Perspective to 5-year hormonal breast cancer therapy: a French national population-based study

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Background: Non-persistence to oral hormonal therapy (HT) in breast cancer (BC) is an emerging health issue, and estimations vary according to the population selected and/or the statistical method applied. This study aimed to estimate non-persistence over 5 years to HT in an unselected sample of women with BC using a French national population-based database and accounting for competing risks.

Methods: A retrospective cohort of 600 women initiating a HT between 2006 and 2007 was constituted using a representative sample of the French national healthcare insurance system database. The Cumulative Incidence Function method was used to estimate the probability of first treatment discontinuation of at least 90 days accounting for competing risk of death from any cause over the theoretical 5-year period of treatment.

Results: Thirty one percent of patients who initiated a HT were identified as non-persistent at the fifth year of follow-up. Patients who switched to another HT (HR 3.10, 95% CI (2.20; 4.36)) or had metastatic BC (HR 3.07, 95% CI (1.73; 5.46)) were more likely to be non-persistent. Women who initiated aromatase inhibitors as compared with tamoxifen (HR 0.62, 95% CI (0.46; 0.83)), had administrative registration for BC (HR 0.21, 95% CI (0.13; 0.32)), or had received an adjuvant chemotherapy (HR 0.65, 95% CI (0.48; 0.89)) were less likely to discontinue.

Conclusions: The estimate of long-term non-persistence in an unselected sample of women treated in France by oral hormonal therapy is substantial, even accounting for competing risks.

Breast cancer is a major worldwide public health challenge. It is the most frequently diagnosed cancer among women in the world and represents the leading cause of cancer death (International Agency for research on Cancer, 2012); in France the annual standardised incidence rate of breast cancer was 88/100 000 and associated mortality was 16/100 000 in 2012 (Binder-Foucard et al, 2013). Over the last decades, the development of new therapies has led to a significant improvement in the prognosis for women with breast cancer. Among such therapies, hormonal therapy (i.e., tamoxifen and aromatase inhibitors) is currently recommended as the standard treatment for hormone receptor positive breast tumours. Many clinical trials have demonstrated that both tamoxifen and aromatase inhibitors are efficient to reduce breast cancer recurrence and mortality (Early Breast Cancer Trialists’ Collaborative Group (EBCTCG), 2005; Dowsett et al, 2010). However, in real life, the optimal effect of hormonal therapy identified through clinical trials may be compromised by women who do not complete the recommended 5-year course of therapy. Available real-life studies designed to estimate non-persistence have been summarised in a qualitative systematic review (Murphy et al, 2012) from which a

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MATERIALS AND METHODS

Data source. This cohort study was conducted using reimbursement data from the Echantillon Généraliste de Bénéficiaires (EGB), a representative 1/97th dynamic random sample of the national healthcare system population-based database that contains data for 670,000 subjects (Roquefeuil et al, 2009; Tuppin et al, 2010). The EGB is an anonymised reimbursement database built by a random selection of individual identification numbers representative of the French population by age and by gender. The EGB includes insured persons, whether they are receiving healthcare or not; all health insurance schemes are included, except some rare special insurance schemes. It contains basic demographic data such as gender and dates of birth or death, all outpatient healthcare reimbursements including characteristics of the prescriber, date of reimbursement, drug dispensations motivating the reimbursement and, for each of these, the dose and the quantity of delivery units (e.g., tablets) dispensed. For each patient, data on affiliation to full healthcare coverage for those on low income (Couvèrure Médicale Universelle, CMU) and registration with a long-standing disease (Affection Longue Durée, ALD) are available. Patients suffering from one of the 30 recognised long-standing diseases, including cancer, may benefit from ALD status that grants patients copayment exempt status for all medical procedures and services related to these diseases. The general practitioner determines eligibility for ALD status by presenting the patient’s medical characteristics to the national health insurance consultant physician who then decides whether or not the patient is eligible for full coverage. The EGB database is linked to a hospital discharge summary database used to assess economic hospital activity (Programme de médicalisation des systèmes d’information, PMSI) that contains hospital data such as diagnoses and medical, surgical, or biological acts. Hospitalisation and ALD medical diagnoses are coded using the International Classification of Diseases, 10th revision (ICD-10). Coding of medical or surgical acts completed during hospitalisations is based on the Common Classification of Medical Acts (CCAM) codes (Supplementary Table).

