Original article

Compliance to antifracture treatments in Tuscany: a regional survey based on institutional pharmaceutical dataset

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Summary

Objective: **compliance to any antifracture therapy is the most important parameter affecting the effectiveness of the treatment. The aim of this study was to evaluate patients compliance to antifracture therapies in the whole Tuscany population who benefit from treatments reimbursed by the Regional Healthcare System.**
Methods: **we have analyzed all antifracture drug prescriptions recorded in Tuscany regional pharmaceutical database concerning year 2009, from both in-hospital distribution database (direct drug delivery, FED), and private pharmacies across the whole region (SPF). Patients who started the treatment in 2008 and those continuing it in 2010 were also considered in the analysis. The sample size consisted in 92,250 people (1:9 male to female ratio). Compliance to antifracture treatments at 3, 6, 9, and 12 months was analyzed by single drug (using the defined daily dose, DDD), and by age group (40-50, 50-60, 60-70, 70-80, 90-100 years).**
Results: **patients compliance decreased under 80% after the first 3 months of treatment, reaching no more than 50% at 1 year. Our results show that compliance to antifracture treatments reflects the age of the patients. People aged 70-80 years old represent the age group most frequently treated with antifracture therapies (36.57% of total prescriptions), with alendronic acid being the most prescribed drug (29.73% of total drug prescribed). Monthly dosing did not increase compliance if compared to oral weekly regimens, while daily oral or s.c. dosing were associated to lower compliance rates.**
Conclusion: **serious efforts need to be implemented to foster patients motivation in assuming their antifracture treatments for at least one year.**

KEY WORDS: antifracture drugs; compliance; efficacy; institutional database.

Introduction

Osteoporosis is a chronic systemic skeletal disorder characterized by low bone density and micro-architectural deterioration resulting in increased susceptibility to fragility fractures (1). Therapeutical options currently available for osteoporosis prevention and treatment include different antiresorptive and anabolic drugs. Adherence to antifracture therapy is the most important parameter affecting the effectiveness of treatments. The primary challenge in treating osteoporosis is that many patients do not take their antifracture therapies correctly. Approximately 50% of all patients do not take bisphosphonates regularly (2) or continue with treatment for at least 12 months (3), with many people discontinuing drug assumption immediately after initiation (4). The suboptimal compliance to oral bisphosphonates may result in negative consequences such as an increased fracture risk (5). Poor compliance to oral medications seems not to be caused by forgetfulness, but to deliberate choice. However, it is very difficult to find out information or studies addressing the issue of patients compliance to antifracture drugs. The aim of this survey was to evaluate patients compliance to antifracture therapies approved for post-menopausal and male osteoporosis in the whole Tuscany population who benefit from treatments reimbursed by Tuscany Regional Healthcare System by analyzing institutional dataset.

Methods

We analyzed all antifracture drug prescriptions anonymously recorded in Tuscany regional pharmaceutical database. The sample size consisted in 92,250 people (males: 9,447; 10.24% - females: 82,803; 89.76%). We have included anonymous data from both in-hospital distribution database (direct drug delivery, FED), and private pharmacies across the whole region (SPF). The analysis was carried out by referring to defined daily dose (DDD) for each drug. In computing patients compliance to therapies, we have considered all patients who were assuming any antifracture drug in year 2009. Patients who had started their antifracture treatment in 2008 and were continuing the therapy in 2009 were also included, as well as those who started the treatment in 2009 and continued drug assumption during the subsequent year 2010. Interruptions of the therapy, such as patients discontinuing the treatment during summertime, were not considered in computing the compliance. Patients compliance to antifracture treatments at 3, 6, 9, and 12 months was analyzed by single drug, and by age group (40-50, 50-60, 60-70, 70-80, 90-100 years). Both for the different age-groups, and for each drug we have also reported the weight (%) on total prescriptions. The analyzed antifracture therapies included: alendronic acid, alendronate plus vitamin D (colecalciferol), risedronate, ibandronate, neridronate, zolendronate, strontium ranelate, teriparatide, parathyroid hormone, and raloxifene. It was impossible to analyze compliance to clodronate because this drug is not reimbursed by the regional healthcare system, unless for a very small category of protected people totally assisted by the State. Neridronate has been included in the analysis, as it is used in Tuscany off-label for the treatment of osteoporosis (one i.m. administration every 3 months). Compliance to zolendronate was obviously considered as 100% because this drugs is administered only once a year. Compliance to daily s.c. teriparatide and parathyroid hormone needs to be evaluated at 6 months, as this drug can only be prescribed respecting a 6 months cycle, and for many patients the therapy is not prolonged after the first cycle. A specific quality control analysis on the dataset was carried out at regional level, fulfilling prescriptions of the current privacy protection laws. Particular attention has been paid to 9 months compliance, as Tuscany Regional Healthcare Service has set a 70% adherence rate to antifracture drug at 290 days as an objective to be reached by all local health authorities across the Region. In order to confirm the results derived from the analysis of data concerning the whole Region provided at central level, a sub-group analysis was performed on a smaller pharmaceutical official datasets concerning only Florence Local Health Authority (ASF), and Careggi University Hospital.

