We developed six IFN monotherapy strategies based on the outcome of pharmacogenomics, and sought to establish the strategy that maximize QALYs (Quality Adjusted Life Years) by age using Markov decision analysis model based on available clinical data and published data.

Methods

In order to visualize the natural course of HCV-1b (F3) and outcome after IFN monotherapy, we developed the Markov decision analysis model by age (40, 50, and 60 years of age). A hypothetical cohort consisting of 1000 patients was made for each age stratification (40, 50, and 60 years of age), and all of the cohort population were followed up until they died, on the assumption that all of them would die before 80 years of age. This assumption was based on the average life expectancy in countries ranking high in life expectancy. Data sources required for preparation of the model were as follows: Data on clinical prognosis of 151 HCV-1b (F3) patients (See "Method of collecting and analyzing NS5A 2209-2248 data" described below and Table 1), 102 HCV-1b (F3) patient QOL score data (See "Method of collecting and analyzing patient QOL data" described below and Table 1), data from literature retrieved from MedLine (1966 to January 2001), and textbooks.

Thus far, several HCV disease progression models have been reported (23) (24) (25) (26) (27). However, these previous models did not do characterize the progression of HCV-1b (F3) alone, and patients did not measure his/her own QOL scores. Further, these previous models did not incorporate recent data (15) (28) (29) on the prognosis for Non responder (NR) patients with HCV-1b after IFN therapy.

<Informed consent for the patients enrolled in the study >

The protocol for IFN treatment for HCV-1b (F3) was in accordance with the Helsinki Declaration. Informed consents were obtained from all 151 HCV-1b (F3) patients before they underwent liver biopsy and received IFN α-2b monotherapy and all 102 HCV-1b (F3) patients in whom patient QOL data were measured. Our study protocol was approved by the institutional review board.

<Assumptions in the Markov decision analysis model> (See, Fig 1)

Natural course of HCV-1b (F3);

The Markov decision analysis model used in our study consists of 4 stages: Severe fibrosis, Cirrhosis, HCC, and Death. Values specified in references were used for the probabilities of transition to disease from HCV-1b required in this analysis.

According to the values, it was assumed that HCV-1b (F3) would progress from

severe fibrosis, cirrhosis, HCC, to death in its natural course.

Definition of health outcome after IFN monotherapy: Patients in whom the level of ALT (alanine aminotransferase) maintains the normal range for 6 months after administration of IFN and HCV RNA disappears 6 months after the end of IFN therapy are defined as "Sustained Response (SR)" and other patients as "Non Response (NR)".

Patients who become SR after receiving IFN monotherapy were assumed to fully recover their health.

Thus far, several reports suggest that HCV-1b progress more rapidly than other genotypes (30) (31), while other reports deny this hypothesis (15) (28) (29) (32) (33) (34) (35) (36). It has not been concluded yet. In this analysis, we extracted 4 reports that indicate annual progression rate of HCV-1b disease and used them for base case analyses (15) (28) (29) (35). Not all of these 4 literatures exclusively indicated the transition probabilities of HCV-1b. Because it is said that there are no differences in the transition probabilities of diseases among genotypes, these literatures were used for the analysis.

According to previous reports, when HCV-1b (F3) takes its natural course, it advances to cirrhosis at an annual rate of 10% (5.9% to 63.3%) in patients who do not receive IFN (15) (29) (35). Also, it advances to HCC at an annual rate of 5.34% in patients with severe fibrosis, and 7.88% in patients with cirrhosis (28). Based on the literature and our clinical data, the annual mortality of cirrhosis and HCC are 5% (5% to 15%) and 63% (50% to 100%), respectively (36) (37) (38) (39). It has been known that the progression rate of liver diseases is affected by the age, sex, and alcohol consumption (35). Therefore, we later performed the sensitivity analyses within a range from the minimum value to maximum value in the references, and examined influences of these factors on results of the base case analyses in detail (See, Fig.1 and Table 1).

In previous reports, clinical effects on patients who were judged as NR after IFN monotherapy were not clear. However, more recent reports have indicated that the progression rate in patients who are judged as NR after IFN therapy is lowered as compared with those who did not receive IFN (15) (28) (29).

