Original Article

Comparative pharmacokinetics, efficacy, and safety of bevacizumab biosimilar to reference bevacizumab in patients with metastatic colorectal cancer

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Abstract

OBJECTIVE: To establish clinical biosimilarity of BevaciRel™ bevacizumab biosimilar (study bevacizumab) with the reference innovator bevacizumab in terms of pharmacokinetics, efficacy, and safety in metastatic colorectal cancer (mCRC). **MATERIALS AND METHODS:** A total of 119 patients with mCRC were enrolled across 20 centers and randomized to receive study and reference bevacizumab in this Phase III clinical study. Of these, 116 patients were administered bevacizumab 5 mg/kg intravenously every 2 weeks with folinic acid, fluorouracil, and irinotecan regimen. The primary endpoint of the study was objective response rate (ORR) at week 25, and the secondary endpoints assessed were progression-free survival (PFS), overall survival (OS), and assessment of pharmacokinetics and safety along with immunogenicity in both treatment arms. **RESULTS:** The ORR was 60.53% in study bevacizumab and 66.67% in reference arm. The proportions of subjects showing CR and PR were comparable in both the arms. The median PFS at 1 year was 3.83 months in test arm and 4.6 months in reference arm. The mean OS was 10.91 months in test arm and 14.68 months in reference arm. The difference in ORR, median PFS, and OS was not statistically significant ($P > 0.05$). The median T_{max} was 6.00 h in both the arms. The median t½ was 330.63 h and 226.14 h, respectively, for test and reference bevacizumab. The adverse event profile of both products was in line with the known profile of bevacizumab. **CONCLUSION:** The study biosimilar bevacizumab was found to be noninferior and clinically biosimilar to the reference bevacizumab, thereby meeting an unmet medical alternative need in mCRC.

Key Words: Bevacizumab, colorectal, comparative, metastatic colorectal cancer

Introduction

Colorectal cancer (CRC) is a formidable health problem worldwide. It is the third most common cancer in men (10.0% of all cancer cases) and the second most common in women (9.4% of all cancer cases).[1,2] Approximately 20% of CRC cases have been metastasized at the time of diagnosis. The most common sites of metastatic disease for CRC are liver, followed by lungs. Metastatic CRC can often present as treatment dilemmas.[3]

The appreciation that tumors induce blood vessel formation, allowing extension beyond a few millimeters in size, stimulated efforts at inhibiting this type of angiogenesis as a means of controlling the growth and spread of cancer cells. The most successful of these efforts to date has focused on neutralizing the vascular endothelial growth factor (VEGF), which is a soluble protein instrumental in angiogenesis. Bevacizumab, a humanized antibody directed against the VEGF, has been examined in combination with chemotherapeutic agents in several clinical studies in patients with advanced colorectal cancer (mCRC).

Bevacizumab binds to all isoforms of VEGF-A, blocks the activation of endothelial cell surface VEGF receptors (VEFGR1 and VEGFR2), and finally leads to the regression of tumor vascularization and inhibition of the tumor nutrition supply.[4]

Clinical studies of bevacizumab in combination with 5-fluorouracil-based regimens have shown that combination therapy is well tolerated and its toxicity is not substantially Greater than that of the chemotherapy alone.[5]

BevaciRel™ (bevacizumab) from Reliance Life Sciences was developed as the first global biosimilar to innovator bevacizumab with comprehensive establishment of physicochemical and biological biosimilarity. The aim of the present study was to establish clinical similarity of the biosimilar bevacizumab with the reference or innovator bevacizumab product in terms of pharmacokinetics, efficacy, and safety in combination with folinic acid, fluorouracil, and irinotecan (FOLFIRI) regimen in patients with metastatic colorectal cancer (mCRC).

Materials and Methods

This was a prospective, multicenter, open-label, two-arm, parallel group, active control, randomized comparative clinical study (CTRI/2013/05/003699) in a total of 119 patients with mCRC. Subjects were randomized to receive biosimilar or reference bevacizumab. The study was conducted in compliance with the ethical principles that originated in the Declaration of Helsinki and ICH-GCP and Indian Schedule-Y regulations. Out of 119 subjects, 116 subjects (83 subjects in biosimilar arm and 33 subjects in reference arm) received bevacizumab in combination with FOLFIRI regimen. Bevacizumab 5 mg/kg was administered intravenously every 2 weeks with chemotherapy (FOLFIRI regimen) in both the arms. FOLFIRI regimen consisted of irinotecan (180 mg/m^2 intravenous [IV] infusion over 2 h), leucovorin (400 mg/m^2 IV infusion over 2 h), and 5-FU (400 mg/m^2 as an IV bolus followed by 2400 mg/m^2 IV infusion over 46 h).

