Author's response to reviews

Title: Pegfilgrastim prophylaxis is associated with a lower risk of hospitalization of cancer patients than filgrastim prophylaxis: A retrospective United States claims analysis of granulocyte colony-stimulating factors (G-CSF)

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Version: 2 Date: 6 September 2012

Author's response to reviews: see over
Dear Mr. de Jesus,

Thank you for reviewing our manuscript, “Pegfilgrastim prophylaxis is associated with a lower risk of hospitalization of cancer patients than filgrastim prophylaxis: A retrospective United States claims analysis of granulocyte colony-stimulating factors (G-CSF)”.

Per the request of BMC Cancer, we have added the following ethics statement to the Methods section of the manuscript:

All patient-identifying information was either encrypted or removed from the study database prior to its release to the study investigators. The study database does not contain any Protected Health Information and is fully compliant with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and federal guidance on Public Welfare and the Protection of Human Subjects. As per the Code of Federal Regulations, Institutional Review Board review and approval is not needed for a study of this nature, as “…subjects cannot be identified, directly or through identifiers linked to the subjects…” (45 CFR 46 §46.101). Use of this fully de-identified and HIPAA-compliant study database for health services research is therefore in full compliance with the Helsinki Declaration.

Referee 1 was concerned that the unbalanced distribution of pegfilgrastim cycles and filgrastim cycles in the study sample may be driven by factors specific to certain practices or prescribers. Unfortunately, the HIPAA-compliant administrative claims database used for the study only contains reimbursed claims with encrypted practice IDs and does not capture detailed characteristics of practices or prescribers. Therefore, we cannot directly detect difference in those variables between cycles with pegfilgrastim and cycles with filgrastim, nor can we control for them in the multivariate regression models. Because the study database comprises data from health plans managed by United Healthcare (the largest health insurer in the US) covering
numerous practices found across the US, the mean number of cycles associated with each unique practice within the study sample is very small (about 5 cycles per practice for pegfilgrastim and about 2 cycles per practice for filgrastim). Consequently, including practice fixed effects (ie, dummy variables representing practices) in the regression models or using practice IDs as instrumental variables is not technically feasible. However, we have accounted for major FN risk factors in the regression models. In the Discussion section of the manuscript, we acknowledge that the study results may be confounded by possible differences in unobserved characteristics, including practice or prescriber characteristics, between pegfilgrastim cycles and filgrastim cycles.

Our point-by-point responses to the referee’s comments are attached below. We have also made minor revisions to improve the precision of the text in the Statistical Analyses subsection. Both clean and tracked-changes copies of the revised manuscript have been provided for your reference.

Thank you for considering our revised manuscript for publication. We sincerely hope that these responses and revisions have sufficiently addressed the referee’s concerns. If you have any questions or comments, please do not hesitate to contact us.

Sincerely,

Arash Naeim, M.D.
Corresponding Author
Referee 1’s question:

There is not a complete answer to my previous requirement about determinants of the choice between filgrastim and pegfilgrastim for the prescribers and questions remain: Are they attached to therapeutic committee rules having in focus only acquisition costs? Are they linked to an old procedure in some centers? Following this question, how many centers still prescribed G-CSF in the database?

Response:

The de-identified and HIPAA-compliant study database only contains reimbursed claims with encrypted practice IDs and does not contain detailed information about practices and prescribers. Therefore, we cannot directly detect difference in those variables between cycles with pegfilgrastim and cycles with filgrastim, nor can we control for them in the multivariate regression models. Additionally, because the study database comprises data from health plans covering numerous practices found across the US, the mean number of cycles associated with each unique practice within the study sample is very small. Consequently, including practice fixed effects in the regression models or using practice IDs as instrumental variables is not technically feasible. We cannot rule out the possibility that certain decisions about using pegfilgrastim or filgrastim were made by oncology practices due to cost concerns or existing procedures. However, examination of practice-level factors may require data collection through interaction with oncology practices and is beyond the scope of this claims-based analysis.

In the study sample, 2,223 practices prescribed 11,683 cycles with pegfilgrastim prophylaxis; 191 practices prescribed 373 cycles with filgrastim prophylaxis.

Referee 1’s question:

Number of centers in GCSF and Peg GCSF; is there for some center a before – after prescription for G and Peg G?

Response:

Please see the previous response for the number of practices associated with filgrastim and pegfilgrastim prophylaxis in the study sample.
Because of the limited sample size (number of cycles) in each stratum of practice in the study sample, there will not be sufficient statistical power for us to conduct any “before-after” trend analysis of G-CSF use patterns at the practice level.

In the Background section of our manuscript, we cited such a “before-after” study published by *JMCP* (Morrison et al. 2007;13(4):337-348, PMID: 17506600). In that study, medical charts in 99 community oncology practices in the U.S. were extracted in 2001 (before FDA approval of pegfilgrastim) and 2003 (after FDA approval of pegfilgrastim). The incidence of FN was found to be 5.3% and 7.3% in filgrastim-treated patients in 2001 and 2003 (N = 583 and 868, respectively), statistically higher than the FN incidence (4.7%) in pegfilgrastim-treated patients in 2003 (N = 1,412). The direction of the findings in Morrison *JMCP* article is consistent with our study results.

**Referee 1’s question:**

Regarding costs of ambulatory care and hospitalizations, what are the total costs, integrating cost of GCSF and Peg GCSF?

**Response:**

The all-cause cost measures reported in the manuscript included the G-CSF (filgrastim and pegfilgrastim) drug costs, as stated in the Utilization and Cost Data subsection of the Methods: “Physician fees, chemotherapy costs, and G-CSF costs were all included in the total all-cause cost measure”.

**Referee 1’s question:**

Nowadays, biosimilars are currently prescribed in these indications and does their lower price counterbalanced the benefit observed in ambulatory and hospitalization costs? That’s an important question for the management of overall costs.

**Response:**

Filgrastim biosimilars have become available on the European G-CSF market since 2008, but none of those biosimilars have been approved by the FDA or are currently available on the US market. Investigation of biosimilars is outside the scope of this retrospective study on comparative effectiveness of G-CSF in the US.
The prices of filgrastim biosimilars vary by brand, setting of care, and region/country in Europe. They also fluctuate over calendar years. Predicting price in the US market if biosimilars were approved by the FDA is difficult. Speculating on the penetration rate and other clinical or economic consequences of filgrastim biosimilars in oncology practices in the US is even more difficult.

We completely agree with the referee about the importance of comparative effectiveness evidence on filgrastim biosimilars vs NEUPOGEN® vs Neulasta® in European clinical practice. The first step in conducting such comparative effectiveness research is to obtain real-world data on the effectiveness, safety, healthcare resource utilization, and costs associated with the use of filgrastim biosimilars in Europe. Unfortunately we are not aware of any published studies reporting such data.
To Whom It May Concern:

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_________________________  Date  _______________________
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