Therefore, it was assumed that diseases would progress at an annual rate of 2% (0% to 17.5%) in HCV-1b (F3) patients who were judged as NR after IFN monotherapy (total dose of IFN: 200 to 800 MU) (28) (29). In HCV-1b (F3) patients who were

judged as NR after IFN monotherapy (mean total dose: 480 MU), the incidence of HCC was lowered from 5.34% to 2.2% per year, and the incidence of HCC originated from cirrhosis was lowered from 7.88% to 5.32% per year (15).

<The disease management strategies> (See, Fig 1)

The disease management strategies are as follows:

Strategy 1: For HCV-1b (F3) patients, when the number of amino-acid mutations in the ISDR is 1 or more, IFN therapy is applied. For patients with absolutely no amino-acid mutation (wild type), IFN therapy is not applied.

Strategy 2: For HCV-1b (F3) patients, when the number of amino-acid mutations in the ISDR is 4 or more (mutant type), IFN therapy is applied. When the number of amino-acid mutations in the region is 1 to 3 (intermediate type), if the virus load is 0.5 Meq/ml or more, IFN therapy is not applied.

Strategy 3: For HCV-1b (F3) patients, when the number of amino-acid mutations in the ISDR is 1 or more, IFN therapy is applied. If the patient is of wild type and the virus load is 0.5 Meq/ml or more, IFN therapy is not applied.

Strategy 4: The NS5A test is not conducted for HCV-1b (F3) patients. If the virus load is 0.5 Meq/ml or less, IFN therapy is applied.

Strategy 5: IFN therapy is applied for all HCV-1b (F3) patients.

Strategy 6: IFN therapy is not applied for all HCV-1b (F3) patients.

<Validity of correlation between the effects of IFN monotherapy on HCV-1b and the number of amino-acid mutations in the ISDR>

At present, the correlation between ISDR and therapeutic effects of IFN monotherapy has been confirmed in Japan, Spain, and Italy (2) (16) (17) (18) (19) (20) (21) (22). For example, the rates of SR after IFN monotherapy in the wild type, intermediate type, and mutant type are 7.2% (10/138), 15.3% (23/151), and 79.6% (58/73), respectively. However, this correlation is not confirmed in some countries of Europe and in the U.S. (40) (41) (42) (43) (44) (45) (46) (47). The reasons why not confirmed in these countries are pointed out as follows: the number of mutants in Europe and the U.S. is smaller than that in Japan (9% (8/93) vs. 19% (76/409)); there is a difference in the total dose of IFN between Japan and Europe/the U.S. (9), and presence of HCV-1b type specific to Japan (J

group) (18). Recently, however, ISDR has been confirmed in Europe for combination therapy (14). At present, the rates of SR after combination therapy in the wild type, intermediate type, and mutant type are 0% (0/6), 18.8 % (3/16), and 75% (3/4), respectively (14). Furthermore, a statistically significant correlation between IFN response and substitutions in ISDR was demonstrated by a recent report (48).

<Method of collecting and analyzing ISDR data>

ISDR was measured by the method of Enomoto et al. (2) in 151 patients who underwent liver biopsy and genotyping by reverse transcription polymerase chain reaction (RT-PCR) at Tokyo Medical and Dental University (Tokyo, Japan) during the period from January 1992 to December 1997 and diagnosed as HCV-1b (F3), and received IFN α -2b (Intron A, Schering-Plough, Kenilworth, N.J.) monotherapy with a total IFN dose of 500 MU or higher (40 to 64 years of age, mean age: 55.0). The 151 HCV-1b (F3) patients enrolled in the study were monitored with serial alanine aminotransferase and HCV RNA determinations (Roche Amplicor version 2.0) during treatment and for 6 months following completion of therapy at Tokyo Medical and Dental University.

In our base case analyses, data on correlation between the therapeutic effects of IFN α -2b monotherapy (total dose of IFN: 500 MU or higher), virus load, and amino-acid mutations in the ISDR in these patients were used (Table 1).

