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ORIGINAL ARTICLE

Tolerance, variability, and pharmacokinetics of bevacizumab biosimilars in Chinese healthy male subjects

Hong Zhang[1] · Qingmei Li[2] · Xiaoxue Zhu[1] · Cuiyun Li[1] · Xiaojiao Li[1] · Chengjiao Liu[1] · Yue Hu[1] · Guiling Chen[1] · Haijing Wei[1] · Jing Wang[1] · Zhenwei Shen[2] · Yanhua Ding[1]

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Abstract

Objective The aim of this study was to explore the tolerance, variability, and pharmacokinetics (PK) of bevacizumab biosimilars (MIL60, BAT1706, IBI305) in Chinese healthy male subjects.

Methods This randomized, double-blind, two-arm, parallel studies included three separate investigations, which were conducted by three sponsors to investigate the bioequivalence of bevacizumab biosimilars (MIL60, BAT1706, IBI305) with that of bevacizumab-EU as a reference drug. Subjects received a single-dose of 1 or 3 mg/kg of the bevacizumab biosimilars or bevacizumab-EU and were followed up for 70–99 days. Serum concentrations of bevacizumab, antidrug antibody (ADA), and neutralizing antibody (NAb) were measured using electrochemiluminescence. In addition, the PK parameters were determined using non-compartmental methods. The safety assessments included adverse events, hematology tests, and biochemistry tests.

Results The three bevacizumab biosimilars exhibited similar PK properties to that of bevacizumab-EU. Bevacizumab demonstrated linear PK properties and a concentration-dependent disposition. When comparing the three biosimilars with bevacizumab-EU, the 90% CIs of the ratios for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were within 80–125%. The inter-CV ranged from 12.6 to 23.3%. Three subjects in the biosimilar groups and bevacizumab-EU were positive for the ADA and negative for the NAb. Treatment-related mild or moderate adverse events were reported in 56–80 and 36–80% of subjects in the biosimilar and bevacizumab treatment arms, respectively.

Conclusions The bevacizumab biosimilars exhibit similar PK characteristics to that of the reference product bevacizumab-EU. The inter-CV is moderate and less than 25% in all cases. The safety profile was similar among bevacizumab biosimilars and bevacizumab-EU with significant adverse events.

Keywords Bevacizumab · Biosimilar · Immunogenicity · Pharmacokinetics · Inter-subject variability

Introduction

Biologics are large complex molecules derived from living cells. Biosimilars are biological products that are highly similar to a natural reference product in terms of safety and efficacy [1]. Biosimilars can improve the overall health outcomes by increasing a patient's access to the biologic-like molecule. Unlike small-molecule drugs that are structurally controllable, the innate complexity of biologics make them difficult to synthesize and small changes in the manufacturing process, also known as product divergence, can result in ineffective final products [2, 3].

The United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) emphasize a stepwise approach for the development of biosimilars [1]. First, the analytical and biofunctional similarity to the reference product is initially demonstrated. Next, the pharmacokinetic (PK) and pharmacodynamic (PD) properties are evaluated and compared. Lastly, the clinical similarity is evaluated in a sensitive patient population to validate its efficacy, safety, and immunogenicity using the same approved dosage and route of administration as the reference product [1–3].

Bevacizumab (Avastin®) is an antibody specific for the human vascular endothelial growth factor (VEGF) protein, allowing it to actively inhibit angiogenesis [4]. In the United

✉ Yanhua Ding
dingyanhua2003@126.com

[1] Phase I Clinical Research Center, The First Hospital of Jilin University, Changchun 130021, Jilin, China

[2] The First Hospital of Jilin University, Changchun, Jilin, China

States and Europe, bevacizumab has been approved for the treatment of non-small cell lung cancer (NSCLC), metastatic colorectal cancer, metastatic renal cell cancer, cervical cancer, platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer. However, the indications can vary in different geographical regions [4–9].

Bevacizumab biosimilars are actively being developed globally, including China. Bevacizumab biosimilars (MIL60, BAT1706, IBI305) have an identical primary structure, and the posttranslational modifications, biochemical properties, and biological functions are similar to the bevacizumab reference product (data not shown). The similarity of bevacizumab biosimilars (MIL60, BAT1706, IBI305) with the bevacizumab reference product has also been tested in cynomolgus monkeys (data not shown). All in vivo studies have supported the clinical development of these bevacizumab biosimilars.

