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Research Paper

Biosimilar G-CSF Based Mobilization of Peripheral Blood Hematopoietic Stem Cells for Autologous and Allogeneic Stem Cell Transplantation

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Abstract

The use of granulocyte colony stimulating factor (G-CSF) biosimilars for peripheral blood hematopoietic stem cell (PBSC) mobilization has stimulated an ongoing debate regarding their efficacy and safety. However, the use of biosimilar G-CSF was approved by the European Medicines Agency (EMA) for all the registered indications of the originator G-CSF (Neupogen®) including mobilization of stem cells. Here, we performed a comprehensive review of published reports on the use of biosimilar G-CSF covering patients with hematological malignancies as well as healthy donors that underwent stem cell mobilization at multiple centers using site-specific non-randomized regimens with a biosimilar G-CSF in the autologous and allogeneic setting.

A total of 904 patients mostly with hematological malignancies as well as healthy donors underwent successful autologous or allogeneic stem cell mobilization, respectively, using a biosimilar G-CSF (520 with Ratiograstim®/Tevagrastim, 384 with Zarzio®). The indication for stem cell mobilization in hematology patients included 326 patients with multiple myeloma, 273 with Non-Hodgkin's lymphoma (NHL), 79 with Hodgkin's lymphoma (HL), and other disease. 156 sibling or volunteer unrelated donors were mobilized using biosimilar G-CSF. Mobilization resulted in good mobilization of CD34+ stem cells with side effects similar to originator G-CSF. Post transplantation engraftment did not significantly differ from results previously documented with the originator G-CSF. The side effects experienced by the patients or donors mobilized by biosimilar G-CSF were minimal and were comparable to those of originator G-CSF.

In summary, the efficacy of biosimilar G-CSFs in terms of PBSC yield as well as their toxicity profile are equivalent to historical data with the reference G-CSF.

Key words: Biosimilar G-CSF, hematopoietic stem cells, mobilization, autologous & allogeneic transplantation, healthy donors

1. Granulocyte colony stimulating factor (G-CSF)

Granulocyte colony stimulating factor (G-CSF) has become a widely used clinical tool used by hematologists and oncologists to treat therapy-induced neutropenia and to accelerate and potentiate engraftment after hematopoietic stem cell transplantation.[1, 2]

2. Biosimilar G-CSF

When conventional drugs produced by chemical synthesis contain the same active substance as the original agent and are similar in terms of quality, safety and efficacy to the original drug, they are termed 'generic'. Hematopoietic growth factors including G-CSF are manufactured by the use of recombinant technology and for regulatory purposes are classified as 'biological medicines' and as such, must comply with specific manufacturing requirements.[3] When biologically equivalent agents are manufactured they are termed "biosimilars".[4] The EMEA stated that "a company may choose to develop a new biological medicinal product claimed to be similar (Similar Biological Medicinal Product) in terms of Quality, Safety and Efficacy to an original, reference medicinal product, which has been granted a marketing authorization in the Community."[3] The manufacture and use of biosimilar G-CSF has a specific set of guidance notes produced by the EMEA, now referred to as EMA.[3] The use of biosimilars in general and in particular for peripheral blood hematopoietic stem cell (PBSC) mobilization has stimulated an ongoing debate regarding their efficacy and safety.[4-8]

3. Extrapolation for biosimilars

The use of biosimilar G-CSF (Ratiograstim®, Tevagrastim®, Biograstim®, Zarzio®, Nivestim®) was approved by the European Medicines Agency (EMA) for all the registered indications of the originator (Neupogen®) including chemotherapy induced neutropenia (CIN), agranulocytosis and neutropenia due to infection with the human immunodeficiency virus (HIV) and mobilization of stem cells in the autologous and allogeneic settings, based on their comparable efficacy and safety profile to the originator G-CSF in CIN.[9] Comparability of biosimilar G-CSF with the originator filgrastim was assessed in three large randomized two-arm comparative studies in a single indication for which the reference G-CSF is approved, i.e. the efficacy of originator versus biosimilar G-CSF in CIN in patients with breast cancer, lung cancer and malignant lymphoma.[10] The extrapolation from these positive results indicating an identical efficacy and safety profile when compared to originator filgrastim (Neupogen®) to the use of the biosimilar G-CSF for the mobilization of CD34+ hematopoietic stem cells in healthy donors was based on European Law.[9] However, this extrapolation in general raised questions.[3-5, 7, 11]

