Adverse Event Reporting of Marketed Biosimilar and Biological Monoclonal Antibody Cancer Treatments in the United States

RWD30

Xiangzhong Xue, MS; Bang Truong, MS; Jingjing Qian, PhD; Auburn University Harrison College of Pharmacy, Auburn, AL, USA

BACKGROUND

- **Cancer** is **the second leading cause of death** in the U.S., leading to more than 1.9 million new cases and 609,360 death in 2022[1].
- **Biological monoclonal antibodies (mAbs)** can exploit antigenic differences between normal and malignant tissues and exact a variety of antitumor responses[2].
- However, the **high prices** of mAbs have led to a substantial economic burden on patients and the healthcare system.
- All early evidence of **marketed cancer treatment biosimilars** was either descriptive or had small sample sizes. Evidence regarding the **post-marketing safety** of mAb biosimilars remains **limited**[3-5].

OBJECTIVES

To examine **adverse event (AE) reporting patterns** and **disproportionate reporting signals** for mAb biosimilars marketed in the U.S. compared to their originator biologics.

METHODS

- **Data Sources**: The public version of 2004-2021 **FDA Adverse Event Reporting System (FAERS)** data
- **Originator Biologic and Biosimilar Product Identification**:
  - All ten mAb biosimilars for cancer treatment marketed before Dec. 31, 2021, in the U.S. and their originator biologics are identified.

Table 1. List of biologic and biosimilar products included in the study

Non-proprietary name	Biological	Biosimilars
Rituximab	Brituxan	Truxima; Ruxience; Riabni
Bevacizumab	Avastin	Mvasi; Zirabev
Trastuzumab	Herceptin	Kanjinti; Ogivri; Ontruzant; Herzuma; Trazimera

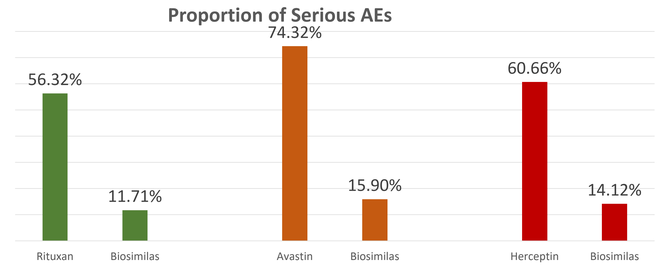
  - AE reports Including criteria:1) from U.S., 2) drug name-manufacturer matched, and 3) after marketing date
- **Data analysis**
  - AE reports were categorized by patients' **age, sex, type of reporters, seriousness, and death**.
    - Chi-squared tests or Fisher-exact tests were used to compare the distribution of AE reports across these variables for each pair of mAb biologics and biosimilars (**combined if multiple biosimilar products are available**).
  - **Disproportionality analysis**
    - The **reporting odds ratio (ROR)** with related **95% confidence intervals (CIs)** to compare reporting rates of **serious**, **death**, and **specific AEs** between an originator biologic/biosimilar (index drugs) and all other drugs (reference drugs) in the FAERS database.
    - **Breslow-Day test** to identify **the homogeneity of mAb biologic's and corresponding biosimilar's ROR**
  - **Main analysis**: Total reports from the entire study duration of 18 years (January, 1,2004 to December 31, 2021)
- SAS (version 9.4; SAS Institute, Cary, NC, USA) was used to conduct all statistical analyses at p<0.05.

RESULTS

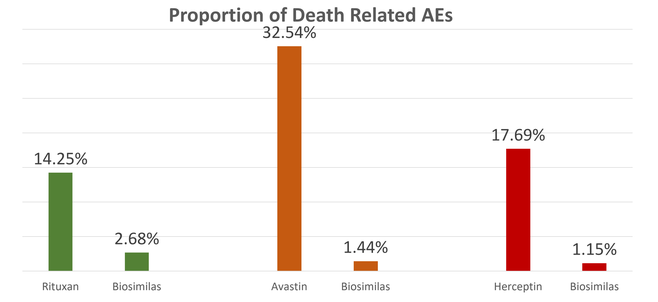
Table 2: Characteristics of adverse event reports for studied mAb biologics and biosimilars in the FAERS between January 1, 2004 and December 31, 2021*

