Leuprolide and Fracture Risk in Patients With Central Precocious Puberty

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INTRODUCTION

- Central Precocious Puberty (CPP) causes early sexual development, rapid bone maturation and early epiphyseal closure, which can result in stunted adult height [1]
- Leuprolide is the most commonly used gonadotropin-releasing hormone (GnRH) analog that helps to delay puberty and epiphyseal closure that ultimately increase adult height [2]
- Fractures have been reported in patients with CPP after childhood leuprolide use [3]

OBJECTIVE

To study the relationship between leuprolide and fracture

METHODS

Design: A retrospective cohort study

Data Source:

U.S. Food and Drug Administration (FDA) Sentinel System -- electronic health care data of primarily commercially-insured patients from 12 data partners during the period between 2000 and 2018

Study Population and Inclusion/Exclusion:

- Eligible patients were classified as the following three cohorts:
  - Leuprolide-exposed cohort with CPP: patients with a CPP diagnosis during 183 days prior to the leuprolide initiation (index date)
  - 1st Leuprolide unexposed cohort with CPP: patients diagnosed with CPP, indexed on median time from the first CPP diagnosis to exposure summarized from the leuprolide-exposed cohort
  - 2nd Leuprolide unexposed cohort without CPP: individuals with no baseline CPP diagnosis, indexed on the first well visit
- Patients meeting the following criteria during the 183-day baseline period prior to the index date were excluded:
  - Age ≥ 11 years on the index date
  - Diagnosis of osteogenesis imperfecta
  - Use of long-acting GnRH agonist
  - Exposure to drugs that affect bone density (anticoagulants, bisphosphonates, antiepileptic drugs, corticosteroids, chemotherapy, cyclosporine, medroxyprogesterone, loop diuretics, proton pump inhibitors, thiazide diuretics, statins, nitrate, beta blocker)
  - Any fracture

Leuprolide Exposure: identified using National Drug Codes (NDCs) and Current Procedural Terminology (CPT) codes recorded in medical and outpatient pharmacy claims

Outcome: Major Fracture

- Composite of humerus fracture, radius/ulna fracture, vertebral fracture, hip fracture, femur fractures
- ICD-9/10-CM diagnosis code with at least one procedure code for the same fracture site within 7 days
- Major trauma excluded

Follow-up: started from the index date until the earliest of the following censoring criteria: major fracture, disenrollment, recorded death, or data end

Statistical Analysis:

- Variable ratio matching (1: ≤10) on continuous age (in days) and calendar month of the index date
- Exploratory data analysis for patient characteristics and outcome events during follow-up
- Proportional hazard modeling comparing the risks of the first fracture in the leuprolide-exposed cohort with the unexposed cohort with CPP and unexposed cohort without CPP for males and females separately
- Post-hoc stratified conditional analysis on age integer (in years) and calendar month of index event to account for the impact of differentially truncated follow-up time due to conditioning on matched sets

RESULTS

- 2,845 female and 439 male leuprolide users
- Mean age:
  - Female: 8 (standard deviation=1.7) years
  - Male: 9 (standard deviation=1.8) years
- Mean duration of cumulative leuprolide use:
  - Female: 327 (max=3,749) days
  - Male: 330 (max=1,941) days
- Mean duration of follow-up from leuprolide initiation:
  - Female: 1,043 (max=6,046) days
  - Male: 1,020 (max= 4,834) days

Female cohorts

- Matched with leuprolide-unexposed children with CPP
  - Leuprolide-exposed children with CPP: 63 fractures from a total of 8,119 person-years (PY) of follow-up
  - Leuprolide-unexposed children with CPP: 751 fractures from a total of 77,552 PY
- Matched with leuprolide-unexposed children without CPP
  - Leuprolide-exposed children with CPP: 63 fractures from a total of 8,124 PY
  - Leuprolide-unexposed children without CPP: 830 fractures from a total of 83,495 PY

