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Adherence in tamoxifen therapy after conversion to a rebate pharmaceutical in breast cancer patients in Germany

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Key words
rebate contract – discount contract – breast cancer – adjuvant therapy – adherence – persistence – compliance – database

Abstract. Background: The aim of this study was to investigate the risk of therapy discontinuation in breast cancer patients treated with tamoxifen with and without conversion to a rebate pharmaceutical (tamoxifen) and to analyze the negative consequences of rebate contracts on the compliance of breast cancer patients among gynecologist and general practitioner practices in Germany. Methods: This retrospective analysis was performed using the IMS Disease Analyzer® database. Women with a diagnosis of breast cancer and first time prescription of tamoxifen in the time from January 2008 until December 2011 were selected. Main outcome measure was the incident the hormone treatment discontinuation rates within 3 years after index date. Treatment discontinuation of tamoxifen was defined as 90 days without this or alternative hormonal therapy (aromatase inhibitors) during that time. Results: In total, 3,620 patients were included in the persistence analysis. 1,712 (47.3%) patients were converted to a rebate product. Within 3 years of follow-up, the discontinuation rates increased to 51.5% for switched patients and 46.3% for patients without switch ($p < 0.01$). Hazard ratios for 3-year risk of tamoxifen therapy discontinuation were adjusted for age, sex, gynecologist care, patient and physician's residency, baseline co-morbidities (osteoporosis, diabetes, depression and thrombosis, side effects). These analyses comprised a significantly increased risk for treatment discontinuation for patients who were switched to a rebate pharmaceutical compared to patients without conversion to a rebate pharmaceutical (HR: 1.27, CI: 1.05 – 1.53, $p = 0.014$). Conclusions: This analysis underlines an association between the initiation of rebate contracts and a negative impact on the compliance of breast cancer patients on an adjuvant hormonal treatment. The impact of rebate contracts on the health of patients and the health care costs should be evaluated in further therapeutic fields through additional research projects.

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Introduction

In the past decade health expenses of medical interventions in Germany increased dramatically. Amongst many other, one attempt of lowering the cost was the decision of the Act on the Stabilization of Contributions to Statutory Health Insurers ("Beitragssicherungsgesetz"), which was introduced in January 2003 and set the compulsory conditions for rebate contracts. The options for statutory health insurance companies regarding the composition of rebate contracts were refined by the Economic Optimization of Pharmaceutical Care Act ("Arzneimittelversorgungs-Wirtschaftlichkeitsgesetz"), which was introduced effect in May 2006, and the health system reform bill ("GKV-Wettbewerbsstärkungsgesetz"). The health system reform bill was implemented in April 2007 and enabled the realization and initiation of rebate contracts, which have been used by many statutory health insurance companies. The German Federal Government aims to lower the costs of pharmaceutical products for statutory health insurance companies through rebate contracts.

The large number of rebate contracts alongside the impossibility to identify the frequency of switches between treatments, which could have implications to therapy compliance, implies uncertainties of patients and doctors [1]. Hereby, the health care system regulates that with every prescription the one with the lowest price must be handed out

to the individual patient irrespective of the manufacturer. According to a statement by the Allensbach Institute, every third prescription a German regularly receives a pharmaceutical product of a different manufacturer than obtained in the past [2]. Furthermore, 7% of the patients affected and 11% of those over 60 years old stated having problems, especially with tolerance and side effects, associated with a pharmaceutical product due to the regulated rebate contract switch. Moreover, even an impairment of the therapeutic effect was reported by patients. Additionally, the German Pharmaceutical Society ("Deutsche Pharmazeutische Gesellschaft") has expressed their concerns towards this procedure especially for some pharmaceuticals, i.e., adjuvant, hormonal treatment of breast cancer [3].

A questionnaire created with general practitioners (GPs) in Germany on their experiences with rebate contracts showed that most GPs have significant problems with switching drugs during chronic treatment due to the effect on patients persistence. A high percentage of the respondents noticed a significant impairment in patient compliance and the doctor-patient relationship [4].

