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ORIGINAL RESEARCH

Peripheral Blood Stem Cell Mobilization and Engraftment after Autologous Stem Cell Transplantation with Biosimilar rhG-CSF

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ABSTRACT

Introduction: Biosimilar versions of filgrastim [recombinant human granulocyte colony-stimulating factor (rhG-CSF)] are now widely available. To date, biosimilar rhG-CSF has demonstrated a comparable quality, safety and efficacy profile to the originator product (filgrastim [Neupogen®], Amgen Inc., CA, USA) in the prevention and management of neutropenia. Biosimilar rhG-CSFs have also been used to induce peripheral blood stem cell (PBSC) mobilization in patients undergoing autologous stem cell transplantation (AHSCT). The authors have examined the effectiveness of a biosimilar rhG-CSF (Zarzio®, Sandoz Biopharmaceuticals, Holzkirchen, Germany) in two retrospective studies across two medical centers in Hungary.

Methods: In Study 1, 70 patients with hematological malignancies scheduled to undergo AHSCT received chemotherapy followed by biosimilar rhG-CSF (2×5 μg) for facilitating neutrophil, leukocyte, and platelet engraftment. In study 2, 40 additional patients with lymphoid malignancies and planned AHSCT received chemotherapy followed by biosimilar rhG-CSF for PBSC mobilization. The effectiveness of treatment was assessed by the average yield of cluster of differentiation (CD) 34+ cells and the number of leukaphereses required.

Results: In Study 1 (patients undergoing AHSCT), the median age was 56 years and most patients were male (60%). The conditioning regimens were mainly high-dose melphalan ($n = 41$) and carmustine (BiCNU®, Bristol-Myers Squibb, NJ, USA), etoposide, cytarabine and melphalan BEAM ($n = 21$).

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Median times to absolute neutrophil and leukocyte engraftment were 9 (range 8–11 days) and 10 (8–12) days, respectively. Median time to platelet engraftment was 10.5 days (7–19 days). In Study 2, the patients' median age was 54 years and the majority (57.5%) were female. The median time interval between day 1 of mobilizing chemotherapy and first leukapheresis was 12 (9–27) days. In the autologous PBSC grafts, the median number of CD34+ cells harvested was 5.2×10^6/kg ($2.22–57.07 \times 10^6$/kg). The median yield of CD34+ cells per leukapheresis product was 2.47×10^6/kg. In total, 58 leukaphereses were performed in 40 successfully harvested patients. ***Conclusions***: In line with previous studies with originator rhG-CSF, the findings of this study indicate that biosimilar rhG-CSF following AHSCT is effective and generally well tolerated in the engraftment setting. In addition, biosimilar rhG-CSF is comparable to the originator rhG-CSF in terms of kinetics of PBSC mobilization and yield of CD34+ cells. In conclusion, the authors have demonstrated that the use of biosimilar rhG-CSF is effective and safe in autologous PBSC mobilization and engraftment after AHSCT.

Keywords: Autologous stem cell transplantation; Biosimilar rhG-CSF; Engraftment; Hematology; Neutropenia; Oncology; Peripheral blood stem cell mobilization

INTRODUCTION

Patients with hematological malignancies are often treated with recombinant human granulocyte colony-stimulating factor (rhG-CSF) to mobilize and collect peripheral blood stem cells (PBSC) for autologous hematopoietic stem cell transplantation (AHSCT). Biosimilars are approved biologics with comparable quality, safety and efficacy to a reference product following loss of patent protection. Biosimilar rhG-CSF has been available since 2009 in Europe, with approval based on having demonstrated comparability with the original filgrastim product (Neupogen®, Amgen Inc., CA, USA). Biosimilar rhG-CSFs have shown to be comparable to the originator rhG-CSF in terms of pharmacodynamic response in healthy volunteers, as well as in overall efficacy and safety when used as prophylaxis for chemotherapy-induced neutropenia [1, 2].