Results

As shown in Table 1 and represented in Figure 1, the most frequently prescribed treatment was alendronate (29.73% of total DDDs), followed by risedronate (21.89%), alendronate plus vitamin D (16.06%), strontium ranelate (15.08%), ibandronate (8.69%), neridronate (4.19%), teriparatide (1.52%), zolendronate (1.32%), raloxifen (0.78%), clodronic acid (0.44%), parathyroid hormone (0.20%), and etidronic acid (0.09%). As reported in the subsequent tables, among patients receiving prescription of any antifracture therapy, the most represented age groups were the following: 70-80 years (36.57% of total DDDs), 80-90 years (23.97%;), 60-70 years (22.95%), 50-60 years (13.04%), 90-100 years (1.78%), and 40-50 years (1.70%). Weekly dosing was the regimen most frequently used both for alendronate and risedronate. Some differences in the weight of each drug among the different age groups were found: monthly ibandronate represented 10-11% of total DDDs in people aged 40 to 70, and 6-8% in older age groups; alendronate (alone) accounted for 25% of total DDDs in people aged 40 to 70 and for 30-35% in patients aged 70 or older; zolendronate was prescribed mostly in younger people (4% of total DDDs in patients aged 40- years old), while daily s.c. anabolic drugs were most frequently assumed by older patients (about 2% of total DDDs between 70 and 90 years old). Risedronate and strontium ranelate accounted for about 21% and 16% of total DDDs in all age groups, respectively. When looking at the three most represented age groups of patients (from 60 to 80 years old), the compliance to the most frequently prescribed bisphosphonates (alendronate, risedronate, alendronate + vitamin D, and ibandronate) were similar at 3, 6, 9, and 12 months (Tables 2 to 5). It must be pointed out that alendronate + vitamin D showed lower compliance rates than alendronate alone, possibly reflecting discrepancies in the reimbursement of this drug by the regional healthcare system. Remarkably, monthly dosing (ibandronate) did not increase compliance if compared to oral weekly regimens, while daily oral or s.c. dosing were associated to lower compliance (Tables 2 to 5).

Specifically people aged 70-80 years represented the most compliant age group to alendronate therapy, while the lowest compliance was observed in between 40 and 50 years old. This trend was confirmed at 3, 6, 9 and 12 months (Tables 2 to 5). Over the time, all age groups showed a decrease in compliance to therapy. After nine months, 65.4% of patients between 70 and 80 years old were still taking alendronate (compliance at 1 year: 56.1%), while only 50.7% of patients between 40 and 50 years old were still compliant at 9 months. Similarly, after nine months, 65.9% of patients aged 70-80 who were assuming risedronate (compliance

Table 1 - Defined Daily Doses (DDDs) of antifracture drugs *(NOTA AIFA 79)* in Tuscany reimbursed by the regional healthcare system.

