The role of biosimilar granulocyte colony stimulating factor (GCSF) Zarzio for progenitor cell mobilization and the treatment of therapy-induced neutropenia in adult hematopoietic stem cell transplantation

by Cherie C. Severson

ABSTRACT
Originator GCSF (Neupogen) has been used to mobilize progenitor stem cells and treat therapy-induced neutropenia in Canadian stem cell transplant settings for years. Although its benefit is not in question, viable alternatives are available. Biosimilar GCSF (Zarzio) is widely in use in Europe since 2009 and was recently approved in the U.S. for the same five indications as Neupogen. Zarzio is reported as safe, equally efficacious, more accessible and cost effective without negatively impacting patient outcomes. This paper summarizes the supporting evidence.

Key words: biosimilar GCSF, Zarzio, autologous transplant, mobilization, neutropenia, cost

As Canadian cancer statistics continue to rise and cancer facilities overflow with patients, the need to investigate novel approaches and cost-effective strategies is required (Canadian Cancer Society’s Advisory Committee [CCSAC], 2015). Canadian hematopoietic stem cell transplant (HCT) programs grapple with budgetary restraints on a daily basis. Measures that facilitate the achievement of budgetary goals are needed to ensure patients receive affordable health care, and HCT programs continue to thrive. One such cost-effective strategy, which can achieve both safety and efficacy while still showing a cost benefit, is the use of a biosimilar granulocyte colony stimulating factor (GCSF), also known as Zarzio (Gascon et al., 2013; Ianotto et al., 2014). The purpose of this manuscript is to introduce biosimilar Zarzio as a cost-effective alternative to the originator Neupogen and compare the two in relation to safety, efficacy, and cost in the setting of hematopoietic stem cell transplant.

Biosimilars are biologics with comparable safety, efficacy and quality as the originator GCSF known as Neupogen (Bonig, Becker, Schwebig & Turner, 2015; Gascon, 2012; Remenyi, et al., 2014). As they are produced by living organisms, biosimilar agents are stringently evaluated on a case-by-case basis prior to approval by regulatory bodies such as the European Medicines Agency, the US Food and Drug Administration (FDA), and the Australian Therapeutic Goods Administration (Bonig et al., 2015; Gascon, 2012; Lefrere et al., 2011). These regulatory bodies provide approval based on robust comparability exercises demonstrating similarity with the originator GCSF Neupogen (Bonig et al., 2015; Gascon, 2012; Lefrere et al., 2011). Similarity is demonstrated through biochemical characterization (i.e., purity, chemical identity, protein structure and receptor on/off kinetics), biologic activity and clinical similarity for at least one indication (Bonig et al., 2015). Biosimilars cannot automatically claim all indications of the originator product (Bonig et al., 2015). They must demonstrate that the mechanism of action and the receptor involved to be identical to those of the originator (Bonig et al., 2015). In this case, both Neupogen and Zarzio have the same mechanism of action, which is direct stimulation of the bone marrow cells through the GCSF surface receptor (Gascon et al., 2013). Bioequivalence of Zarzio and Neupogen was demonstrated in four comparative phase I studies where 146 healthy volunteers were administered either product (Gascon et al., 2013). In tests for efficacy using absolute neutrophil count (ANC) and CD34+ cell count as surrogate markers, both products show comparable effect (Gascon, 2012; Gascon et al., 2013).

Zarzio was initially approved in the European market in 2009. In 2015, it was approved by the FDA for use in the U.S. for the same five indications as its originator Neupogen (Gascon, 2012; Hamburg, 2015; McBride, 2015). These indications include patients with cancer who are receiving myelosuppressive or myeloablative chemotherapy, patients with acute myeloid leukemia receiving induction or consolidation chemotherapy, patients with cancer undergoing blood and marrow transplantation, patients undergoing autologous peripheral blood progenitor cell collection and therapy, and those with severe neutropenia (Hamburg, 2015; Lefrere et al., 2011). Pharmacokinetics and pharmacodynamics studies performed on biosimilar GCSF Zarzio are comparable to the originator GCSF Neupogen (Gascon et al., 2013; Lefrere et al., 2011). Overall, the safety profile is extremely similar to Neupogen with the most common adverse events being headache, bone pain, muscle aches, flu like symptoms, febrile neutropenia, and rash. Rare side effects include splenic rupture, acute