Pharmacokinetic parameters (C_{max}, AUC_{0-336}, $AUC_{0-\infty}$, T_{max}, and t½) were analyzed for single dose of biosimilar

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bevacizumab and reference product in 42 subjects (21 subjects in each arm).

The primary endpoint of the study was objective response rate (ORR) at week 25. The response was evaluated by CT scan performed at week 7, 13, 19, and 25 compared to baseline CT scan data for each subject. The secondary endpoints assessed were progression-free survival (PFS) at 1 year (assessed by RECIST 1.1 criteria) and overall survival (OS) at 2 years. Safety assessment included the incidence of treatment-emergent adverse events and abnormal clinical as well as laboratory results from baseline to the end of the study. Treatment emergent adverse events were followed till their resolution, and adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 16.1. (Oracle Corporation, California, USA). Immunogenicity assessment was included as an additional safety parameter assessed at week 25. Statistical analyses were performed using the SAS® system. Comparative analysis was performed for primary and secondary endpoint data.

The disposition of study subjects

Intent-to-treat (ITT) population included all 119 subjects randomized in the study while safety population included all subjects who were randomized and received at least a single dose of study medication (116 subjects; 83 in the study arm and 33 in the reference arm). Safety analysis was done using both safety and ITT populations. Pharmacokinetic assessment was performed in 42 subjects. Twenty subjects in bevacizumab biosimilar arm and 22 subjects in reference arm were included in pharmacokinetic analysis.

A total of 53 subjects, 38 from study arm and 15 subjects from reference bevacizumab arm, completed the 25-week study for the primary efficacy endpoint. A total of 100 subjects completed at least one post baseline assessment or were early death cases and were considered as response evaluable subjects (73 subjects from study arm and 27 subjects from reference arm) [Figures 1 and 2].

Results

The baseline demographic parameters were comparable in the study and reference arms. Table 1 presents the baseline characteristics of the patients in both treatment arms. The mean age of subjects randomized to the study arm was 46.9 years and the mean weight was 55.7 kg. In the study arm, 28 (32.56%) subjects were females and 58 (67.44%) subjects were male. The mean age of subjects randomized in the reference arm was 51 years with mean weight of 55.4 kg. In the reference arm, 3 (39.39%) subjects were females and 20 (60.61%) subjects were male [Table 1]. Eastern Cooperative Oncology Group performance status was 24.42% in the study arm and 39.39% in the reference arm.

Pharmacokinetic analysis

In the pharmacokinetic analysis, the mean C_{max} was 96.79 and 103.92 µg/mL, AUC_{0-336} was 13682.01 and 15704.93 µgh/mL, and $AUC_{0-\infty}$ was 27518.93 and 25396.16 µgh/mL, respectively, for reference and study bevacizumab. Mean T_{max} was achieved at 9.27 h (median: 6.00 h) and 8.70 h (median: 6.00 h) and t½ was 330.63 h and 226.14 h, respectively, for reference and study bevacizumab. The median t½ observed for reference and study products was 184.4 h and 221.73 h, respectively. Statistically, mean C_{max} was comparable in both arms. The AUC_{0-336} was comparable in both arms, but the concentration achieved over this timeframe is on higher side for study product as compared to reference. The observed variability of the pharmacokinetic parameters lnC_{max} and $lnAUC_{0-336}$ is 23.48 and 32.69, respectively.

Efficacy results

The ORR was observed to be 60.53% in study bevacizumab arm compared to 66.67% in reference arm at 25 weeks. In study arm, 7.9% subjects showed complete response and 52.63% subjects showed partial response. In reference arm, no subjects had shown complete response and 10 (66.67%) subjects showed partial response. The proportions of subjects showing ORR in each arm were

Figure 1: Patient disposition

Table 1: Baseline Characteristics of patients

Parameter	Variable	Biosimilar bevacizumab (*n*=86)	Reference bevacizumab (*n*=33)	Total (*n*=119)	*P*
Age	Mean	46.9	51.0	48.1	*P*=0.0937
	Std Dev	12.23	10.77	11.94	
Body surface area (BSA)	Mean	1.6	1.6	1.6	*P*=1.0000
	Std Dev	0.18	0.18	0.18	
Weight	Mean	55.7	55.4	55.6	*P*=0.8956
	Std Dev	11.28	10.78	11.10	
Sex	Female	28 (32.56%)	13 (39.39%)	41 (34.45%)	
	Male	58 (67.44%)	20 (60.61%)	78 (65.55%)	
ECOG Criteria	0	21 (24.42%)	13 (39.39%)	34 (28.57%)	
	1	58 (67.44%)	17 (51.52%)	75 (63.03%)	
	2	7 (8.14%)	3 (9.09%)	10 (8.40%)	