Defined Daily Dose (DDD) of antifracture drugs	**DDD**	**%**
Alendronic Acid	27,836	29.73%
Risedronic Acid	20,501	21.89%
Alendronic Acid and colecalciferol	15,038	16.06%
Stronzium ranelate	14,123	15.08%
Ibandronic Acid	8,138	8.69%
Neridronate	3,927	4.19%
Teriparatide	1,424	1.525
Zoledronic Acid	1,234	1.32%
Raloxifene	733	0.78%
Clodronic Acid	414	0.44%
Paratiroid Hormon	185	0.20%
Etidronic Acid	86	0.09%
	93,639	100.00%

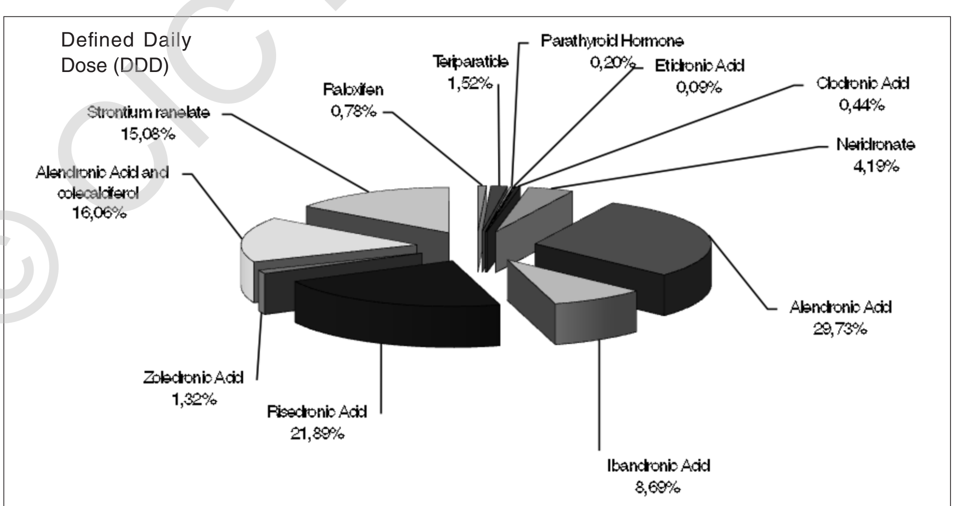

Figure 1 - Distribution (DDDs) of antifracture drugs *(NOTA AIFA 79)* in Tuscany reimbursed by the regional healthcare system.

Table 2 - Three-months compliance to antifracture therapies reimbursed by Tuscany Healthcare System.

3 Months DDD

Age group	DDDs (total = 93.639)	% DDDs per age group over total DDDs	Alendronate (29,73% on total DDDs)	Risedronate (21,89% on total DDDs)	Alendronate + colecalciferol (16,06% on total DDDs)	Strontium ranelate (15,08% on total DDDs)	Ibandronate (8,69% on total DDDs)	Neridronate (4,19% on total DDDs)	Teri-paratide (1,52% on total DDDs)	Zolendronate (1.32% on total DDDs)	Raloxifen (0,78% on total DDDs)	Parathyroid Hormone (0,20% on total DDDs)
40/50	1,591	1.70%	67.41%	65.85%	67.81%	49.11%	68.34%	0.00%	57.14%	–	68.75%	50.00%
50/60	12,206	13.04%	75.58%	77.38%	70.54%	60.99%	77.46%	0.00%	77.42%	–	69.64%	77.78%
60/70	21,492	22.95%	78.88%	80.97%	75.38%	61.31%	79.12%	0.00%	77.57%	–	76.92%	71.11%
70/80	34,240	36.57%	80.85%	81.08%	76.43%	57.28%	77.88%	0.00%	77.16%	–	75.97%	81.71%
80/90	22,442	23.97%	79.77%	78.71%	72.86%	52.38%	75.60%	0.00%	75.27%	–	73.63%	72.09%
90/100	1,668	1.78%	76.28%	76.29%	62.62%	40.85%	63.46%	0.00%	73.33%	–	71.43%	100.00%

Table 3 - Six-months compliance to antifracture therapies reimbursed by Tuscany Healthcare System.