<Method of collecting and analyzing patient QOL data>

In our study, QOL data were collected at Tokyo Medical and Dental University (Tokyo, Japan) during the period from January 1999 to December 2000 by using the time trade off method from 51 patients (40 to 63 years of age, mean age: 48.5) who were diagnosed as HCV-1b (F3) and received IFN α -2b (Intron A, Schering-Plough, Kenilworth, N.J.) monotherapy with a total IFN dose of 500 MU or higher, 36 patients with HCV related cirrhosis who received IFN α -2b monotherapy with a total IFN dose of 500 MU or higher (47 to 63 years of age, mean age: 52.9), and 15 patients with HCC (49 to 68 years of age, mean age: 61.3). QOL data of HCV-1b (F3) patients and patients with HCV related cirrhosis were measured at 3 timepoints, that is, prior to IFN α -2b monotherapy, 6 months after the end of IFN α -2b monotherapy, and during IFN α -2b monotherapy. Patients QOL scores were expressed as values between 0 (death) and 1.0 (perfect health).

Median values in the case of the absence of IFN therapy (Prior to IFN therapy and 6 months after the end of IFN therapy) were used as QOL scores for base case analyses. Sensitivity analyses were made within a range from 0 to 1.0 in order to examine whether IFN monotherapy affected patient QOL in detail (Table 1).

Results

< The base case analyses >

The base case analyses proved that the strategy to perform IFN monotherapy for all HCV-1b (F3) patients aged 40 to 60 years had an advantage. In this case, QALYs of the patients that are shown within the range of 5% discount are as follows: Patients aged 40, 50 and 60 years were 11.97 to 22.87 QALYs, 10.29 to 17.53 QALYs, and 7.48 to 11.04 QALYs, respectively. QALYs decreased with aging.

<Sensitivity analyses>

We performed sensitivity analyses on all values, including discount rate, in order to process data concerning uncertainty of various clinical probabilities. Table 1 shows the scope of sensitivity analyses for each value.

As a result, it was found that three factors influenced the results of the base case analysis: QOL scores of HCV-1b (F3) patients aged 40 to 60 years, the SR rates of these patients after IFN monotherapy, and the transition probabilities of diseases when patients were judged NR after IFN monotherapy. Other values did not influence the results within the range of sensitivity analyses. In order to support the results of the base case analysis, HCV-1b (F3) patients aged 40 to 60 years had to meet the following three requirements. The results are shown with or without 5% discount.

(1) Their QOL scores had to be 0.4 or higher both with and without 5% discount.
(2) The SR rates of IFN monotherapy for the patients aged 40, 50, and 60 years had to be 2.48% or higher, 2.54% to 2.96% or higher, and 8.25% to 8.95% or higher, respectively.
(3) When these patients were judged as NR after IFN monotherapy, the transition probabilities of diseases at the age of 40, 50, and 60 had to be such that the progression of liver diseases were controlled at an annual rate of 9.0% to 10.98% or lower, 9.45% to 10.21% or lower, and 8.31% to 8.42% or lower, respectively. (See, Fig 2-4; Sensitivity analyses for HCV-1b (F3) patients aged 60 years)

Discussion

As a result of the base case analyses, IFN monotherapy was considered favorable for HCV-1b (F3) patients aged 40 to 60 years. However, the results of the sensitivity analyses indicated that the results of this base case analyses were still controversial.

Therefore, we examined the three factors that had great influences on the results in detail.

First, QOL scores of HCV-1b (F3) patients aged 40 to 60 years were examined. Because there is no data on QOL scores of such patients in the literature at present, we studied them in patients who participated in our clinical study. QOL scores of HCV-1b (F3) patients aged 40, 50, and 60 years were 0.75 to 0.87, 0.68 to 0.78, 0.53 to 0.62, respectively, when indicated within the range of presence or absence of IFN monotherapy (total dose of IFN: 500 MU). QOL scores were above the threshold value, that is, 0.4 or above. Therefore, the results of the base case analysis concerning QOL scores were proved.

