

Clinical experience with Zarzio® in Europe: what have we learned?

Pere Gascón · Hans Tesch · Karl Verpoort · Maria Sofia Rosati ·
Nello Salesi · Samir Agrawal · Nils Wilking · Helen Barker ·
Michael Muenzberg · Matthew Turner

Received: 10 January 2013 / Accepted: 12 July 2013 / Published online: 1 August 2013
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Abstract Biosimilars are similar, but non-identical, versions of existing biological drugs for which patents have expired. Despite the rigorous approval process for biosimilars, concerns have been expressed about the efficacy and safety of these products in clinical practice. Biosimilars of filgrastim, based on the originator product Neupogen®, have been available since 2008 and are now in widespread clinical use in Europe and elsewhere. Three biosimilar G-CSFs have been approved based on a combination of physicochemical and biological protein characterisation, pharmacokinetic and phar-

macodynamic assessment in healthy volunteers and efficacy and safety data in patients with cancer. To assess whether biosimilars are effective in the real-world clinical practice setting, a pooled analysis of five post-approval studies of biosimilar G-CSF (Zarzio®) that included 1,302 adult patients who received at least one cycle of chemotherapy with G-CSF support for the prevention of neutropenia was conducted. A total of 36 % of patients had a febrile neutropenia risk of >20 %, while 39.6 % had a risk of 10–20 % based on chemotherapy regimen. The occurrence of severe or febrile neutropenia was within the range of that observed in previous studies of originator G-CSF. In addition, the safety profile of Zarzio® was consistent with that reported for originator G-CSF and the known safety profile of G-CSF. Initial concerns about the use of biosimilars, at least with regard to biosimilar G-CSFs, appear to be unfounded. Adoption of cost-effective biosimilars should help reduce healthcare costs and improve patient access to biological treatments.

P. Gascón (✉)
Division of Medical Oncology, Department of
Hematology-Oncology, Hospital Clinic de Barcelona,
IDIBAPS, University of Barcelona, Calle Villarroel 170,
08036 Barcelona, Spain
e-mail: GASCON@clinic.ub.es

H. Tesch
Onkologisches Zentrum, Bethanien Hospital, Frankfurt, Germany

K. Verpoort
Gemeinschaftspraxis für Hämatologie/Onkologie,
Hamburg, Germany

M. S. Rosati
Policlinico “Umberto I”, Rome, Italy

N. Salesi
Ospedale di Gaeta “M. Di Liegro”, Gaeta, Italy

S. Agrawal
St Bartholomew’s Hospital, London, UK

N. Wilking
Karolinska Institute, Stockholm, Sweden

H. Barker
Rotherham NHS Foundation Trust, Rotherham, UK

M. Muenzberg · M. Turner
Sandoz Biopharmaceuticals, Holzkirchen, Germany

Keywords Biosimilar · Chemotherapy-induced neutropenia · Cost-effectiveness · Filgrastim · G-CSF

Introduction

Biosimilars are similar, but non-identical, versions of originator biological drugs for which patents have expired. Regulatory approval for biosimilars is provided on the basis of comparable quality, safety and efficacy to the originator product rather than on the need to show a positive risk–benefit assessment per se since this has already been proven for the originator. In Europe, the European Medicines Agency (EMA) has developed a specific regulatory pathway for biosimilars [1–3]. In the USA, the Food and Drug Administration released a guidance draft for the regulatory review of biosimilars in early 2012 [4].

Several biosimilar products have now been approved in Europe, including versions of human growth hormone, epoetin alfa and filgrastim. Biosimilars of filgrastim, based on the originator product Neupogen® (Amgen), have been available since 2008 and are now in widespread clinical use. Three biosimilars of filgrastim have been approved, although versions of the same product may be marketed under different names. These are Zarzio®/Filgrastim Hexal® (Sandoz Biopharmaceuticals, a Novartis Company), Tenvagrastim®/Ratiograstim®/Biograstim® (previously referred to as XM02) (Teva) and Nivestim® (Hospira) [5]. Widespread acceptance of biosimilar G-CSF in oncology has been reflected in the most recent EORTC clinical guidelines, which recommend biosimilar filgrastim as well as originator filgrastim to prevent chemotherapy-induced neutropenia, with choice of formulation considered as a matter of individual clinical judgement [6].

