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Concerns about the use of biosimilar granulocyte colony-stimulating factors for the mobilization of stem cells in normal donors: position of the World Marrow Donor Association

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The World Health Organization (WHO) defines biosimilars or Similar Biotherapeutic Products (SBPs) as "a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product (RBP)".[1] As the patents for several of the RBP have recently expired, there has been a surge of interest in developing SBP to broaden access to these drugs through increased global availability and reduced cost. However, manufacturing processes for RBP remain proprietary and, therefore, SBP are manufactured using separately developed and similarly proprietary processes. Thus, despite demonstration of similar efficacy for primary licensing indications, there may be differences in their ultimate clinical efficacy, adverse event profile and immunogenicity. Because of these possible differences, late-effects may also vary.

Two 'branded' versions (RBP) of recombinant G-CSF are available internationally: Granocyte (lenograstim, Chugai, Tokyo, Japan) and Neupogen (filgrastim, Amgen, Vienna, Austria). Their licensed indications include:

reducing the duration of post-chemotherapy (or transplant) neutropenia, congenital neutropenia, cyclical neutropenia, neutropenia associated with HIV, and the mobilization of peripheral blood stem cells (PBSC) for transplantation in patients and healthy donors; but these differ according to national regulations. Both agents are licensed for mobilization of HSC in normal donors in the European Union (EU). Although Neupogen (but not lenograstim) is routinely used for normal donor mobilization in the USA, this is not one of the licensed indications in the product insert and, in view of this, the US Food and Drug Administration (FDA) continues to require close study and oversight of long-term safety.

Prior to the availability of G-CSF, donors could only donate bone marrow. Trials investigating the use of RBP G-CSF in related donors began in the early 1990s, followed by study and data collection in unrelated donors (UD) beginning in 1999. Over the last ten years there has been a marked shift from the donation of bone marrow to PBSC, due largely to donor preference. In 2010, 9,248 unrelated donors donated G-CSF mobilized PBSC (WMDA annual report, *http://www.worldmarrow.org/*). However, in some countries (e.g. the UK) the introduction of G-CSF for UD HSC mobilization was delayed by donor registries due to ethical considerations around the use of a drug in healthy individuals which results in no physical benefit to them. Indeed, some countries have only recently allowed UDs to donate PBSC. The World Marrow Donor Association (WMDA) is an international organization which fosters collaboration to facilitate the exchange of high quality HSC for clinical transplantation and to promote the interests of donors (*http://www.worldmarrow.org/*). The WMDA maintains a database of serious adverse events affecting stem cell donors or the products they donate which all WMDA accredited registries are expected to report to. This global approach is necessary to capture rare adverse events related to G-CSF (e.g. splenic rupture, anaphylaxis) and to recognize trends, as it is likely that very large numbers of donors need to be followed-up for prolonged periods to recognize these low incidence events. Additional information on donor events is available from the European Group for Blood and Marrow Transplantation (EBMT) and several large donor registries such as the German donor registries (ZKRD/DKMS) and National Marrow Donor Program (NMDP) that have published long-term follow-up data on stem cell donor outcomes.[2-4]

Two publications from the mid-90s[5,6] raised concerns about the potential for short course G-CSF to induce chromosomal damage in normal donors which could then predispose to the development of malignancies. The WMDA and several experts in the field produced guidance at that time to indicate that there was insufficient evidence for an increased risk of malignancy in normal donors given G-CSF, and it was not, therefore, recommended to halt the donation of GCSF-mobilized PBSC from UD.[7-10] Two registry based laboratory studies are currently being performed to investigate these claims further. Thus far the studies have shown no increase in chromosomal abnormalities in PBSC donors compared to bone marrow donors or non-donor healthy controls (D Confer and E Nacheva, personal communications, 2011). It is unknown whether the results of these costly studies can be extrapolated to biosimilars.