Second, the transition probabilities of diseases in patients who were judged as NR after IFN monotherapy were examined. Because there are no data on the transition probabilities of liver diseases by age when HCV-1b (F3) patients are judged as NR after IFN monotherapy, we hypothesized that there were no differences in the transition probabilities of diseases between the age groups when patients were judged as NR after IFN monotherapy, based on recent data from the literature. However, it has been known that the progression rate of liver diseases is affected by the age (35). Therefore, we conducted sensitivity analyses within the range from the minimum value to the maximum value in each citation (See Table 1). According to Shiratori et al., when patients were judged as NR after IFN monotherapy, the transition probability of diseases by IFN treatment in a total dose of 200 to 800 MU was 2% (0% to 4%) (28). According to Poynard et al., on the other hand, the probability was 10.9% (2.7% to 17.5%) per year when the total dose of IFN was 216 MU (24 weeks), and 8.5% (3.6% to 16.9%) per year when the total dose of IFN was 432 MU (48 weeks) (29).

In our sensitivity analyses, in order to prove that it was desirable to perform IFN monotherapy for all HCV-1b (F3) patients, the progression of liver diseases in patients aged 40, 50, and 60 years had to be controlled to 9.0% to 10.98% or lower per year, 9.45% to 10.21% or lower per year, and 8.31% to 8.42% or lower per year, respectively. For this

reason, the results of the base case analyses may be true in patients aged 40 years when the total dose of IFN is 216 MU, but it is highly possible that patients aged 50 and 60 years may not be feasible for IFN monotherapy. On the other hand, if the total dose of IFN is 432 MU or higher, the results of the base case analyses are considered to be true in patients aged 40 and 50, but are not in patients aged 60 years.

Third, the SR rates of IFN monotherapy in HCV-1b (F3) patients were examined. In order to validate the results of the base case analyses, the SR rates of IFN monotherapy in HCV-1b (F3) patients aged 40, 50, and 60 years had to be 2.48% or higher, 2.54% to 2.96% or higher, and 8.25% to 8.95% or higher, respectively.

However, there is no literature that describes SR rates of IFN monotherapy in HCV-1b (F3) patients by age. In our clinical study, the SR rates in patients aged 40, 50, and 60 years were 37.1% (13/35), 29.1% (16/55), and 8.2% (5/61), respectively. Only the SR rate in HCV-1b (F3) patients aged 60 years was below 8.25%, that is, the threshold value.

Thus, the results of sensitivity analyses suggest it is highly possible that IFN monotherapy would become the first-line treatment for HCV-1b (F3) patients aged 40 and 50 years if the total dose of IFN was at least 432 MU.

On the other hand, IFN monotherapy was not necessarily the first-line treatment for HCV-1b (F3) patients aged 60 years. Instead, strategy 3 seemd most advantageous to those patients. If IFN monotherapy is performed for them, the NS5A test and virus load test should be conducted prior to the initiation of treatment. IFN monotherapy should be applied at a dose of at least 432 MU only for patients in whom the number of amino-acid mutations in the ISDR is 1 or more and the virus load is 0.5 Meq/ml or less.

In addition, for HCV-1b (F3) patients aged 60 years who are not capable for IFN monotherapy and those living in countries where the correlation between therapeutic efficacy of IFN monotherapy and ISDR has not been confirmed, it would be necessary to examine whether it is possible to apply combination therapy to them. Therefore, we examined whether it was possible to apply combination therapy to HCV-1b (F3) patients aged 60 years by using our decision analysis model for IFN monotherapy in present study. At present, however, there is not enough literature available describing the effects of combination therapy in HCV-1b (F3) patients aged 60 years.

If the QOL scores during IFN monotherapy in HCV-1b (F3) patients aged 60 years are comparable to those during combination therapy, and the progression probabilities of

liver diseases in them are comparable between IFN monotherapy and combination therapy, we can make the following hypothesis by using our Markov decision analysis model in the present study. Combination therapy may be the first-line treatment for HCV-1b (F3) regardless of patient's age, if combination therapy for HCV-1b (F3) patients aged 60 years is proved to: (1) Maintain the patient QOL score at 0.4 or higher, (2) Improve the CR rate to 8.25% to 8.95% or higher, and (3) Reduce the progression probability of liver diseases per year to 8.31% to 8.42% or lower.