Molecular kinetics data at the receptor-binding site have shown direct stimulation of bone marrow cells through the rhG-CSF cell surface receptor with both a biosimilar (Zarzio®, Sandoz Biopharmaceuticals, Holzkirchen, Germany) and the originator rhG-CSF product, thus demonstrating that their mode of action is identical [3]. Therefore, during the approval process of Zarzio®, extrapolation to all indications of the reference rhG-CSF product was considered acceptable, including mobilization of hematopoietic stem cells. Since the approval of other biosimilar rhG-CSFs, the reported clinical experience for hematopoietic stem cell transplantation has suggested similar efficacy and tolerability as with the reference product [2, 4–6].

To further expand the authors' clinical experience of the use of biosimilar rhG-CSF, two separate observational studies were conducted across two large hospitals in Hungary. In the first study, the ability of biosimilar rhG-CSF to facilitate engraftment in patients with hematological malignancies undergoing AHSCT was evaluated. In the second study, the authors examined the efficacy and safety of biosimilar rhG-CSF following chemotherapy for PBSC mobilization in patients with lymphoid tumors.

METHODS

Both studies were retrospective and observational in design and were based on the authors' own clinical experience across two medical centers in Hungary (St. Istvan and St. Laszlo Hospital, Budapest, and the Albert Szent-Györgyi Clinical Centre, University of Szeged, Szeged).

Both studies were approved by the relevant ethics committee and were conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000 and 2008. Informed written consent was obtained from all patients for being included in the study.

Study 1

The primary objective of this study was to evaluate the effectiveness and safety of engraftment following treatment with biosimilar rhG-CSF in patients undergoing AHSCT.

A total of 70 patients with hematological malignancies scheduled to receive biosimilar rhG-CSF after AHSCT for facilitating neutrophil, leukocyte, and platelet engraftment were enrolled between May 2011 and March 2012. Patients aged between 15 and 70 years were eligible for the study if they had an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 [7], with adequate hepatic, cardiac and renal function. The originator rhG-CSF product (Neupogen®) was used for PBSC mobilization in combination with chemotherapy. Neupogen® was administered 24 h after the last day of the mobilizing chemotherapy at a standard daily dose 2×5 μg/kg. Non-Hodgkin's lymphoma patients with B-cell phenotype also received 375 mg/m^2 rituximab as part of their chemotherapy regimen and for in vivo purging.

Autologous Hematopoietic Stem Cell Transplantation

The high-dose conditioning regimens were Carmustine (BiCNU®, Bristol-Myers Squibb, NJ, USA), etoposide, cytarabine and melphalan (BEAM) and total body irradiation plus cyclophosphamide (TBI-CY). BEAM 300 mg/m^2 i.v. on day −6, etoposide 200–400 mg/m^2 i.v. on days −5 to −2, cytarabine 200 mg/m^2 i.v. × 2 on days −5 to −2 and melphalan 140 mg/m^2 i.v. on day −1). TBI-CY comprised total body irradiation (TBI) (12 Gy, fractionated on days −7 to −4) and high-dose cyclophosphamide (CY) (60 mg/kg bodyweight i.v. on days −3 and −2). Non-Hodgkin's lymphoma patients with B-cell phenotype also received 500 mg/m^2 rituximab on day −1. Multiple myeloma patients received 200 mg/m^2 melphalan i.v. on day −1. Reinfusion of stem cells was performed on day 0.

All patients received biosimilar rhG-CSF (Zarzio®) 5 μg/kg/day beginning on day 1 after PBSC infusion and continuing until leukocyte engraftment. Leukocyte engraftment was defined as an absolute neutrophil count of $>0.5 \times 10^9$/L on the first of three consecutive days (with 1×10^9/L considered a safe upper limit), and platelet engraftment was defined as a platelet count of 20×10^9/L for 2 consecutive days without platelet transfusions. Biosimilar rhG-CSF was typically continued beyond first day of leukocyte engraftment to ensure a sustained response. Patients received irradiated red blood cell and platelet transfusion support when hemoglobin was $<80 \times 10^9$/L and platelets were $<10 \times 10^9$/L. Acyclovir, levofloxacin, and fluconazole were used for infection prophylaxis. In addition to demographic data, information on previous chemotherapy regimens, duration of initial response, disease stage at relapse, remission

status before transplant, time to neutrophil and platelet engraftment, hematological and non-hematological complications were extracted from the patients' medical records.