6 Months DDD

Age group	DDDs (total = 93.639)	% DDDs per age group over total DDDs	Alendronate (29,73% on total DDDs)	Risedronate (21,89% on total DDDs)	Alendronate + colecalciferol (16,06% on total DDDs)	Strontium ranelate (15,08% on total DDDs)	Ibandronate (8,69% on total DDDs)	Neridronate (4,19% on total DDDs)	Teri-paratide (1,52% on total DDDs)	Zolendronate (1.32% on total DDDs)	Raloxifen (0,78% on total DDDs)	Parathyroid Hormone (0,20% on total DDDs)
40/50	1,591	1.70%	57.21%	55.49%	57.51%	37.05%	55.28%	0.00%	50.00%	–	50.00%	0.00%
50/60	12,206	13.04%	64.20%	68.24%	59.43%	47.52%	68.36%	0.00%	69.35%	–	62.50%	66.67%
60/70	21,492	22.95%	69.70%	71.12%	66.11%	47.31%	70.18%	0.00%	64.26%	–	69.23%	62.22%
70/80	34,240	36.57%	71.76%	72.22%	66.07%	42.89%	69.18%	0.00%	64.90%	–	63.09%	71.95%
80/90	22,442	23.97%	70.65%	69.26%	63.04%	38.68%	64.68%	0.00%	60.22%	–	65.93%	55.81%
90/100	1,668	1.78%	66.36%	60.22%	51.87%	29.36%	50.00%	0.00%	66.67%	–	71.43%	100.00%

Table 4 - Nine-months compliance to antifracture therapies reimbursed by Tuscany Healthcare System.

9 Months DDD

Age group	DDDs (total = 93.639)	% DDDs per age group over total DDDs	Alendronate (29,73% on total DDDs)	Risedronate (21,89% on total DDDs)	Alendronate + colecalciferol (16,06% on total DDDs)	Strontium ranelate (15,08% on total DDDs)	Ibandronate (8,69% on total DDDs)	Neridronate (4,19% on total DDDs)	Teri-paratide (1,52% on total DDDs)	Zolendronate (1.32% on total DDDs)	Raloxifen (0,78% on total DDDs)	Parathyroid Hormone (0,20% on total DDDs)
40/50	1,591	1.70%	50.75%	48.48%	50.21%	28.57%	48.24%	0.00%	50.00%	–	37.50%	0.00%
50/60	12,206	13.04%	55.96%	61.73%	51.97%	38.08%	60.85%	0.00%	46.77%	–	56.25%	55.56%
60/70	21,492	22.95%	63.42%	64.97%	59.36%	37.75%	63.42%	0.00%	48.67%	–	63.80%	48.89%
70/80	34,240	36.57%	65.41%	65.98%	59.40%	33.60%	62.83%	0.00%	47.50%	–	54.94%	64.63%
80/90	22,442	23.97%	64.28%	62.97%	56.38%	30.55%	57.41%	0.00%	45.43%	–	57.14%	44.19%
90/100	1,668	1.78%	59.22%	53.41%	47.66%	24.26%	43.27%	0.00%	40.00%	–	71.43%	0.00%

at 1 year: 57.6%) were still taking the drug vs. 48.48% of patients aged 40-50. The 9 months compliance with alendronate + vitamin D (colecalciferol) in patients aged 70-80 years old was only 59.4% (compliance at 1 year: 51.8%). In the same age group, 9 months compliance to monthly ibandronate was 63.42% (compliance at 1 year: 54.3%). Compliance to strontium ranelate (administere orally every day, did not exceed 38% at 9 months and 28% at 1 year. Six months compliance to daily s.c. teriparatide and parathyroid hormone did not exceed 66% and 69%, respectively.

Discussion

This is the first study addressing the issue of patients compliance to antifracture therapies in a entire Italian region. The findings of our analyses are quite impressive as only during the first 3 months of treatment there is evidence of a compliance ≥80%, which has been set as a value already corresponding to a reduction of 50% in drug antifracture efficacy (5). This data is of particular concern, as the current knowledge indicates that compliance rates <80%

Table 5 - One year compliance to antifracture therapies reimbursed by Tuscany Healthcare System.

