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ORIGINAL RESEARCH ARTICLE

Pharmacokinetics and Safety of Vedolizumab Following Administration of a Single Intravenous Dose in Healthy Chinese Subjects

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Abstract

Background and Objectives Vedolizumab is a humanized monoclonal antibody, indicated for the treatment of moderately to severely active ulcerative colitis (UC) or Crohn's disease (CD), that specifically binds to the α4β7 integrin. The aim of this study was to assess the pharmacokinetics, safety, and tolerability of vedolizumab following a single intravenous (IV) infusion in healthy adult Chinese subjects.

Methods Sixteen participants received a single IV infusion of vedolizumab (300 mg). Blood samples were collected to measure vedolizumab serum concentrations. The safety of all subjects was monitored.

Results The pharmacokinetic analysis showed that vedolizumab reached the maximum observed serum concentration (C_{max}) at approximately 1.32 hours. The mean C_{max} and area under the concentration–time curve from time 0 to time of the last quantifiable concentration (AUC_{0-t}) and to infinity ($AUC_{0-\infty}$) were 137.25 µg/mL, 2360 days·µg/mL, and 2395 days·µg/mL, respectively. The elimination of vedolizumab was relatively slow, with a mean terminal disposition phase half-life elimination ($t_{1/2}$) of 20.23 days. Six subjects were positive for anti-vedolizumab antibodies (AVAs) on day 106 and day 127. Finally, 4 out of 16 subjects (25.0%) had treatment-emergent adverse events (TEAEs), all of which were upper respiratory tract infections.

Conclusion Vedolizumab was well tolerated in healthy Chinese subjects when administered as a single-dose IV 300 mg infusion. In this study, the rate of AVA positivity was 37.5%, which occurred near the end of the study; no significant differences in pharmacokinetic profiles were observed between the AVA-positive and AVA-negative groups.

Clinical Trial Registration http://www.chinadrugtrials.org.cn: CTR20171528.

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Key Points

Vedolizumab pharmacokinetic parameters and AVA status in healthy Chinese subjects are consistent with anticipated results.

Vedolizumab IV 300 mg was safe and well tolerated in healthy Chinese subjects.

Therefore, vedolizumab pharmacokinetics, AVA status, and safety and tolerability are all appropriate in the Chinese population.

1 Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic idiopathic inflammatory bowel diseases (IBDs) for which no medical cure presently exists. Vedolizumab is a humanized immunoglobulin G1 monoclonal antibody directed against the human lymphocyte integrin α4β7. The α4β7 integrin mediates lymphocyte trafficking to the gastrointestinal (GI) mucosa and gut-associated lymphoid tissue through adhesive interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa [1–4]. Vedolizumab binds to the α4β7 integrin, antagonizing its adherence to MAdCAM-1, and as such, impairs the migration of gut-homing leukocytes into the GI mucosa. Owing to its gut-selective immunomodulatory properties [5], vedolizumab has been developed as a treatment for UC and CD. Pharmacokinetic studies of vedolizumab in Japanese and non-Asian subjects have been reported previously [6, 7]. The main objectives of this study were to assess the pharmacokinetics of vedolizumab in Chinese subjects and to evaluate any potential ethnic differences compared with the pharmacokinetic data previously acquired for other populations.

2 Methods

2.1 Study Population

The eligibility criteria were as follows: healthy Chinese male or nonpregnant, nonlactating female subjects aged 18–45 years (inclusive) who were willing and able to comply with the study schedule and assessments; a body weight of at least 50 kg and a body mass index (BMI) of 19.0–26.0 kg/m^2 (inclusive); and no results showing that the subject had clinically significant abnormalities in physical examinations, medical history, clinical laboratory examinations, vital signs, and electrocardiograms (ECGs). All male subjects who were not sterilized or female subjects of childbearing potential agreed to use adequate contraception throughout the study and for 18 weeks after the last dose.

Subjects were excluded if they had previously received an investigational compound within 30 days of the study or any monoclonal antibody within the past 6 months. The subjects were also excluded if they had clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, GI, urologic, immunologic, or endocrine disease, or psychiatric disease or other abnormality that might impact the ability of the subject to participate or that could potentially confound the study results. Subjects were also ineligible if they had known hypersensitivity to any component of the formulation of the study drug; one or more positive responses on the progressive multifocal leukoencephalopathy (PML) subjective symptoms checklist; a history of cancer, except for basal cell carcinoma that has been in remission for at least 5 years prior to day 1; a positive test result for chronic hepatitis B virus, hepatitis C virus, or human immunodeficiency virus antibody; active or latent tuberculosis (TB) or a positive diagnostic TB test; poor peripheral venous access; or more than 450 mL of blood donated within 45 days. Subjects were excluded if they had a history or evidence of alcohol or drug abuse.