Recently, a number of biosimilar G-CSF products have become available in many countries. Based on cost considerations, there may be pressure brought to bear on health care professionals (HCP) to prescribe a biosimilar drug in place of the originator agent (RBP). While it may be considered reasonable to do so in a number of settings, many HCP caring for normal donors have raised concerns about the use of these agents with very short follow up and minimal data in the normal donor setting. In 2008, the EBMT sent a letter to all of its centers stating that SBP should not be used for the mobilization of HSC in normal donors (related or unrelated). This position was supported by the WMDA.

The aim of this paper is to review the basis of regulatory approval of the biosimilar G-CSF agents, including the available safety data, with reference to the indication for mobilization of PBSC in normal donors and to make recommendations based on these. It is not the intention of this paper to review the entire field of biosimilars for which other comprehensive reviews are already available.[11]

Regulations

To properly assess the safety and efficacy of emerging products, international, regional and national guidelines and policies for the regulatory approval of such agents are necessary.

In the EU, the European Medicines Agency (EMA) produced a guideline in 2006[12] which lays down the requirements for a manufacturer to present to the EMA to obtain a license for an SBP. Unlike chemically derived products (e.g. generics), biosimilars are highly complex and often large protein complexes which differ in their manufacturing processes from each other and from the originator products (RBP). Indeed, because manufacturing details are proprietary, these processes generally cannot be duplicated and even minor differences in manufacture may result in variations of clinical relevance in important parameters, such as the three-dimensional structure, the amount of acido-basic variants and post-translational modifications, e.g. glycosylation profile.[13] Therefore, the main requirement for the manufacturer is to prove 'comparability' with a licensed product. The regulations require the SBP to be compared to an originator product, which must already be licensed on the basis of a full registration dossier. The comparability exercise includes non-clinical and clinical requirements.

Non-clinical studies must be both *in vitro* and *in vivo* and include toxicity analysis as well as immune response. Mutagenicity and carcinogenicity studies are not normally required.[12] Clinical pharmacokinetic (PK), pharmacodynamic (PD) and efficacy studies are required. In addition, the guideline addresses clinical safety, pharmacovigilance (including the need for applicants to present an ongoing risk management and pharmocovigilance plan in line with EU legislation and guidance) and immunogenicity. Immunogenicity must always be investigated in human subjects. These studies generally include antibody testing, characterization of the immune response, and correlation between antibodies and PK/PD. The risk of immunogenicity is also tested for various therapeutic indications.

Other national and international bodies have developed

or are developing regulations and guidelines in this area. In 2009, the WHO produced guidelines for the evaluation of SBPs,[1] with a view to achieving global harmony in regulations. These could be accepted *in toto* or adapted to the individual needs of each National Regulatory Authority (NRA). It is then the responsibility of the NRA to have a regulatory framework for licensing SBPs and, in addition, to set up post-marketing surveillance where necessary. The FDA is in the early stages of deliberation about issuing regulations and/or guidelines in this area (Diane Maloney, personal communication, 2011).

European Union regulations specific to G-CSF

In 2006, the EMA published an annex to the previous guideline which deals specifically with recombinant G-CSF containing products.[14] As in all the regulations, demonstration of comparability is the main requirement. Clinical PK/PD studies are required and these analyses should be made in healthy volunteers and require a single dose crossover study using both subcutaneous and intravenous administration. The EMA annex guideline recommends that in order to assess the clinical efficacy of SBPs for G-CSF, the product must be shown to be comparable to RBP for the indication of "reduction in the duration of neutropenia following chemotherapy". The primary outcome in the model is the duration of neutropenia, with secondary endpoints of the incidence of febrile neutropenia, infections and cumulative G-CSF dose. As the mechanism of action for all of the licensed indications for RBP are believed to be the same, the guidance allows for extrapolation of efficacy to all other indications if the clinical comparability in the above model is proven. Clinical safety and pharmacovigilance are mentioned in the context of the above clinical trials (with at least six months follow up for patients) but no mention is made of normal subjects in this part of the document. While the possibility of rare serious adverse events and immunogenecity is touched upon in terms of ongoing pharmacovigilance, again, the document does not mention normal subjects. Individuals being mobilized with G-CSF are mentioned in the pharmacovigilance plan; however, only in the context of monitoring for lack of efficacy.

