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高病原性鳥インフルエンザの疫学臨床研究に関する研究

平成17年度～19年度　総合研究報告書

主任研究者　工藤　宏一郎

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厚生労働科学研究費補助金（新興・再興感染症研究事業）

総合研究報告書

高病原性鳥インフルエンザの疫学臨床研究に関する総合的研究

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研究要旨　ここ数年の間に、SARS（重症急性呼吸器症候群）、鳥インフルエンザ（H5N1）という 2 つの新興感染症が出現した。いずれも重症感染症であり、人類に脅威を与えているが、特に後者は今後新型インフルエンザへと変異し、世界的大流行を起こすことが懸念されている。しかしながら本疾患はアジアから発生しているにも関わらず、日本国内ではヒトの感染例は報告されていない。今後出現するであろう未知の感染症を含め、近い将来に危惧される新興インフルエンザ等の新興感染症発生に対し、十分な情報収集体制と準備体制、対応出来る人材の育成をすることは、日本の感染症危機管理上、緊急のニーズといえる。本研究は、このような事態に備えることを目的として、ベトナム国及びアジア諸国の現地スタッフと協力した臨床疫学研究を基本としており、新興感染症の予防、治療、感染の封じ込めにつなげるものである。具体的には、

1) 相互交換型の共同診療を可能とする、遠隔診断システム（e-medicine）を構築し、それを維持・発展・有効利用することで、アジア諸国及び世界の国々とネットワークを結び、必要な情報を迅速に効果的に収集・発信する。
2) ベトナムで発生したヒト鳥インフルエンザ症例を使用したヒト鳥インフルエンザ重症化例抑制における oseltamivir の疫学臨床研究を実施する。
3) 高病原性鳥インフルエンザがヒトに感染した場合の病理・病態を解明する。
4) 鳥インフルエンザの臨床に関わる専門家を養成する。
5) 高病原性鳥インフルエンザを封じ込めるための感染対策マニュアルを作成し、ホームページ上で公開する。
6) 肺病変からみた重症化機構の研究
7) ヒト鳥インフルエンザの症例に対して、可能な限りの臨床疫学的調査を実施し、今後の発生防止の一助とする。
8) ヒト鳥インフルエンザ肺炎の治療ガイドラインの策定
9) ヒト型、鳥型インフルエンザウイルスレセプターの発現様式の差異を in vitro の系を用いて解明する。

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A. 研究目的

新興インフルエンザ等の新興感染症発生の事態に備えることを目的として、ベトナムおよびアジア諸国の医療スタッフと協力した疫学臨床研究を中心に、新興呼吸器感染症に関する研究、海外で発生した新興感染症に対応できる専門家の人材養成に関する研究を実施し、ヒト H5N1 の疫学と臨床像を把握する。そのことによって、予防・治療・感染の封じ込め等の具体的方法を探究することにつながり、共同研究相手国（ベトナム）への貢献、及び将来の新型インフルエンザ流行に備える。

B. 研究方法

1. 遠隔診断支援システム（e-medicine）の有効利用―継続、維持及び発展　（工藤主任研究者）
相互交換型の e-medicine を構築し、情報の共有化、迅速化、コミュニケーション強化を図ることで、高病原性鳥インフルエンザの疫学臨床研究の成果向上を促した。

2. 鳥インフルエンザの重症化におけるoseltamivirの疫学臨床研究　(新保分担研究者)
国立感染症熱帯病研究所病院（ハノイ市）に入院したH5N1感染患者の診療録を調査。臨床的特徴を記述し、予後と関連のある所見を oseltamivirの使用も含めて検討した。

3. 高病原性鳥インフルエンザの病理・病態解明　(佐多分担研究者、岡分担研究者)
国立小児病院（ハノイ市）との共同研究としてインフルエンザ剖検例の肺組織を入手し、病理像を検討した。

4. 専門家養成プログラムの開発　(加藤分担研究者)
特定および第一感染症指定医療機関の診療状況を調査した。日本人専門医の海外研修プログラムを構築、実施した。国内研修（輸入感染症講習会）を作成・実施した。

5. 病院感染対策に関する研究　(川名分担研究者)
WHOのパンデミックフェーズ分類1～6に対して、各段階での感染対策の方法をマニュアル化し、インタネットを用いて公開した。マニュアルに従った演習を実施し、問題点を検証した。

6. 肺病変からみた重症化機構の研究
(慶長分担研究者)
ST6GAL1 の各組織での発現、ヒト気道上皮細胞の気相液相培養系における発現、NCI-H292 る発現の検討。

7. ベトナムにおける鳥インフルエンザ症例の臨床疫学調査　(工藤主任研究者)
バクマイ病院に入院した3例のH5N1症例の臨床経過を調査し、H5N1 の治療法について、日越で考察した。

8. ヒト高病原性トリインフルエンザ肺炎の治療ガイドラインの策定　(工藤主任研究者)
国内外のインフルエンザおよび高病原性トリインフルエンザの治療法に関する研究の情報を精査し、有用と思われる治療法を検出し、ガイドラインを作成、インターネットを使って公開する。

9. 動物モデルにおける鳥インフルエンザの治療方法の検討　(切替分担研究者)
培養細胞を用いた *in vitro* 実験とマウスを用いた *in vivo* 実験を行う。この *in vivo* と *in vitro* の感染実験系を中心として薬剤スクリーニングを行う。

C. 研究結果

1. 遠隔診断支援システム（e-medicine）
e-medicine を開発し、日本国内では国立国際医療センター、公立学校共済関東中央病院に設置、ベトナムではバクマイ病院（ハノイ市）に設置して、日越を結ぶネットワークを確立した。同様の TV 医学会議システムを設置されている国立小児病院（ハノイ市）、国立感染症熱帯病研究所病院（ハノイ市）ホーチミン医科薬科大学、熱帯病病院（ホーチミン市）ともインターネットネットワークに迎え入れ、日越を結ぶ医学カンファランスを実施した。また、コンサルテーション、共同診療、プロジェクト会議などに頻回に実施した。加えて、国立感染症熱帯病研究所病院に 2007 年に入院した3例及びバクマイ病院に入院した 2008 年の新規3例の入院時には、e-medicine を利用し、患者の臨床的状況や X 線画像がリアルタイムで提示され、ベトナムの医師チームと共に共同で診療検討を行うことが出来、e-medicine の目的が共同診療、プロジェクトの推進に有益であると確認出来た。

2. 鳥インフルエンザの重症化におけるoseltamivirの疫学臨床研究
国立感染症熱帯病研究所病院(NIITD)の 2004 年 1 月から 2005 年 7 月までに入院した H5N1 感染患者 29 例について、診療録を調査し、臨床的特徴を記述、予後と関連のある所見を Oseltamivir の使用を含めて検討した。調査した 29 例の患者のうち死亡は 7 例 (24.1%)。Oseltamivir は 25 例が使用していた。使用例での死亡は 5/25 例(20.0%)であり、未使用での死亡は 2/4(50.0%)例であった。患者の重症度を調整する為、白血球数を用いて exact logistic regression を行った。Osertamivir 使用例の死亡オッズ比は 0.15(95%信頼区間 0.00-2.57)であり、なお信頼区間は広かった。個々の症例の重症度が調整できないため、白血球数と報告された国を調整した Exact logistic regression を行ったところ、Oseltamivir 使用例の死亡オッズ比は (95%信頼区間 0.12－1.28)であった。この方法では広かった。Fixed effect model による通常のメタ分

析では、Oseltamivir 使用例の死亡オッズ比は 0.98(95%信頼区間 0.002-0.787, P=0.0213)と有意に死亡の抑制効果が認められた。

3. 高病原性鳥インフルエンザの病理・病態解明

国立小児病院（ハノイ市）の協力を得て、2003 年前後の H5N1 症例肺組織を入手し、病理像を検討する機会を得た。肺病理標本 3 例はいずれも DAD を示し、うち発症 6 日目で死亡した症例では A 型インフルエンザウイルス NP 抗原がおもに肺胞上皮細胞に検出できた。ほか 2 例（16 日ないし 17 日後の死亡例）ではウイルス抗原は陰性であった。細胞マーカーとの二重染色を共焦点顕微鏡で観察したところ、1 型及び 2 型肺胞上皮細胞、細気管支上皮細胞、単球/マクロファージ、および血管内皮細胞が感染していることが判明した。これらの成績は世界ではじめて得られたものである。