The development of biosimilars offers many potential benefits to patients, physicians and healthcare providers, including enhanced affordability and increased access to expensive biological treatments. However, the arrival of biosimilars in the clinic has not been without debate, and several questions have been raised over their use [7–11]. These concerns have focused on issues related to consistent product quality and efficacy, immunogenicity, safety, labelling, traceability, automatic substitution, and extrapolation to other indications. As it has been over 5 years since the first biosimilar was approved in Europe, it now seems an appropriate time to review the evidence relating to these topics. Here, we perform this task and report a pooled analysis of post-approval studies of Zarzio® used for the prevention of neutropenia in patients with cancer undergoing cytotoxic chemotherapy.

Biosimilar quality and efficacy

Extensive physicochemical and biological characterisation using an array of standard and advanced analytical tests is a key aspect of the approval process for biosimilars. As a result of this stringent approach, the quality of biosimilars has generally been shown to compare favourably with originator biopharmaceutical products. For instance, analyses have indicated that biosimilar G-CSF may contain fewer impurities and less modified products than the originator [12]. For Zarzio®, protein structure, mass, size, charge and hydrophobicity were shown to be identical to Neupogen® using an array of analytical tests [13]. Bioactivity was also shown to be similar to the originator, with comparable binding to the G-CSF receptor in a surface plasmon resonance-based receptor affinity test and comparable biological activity in an *in vitro* cell proliferation assay. Similar protein characterisation results have been reported for Nivestim® [14] and confirm the physicochemical and biological comparability of biosimilar G-CSF with the originator.

In terms of efficacy, the EMA guidelines on biosimilar G-CSF state that pharmacodynamic (PD) studies may be sufficient to demonstrate comparability [1]. Therefore, clinical development of Zarzio® focused on PD responses in healthy subjects rather than comparative phase III clinical data. Studies in healthy volunteers may be especially useful to evaluate the haematopoietic effect of filgrastim since their bone marrow is more responsive to G-CSF than that of patients with cancer undergoing chemotherapy. The bioequivalence of Zarzio® and Neupogen® was shown in four comparative phase I studies involving a total of 146 healthy adult volunteers [15], in which both products had comparable effects on absolute neutrophil count (ANC) and CD34+ cell count, which were used as surrogate markers of efficacy. Pharmacokinetic (PK) parameters also showed bioequivalence of Zarzio® and Neupogen®.

Data in patients with cancer were provided by a phase III study designed primarily to assess safety. The study was conducted in 170 patients with stage II–IV breast cancer receiving cytotoxic chemotherapy with doxorubicin (60 mg/m²) and docetaxel (75 mg/m²). Zarzio® was shown to be effective in these patients, with the duration of severe grade 4 neutropenia and incidence of febrile neutropenia comparable with published results for the originator product [16, 17].

Similarly, clinical comparability with the originator has been shown for the other two biosimilar G-CSF products. Although there were differences between the clinical development programmes for the three biosimilars, with differing degrees of emphasis on PK/PD characterisation and thus the need for subsequent clinical trial data, all have been approved as being similar to the originator product based on a combination of protein characterisation, PK and PD in healthy volunteers and efficacy and safety in patients. For Tenvagrastim®/Ratiograstim®, development included two PK/PD studies [18, 19] and three phase III studies (in breast cancer, lung cancer and non-Hodgkin's lymphoma) [20–22], while development of Nivestim® involved two PK/PD studies [23, 24] and a single phase III study in patients with breast cancer [25].

Despite the robustness of the non-clinical and clinical evaluations that are necessary for approval of a biosimilar, concerns have been raised over whether biosimilars are effective in the real-world clinical practice setting. To investigate this, we conducted an analysis of pooled data from five post-approval studies in which Zarzio® was used for the prophylaxis of chemotherapy-induced neutropenia in patients with cancer.

