Biosimilar Filgrastim for Progenitor-Cell Mobilization prior to Autologous Transplantation: Retrospective Analysis of Patients with Multiple Myeloma and Lymphomas

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Filgrastim Biossimilar para Mobilização de Células Progenitoras antes do Transplante Autólogo: Análise Retrospectiva de Pacientes com Mieloma Múltiplo e Linfomas

Filgrastim Biosimilar para la Movilización de Células Progenitoras antes del Trasplante Autólogo: Análisis Retrospectivo de Pacientes con Mieloma Múltiple y Linfomas

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Abstract

Introduction: Filgrastim, which plays a key role in peripheral blood progenitor cell (PBPC) harvesting, has been available for nearly 25 years, and several filgrastim biosimilars are available. **Objective:** We assessed whether a biosimilar filgrastim (Filgrastine®) was associated with effective mobilization in patients undergoing PBPC collection for autologous transplantation. **Method:** We reviewed the charts of patients with multiple myeloma and lymphomas treated at three institutions in Brazil. The primary outcome (mobilization success rate, MSR) was the proportion of patients in the intention-to-treat (ITT) group in whom at least 2 x 10^6 CD34+cells/Kg were harvested by leukapheresis on days 5 and/or 6. The per-protocol (PP) group comprised patients who received at least 4 days of Filgrastine and had at least one CD34+ count on days 5 or 6. **Results:** The daily dose of Filgrastine (on D1, with few changes thereafter) ranged from 8.5 to 28.9 mcg/Kg in the 52 patients in the ITT group, with a median of 13.8 mcg/Kg; 51 patients received at least four doses. A mean of 2.84±1.97 x 10^6 CD34+cells/Kg were harvested. MSR was 53.9% (95%CI, 39.5%-67.8%) in the ITT group and 62.2% (95%CI, 46.5%-76.2%) in the 45 patients in the PP group. Mobilization was considered effective by investigators in 80.8% of patients in the ITT group and 88.9% of those in the PP group. **Conclusion:** Despite the study's observational design, the results suggest that Filgrastine® is associated with the expected success rates in PBPC collection for autologous transplantation.

Key words: Granulocyte Colony-Stimulating Factor; Filgrastim; Lymphoma; Multiple Myeloma; Peripheral Blood Stem Cell Transplantation.

Resumo

Introdução: O filgrastim, que desempenha um papel fundamental na coleta de células progenitoras de sangue periférico (CPSP), está disponível há quase 25 anos, e existem vários biossimilares de filgrastim sendo comercializados. **Objetivo:** Avaliar se um filgrastim biossimilar (Filgrastine®) foi associado com mobilização efetiva em pacientes submetidos à coleta de CPSP para transplante autólogo de medula óssea. **Método:** Foram revisados os prontuários de pacientes com mieloma múltiplo e linfomas tratados em três instituições no Brasil. O desfecho primário (taxa de sucesso de mobilização) foi a proporção de pacientes na população intenção de tratar (ITT), em que pelo menos 2 x 106 células CD34+/kg foram coletadas por leucaférese nos dias 5 e/ou 6. A população per protocolo (PP) foi composta por pacientes que receberam pelo menos quatro dias de Filgrastine e tiveram pelo menos uma contagem de CD34+ nos dias 5 ou 6. **Resultados:** A dose diária de Filgrastine (no D1, com pequenas alterações subsequentes) variou de 8,5 a 28,9 mcg/Kg nos 52 pacientes na população ITT, com uma mediana de 13,8 mcg/Kg; 51 pacientes receberam pelo menos quatro doses. Uma média de 2,84±1,97 x 106 células CD34+/kg foram coletadas. A taxa de sucesso de mobilização foi de 53,9% (IC 95%, 39,5% a 67,8%) na população ITT e 62,2% (IC 95%, 46,5% a 76,2%) nos 45 pacientes da população PP. A mobilização foi considerada efetiva pelos pesquisadores em 80,8% dos pacientes da população ITT e 88,9% daqueles na população PP. **Conclusão:** Apesar de sua natureza observacional, este estudo sugere que Filgrastine esteja associado com as taxas de sucesso esperadas na coleta de CPSP para transplante autólogo de medula óssea.

