high dose MTX with or without other disease modifying drugs, the frequency of increased levels of ALT >2x ULN was 6.3/100 patients years, which is lower than previously reported. Also without treatment adjustments, persistence of ALT >2x ULN was rare.

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Table 1. Baseline characteristics of 498 out of 508 recent-onset RA patients in the BeSt study. Patients were categorized with and without an ALT >2x ULN. P-values are calculated to compare patients with and without ALT >2x ULN measurements.

Baseline characteristics	**All patients (n=498)**	**Patients without ALT >2x ULN (n=409)**	**Patients with ALT >2x ULN (n=89)**	**p-value**
Age, mean ± SD years	54 (14)	55 (14)	53 (11)	0.393
Female gender, no. (%)	336 (68)	273 (67)	63 (71)	0.461
Symptom duration, median (IQR) weeks	24 (14-53)	23 (13-53)	25 (14-54)	0.565
DAS, mean ± SD	4.4 (0.8)	4.4 (0.9)	4.3 (0.9)	0.397
HAQ, mean ± SD	1.4 (0.7)	1.4 (0.7)	1.3 (0.6)	0.085
BMI, mean ± SD	26 (4)	26 (4)	26 (3)	0.812
ESR, mean ± SD	41 (27)	41 (28)	39 (27)	0.563
RF positive, no. (%)	324 (65)	258 (63)	66 (73)	0.047
ACPA positive, no. (%)	293 (62)	232 (60)	61 (72)	0.037
Smoking yes, no. (%)	176 (35)	135 (33)	41 (46)	0.020
Alcohol yes, no. (%)	236 (48)	189 (47)	47 (53)	0.284
ALT, mean ± SD	24 (19)	23 (18)	29 (24)	0.035

ALT, alanine transferase; ULN, Upper Limit of Normal; SD, Standard Deviation; IQR, Inter Quartile Range; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; BMI, Body Mass Index; ESR, Erythrocyte Sedimentation Rate; RF, Rheumatoid Factor; ACPA, anti-cyclic citrullinated peptide antibodies

Table 2. Univariate baseline variables predictive of an ALT >2x ULN. Odds ratios with 95% confidence intervals are shown. *P-value <0.05 and **p<0.10.

Baseline variable	**Odds ratio (95% CI)**
Treatment strategy mono	*ref*
Step-up therapy	1.27 (0.68-2.38)
Combo with prednisone	0.58 (0.29-1.17)
Combo with infliximab	1.10 (0.59-2.06)
Age	0.99 (0.98-1.01)
Female gender	1.21 (0.73- 1.99)
Symptom duration	1.00 (1.00-1.00)
DAS	0.89 (0.68-1.17)
HAQ	0.74 (0.52-1.04)**
BMI	1.01 (0.95-1.06)
ESR	1.00 (0.99-1.01)
ALT	1.01 (1.00-1.02)*
History of liver disease	0.57 (0.07-4.61)
ACPA positive	1.72 (1.03-2.88)*
RF positive	1.68 (1.00-2.81)*
Alcohol yes	1.29 (0.81-2.03)
Smoking yes	1.73 (1.09-2.75)*

DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; BMI, Body Mass Index; ESR, Erythrocyte Sedimentation Rate; ALT, alanine transferase ; ACPA, anti-citrullinated protein antibodies; RF, Rheumatoid Factor; CI, Confidence Interval

Table 3. Univariate treatment variables predictive of an ALT >2x ULN. Odds ratios with 95% confidence intervals are shown. *P-value <0.10.

Treatment variable	**Odds ratio (95% CI)**
Number of DMARDs during MTX use	0.71 (0.57-0.90)*
Mean dosage of MTX over time	1.08 (1.02-1.13)*
Time on sulfasalazine	0.70 (0.52- 0.94)*
Time on infliximab	0.72 (0.54-0.95)*
Time on prednisone	0.49 (0.28-0.84)*
Time on hydrochloroquine	0.59 (0.26-1.35)
Time on cyclosporin	1.08 (0.63-1.86)

CI, Confidence Interval; DMARD, disease modifying anti-rheumatic drug; MTX, methotrexate

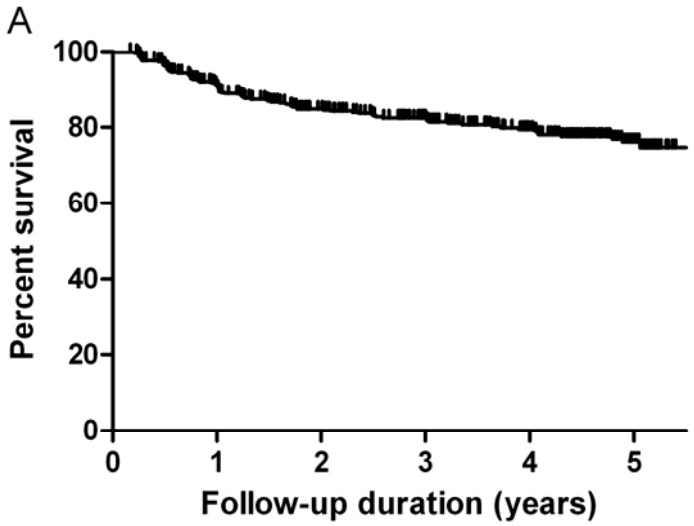

Figure 1A: Kaplan-Meier curve for the time to the first elevated ALT (>2x ULN) for all patients.

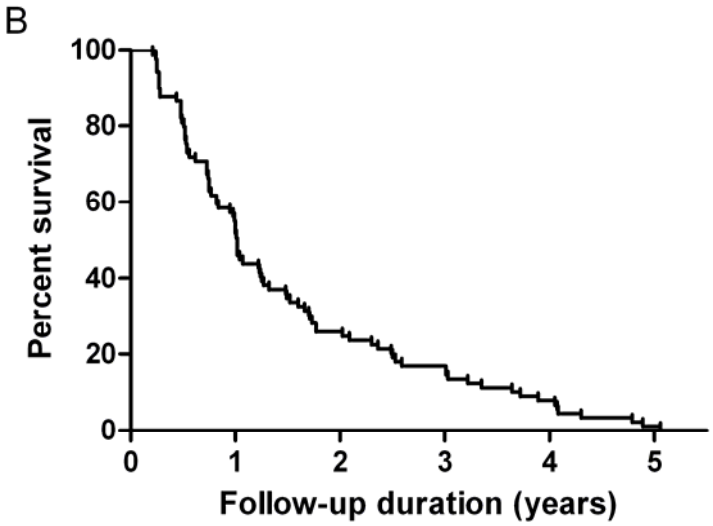

Figure 1B: Kaplan-Meier curve for the time to the first elevated ALT (>2x ULN) for cases (n=89) only.