Pooled analysis of post-approval studies of Zarzio® for prevention of chemotherapy-induced neutropenia

Data were pooled from five studies investigating the real-life clinical usage of Zarzio® for the primary or secondary prophylaxis of chemotherapy-induced neutropenia in patients with cancer (Table 1) [26–30]. These studies were conducted across 12 European countries and consisted of two ongoing multicentre

observational studies (interim data) plus three single-centre observational studies. Patients were included in the analysis if they were aged ≥ 18 years, had a confirmed diagnosis of cancer and received at least one cycle of chemotherapy with Zarzio[®]. Since all studies were non-interventional, patients were treated with Zarzio[®] on the basis of the individual physicians' clinical judgement and according to standard local practice. Patients receiving Zarzio[®] for the treatment of neutropenia (rather than prophylaxis) were excluded from the analysis.

Data from 1,302 patients were included in the analyses. The most frequent cancer types were breast cancer ($n=541$; 42 %), lung cancer ($n=212$; 16 %) and lymphoma/leukaemia ($n=201$; 15 %) (Fig. 1). Based on chemotherapy regimen, 36 % of patients were estimated to have had a febrile neutropenia risk of >20 %, while 40 % had a risk of 10–20 %. A further 12 % of patients received Zarzio[®] despite a febrile neutropenia risk of <10 % (12 % unknown) (Fig. 2). Twice as many patients received biosimilar G-CSF as primary prophylaxis (57 %) compared with secondary prophylaxis (27 %) (16 % unknown) (Fig. 3).

Overall, only 2.2 % ($n=29$) of patients experienced an episode of febrile neutropenia (2.0 % of patients with breast cancer), and 8.5 % ($n=104$) of patients had severe (grade 4) neutropenia (ANC $<500/\mu\text{L}$) (9.4 % in patients with breast cancer). Both

febrile neutropenia and severe neutropenia were approximately twice as likely to occur in patients receiving Zarzio[®] as secondary rather than primary prophylaxis (3.1 versus 1.6 % and 7.4 versus 13.1 % of patients, respectively). Disturbances to chemotherapy regimens (dose reduction or discontinuation) were reported in two studies, occurring in 8/77 patients (10 %) in one study [28] and 27/307 patients (7 %) in the other [27].

The occurrence of severe or febrile neutropenia observed in the pooled analysis was within the range of that observed in previous studies of G-CSF [31, 32]. Overall, this new pooled analysis demonstrates that Zarzio[®] appears to be effective for the prevention of chemotherapy-induced neutropenia in clinical practice across a variety of cancers.

Safety

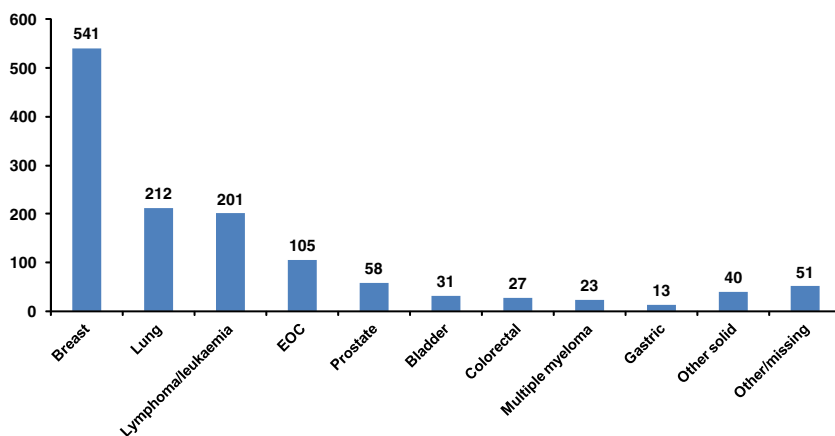
The EMA sets strict guidelines for a market authorisation holder in terms of both product-specific risk management plans and overarching guidance for pharmacovigilance. Since the launch of Zarzio[®] in 2009, the estimated exposure to this biosimilar is approximately 4.5 million patient days (as of June 2013 Sandoz data on file). To date, clinical experience has revealed no striking or new safety signals for Zarzio[®]. In the phase III study, Zarzio[®]