Palavras-chave: Fator Estimulador de Colônias de Granulócitos Humanos; Filgrastim; Linfoma; Myeloma Múltiplo; Transplante de Células-tronco Hematopoiéticas Periféricas.

Resumen

Introducción: El filgrastim, que desempeña un papel fundamental en la colecta de células progenitoras de sangre periférica (CPSP), está disponible desde hace casi 25 años y existen varios biosimilares de filgrastim siendo comercializados. **Objetivo:** Se evaluó si un filgrastim biosimilar (Filgrastine®) se asoció con una movilización efectiva en pacientes sometidos a la colecta de CPSP para el trasplante autólogo de médula ósea. **Método:** Se revisaron los prontuarios de pacientes con mieloma múltiple y linfomas tratados en tres instituciones en Brasil. El resultado primario (tasa de éxito de movilización) fue la proporción de pacientes en la población intención de tratar (ITT) en que al menos 2 x 10^6 células CD34+/kg fueron obtenidas por leucoféresis en los días 5 y/o 6. La población por protocolo (PP) fue compuesta por pacientes que recibieron por lo menos 4 días de Filgrastine y tuvieron al menos un recuento de CD34 + en los días 5 o 6. **Resultados:** La dosis diaria de Filgrastine (en el D1, con pequeños cambios subsiguientes) varió de 8, 5 a 28,9 mcg/Kg en los 52 pacientes en la población ITT, con una mediana de 13,8 mcg / Kg; 51 pacientes recibieron al menos cuatro dosis. Se obtuvo una media de 2,84±1,97 x 10^6 células CD34+/kg. La tasa de éxito de movilización fue del 53,9% (IC 95%, 39,5% a 67,8%) en la población ITT y el 62,2% (IC 95%, 46,5% a 76,2%), en los 45 pacientes de la población PP. La movilización fue considerada efectiva por los investigadores en el 80,8% de los pacientes de la población ITT y el 88,9% de aquellos en la población PP. **Conclusión:** A pesar de su naturaleza observacional, este estudio sugiere que Filgrastine está asociado con las tasas de éxito esperadas en la recolección de CPSP para trasplante autólogo de médula ósea.

Palabras clave: Factor Estimulador de Colonias de Granulocitos Humanos; Filgrastim; Linfoma; Mieloma Múltiple; Trasplante de Células Progenitoras Hematopoyéticas de Sangre Periférica.

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INTRODUCTION

Granulocyte colony-stimulating factor (G-CSF) plays a key role in stem cell transplantation, both for mobilization of peripheral blood progenitor cells (PBSCs) and for hematopoietic recovery[1,2]. G-CSF may be used alone, after chemotherapy, or in combination with plerixafor to mobilize PBPCs, with the choice of mobilization strategy depending in part on the underlying malignancy and on the type of transplantation[3]. In autologous transplantation, PBPC mobilization aims to obtain the required number of cells to ensure hematopoietic recovery with the number of leukapheresis sessions[2]. Among the different types of G-CSF and granulocyte-macrophage-CSF that have been employed, filgrastim is the one used most often.

Filgrastim has been available for nearly 25 years, and several filgrastim biosimilars (similar but not identical versions of the original agent for which the patent has expired) have been available since 2008 and are in clinical use in Europe and elsewhere[4]. In the United States, the first filgrastim biosimilar was approved in March 2015[5], and several filgrastim biosimilars are commercially available in Brazil. Despite the rigorous development and approval processes for biosimilars[6,7] and published evidence that shows no difference in activity between the innovator and biosimilar filgrastim products[4,8-11], concerns have been raised about the efficacy and safety of these products[4,12]. Thus, it is important to assess individual products for their role in clinical practice. The current study aimed to assess a filgrastim biosimilar produced in Brazil (Filgrastine®) for PBPC mobilization among patients with multiple myeloma and lymphomas undergoing progenitor cell harvesting for autologous transplantation.