Study population. Women were eligible for inclusion in the cohort if they were aged 20 years or more and if they initiated a treatment with tamoxifen or AI (i.e., anastrozole, exemestane, or letrozole), between 1 January 2006 and 31 December 2007. Initiation was defined as a first reimbursement without prior reimbursement for one of these drugs during the preceding 12 months. The date of first reimbursement was considered as the index date. Data available within 12 months prior to the first tamoxifen or AI reimbursement were used to identify predictors of non-persistence. The recommended duration of therapy is 5 years (Saint-Paul-de-Vence et al, 2005; Saint-Paul-de-Vence, 2007; Collège de la Haute Autorité de Santé (HAS), 2010) and thus all women selected for the analysis of non-persistence were followed for maximum 5 years after index date, or until death from any cause, or until treatment discontinuation, whichever came first.

Outcome of interest. The outcome measure was non-persistence to hormonal therapy assessed over 5 years after treatment initiation. Treatments delivered during the follow-up were identified using Anatomical Therapeutic Chemical (ATC) codes: exemestane (L02BG06), anastrozole (L02BG03), letrozole (L02BG04), and tamoxifen (L02BA01). Patients were considered non-persistent at the occurrence of the first treatment discontinuation during follow-up. For each woman, the number of days’ supply for each reimbursement was calculated using the overall quantity of reimbursed drugs provided by the prescription, divided by the corresponding Defined Daily Dose (DDD). Overlapping days supplied with successive reimbursements for a same treatment were added to the total duration of exposure. However, when women switched from one hormonal therapy to another one, the overlapping days supplied with successive reimbursements were not included in the total duration of exposure.

Discontinuation was defined as a treatment refill gap of 90 days after the estimated date of last treatment day covered by a given reimbursement. To assess variability, a sensitivity analysis was performed using a 30-day gap, 60-day gap, and 120-day gap. Switching from one hormonal therapy to another one was not considered as a treatment gap or discontinuation.

In order to give a measurable value of the non-persistence issue in France in terms of public health, the estimated proportion of non-persistent women was extrapolated to the whole French population. This calculation was performed using multipliers, standardised on age and gender, for each study year, provided by the national health insurance system.

Covariates. Covariates were chosen based on a review of the literature relating to hormonal therapy adherence and persistence (Verbrugghe et al, 2013) and limited to the variables that were available in the EGB.

As a first step, potential predictors of non-persistence were selected at the time of treatment initiation. The specialties of prescribers responsible for therapy initiation were grouped into three categories: general practitioners, breast cancer specialists (radiotherapists, oncologists, gynecologists), or other. Professional activities of prescribers responsible for therapy initiation were categorised as private practitioners, or salaried physicians. To take better account of the treatment exposure during the follow-up...
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RESULTS

Study population. The study cohort identified from the EGB database included 600 women over the age of 20 years, who had a first reimbursement of tamoxifen or AI between 1 January 2006 to 31 December 2007, and the median follow-up was 1826 days. After a standardised extrapolation to the national French population, this cohort corresponded to 79,793 women in France initiating a hormonal therapy between 2006 and 2007.

Mean age at therapy initiation was 62.0 (standard deviation: 14.1) years. The majority of women had breast cancer ALD registration (86.2%) before initiating hormonal therapy. Three-quarters (71.5%) had invasive breast cancer, and most had been treated by curative surgery (71.8%) within the 12-month period prior to inclusion. For 419 women (69.8%) the first reimbursement for hormonal therapy was for an AI, and among these, 251 (59.9%) had a first reimbursement for anastrozole. During follow-up, 358 women (59.7%) used AIs only, 107 (17.9%) used tamoxifen only, and 135 (22.6%) switched from one treatment to another at least once. Over the study period, 110 (18.3%) women died (all-cause mortality; Table 1).

