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Original article

Efficacy and safety of levofloxacin in patients with bacterial pneumonia evaluated according to the new "Clinical Evaluation Methods for New Antimicrobial Agents to Treat Respiratory Infections (Second Version)"

Hiroshi Mukae [a,*], Toshinori Kawanami [a], Kazuhiro Yatera [a], Katsunori Yanagihara [b], Yoshihiro Yamamoto [c], Hiroshi Kakeya [c], Issei Tokimatsu [d], Junichi Kadota [d], Shigeru Kohno [c]

[a] Department of Respiratory Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan
[b] Department of Clinical Laboratory, Nagasaki University Hospital, Nagasaki, Japan
[c] Department of Molecular Microbiology and Immunology, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan
[d] Department of Respiratory Medicine and Infectious Diseases, Oita University Faculty of Medicine, Oita, Japan

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ABSTRACT

The guideline for the "Clinical Evaluation Methods for New Antimicrobial Agents to Treat Respiratory Infections (Second Version)," published by the Japanese Society of Chemotherapy in January 2012, was proposed to achieve consistency with FDA guidelines based on the concept of clinical evaluation used in Japan. We assessed the clinical efficacy of levofloxacin (LVFX) in patients with bacterial pneumonia according to this new set of guidelines for the first time.

The clinical efficacy of LVFX in patients with community-acquired pneumonia (CAP) and healthcare-associated pneumonia (HCAP) at the test of cure (TOC) was 87.5% (56/64) and 85.7% (6/7), respectively, with an overall efficacy of 87.3% (62/71). The clinical efficacy of LVFX at TOC was as follows: intravenous 81.5% (22/27), oral 88.9% (24/27), switchover from intravenous to oral administration 100% (10/10), respectively. The bacterial eradication rate in the patients with CAP and HCAP and overall efficacy at the end of therapy (EOT) was 95.3% (41/43), 100.0% (4/4) and 95.7% (45/47), respectively. The frequent causative bacterial strains included *Streptococcus pneumoniae* (18), *Haemophilus influenzae* (14) and *Moraxella catarrhalis* (6). The incidence of adverse reactions in the patients whose safety was evaluated was 15.7% (14/89), similar to that previously reported.

The clinical efficacy of LVFX at the early phase, EOT and TOC of CAP, as assessed according to the new and former guidelines, was 70.4% (38/54) and 27.8% (15/54), 87.0% (60/69) and 79.1% (53/67), 87.5% (56/64) and 88.1% (59/67), respectively, with no significant differences. Therefore, the new efficacy evaluation method can be used in exchange for the former evaluation method.

1. Introduction

Clinical trials evaluating new antimicrobials against respiratory infections in Japan are performed according to the "Clinical Evaluation Methods for New Antimicrobial Agents to Treat Respiratory Infections (Draft)" [1] guidelines established in 1997 by the Respiratory Subcommittee of the Committee for the Establishment of Clinical Evaluation Methods for Antimicrobial Agents of the Japanese Society of Chemotherapy (JSC) (former method). However, methods for conducting clinical trials in Japan have changed significantly since the enforcement of the new Good Clinical Practice guidelines in 1997, which make it time- and cost-consuming to perform clinical trials. Therefore, the JSC established a committee to reexamine these methods in order to develop new antimicrobials

* Corresponding author. Department of Respiratory Medicine, University of Occupational and Environmental Health, Japan, 1-1, Iseigaoka, Yahata-nishi-ku, Kitakyushu City, Fukuoka 807-8555, Japan. Tel.: +81 93 691 7453; fax: +81 93 602 9373.
E-mail address: hmukae@med.uoeh-u.ac.jp (H. Mukae).

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for respiratory infections in 2007. The "Clinical Evaluation Methods for New Antimicrobial Agents to Treat Respiratory Infections (Second Version)" [2] (new method) were newly published in January 2012 to ensure consistency with the "Community-acquired bacterial pneumonia: Developing drugs for treatment, Draft Guidance" [3] guidelines of the Food and Drug Administration (FDA guidelines) based on the former evaluation concept used in Japan.

We herein evaluated the efficacy and safety of levofloxacin (LVFX) in patients with bacterial pneumonia according to the new method and discuss points to be kept in mind when using a new method.

2. Patients and methods

2.1. Study design

This was a prospective, open-label, multicenter study that was conducted from 2010 to 2011. The study was conducted with prior approval from the ethics committee of each of the participating institution and was registered on a clinical trial registry (UMIN000004831). The study protocol was explained thoroughly to the patients or their legally acceptable representative before the treatment, and written informed consent was obtained from each patient or their legally acceptable representative. Patients with bacterial pneumonia older than 20 years who visited 17 participating institutions between November 2010 and July 2011 were enrolled.