METHOD

Study design and sponsor's role

This was a retrospective study of patients treated at three public institutions that perform bone marrow transplantation in Brazil: *Hospital das Clínicas de Ribeirão Preto* (HCRP), *Hospital de Clínicas de Porto Alegre* (HCPA), and the Brazilian National Cancer Institute (INCA) in Rio de Janeiro. The study protocol was approved by the institutional review boards of the three participating institutions, and informed consent was waived due to the retrospective methodology. The study was designed and sponsored by Blau Farmacêutica S/A, the manufacturer of the target filgrastim product (Filgrastine®). Data analysis was conducted by an outsourced research organization.

Eligibility criteria and data collection

Eligible patients were those with multiple myeloma, non-Hodgkin lymphoma, or Hodgkin lymphoma who received the target biosimilar filgrastim for PBPC collection prior to autologous transplantation in one of the three participating institutions from January 1st, 2011, to December 31st, 2012. Patients had to be at least 18 years of age, could not have received filgrastim other than Filgrastine®, could not have received chemotherapy concurrently with filgrastim, and could not have participated in any interventional studies within 90 days from the date of the first filgrastim dose. Enrolment was done sequentially, as long as the selection criteria were met. Patient charts were reviewed to collect relevant data onto a specific case report form. Such data included demographic, anthropometric, and clinical features, prior therapies, dates, doses, and route of filgrastim administration, CD34+ counts on various occasions, and whether stem cell collection was considered successful by investigators.

Target outcomes and patient groups

The statistical analysis plan, finalized before database locking, specified that the primary outcome of interest was the proportion of patients in whom at least 2 x 10^6 CD34+ cells/Kg were harvested after a maximum of two sessions of leukapheresis (on days 5 and/or 6 after filgrastim initiation). Secondary efficacy outcome measures were the mean number of CD34+ cells in the leukapheresis product on days 5 and/or 6; the number of days of filgrastim administration required to harvest 2 x 10^6 CD34+ cells/Kg; the proportion of patients in whom at least 5 x 10^6 CD34+ cells/Kg were harvested after a maximum of two sessions of leukapheresis; and the efficacy of mobilization, assessed by investigators on the basis of successful transplantation. Safety was assessed according to adverse events considered by investigators as related to filgrastim administration during the mobilization period. Finally, the patterns of filgrastim use were recorded. The statistical analysis plan provided for two exploratory subgroup analyses of the primary outcome according to institution and underlying malignancy.

Statistical analysis

Since this was a retrospective study, calculation of sample size was not based on statistical assumptions, but on practical considerations regarding feasible patient enrolment. The number of patients enrolled per institutions was estimated at 150 to 180. In recent randomized trials with filgrastim, with or without plerixafor, 2 x 10^6 CD34+ cells/Kg were harvested in 88.3% of patients with multiple myeloma and 47.3% of patients with non-Hodgkin lymphoma.[13, 14] Enrolment of 165 patients would allow detecting a rate of 67.8% (the arithmetic mean of 88.3% and 47.3%) for the proportion

of patients in whom at least 2 x 10^6 CD34+ cells/Kg could be harvested after a maximum of two sessions of leukapheresis, considering a two-tailed confidence interval of 7.5% around the point estimate and 10% losses due to missing data. Therefore, a sample of 165 patients was within the expected range based on feasibility and would allow the detection of a clinically meaningful rate of successful mobilization.

