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Comparison of Osteoporosis Pharmacotherapy Fracture Rates: Analysis of a MarketScan® Claims Database Cohort

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Abstract

Background: Several different classes of medications have been shown to be efficacious at preventing fractures in patients with osteoporosis. No study has compared real world efficacy at preventing fractures between all currently approved medications.
Objectives: To directly compare the efficacy of all currently available osteoporosis medications by using a large population claims database.
Methods: The Truven Health Analytics MarketScan® database from 2008 - 2012 was used to identify all patients who started a new osteoporosis medication. Patients who experienced a fracture after at least 12 months of treatment were identified and risk factors for fracture for all patients were recorded. Logistic regression was used to account for and quantify the contribution of risk factors, and to make direct comparisons between different osteoporosis medications.
Results: A total of 51649 patients were included in the cohort, with an average age of 56 years. The overall incidence rate of fracture was 1.55 per 100 person - years of treatment. Orally administered medications had the lowest fracture rates, led by raloxifene and alendronate (1.24 and 1.54 respectively), while parenterally administered medications including teriparatide and zolerdonic acid had the highest rates (3.90 and 1.98 respectively). No statistically significant differences found between oral or parenterally administered bisphosphonate medications.
Conclusions: While patients taking orally administered drugs including bisphosphonates had less frequent incident fracture no statistically significant differences were found between most drugs in head - to - head comparisons, even considering the route of administration of bisphosphonates. These findings support previous evidence that minimal differences in efficacy exist between different osteoporosis medications. This is the first study using a large database to compare all currently available osteoporosis treatments and will hopefully be augmented by further study to provide more evidence to make clinical decisions on osteoporosis medication use.

Keywords: Osteoporosis, Treatment, Medication, Pharmacotherapy, Fracture, Database

1. Background

The consequences and complications of osteoporosis impose a significant amount of morbidity, mortality and economic burden on patients and societies worldwide. In the United States, approximately one in five men and one in two women over the age of 50 will have an osteoporosis - related fracture (1), resulting in over two million fractures and $19 billion in related costs each year (2).

Pharmacologic treatments for osteoporosis have been shown in randomized controlled trials to reduce the incidence of vertebrae fractures by approximately 50% and non - vertebral fractures by about 30% (3-5). However, despite good compliance the observed incidence of treatment failure or inadequate clinical response has been reported to be considerably higher than in randomized clinical trials. Between 2-26% of compliant patients sustain a fracture each year while being treated with osteoporosis medications (6-8), and increased rates are found in patients who are less compliant (9-13).

Given that there is a relative paucity of evidence that directly compares the effectiveness of different osteoporosis medications, clinical decisions on choosing pharmacotherapy for patients often have an element of trial and

error. Drugs are frequently selected based on reasons other than efficacy, such as cost, insurance coverage, side effects, route of administration and interactions with other drugs or medical conditions. Studies that compare the efficacy of osteoporosis drugs would be useful to lend a quantitative, evidence - based element to making these decisions. This study retrospectively used the MarketScan database to quantify and compare real - world fracture rates among patients on each osteoporosis medication. We hypothesized that patients on medications that are more frequently administered orally would have the highest rate of fractures, followed by self - injectable medications, and then intravenous, intramuscular and medications administered in the hospital and office.

2. Methods

2.1. Data Source

The Truven Health Analytics MarketScan® Commercial Claims and Encounters database from 2008 - 2012 was used to identify patients for the study. The database contains de - identified demographic information and paid claims for inpatient and outpatient medical services and prescriptions for commercial populations.

2.2. Patient Criteria

All patients who started a newly prescribed osteoporosis medication were identified. The medications included in the study were alendronate, calcitonin, denosumab, ibandronate, raloxifene, risedronate, teriparatide and zolendronic acid. Only patients who had a 12 - month period with no filled prescriptions for an osteoporosis medication leading up to starting the new medication were included in the study. Patients who sustained a fracture within the first 12 months of starting a new osteoporosis medication were excluded from the study to allow time for therapeutic levels and results to be obtained.