4. 専門家養成プログラムの開発

1) 特定及び第一種感染症指定病院医療機関の診療状況調査

平成 18 年度、アンケート調査（第一種感染症指定医療機関 13 施設から回答）によって、感染症診療に従事する専門医の不足があること、職員の定期的な研修が半数の施設で行われていないこと、情報の収集が主にインターネットで行われている、などのことが明らかになった。

2) 国内医師研修プログラムの開発

輸入感染症講習会を開催（平成 18 年 10 月、平成 19 年 10 月）した。高病原性鳥インフルエンザについて、e-medicine を使用してベトナムから実際の症例報告をベトナム人医師のが実施し、他に腸チフス、マラリア、デング熱、狂犬病の各論に加え、首都圏の感染症指定医療機関医師による事例検討を行った。第 2 回からは、厚生労働省健康局結核感染症課の後援を頂いた。

3) 海外研修プログラムの開発

平成 18 年度に開発したプログラムを厚生労働省一類感染症等予防・診断・治療研修（ベトナム・ホーチミン市熱帯病院；平成 20 年 3 月）に実施した。高病原性鳥インフルエンザについては、実際に使用された隔離病室の見学、個人防護具の着脱実習、検査・治療に関するベトナム人専門家による講義、フィールド実習を行った。参加者は、第一種感染症指定医療機関医師 7 名、研修資料は、国立国際医療センター国際疾病センターホームページで掲載した。

5. 院内感染対策に関する研究

高病原性鳥インフルエンザを封じ込めるための感染対策の指針として、WHO がガイドラインを発表しているが、本研究では WHO の提唱するフェーズを 3 つのグループに分類し、各段階での感染対策の方法をマニュアルとしてまとめた。このマニュアルをインターネットを用いて公開した。現在、パブリックコメントを取り入れて改訂作業中である。また、本マニュアルに従った訓練も実施し、マニュアルの問題点の検証作業が進行中である。このことで、国立国際医療センターにおいて、インフルエンザの流行早期検出体制を確立した。

6. 肺病変からみた重症化機構の研究

主に NCI-H292 細胞と Calu-3 細胞を用いて、レクチン染色およびレクチン定量系を構築した。また、NCI-H292 細胞と Calu-3 細胞の *ST6GAL1* の転写開始点の相違、サイトカイン等の刺激での発現パターンなどを解析した。

7. H5N1感染患者の臨床疫学研究及び臨床的特徴の検討

バクマイ病院（ハノイ市）に 2007 年度に入院した 3 例について、診療録及び実際に診療にあたった医師達からの聞き取り調査を実施し、臨床的特徴及び治療方法を比較し、検討した。

発症患者はいずれも 20～30 歳の若年者で、トリとの接触が濃厚であると思われる。発症から治療期間は、救命できた Case1 は 3 日で比較的短期であり、死亡した Case2, 3 は 7～12 日と長期であった。Case1 は重症であったが他の Case に比べると重症性は少し弱い。Case2, 3 は重篤で ARDS で集中的な治療を開始するも。治療に反応する間もなく死亡という経過であった。このことから、臨床的観点から早期診断・早期治療が重要であること、また重症肺炎に対しても何らかの集中的治療を要することが強く示唆される。

8. ヒト高病原性トリインフルエンザ肺炎の治療ガイドラインの策定

ヒト H5N1 に対する現時点での保存的療法であるが、WHO の推奨法が最良と思われる。

9. 動物モデルにおける鳥インフルエンザの治療方法の検討

培養細胞を用いた in vitro 実験とマウスを用いた in vivo 実験を立ち上げた。既存薬物の抗インフルエンザ作用をスクーリングする基礎を築いた。手始めに、喘息、COPD 等で頻用され、有用性が確立している吸入ステロイド（気道系での局所療法）単独での抗ウイルス作用は認められなかった。国際ウイルス感染における生体側（マウス）の易感染性を生ずることもなかった。

D. 考察

当初かかげた目的である、今後の H5N1 の治療に向けての治療の開発を目指す基礎となる臨床疫学研究がなされたと思われる。今後、この疾患における臨床的に有用な予防、肺炎の治療の完成が望まれる。

E. 結論

ヒト H5N1 に対する、基礎的な臨床疫学研究がなされた。

F. 研究発表

1. 論文発表

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2) 川名明彦．ヒトの鳥インフルエンザ感染症の臨床的諸問題．臨床とウイルス

2. 学会発表

1) 水野康孝，加藤康幸，岩瀬啓祐，神村麻穂子，工藤宏一郎．国立国際医療センターにおける臨床医を対象とした熱帯医学･旅行医学研修の概要．第56回日本感染症学界東日本地方会学術集会．東京．2007

G. 知的財産権の出願・登録状況（予定を含む）

1. 特許取得

特になし。

2. 実用新案登録

特になし。

3. その他

特になし。

別紙 4

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
新保卓郎	「治る」と「治す」—風邪の抗菌薬問題	尾藤誠司	医師アタマ	医学書院	東京	2007	46-51

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Goto M, Shimbo T, et al.	Influence of loxoprofen use on recovery from naturally acquired upper respiratory tract infections: a randomized controlled trial	Intern Med.	46	1179-1186	2007
Liem NT, Nakajima N, Phat LP, Sato Y, Thach HN, Hung PV, San LT, Katano H, Kumasaka T, Oka T, Kawachi S, Matsushita T, Sata T, Kudo K, Suzuki K.	H5N1-infected cells in lung with diffuse alveolar damage in exudative phase from a fatal case in Vietnam	Jpn J Infect Dis	61	157-160	2008
川名明彦	ヒトの鳥インフルエンザ感染症の臨床的諸問題	臨床とウイルス（日本臨床ウイルス学会）	35巻5号	439－446	2007年
川名明彦	新型インフルエンザ対策医療機関の立場から	臨床検査（医学書院）	52巻1号	64－68	2008年

INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Influence of Loxoprofen Use on Recovery from Naturally Acquired Upper Respiratory Tract Infections: A Randomized Controlled Trial

Masashi Goto[1], Takashi Kawamura[1], Takuro Shimbo[2], Osamu Takahashi[3], Masahiko Ando[1], Koichi Miyaki[4], Takahiko Nohara[5], Hidetsuna Watanabe[6], Isamu Suzuki[7], Mitsuru Aono[1] and for the Great Cold Investigators-II

Abstract

Objective: To investigate whether loxoprofen, one of the nonsteroidal anti-inflammatory drugs, prolongs the recovery process of naturally acquired upper respiratory tract infections (URTIs) in the clinical setting.

Methods: A double-blind, randomized, placebo-controlled trial was conducted in 23 outpatient facilities in Japan. Patients aged 18 through 65 years suffering from URTIs were randomly assigned to receive loxoprofen or its placebo. The primary outcome was duration of illness in days.

Results: A total of 174 patients were available for the analyses. Duration of illness was 8.94 ± 3.20 days in the loxoprofen group compared to 8.39 ± 3.39 days in the placebo group (P=.19). The number of days with limited daily activities was fewer in the loxoprofen group than in the placebo group (2.12 ± 2.05 days vs. 2.68 ± 2.54 days, P=.17). Although severe symptoms were less frequent on days 1, 2, and 3 in the loxoprofen group (27%, 33%, and 29%, respectively) than in the placebo group (32%, 39%, and 37%, respectively), symptoms were more frequent on days 6 through 12 in the loxoprofen group (difference, 5-13%). Adverse events were more common in the loxoprofen group (9.5% vs. 1.1%, P=.051).

Conclusion: Loxoprofen did not significantly modify the recovery process of URTIs except for a slight tendency to delay.