PK studies in humans are essential for demonstrating the bioequivalence between a biosimilar and the reference product. PK profiles between a biosimilar and the reference product should be investigated in a population using various dosages and routes of administration [1–3, 10]. Herein, we evaluated the bioequivalence between bevacizumab biosimilars (MIL60, BAT1706, IBI305) and the European Union (EU)-produced bevacizumab-EU as a reference product in a single-dose PK study in Chinese healthy male volunteers. The single-dose study design should allow for the detection of intrinsic differences in the PK profiles between the bevacizumab biosimilars (MIL60, BAT1706, IBI305) and the bevacizumab reference product. The use of a healthy population avoids confounding factors, such as the variability associated with multidose requirements, multicenter trials, disease conditions, comorbidities, and concomitant therapies. The study specifically focused on males as the PK properties of bevacizumab are gender-specific [4]. For the reference drug, the therapeutic dosage ranged from 5 mg/kg every 2 weeks to 15 mg/kg every 3 weeks [4, 11]. The 1 and 3 mg/kg doses were used in this study because of previous clinical trial plans, and the full PK profile of bevacizumab for the area under the serum concentration–time curve (AUC) estimation.

In this study, we aimed to compare the PK profile of the European Union (EU)-produced bevacizumab, also known as Avastin® from F. Hoffman-La Roche (Basel, Switzerland), with the PK profiles of three different bevacizumab biosimilars [11]. In addition, the bevacizumab biosimilars were assessed in terms of tolerability, safety, and immunogenicity in patients.

Methods

Study design and subjects

This study was conducted in the Phase I Clinical Research Center of the First Hospital of Jilin University between May 5, 2016, and May 5, 2017. The final protocol, any amendments, and informed consent documentation were reviewed and approved by the Institutional Review Board of the First Hospital of Jilin University. The study was conducted in compliance with the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice Guidelines, and local regulatory requirements. All subjects gave their informed consent before their inclusion in this study.

This was a phase I, double-blind, randomized, parallel-group, single-dose, two-arm study. Healthy males aged 18–45 years, with body mass index of 18.5–26.0 kg/m^2 and total body weight of 50–85 kg, were enrolled in the study. At the time of enrollment, all subjects had normal organ function evaluated by the following laboratory tests: bone marrow function, platelet count $\geq$ 125,000/mm^3; and liver function, alanine aminotransferase (ALT) $\leq 1.5 \times$ upper limit normal (ULN) and aspartate aminotransferase $\leq 1.5 \times$ ULN. Subjects with evidence or history of clinically significant diseases, previous history of cancer, hypertension (defined as blood pressure $\geq$ 150/100 mmHg), or heart disease (defined as QT_c > 470 ms) were excluded from the study. Subjects were excluded if they had received blood transfusions, previous anti-VEGF treatment with antibodies or proteins, or were positive for the anti-VEGF antibody.

Bioequivalence studies for the three bevacizumab biosimilars were completed by three sponsors. The screening visit was scheduled 14 days prior to dosing. After the screening, the subjects were admitted to the Clinical Research Unit 1 day before administration of the bevacizumab biosimilars. The subjects were fasted for at least 8 h prior to dosing and then randomized into two groups: the test drug (T) group and the reference drug (R) group in a 1:1 ratio according to a computer-generated randomization schedule. Subjects in the T group received a single intravenous infusion of one of the bevacizumab biosimilars (3 mg/kg MIL60, 1 mg/kg BAT1706, or 3 mg/kg IBI305) for 90 min. In the R group, the subjected received an equivalent dose of bevacizumab-EU. Subjects were discharged 3–5 days after dosing and followed up on an outpatient basis for additional analyses in the clinical research unit on days 5, 8, 15, 22, 29, 36, 43, 57, and 71 for MIL60, on days 8, 11, 15, 22, 29, 36, 43, 57, 71, 85, and 99 for BAT1706, and on days 8, 15, 22, 29, 43, 57, 64, 71, 85, 99 for IBI305. Blood samples for the primary PK analysis were collected before the treatment and through the final follow-up.

Pharmacokinetic evaluations

Blood samples for PK evaluation were collected at 0.5 h before the initiation of dosing (pre-dose), and at 45, 90 min 2.5, 3.5, 5.5, 9.5, 13.5, 24, 48, 96, 168, 336, 504, 672, 840, 1008, 1344, and 1680 h after infusion start for MIL60; and at 45, 90 min, 2.5, 3.5, 5.5, 9.5, 13.5, 24, 48, 72, 96, 168, 240, 336, 504, 672, 840, 1008, 1344, 1680, 2016, and 2352 h after infusion start for BAT1706; and at 90 min, 4, 12, 24, 48, 96, 168, 336, 504, 672, 1008, 1344, 1512, 1680, and 2016 h for IBI305. After collection, the blood samples were allowed to clot for 30 min at room temperature and centrifuged at 1500–1700*g* for approximately 15 min at 2–8 °C. The serum was stored at − 70 °C for further analysis. The concentration of the bevacizumab biosimilars (MIL60, BAT1706 or IBI305) and bevacizumab-EU in the serum were analyzed using an enzyme-linked immunosorbent assay (ELISA) at the United-Power Pharma Tech Co., Ltd. (Beijing, China). The concentration range was 50.00–40,000.00 ng/mL, and the lower limit of quantification (LLOQ) was 0.5 ng/mL. For the PK analysis, concentrations less than the LLOQ were set to zero. The accuracy of the inter-run assay ranged from − 1.5 to 3% and was expressed as the percentage relative error for the quality control samples. The assay precision was less than 15% and was expressed as the inter-run coefficient of variation (COV).

