



Use of a bioinformatics tool, MASE (Molecular Analysis of Side Effects), generates the hypothesis of an association between FGFR2 and bone fractures.

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OBJECTIVE

- ❑ Evaluate a safety-focused bioinformatics tool designed to analyze the underlying mechanisms of safety signals.
- ❑ Test the tool using two well-characterized safety signals: Supraventricular Tachycardia (SVT) and Urinary Retention (UR).
- ❑ Generate a mechanistic hypothesis for bone fracture/osteonecrosis.

BACKGROUND

- ❑ The Office of Clinical Pharmacology OTS/CDER/FDA has research collaborations to assess and assist in the development of safety-focused informatics platforms.
- ❑ One platform, MASE (Molecular Analysis of Side Effects), is a data warehouse integrating a number of public resources to aid in the assessment of molecular mechanisms underpinning adverse events (AE).

RESULTS – Tool Evaluation

Table 1: Target analysis for Supraventricular Tachycardia (SVT).

Target	N	PRR	CI	Top reported drugs		Target MOA
				Drug	N	
Muscarinic acetylcholine receptor m1*	1633	2.2	2.10 - 2.29	Clozapine	225	Peripheral Nervous System (PNS) inhibition via mAChR antagonism blocks vagal stimulation.
				Quetiapine	193	
				Olanzapine	161	
Histamine h1 receptor	1589	2.3	2.20 - 2.40	Clozapine	225	Many neuroleptics antagonize mAChR as well as the histamine H1 receptor. H1 antagonists can also have anticholinergic properties.
				Quetiapine	193	
				Diphenhydramine	174	
Sodium-dependent serotonin transporter	1553	2.05	1.96 - 2.14†	Paroxetine	226	Overstimulation of 5-HT receptors can lead to serotonin syndrome.
				Venlafaxine	198	
				Citalopram	180	
Alpha-1a adrenergic receptor	1521	2.26	2.16 - 2.36	Clozapine	225	Many neuroleptics are also α-1 blockers. Specific α-1 blockers such as doxazosin are known to cause SVT via peripheral vasodilation leading to reflex tachycardia.
				Quetiapine	193	
				Amitriptyline	173	
Beta-1 adrenergic receptor	1463	2.46	2.35 - 2.57	Epinephrine	76	Sympathetic nervous system (SNS) activation can cause SVT.
				Pseudoephedrine	32	
				Norepinephrine	28	
Sodium-dependent noradrenaline transporter	1323	2.1	2 - 2.21	Paroxetine	226	Sympathetic nervous system (SNS) activation via increased NE signaling can cause SVT.
				Venlafaxine	198	
				Amitriptyline	173	
Beta-2 adrenergic receptor	1253	2.54	2.41 - 2.67	Salbutamol	403	Beta-2 AdR stimulation causes vasodilatation and potentially reflex tachycardia.
				Epinephrine	76	
				Salmeterol	50	
Delta-type opioid receptor**	1204	2.6	2.47 - 2.74	Oxycodone	398	Opioid withdrawal is associated with adrenergic hyperstimulation. Opioids can also cause hypotension in patients with depleted blood volume, leading to reflex tachycardia.
				Morphine	279	
				Fentanyl	238	

The SVT cohort consists of 6479 AE case reports containing 1042 drugs, 5534 reactions, 1247 indications, and 1070 biomolecules (targets, enzymes, transporters). 291 targets were significantly associated with SVT (N ≥ 30, PRR lower CI ≥ 2). Top targets are displayed by case report count along with the top 3 reported drugs for each target. N = number of case reports; PRR = Proportional Reporting Ratio; CI = Confidence interval.

* Similar results found for muscarinic acetylcholine receptors m1 and m2.

** Similar results found for kappa-type opioid receptor.

† Lower CI misses cutoff; target included for completeness.

Table 2. Target analysis for Urinary Retention.