4. Similarity of structure and production process of originator and biosimilar G-CSF

The World Health Organization (WHO) stated that "the clinical performance of biotherapeutics can also be much influenced by the manufacturing process and therefore some clinical studies will also be required to support the safety and efficacy of a similar biotherapeutic product (SBP)." [12]

Filgrastim, the active substance of Ratiograstim®/Tevagrastim® is a non- glycosylated recombinant N-methionyl human granulocyte colony stimulating factor expressed in *E. coli* and consisting of 175 amino acids (Figure 1). [13-15]

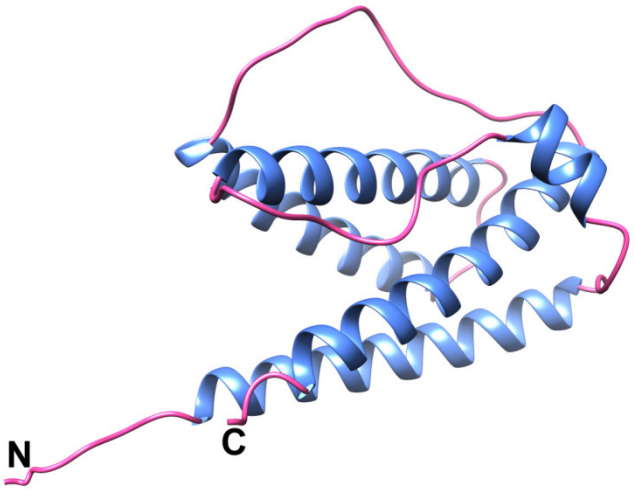

Figure 1. Structure of recombinant human G-CSF. Ribbon representation of the structure of recombinantly produced human G-CSF. The sequence of this biosimilar is identical to the one of filgrastim (Neupogen®). Helical regions are colored in blue, coil regions in pink. The N- and the C-terminus are indicated. Structure co-ordinates (PDB 1GNC; [15]) were used to calculate a mean structure with MOLMOL [13]. The ribbon representation was generated using the UCSF Chimera package [14].

The *E. coli* host strain was transformed with the plasmid using standard techniques to generate the recombinant strain *E. coli* for production of G-CSF. During the biosynthesis process, G-CSF protein is expressed in inclusion bodies in the cells. After a predefined growth time cells are harvested, disrupted and inclusion bodies washed by buffer for removal of contaminants. The inclusion bodies are dissolved in

chaotropic agent and refolded in a reducing-oxidizing system. After refolding, a series of orthogonal chromatographic purification steps are applied. Following purification, the XM02 active substance is filtered and stored at 2 to 8°C.

Ratiograstim®/Tevagrastim® in a concentration of 0.6 mg/ml is supplied in two dosage strengths 30 MIU/0.5 ml and 48 MIU/0.8 ml, filled in 1 ml glass, single-use, pre-filled syringes. The formulation of Ratiograstim®/Tevagrastim® has the same excipients as Neupogen®, i.e. acetic acid, polysorbate 80, sodium hydroxide, sorbitol and water for injections (*as per product information*).

As required for a similar biological medicinal product, comparability to the reference medicinal product Neupogen® has been demonstrated through an extensive head-to-head characterization and stability studies performed for both XM02 active substance and medicinal product. Physical properties, the primary and higher order structures, the biological activity and product related impurities, found to be similar to Neupogen® (*data on file*).

