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Persistence to aromatase inhibitors in the SIDIAP cohort: mortality and influence of bisphosphonates

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Pineda-Moncusí M[1], Vilalta-Carrera A[1], Ovejero D[1], Aymar I[1,2], Servitja S[3], Tusquets I[3], Prieto-Alhambra D[4,5], Díez-Pérez A[1,2], García-Giralt N[1], Nogués X[1,2]

1 Hospital del Mar Institute for Medical Research (IMIM). Center for Biomedical Research Network on Frailty and Healthy Aging (CIBERFES). Barcelona (Spain)
2 Department of Internal Medicine. Hospital del Mar. Autonomous University of Barcelona. Barcelona (Spain)
3. Department of Medical Oncology. Hospital del Mar Institute for Medical Research (IMIM). Barcelona (Spain)
4 Research Group on Prevalent Diseases of the Locomotor System in Primary Care (GREMPAL). Jordi Gol University Institute for Research in Primary Care (IDIAP Jordi Gol) and Center for Biomedical Research Network on Frailty and Aging Healthy (CIBERFES). Autonomous University of Barcelona and Carlos III Health Institute. Barcelona (Spain)
5 Center for Statistics in Medicine (CSM). Nuffield Department of Orthopedics, Rheumatology and Musculoskeletal Sciences (NDORMS). Oxford University. Oxford (UK)

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Summary

Objetive: To assess the persistence of aromatase inhibitor (AI) therapy, mortality associated with treatment discontinuation and the influence of oral bisphosphonates (BP) in routine clinical practice.
Material and methods: Prospective observational study of women with breast cancer undergoing AI treatment between January 2006 and December 2015, registered in the SIDIAP database. Those previously treated with tamoxifen were excluded. AI persistence was studied with a survival analysis: the Kaplan-Meier estimator was calculated, and a proportional hazards model (Cox regression) was performed between users and non-users of BP adjusting for age. A sensitivity analysis was carried out taking into account mortality as a competitive risk (Fine and Gray models). The difference in mortality between groups was compared using a Chi square test.
Results: A persistence to AI of 87% was observed after 5 years of treatment, with an overall mortality of 19.75%. There was 7.7% less mortality in those patients who completed the 5 years of treatment compared to those who did not. Patients with BP showed a decrease in mortality (6.6%) and a decrease in the risk of discontinuing therapy (adjusted SHR: 0.62 [95% CI: 0.55 to 0.70]) compared to non-users.
Conclusions: Persistence to AI and BP use are associated with a decrease in overall mortality. Furthermore, the use of BP increases adherence to AI treatment.

Key words: aromatase inhibitors, bisphosphonates, breast cancer, mortality, persistence.

Introduction

Aromatase inhibitors (AIs) are the recommended adjuvant therapy to treat estrogen receptor-positive breast cancer[1,2]. Its effectiveness in reducing the risk of recurrence and mortality is acknowledged[3]. However, AIs are also associated with various side effects that affect patients' quality of life and therefore compromise adherence to treatment and associated mortality[4].

Reportedly, 30% of patients prescribed with AI discontinue their treatment due to adverse events[5], mainly musculoskeletal[6,7]. Among them, the most frequent are arthralgias[8] and accelerated loss of bone mass[9] associated with an increase in osteoporotic fracture[10,11]. To prevent the loss of bone mass, treating patients with antiresorptives is recommended, with bisphosphonates (BP) being the most used[12-14].

Correspondence: Natalia García Giralt (ngarcia@imim.es)

BP use has been associated with improved mortality associated with reduced bone metastases[13]. Similarly, a study published in a Korean population showed the use of BP was associated with improved adherence[15].

Our study's objective was to evaluate the persistence of AI therapy, the mortality associated with treatment discontinuation, and the influence of oral BPs, in a population-based cohort with data obtained from routine clinical practice.

Material and methods

Data Base

Data from more than 7 million patients, coming from more than 350 Primary Care centers in Catalonia, are registered anonymously by the Information System for the Development of Research in Primary Care (SIDIAP), covering >80% of the total of the Catalan population (http://www.sidiap.org).

This database contains information on sociodemographic variables, lifestyle risk factors (alcohol consumption, obesity, smoking, etc.), comorbidities, and pharmacological dispensations. The data are collected by professionals in the health sector, including the codes of the international classification of diseases and related health problems, 10th edition (ICD-10), as well as structured forms for the collection of clinical variables (tobacco, index of body mass, etc.). SIDIAP also has registered mortality data, obtained from the Central Registry of Insured Persons, as well as migration outside the catchment area[16].

