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Original Research

Different patterns in the risk of newly developed fatty liver and lipid changes with tamoxifen versus aromatase inhibitors in postmenopausal women with early breast cancer: A propensity score–matched cohort study

Namki Hong [a,b], Han Gyul Yoon [a], Da Hea Seo [a], Seho Park [c], Seung Il Kim [c], Joo Hyuk Sohn [d], Yumie Rhee [a,*]

[a] *Department of Internal Medicine, Endocrine Research Institute, Severance Hospital, Yonsei University College of Medicine, Seoul 03722, South Korea*
[b] *Graduate School, Yonsei University College of Medicine, Seoul 03722, South Korea*
[c] *Department of Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul 03722, South Korea*
[d] *Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul 03722, South Korea*

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Abstract ***Background:*** Management of metabolic complications of long-term adjuvant endocrine therapy in early breast cancer remained an unmet need. We aimed to compare the effects of tamoxifen (TMX) and aromatase inhibitors (AIs) on the risk of fatty liver in conjunction with longitudinal changes in the serum lipid parameters.
Methods: Among 1203 subjects who were taking adjuvant TMX or AI (anastrozole or letrozole) without fatty liver at baseline, those taking TMX or AI were 1:1 matched on the propensity score. The primary outcome was newly developed fatty liver detected on annual liver ultrasonography.
Results: Among 328 matched subjects (mean age 53.5 years, body mass index 22.9 kg/m^2), 62 cases of fatty liver in the TMX group and 41 cases in the AI group were detected in a total of 987.4 person-years. The incidence rate of fatty liver was higher in the TMX group than in the AI group (128.7 versus 81.1 per 1000 person-years, P = 0.021), particularly within the first 2 years of therapy. TMX was associated with an increased 5-year risk of newly developed fatty liver (adjusted hazard ratio 1.61, P = 0.030) compared with AI independent of obesity and cholesterol level. Subjects who developed fatty liver had higher triglycerides (TGs) and

* *Corresponding author:* Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea. Fax: +82 2 392 5548.
E-mail address: yumie@yuhs.ac (Y. Rhee).

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lower high-density lipoprotein cholesterol (HDL-C) level at baseline than those without, which was sustained during follow-up despite the serum cholesterol–lowering effect of TMX. ***Conclusions:*** TMX independently increased the 5-year risk of newly developed fatty liver compared with AI in postmenopausal women with early breast cancer. Our findings suggest the need for considering the risk of fatty liver as a different adverse event profile between AI and TMX, particularly in patients with obesity, high TGs and low HDL-C.

1. Introduction

Breast cancer is the most common cancer in women, with an annual incidence of more than 1.7 million worldwide [1]. Adjuvant endocrine therapies such as tamoxifen (TMX), aromatase inhibitors (AIs) or a sequence of these agents are now recognised as the vital strategy based on the improved survival among postmenopausal women with hormone receptor–positive breast cancer, which accounts for most breast cancer cases [2]. As longer durations of endocrine therapies (>5 years) with either ongoing TMX, AI or sequential therapy are now being recommended, there has been increasing attention to the impact of long-term endocrine treatments on metabolic consequences, including the development of fatty liver and derangement of lipid metabolism [2–5]. Given the improved disease-free survival in postmenopausal women with early breast cancer, the proper management of metabolic risk in this population remains an unmet need.

Along with the global epidemic of obesity, non-alcoholic fatty liver disease (NAFLD) is the major cause of liver diseases worldwide, which is linked to type 2 diabetes, increased cardiovascular risk and kidney complications [6,7]. TMX was reported to be associated with hepatic steatosis and steatohepatitis either by directly enhancing hepatic lipogenesis or by precipitating NAFLD through the exacerbation of insulin resistance, central obesity and triglyceridemia [8,9]. However, data on the long-term effects of TMX on the development of fatty liver in postmenopausal women are sparse [10]. Despite the expanding use of AI as the upfront adjuvant endocrine therapy in postmenopausal women, few data are available about the effect of these drugs on the incidence of fatty liver in comparison with TMX [11]. Furthermore, the effect of TMX and AI on the longitudinal changes of serum lipid parameters in conjunction with the development of fatty liver has not been investigated.

In this propensity score–matched cohort study, we aimed to compare the effect of TMX and AI on the risk of newly developed fatty liver and the longitudinal change of serum lipid parameters during 5 years of upfront adjuvant endocrine therapy in postmenopausal women with hormone receptor–positive early breast cancer, along with identifying the independent predictors of incident fatty liver.

2. Methods

2.1. Study design and subjects

We conducted a propensity score–matched retrospective cohort study by using longitudinal data retrieved from the electronic registry of a tertiary-level, university-affiliated single institution (Severance Hospital, Yonsei University College of Medicine, Seoul, Korea). Between January 2006 and May 2015, a total of 5250 subjects received a diagnosis of hormone receptor–positive breast cancer for the first time in their lifetime, and were started on adjuvant hormone therapies after the primary surgery (Fig. 1). The diagnosis of breast cancer was defined by using relevant International Classification of Diseases 10th revision (ICD-10) codes for breast cancer (C50). Adjuvant endocrine therapies were defined as the presence of any prescription of 20-mg TMX daily or non-steroidal third-generation AI (1-mg anastrozole or 2.5-mg letrozole daily). The index date for study entry was defined as the first prescription date of adjuvant endocrine therapies. The baseline data of study subjects within 6 months before the index date, including demographics, cancer stage, pathology reports, liver ultrasonography, comorbidities, alcohol intake, smoking, medications including adjuvant chemotherapy and laboratory values, were obtained by using relevant ICD codes and electronic medical records. The presence of diabetes was defined as having relevant ICD-10 codes plus any prescriptions for diabetes medications or haemoglobin A1c $\geq$ 6.5%. Exclusion criteria were as follows: no available liver ultrasonography data at baseline; metastatic breast cancer; poor Eastern Cooperative Oncology Group performance score (ECOG-PS 3–4); uncertain cancer stage at index date; history of liver cirrhosis, viral or alcoholic hepatitis, non-alcoholic steatohepatitis, hepatitis B or C infection and hyper- or hypothyroidism; current alcohol intake defined as any alcohol intake within 1 year; presence of fatty liver at baseline and potential premenopause status defined as age at index date < 60 years plus baseline follicular stimulating hormone level < 25 mIU/mL [12]. To