2.2 Study Design

This was an open-label, single-center, phase I study in healthy adult Chinese subjects who were administered a single dose of vedolizumab at the Clinical Drug Testing Institute of Peking University First Hospital. The total duration of this study was approximately 7.0 months and involved three periods: screening, treatment, and follow-up. The protocol and informed consent documentations were approved by the Ethics Committee of Peking University First Hospital (China). The study was registered at the China Drug Trials official website (http://www.chinadrugtrials.org.cn: CTR20171528). Sixteen subjects enrolled in this study received a single intravenous (IV) dose of vedolizumab 300 mg on day 1 within 30 minutes. Subjects were kept in the study unit for 3 days after the start of the infusion on day 1 for safety and pharmacokinetic assessments before being discharged. Subjects periodically returned to the study unit according to the predetermined pharmacokinetic sampling schedule until day 127. Additionally, subjects were required to participate in a long-term follow-up safety survey by telephone, 6 months after the single dose of study drug.

2.3 Sample Collection and Assays

Blood samples (5 mL samples taken at the scheduled times) for the pharmacokinetic analysis of vedolizumab were collected within 0.5 hours before the start of the IV infusion, at 15 minutes, 35 minutes, 2 hours, and 8 hours after the start of the IV infusion on day 1, and on days 2, 3, 5, 7, 10, 15, 29, 43, 64, 85, 106, and 127. Serum samples were stored at −70 °C until analysis. Vedolizumab serum concentrations were determined using a validated sandwich enzyme-linked immunosorbent assay [8]. In brief, vedolizumab was bound by immobilized mouse anti-vedolizumab idiotypic antibodies in microtiter plates. Unbound mouse anti-vedolizumab idiotypic antibodies were then blocked, and serum samples added to the wells. Captured vedolizumab was detected with peroxidase-conjugated F(ab')2 fragment mouse anti-human

Ig, Fcr-fragment specific, and visualized using a colorimetric substrate. The lower limit of quantification for this assay was 0.2 μg/mL.

Blood specimens (8.5 mL samples taken at the scheduled times) for determination of anti-vedolizumab antibodies (AVAs) were collected predose on day 1 (within 0.5 hours before dosing), and on days 10, 29, 43, 64, 85, 106, and 127 post dose. Serum samples were stored at –70 °C until analysis. A sample would be assessed for neutralizing AVAs if AVA positivity was detected. AVAs and neutralizing antibodies were detected using electrochemiluminescence assays [9]. In brief, the AVA immunogenicity assay has a sensitivity of 3.9 ng/mL and detects 0.5 μg/mL of anti-vedolizumab positive control (affinity-purified rabbit AVAs) in the presence of vedolizumab concentrations ≥50 μg/mL. The neutralizing assay has a sensitivity of 31.3 ng/mL and detects 0.25 μg/mL of anti-vedolizumab positive control in the presence of vedolizumab concentrations ≥50 μg/mL.

Participants were categorized as being negative for AVAs if they did not have confirmed AVA results at any time of testing; otherwise, they were defined as AVA positive. Participants confirmed to be AVA positive in at least one but not consecutive sample were defined as transiently positive, whereas participants with two or more consecutive positive AVA samples were defined as persistently positive. A sample would be assessed for neutralizing AVAs if AVAs were detected.

2.4 Pharmacokinetic Analysis

The pharmacokinetic parameters of vedolizumab were determined from the concentration–time profiles of all evaluable subjects using a noncompartmental analysis method with WinNonlin Professional, version 8.1. The pharmacokinetic parameters, including the maximum observed serum concentration (C_{max}), time of first occurrence of C_{max} (t_{max}), area under the serum concentration–time curve from time 0 to time of the last quantifiable concentration (AUC_{0-t}), area under the serum concentration–time curve from time 0 to infinity ($AUC_{0-\infty}$), and the terminal disposition phase half-life ($t_{1/2}$) were determined from serum concentration–time data for all evaluable subjects. Actual sampling times were used in all computations involving sampling times.