Non-compliance is fundamental in pharmaceutical therapy. Studies reported that every fifth prescription is refilled at the pharmacy level (primary non-compliance) and that non-compliance is present in ~ 50% of prescribed long-term pharmaceutical treatments [5]. Recently, compliance, persistence and adherence with the hormonal treatment of women with breast cancer have been reported in an increasing number of epidemiological research projects [6].

The most recent database analysis herby indicated that by the end of the 3rd year of treatment, 48% of women with breast cancer on tamoxifen remained on treatment without medication procession gaps exceeding 90 days [7].

The aim of this study was to investigate the risk of therapy discontinuation in breast cancer patients treated with tamoxifen with and without conversion to a rebate pharmaceutical (tamoxifen) and to analyze the negative consequences of rebate contracts on the compliance of breast cancer patients among gynecologist and general practitioner practices in Germany.

Methods

Databases

This retrospective analysis was performed using the IMS Disease Analyzer® database.

The IMS® Disease Analyzer database contains data from Germany, the UK, and France and allows anonymous access to a selected panel of physicians' practices and patients. The data are generated directly from computers in physicians' offices via a standardized interface and provide daily routine information on patients' diseases and therapies. A physician's practice transmits patient data stored in the physician's computer to IMS on a monthly basis. Before transmission, the data are encrypted for protection and contain, in a comparable format and level of detail, information from the patient files in the doctor's practice. Every month the physician receives a feedback report reflecting his/her own prescription pattern and a comparison to those of collaborating colleagues in the IMS panel within that specialty. Altogether, the database contains data from 2,351 practices and ~ 20 million German patients from January 2000 to October 2012. In addition to data from general practitioners and specialists in internal medicine, data for various specialist groups are also recorded in Germany. The Disease Analyzer database provides a complete listing of all relevant patient details for each practice. The data obtained directly from practices are checked for plausibility, linked to relevant additional information such as the price of a pharmaceutical product, ATC and ICD coded, saved, and updated on a monthly basis. The data base includes only anonymized data in compliance with the regulations of the applicable data protection laws. The sampling method for the Disease Analyzer database is based on summary statistics from all doctors in Germany published yearly by the German Medical Association ("Bundesärztekammer"; http://www.baek.de). The statistical unit of IMS uses these statistics to determine the panel design according to the following strata: specialist group, German federal state, community size, and age of physician. This panel design forms the basis for the acquisition of the practices processed in the Dis-

ease Analyzer. Technical support and setup within participating practices is carried out by cooperating software companies using a standardized interface designed for IMS that enables each practice to collect the required data and send them to IMS in an anonymized format [8, 9].

The validity of the Disease Analyzer data was previously evaluated and described [10]. It has been the object of a number of studies and peer-reviewed scientific publications in the fields of epidemiology as well as breast cancer [7].

Study population

Overall, the database included 1,185 general practitioner and 248 gynecological practices continuously reporting to IMS HEALTH during the study period. First-time tamoxifen prescriptions from January 2008 until December 2011 were defined as index dates; maximum follow-up was until June 2012.

First, all subjects diagnosed with breast cancer (ICD 10: C50) were identified (n = 41,465). All subjects with a first-time prescription of tamoxifen (n = 7,792) in the time from January 2008 until December 2011 were selected. Patients with follow-up time of less than 365 days prior to index date were excluded. This exclusion was needed for correct identification of treatment initiation. Additionally, women who were switched from tamoxifen to an aromatase inhibitor were also excluded from the analysis. Further inclusion criteria were age at index date above 18 years. For persistence analyses 3,620 tamoxifen patients were available of who 1,712 (47.3%) patients were switched to a rebate pharmaceutical tamoxifen during the study period.

Study outcome

Main outcome measure was the hormone treatment discontinuation rates within 3 years after index date. Treatment discontinuation of tamoxifen was defined as 90 days without this or alternative hormonal therapy (aromatase inhibitors) during that time.

A longitudinal dataset of medication supply was built for each individual patient and non-persistence with study therapy was calculated. Hereby, the number of days of drug supply was calculated from quantity and dosage information associated with each prescription record. All patients were followed for a duration of at least 3 months to 3 years from their index date to identify the therapy discontinuation.

