Pharmacokinetics of a Single Dose of Fulvestrant Prolonged-Release Intramuscular Injection in Postmenopausal Women Awaiting Surgery for Primary Breast Cancer

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ABSTRACT

Objective: The aim of this study was to describe the pharmacokinetics of 3 different single doses of fulvestrant—a new estrogen receptor (ER) antagonist that downregulates the ER with no known agonist effects—administered as a prolonged-release IM formulation.

Methods: Pharmacokinetic data were obtained in a randomized, partially blinded, placebo-controlled, parallel-group, Phase I/II multicenter trial involving postmenopausal women with primary breast cancer (clinical stages T1–T3, with tumors that were ER positive or of unknown ER status) awaiting curative-intent surgery. Patients received either IM fulvestrant (50, 125, or 250 mg), oral tamoxifen (20 mg, once daily), or oral placebo (once daily). Treatment started 2 to 3 weeks before surgery and blood was taken at various times up to 12 weeks after fulvestrant administration to assess pharmacokinetic variables.

Results: A total of 200 patients entered the trial, of whom 58 took part in the pharmacokinetic analysis (50 mg, n = 20; 125 mg, n = 16; 250 mg, n = 22). Following single IM injections of fulvestrant, the median time to maximum concentration was 6.98, 6.98, and 6.96 days in the 50-, 125,- and 250-mg dose groups, respectively, with an overall range of 2 to 19 days). The plasma concentration–time profiles were primarily controlled by the rate of absorption from the injection site; post-peak plasma concentrations declined over time and were measurable up to 84 days after administration of fulvestrant 125 and 250 mg. Plasma

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concentrations at 28 days were 2- to 5-fold lower than the maximum value. Plasma concentration data for the 250-mg dose were best described by a 2-compartment pharmacokinetic model, with an apparent terminal phase half-life of ~49 days, beginning ~3 weeks after administration. Mean area under the plasma concentration–time curve for days 0 through 28 (AUC_{0-28}) was proportional for fulvestrant 50, 125, and 250 mg. For a doubling of the dose, an analysis of covariance model of the pharmacokinetic data projected an estimated increase in AUC_{0-28} of a factor of 1.84 (95% CI, 1.67 to 2.04).

Conclusions: The IM formulation of fulvestrant used in this study had predictable, dose-linear pharmacokinetics. The prolonged-release properties of this formulation suggested that it may be well suited for the once-monthly dosing schedule intended for clinical use. (*Clin Ther.* 2003;25:1440–1452)

Key words: advanced breast cancer, fulvestrant, estrogen receptor antagonist, antiestrogen, pharmacokinetics.

INTRODUCTION

Although tamoxifen has been a great asset in the treatment of breast cancer,[1,2] some features make it less than ideal. For example, patients with advanced disease who initially respond to tamoxifen may ultimately develop resistance, which may result in disease progression.[3,4] Moreover, tamoxifen treatment may increase the risk of developing endometrial cancer ($P = 0.049$).[5] For these reasons, there has been considerable interest in developing alternative hormonal treatments for breast cancer that improve on the success of tamoxifen.[6,7]

Fulvestrant* (previously known as ICI 182,780) is an estrogen receptor (ER) antagonist with no known agonist effects; it works by downregulating the ER.[8–10] This mechanism contrasts with that of tamoxifen, which acts mainly as an estrogen antagonist but also has estrogen agonist properties.[3,11] Because fulvestrant has a different mode of action than tamoxifen, it has the potential to be effective against tamoxifen-resistant tumors; in vitro, in vivo, and clinical studies have confirmed the lack of cross-resistance.[10,12–14] Moreover, its pure antiestrogenic properties should make it less likely than tamoxifen to have detrimental stimulatory effects on the endometrium; these results have been shown in animal studies.[15]

Following promising results from early clinical trials with fulvestrant,[9,14] 2 Phase III studies[16,17] involving a total of >800 patients have been recently completed. Results of these studies showed similar efficacy and tolerability for fulvestrant 250 mg IM, once monthly, compared with the most appropriate second-