2.5 Immunogenicity Analysis

The proportion of subjects with positive AVAs and neutralizing AVAs were summarized by scheduled sampling times. Titers of AVAs and neutralizing AVAs were listed. The impact of AVAs on pharmacokinetics and safety were explored.

2.6 Safety Analysis

The safety information for all subjects enrolled was monitored throughout the whole study, including opportunistic infections such as PML, liver injury, malignancies, and infusion-related reactions and hypersensitivity, and markedly abnormal vital signs, ECGs, physical examinations, and laboratory tests (clinical chemistry, hematology, coagulation, and urinalysis). The severities (mild, moderate, or severe) of all adverse events (AEs) that occurred during the trial were assessed by the investigator. The likely relationship of the AEs to the study drug was classified as related or not related.

2.7 Statistical Methods

All statistical analyses were conducted using SAS version 9.4. The safety analysis set and pharmacokinetic set consisted of all subjects who were enrolled and received a single dose of the study drug; to be enrolled in the pharmacokinetic set, at least one measurable blood drug concentration was also needed.

The number and percentage of subjects with treatment-emergent adverse events (TEAEs) were summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms, by severity, and by relationship to the study drug. The MedDRA, version 21.0, was used for coding TEAEs.

3 Results

3.1 Participants

A total of 16 subjects were enrolled in the study and received a single infusion of vedolizumab; all 16 subjects completed the study. The detailed demographic characteristics of the subjects are listed in Table 1.

3.2 Pharmacokinetic and AVA Results

All 16 subjects were included in the pharmacokinetic analysis. The mean serum concentration–time curve is shown in Fig. 1. Following a single infusion of vedolizumab IV 300 mg, the mean serum vedolizumab concentration decreased in a generally biphasic elimination fashion, with linear clearance until concentrations reached approximately 1–10 μg/mL. Thereafter, concentrations appeared to decrease in a nonlinear fashion.

Analyses of serum vedolizumab pharmacokinetic parameters are summarized in Table 2. The pharmacokinetic analysis showed that vedolizumab reached C_{max} at approximately 1.32 hours (0.06 days). The mean C_{max}, AUC_{0-t},

Table 1 Demographic and baseline characteristics of healthy Chinese subjects ($n = 16$)

Parameter	Value
Age (years)	
Mean (SD)	30.4 (6.2)
Median	32.0
Min, Max	19.0, 40.0
Sex [*n* (%)]	
Male	9 (56.3)
Female	7 (43.8)
Height (cm)	
Mean (SD)	167.0 (7.5)
Median	169.5
Min, Max	153.0, 182.0
Weight (kg)	
Mean (SD)	63.8 (6.4)
Median	63.0
Min, Max	51.5, 74.5
BMI (kg/m^2)	
Mean (SD)	22.9 (1.6)
Median	22.8
Min, Max	20.0, 25.5

SD standard deviation, *min* minimum, *max* maximum, *BMI* body mass index

and $AUC_{0-\infty}$ were 137.25 µg/mL, 2360 days·µg/mL, and 2395 days·µg/mL, respectively. The elimination of vedolizumab was relatively slow, with an arithmetic mean terminal $t_{1/2}$ of 20.23 days.

The AVA status of subjects administered a single vedolizumab 300 mg IV infusion is summarized in Table 3. All samples were negative in the AVA screening period. A total of six Chinese subjects (37.5%) were AVA positive during the study. Three subjects were positive for AVAs on day 106, two of which were positive for neutralizing AVAs. An additional three subjects were positive for AVAs at the final visit (day 127), one of which was positive for neutralizing AVAs. The three subjects who were AVA positive by day 106 had a titer of 1:250. By the final visit (day 127), four subjects had an AVA titer of 1:250, one subject had a titer of 1:1250, and one subject had a titer of 1:6250.

3.3 Safety Outcomes

Overall, 4 of the 16 subjects (25.0%) had TEAEs that were considered by the investigator to be related to the study drug. The study drug-related TEAEs reported for all four subjects were upper respiratory tract infections, all of which were mild in intensity and self-limited. Of all the upper respiratory tract infections, no trends of decreased white blood cell count, absolute neutrophil count, or total lymphocyte count were observed. Only one subject took ibuprofen sustained-release capsules to control the symptom of fever accompanying the upper respiratory tract infection; no other subjects took extra concomitant medications. None of the subjects had signs or symptoms of PML, hypersensitivity (including injection site reactions), serious infection, or malignancy in this study. Apart from the above four cases of TEAEs, no other apparent abnormalities were observed in subjects' vital signs, ECGs, physical examinations, or clinical laboratory tests throughout the study, and no subjects discontinued as a result of AEs.