5. Statements from WMDA and EBMT on the use of biosimilar G-CSF

Currently, there are few published data regarding the use of biosimilar G-CSF in the context of autologous PBSC for mobilization. Almost no published data exist as for hematopoietic stem cell mobilization from healthy donors. In a recent review by Shaw et al., the World Marrow Donor Association (WMDA) recommends that "biosimilars should only be used in healthy donors where the donor is entered and followed on a clinical study."[16] In 2009, the Executive Committee of the European Bone Marrow Transplantation (EBMT) Association issued a letter stating that "until studies have been performed to provide the required efficacy and safety data, the EBMT does not recommend the use of biosimilar G-CSFs for mobilization of stem cells in healthy donors for stem cell transplantation." The recommendation from the EBMT Executive was that only after collection of comprehensive data G-CSF biosimilars could be considered routinely for the mobilization of peripheral blood stem cells in sibling and volunteer donors.[17]

6. Assessment of the wide use of G-CSF in the real transplantation world

We performed a comprehensive review of published reports covering 904 patients, with hematological malignancies as well as healthy donors that underwent stem cell mobilization with a biosimilar G-CSF for autologous and allogeneic stem cell transplantation, or cellular therapies for tissue regeneration, evaluating mobilization yield and safety profile as well as engraftment and transplantation outcome.

The database pubmed.org and the abstract books of the Annual Meetings of the European Bone Marrow Transplantation (EBMT) Association in 2012 and 2013 were reviewed for peer-reviewed papers and peer-reviewed abstracts respectively regarding the mobilization of stem cells with a biosimilar G-CSF.

An extensive literature review[18-39] produced 904 patients mostly with hematological malignancies as well as healthy donors that underwent successful autologous or allogeneic stem cell mobilization respectively using a biosimilar G-CSF (Ratiograstim®/Tevagrastim® or Zarzio®). A total of 520 patients or donors underwent stem cell mobilization with Ratiograstim®/Tevagrastim®, while 384 patients or donors underwent stem cell mobilization with Zarzio®. The indication for stem cell mobilization in hematology patients included those with multiple myeloma, Non-Hodgkin lymphoma (NHL), Hodgkin's lymphoma (HL), acute and chronic leukemia. Patients with germ cell tumors as well as a small number of patients with cardiac failure who were in cell therapy studies were also included. Sibling or volunteer unrelated donors were mobilized using either Ratiograstim®/Tevagrastim® or Zarzio®. In Figure 2 the total number and the underlying disease of the patients that underwent autologous stem cell mobilization with Ratiograstim®/ Tevagrastim® or Zarzio® is detailed, while Figure 3 summarizes the healthy donors that were mobilized with a biosimilar G-CSF respectively. The details of the specific biosimilar G-CSF used including dose, mode of autologous mobilization and indication are summarized in Table 1, while Table 2 shows the details of the equivalent procedure in healthy donors. It is of note that biosimilar G-CSF was already used for hematopoietic stem cell mobilization not just in sibling donors but also of unrelated volunteer donors from donor registries (Table 2). Mobilization parameters, yield, toxicity and post autologous or allogeneic transplantation engraftment data are detailed in Table 3 and Table 4 respectively. Biosimilar G-CSF based stem cell mobilization for both autologous and allogeneic transplantation resulted in good mobilization of CD34+ stem cells with side effects similar to reference G-CSF. Post transplantation engraftment did not significantly differ from results previously documented with the originator filgrastim (Neupogen®) in historical controls. The side effects experienced by the patients or donors mobilized by biosimilar G-CSF (Ratiograstim® or Tevagrastim® or Zarzio®) were minimal and were comparable to those of originator G-CSF (Table 3 and Table 4).

We could not detect any difference in kinetics of mobilization of PBSC and graft composition between biosimilar and G-CSF. This applies to the cell counts for nucleated cells (NC) as well as to CD34+ progenitor cells, Natural Killer (NK) and T cells. Neither the kinetics nor the ratio of these cell subsets differed between biosimilar and originator G-CSF.

