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ORIGINAL ARTICLE

Tamoxifen use and potential effects on liver parenchyma: A long-term prospective transient elastographic evaluation

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Abstract

Tamoxifen is a commonly prescribed drug in both early and metastatic breast cancer. Prospective studies in Asian populations demonstrated that tamoxifen-related liver steatosis occurred in more than 30% of the patients within 2 years after start of treatment. No well-designed prospective studies on potential tamoxifen-related liver steatosis have been conducted in Caucasian patients so far. Therefore, our prospective study aimed to assess the incidence of tamoxifen-related liver steatosis for a period of 2 years in a population of Caucasian breast cancer patients treated with tamoxifen. Patients with an indication for adjuvant treatment with tamoxifen were included in this study. Data were collected at 3 months (T1) and at 2 years (T2) after start of tamoxifen treatment (follow-up period of 21 months). For the quantification of liver steatosis, patients underwent liver stiffness measurement by transient elastography with simultaneous controlled attenuation parameter (CAP) determination using the FibroScan. A total of 95 Caucasian breast cancer patients were included in this evaluation. Liver steatosis was observed in 46 of 95 (48%) and 48 of 95 (51%) of the patients at T1 and T2, respectively. No clinically relevant increase in liver steatosis was observed during the treatment period of 2 years with tamoxifen (median CAP = 243 ± 49 dB/m (T1) and 253 ± 55 dB/m (T2), respectively; p = 0.038). *Conclusion*: In this prospective longitudinal study in Caucasian breast cancer patients, no clinically relevant alterations in liver steatosis in terms of CAP values and liver/lipid parameters were observed after 2 years of tamoxifen treatment. This study therefore demonstrates an absence of tamoxifen-related adverse events such as steatosis and (early) development of fibrosis or cirrhosis during a treatment period of at least 2 years.

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Tamoxifen is a commonly prescribed drug in both early-stage and metastatic breast cancer.[1] Although the toxicity profile is relatively mild, tamoxifen use is associated with development of fatty liver disease. Prospective studies in Asian populations demonstrated that tamoxifen-related liver steatosis occurred in more than 30% of the patients within 2 years after start of treatment.[2,3] The concept of primary liver steatosis (related to metabolic risk factors) and secondary (e.g., drug use) can intermingle in clinical practice. Earlier, we described a Caucasian patient who developed a severe stage of liver steatosis, 6 months after starting with daily tamoxifen treatment.[4] Despite these data, no well-designed prospective studies on potential tamoxifen-related liver steatosis have been conducted in Caucasian patients so far.

Considering that most patients with early-stage breast cancer have a good prognosis, preventing severe long-term side effects such as fatty liver disease is highly relevant. Moreover, recent data suggest a clinical benefit of extending tamoxifen therapy to 10 years especially in premenopausal, young patients.[5,6] Our prospective, observational study aimed to assess the incidence of tamoxifen-related liver steatosis for a period of 2 years in a population of Caucasian breast cancer patients treated with tamoxifen.

Caucasian patients with an indication for adjuvant treatment with tamoxifen were included in this study. Patients who had longer than 3 months of tamoxifen treatment or started with a dose higher than 20 mg once daily, and patients with a non-Caucasian ethnicity, were not eligible for inclusion. The study was approved as a secondary endpoint by the Local Ethics Committee (Erasmus MC) and was registered in the Dutch Trial Registry (www.trialregister.nl; NL6918).[7] Written informed consent was obtained from all patients participating in this study. All patients were evaluated for a period of 2 years after start of tamoxifen therapy. Data were collected at 3 months (T1) and at 2 years (T2) after start of tamoxifen treatment, during two outpatient visits, including blood sampling for liver function (e.g., alanine aminotransferase, aspartate aminotransferase [AST], gamma-glutamyltransferase, alkaline phosphatase [ALP], total bilirubin [TB]) and lipid spectrum.

