Author’s response to reviews

Title: In search of potential predictors of erythropoiesis-stimulating agents (ESAs) hyporesponsiveness: a population-based study

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REVIEWERS COMMENTS

Reviewer #1:

a) Because ESA dose is increased for ESA-hyporesponsive patients, it would be necessary to have an analysis of ESA exposure even though the exact body weight of each ESA user was not available. The investigators should conduct an analysis of how ESA and iron dose levels affect their main findings.

AUTHOR’S ANSWER: Concerning iron levels, ferritin, transferrin saturation, and iron preparation dispensing, all these variables were considered as potential predictors of the study outcomes. As for their inclusion into the multivariate models, it depended on the univariate relationship of each variable mentioned above with the study outcome as well as on the data availability. When the frequency of missing values for a given variable exceeded a critical threshold (>40%), the variable concerned was not included into the multiple models to avoid
analytical distortions attributable to missingness. Transferrin saturation for CKD and ferritin for cancer, although significantly related to the outcomes at univariate analyses (see legends to Tables 3-4), were not included into the multivariate models because of the relatively high frequency of missing values. Furthermore, as correctly argued by the referee no information on body weight was available and for this reason it was not possible to calculate the ESA exposure. These points are now briefly discussed in the study limitations, as follows: “The high frequency of missing values for some variables considered into the study (namely: transferrin saturation for CKD, as well as ferritin and vitamin B12 for cancer) precluded the possibility to test the independent effect of these risk factors on the study outcome. Furthermore, although we tested into the models a series of laboratory risk factors assessed proximally to the Hb measurement, the possibility of residual time dependent confounding due to unmeasured confounders cannot be excluded”.

We would be happy to carry out sensitivity analyses to increase robustness of the findings if the reviewer and the editor believe so. For example, we may restrict the analyses to those patients having information on ferritin and transferrin saturation (available for around 50%).

b) Because of the time lapse between the baseline Hb value and the follow-up Hb value there needs to be a discussion of time-dependent confounding in the limitations section.

AUTHOR’S ANSWER: As requested by the reviewer, we mentioned the potential problem related to residual time dependent confounding is now briefly commented in the limitation section (see above).

Reviewer #2:

Essentially, the study was conducted for two separate populations, i.e., cancer and CKD patients, so the p-values make little sense in Table 1 Characterization of incident ESA users at baseline. P-values as reported are to evaluate the balance of the characteristics of the two different populations. Baseline characteristics are incomparable between the two study populations. Suggest keep all summary statistics but drop all p-values from table 1. The study didn’t intend to use one patient population as a comparison group for another.

AUTHOR’S ANSWER: As suggested by the reviewer, we deleted all p-values from table 1.

ADDITIONAL REQUESTS/SUGGESTIONS:

a) In Data Analysis section, what % of eligible patients whose indication for use were identified via the alternative algorithm? Plus, it is helpful to provide ESA average/median dose and duration in the time interval of ΔHb measurement if data permitted;

AUTHOR’S ANSWER: All eligible patients were categorized as CKD or cancer patients on the basis of a previously developed algorithm (Ingrasciotta Y, Giorgianni F, Bolcato J, Chinellato A, Pirolo R, Tari DU, et al. How Much Are Biosimilars Used in Clinical Practice? A Retrospective
Italian Population-Based Study of Erythropoiesis-Stimulating Agents in the Years 2009–2013. BioDrugs. 2015 Jul 14). Firstly, the ESA indication for use reported in the electronic therapeutic plan was considered. Secondly, in absence of an electronic therapeutic plan, the indication for use was derived from hospital discharge diagnoses (ICD9-CM for cancer: 140*–239*; ICD9-CM for CKD: 583*, 585*, 586*) and reasons for healthcare service co-payment exemption (cancer: 048; CKD: 023), from the period before to 60 days after the index date. If categorization was still not possible, as a last step, ESA users were categorized by dose, such that those who received a prescription for low-dosage ESA (epoetins: <30,000 IU/mL; darbepoetin alpha: <80–100 mcg/mL) at the index date were considered as CKD patients, while those receiving a high-dosage ESA prescription (epoetins: ≥30,000 IU/mL; darbepoetin alpha: ≥80–100 mcg/mL) were considered as cancer patients. So, 616 CKD patients and 464 cancer patients were identified by this algorithm.

Moreover, as suggested by the reviewer, we calculated the mean (±SD) dosage from Index date to the last Hb measurement within 6 months after ID, stratified by unit of measurement of ESA (Cancer: 34,994.1±9,308.1 IU; 204.7±132.1 mcg; CKD: 8,564.6±4,835.4 IU; 49.9±30.0 mcg); it was added in table 1. The mean (±SD) duration of ESA treatment was still calculated and it was available in Table 1.

b) In Sensitivity Analysis section, should a 2x2 table be reported about the count of patients when ESA hyporesponsiveness were based on two different approaches, one was on ΔHb while the other one on Hb>11? That would provide the info on the magnitude of exposure misclassification or consistence when two different definitions of EAS hyporesponsiveness were used.

AUTHOR’S ANSWER: As suggested by the reviewer, a 2x2 table (Table 2) reporting the proportion of hyporesponsive patients calculated with the two approaches was added and it was described in Results section. For each cohort (ie. CKD and cancer), the results showed that the proportion of ESA hyporesponsive patients was similar using the two definitions of ESA hyporesponsiveness (Cancer: ΔHb<0g/dL: 35.1%; Hb<11g/dL: 32.4%; CKD: ΔHb<0g/dL: 30.3%; Hb<11g/dL: 29.3%).

c) In Statistical Analysis, strongly suggest reporting the Hosmer-Lemeshow goodness of fit tests for logistic regression models. ROC index cannot tell readers how well the models fit the data.

AUTHOR’S ANSWER: As requested by the reviewer, an additional analysis reporting the Hosmer-Lemeshow test for two logistic regression analyses was performed: one for CKD patients and another one for cancer patients. The Hosmer Lemeshow tests were not significant for both models (CKD: Chi Squared=8.70, P-value=0.365; Cancer: Chi Squared=14.19, P=0.077) indicating that estimated and observed odds of the dependent variables were consistent between them. The Hosmer Lemeshow tests performed in the sensitivity analyses showed similar not significant results. We prefer to maintain the ROC curves analysis because this method provides the discrimination ability of a given predictive model whereas the Hosmer Lemeshow test provides the calibration ability of the same model. Thus, the two analyses are complementary between them.