The Application of Mechanism-Based PK/PD Modeling in Pharmacodynamic-Based Dose Selection of muM17, a Surrogate Monoclonal Antibody for Efalizumab

BENJAMIN WU, AMITA JOSHI, SONG REN, CHEE NG

Department of Pharmacokinetic and Pharmacodynamic Sciences, Genentech, Inc., 1 DNA Way, MS 70, South San Francisco, California 94080

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ABSTRACT: muM17 is an anti-mouse CD11a monoclonal antibody (mAb) developed as a surrogate molecule for assessing potential reproductive toxicities of efalizumab, an anti-human CD11a mAb approved for treatment of chronic moderate to severe plaque psoriasis. This article shows the use of a mechanism-based PK/PD model for muM17 to further support the determination of dose equivalency of muM17 in the mouse and efalizumab in humans based on CD11a expression on T-lymphocytes (PD). Patients in clinical studies received 1 mg/kg/week efalizumab subcutaneously for 12 weeks. In the mouse model, a single IV dose of 1 or 10 mg/kg or a single SC dose of 3, 5, or 10 mg/kg muM17 was administered. Drug concentrations and PD were quantitated using ELISA and flow cytometry (FACS) analyses, respectively. The PK/PD model of muM17 in mice was developed and was validated using sparse data from a separate multiple dose PK/PD study. The model was next used to simulate PD profiles with multiple dosing regimens mimicking those of the clinical dose of efalizumab. The model showed that 3 mg/kg/week SC administration of muM17 in mice is the minimum dose that can produce PD effects similar to those produced following 1 mg/kg/week SC of efalizumab in humans.
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INTRODUCTION

Psoriasis is an autoimmune disease mediated by T-lymphocytes and characterized by hyperproliferation of keratinocytes and accumulation of activated T-lymphocytes in the epidermis and dermis of psoriatic lesions.[1–3] Leukocyte function-associated antigen-1 (LFA-1), expressed on activated T-lymphocytes, binds with intracellular adhesion molecule 1 (ICAM-1), facilitating processes related to the pathogenesis of psoriasis, including migration of T-lymphocytes from the circulation into the dermis and epidermis of psoriatic lesions, with subsequent reactivation.[4–7]

Efalizumab is a recombinant humanized IgG1 kappa isotype monoclonal antibody (mAb) that selectively binds to the alpha subunit of LFA-1 (CD11a). Efalizumab was recently approved in the United States and Europe for treatment of adults 18 years and older with moderate to severe plaque psoriasis. In an earlier report, efalizumab demonstrated dose-dependent nonlinear pharmacokinetics (PK) in patients with psoriasis, which can be explained by its saturable binding to its cell surface receptor, CD11a.[8,9] Efalizumab caused a

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Abbreviations: PK, pharmacokinetics; PD, pharmacodynamics; ELISA, enzyme-linked immunosorbent assay; FACS, flow cytometry; MEM, mixed-effect modeling.

Correspondence to: Chee Ng (Telephone: 650-225-3363; Fax: 650-225-6452; E-mail: Ng.chee@gene.com)

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rapid reduction in the expression of CD11a on circulating lymphocytes, typically to 25%–30% of pretreatment levels. The cell-surface CD11a remained at these reduced levels until efalizumab levels decreased below 3 μg/mL, then the drug was rapidly cleared from the circulation and the expression of CD11a return to baseline within 7–10 days.[8,9]

Efalizumab is specific for chimpanzee and human CD11a but does not recognize CD11a from other nonhuman primates.[10,11] This restricted specificity confined nonclinical in vivo safety assessment of efalizumab to chimpanzees. However, assessing safety using the chimpanzee is limited for ethical reasons.

To complete a more comprehensive safety assessment, a chimeric rat anti-mouse CD11a antibody, muM17, was developed and evaluated as a species-specific surrogate molecule for efalizumab. muM17 binds mouse CD11a with specificity and affinity similar to those of efalizumab to human. In addition, muM17 in mice was demonstrated to have similar pharmacological activities as that of efalizumab in human.[12] However, given the different capacity of CD11a, nonlinearity of PK, and other species-specific factors between the mice and human, similar weight-based doses of muM17 and efalizumab may not translate into similar pharmacological effects. To directly compare the PD effects (i.e., CD11a expression levels) of the two molecules, a more informed approach is needed to identify dose equivalence between muM17 in the mice and efalizumab in human. In this study, the initial dose selection was determined based on visual comparison of PD (CD11a expression levels) after a single dose administration in female CD-1 mice. Then, mechanism-based pharmacokinetic/pharmacodynamic (PK/PD) model was developed and provided a quantitative comparison of PD profile between mice and human in a multiple dose study. Therefore, the objectives of this analysis were:

1. To characterize the PKs and PDs of muM17 in mice after single-dose administration and describe the use of the PD marker in the selection of a human-equivalent dose of muM17 for reproductive toxicity studies.
2. To develop a mechanism-based PK/PD model of muM17 in mice and use the model to assess the adequacy of the muM17 dose selected for multiple-dose reproductive toxicity studies in mice.

METHODS

Test Materials

Efalizumab is a humanized full-length mAb that targets human CD11a with a binding affinity of 3.0 ± 1.5 nM.[13] Efalizumab was supplied in single-use glass vials containing sterile, lyophilized drug product. Prior to administration, efalizumab was reconstituted as directed to 100 mg/mL in formulation containing 10 mM L-histidine, 60 mM sucrose, and 0.05% polysorbate 20 at pH 6.0. Efalizumab was stored between 2 and 8°C prior to reconstitution.

muM17 is a chimeric mouse/rat IgG mAb that targets mouse CD11a with a binding affinity of 2.7 ± 1.2 nM.[13] muM17 consists of a murine kappa constant domain for the light chain, and the murine CH1, CH2, and CH3 constant domains for the heavy chain. For the animal study, muM17 was prepared as a liquid formulation (7.6 mg/mL) containing 40 mM L-histidine, 240 mM sucrose, and 0.08% polysorbate 20 at pH 7.0. muM17 was stored between 2 and 8°C before use.

Clinical Study Design

The Phase I clinical study was an open-label, multiple-dose, multi-center study in subjects with moderate to severe plaque psoriasis. Of the 33 subjects who received 12 weekly SC doses of 1 mg/kg efalizumab, 26 subjects were evaluable for PK/PD analysis. Details of the study design and exclusion criteria of the clinical study have been published.[14] Briefly, serum efalizumab concentrations were determined by enzyme-linked immunosorbent assay (ELISA) on Days 0, 7, 28, 56, 77, 78, 79, 80, 84, 91, 98, 112, and 113. For PD analyses, fresh whole blood (1 mL) was collected for analysis of CD11a expression on T-lymphocytes on Days 0, 7, 28, 56, 84, 91, 112, 133, and 168.

Mouse Study Design

PK and PD of muM17 in normal healthy mice were investigated at Genentech, Inc. (South San Francisco, CA). Female CD-1 mice weighing 22.6–28.7 g were purchased from Charles River Laboratories, Inc., (Wilmington, MA). No male mice were used because findings from this study were intended for use in assessing the reproductive toxicity of the drug. Mice were housed in an environmentally controlled animal room with a maintained temperature of 65°F, a relative