It should be possible to draw more precise conclusions by using the results of clinical trials which will be available in the future. While it is likely that more effective treatments will be introduced for the management of HCV disease, such as longer-acting forms of interferon (49), the analyses outlined here will also be applicable to these forms of treatment.

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Current Mailling Addresses
Hisashi Moriguchi [1, 4, 5] MPH, Takamoto Uemura [2] MD, Makoto Kobayashi [3] M. Eng., Raymond T Chung [4] MD, Chifumi Sato [5] MD.

1) Division of Advanced Medical Technology and Intellecual Property Policy, Research Center for Advanced Science and Technology, University of Tokyo. 4-6-1, Komaba Meguro-ku, Tokyo, Japan, 153-8904
2) Department of preventive Medicine and public health, school of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo, Japan, 160-0016
3) Healtheconomics research group, Crecon research and consulting Inc. The pharmaceutical society of Japan, Nagai memorial Bldg., 2-12-15 Shibuya, Shibuya-ku, Tokyo, Japan.150-0002
4) Gastrointestinal Unit, Massachusetts General Hospital and Harvard Medical School., Massachusetts General Hospital, Boston, MA, 02114
5) Department of Health Science, Faculty of Medicine, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo, 113-8519

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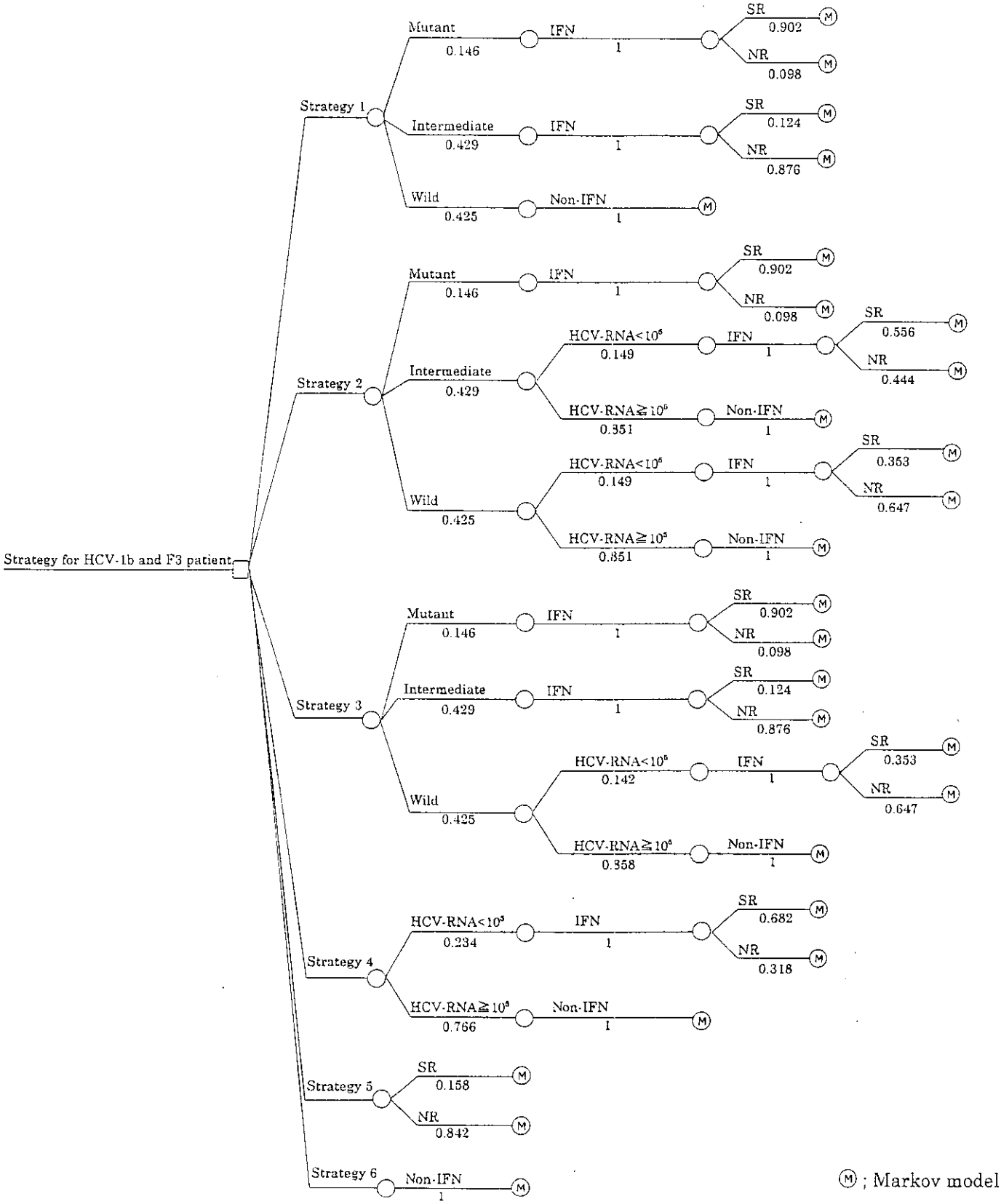