The inclusion criteria were as follows:

1) Suitability for treatment with antibacterial drugs.
2) Acute infiltration on a chest X-ray (CXP) and/or computed tomography (CT) scan obtained within the previous 48 h.
3) At least one of the following clinical symptoms and/or findings: cough, purulent sputum, abnormal findings on auscultation and/or percussion, dyspnea and/or tachypnea, fever (axillary body temperature (BT) $\geq$37 °C), an increased or decreased peripheral white blood cell count (WBC >10,000 or <4500/mm^3), stab leukocytes (>15%), increased serum C-reactive protein (CRP) and hypoxemia.

Patients with hospital-acquired pneumonia were excluded. Bacterial pneumonia was classified into two categories: healthcare-associated pneumonia (HCAP) and community-acquired pneumonia (CAP). HCAP was defined according to the guidelines [4] of the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA).

The exclusion criteria were as follows: bronchial obstruction, a past history of obstructive pneumonia (excluding chronic obstructive pulmonary disease; COPD), lung cancer, cystic fibrosis, acquired immunodeficiency syndrome, *Pneumocystis* pneumonia, active or suspected pulmonary tuberculosis, suspected atypical pneumonia (according to the "Practice Guidelines for Adult CAP" [5] of the Japanese Respiratory Society), the administration of another antimicrobial within 72 h, a past history of hypersensitivity to LVFX or ofloxacin, the use of other antimicrobials (excluding low-dose macrolides) associated with an improvement within one week, pregnancy and a Pneumonia Outcomes Research Team (PORT) class V [6].

2.2. LVFX administration

Cravit® tablets (500 mg once daily) and/or Cravit® Drip Infusion (once daily for 60 min) were continuously administered from seven to 14 days, with a switchover from intravenous to oral administration, if appropriate. LVFX was discontinued, even within seven days, if the treatment effect of LVFX was achieved or for any other reason to discontinue therapy. In patients with renal dysfunction, the dose of LVFX was appropriately reduced.

2.3. Prohibited medications

The concomitant use of other antimicrobials (excluding low-dose macrolides) or corticosteroids ($\geq$10 mg/day of prednisolone) was prohibited.

2.4. Evaluation items and study period

2.4.1. Patient background factors, clinical symptoms and characteristics

The patients' background factors were examined at the start of LVFX treatment (Table 1). Body temperature, pulse rate, respiratory rate, blood pressure, symptoms and the presence of chest rales on auscultation were examined at the start of therapy, three days after the start of therapy, the end of therapy (EOT; the time of LVFX discontinuation) and the test of cure (TOC; five to 10 days after treatment).

2.4.2. Chest imaging and microbiological analyses

CXP was obtained before treatment, three days after the start of treatment and at EOT and TOC. CT was repeatedly evaluated in patients with a chest CT-based diagnosis. Sputum samples were also collected before treatment, three days after the start of treatment and at EOT.

2.4.3. Laboratory examinations

Peripheral blood and blood gas analyses were conducted before the start of treatment and at EOT and TOC. Pneumococcal and *Legionella* urinary antigen tests were also performed before the start of therapy. *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* serum antibodies were examined before the start of treatment and at EOT and TOC, as appropriate.

2.4.4. Adverse events

Adverse events occurring from the start of therapy until three days after the discontinuation of LVFX were assessed and recorded.

2.4.5. Evaluation methods

Eight clinical symptoms and findings were recorded upon registration, as described in the inclusion criteria and sputum Geckler's classification for patients with CAP.

The patients were divided into two groups: those with a PORT class II or less and those with a class III or higher upon registration, based on the recommendation of the ATS/IDSA guidelines [6].

The new method was applied, and the clinical efficacy three days after the start of LVFX (early efficacy) and at EOT and TOC (primary endpoint) was evaluated. The following three-grade rating system for drug efficacy was employed in the early phase and at EOT: "effective," "ineffective" or "indeterminable." The effect at TOC was scored as "cured," "not cured" or "indeterminable."

The microbiologic efficacy at EOT or the time of LVFX cessation was evaluated as follows: "disappeared," "predictably disappeared," "sustained," "predictably sustained" or "indeterminable." "Disappeared" and "predictably disappeared" were categorized as "disappeared," "sustained" and "predictably sustained" were categorized as "sustained" at tabulation.

Adverse events were considered to be adverse reactions if the causal relationship between the adverse event and the administration of LVFX was undeniable.

A central committee was established to provide advice from the standpoint of a third-party, consisting of three committee members