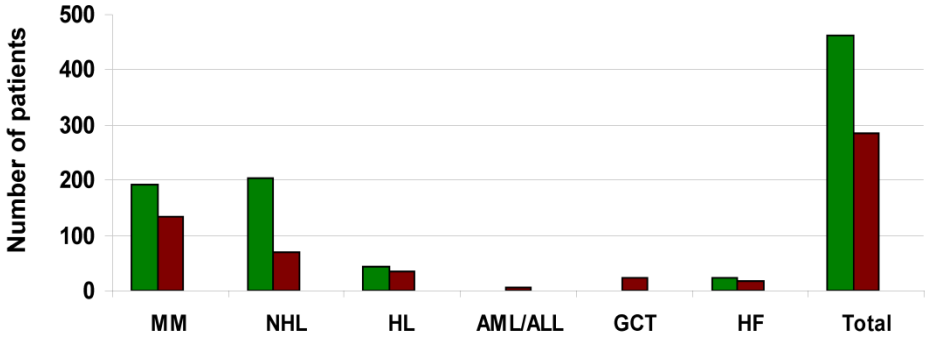

Figure 2. Patients undergoing autologous hematopoietic stem cell mobilization with Ratiograstim® / Tevagrastim® or Zarzio® (Sandoz). The y-axis shows the number of patients with multiple myeloma (MM), non-Hodgkin Lymphoma (NHL), Hodgkin's disease (HL), acute myeloid/lymphoblastic leukemia (AML/ALL), relapsed germinal cell tumor (GCT) or heart failure (HF) as well as the number of all patients (total) undergoing autologous hematopoietic stem cell mobilization with Ratiograstim® / Tevagrastim® [green bars] or Zarzio® (Sandoz) [brown bars].

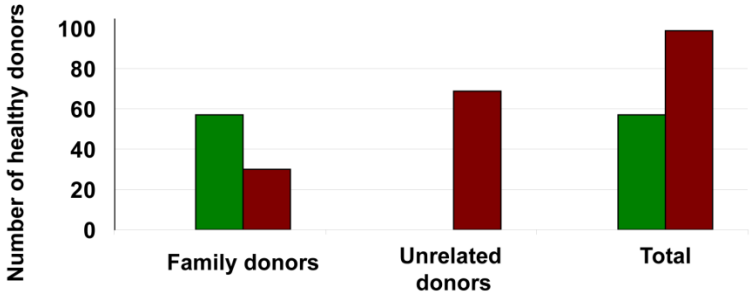

Figure 3. Healthy donors undergoing hematopoietic stem cell mobilization with Ratiograstim® / Tevagrastim® or Zarzio® (Sandoz) for allogeneic stem cell transplantation. The y-axis shows the number of donors, numbers for family donors vs. unrelated donors are specified as well as the number of all patients (total) undergoing hematopoietic stem cell mobilization with Ratiograstim® / Tevagrastim® [green bars] or Zarzio® (Sandoz) [brown bars] for allogeneic stem cell transplantation.

Table 1. Biosimilar G-CSF – Mode and dose for autologous hematopoietic stem cell mobilization

	References	Type of Transplant	Biosimilar used	Dose (µg/kg/day)	Disease category/number of patients					
					MM	NHL	HL	AML/ALL	GCT	HF
1	Publicover A. et al. (2013)[18]	Auto	Ratiograstim®/ Ref. G-CSF + Chemo	NA	76	65	13	-	-	-
2	Kirchner H. (2011)[19]	Auto	Ratiograstim® + Chemo	NA	7	11	1	-	1	-
3	Sammassimo S. et al. (2011)[20]	Auto *	Tevagrastim® + Chemo	300µg/day	6	8	1	-	-	-
4	Sever M. et al. (2012)[21]	Auto	Tevagrastim®	10	-	-	-	-	-	24
5	Andreola G. et al. (2012)[22]	Auto	Tevagrastim® + Pleri + Chemo	10	8	4	2	-	-	-
6	Lanza F. et al. (2012)[23]	Auto	Tevagrastim® + Pleri + Chemo	NA	81	105	25	-	-	-
7	Lazlo D. et al. (2012)[24]	Auto	Ref. G-CSF / Tevagrastim® + Pleri + Chemo	10	10	10	1	-	-	-
8	Morabito L. et al. (2012)[25]	Auto	Ref. G-CSF / Tevagrastim® + Pleri	10	3	1	-	-	-	-
Total					**191**	**204**	**43**	**-**	**1**	**24**
9	Czerw T. et al. (2012)[26]	Auto *	Zarzio®/ Ref. G-CSF	5	55	-	-	-	-	-
10	Dmoszynska A. et al. (2012)[27]	Auto	Zarzio®/ Ref. G-CSF + Chemo	10	23	14	13	4	-	-
11	Yafour N. et al. (2013)[28]	Auto	Zarzio® / Ref. G-CSF	NA	4	-	6	-	-	-