ABOUT THE AUTHOR
Cherie C. Severson, RN, MN, CON(C), BMTCN, Alberta Blood and Marrow Transplant Clinic, Tom Baker Cancer Centre, Calgary, AB

Email: oncnurs@live.com
respiratory distress syndrome, allergic reactions including anaphylaxis, fatal sickle cell crises, capillary leak syndrome, and thrombocytopenia (USA-FDA, 2015). The biosimilar GCSF Zarzio is reported to be as safe, equally efficacious, and more cost effective than the originator GCSF (Aapro, Cornes & Abraham, 2011; Gascon et al., 2013; Lefrere et al., 2011). A review of the pertinent trials regarding the use of biosimilar GCSF Zarzio in the setting of hematology and blood and marrow transplant is on the following pages (see Table 1).

### Table 1: Review of the trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Trial Design</th>
<th>Eligibility</th>
<th>Results</th>
<th>Adverse Events</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bassi et al., 2015</td>
<td>Single institution, retrospective study N=56 minus 1 Noted one patient died prior to engraftment because of disease progression</td>
<td>Male: 34 Female: 22 Median age 57 (r 23-71 years old) NHL: 44%, Myeloma: 44% Hodgkin’s: 12% 1st transplant: 89% Conditioning: Melphalan, BEAM-like regimen Thiotepa MEL All received daily biosimilars (Tevagastim (17) and Zarzio (39) at standard dose starting on day 5 with a median # of days in duration =7 (range 4-9d)</td>
<td>Median CD34+ cells infused 4.05x10^6/kg r (2.2-7.76x10^6/kg) Engraftment 55/56 Median time to neutrophil recovery is 10 (range 8-11 days) Median time to platelet recovery is 12 days (range 8-23 days)</td>
<td>Grade 2 bone pain, sporadic headache, febrile neutropenia lasting a median of 2 days=47% Mucositis post high dose conditioning Rare side effects include a fib, CHF, toxic hepatitis, and 2/55 with erythematous rash covering 50% of body surface No secondary malignancies</td>
<td>Biosimilar GCSF is effective and safe for facilitating bone marrow recovery in autologous HCT and costs less than the originator GCSF Neupogen</td>
</tr>
<tr>
<td>Schmitt et al., 2014</td>
<td>Multicentre analysis involving 904 adult patients with hematological malignancies and healthy donors who underwent stem cell mobilization using a biosimilar agent (Tevagastim or Zarzio)</td>
<td>Tevagastim 520 Zarzio 384 MM 326 NHL 273 HL and other disease including germ cell tumor and cardiac failure 79 Healthy donors 156</td>
<td>Median CD34+ cell count is 3-10.2X 10^6 / kg body weight (range 1-23X 10^6 /kg) The median number of apheresis collection is 1 with few patients undergoing 2 collections and even fewer undergoing 3</td>
<td>Headache, bone and muscle pain, flu like symptoms and mild fever. Rare reporting of neutropenic enterocolitis, grade 3 or 4 infection and sepsis are of note</td>
<td>Autologous No significant difference in the peripheral blood stem cell yield or toxicity profile compared with the historical data of the originator GCSF Neupogen Allogeneic To ensure the safety of healthy donors further long term data regarding biosimilar use in healthy donors is needed.</td>
</tr>
</tbody>
</table>