Table 1 Studies included in pooled analysis of post-approval studies of Zarzio[®] in patients with cancer undergoing cytotoxic chemotherapy

Study	Patients (<i>n</i>)	Cancer types	Type of prophylaxis
MONITOR G-CSF (MC) Gascon et al. 2011 [26]	741	Breast, $n=236$ Lung, $n=160$ Lymphoma/leukaemia, $n=123$ EOC, $n=74$ Prostate, $n=46$ Bladder, $n=29$ Multiple myeloma, $n=22$ Other, $n=51$	PP, $n=409$ SP, $n=129$ Unknown, $n=203$
HexaFil (MC) Tesch et al. 2011 [27]	394	Breast, $n=258$ Lymphoma/leukaemia, $n=61$ Lung, $n=25$ EOC, $n=16$ Other, $n=34$	PP, $n=219$ SP, $n=175$
Hamburg, Germany (SC) Verpoort et al. 2011 [28]	77	Breast, $n=22$ Lymphoma/leukaemia, $n=17$ Colorectal, $n=10$ Other, $n=28$	PP, $n=32$ SP, $n=40$ Unknown, $n=5$
Gaeta, Italy (SC) Salesi et al. 2012 [29]	48	Lung, $n=17$ Colorectal, $n=11$ Breast, $n=10$ Other solid, $n=10$	PP, $n=37$ SP, $n=11$
Rome, Italy (SC) Rosati et al. 2011 [30]	42	Breast, $n=15$ Other solid, $n=27$	PP, $n=42$

EOC endometrial/ovarian cancer, PP primary prophylaxis, MC multicentre, SC single centre, SP secondary prophylaxis

Fig. 1 Pooled analysis of post-approval studies of Zarzio® in patients with cancer undergoing cytotoxic chemotherapy: most frequent solid tumours and haematological malignancies (*n*=1,302)



was generally well tolerated [15], a finding supported by the pooled analysis in which the safety profile of Zarzio® was consistent with that reported for originator G-CSF and the known G-CSF adverse event profile. Of particular note, occurrence of bone pain was 8 % (reported in [27]), consistent with that observed in the phase III study and in line with reported incidence with the originator [16, 17]. The relatively low incidence compared with that observed in clinical studies of originator G-CSF (24 % across all phase II/III studies) may be because bone pain is a recognised common side effect of G-CSF treatment and so may be less likely to be reported in everyday practice than other less expected side effects.

One particular concern with biosimilars has been the potential for an immunological response that may differ from that seen with the originator. EMA states that an appropriate strategy for assessment of unwanted immunogenicity of biological products is essential and should include validated state-of-the-art assays able to detect neutralising and non-neutralising antibodies. For Zarzio®, no neutralising antibodies were detected in any of the clinical studies in healthy volunteers or cancer patients (*n*=316). In addition, no reports of neutralising antibodies have occurred during the ongoing

pharmacovigilance of Zarzio® in clinical use. Pharmacovigilance is necessary to detect rare adverse events that can only be detected in a larger patient population during long-term use and is required for all biologicals, including original products. The lack of reports of antibody development to Zarzio® is unsurprising given that filgrastim is an unglycosylated protein mostly administered to immunocompromised patients and the absence of immunogenicity seen with the originator product.

Traceability and automatic substitution

Traceability refers to the need to be able to identify individual medical products and is essential for accurate pharmacovigilance. Biosimilars generally have the same international non-proprietary name (INN) as the originator product. In the case of biosimilar G-CSFs, their common INN is filgrastim. Several health regulatory agencies have highlighted the need for clinicians to identify specific products by brand name, as did the recent update to EORTC guidelines on the use of G-CSF to reduce the incidence of chemotherapy-induced neutropenia [6].

