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REVIEW

Clinical efficacy and safety of Tevagrastim® (XM02), a biosimilar recombinant human granulocyte colony-stimulating factor

This article was published in the following Dove Press journal:
Biosimilars
26 August 2013
Number of times this article has been viewed

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Abstract: Since the expiration of the patent for filgrastim in Europe in 2006, the European Medicines Agency has approved three biosimilar granulocyte colony-stimulating factors, while the US Food and Drug Administration has approved one of these agents. Using the European Medicines Agency's and the Food and Drug Administration's regulatory reports and scientific publications, we review the evidence about the clinical efficacy and safety of XM02 (Tevagrastim®) relative to the originator product filgrastim (Neupogen®). Clinical efficacy is assessed in terms of equivalence of XM02 and Neupogen®, while safety is evaluated in terms of immunogenicity, bone pain, splenomegaly, allergic reactions, acute respiratory distress syndrome, and mortality. Three Phase III studies in breast cancer patients treated with docetaxel/doxorubicin chemotherapy, lung cancer patients receiving platinum-based chemotherapy, and non-Hodgkin's lymphoma receiving chemotherapy are reviewed. Also included is a postapproval, single-center experience study on peripheral blood stem mobilization. Based on the available therapeutic equivalence and safety data, the clinical and safety outcomes of XM02 are likely to be similar to those of Neupogen®. XM02 and Neupogen® can be considered interchangeable in the approved indications. Patients previously on Neupogen® and converted to XM02 can be expected to show similar efficacy and safety outcomes.

Keywords: biosimilars, biosimilar pharmaceuticals, efficacy, safety, granulocyte colony-stimulating factor, recombinant proteins

Introduction

Neutropenia is a condition characterized by an abnormally low concentration of neutrophils in the blood. White blood cell production is regulated by various growth factors, with the granulocyte colony-stimulating factors (GCSFs) being the most important class for the recovery of neutrophils.[1,2] Cloning of human GCSF was achieved in 1986.[3,4] Exogenous GCSF is produced by means of recombinant deoxyribonucleic acid technology. Filgrastim, the first recombinant human GCSF, was approved for therapeutic use on the basis of two trials[5,6] and has been marketed as Neupogen® (Amgen, Inc, Fort Worth, TX, USA). The patent expired in Europe in 2006, and in the US it will expire later in 2013. On July 24, 2008, the European Medicines Agency (EMA) approved XM02, which has since been marketed as Tevagrastim® (Teva Pharmaceutical Industries, Ltd, Petach Tikva, Israel; but it is also known as Biograstim®, Filgrastim ratiopharm, and Ratiograstim®). On August 29, 2012 the US Food and Drug Administration approved Tbo-filgrastim, which is the same as Tevagrastim® through its Biologics License Application pathway (there was no approval pathway for biosimilars

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at the time). Tbo-filgrastim is expected to enter the US market in late 2013 under the name Tevagrastim®.

XM02 is approved in Europe in the cancer, human immunodeficiency virus, and infections settings (Table 1). In the cancer setting, XM02 is indicated to reduce the duration of neutropenia and the incidence of febrile neutropenia (FN) in patients undergoing cytotoxic chemotherapy, to reduce the duration of neutropenia in high-risk patients undergoing myeloablative therapy followed by bone marrow transplantation, and in the mobilization of peripheral blood progenitor cells. Tbo-filgrastim is approved in the US for the reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of FN.[7,8] The only contraindication for XM02, as specified in the EMA label, is hypersensitivity to the active substance or to any of the excipients.

This article is the first in a series of three reviews of the clinical efficacy and safety of approved biosimilar GCSFs. This series follows a similar set of reviews of biosimilar erythropoietins,[9–11] and uses the same approach (which may be found in a previous paper).[9] We review the clinical evidence on the biosimilar GCSF XM02, including controlled pre- and postauthorization trials and postapproval observational studies. The primary sources of evidence are found in the regulatory reports for XM02 as posted on the EMA and the US Food and Drug Administration (FDA) websites as of January 3, 2013.[7,8] Also included are articles published in peer-reviewed biomedical journals. Excluded are abstracts and posters because of the limited depth of reporting. The manufacturer was not approached for information.