A non-compartmental analysis model was employed to calculate the PK parameters. The concentration–time data included the maximum observable serum concentration (C_{max}), clearance (CL), half-life ($t_{1/2}$), volume of distribution (V), and AUC from zero to the final quantifiable concentration (AUC_{0-t}) and to infinity ($AUC_{0-\infty}$). Actual sample collection times were used for the PK analysis. PK parameters were calculated using an internally validated software system, Phoenix WinNonLin® v6.4 (Certara L.P., Princeton, NJ, USA).

Immunogenicity evaluations

To detect the antidrug antibodies (ADA) and neutralizing antibodies (NAb), blood samples were collected at 0, 8, 15, 29, 43, 71 days post-dose for MIL60 and at 0, 15, 43, 71, 99 days post-dose for BAT1706 and IBI305. ADA samples were analyzed at the United-Power Pharma Tech Co., Ltd. (Beijing, China) using two validated, semi-quantitative electrochemiluminescent assays: one for detecting antibodies against bevacizumab biosimilars and the other one for detecting antibodies against bevacizumab. Samples with ADA positivity were further tested for the presence or absence of neutralizing anti-bevacizumab biosimilars or anti-bevacizumab antibodies, using validated semi-quantitative electrochemiluminescent NAb assays.

Safety evaluations

Adverse events (AEs) were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (V.4.03). The AEs were monitored using several tests, including physical examination, vital signs, pulse oximetry, electrocardiogram, and common laboratory tests like urinalysis and chemistry. All AEs were assessed and scored based on their severity and relation to bevacizumab-EU and its biosimilars. Patients with AEs were monitored until the condition was resolved or stabilized.

Estimation of sample size

According to the current FDA guidelines, the geometric mean ratio (GMR) is set to be 95–105% to achieve 80–90% power ($1-\beta$) at the 5% nominal level ($\alpha=5\%$). The coefficient of variation (CV) is used to denote the inter-subject variability (inter-CV). Since the inter-CV for bevacizumab is known to be between 25–35% [12–14], the initial estimate of sample size was between 62 and 74, calculated by the PASS Version 11 software (NCSS, Kaysville, UT, USA). Considering the 10% drop-out rate, the final sample group sizes were 78–100 (Table 1).

Statistical analysis

PK bioequivalence between bevacizumab-EU and its biosimilars was present if the 90% confidence intervals (CIs) for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were between 80 and 125%. The per-protocol analysis set was used as the study population for the PK analysis. This included the patients who received an entire dose of the study drug with no deviations in the study protocol. All of the patients who received a study drug were used in the safety analysis. Descriptive statistics were

Table 1 Sample size estimation for three different bevacizumab biosimilars

Study	Bioavailability predicted value	α	$1-\beta$	Inter-subject variability (%)	Sample size estimation	Actual sample size
MIL60	0.95–1.05	0.05	0.85	25	62	78
BAT1706	0.95–1.05	0.05	0.9	25	74	82
IBI305	1	0.05	0.85	35	90	100

calculated for PK parameters and demographical data. The *t* test or Wilcoxon ranks tests were used for comparison. All statistical tests were performed by SAS 9.1 Statistical Package (SAS Institute Inc., Cary, NC, USA). $P < 0.05$ was considered statistically significant.

Results

Subjects

A total of 78, 82, and 100 subjects were enrolled and assigned to MIL60, BAT1706, and IBI305 studies, and 77, 80, and 100 subjects received the assigned drugs and were included in the safety analysis set, respectively (Fig. 1). In the MIL60 study, two subjects in the bevacizumab-EU group were excluded from the primary PK analysis due to premature withdrawal from the study. In the BAT1706 study, two subjects in the BAT1706 group withdrew informed consent before dosing and one subject in the bevacizumab-EU group was lost to follow-up. The final per-protocol population used in the PK analysis consisted of 76, 80, and 98 subjects in the MIL60, BAT1706, and IBI305 studies, respectively (Fig. 1). The demographic and baseline characteristics in the per-protocol population were comparable among the different treatment groups (Table 2). There were no significant differences between the demographic and baseline parameters among these groups.