Non-persistence to hormonal therapy. Considering discontinuation as a treatment refill gap of 90 days, 12.0% (95%CI [9.5; 14.8]) of women were non-persistent by the end of the first year of follow-up and this proportion increased to 30.6% (95% CI [26.6; 34.6]) by the end of the fifth year (Figure 1). Among women who experienced a treatment discontinuation, 153 (65.7%) did not resume therapy before the end of the follow-up period.

Transposed to the national French level, the proportion of non-persistent women at 1 year after treatment initiation corresponded to 9,575 (95% CI [7580; 11,809]) and after 5 years to 24,417 (95% CI [21,225; 27,608]) women in France.

Sensitivity analysis. The results from the sensitivity analysis found that for a 30-day refill gap, the most restrictive definition of the outcome, 21.0% (95% CI [17.7; 24.5]) of women were non-persistent at 1 year and 55.1% (95% CI [50.5; 59.5]) were non-persistent at 5 years (Figure 2A), which was significantly greater than that found using a 90-day gap. Applying a 60-day or 120-day gap found no significant difference with results obtained with a 90-day gap: using the 60-day gap 14.1% (95% CI [11.4; 17.1]) of women were non-persistent at 1 year and 37.1% (95% CI [32.9; 41.4]) were non-persistent at 5 years (Figure 2B); using the 120-day gap 10.9% (95% CI [8.5; 13.6]) of women were non-persistent at 1 year of treatment and 28.0% (95% CI [24.1; 31.9]) were so by the end of the fifth year (Figure 2C). Sensitivity analysis also found that among non-persistent women, 142 (38.1%) did not resume therapy before the end of the follow-up period after a 30-day treatment gap, 154 (56.8%) after a 60-day treatment gap, and 129 (65.6%) after a 120-day treatment gap.

Predictors of non-persistence to hormonal therapy. Factors significantly associated with non-persistence to hormonal therapy at 5 years of follow-up were investigated using the 90-day refill gap definition of discontinuation. The factors associated with an increased risk of non-persistence were: being exposed to tamoxifen rather than AI (HR: 1.61, 95% CI [1.20; 2.17]), switching once from an AI to tamoxifen or vice versa (HR: 3.10, 95% CI [2.20; 4.36]) – which was not further increased when switches occurred twice or more, and metastatic breast cancer at treatment initiation which increased with the number of metastases (1 metastasis: HR: 3.07, 95% CI [1.73; 5.46]; ≥ 2 metastases: HR: 4.25, 95% CI [2.06; 8.78]). Women were significantly less at risk of non-persistence (i.e., more likely to persist) if, during the year prior to therapy initiation, they had breast cancer ALD (HR: 0.21, 95% CI [0.13; 0.32]) and at least one session of breast cancer chemotherapy (HR: 0.65, 95% CI [0.48; 0.89]; Table 2).

Analysis restricted on the sub cohort of non-metastatic women. Overall, 564 women had no metastases within the 12 months prior to treatment initiation. Their baseline characteristics were generally similar to those of the full cohort except that a higher proportion of women with no metastasis received a curative surgery before treatment initiation comparing with the full cohort (73.4% vs 71.8%; Table 1). For a 90-day refill gap definition, 12.4% (95% CI [9.8; 15.3]) of women with no metastases were non-persistent at 1 year and 30.8% (95% CI [26.8; 34.9]) were so at the end of the fifth year. For these women, determinants of non-persistence remained similar to those identified in the full cohort (Table 2).