Table 1 Therapeutic indications for XM02 as approved by the European Medicines Agency

Cancer	Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients with established cytotoxic chemotherapy for malignancy.* Reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia. Mobilization of peripheral blood progenitor cells.
Human immunodeficiency virus	Treatment of persistent neutropenia in patients with advanced human immunodeficiency virus infection and to reduce risk of bacterial infections if other treatments are not appropriate.
Infections	Increase levels of neutrophils and reduce risk of infections in patients with neutropenia who have history of severe, repeated infections.

Note: *Also approved by the US Food and Drug Administration. Data from Abraham et al.[12]

Each study is reviewed as to its objectives, endpoints, design, and patient populations studied. Therapeutic equivalence and other efficacy and effectiveness data are reported in detail. Safety data focus on immunogenicity, bone pain, splenomegaly, allergic reactions, acute respiratory distress syndrome, and mortality. Other safety concerns may be found in a comprehensive review of the clinical safety of biosimilar GCSFs.[12]

Clinical studies

Overview

The late-stage clinical development program of XM02 included one Phase III study conducted with 348 breast cancer patients treated with docetaxel/doxorubicin chemotherapy (XM02-02-INT),[13] one Phase III study conducted with 240 lung cancer patients receiving platinum-based chemotherapy (XM02-03-INT),[14] and one Phase III study conducted with 92 chemotherapy-treated patients with non-Hodgkin's lymphoma (NHL) (XM02-04-INT).[15] In addition, one article presented the findings of a postapproval, single-center, experience study on plerixafor and XM02 combination therapy as a first-line peripheral blood stem mobilization strategy in 14 patients who were candidates for autologous bone marrow transplantation.[16]

Study XM02-02-INT: breast cancer

Methods

The primary objective of study XM02-02-INT was to demonstrate the equality of XM02 and Neupogen® in patients with breast cancer during the first cycle of chemotherapy on the duration of severe neutropenia for up to a maximum of four cycles of chemotherapy.[7,8,13] The intent was to document the therapeutic equivalence of XM02 relative to Neupogen® in this population.

The study was designed as a randomized, investigator-blinded, multicenter, Phase III trial in which breast cancer patients were allocated in a 2:2:1 scheme to XM02, Neupogen®, or placebo, respectively. Patients in the placebo arm switched to XM02 after completion of chemotherapy cycle 1. Patients underwent a maximum of four chemotherapy cycles. The chemotherapy regimen in this study consisted of doxorubicin 60 mg/m^2 intravenous (IV) bolus and docetaxel 75 mg/m^2 IV infusion on day 1 of each cycle (3 weeks per cycle). XM02 or Neupogen® administered daily starting 1 day after chemotherapy was completed as a subcutaneous (SC) 5 µg/kg injection for at least 5 days and up to a maximum of 14 days in each cycle. Study medications were stopped if an absolute neutrophil count (ANC) of $\geq 10 \times 10^9$/L was reached after nadir.

The primary endpoint of interest in this review was the duration (in days) of severe neutropenia (ANC $< 0.5 \times 10^9$/L) during cycle 1. Statistically, sensitivity of the assay with respect to the duration of severe neutropenia in cycle 1 was confirmed by comparing XM02 to placebo. A statistically significant two-group analysis of covariance result for a shorter duration in the XM02 arm compared to the placebo arm was then followed by an assessment of equivalence between XM02 and Neupogen®. Equivalence was inferred if the 95% confidence interval (CI) for the difference in duration of severe neutropenia was entirely within the equivalence range of ±1 day. Relevant secondary endpoints were the duration of severe neutropenia for cycles 2, 3, and 4; depth of ANC nadir for cycles 1, 2, 3, and 4; and time to ANC recovery for cycles 1, 2, 3, and 4.

Patients

The sample consisted of male and female adults with high-risk stage 2, 3, or 4 breast cancer who were eligible to receive treatment with docetaxel/doxorubicin as routine chemotherapy; patients were chemotherapy-naïve, had an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, ANC ≥ 1.5×10^9/L, a platelet count ≥100×10^9/L, as well as adequate cardiac, hepatic, and renal functions. In addition to common exclusion criteria for studies in GCSF therapy involving cancer patients, a relevant exclusion criterion was the presence of an underlying neuropathy of grade 2 or higher.