Pharmacokinetic evaluations

The mean serum concentration–time curve for the three tested bevacizumab biosimilars (MIL60, BAT1706, IBI305) similarly exhibited a rapid decrease in serum drug concentration immediately following the end of infusion, which was followed by a slow elimination phase (Fig. 2).

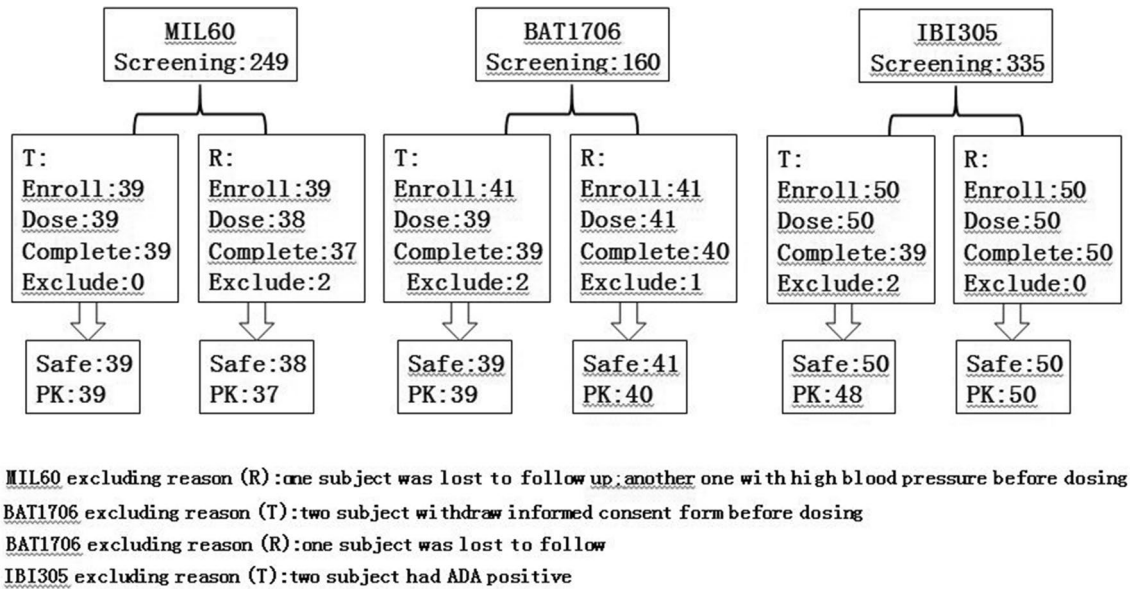

Fig. 1 Flow chart showing the details of the study, including the enrollment number, dosage, completion number, and subject exclusions

Table 2 Demographic characteristics of healthy male volunteers

Study		*N*	Age (years)	Ethnicity (Han/other)	Body Mass Index (kg/m^2)	Body Weight (kg)
MIL60	T	39	31.5 (6.90)	37/2	22.21 (2.12)	63.98 (6.760)
	R	38	30.5 (6.21)	36/2	22.16 (2.25)	64.68 (7.347)
BAT1706	T	41	30.9 (7.60)	41/0	22.86 (3.07)	66.92 (10.20)
	R	41	33.9 (7.48)	40/1	23.47 (2.53)	68.25 (8.159)
IBI305	T	48	36.5 (8.92)	43/5	23.41 (2.73)	67.32 (7.76)
	R	50	34.0 (8.87)	45/5	23.96 (2.04)	68.42 (6.62)

T and R correspond to test drugs and reference drugs, respectively

Age, body max index, and body weight are provided as means (SD)