2.3. Outcomes

This cohort was then divided into subgroups by each medication, and the number of patients who sustained a fracture at least 12 months after starting a new osteoporosis medication was recorded, as well as demographic information. Primary endpoint of fracture was used as this was deemed as treatment failure in our intention to treat analysis. Further discussion of our choice of treatment failure can be found in later sections of this report. Although person years of treatment was used to quantify rate of fracture, we counted each of these as a single incidence of treatment failure, and did not include a time to event analysis.

Type and location of fracture were also identified by ICD - 9 diagnosis code. In addition, information about risk factors were collected for each group, including smoking, alcohol use, rheumatoid arthritis, celiac disease, inflammatory bowel disease, type 1 diabetes, asthma, chronic obstructive pulmonary disease (COPD), osteoarthritis, use of an oral glucocorticoid medication or a fall in the past 12 months. These factors were all identified in the database by diagnosis using ICD-9 codes.

2.4. Statistical Analysis

Absolute numbers and proportion of individual sub - cohorts, as well as unadjusted rates of fracture were recorded and calculated. Logistic regression was also done adjusting for all risk factors. Additionally, the logistic regression models were repeated to compare all drugs head to head with alendronate, which was the most widely prescribed.

3. Results

3.1. Cohort Demographics and Outcomes

A total of 51649 patients met criteria to be included in the cohort. The average age of these patients was 56.0 years with a range from 50 - 63, and the majority was female, with only 3208 males included in the cohort. The average follow up for fracture surveillance was 732 days, approximately 2 years. This means that on average patients were followed for 4 years: one year with no osteoporosis drug use, one year taking a new drug to allow for efficacy to be built up, and two years of fracture surveillance. There were 1610 patients who experienced a fracture, which amounted to 3.1% of patients, and a rate of 1.55 fractures per 100 person years of treatment. The distribution of patients by each drug is listed in Table 1, along with the composition by drug group of risk factors for fracture. Absolute fracture rates for patients by each drug are listed in Table 2, and by type of fracture in Table 3. Absolute fracture rates were lowest for raloxifene and alendronate, and higher for less commonly used, parenterally administered drugs including zoledronic acid and teriparatide. The majority of fractures by location that were capture by ICD - 9 codes were wrist fractures, although almost half of the fractures were not coded as a hip, wrist or vertebral fracture.

Patients taking denosumab were originally included in the study but only 9 such patients met inclusion criteria. Given the relatively small number, they were excluded from the analysis.

Table 1. Demographic Information and Risk Factors for Patients Taking each Osteoporosis Medication[a]

Medication	Alendronate	Calcitonin	Ibandronate	Raloxifene	Risedronate	Teriparatide	Zoledronic Acid	Total
Total number of patients	26395	1074	9956	4753	8815	524	132	51649
Male patients	2035 (7.7)	139 (13.0)	336 (3.4)	8 (0.17)	501 (5.7)	74 (14.1)	12 (9.1)	3208 (6.2)
Average age	56.8	57.1	56.6	56.7	56.5	56.9	56.9	56.0
Smoking	1759 (6.7)	78 (7.3)	585 (5.9)	187 (3.9)	466 (5.3)	46 (8.8)	6 (4.6)	5543 (10.7)
Alcohol abuse	177 (0.67)	8 (0.74)	63 (0.62)	17 (0.36)	35 (0.40)	6 (1.15)	1 (0.76)	580 (1.1)
Rheumatoid arthritis	1287 (4.9)	77 (7.2)	435 (4.4)	159 (3.4)	468 (5.3)	44 (8.4)	12 (9.1)	3947 (7.6)
Celiac disease	183 (0.69)	14 (1.3)	54 (0.54)	23 (0.48)	64 (0.73)	5 (0.95)	1 (0.76)	132 (0.3)
Inflammatory bowel disease	1562 (5.9)	96 (8.9)	626 (6.3)	282 (5.9)	577 (6.6)	41 (7.8)	11 (8.3)	6393 (12.4)
Type I diabetes	625 (2.4)	34 (3.2)	181 (1.8)	77 (1.6)	200 (2.27)	10 (1.9)	5 (3.8)	2086 (4.0)
Type II Diabetes	8657 (32.8)	347 (32.3)	2768 (27.6)	1359 (28.6)	2777 (31.5)	162 (30.9)	44 (33.2)	16114 (31.2)
Use of oral glucocorticoid drug	14867 (56.3)	709 (66.0)	5947 (59.7)	2660 (56.0)	5174 (58.7)	325 (62.0)	90 (68.2)	29772 (57.6)
Asthma, COPD, chronic bronchitis, emphysema	5433 (20.6)	309 (28.8)	2028 (20.4)	891 (18.8)	1808 (20.5)	151 (28.8)	35 (26.5)	10655 (20.6)
Fall in past 12 months	427 (1.6)	21 (2.0)	159 (1.6)	49 (1.0)	118 (1.3)	14 (2.7)	2 (1.5)	790 (1.5)
Osteoarthritis or degenerative joint disease	7092 (26.9)	362 (33.7)	2796 (28.1)	1269 (26.7)	2329 (26.4)	198 (37.8)	47 (35.6)	14093 (27.3)