A total of 348 patients were randomized to the XM02 (n = 140), Neupogen® (n = 136), and placebo (n = 72) arms. As detailed in Table 2, the treatment arms were similar in terms of sex, age, weight, incidence of prior or concomitant medications, and cancer stage at screening/baseline.

Table 2 Patient characteristics in study XM02-02-INT

Characteristic	XM02 (n = 140)	Neupogen® (n = 136)	Placebo/XM02* (n = 72)
Female, n (%)	139 (99.3%)	135 (99.3%)	72 (100.0%)
Age, years (M ± SD)	51.0 ± 9.7	51.4 ± 10.7	49.5 ± 10.3
Body mass index, (kg/m^2) (M ± SD)	27.77 ± 6.11	28.20 ± 5.70	27.42 ± 6.02
Cancer stage, n (%)			
High-risk stage 2	23 (16.4%)	36 (26.5%)	15 (20.8%)
Stage 3	79 (56.4%)	69 (50.7%)	38 (52.8%)
Stage 4	38 (27.1%)	31 (22.8%)	19 (26.4%)
Therapy, n (%)			
Adjuvant	96 (68.6%)	96 (70.6%)	47 (65.3%)
Metastatic	44 (31.4%)	40 (29.4%)	25 (34.7%)

Note: *Patients in this group received placebo in cycle 1 and XM02 afterwards. Data from del Giglio et al.[13]
Abbreviations: n, number; M, mean; SD, standard deviation.

Efficacy

Primary and secondary efficacy endpoints are summarized in Table 3. The mean duration of severe neutropenia in cycles 1–4 was similar in all treatment arms. The mean duration of severe neutropenia was significantly shorter in the XM02 arm (1.141 days) than in the placebo arm (3.823 days), showing the superiority of XM02 in terms of efficacy. The difference in the 95% CI in cycle 1 for XM02 versus Neupogen® was 0.028 days (–0.261 to 0.316), which was within the predefined equivalence range of ±1 day. There was no significant difference in the FN incidence between the treatment arms in all cycles (P = not significant [ns]); however, the Neupogen® and XM02 arms had lower FN incidence rates than the placebo arm. In cycle 1 of the placebo arm, mean ANC decreased after 2 days and reached a nadir on day 11. In contrast, in cycle 1 of the XM02 and Neupogen® arms, the mean ANC increased and reached its maximum on day 3, then it decreased to a nadir on day 7, and it increased again to reach a maximum on day 11. On day 21, mean ANC returned to values as detected on day 1 in all treatment arms. In cycle 1, there was no significant difference in the mean ANC nadir between the XM02 and Neupogen® arms (P = ns). The difference in the 95% CI in cycle 1 was –0.001 days (–0.190 to 0.189). In cycles 2–4, the mean ANC nadir was similar across treatment arms. Further, in cycle 1, there was no significant difference in the mean time to ANC recovery between the XM02 and Neupogen® arms (P = ns). The difference in the 95% CI in cycle 1 was 0.207 days (–0.425 to 0.838). In cycles 2–4, the mean time to ANC recovery was similar in all treatment arms.

Safety

There were three deaths during cycle 1: two in the placebo arm (sepsis and cardiorespiratory arrest) and one in the XM02 arm (ischemic stroke). In addition, one death occurred after the end of the study in the XM02 arm (metastasis in brain). None of these deaths was assessed to be related to the study drug. There were no statistically significant differences between the XM02 and Neupogen® arms with regard to mortality. Additional safety data have been summarized elsewhere.[12]

Study XM02-03-INT: lung cancer

Methods

The primary objective of study XM02-03-INT was to demonstrate the safety profile of XM02 when administered for up to a maximum of six cycles of chemotherapy in patients with lung cancer.[7,8,14] The intent was to document the safety

Table 3 Efficacy endpoints in study XM02-02-INT

	XM02 (n = 140)	Neupogen® (n = 136)	Placebo/XM02* (n = 72)	*P*-value
Mean duration of severe neutropenia (days)				
Cycle 1	1.1	1.1	3.8	
Cycle 4	0.7	0.7	0.6	
ANCOVA estimate and two-sided 95% CI for difference XM02 in cycle 1 (days)	0.028 (–0.261 to 0.316)			
Mean ANC nadir (10^9/L)				
Cycle 1	0.7	0.7	0.2	
Cycle 4	1.0	1.0	1.1	
ANCOVA estimate and two-sided 95% CI for difference XM02 in cycle 1 (days)	–0.001 (–0.190 to 0.189)			
Mean time to ANC recovery (days)				
Cycle 1	8.0	7.8	14.0	
Cycle 4	7.6	7.1	7.2	
ANCOVA estimate and two-sided 95% CI for difference XM02 in cycle 1 (days)	0.207 (–0.425 to 0.838)			
Incidence of FN (%)+				
Cycle 1	12.1	12.5	36.1	ns
Across all cycles	20.7	22.1	41.7	ns