Study design and participants

Prospective observational study of women diagnosed with hormone receptor-positive breast cancer undergoing AI treatment. Patients treated with AI in monotherapy between January 2006 and December 2015 collected in the SIDIAP database were included. AI users were identified using the ATC (European Pharmaceutical Substances and Medicines Coding System) codes: L02BG03 for anastrozole, L02BG04 for letrozole, and L02BG06 for exemestane. Those with a previous history of cancer (except local non-melanoma skin cancer) were excluded.

Patients' follow-up period

For the adherence study, patients were monitored from the start of AI therapy until the first of the following events: cessation or abandonment of AI therapy, death, migration out of the catchment area, or end of availability of data in SIDIAP (December 31, 2015). In the case of mortality, the patients were followed up from their entry into the study until December 31, 2015.

Study variables

The main study variables were adherence to AI, and overall survival. The continued use of AIs was studied through pharmaceutical billing records. Treatment cessation or abandonment was considered in those records without dispensing with intervals of 6 months or more. Overall survival, expressed in mortality, was reported during the follow-up period.

The effect of BPs on persistence and mortality was studied by stratifying in users and non-users: patients with oral BP records (M05BA) were classified as BP users with codes M05BA01 (etidronic acid), M05BA02 (clodronic acid), M05BA04 (alendronic acid), M05BA05 (tiludronic acid), M05BA06 (ibandronic acid), M05BA07 (risedronic acid), and M05BB03 (combination of alendronic acid and cholecalciferol).

Statistical Analysis

Patient characteristics were described using the mean ± standard deviation (SD) in the quantitative variables with normal distribution, and the number and percentage –n (%)– for the categorical variables.

Adherence to AI treatment was studied with a survival analysis: the Kaplan-Meier estimator was calculated and represented by cumulative probability models. A proportional hazards model (Cox regression) was carried out between users and non-users of BP adjusting for age, obtaining the hazard ratio (HR), and its proportionality verified. Additionally, a sensitivity analysis took into account mortality as a competitive risk (Fine and Gray models), estimating the sub-distribution of the risk ratios (SHR).

Finally, the difference in mortality between groups was compared using a Chi square test.

The analyzes were carried out with R 3.5.3 using the foreign, compare groups, splines, survival, and survminer packages. These were defined as significant with $p<0.05$.

Results

18,455 data were collected from women treated with AI. Its baseline characteristics are described in table 1. The persistence [95% CI] to AI treatment was 99.8% [99.7 to 99.9] at 1 year, 98.3% [98.1 to 98 , 5] at 2 years, 95.8% [95.5 to 96.2] at 3 years, 92.9% [92.4 to 93.4] at 4 years, and 87.0% [86.3 to 87.8] after 5 years of treatment (Figure 1).

Mortality was quantified by stratifying the patients taking into account those who completed 5 years of treatment, and, on the other hand, those who did not. An overall mortality of 19.75% (3,644/18,455) was observed: with 21.2% (3,165/14,908) in patients who did not complete 5 years of AI treatment, and 13.5% (479/3,547) in those treated for 5 years or more ($p<0.001$).

Influence of the BP

Of the 18,455 patients included in the study, 21.7% (n=4,009) were treated with oral BP (Table 2). They showed better persistence to AI than those not treated with BP: 99.9% [99.8 to 100] vs. 99.7% [99.6 to 99.8] at 1 year; 99.8% [99.6 to 99.9] vs. 97.8% [97.5 to 98.1] at 2 years; 98.5% [98.1 to 98.9] vs. 94.9% [94.4 to 95.3] at 3 years; 97.2% [96.6 to 97.8] vs. 91.2% [90.5 to 91.8] at 4 years; and 93.3% [92.2 to 94.4] vs. 84.5% [83.5 to 85.5] at 5 years of treatment, respectively (Figure 2). In this way, the risk ratio of abandoning AIs in BP users compared to non-users was as follows: adjusted HR: 0.53 [95% CI: 0.47 to 0.60], and adjusted SHR: 0, 62 [95% CI: 0.55-0.70].

In contrast, mortality in patients with BP was 14.6% (587/4,009), while in non-users it was 21.2% (3,507/14,446) ($p<0.001$).

Discussion

This study evaluates the persistence of AI therapy in a cohort of women diagnosed with hormone receptor-positive breast cancer, as well as mortality and the effect of bisphosphonates, in routine clinical practice. It was observed that the global persistence at 5 years was 87%

with an overall mortality of 19.75%. Mortality in those patients who completed 5 years of therapy was 7.7% lower than those who did not. On the other hand, FB users showed better persistence to AI treatment, with a 47% lower risk of discontinuing therapy, and 6.6% lower mortality than non-users.