	References	Type of Transplant	Biosimilar used	Dose (µg/kg/ day)	Disease category/number of patients					
					MM	NHL	HL	AML / ALL	GCT	HF
12	Kotwica K. et al. (2012)[29]	Auto *	Zarzio® + Chemo	NA	12	4	6	1	-	-
13	Gopcsa L. et al. (2013)[30]	Auto	Zarzio® + Chemo	NA	11	8	2	-	-	-
14	Ostuni A. et al. (2013)[31]	Auto	Zarzio® + Chemo	10	11	22	9	2 (1+1**)	-	-
15	Sever M. et al. (2013)[32]	Auto	Zarzio®	10	-	-	-	-	-	16
16	De Giorgi U. et al. (2012)[33]	Auto	Zarzio® + Chemo	NA	-	-	-	-	22	-
17	Lefrere F. et.al. (2011)[34]	Auto	Zarzio® + Chemo	5 -10	19	21	-	-	-	-
Total					**135**	**69**	**36**	**7**	**22**	**16**

Auto - Autologous mobilization; Auto*- Autologous transplantation; Pleri - Plerixafor; Ref. G-CSF – Reference G-CSF (Neupogen®, Amgen); Chemo- Chemotherapy; MM - Multiple Myeloma; NHL - Non Hodgkin Lymphoma; HL - Hodgkin's Lymphoma; AML / ALL - Acute Myeloid Leukemia / Acute Lymphoblastic Leukemia; ** - Acute Lymphoblastic Leukemia ; GCT- Relapsed Germ cell tumors; HF - Heart failure; NA - not available from abstract

Table 2. Biosimilar G-CSF for hematopoietic stem cell mobilization for allogeneic stem cell transplantation

	References	Type of Transplant	Biosimilar used	Dose (µg/kg/day)	Number of Healthy donors	
					Family Donors	Unrelated donors
1	Schmitt M. et al. (2013)[35]	Allogeneic	Ratiograstim®/ Ref. G-CSF	20	11	-
2	Nagler A. et al. (unpublished)	Allogeneic	Tevagrastim®	24	22	-
3	Nagler A. et al. (2013)[36]	Allogeneic	Tevagrastim®	10	24	-
Total					**57**	**-**
4	Antelo ML. et al. (2013)[37]	Allogeneic	Zarzio® / Ref. G-CSF	5	9	-
5	Becker PSA. et al. (2013)[38]	Allogeneic	Zarzio®	NA	-	69
6	Azar N. Et al. (2012)[39]	Allogeneic	Zarzio®	10	21	-
Total					**30**	**69**

Ref. G-CSF - Reference G-CSF (Neupogen®, Amgen); NA - not available from abstract

Table 3. Mobilization and engraftment data of patients undergoing autologous hematopoietic stem cell mobilization with biosimilar G-CSF

	References	No. of patients	No. of apheresis	$CD34^+$ cell count (X 10^6/kg body weight)	No. of $CD34^+$ cells/µl	Engraftment (Time till regeneration)			Side Effects
						Neutrophils	Platelets		
						>0.5 G/L	>20 G/L	>50 G/L	
1	Publicover A. et al. (2013)[18]	154	66% patients = 1 28% patients = 2 6% patients= 3 1% patients= 4 [Mean=1.4 (± 1.2)]	Median= 4.53 (range= 0.2 – 43.4) [Mean= 6.6 (±13.8)]	Median= 38 (range= 0 – 516)	Median= 13 days (range= 9 - 22 days) [Mean= 13 (± 6) days]	Median= 12 days (range= 7-35 days) [Mean= 13 (± 8) days]	NA	NA
2	Kirchner H. (2011)[19]	20	15 patients= 1 5 patients= 2	15 patients= 7.96 (range= 3.83 - 64.58) 5 patients= range= 2.72 to 13.65	NA	Median= 11 days (range= 9 -19 days)	NA	NA	Bone pain during regeneration phase
3	Sammassimo S. et al. (2011)[20]	15	NA	NA	NA	Median= 11 days (range= 7-13)	Median= 12 days (range= 7- 22)	NA	9/15- Febrile neutropenia
4	Sever M. et al. (2012)[21]	24	NA	NA	Median= 28.49 (range= 7.5-167.72)	NA	NA	NA	4/24- Mild muscle and bone pain
5	Andreola G. et al. (2012)[22]	14	75% patients = 1 25% patients =2	5.2 (range= 2.2 - 10.6)	Day 4: Median=16 (range= 3-42)	Median= 12 days (range= 9	Median= 13 days (range= 9	NA	Bone pain