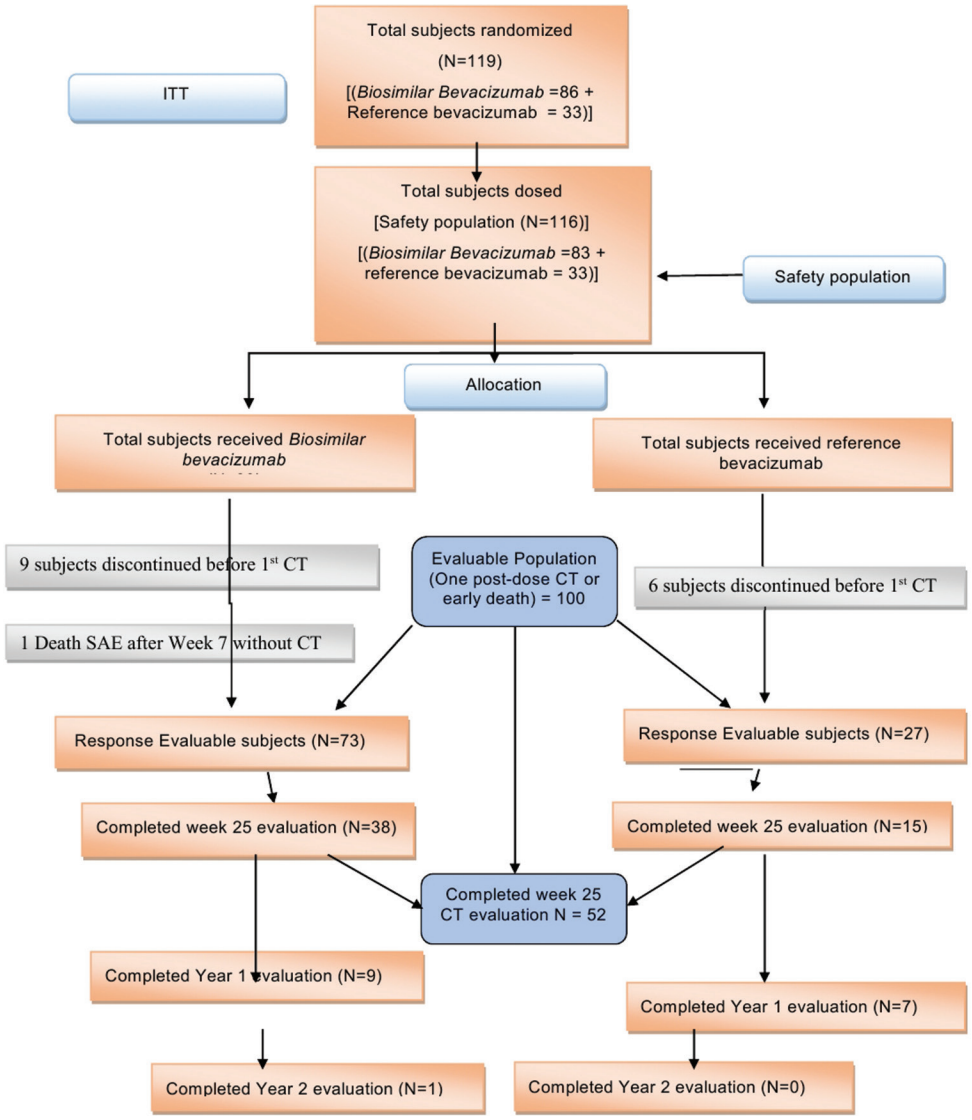

Figure 2: Detailed patient disposition

compared for statistical significance and the difference was found to be nonsignificant ($P > 0.05$) [Table 2].

In the additional analysis to evaluate the response rates (RRs) in subjects missing CT evaluation at week 25, ORR showed comparable response for study and reference arms (49.25% vs. 56%). The proportion of subjects showing ORR in each arm showed no statistical difference ($P > 0.05$).

In secondary efficacy analysis, the median PFS from baseline was 3.83 months in study bevacizumab arm and 4.6 months in reference arm [Table 3]. The PFS in each arm was compared for statistical significance and the difference was found to be nonsignificant ($P > 0.05$).

Overall survival was assessed in all randomized subjects (ITT population; $n = 119$). The mean OS was 10.91 months in study bevacizumab arm and 14.68 in reference arm. The difference was statistically nonsignificant ($P > 0.05$).