Study 2

Forty additional patients with lymphoid malignancy who were scheduled to receive biosimilar rhG-CSF following chemotherapy for autologous PBSC mobilization were recruited from January 2012 to May 2012. Eligible patients (aged 15–70 years) had an ECOG performance status $\geq$2, with adequate hepatic, cardiac, and renal function. The primary objective of Study 2 was to conduct a retrospective analysis of the efficacy and safety of biosimilar rhG-CSF following chemotherapy for PBSC mobilization in patients with lymphoid tumors.

GCSF Treatment and Apheresis

Different induction chemotherapy regimens were administered according to tumor type. The mobilization regimens used for Study 2 included biosimilar rhG-CSF at a standard daily dose 2×5 μg/kg until the end of the leukapheresis. Apheresis was performed when the absolute number of circulating cluster of differentiation (CD) 34+ cells in the peripheral blood was $\geq$20/μL. One or more apheresis were performed until the cumulative yield of CD34+ cells was $\geq 2 \times 10^6$/kg, representing the pre-set threshold to guarantee a safe hematological recovery. All patients were evaluable for the effects of growth factor regimens on toxicity and hematological recovery after mobilizing chemotherapy.

The methodology of PBSC harvest was identical in all patients. Venous access was obtained by a central vein catheter placed in the subclavian vein, to achieve high flow rates. Peripheral blood mononuclear cells (PBMCs) were harvested with a continuous flow cell separator, COBE® Spectra Aphaeresis System (Terumo BCT, CO, USA). For each leukapheresis, whole blood was processed at a flow rate of 50–70 mL/min. The duration of each apheresis depended on blood flow; the number of apheresis procedures depended on the yield of CD34+ cells. All leukapheresis products were processed, frozen, and stored on the day of collection. Quantification of CD34+ cells by flow cytometry was as described for Study 1. Patients were classified into three groups, on the basis of the total yield of CD34+ cells obtained at the completion of the mobilization episode: optimal collection ($\geq 5 \times 10^6$ CD34+ cells/kg), low-yield collection ($\geq 2 \times 10^6$ to $< 5 \times 10^6$ CD34+ cells/kg), and collection failure (apheresis not attempted because of a peripheral blood CD34+ cell count <10/μL).

Hematological and Flow Cytometric Analysis

Blood cell counts were performed to monitor the mobilization or recovery of white blood cells (WBC), with determination of the number of CD34+ cells in peripheral blood when WBC count $\geq 1 \times 10^9$/L.

The ProCount™ progenitor cell enumeration kit (Becton-Dickinson, CA, USA) was used as an in vitro diagnostic test to identify and quantify absolute counts and percentages of CD34+ cells in peripheral blood, mobilized peripheral blood, and leukapheresis samples using flow cytometry. For the CD34+ cell count using the ProCount™ protocol, fresh peripheral blood, or PBSC sample (50 μL) was incubated with control antibodies, anti-CD34 antibody (ProCount™ kit, Becton-Dickinson, CA, USA) or anti-human CD45/fluorescein

isothiocyanate. The CD34+ cell count was carried out by the CellQuest™ program (Becton-Dickinson, CA, USA) and the ProCount™ protocol from Becton-Dickinson. Acquisition and analysis of the data were performed using a flow cytometer (FACSCalibur™, Becton-Dickinson, CA, USA). Results are presented as number of CD34+ cells per milliliter of leukapheresis product.

Safety

Adverse events (AEs) arising during rhG-CSF therapy were monitored and recorded at each visit in both studies.

RESULTS

Study 1

Seventy patients scheduled to receive AHSCT were recruited and treated. Median age was 56 years and the majority were male (60%). Patient characteristics are shown in Table 1. The diagnoses of the patients were: multiple myeloma (41 patients, 59%), non-Hodgkin's lymphoma (19 patients, 27%), and Hodgkin's lymphoma (10 patients, 14%).

The median time from diagnosis to mobilization was 8 months (range 3–187 months). CY was used as the main mobilizing regimen for patients with multiple myeloma ($n = 37$), while dexamethasone + cisplatin + cytarabine (DHAP) was used for lymphoma patients ($n = 18$). In case of unsuccessful collection of CD34+ progenitors ($n = 3$, %), after a rest period of 3–4 weeks, remobilization was attempted by using high-dose etoposide ($n = 2$) or cyclophosphamide ($n = 1$). All remobilization attempts were successful.