DISCUSSION

This study showed that after the first year of treatment, a substantial proportion of women in a representative sample
of women treated in France by oral hormonal therapy were non-persistent to their treatment, even when competing risks are accounted for. This proportion tended to increase over the subsequent four years of treatment. The medication-taking behaviour of these patients is all the more important in light of the findings of recent clinical trials that indicate that continuing endocrine therapy for 10 years rather than stopping at 5 years provides an additional overall and disease-free survival benefit (Davies et al., 2013; Smith et al., 2014).

Overall, these estimates were mostly lower than those obtained from healthcare database studies using the same definition of non-persistence as that used in the present study (Kimmick et al., 2009; Huiart et al., 2011; Nekhlyudov et al., 2011; Weaver et al., 2013). For instance, studies reported by Nekhlyudov et al. (2011), Weaver et al. (2013) and Kimmick et al. (2009) found that between 14% and 20% of women treated by hormonal therapy discontinued treatment for more than 90 days at the end of the first year and that between 46% and 60% of them discontinued treatment at the end of the fifth year. One aspect that may explain this apparent inconsistency is that the probabilities of non-persistence were overestimated by the Kaplan–Meier survival analysis that did not account for competing risks (Huiart et al., 2014). Furthermore, these studies focused on specific subgroups of patients; for instance in studies reported by Weaver et al. (2013) and Kimmick et al. (2009), the study populations included low-income patients covered by Medicaid who are known to be more likely to discontinue their treatment (Streeter et al., 2011). Likewise, in the study reported by Nekhlyudov et al. (2011), authors focused on a specific population

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Table 1. Socio-demographic and treatment characteristics of women initiating a hormonal therapy, with or without metastases, between 1 January 2006 and 31 December 2007 in EGB database

| Age at inclusion – years | All cohort N = 600 | Subcohort of women without metastases N = 564 |
|-------------------------|-------------------|---------------------------------------------|
| <50                     | 121 (20.2)        | 112 (19.9)                                  |
| [50–69]                 | 283 (47.2)        | 266 (47.2)                                  |
| ≥70                     | 196 (32.7)        | 186 (33.0)                                  |

| Hormonal therapy delivered during follow-up, n (%) |
|---------------------------------------------------|
| Tamoxifen only                                     | 107 (17.9) |
| AI only                                           | 358 (59.7) |
| Switch from AI to tamoxifen                        | 40 (6.7)   |
| Switch from tamoxifen to AI                        | 58 (9.7)   |
| Multiple switches                                  | 37 (6.2)   |

| Number of switches during follow-up, n (%) |
|--------------------------------------------|
| 0                                          | 465 (77.5) |
| 1                                          | 98 (16.3)  |
| ≥2                                         | 37 (6.2)   |

| Prescriber specialty for the first hormonal therapy prescription, n (%) |
|------------------------------------------------------------------------|
| Unknown                                                                | 8 (1.3) |
| General practitioners                                                   | 312 (52.0) |
| Breast cancer specialists                                               | 282 (42.7) |
| Other                                                                   | 32 (5.3) |

| Professional activity of prescribers for the first hormonal therapy prescription, n (%) |
|--------------------------------------------------------------------------------------------|
| Unknown                                                                                     | 4 (0.5) |
| Private                                                                                    | 305 (50.8) |
| Salaried                                                                                   | 292 (48.7) |

| Breast cancer diagnosis at the last hospitalisation before inclusion, n (%) |
|----------------------------------------------------------------------------|
| Non identified                                                             | 164 (27.3) |
| Localised breast cancer                                                     | 7 (1.2) |
| Invasive breast cancer                                                       | 429 (71.5) |

| In the 12 month-period before inclusion, n (%) |
|-----------------------------------------------|
| Affiliation to CMU                           | 18 (3.0) |
| Breast cancer ALD                            | 517 (86.2) |