Fig 1. Markov Decision Tree

Sensitivity Analyses (No discount)

Fig.2. Sensitivity analysis on QOL (utility) Score for HCV-1b (F3) patient ,60 years old.

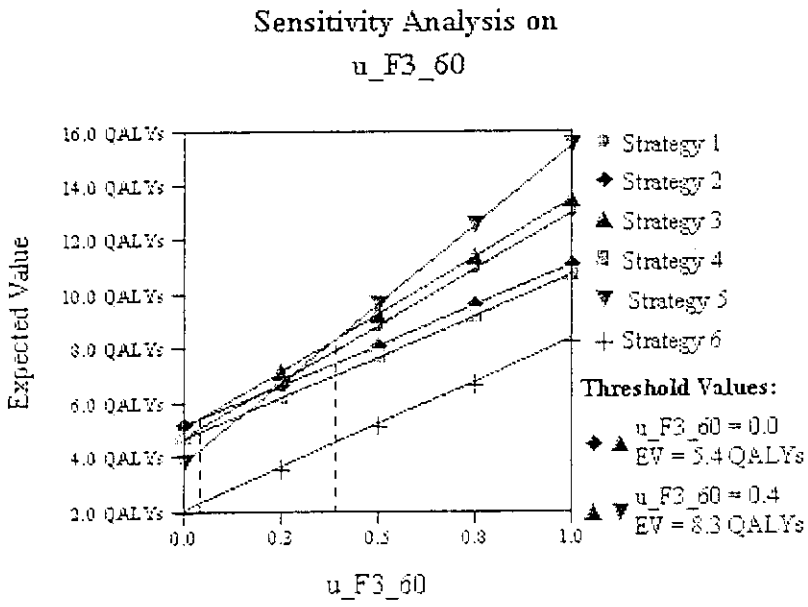


Fig.3. Sensitivity analysis on transition rate for IFN-NR patient with HCV-1b (F3), 60 years old.