Key words: common cold, non-steroidal anti-inflammatory agents, loxoprofen

(DOI: 10.2169/internalmedicine.46.6334)

Introduction

Upper respiratory tract infections (URTIs) are the most frequent acute illness throughout the industrialized world. (1) Although it is associated with an enormous economic burden both in lost productivity and in expenditures for treatment (2), the most appropriate means of management has not yet been thoroughly established. Usage of nonsteroidal anti-inflammatory drugs (NSAIDs) remains controversial. Although NSAIDs would improve acute URTI symptoms such as fever and various types of pain, they could adversely affect the healing stage because they suppress the inflammatory reaction which serves to repair infection-induced acute tissue injury (3).

There have been two types of study populations used to evaluate the effectiveness of NSAID treatments for URTIs. One is experimentally infected subjects and the other is naturally infected ones. Studies of the former type yielded conflicting results. Stanley et al (4) and Graham et al (3) reported that the period of viral shedding increased and immune responses were suppressed by use of NSAIDs.

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Mogabgab and Pollock (5), Hsia et al (6) and Sperber et al, (7, 8) meanwhile, denied influences of NSAIDs on viral shedding. Studies of naturally occurring URTIs (9-12), however, have uniformly focused on the severity of acute symptoms such as nasal discharge, fever, and headache, and little attention has been paid to the duration of illness. Only one study using acetaminophen which has poor anti-inflammatory activity (13) evaluated the duration of symptoms among young children with fever of presumed viral origin (14).

Loxoprofen is a 2-arylpropionic acid anti-inflammatory agent with analgesic and antipyretic properties. It is a prodrug which hardly causes any gastrointestinal problems, and is widely used in Japan. This randomized controlled trial (RCT) was aimed to investigate whether or not loxoprofen prolongs the recovery process of naturally acquired URTIs.

Methods

A double-blind, randomized, placebo-controlled trial was conducted in 23 outpatient facilities including 11 university student health centers, outpatient departments of five university hospitals and two community hospitals, and five private practices during two consecutive winter seasons: from December 1 through March 31, in both 2002-2003 and 2003-2004.

Study participants

Patients aged 18 through 65 years who exhibited symptoms or signs in both nose (rhinorrhea, nasal congestion, sneezing, or snuffling) and pharynx (sore throat or pharyngeal redness), and visited physicians within 48 hours after symptom onset were enrolled in the study.

Patients who were clinically thought to suffer from influenza, pneumonia of any cause, β-streptococcus tonsillitis, and other bacterial infections were excluded. Patients with serious or confusing underlying diseases including bronchial asthma, peptic ulcer, diabetes mellitus, and allergic rhinitis were also excluded from the study as well as immunocompromised or pregnant persons. Patients who were currently using antibiotics, systemic corticosteroids, immunosuppressants, or anticoagulants, and those who had taken NSAIDs or Chinese herbal medicines as cold remedies within 12 hours were ineligible for the study. Written informed consent was obtained from all participants.

Intervention

Each participant was randomly assigned to one of the two treatment arms, intervention and control, by self-drawing a sealed opaque envelope in the physician's sight. Randomization was based on simple computer-generated random digits and the correspondence between the digits and the group assignment was held in the central, secured location by a third party independent of the investigators until data collection was completed. Thus, allocation was concealed and masked from both patients and physicians.

Patients in the intervention group were to take loxoprofen sodium (60 mg/tablet) and those in the control group were to take a placebo which was quite similar to active loxoprofen in shape and taste. In addition to loxoprofen or its placebo, an antihistamine, mequitazine (3 mg/tablet), were also prescribed for both group members. As a rule, participants were to take one tablet of each drug twice a day for at most seven days. They were allowed to increase the daily dose of drugs up to three tablets per day for each drug or decrease and even discontinue them depending on their symptoms. Participants were forbidden to take any other drugs during the study period. However, when they revisited the doctor due to persistence or progression of symptoms, they were allowed to be prescribed other drugs depending on their complaints.

Follow-up

All subjects were requested to fill in the prescribed form (URTI diary) every day from the onset of illness. This form included various URTI complaints such as nasal symptoms (rhinorrhea and sneezing), pharyngeal symptoms (soreness and scratchiness), bronchial symptoms (cough and phlegm) and general symptoms (feverishness, arthralgia, and malaise). Each symptom was classified into four grades, i.e., "none," "mild," "moderate," and "severe," according to the Jackson method (15). "Mild" was defined as when a subject was unaware of the symptom when he/she was busy with something; "moderate" as when one always felt discomfort; and "severe" as when one experienced difficulties in daily life. When a patient felt feverish, he/she was to measure body temperature and record the highest value of the day. Restriction of daily activities was also graded as "none," "partly restricted," "considerably restricted," and "absent from duty." General physical condition was rated on a one-to-ten scale: from 1 (extremely bad) through 10 (extremely good). Adverse events were asked in an open-ended manner. When remedies other than the study drugs were given to the study patients, physicians were to describe the prescription in the URTI diary.

Participants were required to revisit physicians one week later or after recovery to return the URTI diary and unused drugs. If a patient did not make the second office-visit, his/her physician telephoned to remind him/her.

Statistical analysis

Baseline (at the initial office visit and randomization) characteristics and outcome measures were compared between two groups using Student's *t*-test for continuous variables, and Pearson's chi-square test for categorical variables. When the severity of symptoms was evaluated, each symptom grade was replaced by numerical scores, i.e., "none" as 0, "mild" as 1, "moderate" as 2, and "severe" as 3, and Wilcoxon rank sum test was applied. Proportions of rare events were assessed by Fisher's exact test. Daily changes in illness were compared by fitting repeated binary responses to a generalized linear model (16), where treatment group, day

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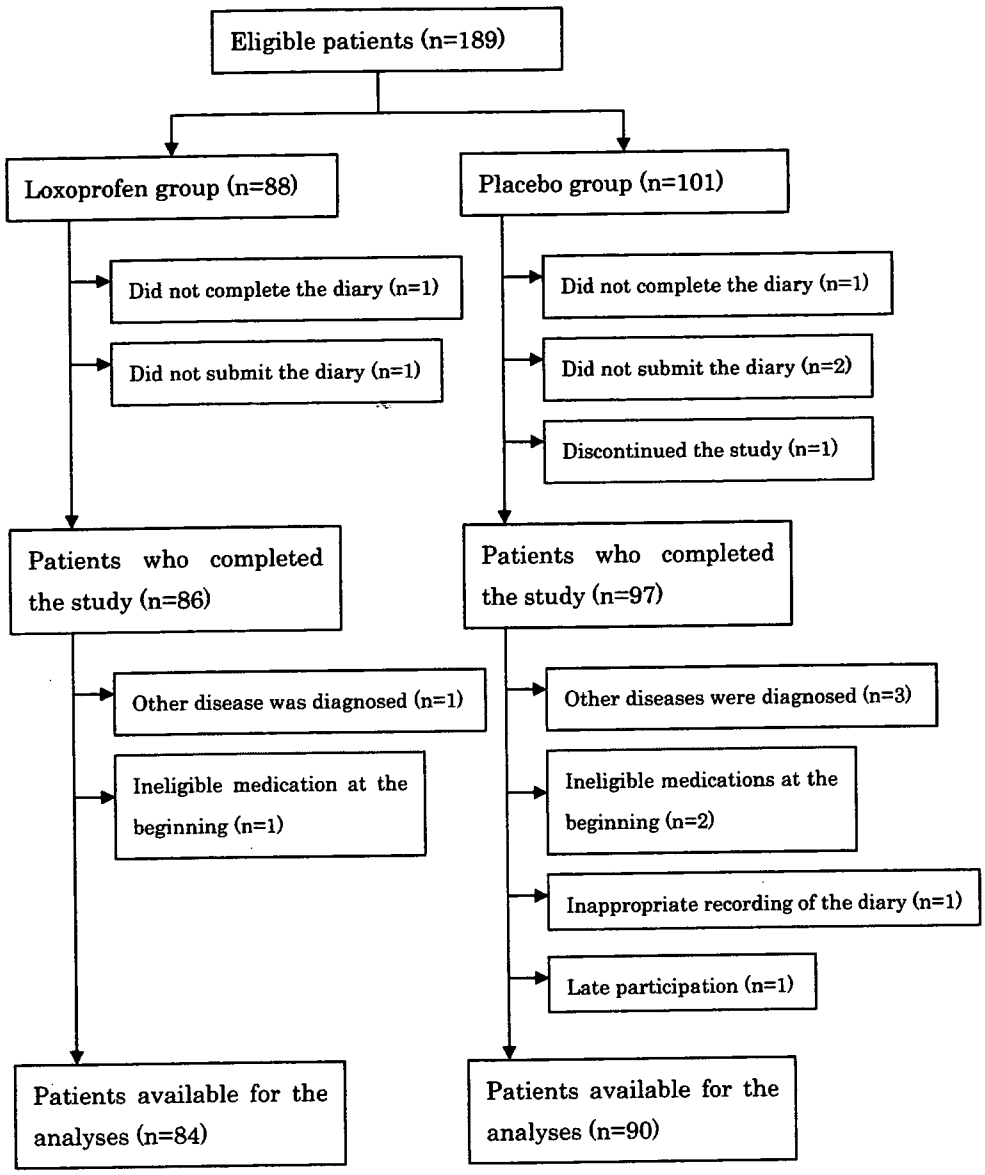