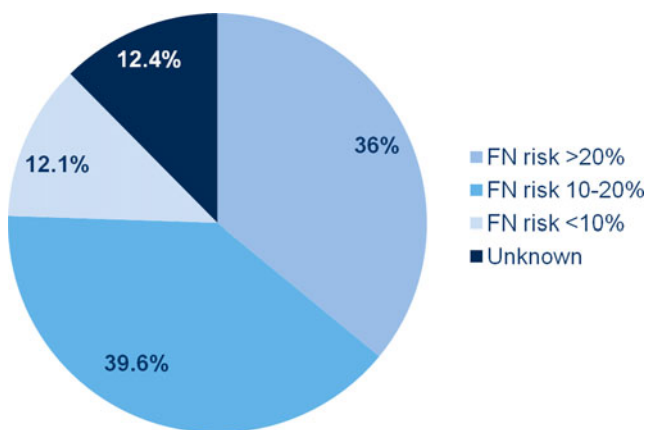


Fig. 2 Pooled analysis of post-approval studies of Zarzio® in patients with cancer undergoing cytotoxic chemotherapy: febrile neutropenia (FN) risk based on chemotherapy regimen (*n*=1,302)

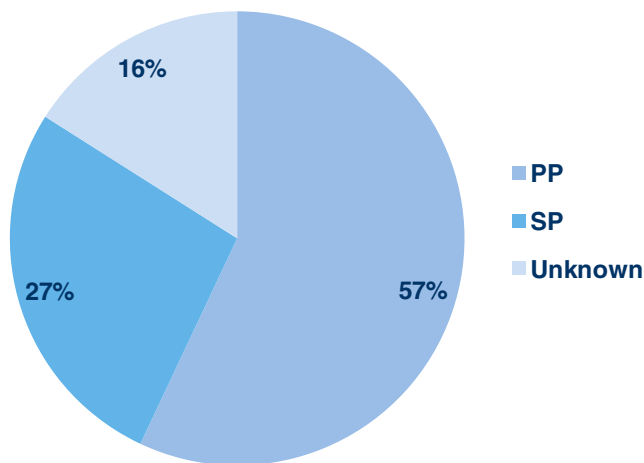


Fig. 3 Pooled analysis of post-approval studies of Zarzio® in patients with cancer undergoing cytotoxic chemotherapy: type of prophylaxis (*n*=1,302). PP primary prophylaxis, SP secondary prophylaxis

In accordance with such guidance, biosimilar manufacturers have marketed products under clearly branded names and packaging.

Another related concern is that of drug substitution, whereby a prescribed product is replaced by another with the same INN by the pharmacist. Generally, the decision to treat a patient with an originator or biosimilar product should be taken by a qualified healthcare professional. EORTC G-CSF clinical guidelines state that no changes in product should be made without informing both physician and patient [6]. The EU allows member countries to set their own policy regarding substitution and many have taken specific measures at a regulatory/legal level to prevent automatic substitution of biologicals, although not all countries have a clear position to date.

Extrapolation to other indications

Another question raised regarding biosimilars relates to the extrapolation of clinical data, a process that may allow the approval of a product for use in indications in which it has not been evaluated in clinical trials. The validity of data extrapolation is dependent on the biosimilar having the same mechanism of action as the originator, and the mechanism of action being the same in different indications. As such, data extrapolation is generally considered rational and appropriate by the EMA when comparability between a biosimilar and originator in one indication can be reasonably assumed to be extended to other indications for which the originator is approved.

In the case of biosimilar G-CSF, approval has been primarily on the basis of studies in healthy volunteers and for the prevention of chemotherapy-induced neutropenia. However, since approval is given for the same indications as the originator, biosimilar G-CSF can also be used for peripheral blood stem cell (PBSC) mobilisation, including neutrophil recovery after stem cell transplantation. Extrapolation to all indications of the reference product was considered acceptable on the basis of phase I data especially since comparable receptor site kinetics of the two products indicate that the mode of action is the same for both, i.e. direct stimulation of bone marrow cells through the G-CSF surface receptor.

