Biosimilars G-CSF versus originator G-CSF in post allotransplant recovery. A case-control study.

Keywords: allogeneic transplantation, growth factor, biosimilars, Hematopoietic recovery.

To the Editor: Biosimilars are new biopharmaceutical agents that are 'similar' but not identical to a reference biopharmaceutical product [1]. Many clinical trials have shown that growth factors administration shortens the neutropenic period, and their administration has became common practice after allogeneic hemopoietic stem cell transplantation (HSCT), despite some controversy [2]. Filgrastim (granulocyte colony-stimulating factor, G-CSF) biosimilars were licensed by EMA for all indications of the reference product on the basis of extrapolation from data in healthy adults and chemotherapy-induced neutropenia [3]. While a survey on the use of biosimilar filgrastim in hematological recovery after autologous HSCT has been recently published [4], there are no published data on the use of G-CSF biosimilars in the post allogeneic HSCT hematopoietic recovery.

From February 2013 to October 2014, 43 consecutive patients were treated in our center with either Tevagrastim® (23 patients) or Zarzio® (20 patients) for febrile neutropenia prophylaxis and count recovery after allogeneic HSCT. These patients where retrospectively compared to 43 consecutive patients who underwent allogeneic HSCT until the date of initial

availability of G-CSF biosimilars (January 2011 - December 2012) and received G-CSF originator (Granulokine®) at the same schedule and indications. The injection of G-CSF (5 μg/kg/day) began at day 7 after HLA-identical sibling or matched unrelated donor (MUD) and at day 6 after haploidentical stem cell infusion and continued until absolute neutrophil count was higher than 1.0 x 10^9/L for three consecutive days. We evaluated the median day of neutrophil, platelet and red blood cell engraftment, the incidence of graft failure, Cytomegalovirus (CMV) infection, early infections and acute graft versus host disease (GvHD), relapse and death rate at six months in the two cohorts. Neutrophil engraftment was defined as a sustained (for more than three consecutive days) absolute neutrophil count of 500/μl without the use of growth factors. Platelet engraftment was defined as the first of three consecutive days with a platelet count ≥20 x 10^9/L without platelet support. Red blood cell engraftment coincided with the last day of red blood cell transfusion. Early infections were defined as occurring from hospital admission until discharge. Engraftment, graft failure and relapse were evaluated in patients who survived at least 15 days after transplant. Acute GvHD was graded according to the revised Glucksberg scale [5] and evaluated in patients who survived at least 15 days and reached engraftment. CMV infection was considered in subjects having at least one serum sample assessed for CMV viremia by PCR-based method. Moreover cost analysis was performed considering drug cost by list price, excluding the value added tax (originator: 115.155 € per vial; mean of the two biosimilars: 88,1 € per vial) and actual cost (originator: 57,00 € per vial; mean of the two biosimilars: 9,22 € per

vial). Mann-Whitney and Pearson Chi-Square tests for continues and categorical variables were used, respectively. Multivariate logistic regression analysis was used to correct for age. The method of general linear models for repeated measures (SPSS version 12.0.1) was used to examine for changes in neutrophils over time. A P-value <0.05 was considered significant. Internal Review Board approved study project. All procedures were carried out in accordance with the ethical standards of the Declaration of Helsinki of 1975, as revised in 2000.

A preliminary analysis revealed no difference between the two biosimilars used; thus data from these patients were analyzed together. Cases and control groups resulted matched for sex, type of disease, Karnofsky score, HCT-Comorbidity Index [6], status of disease at transplant, conditioning regimen, type of donor, HLA-matching, stem cell source and number of stem cells injected. Difference in age was statistically significant but in favor of originator group. The median age was 53 (23-69) in the study group and 44 (19-66) in the control group ($p=0.001$).

We did not observe any statistically significant difference between the study and control group in terms of neutrophil, platelet and red blood cell engraftment, incidence of CMV infection, early infections and graft failure, six month relapse and death. Although immunogenicity is the most important safety issue concerning all biosimilar products [3], G-CSF biosimilars did not increase acute GvHD incidence in the study group.

As the age was significantly different between the two groups, we performed a multivariate logistic regression analysis. When each of the outcome variables was included in the model along with the age, no significant change of p-values was observed (data not shown). Repeated measures general linear model showed no significant within-subjects interaction effect between neutrophils and the two groups (Fig 1. F=0.679; P=0.9). G-CSF vials used in total were 435 in the control group and 380 in the study group. Vials used per patient were 8.5 (range: 3-37) in the control group and 7 (range: 3-40) in the study group. This corresponded to total costs per patient of 1164,94 € versus 778,55 € by list price and of 576,62 € versus 81,47 € actual cost for originator and biosimilars, respectively. Cost saving with biosimilars was of 386,39 (33%) and of 495,15 (85%) per patient by list price and actual cost, respectively.

In conclusion, our study shows that G-CSF biosimilars are equivalent to classical products in terms of safety and efficacy when used for hematopoietic recovery after allogeneic HSCT.

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Competing interests:

The authors declare that there are not competing financial interests in relation to the work described and that this manuscript is original, neither duplicate nor redundant; it has not been published before and is not currently being considered for publication elsewhere. One poster related to this manuscript was presented at Poster Presentation at the European Group for Blood and Marrow Transplantation (EBMT) annual meeting in 2015

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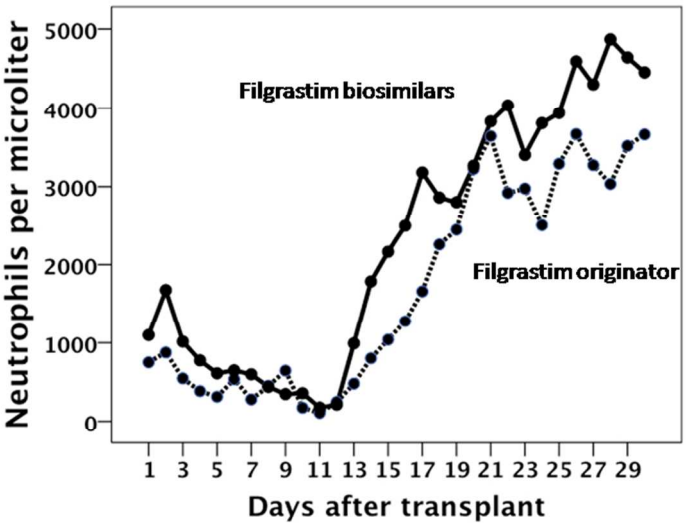
Figure 1: Neutrophils recovery after allogeneic hemopoietic stem cell transplantation. Filgrastim originator versus filgrastim biosimilars. Data from repeated measures of the general linear model F= 0,679 P=0,9. Day 0 is day of allogeneic hemopoietic stem cell infusion.



Neutrophils recovery after allogeneic hemopoietic stem cell transplantation. Filgrastim originator versus filgrastim biosimilars. Data from repeated measures of the general linear model F= 0,679 P=0,9. Day 0 is day of allogeneic hemopoietic stem cell infusion.
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