Pharmacokinetics of Sifuvirtide in Treatment-Naive and Treatment-Experienced HIV-Infected Patients

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ABSTRACT: The pharmacokinetics assessment in two clinical studies of sifuvirtide (a novel HIV fusion inhibitor) was first reported in Chinese HIV patients. Nineteen treatment-naive HIV patients were treated with s.c.(subcutaneous injection) sifuvirtide [10 or 20 mg q.d.(quaque die)] for 28 days in study 1, and eight treatment-experienced HIV patients were treated with s.c. sifuvirtide (20 mg q.d.) in combination with HAART drugs (lamivudine, didanosine, and Kaletra) for 168 days in study 2. In study 1, $T_{1/2}$ was 17.8 ± 3.7 h for 10 mg group and 39.0 ± 3.5 h for 20 mg group; the mean C_{max} of last dose was 498 ± 54 ng/mL for 10 mg group and 897 ± 136 ng/mL for 20 mg group. In study 2, $T_{1/2}$ was 6.71 ± 2.17 h in treatment-experienced patients. C_{max} was 765 ± 288 ng/mL after last 168th dosage. Sifuvirtide showed improved clinical pharmacokinetics characteristics compared with Enfuvirtide, and showed very different pharmacokinetic characteristics between treatment-naive and treatment-experienced patients. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

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INTRODUCTION

HIV fusion inhibitors are the new generation of anti-HIV drugs, which have a unique extracellular mode of action that distinguishes them from the other licensed agents [reverse-transcriptase inhibitors (RTIs) and protease inhibitors (PIs)] that suppress viral replication inside the cell.[1] Most of these inhibitors are synthesized peptides. By mimicking the naturally occurring N-(or C-)heptad repeat regions of HIV-1 gp41 transmembrane glycoprotein (HR1 or HR2), these peptides disrupt the conformational changes that occur following binding of the HIV-1 envelope to the CD4 cell-surface receptor preventing viral entry.[2–5] Among these peptides, Enfuvirtide (T-20, Fuzeon®, DP-178) is the first member of this class of antiretroviral (ARV) agents to be approved by US FDA in 2003. Enfuvirtide is composed of a linear sequence of 36 amino acids derived from the nature-occurring motif (residues 643–678) within the HR2 region.[6] The successful clinical applications of Enfuvirtide clearly indicated that Enfuvirtide has antiviral activity and promising safety profile, both as a monotherapy and in combination with other approved agents in previously treated patients who have multidrug-resistant HIV infection. However, when Enfuvirtide was discovered, the three-dimensional structure of gp41 was not solved, and thus Enfuvirtide covered only two-thirds of the HR2 and missed the deep pocket of gp41. This may ultimately attenuate the efficiency of Enfuvirtide as a fusion inhibitor. Because of its defect in molecular structure and short half-life (3.8 h) *in vivo*, Enfuvirtide must be injected twice daily and 90 mg per dose, resulting in serious injection-site reactions and financial burden for patients. Ultimately, these defects and emergence of Enfuvirtide resistance in some patients are main causes of treatment failure within 6 months.[7,8] The development of better fusion inhibitors with higher efficiency, lower dosage, and much less injection-site reaction would be highly desirable.

A novel anti-HIV fusion inhibitor sifuvirtide (Ac-SWETWEREIENYTRQIYRILEESQ EQQDRNERDLLE-NH2, MW = 4727 Da) was designed based on the three-dimensional structure of HIV-1 gp41 fusogenic core conformation. Sifuvirtide covers the deep hydrophobic pocket that was missed by Enfuvirtide. It has been engineered with 22-amino-acid residues different from Enfuvirtide. The major modification of sequence-included change of the sequence of the N-terminal heptad repeat (NHR)-binding domain (NBD), deletion of the lipid-binding domain (LBD), and addition of the pocket-binding domain (PBD), leading to improvement in stability, pharmacokinetics, and antiviral potency compared with Enfuvirtide.[9,10] The antiviral activity and promising safety profile of sifuvirtide has been shown in *in vitro* experiments and clinical trials. In the cell–cell fusion assay, the effective concentration for 50% inhibition (IC_{50}) of sifuvirtide was 1.2 ± 0.2 nm, compared with 23 ± 6 nm of Enfuvirtide.[11] In cell-mediated viral infections, sifuvirtide had much higher potency than Enfuvirtide in a wide range of primary and laboratory-adapted HIV-1 strains, and Enfuvirtide-resistant HIV-1 strains.[9,12] And for the patients with plasma HIV-1 viral RNA <10,000 copies/mL, the median decline in plasma viral load from baseline was 1.22

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log10 copies/mL for s.c. administration of 20 mg sifuvirtide once daily.[12] This decline in viral load *in vivo* was quite similar to the number of 1.14 log10 copies/mL after s.c. administration of 90 mg Enfuvirtide twice daily.[13] This comparable treatment effect indicated that sifuvirtide had much higher efficacy than Enfuvirtide. Where does this different efficacy come from? Has this high efficacy been related to pharmacokinetics properties? It is believed that different molecular structures result in different pharmacokinetic properties. And the different pharmacokinetic properties may result in different efficacy. To evaluate the efficacy, safety, and pharmacokinetic of sifuvirtide in treatment-naive and treatment-experienced HIV patients and better understand the pharmacodynatics–pharmacokinetics relationship of these fusion inhibitors, clinical phase IIa and IIb trails of sifuvirtide were conducted in Chinese HIV patients. The aim of this paper included characterizing the pharmacokinetics of sifuvirtide in Chinese HIV patients with different treatment history, to better understand the pharmacodynamic–pharmacokinetic relationship of this class of HIV fusion inhibitors, and investigating the action mechanism of HIV fusion inhibitor at the molecular level more precisely.