continued on page 445...
<table>
<thead>
<tr>
<th>Author</th>
<th>Trial Design</th>
<th>Eligibility</th>
<th>Results</th>
<th>Adverse Events</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remenyi et al., 2014</td>
<td>2 retrospective studies of observational design across 2 medical centres in Hungary. Study 1: Primary objective was to evaluate the safety and effectiveness of engraftment following treatment with Zarzio in Auto HCT. Study 2: primary objective: retrospective analysis of the efficacy and safety of biosimilar GCSF (Zarzio) following mobilization chemo in pt with lymphoid tumors.</td>
<td>Study 1: N=70 with hematological malignancies: MM 59%, NHL 27%, HL 14%. Median age 56y 60-40 M/F ratio. ECOG =/&lt;2. Adequate heart, liver and kidney function. Rituximab given to pts with NHL for in vivo purging. Neupogen 2x 5ug/kg admin 24 hr post last day mobilizing chemo. HD conditioning chemo regimens: melphalan, TBI/CYCLO/R or R-BEAM followed by Zarzio 5ug/kg/day beginning on day 1 post Auto. Study 2: Lymphoid malignancies. N=40. Median age 54y. 57.5%: 42.5% F/M ratio. ECOG =/&lt;2 with adequate heart, liver and kidney function. Diagnosis: MM 52.5%, NHL 40%, HL 7.5%. 34/40 pts mobilized with either Cyclo or R-DHAP followed by Zarzio. 4 failed to mobilize and needed Plerixafor.</td>
<td>Study 1: Median # of re-infused CD34+ cells 6.33 X 10⁶/kg. Time to ANC, WBC and PLT engraftment: 9days (r 8-11d), 10 days (r8-12d) and 10.5 days (r7-19d) respectively. Study 2: median time interval btw day1 of mobilizing chemo and first leukophereses: 12 days (r=9-27d). 40 successfully harvested for a total of 58 leukophereses procedure. Median apheresis procedures per pt 1.4 (r 1-2) Median # CD 34 cells harvested: 5.2X 10⁶ /kg (r 2.22-57.07 x 10⁶/kg). Median yield CD 34+ count 2.47X 10⁶ /kg.</td>
<td>Study 1: neutropenic fever &gt;38.0C (64%) related to CVC infection, pneumonia and perianal soft tissue infection. Mucositis grade 1-4: 78%, Diarrhea 58%, Toxicoderma 10% Engraftment syndrome: 13%. Poor graft function 1 Patient. No treatment related deaths before day 100 post Transplant. Study 2: No AE’s mentioned.</td>
<td>Auto transplant only: Study 1: Time to engraftment for WBC, ANC and PLTS are comparable between Biosimilar GCSF (Zarzio) and previous reports of Neupogen. No significant differences between biosimilar GCSF and originator GCSF in the median number of CD 34+ cells mobilized or in the number of GCSF injections and leukophereses procedures to harvest the target CD34+ cell dose. No major differences in safety profile with previous reports of Neupogen. Study 2: Chemotherapy in combination with Biosimilar GCSF enables successful PBSC mobilization and harvesting in the majority of patients (91%).</td>
</tr>
<tr>
<td>Gascon et al., 2013</td>
<td>Pooled analysis N=1302 patients Breast cancer 42% Lung cancer 16% Lymphoma/Leukemia 15% Other: prostate, bladder, myeloma, colorectal, endometrial and ovarian)=27% Febnile neutropenic risk &gt;20% 36% of 1302 Febnile neutropenic risk 10-20%=40% Febnile neutropenic risk &lt;10%=12% Unknown = 12%</td>
<td>Adult patients &gt;18y Confirmed diagnosis of cancer Received at least one cycle of chemotherapy with Zarzio Exclusion: Patients receiving Zarzio for the treatment of neutropenia (rather than prophylaxis) were excluded from the analysis.</td>
<td>An episode of febrile neutropenia N=29/1302=2.2% Severe grade 4 neutropenia N=104/1302=8.5% No risk of immunogenicity with Zarzio as no antibodies have been detected to date demonstrating no or low potential for an immunologic response.</td>
<td>Generally well tolerated Bone pain (8%).</td>
<td>Overall Zarzio is effective in the prevention of chemotherapy-induced neutropenia in a variety of different cancers treated in clinical practice settings.</td>
</tr>
</tbody>
</table>

continued on page 446...
**FEATURES/R Ub RiqUES**

<table>
<thead>
<tr>
<th>Author</th>
<th>Trial Design</th>
<th>Eligibility</th>
<th>Results</th>
<th>Adverse Events</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| Verpoort & Mohler, 2012 | Single centre retrospective review from a large community oncology practice in Germany | Biosimilar group N=77  
Originator group N=25 | Biosimilar GCSF  
Febrile neutropenia=1 pt  
Dose reductions=5 pts (6.5%)  
Dose discontinuation=2 pts (2.5%)  
Originator GCSF  
Febrile neutropenia=1 pt  
Dose reductions=2 pts (8%)  
Dose discontinuation=2 pts (8%). | No unexpected safety findings were observed with the use of biosimilar GCSF. However since this was not a prospective study, adverse events were not recorded | Biosimilar GCSF was effective and prevented dose reductions/discontinuations in the majority of patients. It is considered comparable to the originator Neupogen for the prevention of neutropenia in patients with cancer in routine clinical practice |
| Adult >18y  
Median age 67y (range 20-83y)  
Female 64%  
Male 36%  
Primary prophylaxis =52% of patients  
Secondary prophylaxis=48% of patients  
Originator GCSF  
Median age 64y (range 31-81y)  
Female 64%  
Male 36%  
Primary prophylaxis =36% of patients  | All patients had a confirmed diagnosis of solid tumor (breast, colon) cancer or hematologic malignancy (lymphoma) and received biosimilar GCSF during at least one cycle of combination chemotherapy  
Patients were stratified by risk of febrile neutropenia based on the chemotherapy regimen (>20%, 10-20%, <10%) |

