LETTER TO THE EDITOR

Comment on: "Safety of Marketed Cancer Supportive Care Biosimilars in the U.S.: A Disproportionality Analysis Using the Food and Drug Administration Adverse Event Reporting System (FAERS) Database"

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Dear Editor,

This refers to the original research article by Tanni and colleagues published online on Jan 13, 2021 [1].

The paper aims to explore the post-marketing safety of supportive care cancer biosimilars in the U.S. through comparative analysis based on the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database [2]. Considering the bulk of the evidence of safety and efficacy for biosimilars is from controlled registrational studies, this analysis is a step in the right direction.

The authors acknowledge limitations of this study including over/under reporting bias as well as the suboptimal quality of reports associated with spontaneous reporting in the FAERS database. They also recognize small numbers of specific adverse events (AEs) resulting in reporting odds ratios (RORs) with wider confidence intervals (CIs). In addition, they highlight that causality assessment can't be established from a hypothesis-generating study given patient medical history and concomitant medications.

There are, however, additional methodological limitations that create further challenges to drawing meaningful conclusions regarding product differences from such an analysis and call into question the findings that pertain solely to Fulphila.

First, quantitative comparative analysis of serious AEs (SAEs) for signal detection is not in accordance with good pharmacovigilance (PV) practice and principles of pharmacoepidemiologic assessment [3]. The aim of safety database analysis, which is to identify potential (new) signals associated with a drug–event pair, cannot be addressed with a heterogeneous set of SAEs compared with non-serious AEs. The authors have combined diverse serious events in the disproportionality analysis to suggest a difference, without consideration of individual (serious) AE or causality assessment.

Secondly, the small number of reports limits the ability to identify any possible signal. The authors themselves suggest that caution is required to interpret any difference in bone pain AE reporting between Neulasta and Udenyca as the number of bone pain reports for Udenyca was small and the exposure time period since its marketing launch is short. The small number of reports and limited exposure time would also apply to any individual (serious) AE reported with biosimilar Fulphila. Bone pain-related AEs were not found for Fulphila, further limiting the value of the analysis as bone pain is one of the most frequently reported AEs for pegfilgrastim as appropriately reflected in Neulasta, Udenyca and Fulphila labels.

Thirdly, for Neulasta, most of the AE reports (62.1%) were received from physicians. In contrast, most AE reports received for pegfilgrastim biosimilars were reported by consumers (29.0%) while physicians account for just 23.0% of reports. Reporter type is missing for 9% of the reports received for pegfilgrastim biosimilars but just 3.6% for Neulasta. As the quality of AE reports depends on the accuracy and completeness of the reports made by the reporter, this reporter bias may impact the conclusions from the analysis.

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Furthermore, there are limitations of the statistical analyses. Safety signal detection methods are commonly used to target specific AEs of interest. It is unusual to see these methods applied to a set of diverse individual AEs that are considered serious. One consequence of applying a disproportionality analysis to Fulphila SAEs is that the residual number of non-serious AEs becomes very low (7) leading to an inflated numerator of the ROR.

The proportional risk ratio (PRR) statistic uses the total AEs for Fulphila (120) in the calculation and is not susceptible to inflation in the same way as the ROR statistic. Unfortunately, the authors did not present any results using this statistic. In contrast to the ROR statistic, the PRR for Fulphila (SAEs as a proportion of total AEs) is 1.33 with a 95% CI of 0.63–2.80. The PRR statistic does not exceed the threshold value of 2 and the lower limit of the 95% CI does not exceed the threshold value of 1 [4]. This means that there is no signal of increased reporting of SAEs for Fulphila. This discrepancy between the PRR and ROR may indicate that the findings based on the ROR statistic alone are not robust to draw any firm conclusions. Empirical Bayes Geometric Mean (EBGM), a more sophisticated but increasingly common method, was mentioned but not applied [5].

There are insufficient Fulphila data to make any reliable, formal statistical comparisons against the originator. With only 120 total AEs reported for Fulphila so far in the database, it is not appropriate to perform statistical tests against the originator product, which has 61,608 total AEs reported so far.

The source of data itself also limits the ability to draw conclusions regarding product differences. Regarding the FAERS database, the FDA itself notes, "While FAERS contains reports on a particular drug or biologic, this does not mean that the drug or biologic caused the adverse event. Importantly, the FAERS data by themselves are not an indicator of the safety profile of the drug or biologic." [2]. The FAERS database contains only a small fraction of the side effects that occur with a drug, as there is no requirement for reporters to report side effects to either the FDA or to the manufacturer.

In conclusion, while we agree with the authors that post-marketing safety of supportive care cancer biosimilars is worthwhile, we believe more attention is needed to address limitations highlighted by authors in the study as well as methodologic limitations and alignment with good PV practice discussed above. The conclusions regarding Fulphila from this study are not consistent with the detailed PV analyses conducted regularly with a more comprehensive dataset by the manufacturer.

Declarations

References

1. Tanni KA, Truong CB, Almahasis S, et al. 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. BioDrugs. 2021. https://doi.org/10.1007/s40259-020-00466-3.

2. FDA Adverse Event Reporting System (FAERS) Public Dashboard. FDA. 2020. https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard. Accessed 4 Feb 2021.

3. Guidance for Industry—Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. FDA 2005. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-pharmacovigilance-practices-and-pharmacoepidemiologic-assessment. Accessed 4 Feb 2021.

4. Sakaeda T, Tamon A, Kadoyama K, Okuno Y. Data mining of the public version of the FDA adverse event reporting system. Int J Med Sci. 2013;10(7):796–803. https://doi.org/10.7150/ijms.6048.

5. Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. Drug Saf. 2002;25:381–92. https://doi.org/10.2165/00002018-200225060-00001.