Biosimilar G-CSF agents licensed in the EU

The first biosimilar G-CSF was licensed by the EMA in 2008, and there are currently three biosimilar G-CSF products licensed for use in the EU. These are known by various names (Table 1): 1) Ratiograstim/Tevagrastim/Biograstim (SICOR Biotech UAB, Vilnius, Lithuania); 2) Zarzio/Filgrastim Hexal (Sandoz GmbH, Kundl, Austria.); and 3) Nivestim/Pliva/Mayne filgrastim (Hospira, Zagreb d.o.o., Croatia).

It is recognized that biosimilars differ in a number of aspects from the branded drugs (Table 1). Human G-CSF is a single polypeptide chain protein of 174 amino acids with O-glycosylation at one threonine residue. Lenograstim is also glycosylated, of the same length and is produced in Chinese hamster ovary cells. All of the Filgrastim products (branded and biosimilar) are *E. coli* derived, non-glycosylat-

Table 1. Characteristics of various G-CSF agents.

Feature	Lenograstim (Chugai)	Filgrastim (Amgen)	Ratiograstim/Tevagrastim/ Biograstim XM02 (SICOR Biotech UAB, Vilnius, Lithuania)	Zarzio/Filgrastim Hexal (Sandoz GmbH, Kundl, Austria)	Nivestim/Pliva/Mayne filgrastim (Hospira, Zagreb d.o.o., Croatia)
When licensed (by EMA)	1993	1991	15/09/2008	06/02/2009	18/03/2010
Licensed indications	CIN, post BMT, mobilization	CIN, post BMT, mobilization, congenital neutropenia, cyclical neutropenia, HIV	CIN, post BMT, mobilization, congenital neutropenia, cyclical neutropenia, HIV	CIN, post BMT, mobilization, congenital neutropenia, cyclical neutropenia, HIV	CIN, post BMT, mobilization, congenital neutropenia, cyclical neutropenia, HIV
Characteristics/ manufacturing process	Glysosylated recombinant human G-CSF derived in Chinese hamster ovary cells consisting of 174 amino acids	Non-glycosylated recombinant methionyl human G-CSF expressed in *E. coli* and consisting of 175 amino acids	Non-glycosylated recombinant methionyl human G-CSF expressed in *E. coli* and consisting of 175 amino acids	Non-glycosylated recombinant methionyl human G-CSF expressed in *E. coli* and consisting of 175 amino acids	Non-glycosylated recombinant methionyl human G-CSF expressed in *E. coli* and consisting of 175 amino acids
Product volumes/doses	33.3 MIU/1.0 mL 13.4 MIU/1.0 mL	30 MIU/0.5 mL 48 MIU/0.5 mL	30 MIU/0.5 mL (300 μg) 48 MIU/0.8 mL (480 μg) Differences in the concentration of polysorbate and in the pH value	30MU (300 μg/0.5 mL) 48 MU (480 μg/0.5 mL) The buffer system is glutamate (Neupogen uses acetate)	120 μg/0.2 mL 300 μg/0.5 mL 480 μg/0.5 mL
Stability	24 months at room temperature	24 months at 2-8°C	24 months at 5±3°C.	30 months at 5±3°C	30 months at 2-8°C for the 480 μg/0.5mL presentation 24 months at 2-8°C for the 300 μg/0.5mL and 120 μg/0.2 mL presentations

Table 2. Clinical studies in normal donors.