| Breast cancer medical management |
|----------------------------------|
| Imagery                          | 69 (11.5) |
| Biopsy                           | 20 (3.3) |
| Reconstructive surgery           | 14 (2.3) |
| Curative surgery only            | 208 (34.7) |
| Chemotherapy only                | 28 (4.7) |
| Radiotherapy only                | 5 (0.8) |
| Curative surgery and radiotherapy| 52 (8.7) |
| Curative surgery and chemotherapy | 113 (18.8) |
| Chemotherapy and radiotherapy    | 4 (0.7) |
| Curative surgery, radiotherapy and chemotherapy | 58 (9.7) |

| Breast cancer metastases, n (%) |
|---------------------------------|
| 0                               | 564 (94.0) |
| 1                               | 23 (3.8)  |
| ≥2                              | 13 (2.2)  |

Abbreviations: AI = aromatase inhibitors; ALD = registration with one of the 30 major long-standing diseases (Affection Longue Durée); CMU-c = full healthcare coverage for patients with low income (Couverture Médicale Universelle); EGB = Échantillon Généraliste de Bénéficiaires.
of patients with early-stage breast cancer, and the population was also younger than that of the present study (60% of patients were under 60 years of age). Conversely, our study is population based using data from the French publicly funded health system which provides universal coverage to 99.9% of the French population and thus does not focus on any specific group (Roquefeuil et al., 2009; Tuppin et al., 2010). In contrast, the results of this study are consistent with those of a large population-based cohort of women with breast cancer conducted using the United Kingdom General Practice Research Database, which found that treatment discontinuation reached 29.8% of patients at 5 years (Huiart et al., 2011).

Among previous studies which have studied persistence in patients treated by hormonal therapy, the minimum treatment gap allowable to remain persistent ranged from 45 to 180 days (Murphy et al., 2012). The choice of a 90-day period to define a gap herein is based on the clinical practice in France where a prescription covers at least 30 days and at most 60 days. A discontinuation of 90 days of treatment means that the patient may have missed at least one visit to the physician to renew prescription. Because the use of a unique duration to define a gap may limit understanding about the true pattern of hormonal therapy use, a sensitivity analysis was conducted using shorter and a longer interval of discontinuation. This found no significant difference in estimates using a 60-day or a 120-day gap compared with that found using a 90-day gap, and, as expected, a significant difference using a 30-day gap which is too sensitive to estimate correctly non-persistence in this present study. These results confirm that a 90-day period of treatment discontinuation is robust to assess non-persistence to hormonal therapy in this study.

To further understand non-persistence among these women, the present study also highlights some predictors of discontinuation. Among therapy-related factors, it was found that being exposed to
tamoxifen rather than AI and the occurrence of at least one switch from a hormonal therapy to another during the treatment period increased significantly the risk of being non-persistent. This finding may be related to therapy-related side effects as reported in others studies. For instance, in a meta-analysis women who reported side effects were significantly more likely not to persist with hormonal therapy (OR: 5.73, 95% CI [3.87; 8.47], \( P < 0.001 \)) (Cahir et al., 2015). The main reported adverse effects are related to AI (bone loss and arthralgia) for which effective options are currently available to help patients cope with unwanted symptoms (Monnier, 2007; Dent et al., 2011) and continue their treatment. However, although side effects related to tamoxifen, namely, thromboembolic disease and endometrial cancer, are less frequent, they are more severe and difficult to manage, and their occurrence increases with long-term treatment. Moreover, switching from a treatment to another may be an indicator of unmanaged adverse effects; this is illustrated by Guth et al who found that the majority of women who experienced therapy-related side effects switched hormonal therapy (Guth et al., 2011). The results of the present study are in line with that reported by He et al, who found that patients who switched hormonal therapy during the first year of follow-up were also at increased risk of discontinuation in the following four years (HR: 1.50, 95% CI [1.23; 1.83]; He et al., 2015). Treatment switch may also reflect a lack of treatment efficacy and a progression of the disease, which may lead to a treatment discontinuation initiated by the prescriber.