Notes: *Patients in this group received placebo in cycle 1 and XM02 afterwards (including in cycle 4); +observed or protocol-defined FN. Data from del Giglio et al.[13]
Abbreviations: n, number; ANCOVA, analysis of covariance; CI, confidence interval; ANC, absolute neutrophil count; FN, febrile neutropenia; ns, not significant.

and efficacy of XM02 compared to Neupogen® in this population.

The study was designed as a randomized, controlled, multicenter, Phase III trial in which lung cancer (either small cell or non-small cell) patients were allocated in a 2:1 scheme to treatment with XM02 and Neupogen®, respectively, in the first chemotherapy cycle. In the remaining cycles, all patients received XM02.

Patients underwent a maximum of six chemotherapy cycles at 3- or 4-week intervals. XM02 or Neupogen® administered daily starting 1 day after chemotherapy was completed as a SC 5 μg/kg injection for at least 5 days and up to a maximum of 14 days. Both study medications were stopped if an ANC of $\geq 10 \times 10^9$/L was reached after nadir.

The relevant primary endpoint was the safety profile of XM02 when administered for up to a maximum of six cycles of chemotherapy in patients with lung cancer. Relevant secondary endpoints were the duration of severe neutropenia in cycles 1 and 4, the incidence of observed FN, the depth of ANC nadir in cycles 1 and 4, and the time to ANC recovery in cycles 1 and 4.

Patients

The sample consisted of male and female adults with small cell or non-small cell lung cancer who were eligible to receive a platinum-based myelosuppressive chemotherapy; who were either chemotherapy-naïve or had received no more than one prior chemotherapy regimen; who had an ECOG performance status ≤2, an ANC $\geq 1.5 \times 10^9$/L, a platelet count $\geq 100 \times 10^9$/L, a life expectancy of at least 6 months, as well as adequate cardiac, hepatic, and renal function. In addition to common exclusion criteria for GCSF studies involving cancer patients, a relevant exclusion criterion was the chronic use of oral corticosteroids (except for low-dose chronic treatment with ≤20 mg/day prednisolone or equivalent for chronic obstructive pulmonary disease).

A total of 240 patients were randomized to the XM02 (n = 160) and Neupogen® (n = 80) arms in the first chemotherapy cycle. The treatment arms were similar in terms of sex, age, weight, incidence of prior or concomitant medications, ECOG before cycle 1, and cancer stage at screening/baseline (Table 4).

Efficacy

The mean duration of severe neutropenia in cycles 1 and 4 was similar in all treatment arms (Table 5). The difference in the 95% CI in cycle 1 was 0.157 days (–0.114 to 0.428), which was within the predefined equivalence range of ±1 day. There was no significant difference in FN incidence between the arms in all cycles (P = ns). In the XM02 and Neupogen® arms in cycle 1, the mean ANC increased, reaching its maximum on day 5; it decreased to nadir on days 11 and 12, respectively, and then increased following nadir, reaching a maximum on day 14. In cycle 1, there was a significant difference in the mean ANC nadir between both

Table 4 Patient characteristics in study XM02-03-INT

Characteristic – safety set	XM02 (n = 158)	Neupogen®* (n = 79)
Male, n (%)	127 (80.4%)	61 (77.2%)
Age, years (M ± SD)	58.8 ± 8.8	58.1 ± 10.1
Body mass index, (kg/m^2) (M ± SD)	23.99 ± 4.22	24.41 ± 4.17
Cancer type, n (%)		
Small cell	26 (16.5%)	13 (16.5%)
Non-small cell	132 (83.5%)	66 (83.5%)
Cancer stage, n (%)		
Limited (small cell)	6 (3.8%)	2 (2.5%)
Extensive (small cell)	20 (12.7%)	11 (13.9%)
Stage 3 (non-small cell)	54 (34.2%)	22 (27.8%)
Stage 4 (non-small cell)	78 (49.4%)	44 (55.7%)
ECOG before cycle 1, n (%)		
Status 0	29 (18.4%)	19 (24.1%)
Status 1	100 (63.3%)	43 (54.4%)
Status 2	29 (18.4%)	17 (21.5%)

Note: *Patients in this group received Neupogen® in cycle 1 and XM02 afterward. Data from Gatzemeier et al.[14]

Abbreviations: n, number; M, mean; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group.

