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Original Research

Comparing granulocyte colony–stimulating factor filgrastim and pegfilgrastim to its biosimilars in terms of efficacy and safety: A meta-analysis of randomised clinical trials in breast cancer patients

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KEYWORDS
Granulocyte colony–stimulating factors (G-CSFs) filgrastim; Pegfilgrastim; Biosimilars

Abstract ***Background:*** Granulocyte colony–stimulating factors (G-CSFs) are widely used to prevent neutropenia in cancer patients undergoing myelosuppressive chemotherapy. Several biosimilar medicines of G-CSF are now available, with their development involving a stepwise series of comparisons to demonstrate similarity to reference biologics. Randomised clinical trials (RCTs) are considered confirmatory, and for G-CSF biosimilars, patients with breast cancer (BC) undergoing myelosuppressive chemotherapy are the most sensitive population in which to confirm similarity. This meta-analysis aimed to compare the clinical efficacy and safety of approved or proposed G-CSF biosimilars (filgrastim or pegfilgrastim) with reference G-CSF in patients with BC.

Methods: A Medline literature search up to March 2017 identified RCTs comparing biosimilar G-CSF to reference in BC patients. The primary efficacy end-point was mean difference in duration of severe neutropenia (DSN). Secondary efficacy end-points were differences in depth of absolute neutrophil count (ANC) nadir, time to ANC recovery and incidence of febrile neutropenia. Safety analyses included calculation of risk ratios for bone pain events, myalgia events and serious adverse events. Random effect models were fitted to obtain the pooled estimates of the mean difference for continuous outcomes and the risk ratio for dichotomous outcomes and their corresponding 95% confidence intervals (CIs).

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Findings: Eight eligible RCTs were included in this meta-analysis. Overall difference in DSN between reference and biosimilar medicines was not statistically significant (0·06 d [95% CI −0·05, 0·17]). The analysis of secondary efficacy end-points showed no significant differences between reference biologics and biosimilar medicines, as well as the analysis of bone pain events, myalgia events and serious adverse events.

1. Research in context

1.1. Evidence before this study

We searched PubMed for all meta-analyses up to June 2017, published in any language, with the terms 'filgrastim meta-analysis'. This search identified 30 articles, several of which were meta-analyses comparing short-acting G-CSF with long-acting G-CSF. One meta-analysis was identified that included randomised controlled trials (RCTs) that compared reference filgrastim (Neupogen®, Amgen) with biosimilar filgrastim (tbo-filgrastim/XM02) in patients with breast cancer (BC), lung cancer or non-Hodgkin's lymphoma (NHL). Another meta-analysis included studies comparing G-CSF reference biologics with biosimilar medicines for mobilisation of peripheral blood stem cells. However no meta-analysis was identified that compared G-CSF reference biologics with biosimilars medicines in RCTs performed only in patients with BC receiving cytotoxic chemotherapy.

1.2. Added value of this study

To the best of our knowledge, this meta-analysis is the first to compare G-CSF reference biologics with biosimilar medicines in RCTs of patients with BC. The results reported here show no significant difference between reference and biosimilar G-CSF in terms of duration of severe neutropenia (DSN), as well as secondary efficacy end-points including depth of absolute neutrophil count (ANC), time to ANC recovery and febrile neutropenia (FN). Adverse events such as bone pain events, myalgia events and serious adverse events also showed no significant differences between reference and biosimilar G-CSF.

1.3. Implications of all the available evidence

This meta-analysis of eight RCTs showing similar efficacy and safety of G-CSF reference biologics and biosimilar medicines has implications for clinical practice since this suggests that similar results can be obtained with a biosimilar rather than a reference medicine. Potential cost savings associated with biosimilars can increase patient access to biological treatment and supportive care and has the potential for funds to be redistributed across the healthcare system.

2. Introduction

Current treatment guidelines from the American Society of Clinical Oncology [1], the National Comprehensive Cancer Network [2], the European Organisation for Research and Treatment of Cancer [3], the European Society for Medical Oncology [4] and Canadian supportive care guidelines [5] recommend the prophylactic use of granulocyte colony–stimulating factors (G-CSFs) in patients receiving chemotherapy when the risk of FN is $\geq$ 20%, and in patients with FN risk between 10–20% who have additional risk factors such as age $\geq$65 years, poor performance status and prior FN. In clinical trials and daily practice, primary and secondary prophylaxis with G-CSF has been shown to reduce FN incidence, its complications and improve outcomes of cancer treatment [6–11].

The G-CSF class of therapeutic agents was developed by isolating, purifying, and cloning this haematopoietic regulatory factor [12]. The human G-CSF gene was inserted into *Escherichia coli* using recombinant DNA technology to produce filgrastim, which has been approved for clinical use since 1991 [13]. Because of its relatively short circulating half-life, daily filgrastim injections are required to stimulate neutrophil recovery. In an effort to develop a long-acting form of filgrastim that is as safe and effective as filgrastim, a fusion of filgrastim to polyethylene glycol—pegfilgrastim—was synthetised and finally approved for the clinical use in 2002 [14]. In recent years, several biosimilars of filgrastim and pegfilgrastim and other G-CSF products were developed, including EP2006 (filgrastim, Zarzio®/Zarxio®) [15,16], lipegfilgrastim [17] and Nivestim (Hospira filgrastim) [18]. The development of biosimilars follows a step-wise approach including analytical comparison to the reference medicine and an iterative process development to achieve a product which is equivalent to the reference medicine. The clinical trials in support of this sequential process are focused on confirming this similarity so that the totality of evidence reinforce that the biosimilar is the same biological substance as the reference medicine. For G-CSF biosimilar medicines, patients with breast cancer (BC) are the most sensitive population to confirm similarity between reference biologic and proposed biosimilar.

The aim of this meta-analysis was to compare the clinical efficacy and safety of G-CSF reference biologics (filgrastim and pegfilgrastim) with the efficacy and safety of the G-CSF biosimilar medicines, approved and