Patients restarting the initial treatment or starting another hormonal therapy after 90 days without therapy remained classified as non-persistent along with patients who discontinued Initial therapy and received no further hormonal therapy. Patients restarting the initial therapy or starting alternative hormonal therapy within 90 days was counted as persistent.

Covariates

Co-diagnoses were determined based on primary care diagnoses (ICD-10 codes) for diabetes mellitus (E10, E11, E14), osteoporosis (M80, M81), depression (F32, F33), and thrombosis (I80). Side effects included hot flashes, sweating attacks, and unusual bleeding and were selected using original doctor's text. Demographic data included age, gynecologist care, urban residency, and practice region (East/West Germany).

Statistical analysis

The cumulative non-persistence rate with tamoxifen was estimated using a Kaplan-Meier analysis stratified for patients converted to a rebate product and patients continued with the initial pharmaceutical product. Study subjects were censored at the time of loss to follow-up or treatment discontinuation, whichever occurred first. A Cox proportional hazards regression model was used to estimate the relation between non-persistence with initial molecules and conversion to a rebate product. A stepwise selection procedure with criteria for entry of $p < 0.1$ was used to select the final optimal model. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) are presented for independent variables.

Table 1. Baseline characteristics of the study patients.

Variables	Switch (n = 3,510)	No switch (n = 3,355)	p-value
Age (years)	60.0 (14.1)	60.6 (13.2)	0.105
Region (West Germany) (%)	89.4	87.2	0.035
Urban residency[a] (%)	33.1	33.3	0.918
Gynecologist care (%)	60.2	66.5	0.001
Diagnosed comorbidity[b] (%)			
Osteoporosis	7.3	7.8	0.604
Thrombosis	3.7	3.7	0.948
Diabetes	14.2	11.9	0.013
Depression	21.1	17.1	0.002
Side effects	1.0	1.4	0.247

Data are means (SD) or proportions (%); [a]> 100,000 inhabitants; [b]primary care diagnoses prior to index date.

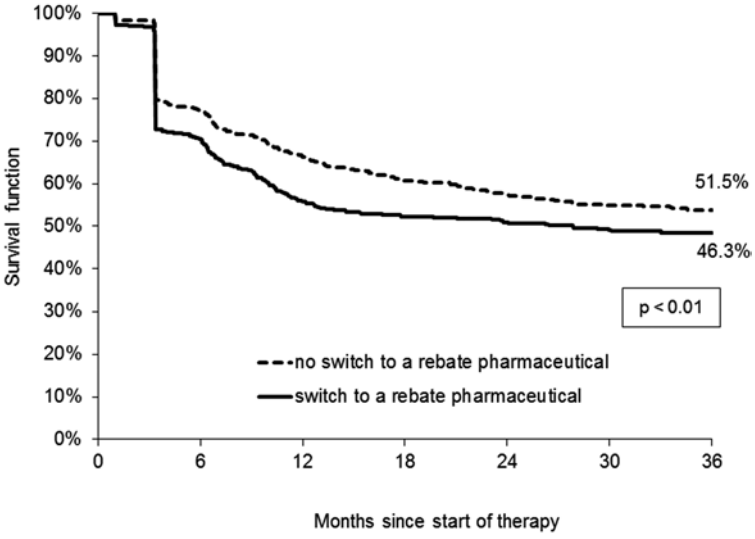

Figure 1. Kaplan-Meier curves for persistence over 3 years in all patients with breast cancer on tamoxifen treatment in Germany (IMS HEALTH Disease Analyzer, Germany).