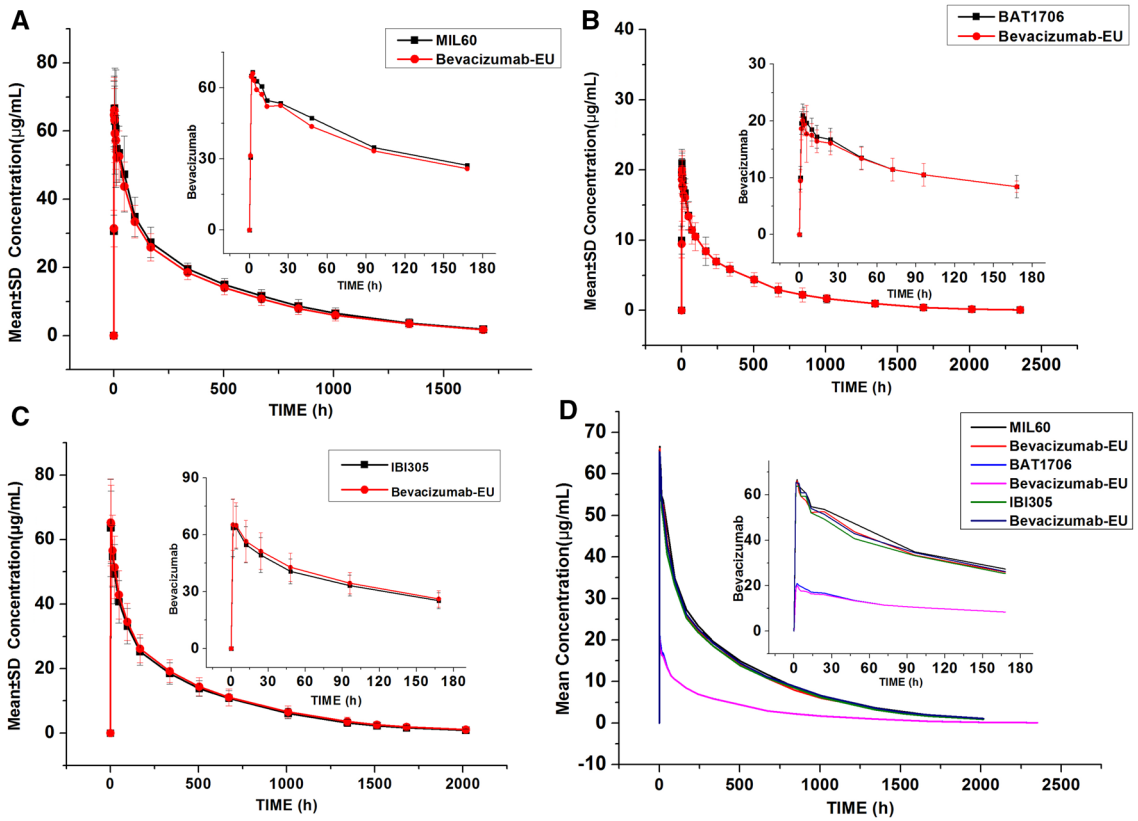

Fig. 2 Mean bevacizumab serum concentration–time profiles for **a** MIL60, **b** BAT1706, **c** IBI305, and **d** all three in comparison to bevacizumab-EU

Bevacizumab-EU exhibited a linear PK and concentration-dependent disposition. The elimination of bevacizumab-EU was linear with a dosage of 1–5 mg/kg. As would be expected, the largest dose of antibody resulted in the highest drug concentration in the blood, along with decreased clearance and increased $t_{1/2}$ (Fig. 3; Table 3).

Consistent with the mean concentration–time profiles, the mean C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ estimates, and inter-CV were similar among all of the tested drugs, with the coefficient of variation values of 14.1–23.3% for C_{max}, 12.6–22.3% for AUC_{0-t}, and 15.3–21.8% for $AUC_{0-\infty}$ (Table 4; Fig. 4). For MIL60, BAT1706, and IBI305, the 90% CIs of the test-to-reference ratios for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were within the bioequivalence window of 80–125% in comparison with bevacizumab-EU (Table 4). The inter-subject variability (inter-CV) of exposure ranged from 12.6 to 22.3%. The 90% CI was wider when the inter-CV was larger. We re-estimated the sample size of the three studies based on their bioequivalence analysis results (GMR and inter-CV), and the sample size was 38–52, which was less than the enrollment size (Table 4).

Immunogenicity evaluations

In the MIL60 study, two subjects, one in the bevacizumab biosimilar group and one in the reference drug group, were positive for ADA at one time point during the study period, yet negative at the other follow-up visits. In the BAT1706 study, all subjects were negative for ADA. In the IBI305 study, two subjects in the bevacizumab biosimilar group were positive for ADA before dosing with one subject being positive during the entire study period and the other subject becoming negative by the day 99 follow-up. Two subjects in the reference drug group were positive for ADA at day 15 and became negative by the next follow-up. However, none of these subjects were positive for NAb. Bevacizumab biosimilars had similar ADA profiles with bevacizumab-EU in this study.

Safety evaluations

There was only one serious AE noted in this study, which was a hand injury in the IBI305 group. However, this was not