*Trademark: Faslodex® (AstraZeneca Pharmaceuticals LP, Wilmington, Delaware).

line therapy, the third-generation aromatase inhibitor anastrozole 1 mg PO, once daily.[16,17]

Unlike tamoxifen—a triphenylethylene—fulvestrant is a steroidal molecule derived from estradiol with a long alkylsulphinyl side chain in the 7-alpha position (Figure 1). Fulvestrant's chemical properties are such that it is poorly soluble and has low and unpredictable oral bioavailability. Thus, a parenteral formulation of fulvestrant has been developed in an attempt to maximize delivery of the drug molecule.

For therapeutic use, fulvestrant is available in a castor oil–based solution for IM injection that slowly releases the drug over a period of at least 1 month. The aim of this article is to describe the pharmacokinetics of 3 different single doses of fulvestrant (50, 125, and 250 mg).

PATIENTS AND METHODS

Study Design

The data for this pharmacokinetic assessment were gathered during a randomized, partially blinded, placebo-controlled, parallel-group, Phase I/II multicenter trial. The primary objective of the study was to compare the antiestrogenic and antiproliferative properties of fulvestrant with tamoxifen and placebo. The methods and results pertinent to the primary objective are reported elsewhere.[18] A prespecified secondary objective of the study was to determine the pharmacokinetic profiles of single doses of fulvestrant, presented here.

Patients with primary breast cancer awaiting curative-intent surgery were randomized to preoperative treatment with fulvestrant, tamoxifen, or placebo. Surgery took place 15 to 22 days after the start of drug treatment. Blood samples for pharmacokinetic analysis were collected up to 12 weeks after the start of drug treatment.

The study was approved by the ethics committee at each center before any patients were enrolled at that center, and was conducted in accordance with the

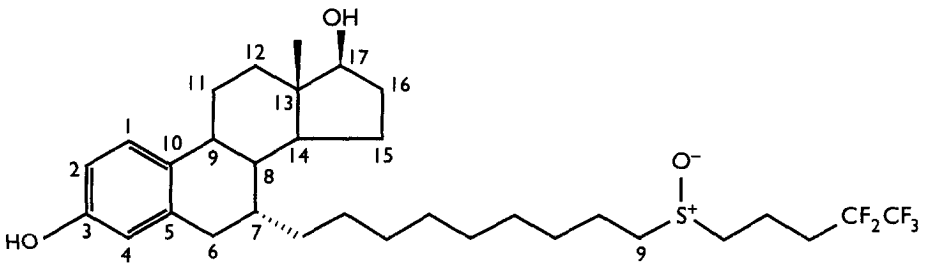

Figure 1. Chemical structure of the estrogen receptor antagonist fulvestrant, 7-alpha-[9-(4,4,5,5,5 penta fluoropentylsulphinyl) nonyl]estra-1,3,5-(10)-triene-3,17-beta-diol.

1964 Declaration of Helsinki as amended in Hong Kong in 1989 and the Republic of South Africa in 1996. All patients gave written informed consent before entering the study.

Patients

Patients were postmenopausal women with primary breast cancer (clinical stages T1–T3) confirmed by histology or cytology. Tumors had to be ER positive or of unknown ER status. The main exclusion criteria were metastatic disease; previous treatment of the tumor with hormonal therapy, chemotherapy, or radiotherapy; treatment with hormone replacement therapy in the previous 4 weeks; abnormal liver function tests; or severe systemic disease. Patients could be withdrawn from the study because of adverse events or protocol violations, as well as at the investigator's discretion or the patient's request.

Treatments

Patients were randomized in a 1:1:1:1:1 ratio to treatment with fulvestrant (50, 125, or 250 mg), tamoxifen (20 mg), or placebo. The placebo matched the tamoxifen tablets to maintain blinding between tamoxifen and placebo. However, fulvestrant doses were not blinded. Thus, patients allocated to fulvestrant knew which treatment they received, whereas those allocated to tamoxifen or placebo did not know which of those treatments they received. Investigators were blinded similarly. Fulvestrant was administered as a single IM injection in the buttock 15 to 22 days before surgery. Tamoxifen and placebo were taken PO once daily from the start of treatment until the day before surgery (ie, for 14 to 21 days).