Except for dates, there was no imputation of missing data. For dates, the 15th of the month was used when only the month and year were available for a given event. When the month was not available, the date was not used for analysis, and the same exclusion applied to variables with missing data on more than 10% of cases. All rates were computed taking the number of patients who met the target outcome criterion as the numerator and the total number of patients in the target group as the denominator. The intention-to-treat (ITT) group consisted of all patients included in the study who received at least one dose of filgrastim. The per-protocol group consisted of all patients in the ITT group who received at least four days of filgrastim for mobilization and had at least one CD34+ count on days 5 or 6. Normally distributed continuous variables were summarized by means and standard deviation (SD), and medians and interquartile range were used for numerical variables with non-normal distribution. Unpaired t-test was used to compare mean values for variables with normal distribution, while the Mann-Whitney test was used for numerical variables with non-normal distribution. Categorical variables were described by absolute and relative frequencies and 95% confidence intervals (CIs) when appropriate, and compared with Fisher's exact test or chi-square test, as appropriate. Two-tailed significance levels of 5% were considered as indicative of statistical significance, and the analyses were performed using MedCalc (Mariakerke, Belgium, version 11).

RESULTS

Patient characteristics and groups

Patient enrolment was lower than expected, mainly because more than one filgrastim product was being used at the participating institutions during the study period. As a result, only 52 patients who received Filgrastine® were registered and analyzed in the ITT group. CD34+ cell count was not performed in 12 patients on D5 and in 27 patients on D6. Since seven patients did not have a CD34+ cell count on either D5 or D6, the per-protocol group consisted of 45 patients. The date of first dose of filgrastim (D1) ranged from December 31st, 2010, to December 15th, 2012. Table 1 shows the main demographic and clinical characteristics of patients in the ITT group. Information on performance status was available for 34 patients (65.4%): performance status was 0/1/2/3/4 in 14/18/1/0/1 cases, respectively. Disease status immediately prior to mobilization, based on investigator opinion, was complete response in 17 patients, partial response in 29, progression in four, and unknown in two cases. Only 11 patients had a history of prior radiotherapy, and two had undergone previous autologous transplantation.

Table 1. Baseline patient characteristics (intention-to-treat group)

Characteristic	Value or N (%)
Gender	
Female	24 (46.2)
Male	28 (53.8)
Age, years	
Range	27 to 67
Mean ± SD	54.0 ± 9.2
Median	56.5
Race/color	
White	41 (78,9)
Brown	8 (15,4)
Black	3 (5,8)
Body mass index, kg/m² (N=48)	
Range	19.9 to 44.3
Mean ± SD	28.7 ± 6.0
Malignancy, %	
Non-Hodgkin lymphoma	3 (5.8)
Hodgkin lymphoma	4 (7.7)
Multiple myeloma	45 (86.5)

Exposure to filgrastim

Table 2 summarizes the patients' exposure to filgrastim. The filgrastim dose administered on D1 ranged from 8.5 to 28.9 mcg/Kg of body weight, with a mean of 15.2 mcg/Kg and a median of 13.8 mcg/Kg. Mean total dose of filgrastim on the first six days of mobilization was 86 mcg/Kg. Fifty-one patients received at least four doses of filgrastim, while one patient received only two doses (this patient collected 10 x 10^6 CD34+ cells/Kg). Filgrastim was always administered subcutaneously. The first dose was administered in the patient's home in 38 cases, in the hospital in three cases, and unrecorded in the remaining 11 cases. The dose of filgrastim administered on D1 was the same as planned in all cases. The administered dose of filgrastim was the same from D1 to D4 in 50 patients, while two patients had changes in their doses. Fifty patients received filgrastim on D5, and 34 received the drug on D6.