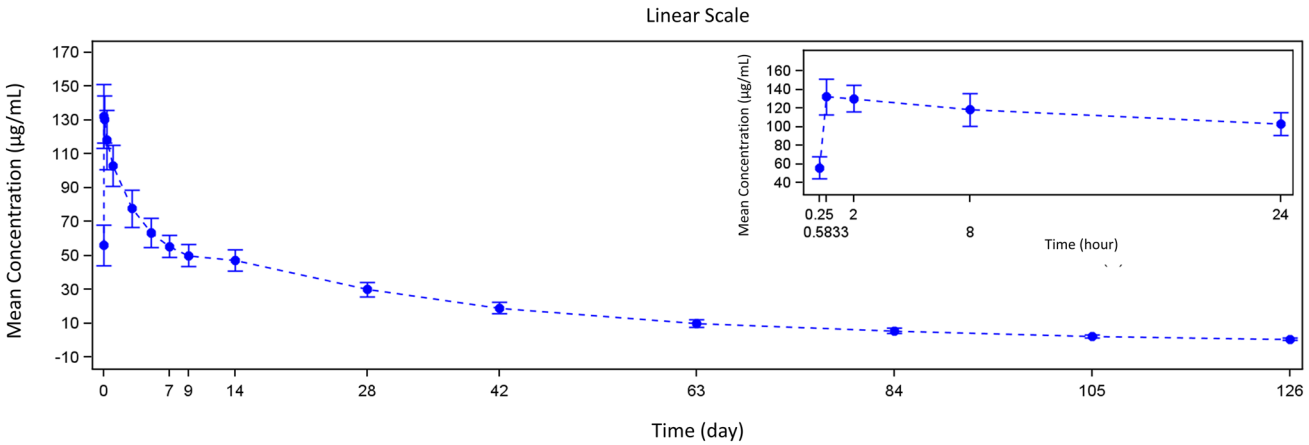

Fig. 1 Mean serum concentration–time curve for vedolizumab 300 mg IV in healthy Chinese subjects. The error bars represent standard deviation(s) and the inset represents vedolizumab pharmacokinetics for the first 24 hours post dose

Table 2 Principal pharmacokinetic parameters following administration of a single vedolizumab 300 mg IV infusion (PK analysis set)

PK parameters	Value
$AUC_{0-\infty}$ (day·μg/mL)	2395 (12.38)
AUC_{0-t} (day·μg/mL)	2360 (12.49)
C_{max} (μg/mL)	137.25 (11.59)
$t_{1/2}$ (days)	20.23 (12.49)
t_{max} (days)	0.06 (0.02, 0.33)

$AUC_{0-\infty}$ area under the serum concentration–time curve from time 0 to infinity, *AUC_{0-t}* area under the serum concentration-time curve from time 0 to time of the last quantifiable concentration, *C_{max}* maximum observed serum concentration, *PK* pharmacokinetic, *$t_{1/2}$* the terminal disposition phase half-life, *T_{max}* time of first occurrence of C_{max}

All data presented as arithmetic means (CV %, pseudo within-subject percentage coefficient of variance) except t_{max}, which was presented as the median (minimum, maximum)

Table 3 Anti-vedolizumab antibody (AVA) status in healthy Chinese subjects after administration of a single vedolizumab 300 mg IV infusion ($N = 16$)

AVA status	Number of subjects (%)
Subjects with ≥1 non-missing AVA sample	16 (100)
AVA negative	10 (62.5)
AVA positive	6 (37.5)
Transiently positive	3 (18.8)
Persistently positive	3 (18.8)
Any neutralizing AVA positive	3 (18.8)

4 Discussion

The mechanism of action of vedolizumab is via binding to the α4β7 integrin only, thus inhibiting adhesion to MAdCAM-1 to selectively block memory T cells from trafficking to inflamed gut tissue; this is a different mechanism of action to natalizumab (which binds to both the α4β1 and α4β7 integrins) [10]. No significant changes in T-lymphocyte population and no systemic immunosuppressive activity have been identified in previous studies [6, 7]. In this study, vedolizumab was well tolerated. Previous studies showed that the most common AEs associated with vedolizumab treatment were GI events and infections, particularly upper respiratory tract infections (range 1–20%) [11, 12]. In this study, the AEs associated with vedolizumab were all (in 4 out of 16 subjects) upper respiratory tract infections, which demonstrated that the safety and tolerability profile of vedolizumab IV in a Chinese population was similar to other populations.