Characteristics		Rituximab			Bevacizumab			Trastuzumab		
		Biologics	Biosimilars	P-Value	Biologics	Biosimilars	P-Value	Biologics	Biosimilars	P-Value
Total Number of Reports		15708	897		22179	975		8585	347	
Patient Age	≤ 18	144 (0.92%)	4 (0.45%)	<.0001	117 (0.53%)	0 (0.00%)	NA	3 (0.03%)	0 (0.00%)	N/A
	19-64	3037 (19.33%)	51 (5.69%)		5210 (23.49%)	175 (17.95%)		2335 (27.20%)	82 (23.63%)	
	65-84	2195 (13.97%)	36 (4.01%)		3287 (14.82%)	148 (15.18%)		897 (10.45%)	27 (7.78%)	
	≥ 85	236 (1.50%)	4 (0.45%)		269 (1.21%)	6 (0.62%)		37 (0.43%)	1 (0.29%)	
	Missing	10096 (64.27%)	802 (89.41%)		13296 (59.95%)	646 (66.26%)		5313 (61.89%)	237 (68.30%)	
Patient Sex	Female	6826 (43.46%)	73 (8.14%)	<.0001	9988 (45.03%)	357 (36.62%)	<.0001	6157 (71.72%)	200 (57.64%)	<.0001
	Male	4828 (30.74%)	35 (3.90%)		7406 (33.39%)	197 (20.21%)		408 (4.75%)	10 (2.88%)	
	Missing	4054 (25.81%)	789 (87.96%)		4785 (21.57%)	421 (43.18%)		2020 (23.53%)	137 (39.48%)	
Type of Reporter	Consumer	3746 (23.85%)	564 (62.88%)	N/A	4143 (18.68%)	74 (7.59%)	N/A	2013 (23.45%)	43 (12.39%)	N/A
	Healthcare professional	10575 (67.32%)	333 (37.12%)		14316 (64.55%)	901 (92.41%)		5562 (64.79%)	304 (87.61%)	
	Missing/ Other	1387 (8.83%)	0 (0.00%)		3720 (16.77%)	0 (0.00%)		1010 (11.76%)	0 (0.00%)	

N/A: not applicable.



All the P-value ≤ 0.01



All the P-value ≤ 0.01

Table 3: Reporting odds ratio (ROR) of seriousness and specific adverse event (AE) reports for studied mAb biologics and biosimilars in the FAERS between January 1, 2004 and December 31, 2021

Outcome/Reaction	Rituximab ROR (95% CI)			Bevacizumab ROR (95% CI)			Trastuzumab ROR (95% CI)		
	Biologics	Biosimilars	P-Value	Biologics	Biosimilars	P-Value	Biologics	Biosimilars	P-Value
Serious AEs	0.89 (0.86, 0.92)	0.09 (0.07, 0.11)	<.0001	1.99 (1.94,2.06)	0.13 (0.11,0.15)	<.0001	1.06 (1.02, 1.11)	0.11 (0.08,0.15)	<.0001
Death	1.86 (1.78,1.95)	0.31 (0.21,0.46)	<.0001	5.43 (5.28,5.59)	0.16 (0.10,0.28)	<.0001^	2.26 (2.13,2.39)	0.13 (0.04,0.35)	<.0001
Neutropenia	4.37 (4.05,4.73)	N/A	N/A	2.24 (2.05,2.45)	0.81 (0.40,1.62)	0.003	6.46 (5.71,7.30)	N/A	N/A
Proteinuria	N/A			15.16 (13.99,16.42)	14.05 (9.51,20.7)	0.14	N/A		
Gastrointestinal hemorrhage				7.20 (6.69,7.75)	N/A	N/A			
Cardiac failure				N/A			3.25 (3.02,3.50)	0.84 (0.43,1.62)	<.0001

^: The result from main analysis were consistent with other two sensitivity analysis.

CONCLUSIONS AND LIMITATIONS

- We observed **no risk signals of serious or death AE reporting for all three mAb biosimilars**. However, **a signal of disproportionate reporting of death was detected between biological and biosimilar bevacizumab (p<0.05)**.
- Due to the passive spontaneous reporting nature, FAERS carry substantial **reporting bias**[6]. Second, FAERS contains **missing, incomplete, and inaccurate information** in AE reporting, which influences the accuracy and completeness of the data. Third, ROR and Breslow-day statistics were not computed due to the **small sample sizes** of some specific AEs of biosimilars.
- Future studies using longitudinal study designs are warranted to conduct and verify our results.