Figure 1. Flowchart of the study.

of illness, and interaction between group and day of illness were included.

The primary outcome measure of this study was the interval in days from the onset of any URTI symptom to the disappearance of all URTI symptoms. The secondary outcomes were severity of URTI symptoms, including general physical condition and performance in daily activities. A power calculation indicated that a sample of 85 per group was necessary to detect a difference in duration of illness between 7 and 8.5 days (7), where power was set at 90%; 2-sided P-value, .05; and standard deviation, 3.0.

Statistical analyses were performed using Stata8.0 (Stata Corporation, College Station, TX, 2003) for univariate analysis and linear regression analysis, and SAS9.1 (SAS Institute, Cary, NC, 2004) for multivariate longitudinal analysis. P values were calculated controlling for possible confounding factors when needed, and the threshold level of .05 was considered statistically significant. All analyses were on an intention-to-treat basis. This study protocol was approved by the Ethics Committee of Kyoto University Faculty of Medicine (No. 404, October 29, 2002).

Results

Figure 1 is the flow chart of this study. A total of 189 patients were randomly assigned to loxoprofen (n=88) and placebo (n=101) groups. Of the 189 participants, six (two in loxoprofen group and four in placebo group) withdrew from the study, because two patients (one in loxoprofen and another in placebo) did not complete the diary, three patients (one in loxoprofen and the others in placebo) did not return the diary, and one patient (placebo) decided not to continue the study after the allocation. We excluded nine more participants (two in loxoprofen and seven in placebo) from analyses, because influenza or acute sinusitis were diagnosed after allocation (one in loxoprofen and three in pla-

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Table 1. Baseline Characteristics of Participants in Loxoprofen and Placebo Groups

	Loxoprofen	Placebo
No. of patients	84	90
Age (years)	29.3 ± 12.5	27.6 ± 11.4
Sex (proportion of men, %)	65.5	65.6
Proportion of smokers (%)	32.8	26.1
Severity of symptoms (scored 0 to 3) *		
Headache	0.71 ± 0.83	0.78 ± 0.89
Rhinorrhea	1.50 ± 0.88	1.67 ± 0.94
Nasal congestion	1.19 ± 0.94	1.35 ± 0.98
Sneezing	0.70 ± 0.72	0.73 ± 0.79
Sore throat	1.51 ± 0.84	1.52 ± 0.95
Scratchiness	1.42 ± 0.91	1.38 ± 0.91
Hoarseness	0.86 ± 0.92	0.82 ± 0.90
Cough	1.15 ± 0.95	1.02 ± 1.00
Phlegm	0.86 ± 0.93	0.73 ± 0.86
Arthralgia/myalgia	0.61 ± 0.86	0.57 ± 0.88
Chilliness	0.65 ± 0.86	0.87 ± 0.89
Feverishness	0.93 ± 0.80	1.12 ± 0.90
General malaise	1.07 ± 0.90	1.20 ± 0.99
Restriction of daily activities (scored 0 to 3) †	0.67 ± 0.84	0.85 ± 0.92
General physical condition (1-to-10 scale)	4.70 ± 1.84	4.99 ± 1.85
Body temperature (℃)	36.9 ± 0.59	36.8 ± 0.70

* "None" was replaced by 0, "mild" by 1, "moderate" by 2, and "severe" by 3.

† "None" was replaced by 0, "partly restricted" by 1, "considerably restricted" by 2, and "absent from one's duty" by 3.

Table 2. Symptoms, Use of Drugs, and Adverse Events in Loxoprofen and Placebo Groups

	Loxoprofen	Placebo	P-values	
			Univariate analysis	Multivariate analysis*
No. of patients	84	90		
Duration of illness (days)	8.94 ± 3.20	8.39 ± 3.39	0.18	0.19
Duration of symptoms (days)				
Headache	2.65 ± 2.92	2.77 ± 3.08	0.93	0.63
Rhinorrhea	6.73 ± 3.78	6.78 ± 3.66	0.93	0.55
Nasal congestion	5.71 ± 3.70	5.89 ± 4.04	0.83	0.86
Sneezing	3.37 ± 3.12	2.56 ± 2.71	0.072	0.096
Sore throat	5.46 ± 3.27	5.00 ± 3.12	0.28	0.28
Scratchiness	5.39 ± 3.42	5.11 ± 3.39	0.64	0.77
Hoarseness	3.89 ± 3.37	3.54 ± 3.31	0.47	0.35
Cough	5.61 ± 4.10	4.99 ± 4.03	0.28	0.31
Phlegm	4.80 ± 3.76	4.02 ± 3.73	0.14	0.16
Arthralgia/myalgia	1.76 ± 2.41	1.97 ± 2.67	0.88	0.34
Chilliness	2.12 ± 2.59	2.40 ± 2.50	0.34	0.37
Feverishness	2.92 ± 2.70	2.96 ± 2.30	0.59	0.70
General malaise	3.58 ± 2.93	3.56 ± 2.89	0.94	0.92
Total symptom score during diseased period	76.4 ± 45.6	75.1 ± 48.0	0.85	0.78
Duration of restriction of daily activities (days)	2.12 ± 2.05	2.68 ± 2.54	0.17	0.17
Average score of general physical condition (1-to-10 scale)	6.35 ± 1.38	6.55 ± 1.32	0.26	0.39
Maximum body temperature (℃)	37.2 ± 0.79	37.2 ± 0.75	0.37	0.68
Consumption of study drugs: Loxoprofen / Placebo (tablets)	11.0 ± 5.01	9.85 ± 4.87	0.12	0.14
Consumption of mequitazine (tablets)	10.1 ± 5.85	9.99 ± 5.01	0.79	0.71
Proportion of patients to whom other drugs were prescribed (%)	10.7	18.9	0.14	0.11
Proportion of patients with adverse events (%)	9.5	1.1	0.015	0.051

* Adjusted for age, sex, smoking, type of the facilities, region, and the year when the patient was included.

cebo), antibiotics or Chinese herbs were used just before the initial visit (one in loxoprofen and two in placebo), recording of the diary was inappropriate (one patient in placebo), and the initial visit was 6 days after the onset (one patient in placebo). Therefore, the remaining 174 patients (84 in loxoprofen and 90 in placebo) were available for the analyses. Table 1 shows the baseline characteristics of the study patients. There was no significant difference in age, sex, and severity in symptoms at randomization between the groups.