	References	No. of patients	No. of apheresis	$CD34^+$ cell count (X 10^6/kg body weight)	No. of $CD34^+$ cells/µl	Engraftment (Time till regeneration)			Side Effects
						Neutrophils	Platelets		
						>0.5 G/L	>20 G/L	>50 G/L	
					Day 5: Median= 60 (range= 14 -138)*	-13 days)	-19 days)		
6	Lanza F. et al. (2012)[23]	211	NA	68% patients= ≥2.0	83% patients ≥20 *	NA	NA	NA	NA
7	Lazlo D. et al. (2012)[24]	21	Median= 1 (range =1-2)	Median= 4 (range= 2.2 - 10.6)	Day 5: Median= 52 (range= 10-138)*	NA	NA	NA	NA
8	Morabito L. et al. (2012)[25]	4	Median=1 (range =1-2)	Median= 5.6 (range= 2.4 - 8.4)	Median= 91 (range= 13-138)*	NA	NA	NA	NA
9	Czerw T. et al. (2012)[26]	55	NA	6.7±3	NA	Median= 12 days (range= 10-13)	NA	Median= 13 (range= 0-19)	9/55- Grade 3 or 4 Infection 3/55-Neutropenic fever
10	Dmoszynska A. et al. (2012)[27]	54	1	Median= 9.1 (range= 0-23)	Median= 62.0 (range= 2-394)	NA	NA	NA	9/54- Neutropenic fever 8/54- Bone pain
11	Yafour N. et al. (2013)[28]	10	Median= 1 (range = 1-2)	Median= 4.09 (range= 0.25 - 4.84)	NA	NA	NA	NA	3/10- Bone pain 3/10- Headache
12	Kotwica K. et al. (2012)[29]	23	NA	Mean±SD= 10.1±4.0	NA	Mean± SD= 13.0±4.0 days	Mean± SD= 16.1±4.4 days	NA	4/23- Neutropenic fever 1/23- Neutropenic enterocolitis 1/23- Sepsis
13	Gopcsa L. et al. (2013)[30]	21	1	Median=3 (range= 0.81 - 24.7)	NA	NA	NA	NA	NA
14	Ostuni A. et al. (2013)[31]	44	Mean= 1.45	Median= 4.3 (range= 0.8 - 6.2)	Median= 58.3 (range= 10 – 503.5)	Median= 12 days (range= 10-23)	Median= 14 days (range= 10-33)	NA	NA
15	Sever M. et al. (2013)[32]	16	NA	NA	Median= 32 (range= 16.94 - 189.76)	NA	NA	NA	NA
16	De Giorgi U. et al. (2012)[33]	22	NA	NA	NA	Median= 15 days	NA	NA	NA
17	Lefrere F. et.al. (2011)[34]	40	Median= 1 (range = 1-3)	Median= 5.50 (range= 1.1-20)	Median= 55.5 (range= 1-196)	Median= 14 days (range= 9-21)	Median= 12 days (range= 6-19)	NA	14/40- Bone pain and/or headache

* - After plerixafor administration, NA - not available from abstract

Table 4. Mobilization and engraftment data of healthy donors that underwent hematopoietic stem cell mobilization with biosimilar G-CSF for allogeneic stem cell transplantation