Table 1 Clinical characteristics of the enrolled patients

Characteristic	Study 1 ($n = 70$)	Study 2 ($n = 40$)
Median age (range), years	56 (24–70)	54 (25–69)
Male, *n* (%)	42 (60)	17 (42.5)
Female, *n* (%)	28 (40)	23 (57.5)
Diagnosis, *n* (%)		
Multiple myeloma	41 (59)	21 (52.5)
Non-Hodgkin's lymphoma	19 (27)	16 (40)
Diffuse large B-cell lymphoma	7	9
Mantle cell lymphoma	7	2
Lymphoplasmacytic lymphoma	2	2
Follicular lymphoma	1	2
Peripheral T-cell lymphoma	1	1
Burkitt's lymphoma	2	0
Hodgkin's lymphoma	10 (14)	3 (7.5)

The following AHSCT conditioning regimens were administered: high-dose melphalan ($n = 41$, 59%), BEAM ± rituximab ($n = 21$, 30%) and TBI-CY ± rituximab ($n = 8$, 11%). At the time of AHSCT, the median number of re-infused CD34+ cells was 6.33×10^6/kg (range 2–17.4×10^6/kg) (Table 2). Median times for achieving absolute neutrophil/leukocyte engraftment were 9 days (range 8–11) and 10 days (range 8–12), respectively (Table 2). The median time for platelet engraftment was 10.5 days (range 7–19 days) and the median duration of biosimilar rhG-CSF administration was 11 days (range 9–13).

Study 2

Forty patients with planned AHSCT received biosimilar rhG-CSF after the last day of

Table 2 Results of Study 1: AHSCT and engraftment following treatment with Zarzio®

Assessment	Study 1 ($n = 70$)
Conditioning regimen	
High-dose melphalan, *n* (%)	41 (59)
BEAM ± rituximab, *n* (%)	21 (30)
TBI-CY ± rituximab, *n* (%)	8 (11)
AHSCT procedure	
Median CD34+ cell count (range), $\times 10^6$/kg	6.33 (2–17.4)
Engraftment results	
Median ANC ($>0.5 \times 10^9$/L)	9 (8–11)
Median ANC ($>1.0 \times 10^9$/L)	10 (8–12)
Median thrombocytes ($>20 \times 10^9$/L)	10.5 (7–19)

AHSCT autologous hematopoietic stem cell transplantation, *ANC* absolute neutrophil count, *BEAM* carmustine (BiCNU®), etoposide, cytarabine and melphalan, *TBI-CY* total body irradiation plus cyclophosphamide

chemotherapy for PBSC mobilization. Median age was 54 years and the majority of patients in this group were female (57.5%). Patients' diagnoses were: multiple myeloma ($n = 21$, 52.5%), non-Hodgkin's lymphoma ($n = 16$, 40%), and Hodgkin's lymphoma ($n = 3$, 7.5%) (Table 1).

The majority of patients received CY ($n = 21$, 48%) or DHAP ± rituximab ($n = 13$, 29%) as a mobilization regimen in combination with Zarzio®. The following mobilizing regimens were administered to the remaining 10 patients: high-dose ifosfamide containing regimens ($n = 4$, 9%), etoposide, dexamethasone, cytarabine (Ara-C), cisplatin (EDAP) ($n = 3$, 7%), hyper-cyclophosphamide, vincristine, adriamycin and dexamethasone (CVAD) arm B ($n = 2$, 5%), and velcade, CVAD, thalidomide, cisplatin, adriamycin, cyclophosphamide and etoposide ($n = 1$, 2%). Four patients received chemotherapy plus Zarzio® due to prior mobilization failure.

CD34+ cells were harvested successfully from the majority of patients ($n = 36/40$, 91%). The incidence of mobilization failure was 10% ($n = 4$), all of these patients received CY+ rhG-CSF. The median time interval between day 1 of the cycle of chemotherapy mobilization and the first leukapheresis session was 13 days (range 9–27). According to type of chemotherapy, the median interval between day 1 of chemotherapy and the first day of apheresis was 11 days (range 9–15) for the CY+ rhG-CSF group and 15 days (range 12–22) for the DHAP + rhG-CSF group.