In support of this, phase I studies showed PD and PK comparability between Zarzio® and Neupogen® at doses typically used for stem cell mobilisation (10 µg/kg) [15]. Subsequently, several studies have indicated that use of biosimilar G-CSF in the haematopoietic stem cell transplant (HSCT) setting is well tolerated and effective, with comparable results to those observed with originator G-CSF. In one study, 40 patients with haematological malignancy who were scheduled to receive Zarzio® following first-cycle chemotherapy for autologous PBSC mobilisation were compared with a matched historical control group ($n=41$) who had been treated with Neupogen® at the same centre [33]. No significant differences between groups were observed in the median number of CD34+

cells collected in the first leukapheresis or in the number of leukaphereses necessary to obtain the minimum CD34+ cell count. Similar results were observed in a study of 38 patients with lymphoma or myeloma who received Zarzio® and who were compared with a historical cohort of such patients treated with Neupogen® ($n=50$) [34]. No significant differences in PBSC stimulation or biological parameters of bone marrow recovery were observed between the two cohorts. Several other studies have also reported comparability of biosimilar G-CSF and the originator when used for stem cell transplantation [35–38].

Relative to the experience gathered in autologous HSCT, use of biosimilar G-CSFs in allogeneic HSCT has been more limited. Accordingly, some concerns have been raised over the use of G-CSFs in healthy donors, especially with regard to long-term safety outcomes. For instance, the World Marrow Donor Association has recommended that biosimilar G-CSF should not be used for mobilisation in healthy donors, unless participating in a clinical study (Shaw et al. 2011) [39]. However, initial data suggest that there are at least no short-term safety concerns. In one small study of 21 donors, Azar et al. reported that Zarzio® was effective and well tolerated [40]. Another biosimilar G-CSF, Ratiograstim®, has been reported to possess similar efficacy to originator G-CSF when given to 22 healthy donors during allogeneic HSCT [41]. A long-term safety study of Zarzio® in 200 healthy stem cell donors is ongoing, with an interim data analysis having reported no unexpected results that would question the safety of Zarzio® for healthy donor stem cell mobilisation (Becker et al. 2012) [42].

Pharmacoeconomic considerations

Global healthcare costs have increased dramatically in recent years, forcing healthcare authorities to consider various means to help contain expenditure [43]. Biosimilars may offer one route to reduced healthcare costs and improved patient access to treatments [44]. However, since biosimilar development and manufacturing involves considerable investment of time and expertise, there were concerns that the cost savings generated may not be as great as was originally predicted. However, these concerns appear to have been largely unfounded, with significant cost savings being reported through the adoption of biosimilars.

Experience from health authority regions that have switched from originator G-CSF to Zarzio® suggests that significant cost savings can be achieved. For instance, across the London region, switching from originator G-CSF to Zarzio® was associated with an estimated annual cost-saving of £1 million, with G-CSF purchasing costs being reduced from £3.3 million in 2010 to £2.3 million in 2011. This saving was predicted to increase to £2 million in 2012 as the switch to biosimilar G-CSF usage continues (personal

communication, Antony Grosso, London Procurement Programme, September 2012). Similarly, in the Southern Health Care region in Sweden (population 1.7 million), the shift from originator to biosimilar G-CSF has led to a fivefold increase in daily G-CSF usage (based on data provided by IMS Health [45], the Swedish Dental and Pharmaceutical Benefits Agency (www.tlv.se) and Skåne University Hospital). Importantly, this region previously had restrictions on G-CSF usage to prevent febrile neutropenia that have been relaxed with the switch to biosimilar. The introduction of biosimilar G-CSF in this region was associated with net savings of €2 million - this represents a saving of 4–5 % of the total drug budget. Moreover, data from IMS suggest that annual savings in 2011 resulting from the use of biosimilar (Zarzio®) rather than originator G-CSF amounted to €85 million across 17 EU countries (estimate based on originator G-CSF prices and sales volume obtained from IMS Health [45] biosimilar G-CSF sales including estimated level of discount based on Sandoz data on file).