	References	No. of donors	No. of apheresis	$CD34^+$ cell count (X 10^6/kg body weight)	No. of $CD34^+$ cells/µl	Engraftment (Time till regeneration)			Side Effects
						Neutrophils	Platelets		
						>0.5 G/L	>20 G/L	>50 G/L	
1	Schmitt M. et al. (2013)[35]	11	1.45	Median= 4.4 (range= 2.0 -7.3)	Median= 65.8 (range= 19.3 to 114.6)	Median = 14 days (range= 11-20 days)	Median = 6 days (range= 0 - 8 days)	Median = 13 days (range= 11-46 days)	1/11 - Flu-like symptoms 1/11 - Back pain
2	Nagler A. et al. (unpublished)	22	21 donors = 1 1 donor = 2	9.44 ± 4.76	Median= 64 (range=18-193)	Median= 15 days (range= 11-20)	Median= 9 days (range= 8-14)	Median =12 days (range= 10-20)	Bone pain
3	Nagler A. et al. (2013) [36]	24	Mean=1.3; 19 donors = 1 4 donors = 2 1 donor = 3	10.2 (range=0.93-35.4)	NA	Median= 13 days (range= 10-21)	Median= 16 days (range= 12-33)	Median = 17 days (range= 12-33)	12/24 = mild arthralgia; 2/24 = Flu-like symptoms
4	Antelo ML. et al. (2013)[37]	9	Median=1 (range= 1-2)	Median= 7.2 (range= 4 - 9.2)	Median= 70.2x10^9/L (range= 24 -114)	NA	25 days	NA	9/9- Mild bone/ muscle pain
5	Becker PSA. et al. (2013)[38]	69	93% donors = 1 7% donors= 2	NA	Mean= 111/L (range= 34-284)	NA	NA	NA	62/69-Bone pain 1/69- Chest pain (SAE)
6	Azar N. et al. (2012)[39]	21	11 donors =1 9 donors = 2 1 donor = 3	Median= 6.0 (range= 2.6 - 9.2)	Median= 72 (range = 16 -145)	NA	NA	NA	8/21-Bone pain

NA - not available from abstract

7. The global use of biosimilar G-CSF for mobilization of progenitor cells in autologous and allogeneic stem cell transplantation centers

We have summarized the available data on the use of biosimilar G-CSF for mobilization of hematopoietic stem cells in patients with a range of hematopoietic malignancies for use in subsequent autologous stem cell transplantation and the mobilization in related and volunteer unrelated normal donors. Biosimilar G-CSF was used for mobilization in more than 900 individuals including patients with hematological malignancies, germ cell tumors and cardiac failure and normal family related (sibling) as well as unrelated volunteer donors from donor registries. Biosimilar G-CSF was found to be safe with limited and transient toxicity, good mobilization yield and transplantation outcomes equivalent to the originator filgrastim (Neupogen®).

Based on the available data in 904 individuals we may conclude that biosimilar G-CSF can be used to mobilize peripheral blood hematopoietic stem cells with equivalent efficiency to that of the originator G-CSF. No significant differences have been demonstrated between biosimilar G-CSF and Neupogen® for the key parameters measured for PBSCs harvest and for engraftment post transplantation as well as to the frequency of occurrence of side effects in donors of both autologous and allogeneic stem cells.

Importantly, published reports have indicated that there was no increase in toxicity or development of side effects either at the time of the mobilization or during follow-up (although still relatively short) using biosimilar G-CSF rather than the originator Filgrastim G-CSF. Pharmacovigilance data for Ratiograstim®/Tevagrastim® are now based on more than 100,000 patients (data on file) who received XM02 because of neutropenia after chemotherapy for a solid tumor, leukemia or lymphoma.[21, 22, 24, 40-46] All three biosimilar G-CSF products currently licensed in the European Union (EU) have similar safety profiles and were equal to originator G-CSF.[47] The increasing body of data summarizing the experience of using biosimilar G-CSF in patients with chemotherapy induced neutropenia and for the mobilization of autologous PBSC shows that biosimi-

lar G-CSF is safe and as effective in PBSC mobilization as the originator G-CSF. In addition, there is a small but significant and growing experience in the use of biosimilar G-CSF in the successful and safe mobilization of PBSC from matched related and unrelated volunteer donors.