Male cohorts

- Matched with leuprolide-unexposed children with CPP
  - Leuprolide-exposed children with CPP: 19 fractures from a total of 1,200 PY of follow-up
  - Leuprolide-unexposed children with CPP:114 fractures from a total of 9,299 PY
- Matched with leuprolide-unexposed children without CPP
  - Leuprolide exposed subjects with CPP: 19 fractures from a total of 1,226 PY
  - Leuprolide unexposed patients without CPP: 172 fractures a total of 12,238 PY

Risk Estimates

- Leuprolide exposed females were 25% (Hazard Ratio [HR]=0.75, 95% Confidence Interval 0.57-1.00) and 34% (HR=0.66, 0.50-0.87) less likely to have fracture than respectively the unexposed females with and without CPP
- Leuprolide exposed males showed no differential fracture risk from the unexposed males with (HR =1.28, 0.75-2.20) and without CPP (HR=1.07, 0.64-1.77)
- In the post hoc stratified conditional analysis, the HRs were 0.80 (0.62-1.05) and 0.70 (0.54-0.91) when compared to the unexposed females respectively with CPP and without CPP, and the HRs were 1.27 (0.76-2.12) and 1.17 (0.72-1.91) when compared to unexposed males respectively with CPP and without CPP

Table 1. Follow-up Time and Age Distribution of Children with and without Leuprolide Exposure, U.S. FDA Sentinel Distributed Database, January 1, 2000 - August 31, 2018

	Exposed with CPP (# Subjects)	Unexposed with CPP (#Matched Sets)		Exposed with CPP (# Subjects)	Unexposed without CPP (#Matched Sets)
Female					
Patients (N)	2,841 (100.0%)	2,841 (100.0%)		2,845 (100.0%)	2,845 (100.0%)
Follow-up time (person-days; mean, SD)	1,043.8 (981.0)	1,079.0 (1018.8)		1,043.0 (981.1)	1,077.7 (1145.6)
Mean age (years)	8.0 (1.7)	8.0 (1.7)		8.0 (1.7)	8.0 (1.7)
Age (years)					
0-2	78 (2.7%)	80 (2.8%)		79 (2.8%)	79 (2.8%)
3-4	100 (3.5%)	98 (3.4%)		101 (3.6%)	101 (3.6%)
5-6	373 (13.1%)	377 (13.3%)		374 (13.1%)	373 (13.1%)
7-8	1,479 (52.1%)	1,471 (51.8%)		1,479 (52.0%)	1,479 (52.0%)
9-10	811 (28.5%)	816 (28.7%)		812 (28.5%)	813 (28.6%)
Male					
Patients (N)	432 (100.0%)	432 (100.0%)		439 (100.0%)	439 (100.0%)
Follow-up time (person-days; mean, SD)	1,014.5 (918.8)	1,021.1 (962.1)		1,020.3 (918.7)	1,018.2 (1050.9)
Mean age (years)	9.1 (1.8)	9.1 (1.7)		9.1 (1.8)	9.1 (1.8)
Age (years)					
0-2	9 (2.1%)	10 (2.2%)		11 (2.5%)	11 (2.5%)
3-4	5 (1.2%)	4 (0.9%)		5 (1.1%)	5 (1.1%)
5-6	25 (5.8%)	26 (6.1%)		26 (5.9%)	26 (5.9%)
7-8	120 (27.8%)	118 (27.2%)		123 (28.0%)	123 (28.0%)
9-10	273 (63.2%)	274 (63.5%)		274 (62.4%)	274 (62.4%)

Table 2. Estimated Hazard Ratios of Major Fracture between Leuprolide-Exposed and the Matched Leuprolide-Unexposed Children with CPP, U.S. FDA Sentinel Distributed Database, January 1, 2000 - August 31, 2018