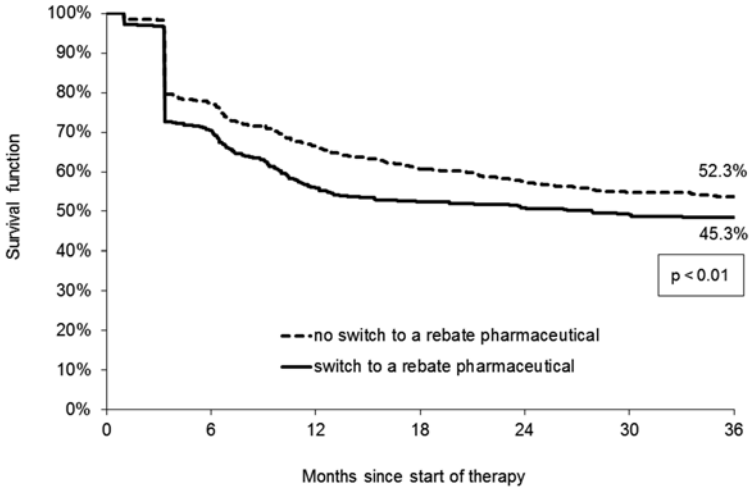

Figure 2. Kaplan-Meier curves for persistence over 3 years in patients over 65 years with breast cancer on tamoxifen treatment in Germany (IMS HEALTH Disease Analyzer, Germany).

The proportional hazards assumption was assessed and upheld for all analyses. Furthermore, potential confounders (age, gynecologist care, urban residency, practice in East-Germany), and co-morbidity (diabetes, osteoporosis, depression, thrombosis) were included as independent variables. Two-sided tests were used and a p-value of < 0.05 was considered as statistically significant. All analyses were carried out using SAS 9.2. (SAS Institute, Cary, NC, USA). Good practice methods for retrospective database studies were considered [28].

Results

Study population

In total, 3,620 patients with a diagnosis of breast cancer and first-time prescriptions of tamoxifen were included in the persistence analysis using the Disease Analyzer database. We found that 1,712 (47.3%) patients were converted to a rebate product. The demographic characteristics of the study patients are shown in Table 1.

Mean age was equivalent (60.0 and 60.6 years) and statistically not significantly different between the groups ($p = 0.105$). The proportions of patients with diagnosis of diabetes (14.2 vs. 11.9) and depression (21.1 vs. 17.1) were slightly but significantly ($p = 0.013$; $p = 0.002$) higher in the group who were switched to a rebate pharmaceutical. The number of patients treated in a gynecological practice (60.2 vs. 66.5) was significantly lower in the group who were switched to a rebate pharmaceutical ($p = 0.001$).

Kaplan-Meier survival analyses

After 1-year of follow-up, 44.2% of patients with a switch to a rebate pharmaceutical and 33.8% of patients without switch discontinued their treatment ($p < 0.01$). Within 3 years of follow-up, the discontinuation rates increased to 51.5% for switched patients and 46.3% for patients without switch ($p < 0.01$) (Figure 1). This effect could also been shown in patients over 65 years, where the discontinuation rates within 3 years of follow-up increased to 52.3% for switched

Table 2. Association of tamoxifen treatment discontinuation within 3 years with regard to predefined outcome variables (Cox regression model analyses).

Outcome variables	Hazard ratio[a] (95%CI)	p-value
Switch to a rebate pharmaceutical	1.27 (1.05 – 1.53)	0.014
Gynecologist care[b]	0.45 (0.37 – 0.55)	< 0.001
Age ≤ 50[c]	1.30 (1.00 – 1.69)	0.049
Diabetes	0.68 (0.49 – 0.93)	0.017

[a]Discontinuation of treatment adjusted for age, region (West Germany), urban residency, gynecologist care, co-diagnoses, and side effects; [b]vs. general practitioner care; [c]reference is age > 70.

patients and 45.3% for patients without a switch ($p < 0.01$) (Figure 2).

Cox regression analysis

The multivariate hazard ratios of the Cox regression models are shown in Table 2. Hazard ratios for the 3-year risk of tamoxifen therapy discontinuation were adjusted for age, sex, gynecologist care, patient and physician's residency, baseline co-morbidities (osteoporosis, diabetes, depression and thrombosis, side effects).

These analyses comprised a significantly increased risk for treatment discontinuation for patients who were switched to a rebate pharmaceutical compared to patients without conversion to a rebate pharmaceutical (HR: 1.27, CI: 1.05 – 1.53, $p = 0.014$).

Patients treated in a gynecologist practice had significantly longer persistence than patients who obtained their prescriptions in a general practitioner practice ($p < 0.001$). Patients younger than 50 were most likely to discontinue initial therapy when compared with the reference group of women over 70 ($p = 0.049$). Diabetes as co-morbiditiy was associated with decreased risk of treatment discontinuation ($p = 0.017$). No significant effect was found for West Germany, urban residency, other co-morbidities, side effects, and other age groups investigated.