Patients did not receive any systemic anticancer therapies, other than the study medication, for the duration of the study. Estrogen replacement therapy was also prohibited during the study.

Blood Sampling and Analysis

Blood samples (10 mL) were drawn into heparin tubes for assay of plasma fulvestrant before and at 2, 7, 10, 14, 21, 28, 35, 42, 56, and 84 days (12 weeks) after administration. Samples were centrifuged at 1000*g* for 10 minutes and the plasma was removed and stored at –20°C until analysis. Plasma samples were packed in dry ice at –80°C and transported to the laboratory for pharmacokinetic analysis. Fulvestrant was extracted from 0.5 mL of plasma by mixing with 2.0 mL of hexane/propan-2-ol. Following centrifugation, the organic layer was separated and evaporated to dryness. The extract was reconstituted and injected into a high-performance liquid chromatography (HPLC) system with an Inertsyl YMC-ODS-AQ 3F HPLC column (Hichrom Ltd., Berkshire, United Kingdom) coupled to a Sciex API III+ triple quadruple mass spectrometer fitted with a heated nebulizer interface (Applied Biosystems, Foster City, California). Fulvestrant was monitored

in positive multiple reaction mode using 607 m/z for the precursor ion and 589 m/z for the product ion. Fulvestrant was quantified using a 1/× weighted linear least squares regression line generated from spiking standard amounts of fulvestrant over the concentration range 0.25 to 50.0 ng/mL. The limit of quantification for the assay was 0.25 ng/mL and the coefficient of variation ranged from 7.70% to 17.1% for standards of 40.0 ng/mL and 1.0 ng/mL, respectively.

Pharmacokinetic Analysis

Maximum plasma fulvestrant concentration (C_{max}), plasma concentration at 28 days (C_{min})—the minimum time between doses—and time to maximum concentration (T_{max}) were determined by inspection of individual patient data. Area under the concentration-time curve in the first 28 days (AUC_{0-28}) and AUC from time 0 to the last quantifiable plasma concentration (AUC_{0-t}) were calculated using the linear trapezoidal rule.

Estimates of half-life ($t_{1/2}$) and AUC from time 0 to infinity ($AUC_{0-\infty}$) were obtained from a first-order, 2-compartment, pharmacokinetic model fitted to the 250-mg dose data using a naive pooled data approach; that is, it was assumed that all plasma concentrations had come from the same patient. Thus, although there were concentration data from a number of patients at each dose level, this approach did not allow for estimation of intersubject variability. Although it is also possible to describe the data for each dose with 1-compartment models, the 2-compartment model was chosen as more representative of the observed data at all 3 dose levels. More complex models were not evaluated due to the relatively infrequent data obtained during the initial absorption phase. Data were weighted by the reciprocal of the concentrations as a compromise between overweighting low concentrations and obtaining an adequate fit to the initial data. Analysis was performed using the validated software package WinNonlin version 1.5 (Pharsight Corporation, Mountain View, California). Model-generated parameters were also used to simulate the plasma concentration–time curves for comparison with observed data for the 50- and 125-mg dose groups.

Statistical Analysis

Descriptive statistics were calculated for pharmacokinetic parameters; for parameters with a log-normal distribution [AUC_{0-28}, C_{max}, and C_{min}], the data were log [base e] transformed and summarized as geometric means with coefficients of variation.

Any center by treatment interaction was tested using an analysis of covariance (ANCOVA) model with center, log (dose), and the interaction as covariates, performed using the SAS procedure PROC MIXED (SAS Institute Inc., Cary, North Carolina). If the center by log (dose) interaction was not significant at the 1% level, then this was dropped from the model; subsequently, the hypothesis that

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