1 Year DDD												
Age group	DDDs (total = 93.639)	% DDDs per age group over total DDDs	Alendronate (29,73% on total DDDs)	Risedronate (21,89% on total DDDs)	Alendronate + colecalciferol (16,06% on total DDDs)	Strontium ranelate (15,08% total DDDs)	Ibandronate (8,69% on total DDDs)	Neridronate (4,19% on total DDDs)	Teri-paratide (1,52% on total DDDs)	Zolendronate (1.32% on total DDDs)	Raloxifen (0,78% on total DDDs)	Parathyroid Hormone (0,20% on total DDDs)
40/50	1,591	1.70%	41.29%	40.55%	42.06%	21.88%	35.68%	100.00%	35.71%	100.00%	31.25%	0.00%
50/60	12,206	13.04%	46.03%	52.30%	44.66%	27.63%	51.53%	100.00%	35.48%	100.00%	51.79%	22.22%
60/70	21,492	22.95%	53.45%	56.48%	51.44%	26.82%	54.89%	100.00%	37.64%	100.00%	56.11%	35.56%
70/80	34,240	36.57%	56.17%	57.66%	51.79%	24.30%	54.31%	100.00%	36.91%	100.00%	49.79%	50.00%
80/90	22,442	23.97%	53.66%	54.02%	48.90%	22.07%	50.60%	100.00%	36.56%	100.00%	51.65%	39.53%
90/100	1,668	1.78%	49.46%	43.05%	40.65%	19.57%	35.58%	100.00%	26.67%	–	57.14%	0.00%

remarkably reduce the drug efficacy in terms of fracture prevention, with protective effects being almost lost in case of compliance <50%. However, a certain degree of antifracture effects cannot be excluded even after 6 months of therapy both for antiresorptive and anabolic treatments. Our results also show that adherence to the treatment reflect the age of the patients. The worst compliance rates were generally observed in the youngest (40-50) and oldest (90-100) age groups. Despite these subgroups represented a small percentage of treated patients (about 1.7%), the observed effect may reflect difficulties in getting a reimbursed therapy from the regional healthcare system. This could also explain why the compliance to alendronate + vitamin D (which is still a branded drug) is currently lower than adherence to therapy with alendronate alone. Gender differences and other variables such as the organization of healthcare system may also play a role (6). Moreover epidemiologic studies have shown that adverse upper gastrointestinal effects, more frequent dosing, treatment cost, lack of disease symptoms, and practical difficulties in the administration regimen are independent predictors of poor adherence to bisphosphonate therapy (7). Silverman et al. suggest that psychobehavioral interventions may help to improve motivation. It is important to understand the reasons for poor compliance, and patient preferences must be considered in medication decision making (6). Siris et al. have reported a linear association between adherence with osteoporosis medications and incidence of fractures during a 2-year treatment period (5). Increasing refill compliance levels are associated with progressively lower fracture rates (5). These findings suggest that incremental changes in medication-taking habits could improve clinical outcomes of osteoporosis treatment. Curtis et al. showed a similar linear effect by evaluating adherence in a time varying manner over 2.5 years (8). Samapalis et al. comfirms that the adherence with osteoporosis treatment in patients with osteoporosis is suboptimal and that it decreases at significant rates with longer treatment duration, increasing risk of osteoporotic fractures (9). This type of information may be more relevant for daily clinical practice because it provides an assessment of the benefits of medications across the range of possible adherence rates. However, it is clear that physicians play an important role fostering motivation of the patients to assume the therapy for the whole period indicated in their prescriptions.

Conclusion

Our data show that patients compliance to any antifracture therapy in Tuscany decreased under 80% immediately after the first 3 months of treatment, and up to 50-55% at one year. This data is of particular concern, as the current evidences have showed that compliance rates <80% remarkably reduce the drug efficacy in terms of fracture prevention, with protective effects being almost lost in case of compliance <50%. Major efforts should be performed in motivating patients to continue assuming their antifracture therapy for the entire period indicated in medical prescription.

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