BioDrugs (2021) 35:375–377
https://doi.org/10.1007/s40259-021-00474-x

LETTER TO THE EDITOR

Author's Reply to Joerg Putzke et al. Comment on: "Safety of Marketed Cancer Supportive Care Biosimilars in the US: A Disproportionality Analysis Using the Food and Drug Administration Adverse Event Reporting System (FAERS) Database"

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Accepted: 6 March 2021 / Published online: 16 April 2021

We appreciate the opportunity to clarify and expand on the results of our recently published paper [1]. The Putzke et al. letter appropriately highlights important limitations of our methods that are inherent in the US Food and Drug Administration (FDA)'s Adverse Event Reporting System (FAERS) data [2]. While not explicitly addressed in the Putzke and colleagues' commentary, we would like to highlight our own conclusion that "future studies using larger data sources, longer observation period, and rigorous study designs to test these adverse event (AE) signals detected from our study are warranted" [1]. Indeed, we should all recognize that the spontaneous AE reporting data by themselves are not an indicator of the safety profile of the drug or biologic product [3]. Such analyses should consider all of the methodological implications and limitations, and explicitly focus on hypothesis generation instead of hypothesis testing. Even more importantly, patients and healthcare providers should not make therapeutic decisions based on our published analyses. Instead, the intent of our paper was a call to action for further study of safety of biosimilar products, and we believe our paper appropriately calls for further analyses.

We would like to stress the importance of several of the Putzke and colleagues' comments. First, we respect the limitation such as over/under reporting bias and the suboptimal quality of reports (i.e., missing data in the manufacturer names and concomitant medications) associated with spontaneous reporting system like the FAERS. Second, we recognize small numbers of specific AEs that resulted in reporting odds ratios (RORs) with wider confidence intervals (CIs). This is stressed in our conclusions that additional analyses and longer observation periods are needed.

The Putzke and colleagues' commentary made several points that we would like to clarify. First, Putzke and colleagues brought up the concern about the use of serious AEs to compare the "heterogeneous set of SAEs compared with non-serious AEs" in our analyses. The definition of serious AEs used in our study was based on the US FDA definition of such events, including one or more of the following outcomes, which were documented in the report: death, hospitalization, life-threatening, disability, congenital anomaly, and/or other serious outcome [3]. The US FDA regularly reports the proportion of these aggregated serious AEs to the public [4] and through their FAERS public dashboard. In addition, the use and comparison of the group of these serious AEs as the key outcome for post-marketing safety signal detection for pharmaceutical products has been widely published in the pharmacovigilance literature [5, 6]. While we agree there are limitations with the use of these serious AEs due to their heterogeneous nature, our approach of analyzing both serious and individual AEs for each biologic–biosimilar pair provided more complete information in reported AEs for both the biologic and corresponding biosimilar products. Further, given that we focused on serious and known AEs in our original analyses, we acknowledged that we might have

This reply refers to the comment available at: https://doi.org/10.1007/s40259-021-00476-9.

This reply refers to the article available at: https://doi.org/10.1007/s40259-020-00466-3.

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Table 1 Proportional risk ratios for signal detection in serious AEs related to pegfilgrastim biosimilar product Fulphila

	Main analysis			Sensitivity analysis*		
	Cases	Controls	PRR (95% CI)	Cases	Controls	PRR (95% CI)
Fulphila	113	7	5.04 (2.45–10.34)	113	7	7.42 (3.62–15.23)
Non-Fulphila	65,760,322	27,364,767	1	6,312,971	4,820,675	1

Serious AEs: including one or more of the following outcomes, which were documented in the report: death, hospitalization, life-threatening, disability, congenital anomaly, and/or other serious outcome

AEs adverse events, *CI* confidence interval, *PRR* proportional risk ratio

*Limiting to first biosimilar entry and forward (Fulphila® entered the US market on July 9, 2018)

missed detecting potential new or rare, as well as important, AE signals such as immunogenic AEs for the studied drugs. Future analyses should address signal detection for these potential new AEs.

Second, Putzke and colleagues made another point that we acknowledged the small number of AE reports and short marketing exposure time for Udenyca for the analysis of bone pain-related AE reports, but not for Fulphila. However, we did not analyze ROR for bone pain-related AE for Fulphila because our AE detection algorithm did not detect any such report in the timeframe of the FAERS analyzed in our study. Regarding serious AEs, both Udenyca and Fulphila had considerable numbers of serious AE reports ($n = 76$ for Udenyca and $n = 113$ for Fulphila) during the short observational period of < 2 years of marketing. However, for the purpose of early signal detection using the spontaneous reporting data, our analysis of calculating RORs for serious AEs for Udenyca and Fulphila was appropriate, with an adequate number of AE reports for both biosimilar products (≥ 3) [7]. In addition, we performed multiple sensitivity analyses, including limiting observational duration and role of drug exposure mentioned in AE reports, to verify our main results, and all findings were consistent.

Third, Putzke and colleagues commented on potential reporter bias that might impact the quality of reports for Neulasta and pegfilgrastim biosimilars. Specifically, the proportion of AE reports for Neulasta that was missing in reporter type or came from healthcare professionals was lower than it was for pegfilgrastim biosimilars. However, existing literature did not identify any difference in quality of AE reports from consumer and healthcare professionals. Instead, Toki and Ono found that the completeness of FAERS reports from consumers was generally greater than reports from healthcare providers [8]. Therefore, we do not have prior reason to believe that the difference in AE reporting between Neulasta and pegfilgrastim biosimilars was caused by type of reporter.

Finally, Putzke and colleagues challenged us in the use of ROR instead of proportional risk ratio (PRR) for signal detection in our original analyses. Both disproportionality analysis measures have been widely used in pharmacovigilance literature. However, the ROR methodology has shown better control for certain types of under reporting compared with other disproportionality metrics [9]. Putzke and colleagues further highlighted that their internal serious AE PRR calculation for Fulphila was 1.33 (95% CI 0.63–2.80), which implied no signal of increased reporting of serious AEs for Fulphila [2]. However, Putzke and colleagues did not provide adequate details of their data source and PRR calculation in their commentary. Using the same FAERS data from January 1, 2004 to March 31, 2020 as in our original analyses, we went ahead and calculated PRRs with 95% CIs for Fulphila-related serious AEs (Table 1). Different from Putzke and colleagues, our PRR results confirmed the same finding as in our original paper, which is increased reporting of serious AEs for Fulphila (PRR 5.04 [95% CI 2.45–10.34] in the main analysis, and PRR 7.42 [95% CI 3.62–15.23] in the sensitivity analysis) compared with all other drugs. However, as mentioned in our paper, we do recommend future analysis using the more conservative Bayesian confidence propagation neural network (BCPNN) to confirm our findings [10].

In conclusion, we hope our paper stimulates further discussion and analyses to support the safe use of biologic and biosimilar products. The availability of more biosimilar products brings competition to the marketplace and improves patients' access to expensive biologics. We hope that public analyses such as ours continue to stimulate discussion and enhance pharmacovigilance research.

Declarations

Funding No financial assistance was used to conduct the study described in the manuscript and/or used to assist with the preparation of the manuscript.

Conflict of interest No conflicts of interest to report for all authors.

Ethics approval The original study was granted exemption by the Auburn University institutional review board (IRB).

Consent Not applicable.

Data availability The US FDA FAERS data supporting the results reported in the article can be accessed and downloaded from https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

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