Reports indicate the side effects of AI negatively influence adherence to treatment[5]. Several randomized controlled trials (RCTs) have published persistence rates that vary between 76-90%[17,18]. However, the reliability of these percentages may be questioned by the lack of discontinuity results from some RCTs. Several studies of adherence in population databases show values of around 69-88% in short observation periods (one year of adherence)[19-21], and of 61-79% in longer follow-up periods (3-4,5 years)[20,22]. Hershman et al. (2010)[22] observed a 30% discontinuation rate in patients with AI at 4.5 years of follow-up, while Hadji et al. (2013)[23] described a discontinuation between 44-55% at 3 years. Among other factors, the age of the patients (younger, less adherence), and the cost of medicines and/or derived medical expenses –especially in private health systems–, have been described as variables associated with greater discontinuity[21]. The high persistence observed in our population could be explained by a high mean age (mean ± SD: 67.6 ± 11.6) compared to that reported in the RCTs (mean ± SD: 64.1 ± 9.0 in the study ATAC[24], and 64.3 ± 8.1 in the IES study[25]; median [range]: 61 [38-89] in the BIG 1-98 study[26]; and median of 63.9 and 64.3 in patients with exemestane and anastrozole in study MA.27[27]) and a public health system, where the cost of treatment is practically negligible.

In the case of global mortality, there is a certain diversity of results depending on the design of the RCT. In the BIG 1-98 study, a mortality of 12.3% was observed[28]. The ATAC safety study detected a mortality of 23.5% in all AI monotherapy users, and 21.5% in the subpopulation of women with known hormone receptor-positive tumor status[29]. In contrast, study MA.27, published by Goss et al. (2013), showed a mortality of 5.7% at 5 years[27]. Unlike RCTs, our study uses data from the general population visited in primary care, achieving a more representative population of the usual clinic. Interestingly, the mortality values of our study population are similar to those described in the ATAC study. This fact could be attributed to the fact that both report mortality results of up to 10 years of follow-up.

On the other hand, and in agreement with our results, the use of BP was reported by Lee et al. (2014)[15] as a factor that improves adherence to AI treatment. Likewise, the use of BP was associated with a 34% decrease in the incidence of bone metastases and a 17% reduction in mortality[13]. In general, the use of BP decreases overall mortality, increases life expectancy and prevents the appearance of various cancers in the general population[30]. This improvement in life expectancy is not only attributed to the decrease in fractures[31], but also to a possible prevention of frailty and a greater capacity of the individual to cope with different conditions[32].

Table 1. Baseline characteristics of the participants included in the study

Variable	AI users (N=18,455)
Age (mean ± SD)	67.6 ± 11.6
BMI (mean kg/m² ± SD)	29.7 ± 5.36
Not available [n (%)]	*13,555 (73.45%)*
Smokers [n (%)]	
No smokers	10,269 (81.44%)
Smokers	1,343 (10.65%)
Ex-smokers	997 (7.91%)
Not available [n (%)]	*5,846 (31.68%)*
Risk of alcoholism [n (%)]	
Without/Low	2,410 (85.58%)
Moderate	390 (13.85%)
High/Alcoholism	16 (0.57%)
Not available [n (%)]	*15,639 (84.74%)*
Charlson comorbidity index [n (%)]	
0	2,315 (12.54%)
1	704 (3.81%)
2	9,840 (53.32%)
3	3,553 (19.25%)
≥4	2,043 (11.07%)
MEDEA deprivation index [n (%)]	
Rural area	3,450 (20.28%)
Urban area 1	3,498 (20.56%)
Urban area 2	2,960 (17.40%)
Urban area 3	2,692 (15.83%)
Urban area 4	2,399 (14.10%)
Urban area 5	2,012 (11.83%)
Not available [n (%)]	*1,444 (7.82%)*
BP users [n (%)]	4,009 (21.7%)

BP: bisphosphonates; SD: standard deviation; BMI: body mass index; MEDEA: mortality in small Spanish areas and socio-economic and environmental inequalities.

Figure 1. Persistence to AI treatment. The graph presents a Kaplan-Meyer curve that shows the risk of AI abandonment in cumulative terms. Abbreviations: AI: aromatase inhibitors