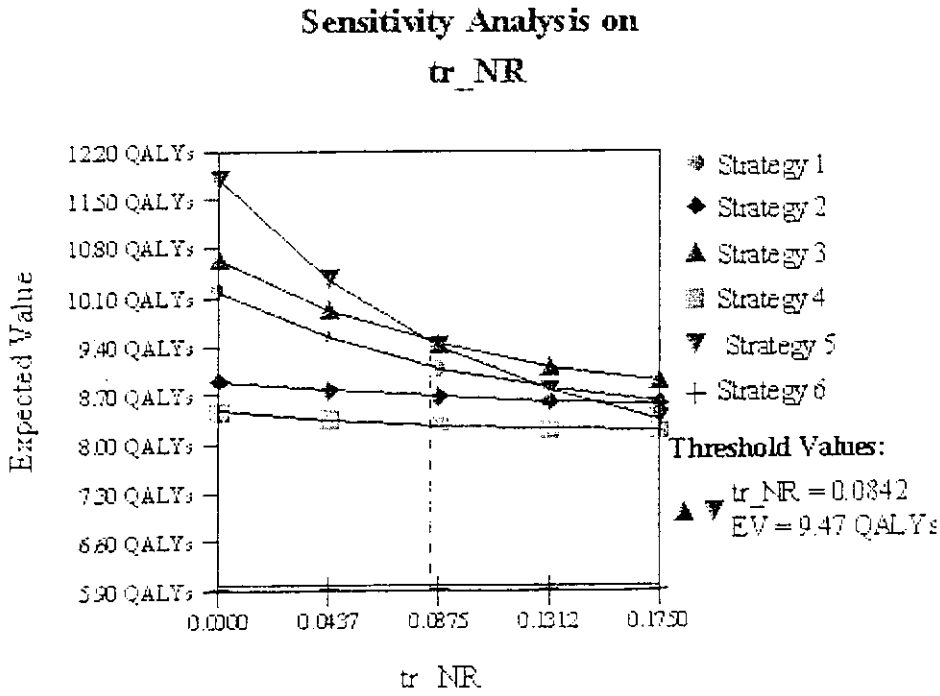
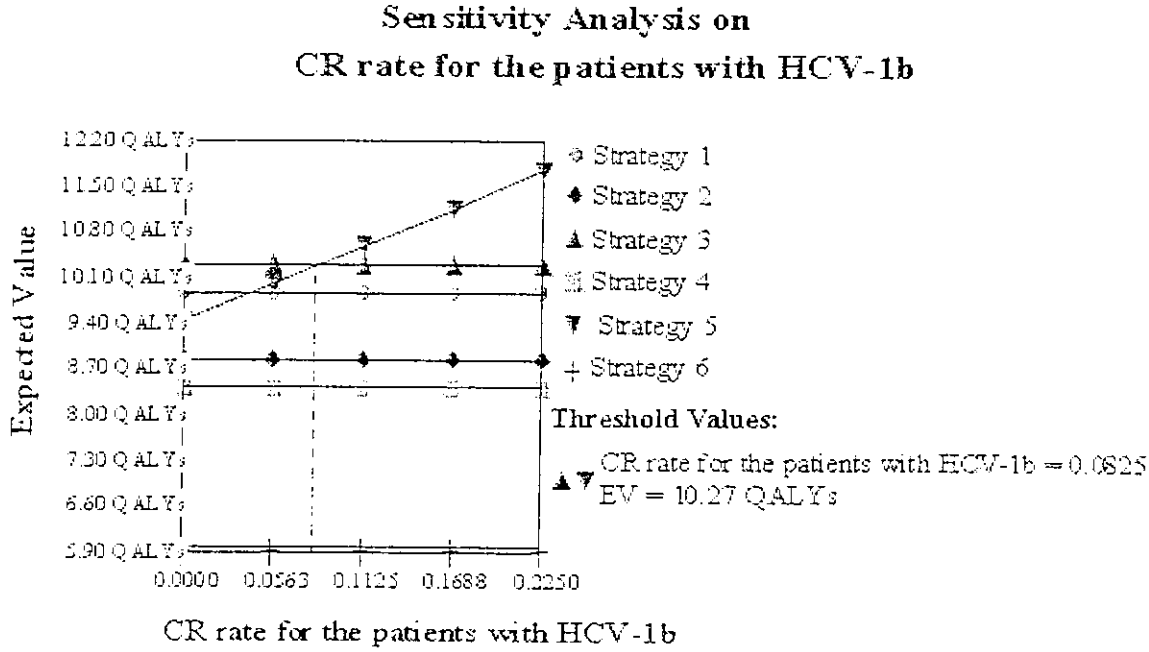


Fig.4. Sensitivity analysis on IFN-SR rate for the patient with HCV-1b (F3), 60 years old.