Discussion

Our results indicated that women who were switched to a rebate pharmaceutical had a significantly higher risk of therapy discontinuation compared to women continued with the initial compound. This may be interpreted as a result of patient lack of confidence due to the rebate pharmaceutical or may be a consequence associated with the rebate medication, such as decreased effectiveness.

Breast cancer is the most common cancer among women in Europe that accounted for ~ 30% of cancer incidence among women and 15% of cancer deaths in 2009 [12]. In Germany, ~ 71,600 women are diagnosed with breast cancer in 2008 and ~ 17,000 women died of the disease [13].

Studies have shown that hormonal therapy for breast cancer may increase the chance of long-term survival by preventing a recurrence [14]. Tamoxifen and aromatase inhibitors are hereby a standard in the adjuvant treatment of early hormone receptor-positive breast cancer [14, 15]. Women who undergo hormonal therapy need to take tamoxifen or aromatase inhibitor orally, on a daily basis for a total of 5 years. However, epidemiological studies based on different databases and different methodologies concluded that adherence and persistence to adjuvant hormonal therapy among breast cancer survivors is suboptimal [16, 17, 18, 19, 20, 21, 22, 23]. For example, in line with our rather long term study results, the French National Health Insurance System database reported a discontinuation rate of 39.5% (95% CI 32.9 – 47.0) after 3 years of tamoxifen intake [19].

But these studies were published either before rebate contracts were initiated or in countries where no such rebate contracts existed at the time of the study. Several studies indicate non-compliance due to a switch to another pharmaceutical product in patients other than those with breast cancer [24, 25, 26, 27]. Often, patients feel less confident in the effectiveness of their switched medication and failure in drug application and dosing have been reported [24]. The majority of patients who convert to a rebate compound experience adverse events due to the new drugs or report serious problems regarding medication intake [25]. Additionally, a massive pressure on physicians due to rebate contracts was reported [26, 27].

Switches to a rebate TAM or AI product have "economic" reasons. Such changes in treatments are often followed by a total discontinuation rather than the tapering of hor-

monal drugs at the end of treatment. Notably, non-compliance in this group of patients could increase the risk of cancer recurrence and death.

Non-compliance is often followed by therapeutic failure leading to significant increase in further treatments and costs to the health care system and society [28]. Therapeutic failure and the associated consequences including the aggravation of disease can lead to an increase of physician visits and additional examinations, prescriptions, hospitalizations, and the associated direct and indirect costs [29].

Some limitations of the dataset used in our study should be taken into consideration when interpreting the results. At first, no valid information on TNM status and detailed documentation of side effects of endocrine treatment were available in the database. Data on socioeconomic status and lifestyle-related risk factors (smoking, alcohol, physical activity), which might have a significant impact on persistence, was not available. Patients could be observed in one practice only; when they received prescription by another doctor, which in Germany is not gynecological practice, these prescriptions are not documented. A further limitation of our study is the unavailability to exact data on patient compliance. We had to estimate compliance using information about prescribed daily dosage, number of prescribed refills and day of the next prescription.

However, our study has several strengths. The size of the database enabled the selection of large subsamples and information on the influence covariates of non-compliance. Additionally, this study used real life data from gynecological practices and GPs indicating a realistic impact of the access to medical care on compliance. Finally, several recent reports have proven the high validity of the information recorded by the Disease Analyzer database [8, 10].

In conclusion, this analysis underlines an association between the initiation of rebate contracts and a negative impact on the compliance of breast cancer patients on an adjuvant hormonal treatment. The impact of rebate contracts on the health of patients and the health care costs should be evaluated in further therapeutic fields through additional research projects.

German Federal Government should maintain the initial pharmaceutical drug for 5 years without rebate contract change for negative impact on the compliance of breast cancer patients on an adjuvant hormonal therapy.

Conflict of interest

PH received speaker's fee, educational and research funding from Amgen, Astra Zeneca, Elli Lilly, Novartis, Pfizer, and Roche.

There are no declarable financial or other relationships

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