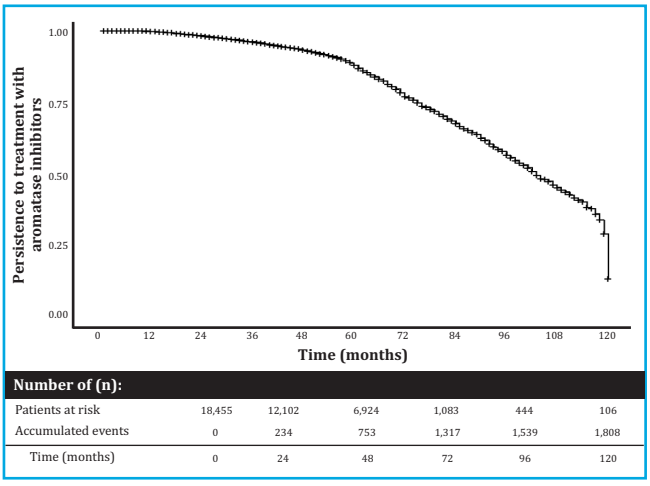
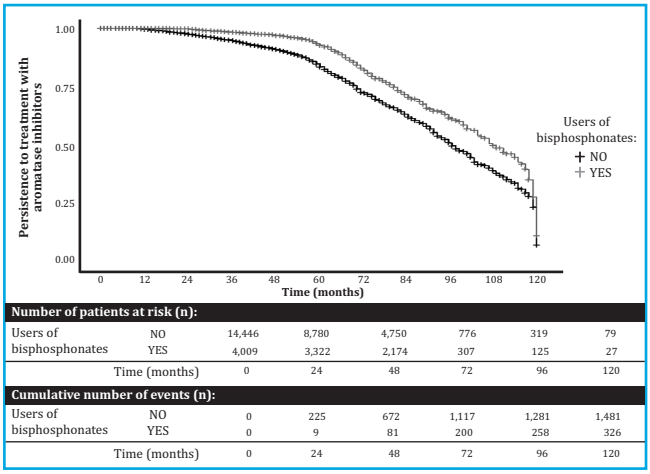


Table 2. Baseline characteristics of women treated with AI according to their use of BP

Variable	Non-BP users (N=14,446)	BP users (N=4,009)
Age (mean ± SD)	67.5 ± 12.0	68.0 ± 10.1
BMI (mean kg/m² ± SD)	29.9 ± 5.45	29.0 ± 4.94
Not available [n (%)]	*10,602 (73.4%)*	*2,953 (73.7%)*
Smokers [n (%)]		
No smokers	8,006 (80.7%)	2,263 (84.2%)
Smokers	1,088 (11.0%)	255 (9.48%)
Ex-smokers	826 (8.33%)	171 (6.36%)
Not available [n (%)]	*4,526 (31.3%)*	*1,320 (32.9%)*
Risk of alcoholism [n (%)]		
Without/Low	1,901 (85.4%)	509 (86.1%)
Moderate	313 (14.1%)	77 (13.0%)
High/Alcoholism	11 (0.49%)	5 (0.85%)
Not available [n (%)]	*12,221 (84.6%)*	*3,418 (85.3%)*
Charlson comorbidity index [n (%)]		
0	1,753 (12.13%)	562 (14.02%)
1	552 (3.82%)	152 (3.79%)
2	7,573 (52.42%)	2,267 (56.55%)
3	2,847 (19.71%)	706 (17.61%)
≥4	1,721 (11.91%)	322 (8.03%)
MEDEA deprivation index [n (%)]		
Rural area	2,809 (21.13%)	641 (17.25%)
Urban area 1	2,680 (20.16%)	818 (22.01%)
Urban area 2	2,304 (17.33%)	656 (17.65%)
Urban area 3	2,040 (15.35%)	652 (17.54%)
Urban area 4	1,890 (14.22%)	509 (13.69%)
Urban area 5	1,571 (11.82%)	441 (11.86%)
Not available [n (%)]	*1,152 (7.97%)*	*292 (7.28%)*

BP: bisphosphonates; SD: standard deviation; BMI: body mass index; MEDEA: mortality in small Spanish areas and socio-economic and environmental inequalities.

Figure 2. Persistence of AI treatment among users and non-users of BP. The graph presents a Kaplan-Meyer curve that shows AI drop out risk in cumulative terms between the study groups: users and non-users of BP. Abbreviations: AI: aromatase inhibitors; BP: bisphosphonates



Taking all this into account, the greater adherence to AI in patients treated with BP could be explained by improved treatment of adverse events that would have a positive impact on the patient, while the decrease in overall mortality derived from the use of the BP could be attributed both to a decrease in bone metastases and to greater adherence to AIs.

One limitation of this study is that the SIDIAP database does not have data referring to the cause of mortality or the reason for discontinuation of treatment. Thus, our study only considers overall mortality, but there is a risk of bias in that mortality before 5 years is not a consequence of discontinuing therapy. Additional studies are needed to verify that the observed difference in mortality is not due to a bias in the populations studied (between those patients who completed 5 years vs. those who did not, and between users and non-users of BP). However, our study corroborates the results observed in previous studies.

In conclusion, a 5-year persistence to AI of 87% has been observed in routine clinical practice, which improves with the use of BP. On the other hand, completing 5 years of AI therapy and the use of BP would be associated with a decrease in mortality.

Ethics statement: This study was approved by the IDIAP Jordi Gol Research Ethics Committee (CEI) and the SIDIAP Scientific Committee (P16/031). The data from the SIDIAP database were anonymized, with a null identification risk, in accordance with Organic Law 15/1999, of December 13. Therefore, the signing of an informed consent by the patients was not required.

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Conflict of interests: The authors declare no conflict of interest.

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