**COST**

Biosimilar products are used widely across the European market (Verpoort & Mohler, 2012). In some cases, biosimilars are used more often than the originator product (Bonig et al., 2015). The benefit to using biosimilar GCSF Zarzio is increased affordability and improved access for a hematopoietic stem cell transplant program (Verpoort & Mohler, 2012, Bonig et al., 2015). Originally, the cost of Zarzio was reported as 15% lower than the originator GCSF (Schmitt et al., 2014). However, in a 2014 report, Zarzio was variably reported between 25% and 86% less in cost than Neupogen (Schmitt et al., 2014; Verpoort & Mohler, 2012) (see Table 2). The second benefit to using biosimilar GCSF Zarzio over Neupogen is access (Verpoort & Mohler, 2012). Due to Zarzio’s affordability, access is easier (Verpoort & Mohler, 2012) This allows physicians to follow the recommended European Organization for Research and Treatment of Cancer (EORTC) clinical guidelines including wider use of GCSF as a primary prophylaxis (Verpoort & Mohler, 2012). It is of note that global hospitalization costs may not be significantly impacted by the use of biosimilars taking into consideration the total cost of a transplant procedure (Ianotto et al., 2012).

**IMPLICATIONS FOR CLINICAL PRACTICE**

Biosimilar Zarzio formulation comes in a prefilled syringe (300ug/0.5ml and 480ug/0.8ml) and is administered subcutaneously (US Food and Drug Administration [FDA], 2015). Patient teaching is expected to take the same amount of time, as the side effect profile is similar to the originator product Neupogen. Since the safety, efficacy, and method of administration are comparable between the two, the change to biosimilar Zarzio does not have great impact on frontline staff nurses. The greatest implication for clinical practice in a hematopoietic stem cell program is cost and access. This is significant to ambulatory clinic nurses and physicians who grapple with getting approval for cancer treatments due to high costs (Turner & Associates, 2008). If drugs are more expensive, in general, they are more difficult to access and have fewer indications approved for use (Turner & Associates, 2008). According to the EORTC guidelines, both the biosimilar GCSF and the originator GCSF are recommended for prevention of febrile neutropenia, but the choice of which formulation to use is left with the individual provider (Verpoort & Mohler, 2012). Due to the high expense of Neupogen for transplant programs, health care providers are not using it as...
widesely as its approval would implicate (Verpoort & Mohler, 2012). If biosimil- lar Zarzio is less expensive, it could be argued that it should be easier to access and, logically, be utilized more widely in accordance with the EORTC guidelines (Verpoort & Mohler, 2012). Further, it is significant to patients who should benefit if physicians could more widely prescribe for indications where they may have hesi- tated before, such as primary prophylaxis (Verpoort and Mohler, 2012).

CONCLUSION

Although originator GCSF (Neupogen) is the current drug of choice for stem cell mobilization, post-transplant engraftment and chemotherapy-induced neutropenia, alternatives such as biosimilar GCSF (Zarzio) are available (Remenyi et al., 2014; Verpoort & Mohler, 2012). This alternative is widely utilized in the European market and will soon be available in the USA (Aapro et al., 2011; Verpoort & Mohler, 2012). Due to limited availability of long-term follow-up data, the European Bone Marrow Transplantation Association does not recommend the use of biosimilars in healthy donors (Schmitt et al., 2014). The use of biosimilar Zarzio is a safe and cost-effective alternative to the originator product Neupogen, and may facilitate easier access for physi- cians and patients in Canadian stem cell transplant programs without impacting patient outcomes negatively (Verpoort & Mohler, 2012).

DISCLOSURES

There are no disclosures or conflict of interests.

REFERENCES