Target	N	PRR	CI	Top reported drugs		Target MOA
				Drug	N	
Muscarinic acetylcholine receptor m1*	1780	2.86	2.75 - 2.97	Tiotropium	401	Anti-cholinergic activity increases bladder muscle tone and increases urethral sphincter tone as part of the micturition reflex.
				Quetiapine	170	
				Tolterodine	136	
Alpha-1a** adrenergic receptor	1342	2.37	2.27 - 2.49	Quetiapine	170	Alpha-1 antagonism can relax smooth muscle in the bladder neck and prostate. Quetiapine and risperidone also possess anticholinergic activity.
				Risperidone	132	
				Olanzapine	118	
Kappa-type opioid receptor	797	2.1	1.97 - 2.24†	Oxycodone	230	UR is a well recognized AE with many opioids. Mechanism unknown.
				Morphine	146	
				Fentanyl	138	
Gamma-aminobutyric-acid receptor subunit beta-3***	747	2.2	2.05 - 2.35	Clonazepam	160	Both UR and urinary incontinence have been reported with benzodiazepines. Blockade of GABA-A and GABA-B receptors in the spinal cord and brain stimulates micturition in rats.
				Diazepam	147	
				Zolpidem	73	
Alpha-7 nicotinic cholinergic receptor subunit	181	2.64	2.28 - 3.04	Tramadol	135	Activation of nicotinic receptors in parasympathetic bladder neurons contracts the detrusor muscle.
				Memantine	39	

The Urinary Retention cohort consists of 5,435 AE case reports containing 966 drugs, 4043 reactions, 992 indications, and 1029 biomolecules (targets, enzymes, transporters). 107 targets were significantly associated with UR (N ≥ 30, PRR lower CI ≥ 2). Top targets are displayed by case report count along with the top 3 reported drugs for each target. N = number of case reports; PRR = Proportional Reporting Ratio; CI = Confidence Interval.

* Similar results found for muscarinic acetylcholine receptors m2, m3, m4, and m5.

** Similar results found for alpha adrenergic receptors 1b and 1d.

*** Similar results found for other GABA-A subunits.

† Lower CI misses cutoff; target included for completeness.

CONCLUSIONS

- ❑ A bioinformatics tool can successfully identify known molecular targets underlying well-studied AEs such as Supraventricular Tachycardia and Urinary Retention.
- ❑ A bioinformatics tool can be used to generate biologically plausible hypotheses for novel mechanisms underlying AEs. In this case, a possible association between FGFR2 and bone fracture is hypothesized.
- ❑ Virtual cohort analysis can be used to assess the contribution of confounding co-medications and co-morbidities to further refine hypotheses. In this case, bisphosphonate co-administration and hematological malignancies/metastases to bone are investigated with respect to FGFR2 and bone fracture/osteonecrosis.

METHODS

- ❑ Construction of MASE data warehouse Data warehouse integrates AE-drug data from public FAERS (FDA Adverse Event Reporting System); target, enzyme, and transporter data from Drugbank; signaling pathways from Reactome, NCI-Nature, and Biocarta.
- ❑ Patient Virtual Cohorts and Search Criteria The software enables the construction and analysis of “virtual cohorts” of AE cases, using combinations of clinical and molecular parameters including user defined groups of MedDRA Preferred Terms (PT), biomolecules (drug targets, transporters, enzymes), and pathways.
Cohort Definitions: 1) SVT cohort was generated from three MedDRA PTs: Sinus tachycardia, Supraventricular tachycardia, Atrial tachycardia; 2) the Urinary Retention cohort was generated using the single MedDRA term: Urinary Retention. 3) The FGFR2 (Fibroblast Growth Factor Receptor 2) cohort was generated by the software and consists of all AE cases that report the use of a drug mapped to FGFR2 in the database.
- ❑ Statistical Analysis and Preliminary Tool Validation Disproportionality Analysis used the Proportional Reporting Ratio (PRR) measure described in van Puijenbroek, *et al*¹. To qualify as a positive signal, target-AE associations had to meet two criteria: 1) the lower bound of the 95% CI of PRR ≥ 2 and 2) case number (N) of target-AE reports ≥ 30. For each target-AE pair meeting the significance criteria, the three most frequently co-reported drugs were assessed as causing the AE according to the Clinical Pharmacology² database (Elsevier) and UpToDate³ (Wolters Kluwer).
- ❑ Hypothesis Generation A target-AE profile is generated for each biomolecule in the database via integration of drug-target data with AE data.

RESULTS – Hypothesis Generation

Table 3. Hypothesis Generation: Bone pathologies associated with FGFR2 in MASE.