Among patient clinical factors, age does not appear to be a predictor of non-persistence. This contrasts with results of others studies, which found that extreme ages (i.e., older or younger) were negatively associated with non-persistence (Owsusu et al., 2008; Hershman et al., 2010). Concerning disease-related factors, it was found that women with metastatic breast cancer before treatment initiation were more likely to discontinue treatment. At this stage of the disease benefit of endocrine therapy may be low especially considering toxicity of these drugs. Discontinuation of treatment may be a prescriber decision or the choice of patients who might not expect any significant improvement from the hormonal therapy and who want to avoid the toxicity of the treatment, considering it of low benefit. This ties in with that reported by Fink et al (2004), who have previously identified that lack of belief in the efficacy of hormonal therapy was associated with hormonal therapy non-persistence. By contrast, women who received an adjuvant chemotherapy for breast cancer were likely to be persistent as previously reported by several other studies (Fink et al., 2004; Lash et al., 2006; Kimmick et al., 2009; Hershman et al., 2010).

The medical-social-related predictor of persistence that was identified is the ALD registration status before treatment initiation. According to the findings of the present study, women who have this ALD registration were more likely to persist. The ALD system is specific to the French healthcare system and its eligibility is based only on medical criteria. Women who benefit from an ALD registration have a better follow-up then those who do not because these women need to visit their general practitioner to submit an application to the national health insurance consultant physician. It could be surprising that patients would not want to benefit from the ALD status, but for some the recognition of breast cancer as long-standing disease is psychologically difficult and may significantly impact on their social and professional life (Préau et al., 2008).

Additional analyses showed that women supposedly in early BC stage (i.e., with no metastasis) at treatment initiation had similar estimate and predictors of non-persistence than those assessed in the full cohort. Similar considerations than those described above may thus be applicable to these women.

The present study has several important strengths. It relies on a high-quality database, the EGB, which is widely used to study patterns of drug use. The EGB is a dynamic and representative sample of 1/97th of the French national healthcare system population-based database which provides a coverage of practically the entire population in France. The EGB includes insured persons, whether they are receiving healthcare or not. All health insurance schemes are included, except some rare special insurance schemes.
Thus EGB gives an representative overview of healthcare consumption of patients treated with hormonal therapy in a ‘real-world’ practice and it is well suited to study disease with high prevalence such as breast cancer (Martin-Latry and Bégaud, 2010; Mouls et al., 2015). As for any other healthcare databases, it also avoids reporting bias associated with self-reported drug use. There are, however, certain limitations. These mainly concern those common to most healthcare databases, namely the assumption that treatment dispensation equates to intake, but these databases have been frequently used and validated for the assessment of medication-taking behaviour (Silka et al., 2005; Andrade et al., 2006). Furthermore, there is limited detailed clinical information regarding comorbidities (e.g., smoking and nutritional status), paraclinical examination results and the exact reason for discontinuation. Thus, it was difficult with electronic medical data, to reliably identify situations where the discontinuation or switch of therapy was mandatory, such as as breast cancer recurrence, treatment toxicity (deep veinous thrombosis or endometrial cancer), or other medical reasons not related to breast cancer (palliative treatment of other malignant disease, pregnancy, etc.). In some of these situations, non-persistence may reflect appropriate care. In some others, patient willingness to stop therapy may be justified by a medical reason such as a desired future fertility (Llarena et al., 2015). But in any of these cases, it remains very complex to determine the real reason of treatment discontinuation and field surveys are valuable tools to complement these results. Another limitation of this study, is the choice of the duration of the time-window, preceding treatment initiation and where basic data were collected. Some data may thus be incomplete because information was provided before the 12 months prior to treatment initiation.

In summary, the estimate of long-term non-persistence measured in an unselected sample of women treated in France by oral hormonal therapy, is substantial in the first year of therapy and rose in subsequent years. These results suggest the need for early detection of non-persistence and intervention to assist in resumption of therapy.

CONFLICT OF INTEREST

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