8. Future directions

The possibility for functional differences between biosimilars and their originator products has led to the development of specific guidelines by the European Medicines Agency (EMA) specifying the minimum requirements for the approval of biosimilars. In the guidelines, the basic premise is that biosimilars must demonstrate comparable efficacy and safety to the originator product. The guidelines require evidences related to the pre-clinical pharmacodynamics and toxicity, clinical pharmacokinetic and pharmacodynamic data and clinical efficacy (phase III) studies. The EMA recommended that if the efficacy of G-CSF is demonstrated in the setting of chemotherapy induced neutropenia, then extrapolation to other indications is allowed. Clinical safety data should be collected for a minimum of six months and the importance of ongoing pharmacovigilance is also stressed.

9. Health economy aspects

Use of a biosimilar G-CSF has significant cost advantages for a transplant unit.[18] When first introduced in 2008, biosimilars were approximately 15% cheaper than the originator. Today the price of biosimilars has been reduced rapidly, up to 80% lower in cost.[18] Thus, the use of biosimilar G-CSF is cost-effective strategy permitting a reduction of cost compared with the use of originator G-CSF. The savings can be re-invested in other services.[48]

An important concern frequently raised regarding the use of biosimilars is the potential for immunogenicity. Any protein used as a drug has the potential to cause immunogenicity. In a thorough literature search we performed we found only very limited data relating to immunogenicity for any type of G-CSF.[16] In this regard, there are some published data suggesting that G-CSF is non-immunogenic.[49] Conversely, anti-G-CSF antibodies were found in 15/135 healthy individuals who had never been exposed to G-CSF.[50] Data submitted to the EMA found no significant difference between biosimilar G-CSF (Nivestim®, Hospira) and the reference G-CSF Neupogen® in terms of immunogenicity. Continuous long term follow-ups in very large cohorts of healthy donors are obviously needed for the evaluation of immunogenicity, a still rare but potentially important side effect to be ruled out.

10. Conclusions

This report summarizes the currently available experience using biosimilar G-CSF for stem cell mobilization and may help to dispel some of the concerns appropriately raised regarding their use in this clinical setting,[4-8] especially in healthy related donors and unrelated volunteer donors. As healthy donors gain no personal benefit from the procedure, absolute assurance of no harm to them is mandatory. Correctly detailing these concerns a recent review regarding the use of biosimilar G-CSF, in healthy donors, suggested that safety data can only be obtained by performing an adequate number of stem cell mobilization procedures and conducting long-term follow up in patients undergoing allogeneic stem cell transplantation.[16] The parameters to be analyzed were not specified. Currently both the WMDA and EBMT do not advise the use of a biosimilar G-CSF in the healthy donor setting unless in the context of clinical trials where both patients and donors give informed consent. This review analyses in retrospective more than 900 patients and healthy donors that have been mobilized with biosimilar G-CSF for both autologous and allogeneic transplantations and to our knowledge all data published at present have shown equivalence for biosimilar G-CSF when used for stem cell mobilization. Our study is not a randomized study but a summary of data from various institutions possibly involving different protocols including the use of variable doses of originator/biosimilar G-CSF. Biosimilar G-CSF products were approved by the EMA in 2008 and have been licensed only in the last few years. Therefore long-term safety for both donor and recipient of the graft can be only evaluated over the forthcoming years. Indeed, long-term follow-up data will be collected in ongoing studies.

In summary, we present the published experience for the use of biosimilar G-CSFs in more than 900 patients and normal family related and volunteer unrelated donors. The toxicity profile, PBSC yield and efficacy seem equivalent to historical data with the reference G-CSF filgrastim. Until results from multi-center randomized clinical trials that directly compare biosimilar G-CSF with the originator G-CSF are reported, it is important to collect and summarize all of the available clinical experience in order to allow the transplant community to make informed decisions regarding the choice of G-CSF.

Competing Interests

AS, MS, AP, KHO, AN received travel grants. AN, KHO and MS received research grants and speaker's honoraria from TEVA. MG received speaker's and consultant's honoraria from TEVA. AP re-

ceived an unrestricted educational grant from TEVA Ltd. MS received speaker's honoraria from AMGEN Ltd. JM, LW, PT and RK declare no conflict of interest.

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