	The use of biosimilar rHu-GCSF			
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The use of biosimilar recombinant human Granulocyte Colony Stimulating Factors for the mobilisation of haematopoietic stem cells in volunteer unrelated donors.

A statement of the Medical Working Group of the World Marrow Donor Association.

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Introduction

Recombinant human G-CSF (rHu-GCSF) Granulocyte Colony Stimulating Factor (GCSF) is routinely used for the mobilisation of haematopoietic stem cells (HSC) from the bone marrow into the peripheral blood for collection by apheresis for transplantation. The Amgen originator filgrastim (Neupogen) has expired patent protection. Copies of biological agents that have expired patent protection and that are similar in terms of quality, safety and efficacy to the previously licensed reference product are available. For these agents, different regulatory processes apply compared to generic drugs. Filgrastim biosimilars have been shown to have high similarity with the reference product (e.g. treatment of neutropenia, mobilisation of CD34-pos. cells).

A statement regarding the use of biosimilars has recently been published and urges a degree of caution with the statement that "The reliability of biosimilars should not be compromised by our urgent need to provide access to treatments. Quality comes first".[1]

In 2012 the WMDA published a statement on the use of biosimilar filgrastim states:
"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."

This formed the basis of WMDA Document 2012 (20121010-WGME-GCSF) which stated that "These large studies on donors were performed using the types of GCSF called Neupogen (filgrastim, Amgen) or Granocyte (lenograstim, Chugai). Other types of GCSF called biosimilars (or follow-on biologics) and other medicines used for mobilization of stem cells, such as GM-CSF or plerixafor, have differences in them that may lead to differences in early and late side effects compared with Neupogen or Granocyte. Further study of how donors react to all of these agents will help establish if there are any positive or negative long-term effects from receiving GCSF".

Update 2017 – results of global survey

In 2017, the WMDA member organisations were invited to participate in a survey on the use of biosimilar mobilising agents in unrelated donors to establish patterns of practice based on a growing body of evidence. The survey aimed to determine:

- How agents for mobilising of CD34-pos. cells were being used for unrelated donors.
- Whether stem cell donor registries had changed or were planning to change mobilising agent for their unrelated donors.
- The reasons for a change in mobilising agents.

Forty-two organisations that were surveyed responded. Data were sought with regard to unrelated donors and where available, transplant centre protocols for family-member donors as well.

Unrelated donors

The majority of the organisations (33) used Neupogen, nine (9) used Granocyte, eight (8) used one of five available biosimilar filgrastims (Nivestim, Neukine, Granulokine, Grafeel, Zarzio) and two (2) used either Neupogen or Granocyte.

Related donors

Of 33 responding organisations, 18 used Neupogen, four (4) Granocyte, nine (9) a biosimilar filgrastim, two (2) either filgrastim or lenograstim and one centre used plerixafor after an unspecified rHu-GCSF.

Change in practice after 2013

Thirty-one (31) organisations had not changed practice between 2013 and 2017. Eleven organisations had change their practice: ten organisations from a filgrastim agent to another filgrastim agent, one organisation from filgrastim to lenograstim.

Planned changes in practice

Eighteen organisations are planning to change mobilising agent, the majority (11) because of price. Other factors stated included efficacy, safety, quality and accessibility.

Evidence base

An informal review of published literature as of August 2017 identified that biosimilar filgrastims have been studied in at least 553 patients and 1,200 donors[2-8].

Based on a recent survey of forty-two organisations, and a review of the literature, the 2012 WMDA recommendation on the use of biosimilar filgrastims has been revised as follows:

- Stem cell donor registries or their affiliated organisations may use filgrastim biosimilars, provided that they are approved by national and/or regional agencies *for CD34-positive cell mobilisation in healthy donors* or equivalent wording. Donors on approved research protocols are exempt from this restriction.
- If a new filgrastim biosimilar is used by a registry or its affiliated organisation, the registry should have a policy to continue to follow donors to identify any adverse effect possibly caused by the biosimilar.
- Stem cell donor registries must report adverse events and reactions (SEAR and SPEAR) as per usual prospective, in addition registries MUST record the specific brand of mobilising agent in the S(P)EAR report.

Currently, WMDA cannot recommend the routine use of plerixafor or similar mobilizing agents, but recognises that there may be situations where their use is appropriate per individual situations[9,10].

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