Preliminary Report on DU-6859a for Lower Respiratory Tract Infection

Toshihiro Nukiwa,1,2 Kaoru Shimada,3 Kohei Hara,3 Shigeki Odagiri,4 and Hiroyuki Kobayashi5

1Department of Respiratory Oncology and Molecular Medicine, Institute of Development, Aging, and Cancer, Tohoku University, Sendai, Japan,
2Department of Infectious Diseases, Institute of Medical Science, University of Tokyo, Tokyo, Japan,
3The Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan,
4Department of Respiratory Diseases, Kanagawa Prefectural Cardiovascular and Respiratory Disease Center, Yokohama, Japan, and
5The First Department of Internal Medicine, School of Medicine, Kyorin University, Mitaka, Japan

INTRODUCTION

New quinolone antibacterial agents have been widely used as oral treatment for patients with lower respiratory tract infection (RTI), because of their broad spectrum and strong antibacterial activity against various kinds of organisms causing RTI. More active drugs, however, are required to improve responses in refractory infections due to *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*.

DU-6859a (Fig. 1), a novel “new quinolone,” which was synthesized by Daiichi Pharmaceutical Co., Ltd. (Tokyo, Japan), in 1988, has a broad spectrum of antibacterial activity against aerobic and anaerobic gram-positive and gram-negative bacteria, as well as *Chlamydia* and *Mycoplasma* species. One of the most important characteristics of DU-6859a, as compared with other currently available new quinolones, was its significantly higher activity against quinolone-resistant, methicillin-resistant *Staphylococcus aureus*, *S. pneumoniae*, quinolone-resistant *P. aeruginosa*, and *Bacteroides fragilis*.1

A satisfactory distribution of DU-6859a to respiratory tract tissues was observed in preclinical pharmacokinetic studies in rats (data on file, Daiichi Pharmaceutical Co., Ltd.). No evidence of overt toxicity that would contraindicate clinical studies has been shown in various animal species used for toxicity studies (data on file, Daiichi Pharmaceutical Co., Ltd.). The maximum serum concentration of DU-6859a showed dose dependency, and the elimination half-life was 4 to 5 hours in the phase I study.2 Approximately 70% of the administered dose was excreted unchanged in the urine within 48 hours. No accumulation of DU-6859a was observed during a 7-day administration period.

A preliminary multicenter study (an early phase II study) on DU-6859a, in patients with RTI, was performed with the cooperation of 20 leading hospitals in Japan (Appendix). The results obtained are reported herein.

PATIENTS AND METHODS

**Subject selection**

The objective diseases of this study were moderately advanced bacterial pneumonia or acute infectious exacerbation of chronic bronchitis, diffuse panbronchiolitis, infectious bronchiectasis, bronchial asthma with infection, and infection combined with chronic respiratory diseases such as pulmonary emphysema and pulmonary fibrosis. The inclusion criteria with regard to pneumonia were fever, leukocytosis, elevated C-reactive protein (CRP), and/or radiologic findings indicative of the disease. Other criteria include elevated CRP and increased purulent sputum associated with chronic RTI.
Patients who visited the participating hospitals during the period from November 1993 to May 1994 served as study subjects. The age range was previously limited to 20 to 79 years. Patients with the following conditions had previously been excluded: 1) severe infection, 2) severe underlying diseases or complications, 3) symptomatic improvement by prior treatment with another antibacterial agent, 4) a history of allergic or other serious reactions to quinolones, 5) pregnancy, possible pregnancy, or breastfeeding. Verbal or written consent to participate in the study was obtained from all patients.

**Test drug and administration**

DU-6859a tablets containing 50 mg of DU-6859 (the anhydride of DU-6859a) were used in this study. Based on the antibacterial activity of DU-6859a and the results of the phase I study on pharmacokinetics and tolerance, the drug was administered orally in the dose range of 50 to 100 mg once or twice daily. The administration period of DU-6859a was initially determined as 3 to 14 days.

Systemic administration of corticosteroids was prohibited, but nonsteroidal anti-inflammatory agents and theophylline were used with caution.

**Assessment of symptoms and laboratory variables**

The background of each patient was examined before starting the treatment. Clinical symptoms and adverse events were recorded during the trial. Laboratory findings such as hematology tests, biochemistry tests, and/or urinalysis were checked at the beginning and just after completion of the trial. The clinical efficacy of DU-6859a was assessed at the end of treatment and was based on an overall evaluation of clinical prognosis, including laboratory findings. Clinical efficacy was classified into the following grades: 1) excellent, clinical signs and symptoms improved shortly after the start of treatment; 2) good, clinical signs and symptoms improved by the end of the treatment period; 3) fair, clinical signs and symptoms improved slightly by the end of the treatment period; and 4) poor, clinical signs and symptoms were unimproved.

**Bacteriologic evaluation**

Bacteriologic examination of sputum or other suitable specimens was performed before, during, and after the treatment period. Microbial susceptibility was also determined at Mitsubishi Yuka Bio-Clinical Laboratories, Inc. (Tokyo, Japan).

The bacteriologic response to DU-6859a was observed on an individual patient basis. When replacement organisms were detected, a judgment of superinfection was made based on positive clinical symptoms and laboratory findings. Other organisms were recorded only as nonpathogenic bacteria.

**Evaluation of side effects**

When adverse events or abnormal laboratory test changes were noted, the severity was graded (mild, moderate, or severe) by the attending physician, taking into consideration whether administration of the drug was discontinued and/or whether treatment was required. The causal relationships to DU-6859a were recorded as definite, probable, possible, unlikely, or none, and the designations definite, probable, or possible were used to assess side effects or abnormal laboratory findings.

Overall safety was evaluated on the basis of side effects and abnormal laboratory findings, and the drug was classified into the following grades: 1) safe, no side effects or abnormal laboratory findings; 2) almost safe, side effects or abnormal laboratory findings were noted, but medication was continued with no additional treatment; 3) problematic, side effects or abnormal laboratory findings were noted, but medication was continued with concomitant treatment; and 4) unsafe, side effects or abnormal laboratory findings were noted, medication was withdrawn, or should have been stopped.

**Evaluation of clinical utility**

In terms of the clinical efficacy and safety in each case, the clinical utility of DU-6859a was classified by the attending physicians as very useful, useful, slightly useful, or not useful.

**RESULTS**

**Case selection**

Of the 109 patients enrolled in this trial, the following patients were excluded due to failure to meet the study protocol. One patient whose course was complicated by advanced lung cancer was excluded from all evaluations. Eight patients were excluded from evaluations of clinical and bacteriologic efficacy and clinical utility, because four were more than 80 years of age, two had acute bronchitis, and the others took an only one dose, due to the development of side effects (one case) and the withdrawal at the patient's request (one case). The causative organism was determined in 50 cases; of these, bacteriologic examination after the treatment was not done in one patient. The overall safety and clinical utility could not be determined in one patient who developed an adverse event judged unlikely to be related to the test drug. In addition, data considered unevaluable by the attending physicians for each patient were excluded from the assessment.