Feature	Ratiograstim/Tevagrastim/ Biograstim XM02 (SICOR Biotech UAB, Vilnius, Lithuania)	Zarzio/Filgrastim Hexal (Sandoz GmbH, Kundl, Austria.)	Nivestim/Pliva/Mayne filgrastim (Hospira, Zagreb d.o.o, Croatia,)
Type of study	Phase 1 (PK/PD)	Phase 1 (PK/PD)	Phase 1 (PK/PD)
Study outlines	**XM02-01-LT** 56 healthy male volunteers randomized to receive a single dose of biosimilar *versus* comparator at either 5 μg/kg or 10 μg/kg subcutaneously. **XM02-05-DE** 144 healthy male and female volunteers randomized to receive a single dose of biosimilar *versus* comparator at either 5 μg/kg or 10 μg/kg subcutaneously or intravenously (4 groups).	**EP06-101.** 40 healthy volunteers in a randomized, double-blind, 2-way crossover using multiple s.c doses of drug at 10 μg/kg/day **EP06-102.** 26 healthy volunteers in a randomized, double-blind, 2-way crossover using a single i.v. dose of 5 μg/kg/day **EP06-103.** 2x28 healthy volunteers in a randomized, double-blind, 2-way crossover using multiple s.c doses in two dose groups of 2.5 μg/kg/day and 5ug/kg/day **EP06-105.** 24 healthy volunteers in a randomized, double-blind, 2-way crossover using a single s.c dose of 1 μg/kg	**GCF061.** 44 healthy volunteers randomized to a single dose of 10 μg/kg IV or s.c in a 2-way crossover study. **GCF062.** 48 healthy volunteers in a randomized, 2-way crossover, multiple-dose (a total of 5 doses at 5 μg/kg or 10 μg/kg s.c.) study
Comparator	Neupogen Filgrastim (Amgen)	Neupogen Filgrastim (Amgen)	Neupogen Filgrastim (Amgen)
Study objectives	Primary: PK (05) and PD (01) Secondary: PK/PD	Primary: PK (101/102) or PD (103/105) bioequivalence Secondary: PK (103/105), PD (101/102), safety	Primary: PK (061) or PD (062) bioequivalence Secondary: PK (062), safety (062)
Results of study	Equivalence for all the study outcomes in both studies (except for non-log transformed variable ANCtmax in the 10 μg/kg dose in the first study)	Small differences observed in the pharmacokinetic profile of the study drug were expected not to translate into significant differences in the PD response	No important differences in bioequivalence found
Safety in studies	No specific data reported	Adverse events in the 146 healthy volunteers were consistent with those expected with Neupogen and were similar with both products Ongoing safety follow up will be performed on healthy subjects included in one of the phase I studies and in a post-marketing study following-up healthy stem cell donors undergoing mobilization (5 years after mobilization)	Equally numbers of expected adverse events reported in normal donors with both products. Two severe adverse events reported, one with each product Bone pain and myalgia were more common in the Nivestim group
Immunogenicity	No data reported in this study group	Samples for evaluation of antibodies were taken in 3 of the studies. None of the volunteers tested developed anti-rhG-CSF binding antibodies	In the GCF062 study, 2 subjects gave a positive antibody response following treatment. Three patients in the Nivestim treatment group (1.6%) had one or more post-treatment samples with a borderline positive result. NAbs were not found in 3 samples having borderline positive responses in the anti-G-CSF antibody screening
Additional conclusion of studies from licensing body	"Screening for rare immunological adverse effects in the post-marketing setting is difficult. In principle, it must be driven by reported adverse events that have a potential immunological origin. These events should be investigated for immunogenicity as agreed in the Risk Management Plan. A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product. No additional risk minimisation activities were required beyond those included in the product information"	"A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product"	"Follow-up measures for determining the possible development of immunogenicity should be implemented as there is not enough data to demonstrate sensitivity and detection of anti-G-CSF antibodies. Additional long-term safety and immunogenicity data will be collected in the post-marketing phase"

ed products of 175 amino acids in length. Most countries/centers use both RBPs, and while they differ in their overall licensed indications, and there is some evidence to show that differences in activity and action are found,[15,16] they appear to be of equal clinical efficacy.

All of the licensed biosimilars have used Neupogen (Amgen filgrastim) as the comparator and, based on the EMA requirements outlined above, have been successful in obtaining a license for all of the same indications as the RBP.

Evidence for efficacy in mobilization of HSC

For each of the biosimilar drugs phase I studies (PK/PD) have been carried out in healthy volunteers, representing a total of 438 normal individuals (Table 2). In all cases, the primary PK/PD objectives were met. These included an assessment of the kinetics of $CD34^+$ cell counts in the peripheral blood which in all cases was reported to be equivalent to the comparator. However, the actual success of these agents at mobilizing HSC (the number of CD34 cells harvested and the subsequent successful engraftment of the patient) is only extrapolated, as these aspects have not been tested. This may raise concerns for the allogeneic transplant recipient, particularly if the mobilized product differs from that expected with the RBP.