Table 5 Efficacy endpoints in study XM02-03-INT

Full analysis set (n)	XM02 (n = 160)	Neupogen®* (n = 80)	*P*-value
Mean duration of severe neutropenia (days)			
Cycle 1	0.5	0.3	
Cycle 4	0.4	0.3	
ANCOVA estimate and two-sided 95% CI for difference XM02 in cycle 1 (days)	0.157 (–0.114 to 0.428)		
Mean ANC nadir (10^9/L)			
Cycle 1	2.1	2.9	<0.05#
Cycle 4	2.3	3.2	
ANCOVA estimate and two-sided 95% CI for difference XM02 in cycle 1 (days)	–0.660 (–1.146 to –0.173)		
Mean time to ANC recovery (days)			
Cycle 1	6.3	4.5	<0.05
Cycle 4	6.4	4.5	
ANCOVA estimate and two-sided 95% CI for difference XM02 in cycle 1 (days)	1.686 (0.092 to 3.280)		
Incidence of FN (%)+			
Cycle 1	15.0	8.8	ns
Across all cycles	33.1	23.8	ns

Note: *Patients in this group received placebo in cycle 1 and XM02 afterwards (including in cycle 4); +observed or protocol-defined FN; #in all cycles. Data from Gatzemeier et al.[14]

Abbreviations: n, number; ANCOVA, analysis of covariance; CI, confidence interval; ANC, absolute neutrophil count; FN, febrile neutropenia; ns, not significant.

arms ($P < 0.05$). The difference in the 95% CI in cycle 1 was –0.660 days (–1.146 to –0.173). In cycle 4, the mean ANC nadir was similar across treatment arms. In cycle 1, there was a significant difference in mean time to ANC recovery between both arms ($P < 0.05$). The difference in the 95% CI in cycle 1 was 1.686 days (0.092 to 3.280). In cycle 4, the mean time to ANC recovery was similar in all treatment arms.

Safety

There were no statistically significant differences in mortality between the XM02 and Neupogen® arms. There were 31 deaths during the study: 19 in the XM02 arm and 12 in the Neupogen® arm. None of these deaths was assessed to be related to the study drug. Additional safety data have been summarized elsewhere.[12]

Study XM02-04-INT: non-Hodgkin's lymphoma

Methods

The primary objective of study XM02-04-INT was to demonstrate the safety and efficacy of XM02 when administered for up to a maximum of six cycles of chemotherapy in patients with NHL.[7,8,15] The intent was to document the safety and efficacy of XM02 compared to Neupogen® in NHL patients.

The study was designed as a randomized, controlled, multicenter, Phase III trial in which NHL patients were allocated in a 2:1 scheme to the XM02 or Neupogen® arms, respectively, in the first chemotherapy cycle. In subsequent cycles, all patients received XM02.

Patients underwent a maximum of six chemotherapy cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone with or without adjuvant rituximab (cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone, and rituximab; or cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone) at 3-week intervals. XM02 or Neupogen® administered daily starting 1 day after chemotherapy was completed as an SC 5 µg/kg injection for at least 5 days and up to a maximum of 14 days in the first cycle only. Both study medications were stopped if an ANC of $\geq 10 \times 10^9$/L was reached after nadir.

The primary endpoint of interest to this review was the safety of XM02 when administered for up to a maximum of six cycles of chemotherapy in patients with NHL. Relevant secondary endpoints were the duration of severe neutropenia in cycles 1 and 4, the incidence of observed FN, the depth of ANC nadir in cycles 1 and 4, and the time to ANC recovery in cycles 1 and 4.