Table 2 summarizes the symptoms. Duration of illness, the number of days from the onset to the complete disappearance of URTI symptoms, was 8.94 ± 3.20 days in the loxoprofen group compared with 8.39 ± 3.39 days in the placebo group (P=.19). While sneezing and productive

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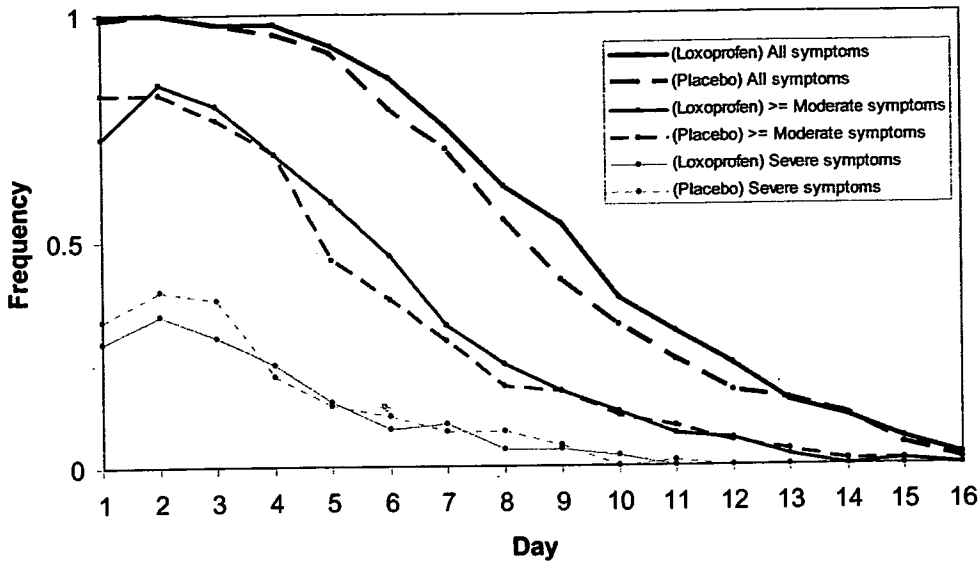

Figure 2. Changes in frequency of overall symptoms according to severity and day of illness.

cough tended to continue longer, days with limited daily activities were fewer in the loxoprofen group than in the placebo group (2.12 ± 2.05 days vs. 2.68 ± 2.54 days, P=.17). Total symptom scores during the diseased period were then almost identical between the two treatment groups (76.4 ± 45.6 in the loxoprofen group vs. 75.1 ± 48.0 in the placebo group, P=.78).

Figure 2 demonstrates the changes in frequency of overall symptoms according to severity and day of illness. Severe symptoms of any kind were less frequent on days 1, 2, and 3 in the loxoprofen group (27%, 33%, and 29%, respectively) than in the placebo group (32%, 39%, and 37%, respectively) even though statistically insignificant (P=.49, .45, and .26, respectively). Symptoms regardless of grade were, however, more frequent on days 6 through 12 in the loxoprofen group than in the placebo group (difference, 5-13%; P=.10-.46).

Change in frequency of each symptom with the day of illness was examined by the generalized linear model. Moderate or severe sneezing was more frequent in the recovery phase of illness, after day 3, in the loxoprofen group than in the placebo group (P=.011), whereas moderate or severe headache, severe arthralgia, and severe chills were less frequent (P=.001, .006, and .018, respectively) in the acute phase of illness, days 1 through day 3.

The number of loxoprofen tablets taken during illness was greater than that of placebo tablets (11.0 ± 5.0 tablets vs. 9.9 ± 4.9 tablets, P=.14; Table 2), although the consumption of mequitazine was similar in both groups (10.1 ± 5.9 tablets vs. 10.0 ± 5.0 tablets, P=.71). However, other drugs were less likely to be prescribed in the loxoprofen group than in the placebo group (10.7% vs. 18.9%, P=.11). Drugs additionally prescribed included acetaminophen (five in loxoprofen and six in placebo), other antihistamines (six in loxoprofen and 10 in placebo), and antitussives (two in loxoprofen and six in placebo). Some NSAIDs were prescribed for two cases of the placebo group. Most of those drugs were taken after day 8; otherwise, they were used within 2 days of the first visit.

Eight patients in the loxoprofen group (9.5%) complained of several kinds of adverse events including drowsiness (in three) and thirst (in two) during the follow-up period, which was higher than the one patient in the placebo group (1.1%) with drowsiness (P=.051, Table 2).

Discussion

This randomized placebo-controlled trial suggested that use of loxoprofen may slow down the recovery from URTIs (by approximately 13 hours) instead of providing some alleviation for severe symptoms and improved performance in daily activities, even though most of the effects were statistically insignificant. It also demonstrated that loxoprofen could increase adverse events.

Several studies on experimentally infected subjects suggested that the period of viral shedding increased by use of NSAIDs (3, 4). These findings are consistent with the theoretical inference from the fact that NSAIDs suppress biological responses essential to eradicate pathogens (13). Studies of naturally occurring URTIs (9-12), however, did not examine the duration of URTI symptoms. An RCT showed that acetaminophen which has little anti-inflammatory activity (13) did not change the duration of fever and other symptoms (14). Thus, this is the first RCT that examined how an NSAID would affect the recovery process of naturally acquired URTIs in clinical settings. Although loxoprofen is not available in most western countries, these findings are still worthwhile due to the frequent use of similar NSAIDs for uncomplicated URTI patients throughout the world.

The loxoprofen-induced clinical effects were smaller than expected. We performed the sample size calculation based on a study of an experimental infection model. In naturally acquired URTIs, there might be a wide variation in their na-

ture and clinical profiles. Another presumable reason is the relatively low dose of loxoprofen used in this study. Although three tablets of loxoprofen had been used daily in the phase-III clinical trial for the Government approval (17), we set the standard dose at two tablets daily in this study to reduce adverse events. This restriction could attenuate the difference of the effects. A study with larger sample size and heavier dosing might yield definite results. However, the present findings should help clinicians and patients make clinical decisions. Then, further studies are not necessarily required from the ethical point of view.

Several patients in the loxoprofen group complained of adverse events during the follow-up period as compared with only one in the placebo group. Most complaints, however, were deemed to be mequitazine induced. There may be some synergistic effects between mequitazine with loxoprofen, although to our knowledge, no report has been made on the pharmacokinetic or pharmacodynamic interaction between co-administered loxoprofen and mequitazine. In any case, clinicians should pay attention to the negative side of the drugs.

Other drugs such as antihistamines and antitussives were prescribed more frequently among the placebo patients than the loxoprofen patients. This fact may be attributed to a lower frequency of symptoms on day 6 through day 12 in the placebo group. However, most of the drugs additionally prescribed were taken after day 8 or just after the initial visit. Therefore, the influence of additional medications would be minimal on day 6 through day 8.

The present study has some admitted limitations. First, all of the outcomes measured were solely based on the patients' self-report, and no objective markers were used except for body temperature. However, their uncertainty was equal in both treatment groups because of the blindness, and comparability was ensured. Second, other diseases such as influenza and some bacterial infections were not completely ruled out, because diagnosis of URTIs was made only by subjective symptoms and physical findings. Since complete diagnosis is costly and even influenza and β-hemolytic streptococcus infections are self-limited in healthy people, symptom/sign-based diagnosis would be acceptable in community healthcare settings. Third, generalizability of our results was somewhat limited by the strict inclusion/exclusion criteria. Drug effects on patients who develop URTIs two days before or earlier and those with underlying diseases are unknown. In addition, our results are not applicable to children and elderly patients.

In conclusion, loxoprofen, one of the NSAIDs, did not significantly modify the recovery process from URTIs among naturally infected patients except for a slight tendency to delay complete recovery.

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Short Communication

H5N1-Infected Cells in Lung with Diffuse Alveolar Damage in Exudative Phase from a Fatal Case in Vietnam

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SUMMARY: Necropsied lung tissues of three fatal cases with avian influenza A virus (H5N1) infection in Vietnam were analyzed to detect H5N1 virus-infected cells. Formalin-fixed and paraffin-embedded lung tissue sections showed typical histological features of diffuse alveolar damage (DAD) in all cases. Immunohistochemistry for the influenza A virus nucleoprotein antigen revealed positive signals of bronchiolar and alveolar epithelial cells in only one patient, who exhibited DAD with an exudative phase and died on the 6th day after onset. However, no signal was detected in the other two cases of DAD with a proliferative phase. These patients died on day 16 and day 17 after onset, respectively. H5N1 virus antigens were detected predominantly in epithelial cells in terminal bronchioles and in alveoli, i.e., type I and type II alveolar pneumocytes, and in alveolar macrophages. The pathogenesis of exudative DAD caused by H5N1 infection is discussed.