One of the main purposes of this study was to evaluate the pharmacokinetic parameters of a single infusion of vedolizumab in healthy Chinese volunteers. These pharmacokinetic parameters are consistent with previous studies conducted in non-Asian populations [6] and Japanese patients with UC [13], and with the previously published population pharmacokinetic model [7]. For example, the estimated vedolizumab half-life of 20.23 days in Chinese subjects is slightly shorter than, but similar to, the 25.5 day half-life in the population pharmacokinetic model. According to the results of previous studies and the population pharmacokinetic model, extremely high body weight or extreme differences in serum albumin are potentially clinically important predictors of vedolizumab clearance rate (CL) [14]; however, body weight and serum albumin were comparable across populations, so they were not anticipated to differentially impact the pharmacokinetic parameters in Chinese subjects. For instance, the C_{max} and AUC in Chinese subjects were also comparable to the non-Asian population (considering different single doses) [6]. Furthermore, the C_{max} of 137.25 μg/mL in the Chinese subjects was also comparable to, but slightly higher than, the single-dose (first dose administered) C_{max} of 99.6 μg/mL in Japanese patients with UC [13]. Therefore, ethnicity is not considered to be a clinically relevant factor that affects the pharmacokinetics of vedolizumab in the Chinese population. As such, the standard 300 mg IV infusion regimen will achieve appropriate pharmacokinetic parameters in Chinese patients with IBD.

AVA statuses for subjects administered a single vedolizumab 300 mg IV infusion are summarized in Table 3. In this study, a total of six Chinese subjects (37.5%) were AVA positive during the study. This percentage of AVA positivity was comparable and slightly lower than a previous study in non-Asian subjects (54%) [6]. In the current study, AVA positivity occurred near the end of the study (on days 106 and 127), and the titers of the first detected AVA positivity were all started at 1:250. The AVA titers of the two subjects who were positive for neutralizing AVAs by day 106 increased to 1:1250 and 1:6250, respectively, by day 127. According to the protocol, no more samples were collected for AVA testing after day 127; therefore, the follow-up AVA status still needs to be studied in future research. Though other studies have reported that vedolizumab trough serum concentrations decreased when patients were persistently AVA positive during treatment [14], in this study, no significant difference in pharmacokinetic profiles was observed between the AVA-positive and AVA-negative groups, which might be related to the single infusion of vedolizumab.

5 Conclusions

Vedolizumab's pharmacokinetic parameters were determined and it was found to be well tolerated in healthy Chinese subjects when administered as a single-dose 300 mg IV infusion. In this study, the rate of AVA positivity was 37.5%, which occurred near the end of the study; there were no significant differences in pharmacokinetic profiles observed between the AVA-positive and AVA-negative groups. Finally, ethnicity is not considered to be a clinically meaningful factor that affects vedolizumab pharmacokinetics or AVA status in the Chinese population.

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Declarations

Funding This work was supported by Takeda Development Center Asia, Pte. Ltd.

Conflict of interest Lili Yang, Alexander Prokopienko, and Hiroyuki Okamoto are employees of Takeda, which sponsored the clinical trial. Lili Yang, Alexander Prokopienko, and Hiroyuki Okamoto also own stock and/or stock options in Takeda. Other authors have no relevant conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki and Good Clinical Practice Guidelines. The study was approved by the Ethics Committee of Peking University First Hospital (China).

Informed consent All subjects provided written informed consent prior to participation.

Consent for publication Not applicable.

Availability of data and material Considered upon request.

Code availability Not applicable.

Author Contributions Y.C. and X.Z. contributed to the design of the study. Y.C., X.Z., R.X., N.Z., and B.J. performed the research and interpreted the data. Preparation of the initial manuscript was carried out by R.X. and N.Z. The manuscript was revised and approved by R.X., N.Z., B.J., X.Z., and Y.C. L.Y. contributed to exporting serum samples from China by providing technical/scientific rationale to OHGRA, overseeing the smooth running of the technical operations during the study in China, answering Chinese regulatory immunogenicity and neutralizing questions, providing the assay information, and reviewing this manuscript. A.P. contributed to the interpretation of the data and writing and reviewing the manuscript. H.O. contributed to the design of the study, analysis, and interpretation of the data.

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