The median duration of treatment with Zarzio® until PBSC harvest was 10 days (range 6–24) (Table 3). A second remobilization attempt was made in four patients. For remobilization, the following regimens were used: EDAP ($n = 1$), ifosfamide, etoposide, Ara-C, methotrexate ($n = 1$), DHAP ($n = 1$), and CY ($n = 1$). These included three patients who received plerixafor because they did not reach the number of CD34+ cells required to start leukapheresis (Table 3). A remobilization attempt was eventually successful (CD34+ cells were collected, although with suboptimal yields). Ultimately, four patients received plerixafor including one case where its administration was used first-line with the CY + rhG-CSF regimen. None of these patients underwent bone marrow harvesting.

In 40 successfully harvested patients, a total of 58 leukaphereses procedures were performed. Most patients (62.5%) underwent just one leukapheresis, while 35% of patients received the procedure twice, with a median of 1.4 leukaphereses per patient (Table 3). The median number of CD34+ stem cells in the peripheral blood at the start of PBSC collection was 51/μl (range 8–393/μl). In the autologous

Table 3 Results of Study 2: chemotherapy in combination with Zarzio® for autologous PBSC mobilization

PBSC mobilization results	**Total (n = 44)[a]**
Successful mobilization, n (%)	40 (91)
Mobilization failure, n (%)	4 (9)
Mobilization regimen[b] plus plerixafor, n (%)	4 (9)
Median interval between chemotherapy and PBSC apheresis, days (range)	13 (9–27)
Median treatment duration with cyclophosphamide and Zarzio®, days (range)	11 (9–15)
Median treatment duration with DHAP and Zarzio®, days (range)	15 (12–22)
Median treatment duration with Zarzio® until starting PBSC harvest, days (range)	10 (6–24)
PBSC harvest results	**n = 40**
1 PBSC apheresis	25 (62.5)
2 PBSC aphereses	14 (35)
4 PBSC aphereses	1 (2.5)
Total number of leukaphereses	58
Number of leukaphereses per mobilization	1.4
Peripheral blood CD34+ cell count (per μl) at the start of leukapheresis (range)	51 (8–393)
Median (range) number of CD34+ cells harvested ($\times 10^6$/kg)	5.2 (2.22–57.07)
Median (range) number of CD34+ cells per leukapheresis ($\times 10^6$/kg)	2.47 (0.54–57.07)

CD cluster of differentiation, *CY* cyclophosphamide, *DHAP* dexamethasone + cisplatin + cytarabine, *EDAP* etoposide, dexamethasone, Ara-C, cisplatin; *PBSC* peripheral blood stem cell

[a] Four patients underwent a second mobilization procedure due to mobilization failure at the first attempt

[b] CY, DHAP and EDAP. Four of the 40 successfully mobilized patients received this regimen

PBSC grafts, the median number of the CD34+ cells harvested per patient was 5.2×10^6/kg (range 2.22–57.07 $\times$ 10^6/kg). In total, 67.5% of patients achieved optimal stem cell collection (defined as $\geq 5 \times 10^6$ CD34+ cells/kg); among these patients the median number of harvested CD34+ cells was 9.74×10^6/kg (range 5.05–57.07 $\times$ 10^6/kg). Attempted collections were sub optimal for the remaining 32.5% patients, whose median number of harvested CD34+ cells was 3.65×10^6/kg (range 2.22–4.9 $\times$ 10^6/kg). The median yield of CD34+ cells per leukapheresis product was 2.47×10^6/kg, with a high degree of variability between patients (Table 3).

Safety

The AE profile of biosimilar rhG-CSF during Study 1 was comparable to that previously reported for the reference product (Neupogen®), with a similar occurrence of common AEs such as neutropenic fever (>38 °C), which was observed in 45 patients (64%) including five patients with sepsis, five patients with central-catheter associated infection, two patients with pneumonia, and two patients with perianal soft tissue infection. Other non-hematological toxicities related exclusively to the conditioning regimen were: 55 cases (78%) of grade 1–4 mucositis; 41 cases

(58%) of diarrhea; and 7 cases (10%) of toxicoderma. Engraftment syndrome (fever and rash following transplantation) occurred in nine patients (13%). Poor graft function was observed in one patient. There were no treatment-related deaths before day 100 after transplantation.