Highly pathogenic avian influenza A H5N1 virus (H5N1) infection has been reported to cause severe respiratory disease. In 1997, H5N1 was first isolated in Hong Kong from tracheal aspirates of a 3-year-old boy with a fatal respiratory illness (1-3). In 2003, human disease associated with H5N1 re-emerged (4). Since then, the number of confirmed fatal human H5N1-infected cases has increased and now totals approximately 200 cases. These cases occurred, predominantly, in Vietnam, Thailand, and Indonesia (5-9). The histopathological data for H5N1 virus infection in humans were, however, limited (3,4,6,8,10-12), and the pathogenesis of the disease remains unclear. Examination of ex vivo infected lung tissues showed that influenza A virus nucleoprotein (InfA-NP) was detected in pneumocytes and in alveolar macrophages (13). Also the pattern of viral attachment in human respiratory tract sections showed that H5N1 attached to the apical cell membrane of bronchiolar cells, type II pneumocytes and alveolar macrophages (14,15). The postmortem study of H5N1-infected patients has recently been published for the first time (16).

In the present study, we describe the histopathological findings from three fatal cases of H5N1 infection from the National Hospital of Pediatrics in Hanoi, Vietnam. The detailed clinical findings of Case 1 and Case 2 have been described previously (5). On admission, all patients presented with fever, cough, and dyspnea, and H5N1 virus was detected in tracheal fluids by reverse-transcriptase polymerase chain reaction (RT-PCR) before death occurred. The duration of the disease in Case 1, 6 days, was much shorter than in the other two cases (Table 1). Small pieces of lung tissues in the lower respiratory tract were necropsied and histological and immunohistochemical examinations were carried out on formalin-fixed and paraffin-embedded lung tissues.

The hematoxylin and eosin-stained lung sections of Case 1 demonstrated typical histological features of diffuse alveolar damage (DAD) with an exudative phase (Fig. 1a). Eosinophilic hyaline membrane was found on alveolar ducts and on alveoli. The alveolar space was filled with proteinaceous exudates containing erythrocytes, macrophages, and cell debris. The alveolar septa were thickened by edema with mild inflammatory infiltration, consisting of lymphocytes and macrophages. In Cases 2 and 3, hyaline membrane formation was focally found, and the proliferation of fibroblasts in the interstitial space was marked in comparison to Case 1. Mild interstitial inflammation and proliferation of type II pneumocytes with bizarre and cuboidal features were observed (Fig. 1c), indicating that Cases 2 and 3 were in the proliferative (repair) phase of DAD. Squamous cell metaplasia in the bronchiolar epithelium was also observed (Fig. 1d). Focal accumulation of neutrophils in the alveolar space was found in Case 3, suggesting pulmonary bacterial infection. These histological features were similar to those reported previously in fatal human H5N1 influenza A virus-infected cases (4,8,10,11).

To detect the influenza A virus antigen, the sections were immunostained with an avidin-biotin complex immunoperoxidase method (LSAB2 kit/HRP/DAB; Dako Cytomation, Copenhagen, Denmark) using a mouse monoclonal antibody against InfA-NP (17). Positive signals for InfA-NP were detected in 6 of 6 blocks of lung tissue from Case 1, whereas they were not found in those from Case 2 or 3. The signals were found mainly in alveolar epithelial cells and in interstitial cells (Fig. 1b). The many positive cells were interpreted as type II pneumocytes and/or alveolar macrophages, but the positive cell presented in the inset in Fig. 1b was considered to be a type I pneumocyte based on its histological location and morphology. H5N1-RNA was also detected by real-time RT-

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**Deceased after the contribution of this study.

Table 1. Histopathological findings in the lung of H5N1 fatal cases in Vietnam

Case	Age (y)/ Sex	Days from onset to death	Histology in lung sections	RT-PCR for H5N1 (tracheal fluids)	RT-PCR for H5N1 (paraffin-embedded sections of lung)	Immunohistochemistry for InfA-NP antigen and co-localization with cell marker proteins
1[1]	12/F	6	DAD with an exudative phase, Hyaline membrane formation Hemmorhagic necrosis	Positive	Positive	Positive for InfA-NP antigen, and colocalized with AE1/AE3, EMA, SPA, SPD, CD68, CD34
2[2]	5/M	17	DAD with a proliferative (repair) phase Hyaline membrane formation	Positive	Negative	Negative for InfA-NP antigen
3	4/M	16	DAD with a proliferative (repair) phase Hyaline membrane formation Microabscess	Positive	Negative	Negative for InfA-NP antigen

[1]: Patient 1 in Ref (5).
[2]: Patient 2 in Ref (5).
M, male; F, female; DAD, diffuse alveolar damage; InfA-NP, influenza virus A nucleoprotein; EMA, epithelial membrane antigen; SPA, surfactant protein A; SPD, surfactant protein D.

Table 2. Antibodies used for double immunofluorescence staining

Antigen	Antibody type	Stained cells	Source
cytokeratin (AE1/AE3)	mouse monoclonal	epithelial cell of bronchiole	Dako
epithelial membrane antigen (EMA)	mouse monoclonal	epithelial cell	Dako
surfactant apoprotein A (SPA)	mouse monoclonal	type II alveolar pneumocyte	Dako
surfactant apoprotein D (SPD)	rabbit polyclonal	type II alveolar pneumocyte	Chemicon[1]
CD68 (KP1)	mouse monoclonal	alveolar macrophage	Dako
CD68 (PG-M1)	mouse monoclonal	alveolar macrophage	Dako
CD34	mouse monoclonal	endothelial cell	Immunotech[2]
influenza A virus nucleoprotein	mouse monoclonal	influenza A virus infected cell	in-house Ref. (17)
influenza A virus nucleoprotein	rabbit polyclonal	influenza A virus infected cell	in-house Ref. (17)

[1]: Chemicon, Temecula, Calif., USA.
[2]: Immunotech, Marseille, France.

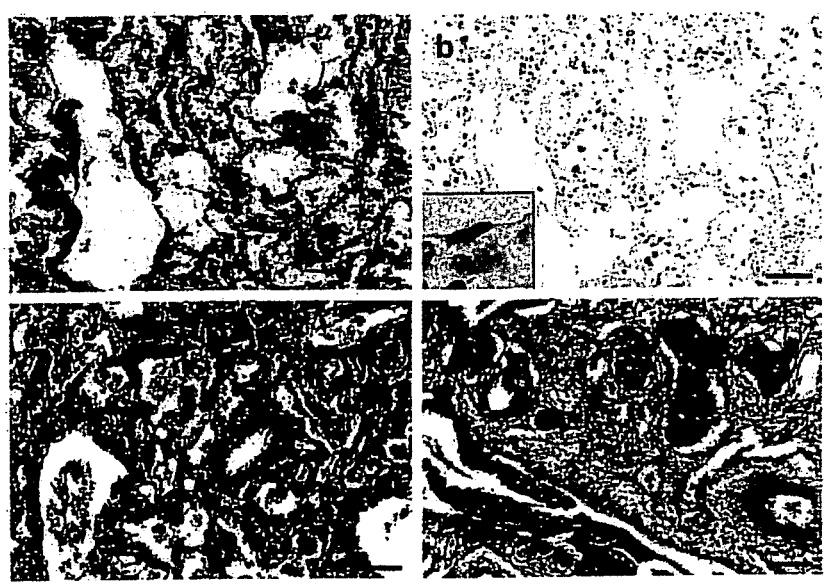

Fig. 1. Hematoxylin and eosin stainings and immunohistochemistry for influenza virus A nucleoprotein (InfA-NP) in Case 1. (a) Hyaline membrane formation is observed on the alveolar walls. In the interstitial space, edema and mild inflammatory cell infiltrates are observed (Case 1). (b) InfA-NP antigens are detected in alveolar epithelial cells and in the interstitial space. InfA-NP-positive, type I pneumocyte is indicated in the inset. (c) Mild interstitial inflammation and proliferation of type II pneumocytes with bizarre and cuboidal features were observed (Case 3). (d) Squamous cell metaplasia in the bronchiolar epithelium was also observed (Case 2). Scale bar = 100 μm.