Cohorts	Number of Indexed children	Person Years at Risk	Average Person Years at Risk	Number of Events	Incidence Rate per 1,000 Person Years	Risk per 1,000 Indexed Children	Hazard Ratio (95% CI)
Female							
Unmatched Analysis (Site-adjusted only)							
Exposed with CPP	2,845	8,124.33	2.86	63	7.75	22.14	0.81
Unexposed with CPP	65,313	199,566.94	3.06	1,780	8.92	27.25	(0.63, 1.04)
1:many Matched Conditional Analysis							
Exposed with CPP	2,841	7,478.99	2.63	56	7.49	19.71	0.75
Unexposed with CPP	26,811	39,149.67	1.46	445	11.37	16.60	(0.57, 1.00)
Male							
Unmatched Analysis (Site-adjusted only)							
Exposed with CPP	439	1,226.34	2.79	19	15.49	43.28	1.35
Unexposed with CPP	10,509	29,996.24	2.85	341	11.37	32.45	(0.85, 2.15)
1:many Matched Conditional Analysis							
Exposed with CPP	432	1,064.22	2.46	18	16.91	41.67	1.28
Unexposed with CPP	3,474	4,880.93	1.40	66	13.52	19.00	(0.75, 2.20)

Table 3. Estimated Hazard Ratios of Major Fracture between Leuprolide-Exposed and the Matched Leuprolide-Unexposed Children without CPP, U.S. FDA Sentinel Distributed Database, January 1, 2000 - August 31, 2018

Cohorts	Number of Indexed Children	Person Years at Risk	Average Person Years at Risk	Number of Events	Incidence Rate per 1,000 Person Years	Risk per 1,000 Indexed Children	Hazard Ratio (95% CI)
Female							
Unmatched Analysis (Site-adjusted only)							
Exposed with CPP	2,845	8,124.33	2.86	63	7.75	22.14	0.86
Unexposed without CPP	6,547,116	19,008,132.21	2.90	162,613	8.55	24.84	(0.67, 1.10)
1:many Matched Conditional Analysis							
Exposed with CPP	2,845	7,599.92	2.67	58	7.63	20.39	0.66
Unexposed without CPP	28,450	40,316.85	1.42	510	12.65	17.93	(0.50, 0.87)
Male							
Unmatched Analysis (Site-adjusted only)							
Exposed with CPP	439	1,226.34	2.79	19	15.49	43.28	1.45
Unexposed without CPP	6,739,063	19,523,714.76	2.90	193,777	9.93	28.75	(0.93, 2.28)
1:many Matched Conditional Analysis							
Exposed with CPP	439	1,146.65	2.61	19	16.57	43.28	1.07
Unexposed without CPP	4,390	6,169.19	1.41	98	15.89	22.32	(0.64, 1.77)

Table 4. Estimated Hazard Ratios of Major Fracture between Leuprolide-Exposed and the Matched Leuprolide-Unexposed Children with or without CPP (Stratified Conditional Analysis), U.S. FDA Sentinel Distributed Database, January 1, 2000 - August 31, 2018

Cohorts	Number of Indexed Children	Person Years at Risk	Average Person Years at Risk	Number of Events	Incidence Rate per 1,000 Person Years	Risk per 1,000 Indexed Children	Hazard Ratio (95% CI)
Female							
Exposed with CPP	2,841	7,957.46	2.80	62	7.79	21.82	0.80
Unexposed with CPP	26,811	64,408.29	2.40	679	10.54	25.33	(0.62, 1.05)
Exposed with CPP	2,845	8,042.14	2.83	62	7.71	21.79	0.70
Unexposed without CPP	28,450	65,972.84	2.32	750	11.37	26.36	(0.54,0.91)
Male							
Exposed with CPP	432	1,109.90	2.57	18	16.22	41.67	1.27
Unexposed with CPP	3,474	6,551.65	1.89	91	13.89	26.19	(0.76, 2.12)
Exposed with CPP	439	1,185.45	2.70	19	16.03	43.28	1.17
Unexposed without CPP	4,390	8,053.54	1.83	124	15.40	28.25	(0.72, 1.91)

CONCLUSIONS

- Compared separately to the leuprolide-unexposed children with or without CPP, the study observed a lower risk of fracture in female leuprolide users with CPP, but no statistically significant difference in male leuprolide users with CPP
- There were consistent results from the post hoc analysis, accounting for the impact of differentially truncated follow-up time due to conditioning on matched sets
- Results from this study provided no evidence for an increased risk of fracture following leuprolide use during childhood

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