DISCUSSION

The authors' studies examined the effectiveness of a biosimilar rhG-CSF (Zarzio®) to facilitate engraftment (Study 1) or PBSC mobilization (Study 2) in patients with hematological malignancies. The findings from Study 1 indicate that the median number of re-infused CD34+ cells (6.33×10^6/kg) and the time to engraftment (9–10 days) are comparable to those previously reported with the reference product (Neupogen®) in the literature [8, 9] and in the author's own experience. Similarly, the results from Study 2 showed that chemotherapy in combination with biosimilar rhG-CSF enables successful PBSC mobilization and harvesting in the majority of patients (91%). The median number of CD34+ cells collected at each leukapheresis and the number of leukapheresis necessary to harvest the required number of CD34+ cells was also comparable to the reference product when combined with chemotherapy [10].

Due to the nature of our studies (Study 1 and 2), they carry certain intrinsic limitations, such as being retrospective, open label, non-comparative, non-controlled, and having a relatively small sample size. Nonetheless, the authors' experience with biosimilar rhG-CSF is consistent with the data reported in the literature. For instance, a French study of patients with hematological malignancies who received rhG-CSF for autologous PBSC mobilization reported no significant differences between biosimilar and originator rhG-CSF in the median number of CD34+ cells mobilized, or in the number of rhG-CSF injections and leukaphereses required to harvest the minimum CD34+ cell count [4]. In addition, a follow-up study examining the use of rhG-CSF biosimilars for PBSC mobilization and transplantation in lymphoma and myeloma patients reported that the results achieved after 1 year with biosimilar rhG-CSF were comparable with a historical cohort of patients treated with the reference product; i.e., there were no significant differences between the two formulations in terms of PBSC stimulation or biological parameters of bone marrow recovery [5].

Many ongoing studies are continuing to evaluate the long-term safety of biosimilar rhG-CSF in a variety of clinical settings and patient populations. Given the equivalent pharmacokinetic and pharmacodynamic properties and mode of action of biosimilar versus reference rhG-CSF, as well as their lack of immunogenicity [1, 3], no major differences in their long-term safety profiles are expected. In the authors' own experience, they have noted a similar safety profile with the biosimilar as with the reference rhG-CSF, although longer-term observations are not yet available. Furthermore, the use of biosimilars may offer significant cost savings and help reduce hospital expenditure. In an analysis of rhG-CSF use for the prevention of chemotherapy-induced neutropenia, biosimilars were associated with cost savings of around 25%, compared with the reference product [11]. Other studies have also indicated substantial cost savings through the use of biosimilar rhG-CSF for autologous PBSC mobilization and transplantation [4, 5]. In addition, recent data from the literature, combined with the findings of this study,

support the use of a combination regimen of biosimilar rhG-CSF with plerixafor in patients proven or predicted to be poor mobilizers, in order to improve the likelihood of obtaining optimal stem cell yields for AHSCT in just a few days of apheresis [12].

CONCLUSION

Biosimilar rhG-CSF products are becoming widely used in primary and secondary prevention of neutropenia after salvage chemotherapy in patients with lymphoid malignancies. On the basis of the authors' own clinical experience, Zarzio® showed a similar efficacy and safety profile as its reference product when administered after AHSCT in the engraftment setting, and has also shown comparable results to Neupogen® in terms of kinetics of PBSC mobilization and yield of stem cells collected. These findings are consistent with the authors' earlier observations. In addition, the use of biosimilar rhG-CSF is feasible in the management of post-autograft neutropenia. In conclusion, the use of a biosimilar rhG-CSF is effective in the setting of autologous PBSC mobilization and engraftment after AHSCT in patients with hematological malignancies, without any additional safety concerns and potential cost savings.

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Conflict of interest. P. Reményi, L. Gopcsa, I. Marton, M. Réti, G. Mikala, M. Pető, A. Barta, Á. Bátai, Z. Farkas, Z. Borbényi, Z. Csukly, I. Bodó, J. Fábián, Á. Király, L. Lengyel, K. Piukovics, É. Torbágyi, and T. Masszi declare no conflict of interest.

Compliance with ethics guidelines. Both studies were approved by the relevant ethics committee and were conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000 and 2008. Informed written consent was obtained from all patients for being included in the study.

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