Patients

The sample consisted of male and female adult patients with aggressive NHL, defined as diffuse large B-cell lymphoma, mediastinal large B-cell lymphoma, grade 3 follicular lymphoma, or anaplastic large cell lymphoma; patients who were chemotherapy-naïve; patients who had an ANC $\geq 1.5 \times 10^9$/L, a platelet count $\geq 100 \times 10^9$/L, a life expectancy of at least 6 months, as well as adequate cardiac, hepatic, and renal function.

A total of 92 patients were randomized to the XM02 (n = 63), and Filgrastim (n = 29) arms in the first chemotherapy cycle. As detailed in Table 6, the treatment arms were similar in terms of sex, age, weight, and incidence of prior or concomitant medications.

Efficacy

Primary and secondary efficacy endpoints are summarized in Table 7. The mean duration of severe neutropenia in cycles 1 and 4 were similar in all treatment arms. The difference in the 95% CI in cycle 1 was −0.378 days (−0.837 to 0.081), which was within the predefined equivalence range of ±1 day. There was no statistically significant difference in the FN incidence rate between the arms in all cycles (P = ns). In cycle 1, the mean ANC in both the XM02 and Filgrastim arms increased and reached their maximum on day 4, then decreased to a nadir on day 9, then increased again to reach a maximum level on day 11. In cycle 1, there was no significant difference in the mean ANC nadir between both arms (P = ns). In cycle 4, the mean ANC nadir was similar across treatment arms. In cycle 1, there was no significant difference in the mean time to ANC recovery between both arms (P = 0.4939).

Safety

There were no fatal treatment-emergent adverse events in either study arm. One patient who had withdrawn prematurely from the study due to progressive disease died during the observation period. Additional safety data have been summarized elsewhere.[12]

Table 6 Patient characteristics in study XM02-04-INT

Characteristic	XM02 (n = 63)	Filgrastim *(n = 29)
Female, n (%)	32 (50.8%)	12 (41.4%)
Age, years (M ± SD)	50.2 ± 16.1	56.7 ± 15.4
Body mass index, (kg/m^2) (M ± SD)	25.16 ± 4.07	26.13 ± 5.91
Baseline ANC (10^9/L) (M ± SD)	4.99 ± 2.55	4.46 ± 2.36

Note: *Patients in this group received filgrastim in cycle 1 and XM02 afterwards. Data from del Giglio et al.[13]
Abbreviations: n, number; M, mean; SD, standard deviation; ANC, absolute neutrophil count.

Table 7 Efficacy endpoints in study XM02-04-INT

Full analysis set (n)	XM02 (n = 63)	Filgrastim *(n = 29)	*P*-value
Mean DSN (days)			
Cycle 1	0.5	0.9	0.1055
Cycle 4	0.2	0.7	NA
Incidence of FN (%)			
Cycle 1	11.1	20.7	0.1232
Across all cycles	31.7	41.4	0.2094
Mean ANC nadir (10^9/L)			
Cycle 1	1.7	1.1	0.1531
Cycle 4	2.1	1.8	NA
Mean time to ANC recovery (days)			
Cycle 1	6.0	6.7	0.4939
Cycle 4	4.9	6.1	NA

Note: *Patients in this group received filgrastim in cycle 1 and XM02 afterwards. Data from Engert et al.[15]
Abbreviations: n, number; DSN, duration of severe neutropenia; NA, not assessed; FN, febrile neutropenia; ANC, absolute neutrophil count.

Plerixafor and XM02 (Tevagastrim®) as a first-line peripheral blood stem cell mobilization strategy in patients with multiple myeloma and lymphoma candidated to autologous bone marrow transplantation

Methods

The primary objective of this single-center report was to evaluate the safety and efficacy of the combination of XM02 and plerixafor as a first-line strategy to mobilize peripheral blood stem cells in patients with lymphoproliferative disease and multiple myeloma (MM).[7,8,16]

Peripheral blood stem cells were collected for autologous transplantation after induction therapy of a combination of XM02 and plerixafor. XM02 was given for 4 days (10 µg/kg/day). If peripheral blood CD34+ cells were <20 cells/µL, plerixafor was given at a dose of 0.24 mg/kg body weight.

Patients

The study included four patients with NHL, two patients with Hodgkin's disease, and eight patients with MM.