Table 2. Exposure to filgrastim

Doses	N (%)
Nominal dose on D1	
600 mcg	8 (15.4)
900 mcg	20 (38.5)
1,200 mcg	17 (32.7)
1,500 mcg	2 (3.9)
1,800 mcg	1 (1.9)
2,100 mcg	3 (5.8)
2,400 mcg	1 (1.9)
Summary of D1 dose, mcg	
Mean ± SD	1,090 ± 407
Median	900

Efficacy and safety outcomes

Of the 52 patients in the ITT group, 28 had at least 2 x 10^6 CD34+ cells/Kg harvested on D5 and/or D6. Therefore, the mobilization success rate in the ITT group was 53.9% (95%CI, 39.5-67.8%). All those 28 patients were part of the per-protocol group. Thus, the mobilization success rate in the per-protocol group was 62.2% (95%CI, 46.5-76.2%).

A mean of 2.84 ± 1.97 x 10^6 CD34+ cells/Kg were harvested on D5 and/or D6. Of the 28 patients with at least 2 x 10^6 CD34+ cells/Kg harvested on D5 and/or D6, 14 achieved that threshold on D5, and 14 required administration on D6 as well. The proportions of patients in whom at least 5 x 10^6 CD34+ cells/Kg were successfully harvested after a maximum of two sessions of leukapheresis were 13.5% (95%CI, 5.6% to 25.8%) in the ITT group and 15.6% (95%CI, 6.5% to 29.5%) in the per-protocol group. Mobilization was considered effective by investigators in 42 patients (80.8%) from the ITT group and 40 (88.9%) from the per-protocol group. As a result, 10 patients in the ITT group and five in the per-protocol group were not able to receive the planned autologous transplantation. No adverse events were reported by investigators. Seven deaths were reported, occurring from 1 to 25 months after the first day of filgrastim administration.

Exploratory analyses

The planned subgroup analysis of the primary outcome according to institution showed nominally (but not statistically) different mobilization success rates according to institution (72.2% for HCRP, 58.8% for HCPA, and 35.7% for INCA, P=0.277 in the ITT group and 81.3%, 62.5%, and 38.5%, respectively, P=0.061, in the per-protocol group). The planned analysis according to underlying malignancy showed that only patients with multiple myeloma achieved the minimum threshold of 2 x 10^6 CD34+ cells/Kg harvested on D5 and/or D6 (P=0.009 in the ITT group; P=0.010 in the per-protocol group).

Unplanned exploratory analyses suggested no association between the primary outcome and gender, age, or history of radiotherapy. On the other hand, there were significantly different proportions of patients with history of radiotherapy in the three institutions: 19.0% at HCRP, 5.9% at HCPA, and 42.9% at INCA (P=0.041). This imbalance was apparently not due to the underlying disease, since there were no differences in distributions of underlying disease according to institution, or of underlying disease according to history of radiotherapy (data not shown). The potential influence of radiotherapy on the number of CD34+ cells/Kg was also explored. Of 11 patients with previous radiotherapy, 10 had available CD34+ cell counts. Of the 41 patients without previous radiation therapy, 35 had such counts. Median number of CD34+ cells was 1.7 x 10^6 in patients with previous radiotherapy and 2.2 x 10^6 in those without (P=0.133).

DISCUSSION

This retrospective study showed a 53.9% success rate in the ITT group, the primary group for analysis (with success defined as the collection of at least 2 x 10^6 CD34+ cells/Kg body weight, with a maximum of two leukapheresis sessions). Although the success rate in the ITT group was lower than expected at the time of the study design (67.8%), the latter figure is identical to the upper limit of the 95%CI for the observed success rate. Nevertheless, due to the absence of a statistical hypothesis for testing, it is not possible to classify this study as positive or negative, based on formal criteria. Moreover, the success rate in the per-protocol group was 62.2%, which is closer to the rate expected at the time of the study design. Furthermore, if successful mobilization is considered as a relevant outcome parameter (as measured indirectly according to the investigator's opinion), the rates observed in this study were 80.8% and 88.9 % in the ITT and per-protocol groups, respectively. Importantly, the investigator's assessment takes into account the patient's full history and not only the results of two days of leukapheresis. It is also widely acknowledged that nearly 20% of multiple myeloma patients do not achieve successful mobilization, regardless of the schedule of filgrastim used[13,14].