Table 3 The pharmacokinetic parameters of bevacizumab in each study

Study	Treatment group	Dose (mg/kg)	*N*	$AUC_{0-\infty}$ (h μg/mL)	AUC_{0-t} (h μg/mL)	Ratio[a]	CL (mL/h/kg)	$t_{1/2}$ (h)	*V* (mL/kg)	C_{max} (μg/mL)	T_{max} (h)
BAT1706	T	1	39	6127 ± 1070	6058 ± 1060		0.184 ± 0.032	318.27 ± 48.41	83.61 ± 12.79	21.51 ± 3.41	2.96 (1.5, 5.5)
BAT1706	Bevacizumab-EU	1	40	6066 ± 1352	5984 ± 1303		0.193 ± 0.032	315.73 ± 47.18	86.98 ± 12.30	20.65 ± 3.99	4.51 (1.5, 72)
MIL60	T	3	39	22,652 ± 3827	21,487 ± 2868	3.59	0.130 ± 0.018	379.92 ± 89.67	72.49 ± 9.01	70.93 ± 16.11	2.50 (1.5, 24.0)
MIL60	Bevacizumab-EU	3	37	21,230 ± 3346	20,214 ± 2881	3.38	0.140 ± 0.025	378.01 ± 64.64	77.49 ± 9.21	67.68 ± 9.47	2.50 (1.5, 5.5)
IBI305	T	3	48	20,647 ± 3542	20,170 ± 3493	3.37	0.150 ± 0.029	340.20 ± 51.10	73.30 ± 16.10	67.40 ± 15.10	4.00 (1.50, 12.0)
IBI305	Bevacizumab-EU	3	50	21,786 ± 4309	21,205 ± 4049	3.54	0.140 ± 0.028	356.50 ± 69.60	72.00 ± 12.70	70.00 ± 20.70	4.00 (1.50, 12.0)
Literature [13]	Bevacizumab-EU	5	33	43,830 ± 8326	41,010 ± 6711	6.85	0.117 ± 0.022	417 ± 90	64.9 ± 9.6	137.0 ± 20.5	NA

Data are shown as mean ± SD or median (min, max)

[a]Ratio of AUC_{0-t} at each group vs. bevacizumab-EU 1 mg/kg

related to the study drug. In addition, there were no deaths or discontinuations due to AEs. Most AEs were grade 1 or 2, and there were no abnormal reactions at the injection site.

In the MIL60 study, of the 77 subjects who received the study drug, 22 (56.4%) and 24 (63.2%) experienced drug-induced AEs in the bevacizumab biosimilar (MIL60) and bevacizumab-EU groups, respectively. Hypertriglyceridemia (grade 3 AE, not related to the drug) occurred at 70 days after dosing in the bevacizumab biosimilar (MIL60) group, and nettle-rash (grade 3 AE, related to the drug) occurred at 41 days after dosing in the bevacizumab-EU group. The AEs disappeared without additional medical treatment.

In the BAT1706 study, of the 80 subjects who received study drug, 25 (64%) and 14 (35%) subjects experienced drug-induced AEs in the bevacizumab biosimilar (BAT1706) and bevacizumab-EU group, respectively. Hypertriglyceridemia (grade 3 AE, not related the drug) and hypokalemia (grade 3, not related the drug) occurred after dosing in the bevacizumab biosimilar (BAT1706) and bevacizumab-EU groups, respectively. Again, the AEs required no additional medical treatment.

In the IBI305 study, of the 100 subjects who received study drug, 40 (80%) subjects in each group experienced drug-induced AEs. Eight subjects in the bevacizumab biosimilar (IBI305) group had grade 3 AEs, which included hypertriglyceridemia, neutrophilia, and increased aspartate aminotransferase (AST) levels. In addition, four subjects in the bevacizumab-EU group had grade 3 hypertriglyceridemia. All of drug-induced AEs were reported to the Institutional Review Board of The First Hospital of Jilin University.

Discussion

This phase I study demonstrated that bevacizumab biosimilars (MIL60, BAT1706, IBI305) have similar PK profiles to that of bevacizumab-EU when accessed in healthy volunteers. The 90% CIs of the test-to-reference ratios for C_{max} and AUC were within the predefined bioequivalence acceptance range of 80–125% for the biosimilars in comparison with bevacizumab-EU. The PK similarities between the licensed bevacizumab-EU products and biosimilars justifies the use of the biosimilars in phase II clinical studies [1–3, 15].

PK studies in humans have shown that bevacizumab is cleared from the blood with an initial rapid phase, which is followed by a slow clearance phase. The antibody has a high volume of distribution and displays a long half-life of 15 days [4, 12–14]. Similar findings have been reported for other bevacizumab biosimilars, such as BS-503a (Daiichi Sankyo), PF06439535 (Pfizer), and Boehringer Ingelheim BI 695502 (Boehringer represents Ingelheim), which have