Adverse Event	N	PRR	CI
Osteonecrosis	562	6.78	6.24 - 7.37
Osteonecrosis of jaw	119	6.57	5.47 - 7.89
Aseptic necrosis bone	93	14.7	11.89 - 18.17
Hip fracture	83	2.99	2.41 - 3.72
Bone lesion	82	20.5	16.29 - 25.81
Spinal compression fracture	61	6.99	5.41 - 9.04
Pathological fracture	57	9.62	7.36 - 12.56
Compression fracture	47	9.62	7.16 - 12.91
Primary sequestrum	46	12.85	9.52 - 17.36
Osteopenia	44	3.76	2.79 - 5.07
Osteolysis	32	10.31	7.21 - 14.74

A number of bone pathologies including fracture and osteonecrosis are significantly associated with FGFR2 by our criteria, suggesting a possible association with drugs targeting FGFR2. A critical role for FGF signaling and bone development has been described in the literature^{4,5}. N = number of case reports; PRR = Proportional Reporting Ratio; CI = Confidence Interval.

Table 4. Reporting of bone related pathologies in MASE with drugs targeting FGFR2: comparison of cohorts with and without co-reporting of cancer indication.

Adverse Event	FGFR2 w/ cancer indication (10791 AEs)			FGFR2 w/o cancer indication (4836 AEs)		
	N	PRR	CI	N	PRR	CI
Osteonecrosis	474	8.24	7.53 - 9.01	88	3.32	2.70 - 4.09
Bone disorder	234	11.38	10 - 12.97	36	3.75	2.71 - 5.21
Osteomyelitis	149	8.73	7.42 - 10.27	28	3.56	2.45 - 5.15
Aseptic necrosis bone	83	18.84	15.07 - 23.55	10	4.72	2.54 - 8.80
Hip fracture	71	3.71	2.93 - 4.68	12	1.38	0.78 - 2.43
Osteonecrosis of jaw	70	5.51	4.35 - 6.98	49	8.57	6.47 - 11.35
Bone lesion	68	24.12	18.79 - 30.95	14	10.22	6.03 - 17.34
Pathological fracture	51	12.4	9.36 - 16.44	6	3.11	1.39 - 6.94
Spinal compression fracture	49	8.08	6.08 - 10.74	12	4.31	2.44 - 7.60
Primary sequestrum	39	15.61	11.29 - 21.59	7	5.93	2.81 - 12.48

Hematologic malignancies such as multiple myeloma can cause bone pathologies. To address this potential confounder, virtual cohorts were generated for FGFR2 with and without reporting of cancer indication and then examined for bone pathologies. There is an overall reduction in signal as assessed by decreased PRR, but the signal remains for osteonecrosis and some fractures. N = number of case reports; PRR = Proportional Reporting Ratio; CI = Confidence Interval.

Table 5. Reporting of bone related pathologies in MASE with drugs targeting FGFR2: comparison of cohorts with and without co-reporting of bisphosphonate usage.

Adverse Event	FGFR2 + Bisphosphonates (1457 AEs)			FGFR2 - Bisphosphonates (14069 AEs)		
	N	PRR	CI	N	PRR	CI
Osteonecrosis	540	70.12	65.43 - 75.14	22	0.28	0.19 - 0.43
Bone disorder	253	91.85	81.81 - 103.13	17	0.6	0.38 - 0.97
Osteomyelitis	160	69.87	60.15 - 81.14	17	0.74	0.46 - 1.19
Osteonecrosis of jaw	114	67.76	56.59 - 81.13	5	0.29	0.12 - 0.71
Aseptic necrosis bone	89	151.03	122.30 - 186.50	4	0.64	0.24 - 1.72
Bone lesion	72	190.98	150.44 - 242.44	10	2.48	1.33 - 4.64
Primary sequestrum	46	138.61	103.04 - 186.46	N/A	N/A	N/A - N/A
Spinal compression fracture	31	37.47	26.35 - 53.30	30	3.74	2.60 - 5.36
Compression fracture	29	62.47	43.27 - 90.19	18	3.94	2.47 - 6.29
Pathological fracture	26	45.73	31.08 - 67.29	31	5.65	3.95 - 8.08
Hip fracture	12	4.59	2.61 - 8.07	71	2.84	2.25 - 3.59

Use of bisphosphonates such as zoledronate has been frequently reported with bone pathologies such as osteonecrosis and femoral neck fracture. To address this potential confounder, virtual cohorts were generated for FGFR2 with and without bisphosphonates and then examined for bone pathologies. There is a loss of association between osteonecrosis and FGFR2 by our criteria, but some signal remains for bone fracture. N = number of case reports; PRR = Proportional Reporting Ratio; CI = Confidence Interval.

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