[a]All values listed are number of patients with percent in brackets, except for age, which is expressed in years.

Table 2. Fracture Rate and Follow - up Period for Patients by each Osteoporosis Medication[a]

Medication	Alendronate	Calcitonin	Ibandronate	Raloxifene	Risedronate	Teriparatide	Zoledronic Acid	Total
Total number of patients	26395	1074	9956	4753	8815	524	132	51649
Fractures	804	37	325	119	280	40	5	1610
Patients with fracture(s) (%)	3.05	3.45	3.26	2.50	3.18	7.63	3.79	3.12
Average follow-up (days)	724	717	741	735	751	714	697	732
Fracture rate per 100 person years	1.54	1.75	1.61	1.24	1.54	3.9	1.98	1.55

[a]No statistically significant differences were found in fracture rates aside from the rate for teriparatide being higher than all other ones. A more detailed and controlled head - to - head analysis can be seen in Table 5.

Table 3. Number of Fractures in Different Sites by each Osteoporosis Medication

Medication	Alendronate	Calcitonin	Ibandronate	Raloxifene	Risedronate	Teriparatide	Zoledronic Acid	Total
Total number of patients	26395	1074	9956	4753	8815	524	132	51649
Hip fractures	87	5	31	13	26	6	0	168
Wrist fractures	273	4	103	34	99	3	2	518
Vertebrae fractures	89	8	45	19	34	2	0	197
Other fractures	355	20	146	53	121	29	3	727
Total Fractures	804	37	325	119	280	40	5	1,610

3.2. Logistic Regression Analysis

Logistic regression analysis yielded a controlled contribution towards fractures for different risk factors to fractures, as seen in Table 4. Most risk factors had statistically significant odds ratios greater than 1, indicating an increased risk of fracture. Experiencing a fall in the 12

months prior to starting an osteoporosis medication was by far the most significant risk factor for experiencing a fracture while being treated for osteoporosis in our cohort. In descending order of magnitude of risk, having a prior fall was followed by carrying a diagnosis of diabetes, osteoarthritis, alcohol abuse, and being a smoker. Other risk factors that appeared to contribute to fractures included inflammatory bowel disease, use of an oral glucocorticoid, asthma and COPD. Factors found not to have a statistically significant correlation included rheumatoid arthritis and celiac disease. Table 5 shows the results of the logistic regressions directly comparing each drug to alendronate. For this analysis, confounders that were adjusted for were smoking, alcohol abuse, rheumatoid arthritis, inflammatory bowel disease, celiac disease, type 1 diabetes, type 2 diabetes, use of oral glucocorticoid, asthmas, COPD, chronic bronchitis, emphysema, fall in past 12 months, osteoarthritis and degenerative joint disease. Except for raloxifene, the odds ratios were above 1, indicating increased risk of fracture relative to alendronate, but only teriparatide was statistically significant (OR 2.347, 95% CI 1.676 - 3.286). Although the odds ratio for raloxifene was less than 1, indicating decreased risk of fracture, it was not statistically significant.