Table 2: Efficacy evaluation with complete response (CR), partial response (PR) and objective response rate (ORR) at Week 25 (*n*=53)

Assessment at	Response	Reference bevacizumab *n*=15 (%)	Biosimilar bevacizumab *n*=38(%)	*P*
Week 25	CR	0 (0.00)	3 (7.90)	NA
	PR	10 (66.67)	20 (52.63)	0.390
	ORR	10 (66.67)	23 (60.53)	0.622

Table 3: Progression free survival from baseline

Progression free survival (months)	Reference bevacizumab (*n*=33)	Biosimilar bevacizumab (*n*=83)	*P**
Mean PFS at Week 25	3.63	3.58	0.922
Mean PFS at Year 1	4.18	3.64	0.444

Safety results

There were 83 subjects in study bevacizumab arm and 33 subjects in reference arm who had received at least a single dose of study medication and were consider for safety analysis. Overall 715 adverse events were reported. Out of 715 adverse events, there were 70 (84.34%) subjects in study arm and 27 (81.82%) subjects in the reference arm who had at least one adverse event in the study. In the study, 50 serious adverse events (SAEs) were reported. As per the MedDRA coding, these 50 SAEs were coded

into 70 SAE terms. There were 27 (32.53%) subjects in the study bevacizumab arm and 14 (42.42%) subjects in the reference arm with at least one SAE in the study. There was no infusion-related reaction reported in this study. One subject from study arm discontinued the study due to an adverse event. A total of 18 deaths were reported in the study, i. e, 14 (16.87%) in study bevacizumab arm and 4 (12.12%) in reference bevacizumab arm.

In the study bevacizumab arm, the most commonly reported SAEs were in the gastrointestinal disorder SOC observed in 13 (15.66%) subjects, followed by blood and lymphatic system disorders SOC in 10 (12.05%) subjects and general disorders and administration site conditions SOC in 9 (10.84%) subjects. As per SOC terms, in reference bevacizumab arm, the most commonly reported SAEs were in the blood and lymphatic system disorders SOC observed in 5 (15.15%) subjects followed by infections and infestations SOC observed in 3 (9.09%) subjects. The percentage of subjects with adverse events in each arm was compared for statistical significance and the difference was found to be nonsignificant ($P > 0.05$). The above observations are consistent with safety profile of bevacizumab.

To analyze immunogenicity, 40 samples were analyzed in this study from both arms and all samples were found to be negative. In this study, no new confirmed immunologically mediated major clinical observation related to safety or efficacy was reported.

Discussion

The inhibition of VEGF with bevacizumab has been shown to result in tumor reduction of colon cancer and acts in synergy with chemotherapy. Bevacizumab is a humanized recombinant monoclonal antibody which binds to and blocks the activity of all isoforms of VEGF-A. Addition of bevacizumab to irinotecan plus bolus fluorouracil and leucovorin (FOLFIRI) is established to confer clinically significant improvements in OS, PFS, as well as RR, in patients with previously untreated mCRC.[6]

Biosimilar of bevacizumab from Reliance Life Sciences Pvt. Ltd., for mCRC, was evaluated for clinical biosimilarity. The study was conducted in two stages. In the first stage, the 42 subjects were analyzed for pharmacokinetic similarity, and in the second stage, a total of 119 subjects were randomized for the evaluation of efficacy and safety in mCRC. The study and reference arm dosages were according to the approved standard.

Pharmacokinetic parameters were calculated for single dose of study and reference product in 42 subjects distributed equally in study and reference arm. Statistically, mean C_{max} was comparable in both arms. The $AUC_{0\text{-}336}$ was comparable in both arms, but the concentration achieved over this timeframe is on higher side for study product as compared to reference. The observed PK results of study bevacizumab have no bearing on the safety and efficacy profile of the biosimilar product.

The study confirms that biosimilar bevacizumab improves the overall response rate, PFS, and OS when combined with chemotherapy for mCRC. The effect size was similar to the reference innovator bevacizumab with no significant statistical difference. The safety profile of biosimilar bevacizumab documented in this study was similar to that observed for the reference bevacizumab. The percentage of subjects with adverse events in each arm was compared for statistical significance and the difference was found to be nonsignificant ($P > 0.05$). No new confirmed immunologically mediated major clinical observation related to safety or efficacy was reported in this study. The adverse event profile in the two arms was in line with known profile of bevacizumab.

Conclusion

The study was conducted with the intention to establish clinical biosimilarity to the reference innovator bevacizumab and bridge the unmet medical need of clinically equivalent biosimilar of bevacizumab in mCRC. The results demonstrate that the subjects receiving biosimilar or reference bevacizumab had comparable primary and secondary response. The pharmacokinetic data revealed comparable concentration data for bevacizumab biosimilar and reference product. The observed safety profile in this trial is in line with known safety profile of bevacizumab.

The combination of BevaciRel™ (biosimilar bevacizumab) with chemotherapy[7] as compared to the reference innovator bevacizumab with chemotherapy was found to be noninferior or clinically biosimilar to reference bevacizumab and will be a suitable treatment option for the medical fraternity in their real-time practice in the management of mCRC.

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Conflicts of interest

All the authors are employees of Reliance Life Sciences.

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