International Society of Chemotherapy

7TH WESTERN PACIFIC CONGRESS OF CHEMOTHERAPY & INFECTIOUS DISEASES

第七屆西太平洋化療及傳染病會議

11 - 14 DECEMBER 2000

MEETING THE CHALLENGES OF THE NEW MILLENNIUM

Dr. Moriguchi Hisashi
University of Tokyo
4-6-1 Komaba Heguro-ku
Tokyo
Japan

10 September 2000

Dear Dr. Monriguchi,

Re: 7th Western Pacific Congress of Chemotherapy & Infectious Diseases (7th WPCCID) Abstract acceptance

We are pleased to inform you that your abstract has been accepted for presentation at the above Congress. Please find the details confirmed as below:

Category	:	Clinical trials
Your abstract title	:	Evaluation of the usefulness of various antibiotics for acute upper respiratory tract infections –A pilot study-
Form of presentation	:	**Poster**

We will soon send you a confirmation letter to advise the arrangement such as the presentation sessions, days, times and other relevant information in October. Meanwhile, please be advised all authors are requested to register for the Congress before 01 November 2000. If the registration fee from the author is not received by this date, the abstract will not be published in the program book or any other forms.

By registering early, you can save up to US$40. We urge you to register before 15 Oct 2000.

Once again, we thank you for your support of the Congress. Should you require any further information, please do not hesitate to contact us.

Yours sincerely,

Dilys Liu
Congress Secretariat
7th Western Pacific Congress
of Chemotherapy & Infectious Deseases

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Tel: (852) 2735 8118 Fax: (852) 2735 8282 E-mail: moreview@mvdmc.com

西太平洋化学療法・感染症学会にて発表.
(2000年11月, 香港)

急性上気道感染症に対する抗菌薬の評価-第一次試行調査-

森口尚史（東京大学先端科学技術研究センター 客員助教授）
上村隆元（慶応義塾大学医学部 助手）
佐藤千史（東京医科歯科大学医学部 教授）

背景

現在、急性上気道感染症治療については市販されている抗菌薬の多くが高い有効性を示しており、薬物治療における充足度が高い領域である。

一方、本疾患は治癒率が高くエンピリック・セラピー（経験的な治療）が中心となるため、細菌学的検査による起炎菌の消失時期や治癒日数を正確に把握することが困難である。

しかし、最近、Evidence Based Medicine (EBM；根拠に基づく医療)概念の臨床導入に関する大きな盛り上がりの中で、EBM による抗菌薬の効果的かつ効率的な使用戦略の構築が必要とされている。

MedLine による文献検索（1966 年～2000 年 12 月）によれば、現時点で扁桃炎・咽喉頭炎に対する抗菌薬の比較試験は十分でない（1）（2）。

患者数が多いにも関らず、扁桃炎・咽喉頭炎に対しては「ニューキノロン・セフェム・マクロライド系抗菌薬」に関する比較試験はほとんどなく、これらの疾患に、いつ・どのような抗菌薬をどのように使用すればいいのかを考える際の基盤となる「科学的証拠」は国際的にみても脆弱であるといわざるを得ない。

さらに、最近では、風邪・インフルエンザでの抗菌薬・解熱鎮痛剤の併用による重篤な副作用が日本でも問題となっている。

この点に関し、アメリカでは 1993 年度ベースで薬の副作用死は 7391 件であり、そのうち 2098 人が解熱鎮痛剤で死亡しているというデータが示された（3）。したがって、扁桃炎・咽喉頭炎に対する抗菌薬・解熱鎮痛剤の併用の是非についても、十分な評価検討がなされる必要がある。

目的

体温 38.6℃以上の扁桃炎・咽喉頭炎患者（重症例）に対し体温を指標とした治癒判定を行い、治癒率を比較することで、「ニューキノロン・セフェム・マクロライド系抗菌薬」の臨床上の位置付けを客観的に評価する。また、Visual Analogue Scale (VAS)を用いた患者 QOL の推移、更に 5 日以内の再診率を比較することにより、各抗菌薬に対する患者自身の医療満足度を評価する。以上により、扁桃炎・咽喉頭炎（重症例）に対し、いつ・どのような抗菌薬をどのように使用すればいいのかに関するエビデンスに基づく「診療ガイドライン」作成のための参照情報を得ることが目的である。