4. Discussion

The results of the direct comparison of different osteoporosis medications were opposite of our hypothesis. No statistically significant results were found based on route of administration of bisphosphonates, nor between raloxifene and alendronate. Previous randomized trials and retrospective studies have found no difference between alendronate and raloxifene, and other reviews and analyses have concluded that minimal differences in efficacy exist between different medication options (4, 14-16). The fact that our study did not find statistically significant differences supports the results from these studies.

The only statistically significant difference in fracture rate found by the study was between teriparatide and alendronate. This likely represents confounding by indication, since many patients taking teriparatide are prescribed it due to an indication of previous fractures, or especially low bone mineral density.

For almost all risk factors that were captured by available data, analysis showed statistically significant results for them increasing the likelihood of experiencing a fracture. The risk factors that were chosen in the study were identified to mirror the validated FRAX model risk factors, as much as was possible by using ICD - 9 codes. This analysis showed experiencing a recent fall to be by far the most significant risk factor. It is worth keeping in mind that most studies evaluating risk factors looked at general populations, whereas our cohort included only patients currently being treated for osteoporosis. Similar results have also been found by studies that have identified risk factors for treatment failure while on an osteoporosis medication (17, 18). Given the significant magnitude of risk found in this study and other for patients who have had a recent fall or fracture, it may be worth considering more intensive therapy for these patients, including possibly using multiple agents when initiating therapy.

The overall fracture rate for all patients included in the study of 1.55 fractures per 100 person years of treatment was at the lower end of the spectrum from previous studies. Although no studies have looked at such a wide range of medications in a single study, rates of fractures per 100 person years have been reported between 0.8 and 9.5, with most between 1 and 4 (6-8, 12, 15, 17, 19-26). These rates, as well as data from randomized controlled trials have found relative risk reduction of approximately 0.60 compared to patients not taking osteoporosis medications (16). The results in our study therefore lie somewhere in between the greater efficacy found in trials and the lesser efficacy that has been noted in "real world" retrospective studies. A control group cohort was initially included in this study but removed in favor of directly comparing medications to each other.

Ultimately it is a difficult comparison to make between this study and others since there are many parameters that vary between them, including assessments of compliance, duration of follow up and the medications that were studies. In the present study, no assessment of compliance was made, but inclusion criteria required a one - year "wash out" period and a one - year period for efficacy to be achieved. It is possible that we included patients who had been on past long term (i.e. 5 or more years of oral bisphosphonates or 3 or more years of I.V. bisphosphonates), and despite a "wash out" period of one year, that they were still exhibiting an effect of the bisphosphonate given the known long half - life of these drugs in bone. If they were restarted on a bisphosphonate after a "drug holiday" it may have accounted for the lower fracture rate in this group, but there's no way in knowing that from this database analysis.

Although many other studies have reported treatment failure as 2 or more fractures, and most efficacy studies control for patient compliance, we specifically did not want to use these methods (6, 26). We felt that without controlling for compliance we would capture a true, intention - to - treat efficacy for each drug, and have compliance (or non - compliance) contribute to their overall efficacy versus other medications. We also reported rates of a single fracture since we felt that there is a more significant

Table 4. Logistic Regression Results Indicating Risk Associated with Fracture While Being Treated for Osteoporosis, for each Factor