The two chief limitations of this study were its retrospective design and final sample size, which was lower than expected. Although the study was retrospective, it had an approved protocol and statistical analysis plan,

and data were collected with a standardized case report form. Moreover, every effort was made to collect all the required data, and the analyses were performed by a third party not involved in data collection. It was possible to trace the target filgrastim product using prescription and pharmacy records, and patient enrolment was short of expectations. This lower patient accrual definitely impacted the precision of the estimated success rates (i.e., the 95% confidence intervals). Meanwhile, the possibility of bias resulting from this lower accrual could not be ascertained, since systematic differences between patients receiving the target filgrastim product and other filgrastim formulations were not assessed.

The reason for the nominally lower success rate at INCA (35.7% in the ITT group) when compared to the other two institutions (72.2% and 58.8%) is not completely clear. However, prior radiotherapy rates differed statistically between the institutions, with 42.9% of patients from INCA having such history. Meanwhile, the difference between the median numbers of CD34-positive cells in patients with and without prior radiotherapy was not statistically significant, possibly because of the small sample size. Similarly, there was no statistically significant association between history of radiotherapy and successful mobilization. Finally, the difference between the institutions in relation to prior radiotherapy does not appear to be due to the underlying disease. Of note, all patients treated in the institution with the highest success rate (HCRP) had multiple myeloma, but this finding's relevance is uncertain. It is thus possible that patients in the three institutions differed in terms of unmeasured confounders associated with successful mobilization, such as intensity of prior treatment and disease status or bone marrow status at the time of PBPC collection.

The current study's results can be compared to those of other published studies. To our knowledge, no previously published Brazilian study is available for comparison. Gabús *et al.* reported on their experience with PBPC harvesting for autologous transplantation using another filgrastim biosimilar, Filgen JP (Clausen Filgrastim), as well as other filgrastim products available in Uruguay.[15] There was no difference in effectiveness between Filgen JP and other filgrastim products, and the mean number of CD34+ cells harvested in that study was 4.98 x 10^6 CD34+ cells/Kg, almost twice as high as the mean number found in the current study (2.84 x 10^6 CD34+ cells/Kg). The reason for this difference is not entirely clear. Gabús *et al.* reported a mean filgrastim dose of 105 mcg/Kg, while in our study the mean total dose on the first six days of mobilization was 86 mcg/Kg. The fact that no data were collected systematically beyond D6 does not allow concluding that a lower total dose of filgrastim administered in our patients explains the differences in the mean number of CD34+ cells harvested. Higher CD34+ cell yields have been reported in other studies with biosimilar filgrastim,[9, 11, 16] but whether this is due to differences in the filgrastim products, patient profiles, methods for CD34+ quantification, or institutional policies on PBPC mobilization and harvesting remains unclear.

Biosimilars offer potential benefits to patients and the healthcare system, especially by increasing affordability and allowing greater access to expensive treatments. Previous studies have shown that the use of biosimilar filgrastim offers cost savings with similar efficacy when compared to the innovator product[17,18]. These findings and the apparent lack of differences in activity or safety between the innovator and biosimilar filgrastim products[4, 8-11, 15] support the use of biosimilar filgrastim in clinical practice.

In conclusion, despite the study's observational design, the results suggest that the target biosimilar filgrastim (Filgrastine®) is effective in clinical practice, based on the success rates of 53.9% and 62.2% in the ITT and per-protocol groups and the success rates assessed by investigators (80.8% and 88.9%, respectively). Ideally, these findings should be confirmed by a comparative clinical trial.

AUTHOR CONTRIBUTIONS

All authors worked on the research project's design and planning, data collection and analysis, and writing and revision of the manuscript.

CONFLICT OF INTEREST:

None.

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