For the quantification of liver steatosis, patients underwent liver stiffness measurement (LSM) by transient elastography with simultaneous controlled attenuation parameter (CAP) determination using the FibroScan Touch 502 software version C 3.2 (Echosens). Experienced operators performed all FibroScan examinations as per the manufacturer's recommendations. Primary endpoint in this observational study was the alteration in liver steatosis 2 years after start with tamoxifen treatment compared with baseline measurements (T1). Statistical differences between groups or paired data points were calculated by appropriate parametric or nonparametric tests. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Five percent of our patients were excluded from analysis due to loss to follow-up (not for a medical reason); therefore, a total of 95 Caucasian breast cancer patients (age = 55.9 ± 12.0 years and body mass index [BMI] = 25.5 ± 3.8 kg.m^{-2}) were included in this evaluation, and all 190 FibroScan assessments were performed and eligible for analyses. The FibroScan was performed 3 months after initiation of tamoxifen due to practical considerations. Generally, development of liver steatosis progresses slowly; however, a rapid development (within a few months after tamoxifen initiation) may not be excluded in rare cases. Liver steatosis (defined by a CAP > 248 dB/m according to a validation report by Echosens) was observed in 48% and 51% of the patients at T1 and T2, respectively. No clinically relevant increase in liver steatosis was observed during the treatment period of 2 years with tamoxifen (median CAP = 243 ± 49 dB/m [T1] and 253 ± 55 dB/m [T2], respectively; $p = 0.038$). Also, no alterations were observed in fibrosis scores between 3 months and 2 years of treatment with tamoxifen (4.6 ± 1.4 kPa [T1] and 4.4 ± 1.4 kPa [T2], respectively; $p > 0.05$). Results of the FibroScan assessments are presented in Table 1.

Liver fibrosis, defined by LSM > 7.0 kPa, was diagnosed in 9 patients (9%) at T1 and in 6 patients (6%) at T2, respectively. In case of a suspicion of severe liver fibrosis (>9.5 kPa), patients were referred to a hepatologist for a second opinion. In all cases, no diagnosis of hepatitis was made by the hepatologist. Lifestyle advices (limited alcohol intake, exercise, diet etcetera) were given, and follow-up for liver fibrosis was advised. These consultations did not lead to dose alterations, interruptions, or discontinuations. Furthermore, the liver parameters were stable over time in these patients. A statistically significant difference was found between biochemistry parameters at 3 months compared with 2 years of tamoxifen treatment, including an increase in mean AST, triglycerides, apolipoprotein B and glucose, and a decrease in mean TB, ALP, and low-density lipoprotein. No differences were observed between T1 and T2 for weight and BMI. In our population, 13 of 95 (14%) patients used drugs for diabetes mellitus, hypertension, or hypercholesterolemia. No association between those drugs and liver steatosis at T1 or T2 was found ($p > 0.05$). In addition, liver fibrosis stiffness score was stable over time in patients with steatosis (mean 4.9 ± 1.5 kPa at T1 vs. 4.6 ± 1.6 kPa at T2; $p > 0.05$). In general, patients with a CAP > 248 dB/m were characterized by a higher BMI (26.9 ± 3.7), age (58.9 ± 11.6), or triglycerides levels (1.8 ± 0.8) compared with the population below 248 dB/m. These findings clearly indicate “lifestyle factors” as major risk factor for the development of liver steatosis. The main parameters of the population tamoxifen users are depicted in Table 1.

TABLE 1 Main parameters of evaluable patients 3 months (T1) and 24 months (T2) after start with tamoxifen treatment (n = 95)

	T1 (n = 95) N (%) or mean ± SD	T2 (n = 95) N (%) or mean ± SD	p-value
Age, years	55.9 ± 12.0	—	—
Weight, kg	72.1 ± 10.8	72.5 ± 10.5	0.28
BMI, $kg.m^{-2}$	25.5 ± 3.8	25.7 ± 3.8	0.22
Medication			
DM, hypertension, hypercholesterolemia	13 (14)	n.a.	
Liver steatosis			
CAP (dB/m)	243 ± 49	253 ± 55	0.038*
Steatosis (CAP > 248[a] dB/m), %	46 (48)	48 (51)	—
Liver fibrosis			
LSM (kPa)	4.6 ± 1.4	4.4 ± 1.4	0.9
Fibrosis (>7.0 kPa), %	9 (10)	6 (6)	—
Biochemistry			
ALT, U/L	20.7 ± 7.6	20.7 ± 9.7	0.9
AST, U/L	22.6 ± 5.3	24.7 ± 6.2	<0.001***
GGT, U/L	32.0 ± 26.0	30.2 ± 25.2	0.34
Total bilirubin, μmol/L	5.6 ± 2.6	4.7 ± 2.4	<0.001***
ALP, U/L	63.9 ± 18.7	58.7 ± 18.7	0.004*
Triglycerides, mmol/L	1.5 ± 0.7	1.9 ± 1.5	0.001**
Total cholesterol, mmol/L	4.9 ± 1.0	4.8 ± 0.9	0.59
HDL, mmol/L	1.7 ± 0.5	1.8 ± 0.5	0.02*
LDL, mmol/L	2.9 ± 0.9	2.6 ± 0.7	<0.001***
APO-A1, g/L	1.7 ± 0.3	1.7 ± 0.3	0.09
APO-B1, g/L	0.8 ± 0.2	0.8 ± 0.2	0.02*