Fracture Risk Factor	Wald Chi - Square	P value	Odds Ratio	95% Confidence Limits	
Smoking	17.97	< 0.0001	1.457	1.224	1.733
Alcohol abuse	5.19	0.023	1.665	1.074	2.582
Rheumatoid arthritis	0.21	0.65	1.049	0.852	1.292
Celiac disease	0.51	0.48	1.227	0.700	2.148
Inflammatory bowel disease	4.35	0.037	1.215	1.012	1.460
Type I diabetes	19.89	< 0.0001	1.786	1.384	2.305
Use of oral glucocorticoid drug	6.31	0.012	1.149	1.031	1.280
Asthma, COPD, chronic bronchitis, emphysema	24.22	< 0.0001	1.337	1.191	1.501
Fall in past 12 months	438.44	< 0.0001	7.328	6.082	8.830
Osteoarthritis or degenerative joint disease	105.43	< 0.0001	1.731	1.559	1.922

Table 5. Logistic Regression Results for Head - to - head Drug Comparisons to Alendronate, with Regards to Fracture Incidence[a]

Drug	Unadjusted Odds Ratio	95% Confidence Limit		Odds Ratio	95% Confidence Limit	
Calcitonin	1.14	0.81	1.59	1.03	0.73	1.44
Ibandronate	1.07	0.94	1.22	1.08	0.94	1.23
Raloxifene	0.82	0.67	0.99	0.87	0.72	1.07
Risendronate	1.04	0.91	1.20	1.07	0.93	1.23
Teriparatide	2.63	1.89	3.66	2.35	1.68	3.29
Zolendronic Acid	1.25	0.51	3.07	1.16	0.47	2.86

[a]Variables adjusted for: smoking, alcohol abuse, rheumatoid arthritis, inflammatory bowel disease, celiac disease, type 1 diabetes, type 2 diabetes, use of oral glucocorticoid, asthma, COPD, chronic bronchitis, emphysema, fall in past 12 months, osteoarthritis and degenerative joint disease.

clinical difference between one and zero fractures, than between two and one fractures. For this reason we also gave a significant amount of time for drug efficacy to be achieved (12 months), before looking for patients who experienced a fracture.

The weaknesses of this study include many of the well - reported drawbacks of large claims database studies. Most important among these, is that the data integrity is dependent on the accuracy of the coding within the database and that the sub - population within the database may or may not represent the composition of other populations. The lack of available bone mineral density data for all patients, as mentioned above, is also a significant drawback of the data set and study. Another difficulty in our study specifically was that limited use of newer drugs reduced the ability to identify statistically significant differences in comparing different medications. As previously mentioned, more recently approved drugs account for a small proportion of patients included in the study. The average age is also a limitation of the study, as the patients captured in this cohort were relatively young, with an average age of 56 and a range of 50 to 63 years of age. Although this does not capture the age range of all patients who use osteoporosis medications, this is still an age group where fracture prevention and osteoporosis is a significant health problem, as evidenced by the over 100000 patients captured in our study. Finally, having a longer follow up period would also be useful but was limited by the available data.

More studies comparing the efficacy of osteoporosis medication would certainly serve to help direct evidence - based decision making for health care providers. This may be more achievable as use of new agents become more prevalent. Consideration of drug efficacy in specific type of patients and populations may also identify more specific indications for individual drugs.

Overall, this study reaffirmed the efficacy of all osteoporosis medications in a large population database study. Patients taking orally administered drugs including bisphosphonates had less frequent incident fracture, however statistically significant differences were not found in head - to - head comparisons that accounted for risk factors. Ultimately this supports previous findings that minimal differences in efficacy exist between the different medications, and highlights the paucity of data available for patients taking more recently approved medications. Previously established risk factors for fracture were also con-

firmed to be risk factors for treatment failure across this large cohort. This is the first study to use a large database to compare all currently available osteoporosis treatments and will hopefully be augmented by further study to provide more evidence to make clinical decisions on osteoporosis medication use.

Footnotes

Authors' Contribution: Study concept and design: Fox, Kocis; Acquisition of data: Liu; Analysis and interpretation of data: Liu, Reynolds; Drafting of the manuscript: Reynolds, Skowronski, Liu; Critical revision of the manuscript for important intellectual content: Fox, Leslie, Kocis; Statistical analysis: Liu; Administrative, technical and material support: Reynolds; Study supervision: Fox, Kocis.

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