Efficacy

On day 4, the median number of CD34+ cells during the administration of XM02 was 16 per µL. Two patients with MM received plerixafor. On day 5, the median number of

CD34+ cells after plerixafor administration had risen to 60 per μL. For all patients, the median number of CD34+ cells/kg collected after the transplantation procedure was 5.2×10^6 in 75% of patients in a single procedure. The remaining 25% of patients collected in two apheresis.

Safety

No deaths were observed. Additional safety data have been summarized elsewhere.[12]

Comments

The clinical efficacy and safety of XM02, a biosimilar GCSF, were evaluated in randomized controlled Phase III studies in breast cancer, lung cancer, and NHL. These studies were submitted as part of the EMA and FDA authorization process and were also published in refereed journals. These studies provide adequate evidence about the therapeutic equivalence of XM02 relative to originator filgrastim and its superiority over placebo.

While these studies aimed to compare XM02 to Neupogen®, and in study XM02-02-INT also to placebo, they also attempted to optimize patients' exposure to XM02. In study XM02-02-INT, patients randomized to the placebo arm were switched to XM02 after cycle 1 and patients received the treatment for the remainder of the study. In studies XM02-03-INT and XM02-04-INT, patients randomized to the Neupogen® arm were treated with this agent in the first cycle, but they were treated with XM02 in subsequent cycles. These conversions increased the number of patients exposed to XM02 and the number of chemotherapy cycles within and across patients in which XM02 was used.

In addition to cancer patients receiving cytotoxic chemotherapy, the EMA-approved label for XM02 includes cancer patients at risk for prolonged severe neutropenia and designated to undergo myeloablative therapy followed by bone marrow transplantation. The EMA dossier did not include a study to get approval for bone marrow transplant, and this indication was received by extrapolation. Since the approval of XM02 by the EMA, a single-center experience study on 14 patients with MM and lymphoma, and who were treated with plerixafor and XM02, was published.[17] This combination of drugs was found to be an effective nontoxic method to mobilize stem cells. The study provides preliminary evidence in support of the stem cell mobilization indication. Extrapolation may also have been applied in the inclusion, in the EMA label, of the indications related to human immunodeficiency virus and infections. Note that the FDA label for XM02 is limited to the reduction of severe neutropenia and FN in patients with nonmyeloid malignancies treated with cytotoxic chemotherapy. The XM02 dossier was submitted under the Biologics License Application pathway, as the FDA had not yet established a biosimilar pathway.

Based on the available data in routine clinical practice, the clinical and safety outcomes of XM02 are likely to be similar to those of Neupogen®. XM02 and Neupogen® can be assumed to be interchangeable in the approved indications. Patients previously treated with Neupogen® and who switched to XM02 can be expected to show similar efficacy and safety outcomes. XM02 has not been compared to EP2006 (Zarzio®; Sandoz International GmbH, Holzkirchen, Germany), or the Hospira product Nivestim™ (Hospira, Inc, Lake Forest, IL, USA) (no code available). Eporatio (Merckle Biotec GmbH, Ulm, Germany) and Teva are the two other EMA-approved biosimilar GCSFs. The three biosimilar products should not be assumed to be interchangeable.

Acknowledgments

Alaa Bagalagel and Abdulaziz Mohammed were supported as Fellows and Ivo Abraham as Director of the Postdoctoral Fellowship Program in Clinical Research in Human Therapeutics at the University of Arizona and funded by King Abdulaziz University, Jeddah, Saudi Arabia. Ivo Abraham was also supported as Director of the Arizona Area Health Education Center (AzAHEC) Interprofessional Fellowship Program in Clinical Outcomes and Comparative Effectiveness Research, funded by the Bureau of Health Professions, US Department of Health and Human Services through the AzAHEC Program. The services of Karen MacDonald were contributed pro bono by Matrix45.

Disclosure

Karen MacDonald and Ivo Abraham are principals of Matrix45, which has received research grants and contracts related to GCSF from Sandoz/Novartis. By company policy, they cannot hold equity in sponsor organizations, nor receive direct personal benefits, financial or other, from sponsor organizations. Matrix45 provides similar services to other biopharmaceutical companies without exclusivity constraints. The present paper was prepared independently. The manufacturer of the biosimilar reviewed here was not contacted for data, publications, or other sources of information, nor did it have any input on the review activities or in the preparation of the manuscript. Alaa Bagalagel and Abdulaziz Mohammed report no conflicts of interest in this work. The authors report no other conflicts of interest in this work.

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