PCR in paraffin-embedded lung sections from Case 1 only (18). In DAD with a proliferative phase, as in Cases 2 and 3, viral antigens and nucleic acids were not detected.

To characterize virus-infected cells, confocal laser scanning microscopy was used to visualize double immunofluorescence staining for InfA-NP and for cell-type specific marker proteins of epithelial cells, macrophages, and endothelial cells. The antibodies used are shown in Table 2. Alexa Fluor 568-conjugated anti-mouse or anti-rabbit IgG (Molecular Probes, Eugene, Oreg., USA) and Alexa Fluor 488-conjugated anti-rabbit or anti-mouse IgG (Molecular Probes) were used as secondary antibodies. InfA-NP signals were detected most

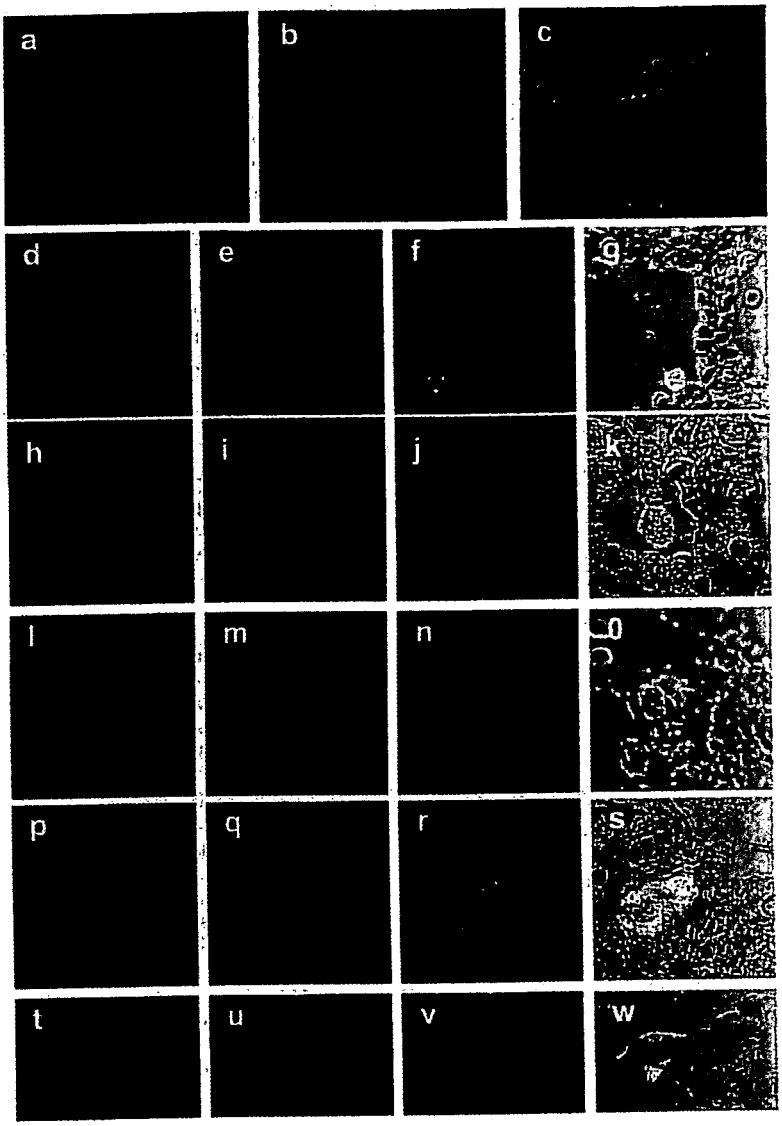

Fig. 2. The phenotype of influenza virus A nucleoprotein (InfA-NP) positive cells. InfA-NP immunoreactivity (a, d, h, l, p, t) (red color) and cytokeratin (b), EMA (e), SPD (i), CD68 (Kp1) (m), CD68 (PGM-1) (q) or CD34 (u) immunoreactivity (green color). Co-localization is presented respectively (c, f, j, n, r, v). Differential interference contrast (DIC) images are also shown (g, k, o, s, w). Original magnifications, ×400.

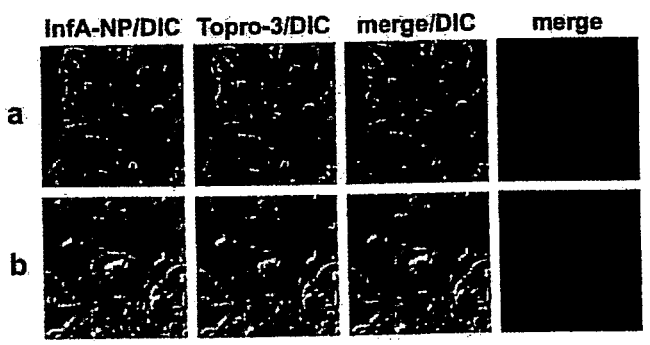

Fig. 3. Immunofluorescence staining of InfA-NP antigen in infected epithelial cells. InfA-NP immunoreactivity (red color), TO-PRO-3 nucleic acid staining (blue color) and merged images (pink color) are shown. Some were analyzed with differential interference contrast (DIC) images. The InfA-NP antigen was localized in nuclei (a) or in cytoplasm (b). Original magnifications, ×400.

frequently in epithelial (EMA-positive) cells. They were also detected in AE1/AE3, SPD, SPA, and CD68-positive cells (Fig. 2), indicating that H5N1 virus antigens were present predominantly in the epithelial cells in terminal bronchioles and alveoli, mainly in type II alveolar pneumocytes and in alveolar macrophages. A few H5N1 virus-infected type I pneumocytes were also suggested by double-positive staining for InfA-NP and for EMA, in combination with distinctive morphology. Although the number was very few, the InfA-NP signal was also detected in CD34-positive cells, suggesting that the H5N1 had infected some CD34-positive endothelial cells. Further investigation will be necessary to confirm the H5N1 infection of human endothelial cells, as has been observed in the endothelial cells of chickens and other birds (19). The localization of InfA-NP antigen within the cell was determined by counterstaining with TO-PRO-3 nucleic acid staining (Molecular Probes). Some InfA-NP signals were detected in nuclei (Fig. 3a) and others were detected in the cytoplasm (Fig. 3b). Histologically, in the early phase of infection, InfA-NP antigen was localized in the nucleus, while in the late phase of infection, InfA-NP antigen was localized in the cytoplasm (20). These observations suggested that viruses were in the proliferative stage in the early phase of H5N1 infection. The histopathological data

are summarized in Table 1.

Avian influenza viruses have been found to preferentially bind to sialic acid-α-2,3-Gal (SAα2-3)-linked oligosaccharides, while human influenza viruses were found to bind to SAα2-6-linked oligosaccharides (21), although these findings were made in vitro or ex vivo experiments. As an in vivo examination, we performed an analysis with the double-staining technique using a monoclonal antibody against InfA-NP in combination with either biotinylated *Maackia amurensis* agglutinin (MAA) lectin (Vector Laboratories, Burlingame, Calif., USA) which is specific for SAα2-3-linked oligosaccharides, or with *Sambucus nigra* agglutinin (SNA) lectin (EY Laboratories, San Mateo, Calif., USA), which is specific for SAα2-6-linked oligosaccharides. In the alveoli, many cells were not stained by SNA lectin but were stained by MAA lectin, suggesting that they express SAα2-3-linked oligosaccharides, as found in previous reports (21). Unexpectedly, the InfA-NP-positive cells were not double-stained by MAA lectin.