As shown by the Swedish example, the increased affordability of biosimilar G-CSF may improve patient access to G-CSF and encourage physicians to more closely adhere to clinical guideline recommendations. Evidence to support this is also provided from the UK, where the availability of biosimilar G-CSF (September 2008) resulted in a 13 % increase in overall G-CSF use from 2008 to 2009 and a further 17 % increase from 2009 to 2010. This increase in use is illustrated by the experience of the Haematology Department, Rotherham Hospital, Rotherham, UK, where the decision to switch from originator G-CSF to Zarzio® by the purchasing consortium was a factor contributing to a shift in treatment practice from secondary prophylaxis to increased primary prophylaxis, especially in patients receiving chemotherapy with a febrile neutropenia risk of 10–20 %. Recently published experience from a single centre in Hamburg, Germany, also reports that switching from originator to biosimilar G-CSF was accompanied by a trend towards an increased use of G-CSF as primary prophylaxis (52 % versus 36 % of patients), which may have reflected increased willingness to use G-CSF earlier, given its lower cost [28].

In addition to increased access to G-CSF, cost savings achieved through biosimilar use can be redistributed to offset budgetary constraints elsewhere, in particular, to improve access to new cancer treatments and/or reduce workforce cost-saving pressures.

Conclusions

Biosimilar products have been available in Europe and elsewhere for several years. These products are manufactured with state-of-the-art technology and have passed the regulatory requirements for approval. A recent review authored by members and experts of the Working Party on Similar Biological Medicinal Products of the EMA concluded that principles guiding

biosimilar development are scientifically sound and that approved biosimilars can be considered as therapeutic alternatives to the reference product [46]. Initial concerns about efficacy and safety appear to be unfounded as, for example, an increasing body of clinical evidence suggests that biosimilar G-CSFs compare favourably with the originator product. Recent EORTC guidelines for the prevention of chemotherapy-induced neutropenia now recognise biosimilar G-CSF as an alternative to the originator [6]. However, it should be noted that implementation of EORTC guidelines is varied with many scenarios where physicians chose to ‘wait and see’, often waiting for neutrophils to decrease or neutropenic symptoms to occur before intervening. There are many reasons for this, but cost containment is very likely to be one of them. One benefit of biosimilars is that their greater affordability may encourage earlier use of G-CSF and improve congruence with guidelines. Strict pharmacovigilance and data monitoring should continue to examine the long-term efficacy and safety of biosimilars, and this information must be clearly disseminated to patients, clinicians and other stakeholders. Nevertheless, in the current climate of growing financial constraints on healthcare cost systems, biosimilars offer an affordable, high-quality and clinically effective alternative. Thus, increasing adoption of biosimilars should help reduce healthcare budgets and improve access to expensive biological treatments for patients.

Acknowledgments Collection and analysis of pooled data for Zarzio® was funded by Sandoz Biopharmaceuticals. Medical writing support was provided by Andy Bond of Spirit Medical Communications and funding was by Sandoz Biopharmaceuticals.

Conflicts of interest PG has received honoraria from Sandoz Biopharmaceuticals for speaking at educational events and attending advisory boards. HT is principal investigator of the Sandoz/Hexal funded HEXAFIL trial and has received honoraria for related congress presentations and advisory boards. KV has received a research grant from Sandoz Biopharmaceuticals. HB has received honoraria for speaking at a Sandoz Biopharmaceuticals-sponsored educational event and educational support to attend a haematology educational congress and for attending an advisory board. SA has received honoraria from Sandoz Biopharmaceuticals for attendance at educational meetings and for consultancy and research grants for clinical audit projects. MM and MT are employees of Sandoz Biopharmaceuticals. MSR, NS and HW have declared no conflicts of interest.

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