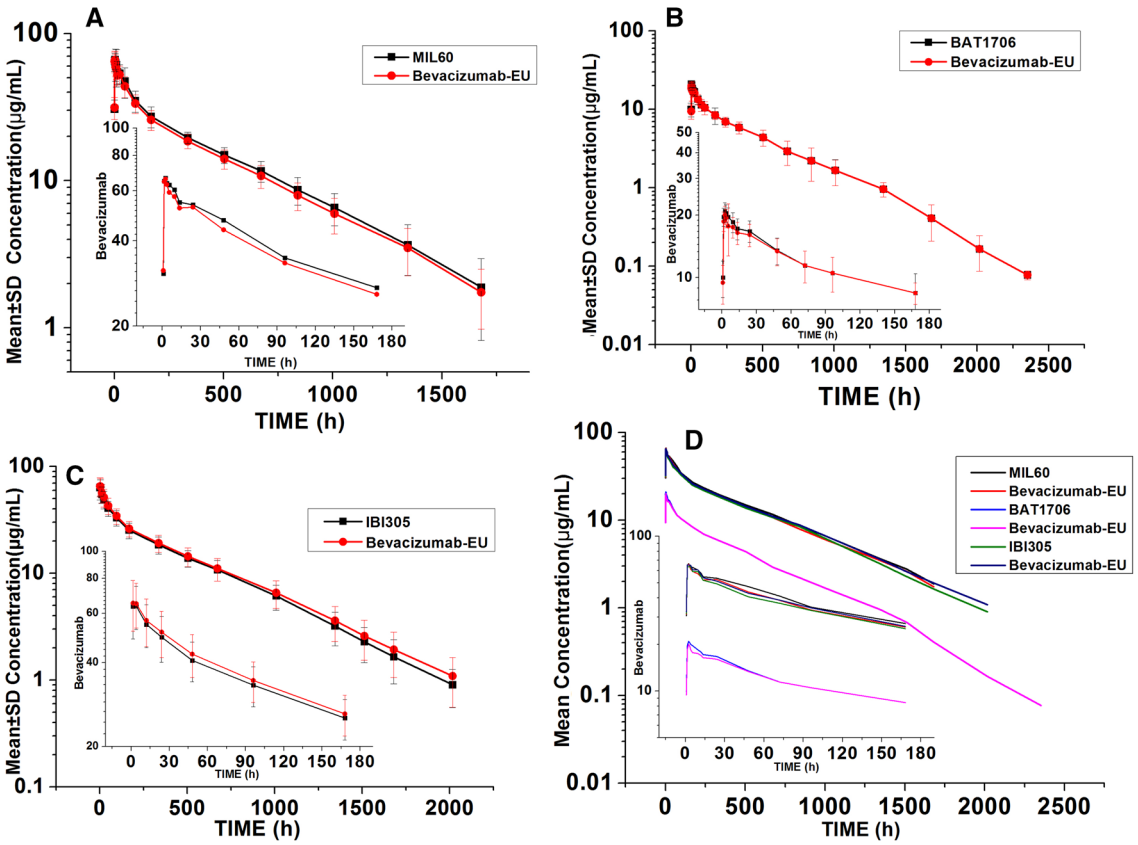

Fig. 3 Mean log bevacizumab serum concentration–time profiles for **a** MIL60, **b** BAT1706, **c** IBI305, and **d** all three in comparison to bevacizumab-EU

Table 4 Bioequivalence assessment summary and re-estimation of sample size

Study	PK parameter[a]	C_{max}	AUC_{0-t}	AUC_{0-inf}	Re-estimated Sample Size
MIL60	GMR (90% CI)	1.04 (0.97–1.11)	1.07 (1.01–1.12)	1.07 (1.01–1.13)	38
	Inter-CV (%)	14.14 vs. 18.9	15.0 vs. 12.6	16.6 vs. 15.3	
	90% CI interval	0.14	0.11	0.12	
BAT1706	GMR (90% CI)	0.95 (0.88–1.03)	0.98 (0.92–1.05)	0.98 (0.92–1.06)	
	Inter-CV (%)	15.87 vs. 19.33	17.47 vs. 22.30	17.51 vs. 21.78	
	90% CI interval	0.15	0.13	0.14	52
IBI305	GMR (90% CI)	0.97 (0.90–1.04)	0.95 (0.89–1.01)	0.95 (0.89–1.01)	
	Inter-CV (%)	21.6 vs. 23.3	18.5 vs. 19.2	18.3 vs. 19.8	
	90% CI interval	0.14	0.12	0.12	52

[a]T vs. R(Bevacizumab-EU)

been evaluated in phase I bioequivalence studies in healthy subjects [12–14].

In this study, AUC and C_{max} were almost linear from 1 to 5 mg/kg, which is warranted by the ratio of exposure (about three- and five-times) and according to the bevacizumab label [4]. The PK parameters were similar between MIL60 and IBI305, suggesting that the study designs were appropriate. However, the clearance decreased in subjects receiving 1 mg/kg of antibody compared with those subjects receiving 5 mg/kg. This may be explained by a nonlinear elimination at large dose scale [4].The inter-CV of bevacizumab among Chinese subjects is small, and in the future, we recommend that the sample size of 26 subjects be enough for bioequivalence of bevacizumab biosimilars at each arm, in consideration of inter-CV (12.6–23.3%) [16–19].