Although the materials were restricted to small pieces of lung tissue in the lower respiratory tract, the evidence in the present study showed that several types of cells in the lung, namely type I and type II alveolar pneumocytes, epithelial cells in terminal bronchioles, macrophages in the alveolar space and CD34-positive endothelial cells in the interstitial tissues, were involved in the disease. The evidence in Case 1, the case with H5N1 infection who died on day 6 after onset, strongly suggests that H5N1 may infect the epithelial cells of alveolar tissues in the early clinical phase and can thereafter be transmitted to adjacent cells. The dissemination of infection among these cells was supposed to be accompanied by the release of pro-inflammatory cytokines from the infected alveolar macrophages (4,10,12), resulting in rapid progression from DAD with an exudative phase to that with a proliferative phase.

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ヒトの鳥インフルエンザ感染症の臨床的諸問題
—H5N1を中心に—

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1. はじめに

かつては鳥のインフルエンザウイルスが直接ヒトに感染症を起こす事はないと考えられていた．しかし，1997年香港においてインフルエンザウイルスA/H5N1亜型（以下H5N1と略す）のヒト感染例が報告されて以来，鳥のインフルエンザウイルスもヒトに重症感染症を起こし得ることが広く認識された．H5N1のヒトへの感染力は弱く，またヒト—ヒト感染も認められなかったため，ウイルス保有の疑いのある鳥を大量に殺処分することで1997年のH5N1流行は終息した．しかしその後も鳥の間での流行を背景として，2003年末頃より再びH5N1ヒト感染事例が報告されるようになり，現在もその状況は続いている．H5N1が世界的に注目されているのは，ヒトに感染発病した場合の致死率が高いことのほかに，本ウイルスが近い将来ヒトへの強い感染力を獲得し，パンデミック（世界的な大流行）をおこしうる新型ウイルスに変異する可能性があるからである．現実味を帯びてきた次のパンデミックにむけて，WHO(世界保健機関）は2005年5月，新型インフルエンザパンデミックプランを大幅に改訂[1]，それに伴いわが国も2005年12月「新型インフルエンザ対策行動計画」を発表した[2]．また，2006年6月には感染症法の一部改正により，それまで四類感染症であった鳥インフルエンザのうち，H5N1は指定感染症に組み替えられ，入院勧告や就労制限などが適用されることとなった．本稿では，ヒトのH5N1感染症について，臨床的な側面からまとめてみたい．

2. ヒトの感染症の成立

a. 種の壁について

鳥のインフルエンザウイルスが鳥からヒトに直接感染することは稀である．鳥からヒトへ，種を超えた感染が成立しにくい理由として強調されているのは，レセプター特異性の存在である．すなわち，鳥インフルエンザウイルスと結合するレセプターは，ヒトには無いとされていた．しかし，最近の研究の結果，ヒトの気道にもわずかながら鳥ウイルスと結合するレセプターがあること[3]や，肺胞（Ⅱ型肺胞上皮細胞）には同レセプターが多く発現していること[4]，また，角膜や鼻涙管上皮にも同レセプターがあること[5]が示されている．これらの研究成果は，濃厚なウイルス曝露があれば鳥のインフルエンザは種の壁を越えてヒトに感染しうることを説明している．

b. ウイルスのヒトへの適応

レセプター特異性が宿主特異性を規定する大きな要因であるが，近年鳥型のみならずヒト型のレセプターとも結合しうるH5N1ウイルスが報告されている[6]．これらの知見は，今後ウイルスがわずかな変異により容易にヒトに感染するタイプに変わる可能性を示唆している．また，H5N1のRNAポリメラーゼのPB2サブユニットの627番目のアミノ酸がグルタミン酸からリジンに変わると同ウイルスが鳥だけでなく哺乳類

Clinical considerations of avian influenza A (H5N1) infection in humans
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の細胞で効率よく増殖することが示された[6,7]が，すでにこのような変化を認めるウイルスも見つかっているという．

c. ヒト—ヒト感染の問題

これまでのところH5N1のヒト—ヒト感染は稀である．しかし，ウイルスに対するレセプター特異性も絶対的なものではなく，またH5N1が徐々にヒトへの適応を進めている状況を考慮すると，現状においても濃厚なウイルス曝露があればヒト—ヒト感染も起こりうることは充分考えられる．すでにヒト—ヒト感染と推定される事例もベトナム，タイ，インドネシアから報告されている．特にインドネシアの例は，母親から6人の家族へ，そしてさらにそのうちの1人からもう1人へと3代に及ぶ感染であった可能性が示されている．

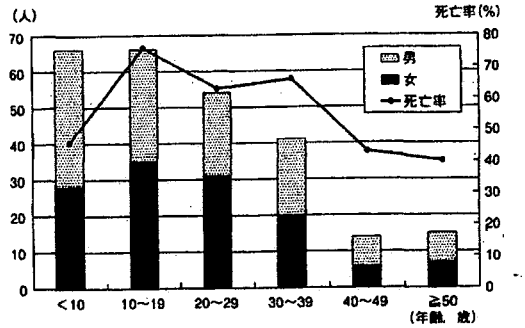
3. ヒト感染症の臨床的特徴

a. 疫学

疫学についてはWHOの報告[8]が最も大規模かつ包括的である．これは，2003年11月から2006年11月までの3年間にウイルス学的に確定されたH5N1報告例256例をまとめたものである．以下それに従い，疫学的特長を記す．

症例の報告は，いずれも北半球の冬から春の時期に集中しているように見える．患者の年齢別報告数と死亡率を図1[8]に示した．年齢は3ヶ月から75歳に分布するが，その中央値は18歳で，20歳未満が全体の52%，40歳未満が89%を占める．報告数に性差は無い．発症から入院までの日数の中央値は4日（分布は0～18日）である．全体の致死率は60%であるが，男性55%，女性65%と女性の死亡率が高い傾向にある．致死率が最も高い年齢階級は10～19歳で76%，最も低いのは50歳以上の40%である．発症から死亡までの期間の中央値は9日（範囲2～31日）である．

図1　インフルエンザA/H5N1患者の年齢別報告数と死亡率



WHOの報告[8]をもとに作図

以上のように本疾患が若年層に多く，また致死率も若年層で高い理由は明らかでない．1918年のインフルエンザパンデミック時も，20代～30代前半といった比較的若い年代での死亡率が高かったことが知られている[9]．新型インフルエンザウイルスが出現した場合，若年層が脆弱である可能性が示唆される．一方，2003年に世界で流行したSARS(重症急性呼吸器症候群)は，若年者の感染例が少なく，高齢者ほど罹患率・致死率共に高いという特徴を有していた[10]．このような年齢と罹患率・予後との関連が見られる理由については今後の研究が必要である．

b. 臨床像

H5N1感染症の臨床像は，WHOの専門家委員会が，香港，タイ，ベトナム，カンボジアからの報告をまとめた論文[11]に詳しい．その知見を以下に引用する．

患者の70～100%で病鳥，死鳥との接触歴がある．ほぼ全例で38℃以上の発熱，咳嗽を認めるほか，呼吸困難（報告により幅があり6～100%，以下同）咽頭痛・鼻汁（25～71%），下痢（17～70%），筋肉痛（0～53%），頭痛（10～100%）など呼吸器外症状もみられる．H7N7でみられた結膜炎症状はほとんど見られない．上気道症状は必須ではなく，早い段階から下気道症状を合併する．呼吸困難は発症後5日目頃に出現し，ほぼ全例が臨床的に肺炎となる．肺炎を合併すると頻呼吸となり，聴診上crackles が出現する．

胸部X線写真では，びまん性，多発性，斑状，すりガラス状，区域性，コンソリデーションなどと表現される多彩な所見が混在する．胸部X線上の異常陰影は発症後3，4日目頃から出現し始め，その進行は早い．陰影は融合しARDS (acute respiratory distress syndrome；急性呼吸窮迫症候群）の状態となる．検査では，末梢血白血球数減少，特にリンパ球減少（50～80%）ならびに血小板減（33～80%）がみられる．軽