Abbreviations: Apo-A, apolipoprotein A; Apo-B, apolipoprotein B; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; DM, diabetes mellitus; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LSM, liver stiffness measurement; T1, assessment 3 months after start with tamoxifen treatment; T2, assessment 2 years after start with tamoxifen.

[a]CAP value based on validation reports of the manufacturer of the FibroScan Touch 502.

*p-value < 0.05; **p-value < 0.01; ***p-value < 0.001.

Previously, a prospective observational study in 175 Chinese patients demonstrated a cumulative incidence of liver steatosis of 38% after 2 years of tamoxifen use.[3] This is prospective, observational study investigates the potential effect of tamoxifen on liver steatosis in a Caucasian population. Both studies show no clinically relevant alterations of liver enzymes after extensive tamoxifen use during 2 years.[3] In contrast to an Asian population, no increase in liver steatosis was observed in our Caucasian population.

The mechanism of development of fatty liver disease in (Asian) tamoxifen users is not fully elucidated, although there are indications of disturbance of the lipid homeostasis due to antagonism of the estrogen receptor.[8] In line with historical data, 48% of our patients were diagnosed with liver steatosis at T1.[9] Among a study population in the United States, liver steatosis prevalence was low in Asian patients (18%) and high among Mexican Americans (48%).[10] Therefore, apart from traditional risk factors ("lifestyle") and adaption of the Western culture, ethnic factors appear to play a significant role in the development of liver steatosis. The absence of lifestyle-related risk factors (e.g., hip–waist circumference, alcohol consumption) is a minor limitation of our study. In addition, a follow-up of 2 years is limited to identify serious complications of steatosis, such as nonalcoholic steatohepatitis or liver fibrosis. The data of this study may not be generalizable to other populations that are more ethnically diverse (non-Caucasians) or have a higher mean BMI.

In conclusion, in this prospective longitudinal study in Caucasian breast cancer patients, no clinical relevant alterations in liver steatosis in terms of CAP values and liver/lipid parameters were observed after 2 years of tamoxifen treatment. This study therefore demonstrates an absence of tamoxifen-related adverse events such as steatosis and (early) development of fibrosis or cirrhosis during a treatment period of at least 2 years.

AUTHOR CONTRIBUTIONS

Study concept: C. Louwrens Braal, Stijn L. W. Koolen, Agnes Jager, Robert J. de Knegt, Ron H. J. Mathijssen, and Karel Eechoute. *Data acquistion*: C. Louwrens Braal. *Formal analysis*: C. Louwrens Braal and Karel Eechoute. *Statistical analysis*: C. Louwrens Braal. *Funding acquisition*: Agnes Jager, Stijn L. W. Koolen, Ron H.J. Mathijssen, and Robert J. de Knegt. *Investigation*: C. Louwrens Braal, Robert J. de Knegt, Agnes Jager, Stijn L. W. Koolen, Ron H.J. Mathijssen, and Karel Eechoute. *Methodology*: C. Louwrens Braal and Karel Eechoute. *Project administration*: C. Louwrens Braal. *Supervision*: Robert J. de Knegt, Ron H. J. Mathijssen, and Karel Eechoute. All authors contributed to the data interpretation and preparation of the research letter for publication, and they approved the final version.

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CONFLICT OF INTEREST

Robert J. de Knegt received a research grant from Echosens.

ETHICS STATEMENT

The study was approved by the Local Ethics Committee (Erasmus MC, Rotterdam, the Netherlands; MEC 17–548) and was registered in the Dutch Trial Registry (www.trialregister.nl; NL6918). Written informed consent was obtained from all patients participating in this study.

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