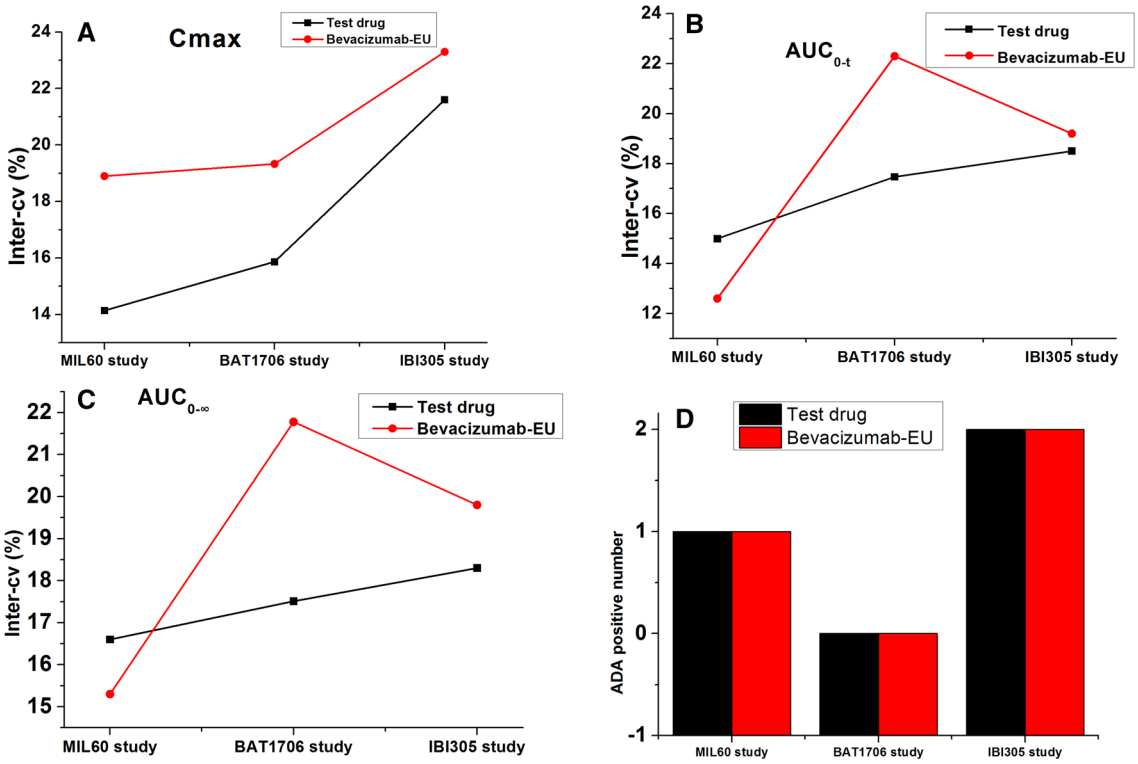

Fig. 4 **a**–**c** The inter-subject variability of bevacizumab biosimilars and the **d** positive number of antidrug antibody (ADA)

Immune responses may develop following bevacizumab administration. In this study, comparable ADA profiles were found among the tested drugs with no NAb in any of the ADA-positive samples, which was consistent with a previous report showing the low immunogenicity for bevacizumab [4]. Earlier studies have shown that the incidence of positive ADA was low for bevacizumab biosimilars with 6.1% ($n=2$) of cases for PF-06439535, 2.9% ($n=1$) of cases for Bevacizumab-EU and 6.1% ($n=2$) of cases for Bevacizumab-US [12–14]. Therefore, bevacizumab exhibits low immunogenicity in humans [20–22].

The most common AEs (incidence rates of > 10% and at least twice the control arm rate) associated with the use of bevacizumab include epistaxis, headache, hypertension when administered as anti-cancer therapy for long-term [4]. Our study showed that the safety profiles were comparable between the biosimilars (MIL60, BAT1706, IBI305) and bevacizumab-EU after a single-dose with no clinically meaningful differences. Previous studies have reported that 48.5 and 62.9% of subjects who receive PF-06439535 and Bevacizumab-EU experienced drug-induced grade 1 or 2 AEs, respectively [12–14]. Since these AEs were non-specific and occurred similarly among the biosimilars and bevacizumab-EU groups, it seems that bevacizumab and its biosimilars have similar tolerability profiles in healthy subjects [23].

Conclusions

The present study showed that the PK profiles of bevacizumab biosimilars (MIL60, BAT1706, IBI305) were similar to that of bevacizumab-EU. The bevacizumab biosimilars had a similar ADA profile with no detection of NAb and a comparable safety profile in comparison with the reference drug. The inter-CV of bevacizumab was low among Chinese subjects. These data support the clinical development of MIL60, BAT1706, and IBI305 as bevacizumab biosimilars.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interests.

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