Two of the three agents included safety as a secondary objective in one or more of their studies (Table 2). Where it was analyzed, the conclusions are that the adverse events associated with the study drug were expected (i.e. known adverse effects associated with the comparator drug) and similar in frequency to the comparator drug. No specific safety data are reported on the SICOR product. It was noted that there was increased bone pain and myalgia with the Hospira product *versus* the comparator. This has been included in the product specifications.

It is important to emphasize that all of the adverse event data reported represents immediate or short-term effects, and no long-term data are currently available. Long-term follow up is planned for one of the agents (Sandoz) which will include some of the healthy volunteers included in the phase I studies, as well as a post-marketing study reporting adverse events at 5-years post mobilization. It is worth remembering that there are a number of rare, but known, severe adverse events related to branded G-CSF (e.g. anaphlyaxis, splenic rupture). Knowing whether these and other possible severe adverse events could occur with SBPs will require larger numbers of donors to be tested and longer follow up.

A further concern with normal donors, and one which is only partially addressed, is the potential for immunogenicity and antibody formation. This is of particular concern with biosimilar agents. Based on the phase I studies of the biosimilar agents tested to date (as well as the animal studies) there is no increase in the incidence of antibodies compared to the comparator (Table 1). These studies have, however, only been performed in a very small number of healthy volunteers and thus it is possible that altered immunogenicity could be undetected. Based on this concern, the Committee for Medicinal Products for Human Use (CHMP), which is responsible for preparing the EMA's opinions on all questions concerning medicines for human use, recommended for Nivestim that "follow-up measures with regards to immunogenicity should be implemented in the event of a possibility of low-level immunogenicity not detected by the analytical method used".

Clinical use of biosimilar G-CSF for mobilization

There are two published reports showing efficacy of biosimilar G-CSF in the mobilization of stem cells in the autologous setting. One study[17] compared the outcome for 29 patients mobilized using Ratiograstim to 34 historical controls using branded filgrastim. GCSF mobilization was performed along with chemotherapy for patients with myeloma and lymphoproliferative diseases. The study showed no difference in the time from the start of injections to apheresis or the number of apheresis sessions required. A second study reports the outcome of mobilization in 414 patients using Neutromax, a biosimilar approved in Argentina, but not in the EU, in patients with myeloma and lymphoma.[18] Neutromax was used for mobilization as well as post transplant to accelerate neutrophil recovery. Although there is no direct comparision, the results for $CD34^+$ cell harvesting and engraftment post transplant are similar to those in the published literature. To our knowledge, no data in normal donor mobilization have been published.

Conclusions and recommendations

In conclusion, the license for G-CSF to be used for mobilization of stem cells has been granted to several biosimilar agents in Europe on the basis of extrapolated data. Although healthy volunteers have received these drugs, this has only been in the context of phase I pharmacodynamic and pharmacokinetic studies. Short-term adverse events were only assessed in a small number of these volunteers and long-term follow-up studies have not been published. Limited data are now available for the efficacy of biosimar G-CSF for mobilization in the autologous setting (patients) but not in normal donors.

As the efficacy for mobilization is extrapolated, with little safety analysis and no long-term follow up, the WMDA recommends that biosimilars not be used for mobilization in normal donors unless the donor is followed on a study looking at this question with both the recipient and the donor providing appropriate consent. Only when comprehensive data to confirm long-term safety and efficacy is available should use of G-CSF biosimilars be considered routine.

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Editorial note: *this article is a position paper on the use of G-CSF biosimilars. As stated by Kassirer and Angell [Kassirer JP, Angell M. Financial conflicts of interest in biomedical research. N Engl J Med. 1993 Aug 19;329(8):570-1] "unlike reports of original research, these articles represent the judgment of their authors, based on their evaluation of the literature. What studies they select to discuss and their analysis of them are necessarily subjective". In accordance with Haematologica policy, in the process of manuscript submission the authors of this paper have attested that it has not*

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