Treatment of Osteoporosis with Anabolic Agents and the Risk of Primary Bone Cancers: A Study of 44,728 Patients Treated with Teriperatide and Abaloparatide

Daniel James Alsoof, Christopher McDonald, Keir Gene Johnson[1], Janine Molino, Mariah Balmaceno-Criss, Alan H Daniels[2]

[1]Warren Alpert Medical School of Brown University, [2]University Orthopedics, Inc.

INTRODUCTION:

Primary bone malignancies are rare but serious cancers. Osteosarcoma is the most common primary bone malignancy with a bimodal age distribution. It exists in both a primary form, driven by p53 mutations, and secondary forms subsequent to Paget's disease, radiation, or other causes. Bone anabolic agents such as teriparatide and abaloparatide can benefit orthopaedic patients perioperatively and improve outcomes after fragility fractures. However, preliminary animal data raised concern for the potential development of bony malignancies following treatment with these medications.

METHODS:

This investigation examined 44,728 patients over 50-years-old who were prescribed teriparatide or abaloparatide, and compared them to a matched control group to evaluate risk of primary bone cancer development. Patients under 50, with a prior history of cancer, or other risk factors for bony malignancy were excluded. A separate cohort of 1,241 patients prescribed teriparatide or abaloparatide and with risk factors for primary bone malignancy, along with 6,199 matched controls, was created to evaluate the effect of anabolic agents in this population. Cumulative incidence and incidence rate per 100,000 person years was calculated as were risk ratios and incidence rate ratios. Anabolic agents exposed and unexposed cohorts were compared using the Pearson Chi-square method and two-sided t-test where applicable.

RESULTS:

The overall risk of primary bone malignancy development for risk factor excluded patients in the anabolic agent-exposed group was 0.02%, compared to 0.05% in the non-exposed group. Incidence rate per 100,000 person years was calculated at 3.61 for the anabolic exposed patients and 6.46 for controls. There was a risk ratio of 0.47 (p=0.03) for development of primary bone malignancies in patients undergoing treatment with bone anabolic agents and an incidence rate ratio of 0.56 (p=0.052). Among patients with osteosarcoma risk factors, 5.96% of anabolic exposed cohort developed primary bone malignancies and 8.13% developed primary bone malignancy in non-exposed patients. Incidence rate per 100,000 person years among osteosarcoma risk factor cohorts was 1025.99 for anabolic exposed and 2083.40 for non-exposed. The risk ratio was 0.73 (p=0.01) and incidence rate ratio was 0.95 (p=0.67).

DISCUSSION AND CONCLUSION:

Bone anabolic agents such as teriparatide and abaloparatide can safely be used for osteoporosis and orthopaedic perioperative management without increased risk of development of primary bone tumors such as osteosarcoma.

Figure 1. Incidence Rate Ratio (IRR) of osteosarcoma and primary bone malignancies given exposure to teriparatide compared to previously reported data

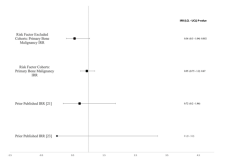

Table 1. Comparison of medications, malignancies, and primary bone malignancy risk factors between anabolic exposed and unexposed patients before matching and exclusion criteria. *The number patients in a cohort size <11 are not reportable per HIPAA (Health Insurance Portability and Accountability Act).

	Exposed	%	Controls	%	P-value
Total	60,254	100	5,405,890	100	
Osteoporosis drugs					
Bisphosphonates	25503	42.46%	1634802	30.24%	<0.001
Vitamin D	23152	38.42%	1358640	24.78%	<0.001
Denosumab	7558	12.54%	124957	2.31%	<0.001
Malignancies					
Multiple Myeloma	518	0.86%	44154	0.82%	0.2886
AML	81	0.13%	8573	0.16%	0.1523
ALL	53	0.09%	6182	0.11%	0.0644
CML	75	0.12%	7998	0.14%	0.2421
CLL	250	0.41%	27479	0.51%	0.0815
Osteosarcoma	104	0.17%	12737	0.24%	0.0854
Primary Bone Malignancy Risk Factors					
Paget's Disease	166	0.28%	11440	0.21%	0.1151
Hereditary Multiple Osteochondromatosis	23	0.04%	1198	0.02%	0.0233
Polyostotic Fibrous Dysplasia	*	*	312	0.01%	0.1096
Retinoblastoma	*	*	348	0.01%	0.9307
Li Fraumeni Syndrome	*	*	357	0.01%	0.7705
Irradiation Exposure	901	1.50%	116762	2.19%	<0.001
Alkylating Agent Exposure	181	0.30%	13269	0.25%	0.0802

Table 2. Comparison of demographics between anabolic exposed and unexposed cohorts after matching and exclusion criteria applied.

	Exposed	%	Controls	%	P-value
Total	44,720		223,603		
Gender					
Female	40649	90.88%	203263	90.87%	>0.999
Male	4079	9.12%	20388	9.12%	>0.999
CCI					
Average CCI score	1.24		1.69		0.998
Median CCI score	1		1		
Standard Deviation for CCI score	1.8		2.06		
Age Range					
40-44	85	0.19%	426	0.19%	>0.999
45-49	645	1.44%	3226	1.44%	>0.999
50-54	2866	6.41%	14328	6.41%	>0.999
55-59	6009	13.43%	30046	13.43%	>0.999
60-64	7812	17.47%	39060	17.46%	>0.999
65-69	7339	16.41%	36695	16.41%	>0.999
70-74	12118	27.09%	60590	27.09%	>0.999
75-79	6617	14.79%	33085	14.79%	>0.999
80+	1227	2.77%	6185	2.77%	>0.999

Table 3. Risk Factor Cohorts: Comparison of demographics between anabolic exposed and unexposed patients after matching.

	Exposed	%	Controls	%	P-value
Total	1,241		6,199		
Gender					
Female	1087	87.59%	5431	87.61%	>0.999
Male	154	12.41%	768	12.39%	>0.999
CCI					
Average CCI score	3.15		3.26		0.998
Median CCI score	2		2		
Standard Deviation for CCI score	3.28		3.51		
Age Range					
40-44	15	1.21%	75	1.21%	>0.999
45-49	35	2.82%	175	2.82%	>0.999
50-54	82	6.61%	411	6.63%	>0.999
55-59	150	12.01%	746	12.04%	>0.999
60-64	230	18.53%	1150	18.55%	>0.999
65-69	222	17.89%	1110	17.91%	>0.999
70-74	342	27.56%	1707	27.54%	>0.999
75-79	127	10.23%	635	10.24%	>0.999
80+	<11		<11		>0.999

Table 4. Primary bone malignancy risk for patients who received anabolic agents compared to a matched cohort who did not receive any bone-forming medications

	Exposed	Controls	RR or IRR (95% CI)	P-value
Risk Factor Excluded Cohorts				
Cumulative Incidence	11 (0.02%)	116 (0.05%)	0.47 (0.26-0.88)	0.03
Incidence rate per 100,000 person years	3.61	6.46	0.56 (0.30-1.04)	0.052
Average follow up time (years)	5.81	6.29	-	<0.001
Total person-years	304,251	1,795,300	-	-
Risk Factor Cohorts				
Cumulative Incidence	74 (5.96%)	504 (8.13%)	0.73 (0.56-0.93)	0.01
Incidence rate per 100,000 person years	1025.99	1083.40	0.95 (0.72 - 1.26)	0.67
Average follow up time (years)	5.59	6.12	-	<0.0001
Total person-years	7213	46,520	-	-

RR=Risk Ratio; IRR=Incidence Rate Ratio