METHODS

Ethical approvals of the following two studies were obtained by an independent Ethics Committee at the study site (Ethic committee of Beijing Youan Hospital, Beijing, People's Republic of China). Before the studies began, the protocol and the informed-consent provisions were reviewed and approved by the independent institutional review board at the study site. All Chinese subjects were given written informed consent to participate in the studies, and agreed to abstain from nonstudy medication.

Patients ranged in age from 18 to 45 years (mean age = 38 years) and body mass index (BMI) ranged from 18.0 to 27.0 Kg/m^2 (BMI = weight/stature^2) were screened. After they had a thorough physical examination (including a general physical examination, urinalysis, blood biochemical tests, chest X-ray, B ultrasound and electrocardiogram, etc.), subjects without severe liver and kidney damage and other indicators in the basic normal range were considered to enroll. Subjects were excluded from entry into the two studies based on any of the following: if they were smokers and drinkers; pregnant or lactating; using any not mentioned prescription drugs in the 4-week period prior to dosing or used over-the-counter medication in the 2-week period prior to dosing; had a significant illness (e.g., in the acute phase of infection, serious chronic diseases, metabolic diseases, and pancreatitis), or transaminases exceeding three times the upper limit of normal, creatinine above normal within 2 weeks prior to dosing. The following two clinical studies were registered at Chinese Clinical Trial Registry and in full compliance with the WHO International Clinical Trials Registry Platform (WHO ICTRP) and the International Committee of Medical Journal Editors (ICMJE) criteria.

Study 1

Study Design

This pharmacokinetic assessment was part of the FS0103 study of sifuvirtide (registration number ChiCTR-TRC-08000211), a phase IIa clinical study for safety and pharmacokinetics of multiple dose administration of sifuvirtide in HIV-infected volunteers. The primary objective of FS0103 study was to evaluate the safety, tolerability, and pharmacokinetics of multiple doses of sifuvirtide for s.c. injection in HIV-infected volunteers, along with efficacy evaluation. Except for the additional blood sampling, the procedures for this substudy were part of the FS0103 study protocol. Study 1 was conducted at Beijing Youan Hospital from August 2006 to July 2007.

It was a 4-week, double-blind, two doses, and randomized parallel control pharmacokinetic study in treatment-naive HIV-1-infected patients. Inclusion criteria for HIV-1-infected adults with HIV viral RNA in plasma were greater than 5000 copies/mL (bDNA detection), and CD4$^+$ lymphocyte counts greater than 250 cells/mL (absolute counting) were enrolled. Treatment-naive patients were defined as subjects who stopped receiving anti-HIV drug over half a year or subjects who never received any anti-HIV drug. So HIV subjects who stopped receiving anti-HIV drug less than half a year before admission were excluded. During study 1, subjects, care providers, and investigators are all blinding. All the research process should ensure blinding implemented. Patients and care provider were all blinded after assignment to interventions. They do not know the exact dose.

A total of 24 subjects were randomized to two groups; subjects in 10 mg group were received 10 mg sifuvirtide s.c.(subcutaneous injection) once daily, and subjects in 20 mg group were received 20 mg sifuvirtide s.c. once daily. Randomization procedure was generated by random number table.

Anti-HIV Treatment

Sifuvirtide (FusoGen Pharmaceuticals, Inc., Tianjin, People's Republic of China) was administered as s.c. injection (10 or 20 mg dose for each group) once daily for 28 consecutive days. The contents of each vial of sifuvirtide were dissolved in water for injection. Injection site is the abdomen, and each injection should choose a different part of the last injection. The site of injection should not be chosen before the reactions had subsided again.

Study 2

Study Design

Study 2 was pharmacokinetic assessment part of FS0105 study (registration number ChiCTR-TRC-08000238), a phase IIb clinical study for efficacy, safety, and pharmacokinetics of sifuvirtide for injection in combination with HAART therapy in HIV-infected subjects. Except for the additional blood sampling, the procedures for this substudy were part of the FS0105 study protocol. FS0105 study was conducted at Beijing Youan Hospital from August 2007 to December 2009. It was a 24-weeks, open-label, randomized parallel control study for efficacy, safety, and pharmacokinetics of sifuvirtide for injection in combination with HAART therapy in HIV-infected subjects. One hundred and eight patients with HIV infection who were receiving HAART therapy for more than 6 months were enrolled in the FS0105 study. HIV viral RNA for all patients was greater than 5000 copies/mL, and CD4 cell count was greater than 50 cells/mm^3. At the screening phase, treatment-experienced HIV patients who fulfilled inclusion criteria with HIV viral RNA in plasma were greater than 5000 copies/mL (bDNA detection), and CD4$^+$ lymphocyte counts greater than 50 cells/mm^3 (absolute counting) were considered to enroll in study 2. The

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